Risk of rebleeding from gastroesophageal varices after initial treatment with cyanoacrylate: a systematic review and pooled analysis.

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Abstract

Background Cyanoacrylate alone or in combination with other interventions, can be used to achieve variable rates of successes in preventing rebleeding. Our study aims to assess the pooled risk of gastric and esophageal varices rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments, by systematic review of literature and pooled analysis.

Methodology PubMed, EMBASE, SCOPUS and the Cochrane library were searched for studies that reported the risk of rebleeding during the follow-up period after treatment of gastric or esophageal varices with either cyanoacrylate alone or in combination with other treatments. Standard error, upper and lower confidence intervals at 95% confidence interval for the risk, were obtained STATA Version 15 which was also used to generate forest plots for pooled analysis. Random or fixed effect model was used depending on the heterogeneity (I2).

Results A total of 39 studies were found to report treatment of either gastric or esophageal varices with either cyanoacrylate alone or in combination with other treatments. When gastric varices are treated with cyanoacrylate alone, the risk of rebleeding during the follow-up period is 0.16(Confidence Interval: 0.13-0.18). When combined with lipiodol; polidocanol or sclerotherapy the rebleeding risks are 0.13 (CI:0.03-0.22), 0.10(CI:0.02-0.19) and 0.10(CI:0.05-0.18), respectively. When combined with percutaneous transhepatic variceal embolization; percutaneous transhepatic variceal embolization; endoscopic ultrasound guided coils; or with ethanolamine, the rebleeding risk are 0.10(CI:0.03-0.17), 0.10(CI:0.03-0.17), 0.07(CI:0.03-0.11) and 0.08(CI:0.02-0.14), respectively. When esophageal varices are treated with cyanoacrylate alone, the risk of rebleeding is 0.29(CI:0.11-0.47). When combined with percutaneous transhepatic variceal embolization; sclerotherapy; or band ligation, the risks of rebleeding are 0.16(CI:0.10-0.22), 0.12(CI:0.04-0.20) and 0.10(CI:0.04-0.24), respectively. When combined with transjugular intrahepatic portosystemic shunt; or ethanolamine, the risks of rebleeding are 0.06(CI:-0.01-0.12) and 0.02 (CI:-0.02-0.05), respectively.

Conclusion In treating both gastric and esophageal varices, cyanoacrylate produces better results in terms of lower risk of rebleeding when combined with other treatments than when used alone. The combination of cyanoacrylate with ethanolamine or with endoscopic ultrasound guided coils produces lowest risk of rebleeding in esophageal and gastric varices, respectively. We call upon randomized trials to test these hypotheses.

Introduction

Liver cirrhosis is the leading cause of portal hypertension which in turn, leads to portal hypertension and gastrointestinal varices. Up to 17% of liver cirrhosis patients will develop esophageal varices, while 15% will develop gastric varices. Up to 30% gastroesophageal varices will bleed within 2 years (1). Bleeding from varices is one among gastrointestinal emergencies that account for majority of mortalities and morbidities among portal hypertension patients despite the cause (2). About 50–80% of patients who survive the first episode of variceal hemorrhage will have a recurrent early or late rebleeding episode (3). Up to 20% of patients with rebleeding a episodes will not survive (4).

From an older literature, half of variceal hemorrhages would stop spontaneously however, the risk of rebleeding and mortality increases significantly (5). Current studies, however, report that, in patients with cirrhosis Child-Pugh of class C or with hepatic venous pressure of higher than 20millimeters of mercury are less likely to spontaneous stoppage of bleeding. These patients would require interventional hemostatic measures with pharmacological drugs such as octreotide, somatostatin and beta blockers; endoscopic sclerotherapy, band ligation or tissue adhesives injection; and/or shunting by surgery or by transjugular intrahepatic portosystemic shunt to achieve hemostasis. A selective combination of these approaches has also been reported (1). Different hemostatic approaches differ in terms of their success rates in achieving hemostasis, preventing rebleeding and reducing mortality and morbidity. With advancing technology, each approach has evolved, and tissue adhesives have increasingly being used as the first line of therapy during the last decades (6, 7).

Also known as “tissue glue”, tissue adhesives were approved by the United States of America’s Food and Drug Authority in 1998, however, there have been previous studies reporting their use as back as the year 1981 (8). Primarily containing n-butyl-2 cyanoacrylate or 2-octyl cyanoacrylate, tissue adhesives are liquid monomers that undergo chemical reactions upon contact with moisture, to form polymers that can strongly attach to tissue (9). Despite a number of reported complications associated with their use such as embolism and needle impaction (10), cyanoacrylate has been reported to have higher hemostasis and lower rebleeding rates than traditional band ligation and sclerotherapy in gastroesophageal varices (2). Moreover, they have been reported to have antibiotic activity towards gram-positive bacteria (11).

Cyanoacrylate can be used alone or in combination with other interventions, to achieve variable rates of successes in hemostasis, reducing mortality and prevention of rebleeding. Our study was aimed at assessing the overall risk of gastroesophageal rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments, by systematic review of literature and pooled analysis.

Methods

Eligibility criteria

The current study involved participants with bleeding gastroesophageal varices who underwent hemostasis by cyanoacrylate injection alone or in combination with other treatments. Observational and interventional studies reporting the risk of rebleeding after hemostasis treatment were included. Expanding the external validity, eligible English published literature from across the world were included.

Information sources

Four online databases, namely PubMed, EMBASE, SOPUS and the Cochrane library were systematically searched with no time range specified. Secondary referencing of eligible studies extended the search scope. The last search was conducted on 4th March 2020.

The search

Advanced search tool employing MeSH and keywords, was utilized in all three online databases. Using PubMed, advanced search was done as; (((((cyanoacrylate[MeSH Terms]) AND endoscopic hemostasis[MeSH Terms]) AND esophageal varices[MeSH Terms]) OR gastric varices[MeSH Terms])) AND reble*. The search was repeated as; (((adhes*) AND endosc*) AND varic*) AND reble*. The searches were independently performed by two authors; ZH and JS. Results were exported to *EndNote X9 (Builld 12062)* which kept track of references.

Study selection process

Two authors screened titles and abstracts of all articles from online database searches to identify the most relevant articles in line with our study question. The relevant articles were sought for full texts and final included studies were identified after thorough reading full text articles to assess inclusion and exclusion criteria. This process was done by two authors; ZH and JS with the third author, TL assisting to resolve discrepancies. The search, screening and study identification process is summarized in **Figure 1.**

Data extraction

Before data extraction process from full-text articles meting eligibility criteria for inclusion, assessment for methodological biases was done by using the Joanna Briggs institute meta-analysis of statistics assessment and review instrument. PRISMA (12)(preferred reporting items for systematic reviews and meta-analyses) tool was used to minimize reporting bias upon write-up of this study.

Data collected included Author name, year of publication, country of study, study design, what comparison groups involved, varicose lesion location, study sample size, definitive diagnoses, number/ proportion of rebleeding events among followed up patients, the name of tissue adhesive utilized and follow-up duration. This was independently performed by two authors, namely; ZH and DZ with SL to resolve discrepancies. The current study had on outcome, the risk of rebleeding.

Analysis

The risk of rebleeding among gastric and esophageal varices patients were analyzed separately. Moreover, the risk of rebleeding in gastric or esophageal varices groups were analyzed separately depending on whether the cyanoacrylate was utilized alone or in combination with other treatments. This gave rise to five separate analyses on which quantitative analysis was conducted: (1) Analyzing pooled risk of rebleeding in gastric varices treated with cyanoacrylate alone; (2) analyzing pooled risk of rebleeding in esophageal varices treated with cyanoacrylate alone; (3) analyzing pooled risk of rebleeding in gastric varices treated with cyanoacrylate with ethanolamine; (4) analyzing pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils; and (5) analyzing a pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization. A qualitative narrative (i.e. descriptive) approach was utilized in assessing the risk of rebleeding in gastroesophageal varices treated with cyanoacrylate with sclerotherapy as the eligible studies involved different participants.

The risk of rebleeding was calculated dividing the number of patients rebleeding during the follow-up period after endoscopic hemostasis by the total number of patients that initially underwent the endoscopic hemostasis procedure. The denominator did not include patients lost during the follow up. Standard error, upper and lower confidence intervals (at 95% confidence interval) for the risk, were obtained from the “generate command” in computer software ***STATA Version 15*** which was also used to generate forest plots for pooled analysis. The software was customized to random or fixed effect model depending on the heterogeneity (I^2) of the studies when analyzing the outcomes. Fixed effect model was used when I^2 was less than 50% and random effect model was used when I^2 was more than 50% indicating significant heterogeneity.

Assumptions

Participants were considered to have been correctly diagnosed with upper gastrointestinal bleeding due to gastric or esophageal varices, and not due to other causes such as Mallory-Weiss tear or gastritis. Despite the country under which treatment was given, all patients were considered to have received standard care.

Results

A total of sixty (60) studies that seemed to be relevant to our study basing on screening titles and abstract, were sought for full texts. Five of these were eliminated after thorough full-text reading. *Webb* et al (1981)(8) did not report our outcome of interest; *Datta* et al. (2003)(13) and *Smith* et al. (2014)(14) utilized fibrin glue; *Noh* et al. (2004)(15) and *Zhang* et al. (2007)(16) used Korean and Chinese language, respectively. A total of 55 studies were included in the systematic review while 39 studies were pooled for statistical analysis.

Characteristics of included studies

Table 1 illustrates characteristics of all included studies in our pooled analysis. These were published between the year 1989 and 2019 from countries in Africa, Europe, Asia, and North America. Eleven studies were retrospective observational; sixteen were prospective observational; two were case series; and ten were randomized clinical trials. Thirteen studies were comparative, one arm of which was cyanoacrylate. Eleven studies were non-comparative involving only cyanoacrylate outcome assessment while of the two studies, one involved comparing different doses of cyanoacrylate (i.e. 0.5mls versus 1.0mls) while another compared diluted versus undiluted cyanoacrylate. Follow-up duration after treatment with cyanoacrylate ranged from six weeks to fifteen years in another study. One study did not report duration of follow-up.

A total of 39 studies reported 3630 who had either gastric or esophageal variceal and underwent hemostasis with cyanoacrylate alone or in combination with other treatments. A total of 497 had gastric or esophageal recurrent bleeding episodes during the follow-up period.

Table 1. Study characteristics

Author (Year)	Country of study	Study design	Comparison groups	Lesion location (Sample size)	Diagnoses	Participants rebleed	Type of tissue adhesive utilized	Follow-up duration
Ramond (1989)(17)	France	Case series	butyl cyanoacrylate versus Sclerosant	Gastric 27	Cirrhosis; Portal vein thrombosis	10 out of 27 followed up	butyl cyanoacrylate	1-38 Months (Mean: 14.7 ±11.0)
Oho 1995(18)	Japan	Randomized trial	ethanolamine oleate (n = 24) or butyl cyanoacrylate (n = 29	Gastric	Gastric varices	9 out of 29 in the cyanoacrylate group	cyanoacrylate	14 months
D'Imperio 1996(19)	Italy	Prospective	N-butyl-2-cyanoacrylate	Esophageal 24; Gastric 54; Duodenal 2	Upper gastrointestinal tract varices	2 from gastric varices; 0 from duodenal varices; Esophageal not reported	N-butyl-2-cyanoacrylate	6 Months
Omar 1998(20)	Egypt	Prospective trial	Polidocanol, Ethanolamine, Cyanoacrylate	Esophageal 60	Schistosoma hepatic fibrosis	0	Cyanoacrylate	Not accessed
Kind 2000(21)	Italy	Retrospective	One arm study: Bucrylate	Gastric 174	Gastric varices	27 (Occurred during the firt 30 days)	Bucrylate	12 years
Evrad 2003(22)	Belgium	Retrospective	N-butyl-2-cyanoacrylate versus Proprenolol	Esophageal 16; Gastric 5	Esophagogastric varices	Esophageal 4; Gastric 2	N-butyl-2-cyanoacrylate	6 weeks
Noophun 2005(23)	Thailand	Prospective	One arm study: cyanocrylate	Gastric 24	Gastric varices	10	N-butyl-2-cyanoacrylate	Minimum of 4 weeks
Tan 2006(24)	Taiwan	Prospective	Band ligation Vesus N-butyl-2-cyanoacrylate	49	Liver cirrhosis	11	N-butyl-2-cyanoacrylate	680.67 ±710.54 days
Cheng 2007(25)	China	Retrospective	One arm study: N-	Gastric 635	Gastric varices	44 out of 550 followed up	N-butyl-2-cyanoacrylate	Up to 10 years

			butyl-2-cyanoacrylate					
Kuo 2007(26)	China	Randomized trial	Histoacryl versus Histoacryl + hypertonic glucose solution	Gastric 67	Gastric varices	2 out of 34 who received Histoacryl alone	N-butyl-2-cyanoacrylate	37.9 ±18.5 months
Hong 2009(27)	Korea	Randomized trial	Endoscopic N-butyl-2-cyanoacrylate injection versus balloon-occluded retrograde transvenous obliteration	Gastric 27	gastric variceal hemorrhage	10 out of 14 in the N-butyl-2-cyanoacrylate group	N-butyl-2-cyanoacrylate	Up to 17 Months
Hou 2009 (28)	Taiwan	Randomized trial	0.5 mL Versus 1.0 mL of cyanoacrylate	Gastric 44	gastric variceal hemorrhage	14 out of 47 in the 0.5mls group; 17 out of 44 in the 1ml group	N-butyl-2-cyanoacrylate	Up to two years
Procaccini 2009(29)	USA	Retrospective	Cyanoacrylate versus TIPS	Gastric 105	gastric variceal hemorrhage	13 out of 61 in the Cyanoacryl group (4/58 at 72hrs; 5/47 at 3 months; 4/40 at 1year)	Cyanoacrylate	Up to one year
Rivet 2009(30)	France	Prospective	Cyanoacrylate versus Band ligation	Esophageal 8	Portal hypertension due to portal vein thrombosis, biliary atresia and antitrypsin deficiency	3 out of 8 in the cyanoacrylate group	Cyanoacrylate	12.5 10.6 weeks
Cheng 2010(31)	China	Retrospective	Butyl cyanoacrylate	Gastric varices 753	Gastric varices due to viral	33	Butyl cyanoacrylate	Up to 6 months after

					hepatitis and others			initial endoscopy
Choudhuri 2010(32)	India	Prospective	N-butyl-2-cyanoacrylate	Gastric varices 170	Gastric variceal hemorrhage	23 out of 158 that were followed-up	N-butyl-2-cyanoacrylate	30.7 + 17.2 months
Mishra 2010(33)	India	Prospective	Cyanoacrylate versus beta blocker	Gastric 33; Esophageal 26	Gastric varices	3 out of 33	cyanoacrylate	26 Months
Soga 2010(34)	Japan	Case report	N-butyl-2-cyanoacrylate cyanoacrylate	Gastric 1; Duodenal 1	Gastroduodenal varices	No rebleeding recorded	N-butyl-2-cyanoacrylate cyanoacrylate	53 days
Binmoellar 2011(35)	USA	Retrospective	N-butyl-2-cyanoacrylate cyanoacrylate	Gastric 30 (24 variceal; 6 non variceal)	Gastric varices; Non variceal lesion	No bleeding recorded from 24 variceal group	N-butyl-2-cyanoacrylate cyanoacrylate	193 (24-589) days
Kang 2011(36)	Korea	Retrospective	N-butyl-2-cyanoacrylate cyanoacrylate	Gastric varices 127	Gastric varices	29 out of 127	N-butyl-2-cyanoacrylate cyanoacrylate	One year
Liao 2013(37)	Taiwan	Prospective	Cyanoacrylate	Gastric varices 69	Gastric varices	10 out of 69	Cyanoacrylate	More than 30 months
Tantau 2013(38)	Romania	Prospective	Cyanoacrylate versus Band ligation	Gastric 37	Gastric varices	6 out of 19 in the Cyanoacrylate group	Cyanoacrylate	27.26 ± 214.16 days
Al-Bawardy 2016(39)	USA	Retrospective	2-octyl cyanoacrylate	Gastric 95	Gastric Variceal Hemorrhage	8 out of 95	2-octyl cyanoacrylate	Up to 15 years
Singh 2016(10)	India	Prospective	Diluted versus undiluted Cyanoacrylate	Gastric 30	Gastric Variceal Hemorrhage	5 out of 30	Cyanoacrylate	Up to one year
Liu 2019(40)	China	Prospective	Cyanoacrylate with Versus without antibiotic	Gastric varices 107	Gastric varices	106 out of 107	Cyanoacrylate	4.59 ± 1.63; 4.30 ± 1.48 Days
Xiaoqing 2019(2)	China	Prospective	Cyanoacrylate versus Cyanoacrylate	Gastric varices 130	Gastric varices	8 out of 62 in the	Cyanoacrylate	38.8 months for

			+ Lauromacrogo			Cyanoacrylate group		Cyanoacrylate group
Thakeb 1995 (41)	Egypt	Randomized trial	N-butyl-2-cyanoacrylate plus ethanolamine oleate 5% versus ethanolamine alone	Gastric varices 57; Esophageal varices 59	Gastroesophageal varices	3 out of 57 gastric varices; 1 out of 59 esophageal varices.	N-butyl-2-cyanoacrylate	Up to 32 months
Maruyama 2010(42)	Japan	Retrospective	Cyanoacrylate plus ethanolamine	Gastric varices 20	Gastric varices	10 out of 20 gastric varices	Cyanoacrylate	28.1 months
Bhat 2016(43)	United States of America	Retrospective	cyanoacrylate and coils guided by endoscopic ultrasound	Gastric varices 125	Gastric varices	10 out of 125 gastric varices	cyanoacrylate	Median: 436 days;
Robles-Medranda 2019(44)	Eqcuador	Prospective	cyanoacrylate and coils guided by endoscopic ultrasound	Gastric varices 30	Gastric varices	1 out of 27 gastric varices patients followed up	cyanoacrylate	Up to 12 months
Zhang 2007(16)	China	Randomized trial	Cyanoacrylate with percutaneous transhepatic variceal embolization	Esophageal varices 92	Esophageal varices	14 out of 86 esophageal varices patients followed up	cyanoacrylate	Mean: 31.5 months
Zhang 2008 (45)	China	Randomized trial	Cyanoacrylate with percutaneous transhepatic variceal embolization	Esophageal varices 52	Esophageal varices	8 out 0f 52 esophageal varices patients followed up	cyanoacrylate	Median: 25 months
Tian 2011(46)	China	Prospective	Cyanoacrylate with percutaneous transhepatic	Gastric varices 71	Gastric varices	7 out of 71 gastric varices	cyanoacrylate	Mean; 24.2 ± 12.4 months

			variceal embolization			patients followed		
Feritis 1995(47)	Greece	Randomized trial	cyanoacrylate with sclerotherapy	Esophageal varices 126	Esophageal varices	8 out of 67 esophageal varices patients followed up	N-butyl-2-cyanoacrylate	30 days
Dhiman 2002(48)	India	Prospective	cyanoacrylate with sclerotherapy	Gastric varices 29	Gastric varices	3 out of 29 esophageal varices patients followed up	N-butyl-2-cyanoacrylate	Up to 6 months
Shi 2014(49)	China	Retrospective	transjugular intrahepatic portosystemic shunt alone versus combined with Cyanoacrylate	Esophageal Variceal 53	Esophageal Variceal Bleeding	3 out of 53 esophageal varices patients followed up	Cyanoacrylate	35.8 months
Ma 2018(50)	China	Prospective	combined cyanoacrylate with balloon-occluded retrograde transvenous obliteration	gastroesophageal varices 28	gastroesophageal varices and reported a rebleeding risk of 0.31	8 out of 26	cyanoacrylate	90 days
Dai 2017(51)	China	Randomized trial	band ligation alone versus in combination with cyanoacrylate	Gastroesophageal varices 97	gastroesophageal varices	7 out of 49 esophageal varices patients followed up	Cyanoacrylate	20 months
Zeng 2017(52)	China	Randomized trial	cyanoacrylate plus Polidocanol versus cyanoacrylate plus lipiodol in	gastric varices 96	gastric varices	11 out of 94 gastric varices patients followed up	cyanoacrylate	6 months

Pooled risk of rebleeding in gastric varices treated with cyanoacrylate alone

Figure 2 illustrates a forest plot of pooled risk of rebleeding for gastric varices after cyanoacrylate treatment. A total of twenty-five studies reported 2590 gastric variceal patients, of whom 402 had had rebleeding after initial treatment with cyanoacrylate hemostasis. The risk ranged from the minimum of 0.04 (4%) to a maximum of 0.99 (99%) in another study. Two studies were excluded for not having rebleeding incidences during the follow up period. The pooled overall risk of rebleeding was 0.30 (confidence interval: 0.30-0.31).

There was a significant heterogeneity observed with I^2 of 99.7%, p-Value<0.05. This led us to conduct sensitivity analysis, eliminating peculiar studies from the analysis. **Figure 3** illustrates a sensitivity analysis forest plot of pooled risk of rebleeding for gastric varices after elimination of peculiar studies. *Ramond* et al (1989)(17) and *Soga* et al (2010)(34) were case series and case report respectively; *D'Imperio* et al. (1996)(19), *Omar* et al. (1998)(20), *Noophun* et al. (2005)(23), *Rivet* et al (2009)(30), *Cheng* et al (2010)(31), *Binmoellar* et al (2011)(35) and *Tantau* et al. (2013)(38) had less than one-year of follow-up; while *Kind* et al. (2000)(21), *Tan* et al. (2006)(24), *Procaccini* et al. (2009)(29), *Choudhuri* et al. (2010)(32), *Mishra* et al. (2010)(33), *Liao* et al. (2013)(37), *Singh* et al. (2016)(10), *Cheng* et al. (2007)(25), *Kuo* et al (2007)(26), *Huo* et al. (2009)(28), *Kang* et al. (2011)(36), *Al-Baward* et al. (2016)(39) and *Xiaoqing* et al. (2019)(2) were excluded by meta-regression. *Evrad* et al. (2003)(22), *Hong* et al. (2009)(27), *Soga* et al. (2010)(34) and *Liu* et al. (2019)(40) were excluded because their findings did not fulfill normality test criteria for calculation of confidence interval (i.e.N(1-Pe) $\geq$10). The resulting overall pooled risk was 0.16 (Confidence interval: 1.13-0.18) with no significant heterogeneity (i.e. I^2=0.0%, p-Value=0.619).

Pooled risk of rebleeding in esophageal varices treated with cyanoacrylate alone

Figure 4 illustrates a forest plot of pooled risk of rebleeding for esophageal varices after cyanoacrylate treatment. A total of five studies reported 134 esophageal variceal patients, 7of whom had had rebleeding after initial treatment with cyanoacrylate hemostasis. The risk of rebleeding ranged from the minimum of 0.25 (25%) to a maximum of 0.38 (99%) in another study. Three studies were excluded for not having rebleeding incidences during the follow up period. The pooled overall risk of rebleeding was 0.29 (confidence interval: 0.11-0.47). There was no significant heterogeneity observed; I^2 of 0.0%, p-Value=0.53.7).

Pooled risk of rebleeding in gastric varices treated with cyanoacrylate with ethanolamine

Two studies illustrated treatment with a combination of cyanoacrylate and ethanolamine; *Thakeeb* et al. (1995)(41) and *Maruyama* et al. (2010)(42). Thakeeb reported 3 (i.e. risk= 0.052) rebleeding events among gastric variceal patients; and one (risk=0.017) rebleeding events among esophageal varices patients. Maruayama reported 10 (i.e. risk =0.5) rebleeding events among gastric varices patients. **Figure 5** illustrates a forest plot of pooled risk, 0.08(0.02-0.14) of rebleeding in gastric varices treated with a combination of cyanoacrylate with ethanolamine.

Pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils

Two studies illustrated treatment with a combination of cyanoacrylate and coils guided by endoscopic ultrasound; *Bhat* et al. (2016)(43) and *Robles-medranda* et al. (2019)(44). *Bhat* et al. (2016) reported 10 rebleeding events out of 125 gastric varices patients who were followed-up. This corresponds to the risk of 0.08 (Confidence interval: 0.03-0.13). *Robles-medranda* et al. (2019) reported 1 rebleeding event out of 27 gastric varices patients, which corresponds to the risk of 0.04(Confidence interval: -0.03-0.11). **Figure 6** illustrates a forest plot of pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils.

Pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization

Three studies illustrated treatment with a combination of cyanoacrylate and percutaneous transhepatic variceal embolization in gastroesophageal varices; *Zhang* et al. (2007)(16) and *Zhang* et al. (2008)(45) involved esophageal varices patients, and reported rebleeding risks of 0.16(confidence interval: 0.08-0.24) and 0.15 (confidence interval: 0.06-0.25), respectively. *Tian* et al. (2011)(46) involved gastric varices patients and reported rebleeding risk of 0.10(confidence interval: 0.03-0.17). **Figure 7** illustrates a forest plot of pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization.

Risk of rebleeding in gastroesophageal varices treated with cyanoacrylate with sclerotherapy

Two studies assessed the efficacy of combination of cyanoacrylate and sclerotherapy in the treatment of gastroesophageal varices. In one study, *Feretis* et al. (1995)(47) compared the combination versus sclerotherapy alone in the treatment of esophageal varices and reported the risk for rebleeding in the combination group to be 0.12 (Confidence interval: 0.04-0.20). In another one arm study, *Dhiman* et al.(48)(2002) assessed the outcome of the combination therapy in the treatment of gastric varices and reported a risk of 0.10 (Confidence interval: 0.05-0.18). Forest plot was not constructed as the two studies involved different participants (i.e. gastric and esophageal varices).

Other combination treatments with cyanoacrylate

In their study *Shi* et al. (2014)(49) compared between transjugular intrahepatic portosystemic shunt alone versus combined with Cyanoacrylate for Esophageal Variceal Bleeding. The combination therapy reduced the rebleeding risk to a third of one observed in transjugular intrahepatic portosystemic shunt alone. That is from 0.19 to 0.06, p-Value of 0.04. In another study, *Ma* et al. (2018)(50) combined cyanoacrylate with balloon-occluded retrograde transvenous obliteration in 28 patients with gastroesophageal varices and reported a rebleeding risk of 0.31 (confidence interval: 0.13-0.49).

Dai et al. (2017)(51) compared band ligation alone versus in combination with cyanoacrylate in the treatment of gastroesophageal varices. The risk of rebleeding in the combination therapy was reduced to a quarter that recorded in band ligation alone. That is from 0.56 to 0.14, p-Value<0.01. *Zeng* et al. (2017)(52) compared two combinations; cyanoacrylate plus Polidocanol versus cyanoacrylate plus lipiodol in the treatment of gastric varices. The later showed the risk of rebleeding of 0.13 (Confidence Interval: 0.03-0.22) as compared to 0.10 (Confidence interval: 0.02-0.19) in the polidocanol combination.

Table 2 summarizes risks of rebleeding in gastric and esophageal varices when treated with cyanoacrylate alone or in combination with other treatments as discussed earlier.

Table 2 risks of rebleeding in gastric and esophageal varices when treated with cyanoacrylate alone or in combination with other treatments

Key: * Calculated from a single study (Not pooled); ** Gastric or esophageal varices not specified (Gastroesophageal)

Note: The values in the table are independently calculated and the table does not mean statistical comparison between them.

Discussion

Through decades-long progressive improvements in the treatment of gastroesophageal varices, cyanoacrylate has evolved to be one of favored first line of treatment. The current study was aimed at utilizing systematic review of literature and pooled analysis to assess the overall risk of gastroesophageal rebleeding after an initial treatment with cyanoacrylate alone and/or in combination with other treatments.

Hemostasis treatment type	Pooled risk of gastric varices rebleeding (Confidence interval)	Pooled risk of esophageal varices rebleeding (confidence interval)
Cyanoacrylate alone	0.16 (0.13-0.18)	0.29 (0.11-0.47)
Cyanoacrylate combined with ethanolamine	0.08(0.02-0.14)	0.02 (-0.02-0.05).
Cyanoacrylate combined with endoscopic ultrasound guided coils	0.07(0.03-0.11)	-
Cyanoacrylate combined with percutaneous transhepatic variceal embolization	0.10(0.03-0.17) *	0.16(0.10-0.22)
Cyanoacrylate combined with transjugular intrahepatic portosystemic shunt	-	0.06(-0.01-0.12) *
Cyanoacrylate combined with sclerotherapy	0.10 (0.05-0.18) *	0.12 (0.04-0.20) *.
Cyanoacrylate combined with band ligation	-	0.10(0.04-0.24) *
cyanoacrylate combined with polidocanol	0.10 (0.02-0.19) *	-
cyanoacrylate combined with lipiodol	0.13 (0.03-0.22) *	-
Cyanoacrylate combined with balloon-occluded retrograde transvenous obliteration	0.31 (0.13-0.49) **	

Following treatment of gastric varices with cyanoacrylate alone, twenty-five studies demonstrated different risks of rebleeding from the minimum of 0.04 to a maximum of 0.99 in another study, with the overall pooled risk of 0.30 (confidence interval: 0.30–0.31). However, after getting rid of peculiar studies that increased heterogeneity, the resulting overall pooled risk was 0.16 (Confidence interval: 0.13–0.18). This risk of rebleeding coincides with that previously reported by Hou et al. (2009)(28) but differed from majority of other studies. Authors believe that the reason for the differences among studies to be technological advancement with time. This can be demonstrated majority of studies from the year 2010 forward having lower risk of rebleeding than studies before 2010. Different sample sizes and different study methodologies could also explain the differences.

Esophageal varices treated with cyanoacrylate alone showed the risk of rebleeding ranging from the 0.25 to 0.38 in different studies with the pooled overall risk of 0.29 (confidence interval: 0.11–0.47). Following a fewer number of studies, a meta regression could not be conducted. However, authors believe that the reason for the differences between studies to be due to different methodological approaches between the studies as Rivet et al. (2009)(30) followed up their patients for twice the duration used by Evrad et al. (2003)(22). Authors of this study hypothesize that; gastric varices respond better to cyanoacrylate as compared to esophageal varices in terms of lower risk of rebleeding. We call upon randomized clinical trials comparing the risk of rebleeding between gastric varices and esophageal varices treated with Cyanoacrylate alone.

When cyanoacrylate is combined with ethanolamine in the treatment of gastric varices the pooled risk of rebleeding after treatment is 0.08(Confidence interval: 0.02–0.14). The result aligns with that reported by Thakeb et al. (1995) but differs from Maruyama who reported higher risk of 0.5. The difference is accounted fewer sample size by Maruyama. On the other hand, when the combination is used to treat esophageal varices the risk of rebleeding is 0.017(confidence interval: -0.02-0.05). From an otherwise weak basis, we hypothesis that esophageal varices in contrast to gastric varices, respond better to the combination of cyanoacrylate and ethanolamine, in terms of lower risk of rebleeding. We call upon clinical randomized clinical trials to test this hypothesis.

From our findings, when cyanoacrylate is combined with endoscopic ultrasound guided coils to treat gastric varices the pooled risk of rebleeding is 0.07(confidence interval: 0.03–0.11). This finding is more or less similar to that reported by Bhat et al. (2016)(43), but is higher than that reported by Robles-medranda et al. (2019)(44). The reason for the differences could be explained by different sample sizes among studies pooled. One study had nearly five times the sample size used by the other.

When esophageal varices are treated with a combination of cyanoacrylate and percutaneous transhepatic variceal embolization the pooled risk of rebleeding is 0.16(confidence interval: 0.10–0.22). This is coinciding with findings previously reported by Zhang et al. (2007)(16). In another study by Tian et al. (2011)(46) when the combination is used to treat gastric varices, the risk of rebleeding is 0.10(confidence interval: 0.03–0.17). We hypothesize that esophageal varices in contrast to gastric varices, respond better to the combination of cyanoacrylate and percutaneous transhepatic variceal embolization in terms of lower risk of rebleeding. Authors call upon randomized clinical trials to test this hypothesis.

The risk of rebleeding in gastric varices treated with cyanoacrylate with sclerotherapy was lower by 0.02 from that of esophageal varices treated with the same combination. The difference could partly be due to more or less same number of sample sizes among the two studies descriptively analyzed. In combination with other treatments such as transjugular intrahepatic portosystemic shunt and balloon-occluded retrograde transvenous obliteration, it is evident that, cyanoacrylate improves efficacy of the treatment of gastroesophageal varices in terms of lowering rebleeding risk.

Study Limitation And Measures Taken

Our study search was limited to English published literature; involved pooling of studies with different sample sizes, different study designs and different follow-up durations. These were thought to introduce heterogeneity in the pooled analysis. However, authors appraised eligible studies; performed sensitivity analyses, meta-regression and used random effect models to deal with high heterogeneity among pooled studies. We also utilized PRISMA tools to minimize reporting biases.

Conclusion

Conclusion: In treating both gastric and esophageal varices, cyanoacrylate produces better results in terms of lower risk of rebleeding when combined with other treatments than when used alone. The combination of cyanoacrylate with ethanolamine or with endoscopic ultrasound guided coils produces lowest risk of rebleeding in esophageal and gastric varices, respectively. We call upon randomized trials to test these hypotheses.

Abbreviations

PRISMA – preferred reporting items for systematic reviews and meta-analyses

MeSH – Medical Subject Headings

ZH - Zixuan Hu (Author)

DZ - Decai Zhang (Author)

JS - Joel Swai (Author)

TL - Tao Liu (Author)

SL - Shaojun Liu (Author)

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: Authors declared no competing interests

Funding: No funds were given

Author's contributions: Study designing: JS; data search ZH, JS and TL; data extraction: ZH, DZ, and SL; data analysis and interpretation: JS and ZH; Manuscript drafting: JS; manuscript critical intellectual content revision: SL, TL and DZ. All authors read and approved the final version of the manuscript.

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Figures

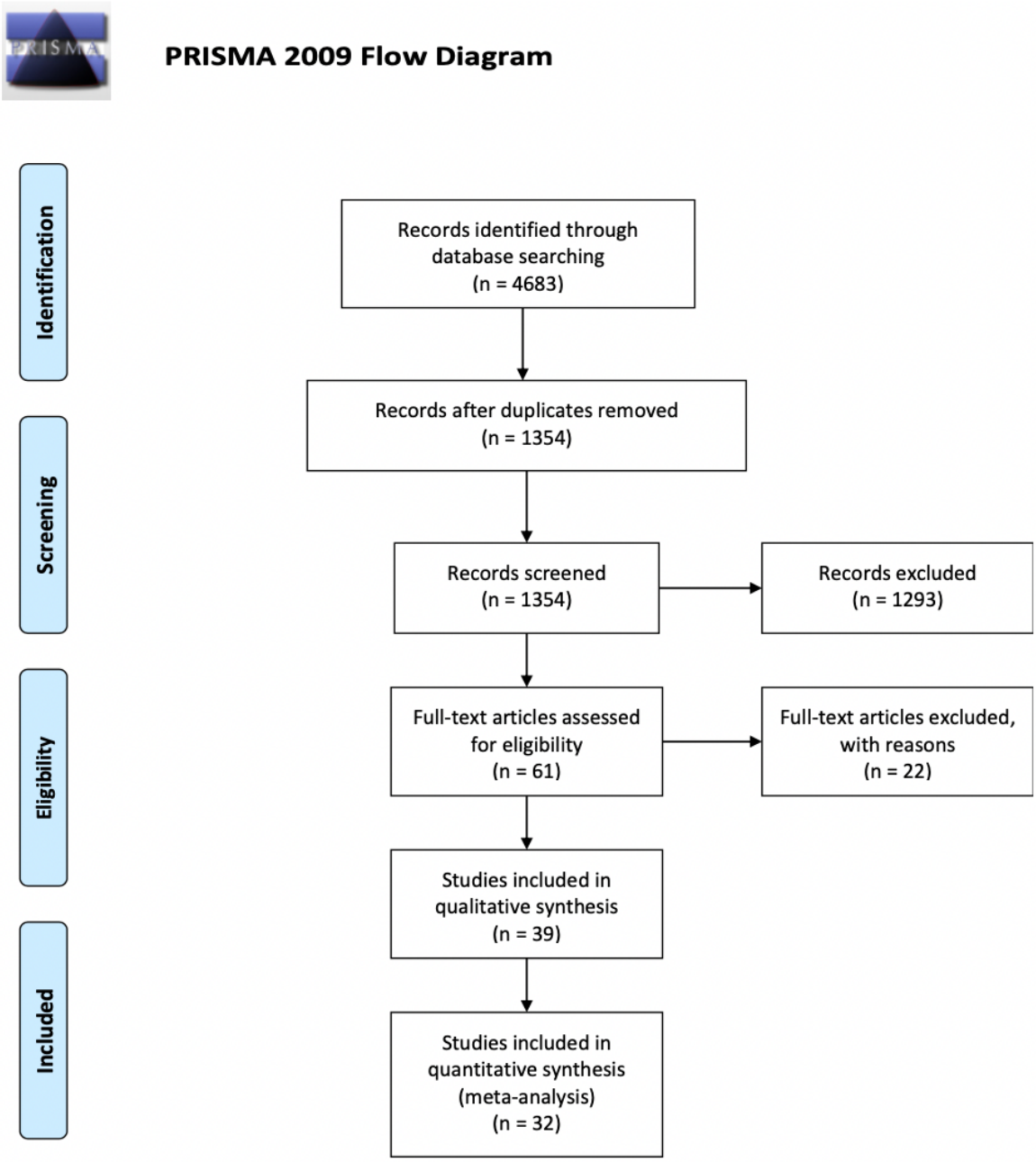

Figure 1

PRISMA 2009 Flow Diagram

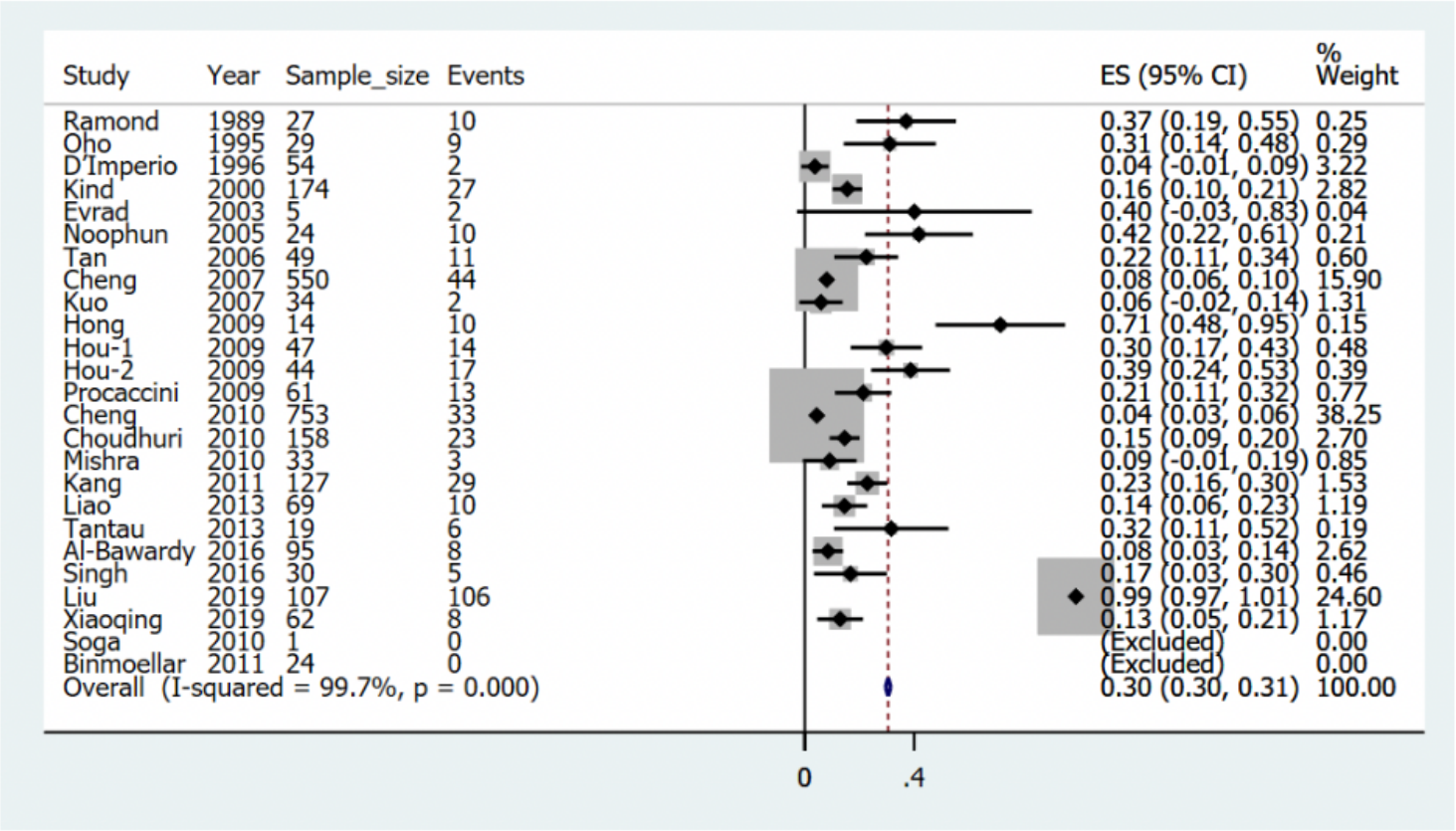

Figure 2

A forest plot of pooled risk of rebleeding for gastric varices after cyanoacrylate treatment.

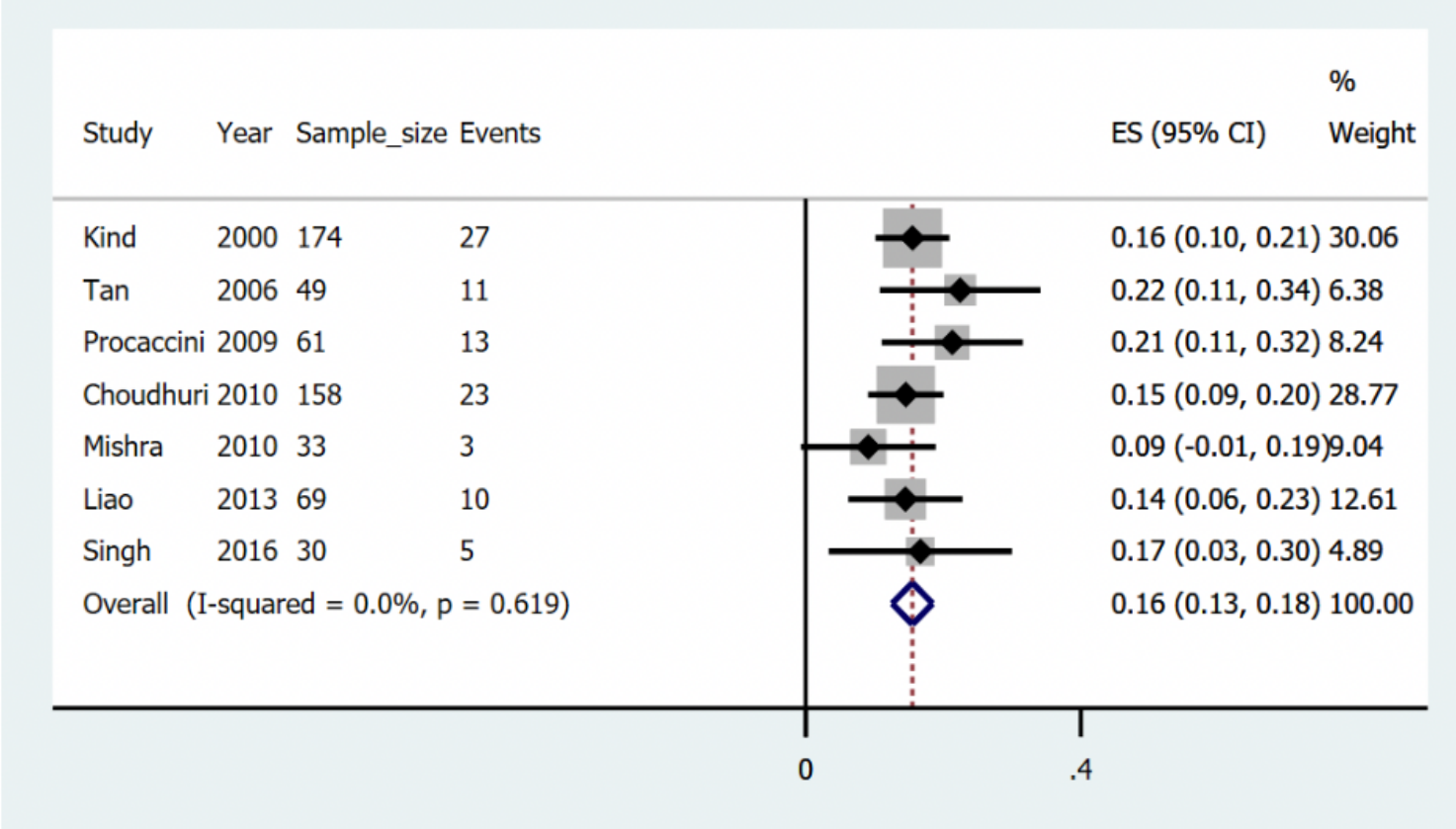

Figure 3

Forest plot after sensitivity analysis of pooled risk of rebleeding for gastric varices

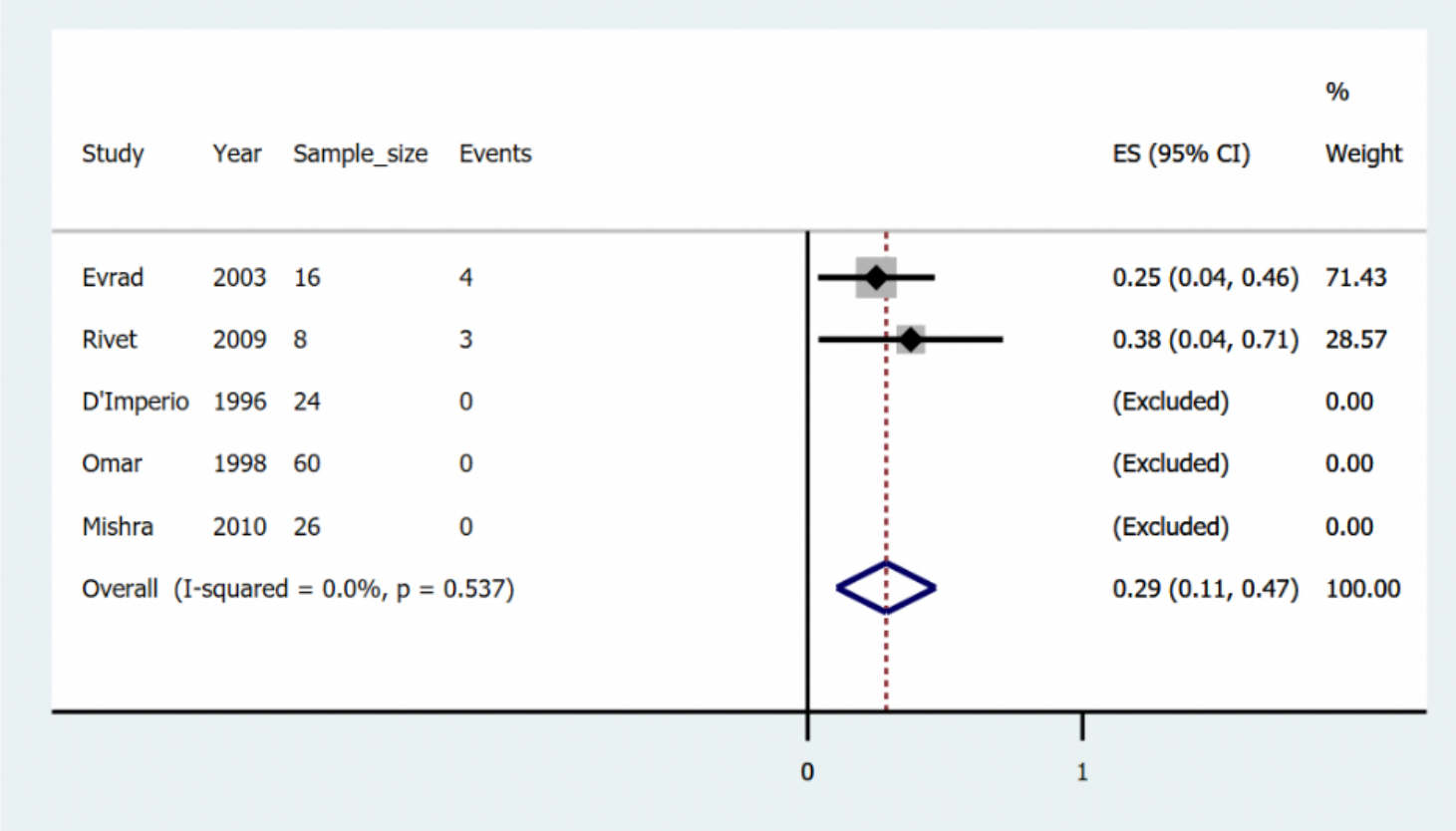

Figure 4

A forest plot of pooled risk of rebleeding of esophageal varices after cyanoacrylate treatment.

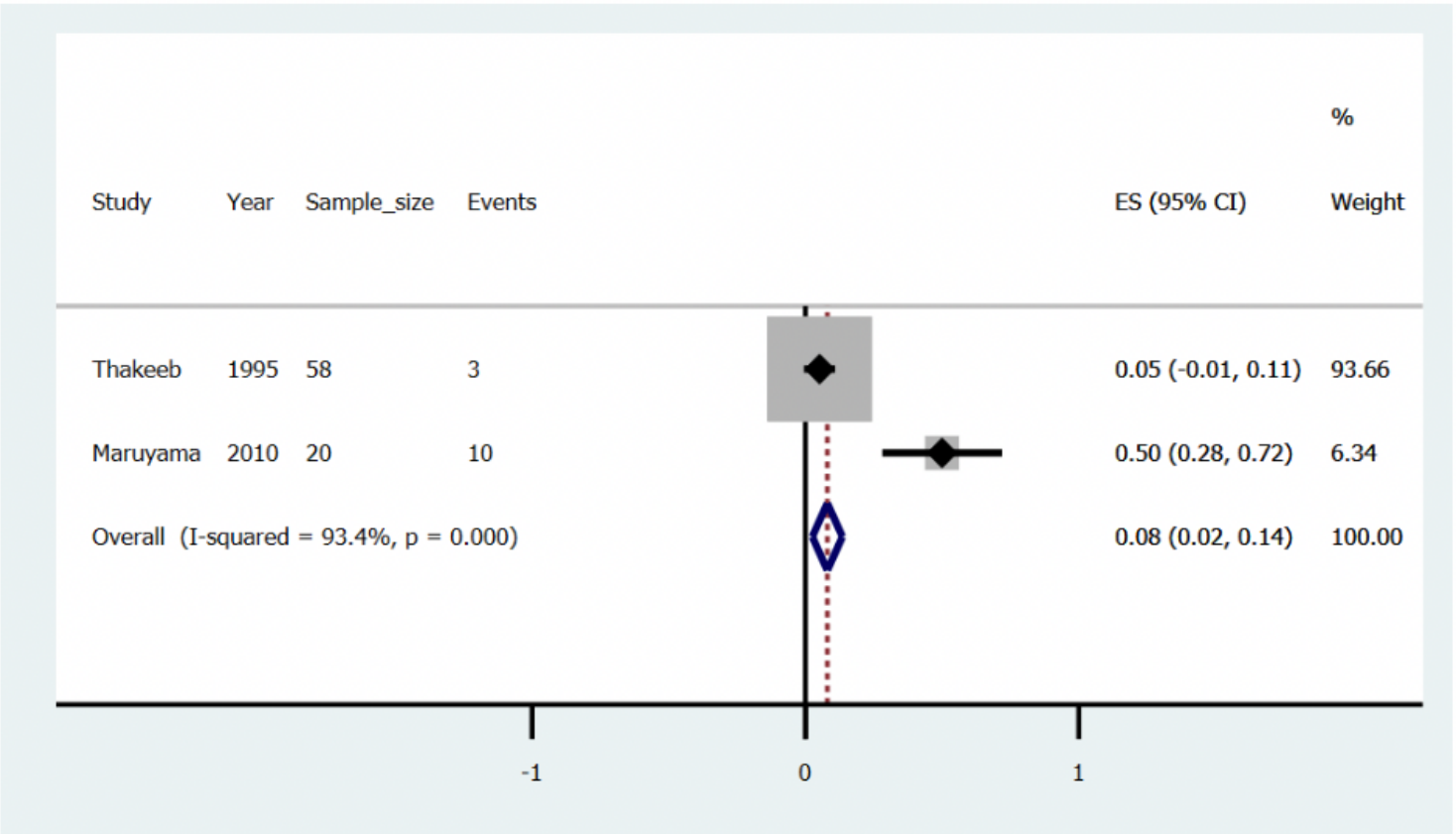

Figure 5

Illustrates a forest plot of pooled risk of rebleeding in gastric varices treated with a combination of cyanoacrylate with ethanolamine.

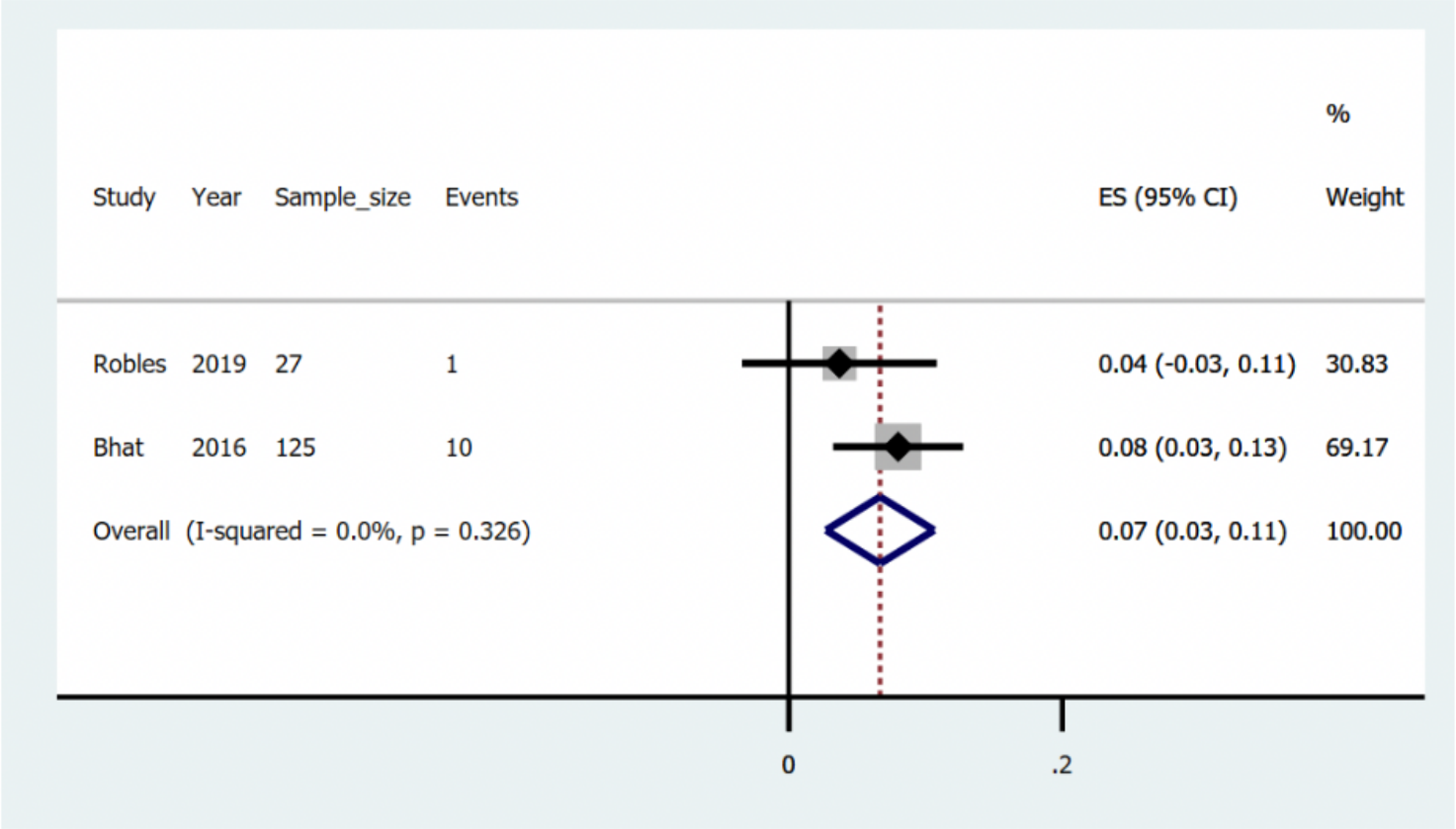

Figure 6

A forest plot of pooled risk of rebleeding in gastric varices treated with cyanoacrylate with endoscopic ultrasound guided coils.

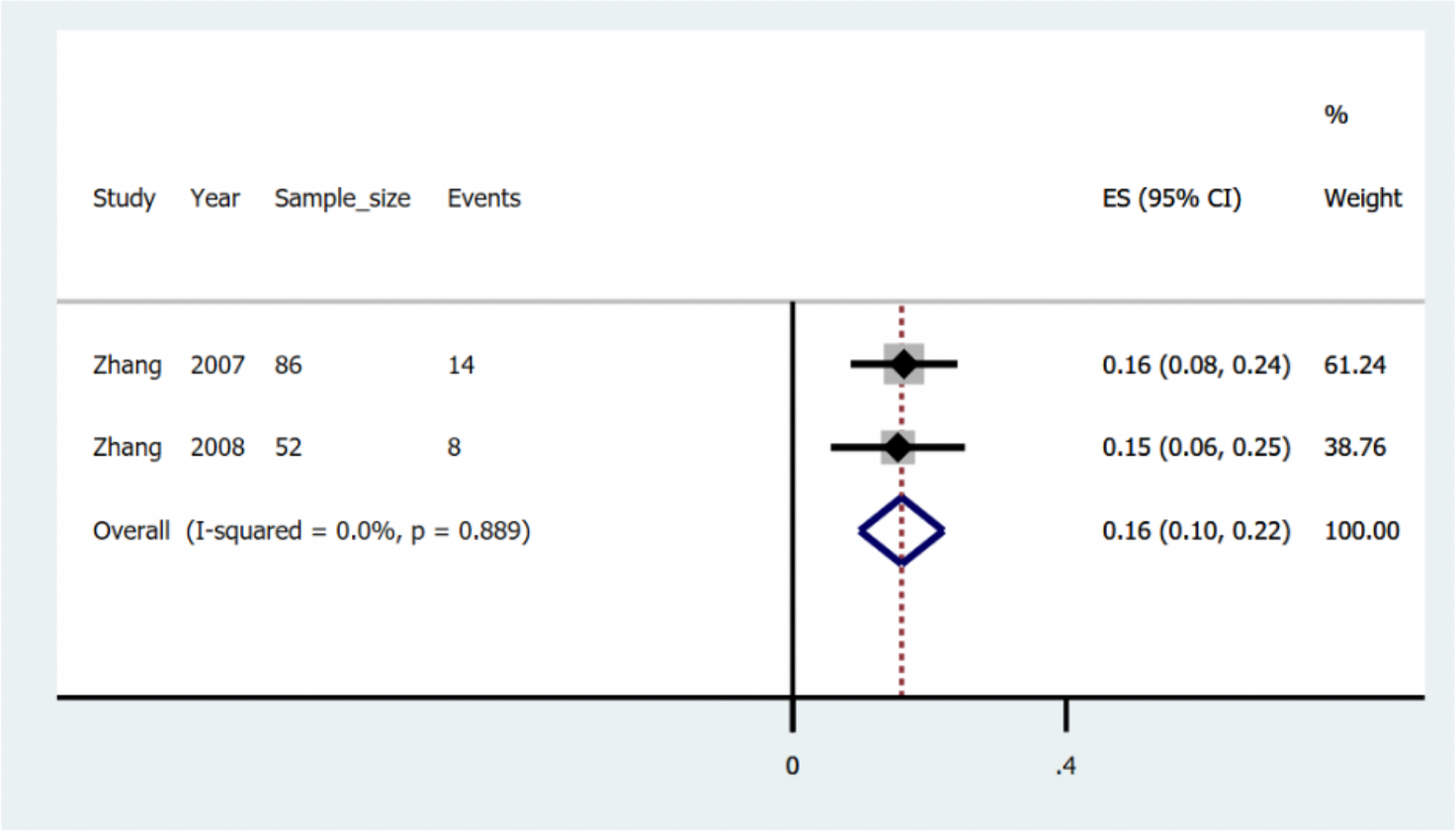

Figure 7

Illustrates a forest plot of pooled risk of rebleeding in esophageal varices treated with cyanoacrylate with percutaneous transhepatic variceal embolization.