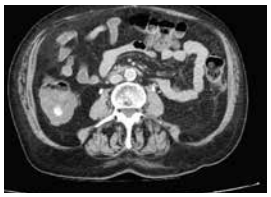

SENSITIVITY AND SPECIFICITY OF COMPUTER AXIAL TOMOGRAPHY IN THE DIAGNOSIS OF GASTROINTESTINAL BLEEDING: META-ANALYSIS

Sensibilidad y especificidad de la tomografía axial computarizada para el diagnóstico de hemorragia de vías digestivas: metaanálisis

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Key words (MeSH)
Tomography, X-Ray Computed
Endoscopy
Meta-Analysis

Palabras clave (DeCS)
Tomografía computarizada por rayos x
Endoscopia
Metaanálisis

Summary

Objective: To perform a meta-analysis through a systematic review of the literature, of the diagnosis studies with higher methodological quality according to the quality assessment tool for diagnostic accuracy studies (QUADAS-1). ***Methods:*** We evaluated the diagnostic efficacy of CT for gastrointestinal bleeding compared with angiography, endoscopy, colonoscopy, medical assessment, surgery, nuclear medicine procedures, or a combination of any of these methods; A systematic review was made from January 1998 to August 2013-in PubMed, National Guideline Clearinghouse, Canadian Medical Association Infobase, The Cochrane Library and the Database of Abstracts of Reviews of Effectiveness (DARE)-of papers that assessing the CT compared to the above procedures, 13 articles with adequate methodological quality according to QUADAS-1 (more than 6) were chosen, in which the heterogeneity results were evaluated and according to it, the statistical analysis was performed. ***Results:*** The combined average of the 13 studies is the following: sensitivity 88%, specificity 96%, positive predictive value 22.5, negative predictive value 0.12, Diagnostic Odds Ratio 182 and AUC 0.91. ***Conclusions:*** The results indicate that CT has a good diagnostic accuracy with which we can conclude that CT is a modality with high performance in the diagnosis of gastrointestinal bleeding.

Resumen

Objetivo: Hacer un metaanálisis mediante una revisión sistemática de la literatura, de los estudios de diagnóstico con mayor calidad metodológica según el *quality assessment tool for diagnostic accuracy studies* (QUADAS-1). ***Métodos:*** Se evaluó la eficacia diagnóstica de la TC para HVD en comparación con la angiografía, la endoscopia, la colonoscopia, el seguimiento médico, la cirugía, los procedimientos de medicina nuclear o la combinación de cualquiera de estos métodos; se realizó una búsqueda sistemática de la información de enero de 1998 a agosto de 2013 en PubMed*, National Guideline Clearinghouse, Canadian Medical Association Infobase, The Cochrane Library* y en el *Database of Abstracts of Reviews of Effectiveness (DARE),* de artículos que evaluaran la TC en comparación con los procedimientos mencionados anteriormente; se escogieron 13 artículos con calidad metodológica adecuada de acuerdo al QUADAS-1 (mayor de 6), en los cuales se evaluó la heterogeneidad y,

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posteriormente, de acuerdo con estos resultados, se realizó el análisis estadístico. ***Resultados:*** Las medias combinadas de los 13 estudios son las siguientes: Sensibilidad 88 %, especificidad 96 %, valor predictivo positivo 22,5, valor predictivo negativo 0,12, *Diagnostic Odds Ratio* 182 y área bajo la curva 0,91. ***Conclusión:*** Los resultados indican que la TC presenta una buena exactitud diagnóstica, por lo que se puede concluir que la TC es una modalidad con alto rendimiento en el diagnóstico de HVD.

Introduction

Gastrointestinal bleeding leads to approximately 300,000 hospitalizations annually (1,2); close to 75% of the bleeding cases spontaneously recede**,** however, bleeding will reoccur in approximately 25% of theses cases, which causes an important morbidity and mortality (1,2). It is estimated that high acute and massive gastrointestinal bleeding has an incidence of 40 to 150 episodes per 100,000 persons annually, with a mortality rate of 6 to 10% (3,4), and low gastrointestinal bleeding presents and incidence of 20 to 27 episodes per 100,000 persons per year, with a mortality rate of 4 to 10% (4,5), which can even reach 23% in cases of massive bleeding and/or if bleeding is recurrent after hospitalization (4).

In the assessment, gastrointestinal bleeding is classified as high or low depending on whether bleeding is acute and massive or, if on the contrary, it is chronic and intermittent; the main causes of gastrointestinal bleeding are listed in tables 1 (5,6) and 2 (4-8).

Table 1. Main causes of massive haematochezia

Cause	Prevalence %
SDT	
Peptic Ulcer	40-79
Gastritis/duodenitis	5-30
Esophageal varicose veins	6-21
Mallory-Weiss rip	3-15
Esophagitis	2-8
Gastric cancer	2-3
Others*	<1
IDT	
Small Intestine	
Angiodysplasia	70-80
Others**	30-20
Large Intestine	
Diverticular disease	17-49
Arteriovenous malformation	2-30
Colitis	9-21
Colonic Neoplasia/Pospolipectomy	11-14
Ano-rectal causes	4-10

Acronyms: Superior digestive tract (SDT), Inferior digestive tract (IDT). *Dieulafoy's lesion, gastric arteriovenous malformations, portal gastropathy. **Jejunoileal Diverticulum, Meckel's Diverticulum, neoplasias, lymphoma, enteritis, Chron's disease, aortoduodenal fistula.

Table 2. Main causes of chronic intermittent rectal bleeding

Cause	Prevalence %
SDT	
Gastritis	18-35
Esophagitis	18-35
Gastric ulcer	18-21
Duodenal ulcer	3-15
Angiodysplasia	5-23
Gastric cancer	3-6
Others*	--
IDT	
Small Intestine	
Angiodysplasia	40
Small intestine tumours	33
Otras**	--
Large Intestine	
Haemorrhoids	59
Colorectal polyps	38-52
Diverticulosis	34-51
Colorectal cancer	5-8
Proctitis/Ulcerative colitis	2-6
Arteriovenous malformation	0-5
Colonic narrowing	2
Others***	--

Notes: * Esophageal cancer. **Small intestine erosions and ulcers, Chron's disease, small intestine diverticular disease, celiac sprue, post radiation enteritis, Meckel's diverticulum, small intestine varicose vein, lymphangioma, Blue Rubber Bled Nevus syndrome, Osler-Weber-Rendu syndrome, Von Willebrand disease, intestinal polyposis syndrome, Gardner's syndrome, aortoenteric fistula, amiloidosis, hemosucces pancreaticus with haemobilia. *** Pospolipectomy bleeding, other colitis, anal neoplasia.

As to acute rectal haemorrhage, its study generally begins with an esophagogastroduodenoscopy (EGD) when there is the suspicion of superior gastrointestinal bleeding. When it is unlikely that the source of bleeding is high, diagnostic efforts should be directed to the large intestine by means of a colonoscopy (9). Several studies have demonstrated that colonoscopy detects the definitive locations of bleeding in more than 70% of the patients (10-12). The advantages of colonoscopy include direct visualization, the possibility to perform a biopsy and the capacity to treat bleeding lesions with a heat probe, epinephrine injection, laser therapy, band ligation or haemostatic clip (11-13). As

a first diagnostic method, colonoscopy has a higher performance and a lower rate of arteriographic complications than arteriography (5,8,14), and, although in cases of massive bleeding visibility can be hindered, when it is used to assess low sub massive gastrointestinal bleeding, colonoscopy can be highly efficient (5).

In situations in which the massive bleeding does not allow to detect the source by means of an endoscopic tool, arteriography is the second choice exam (5,8,14). However, several studies have found a wide margin of sensitivity with this exam, which varies from 40 to 78% (14).

Another useful study in gastrointestinal bleeding is scintigraphy with red blood cells marked with technetium 99. This nuclear diagnostic method is used to detect slow bleeding sources, with indices of 0.1 to 0.4 ml per minute (5,11,14-17). However, it is not as sensitive as arteriography to detect the exact bleeding location. Notwithstanding, when used in conjunction with arteriography, a sensitivity of 61 to 72% can be achieved (17).

When the source of bleeding is not identified with either of the previously mentioned methods, the patient must undergo an exploratory laparotomy (5,1,,17), which, in many occasions is accompanied by an intra-operative endoscopy (17), which has a sensitivity above 70% in identifying the source of bleeding and additionally provides the limits for surgical extension in approximately 10% of cases (14,17,18). However, removing the colon lesion, visualized and suspect, not always stops bleeding (17); in this cases intra-operative arteriography is used a accompanying method to localize the source of bleeding and to avoid unnecessary segmentary resection of the colon, caused by a blind hemicolectomy (17).

It is important to distinguish that, depending on the clinical suspicion, the superior or inferior endoscopy must be repeated given that high or low gastrointestinal lesions, occasionally, are not detected in the first endoscopy; especially in the erosions of hiatal hernias of big dimensions, in arteriovenous malformations, in peptic ulcers and neoplasias (17).

As to chronic and intermittent rectal bleeding, colonoscopy or rectosigmoidoscopy are the tests of choice given a sensitivity of 92% and a specificity of 100% (6,17).

Gastrointestinal bleeding from the small intestine is uncommon, and is present in only 2 to 10% of all cases; it is technically difficult to evaluate given its location (19). However, every time that colonoscopic procedures (colonoscopy or endoscopy of the upper digestive tract) do not make a diagnosis, the small intestine should be evaluated (17,19,20). One of the diagnostic tools for this type of patients is enteroscopy, an extension of endoscopy of the digestive tracts with which between 15 and 160 cm distal to Treitz's ligament can be visualized (14,17,19,21), and can be conclusive in up to 54% of cases. With this diagnostic tool biopsies and treatment can also be performed; however, its use is limited up to 160 cm distal to Treitz's ligament. For these cases two radiographic tools exist that can help. The first is the upper gastrointestinal with barium swallow series, and the second is the enteroclysis; these tools have low sensitivity of 0 to 5.6% and of 10 to 21% respectively (17). Enteroclysis requires a previous endoscopy, with posterior direct application of contrast dye in the proximal area of the small intestine. Its advantages when compared to the upper gastrointestinal series are higher sensitivity, a shorter duration of examination and its high usefulness for the evaluation of unconscious or uncooperative patients (17). When enteroclysis is used in combination with enteroscopy, a diagnostic performance of up to 58% can be achieved (17). Two nuclear medicine exams also exist for the evaluation of small intestine lesions, one is scintigraphy with red blood cells marked with technetium 99 and the other is the Meckel scintigraphy for the search of ectopic gastric mucose, which uses pertecnatum of technetium 99 (17,22). This last one is highly sensitive (75 to 100%) to detect gastric mucose in the small intestine, which can be considered the probable source of bleeding, but has the disadvantage that does not identify the site of bleeding *per se* (22).

It is also important to mention the endoscopic capsule, which is a relatively new exam for the diagnosis of gastrointestinal bleeding. Only some small studies have analyzed the usefulness of this diagnostic tool in the identification of the cause of bleeding in the small intestine, with promising preliminary results (19,20,23,24).

Whenever there are contraindications for the upper endoscopic procedures, the upper gastrointestinal series with barium swallow can be considered (sensitivity 54% and specificity 91%) and, for the colon, the barium enema with double contrast, which although it has a low sensitivity and specificity, can be an acceptable alternative (6,25,26).

Finally, when all diagnostic tools have failed in the identification of the source of bleeding and anemia persists or worsens, a laparatomy with an intra-operative enteroscopy must be performed (18). This procedure is considered as the last diagnostic option in the assessment of cases not considered an emergency, given it is an invasive exam and is associated with a high rate of morbidity and mortality (17).

Recent advances in CT, such as a finer collimation, better scanning times, higher anatomical coverage and improved multi-planar reconstructions, have widely extended its diagnostic usefulness as much in patients with upper and lower gastrointestinal bleeding, as well as in patients with massive and intermittent bleeding. However, its function has not yet been precisely established (27-29).

In porcine models, helicoidal CT has described active colonic bleeding with bleeding rates as low as 0.3 ml/min, which is below the threshold reported for angiography with selective catheter, and approximates the bleeding rates detected with scintigraphy with marked red blood cells (30).

Active gastrointestinal bleeding diagnosis with the use of CT is basically performed when the high attenuation produced by the extravased contrast dye is observed in the intestinal lumen, which can have several radiological patterns: linear, jet, swirling, ellipsoidal, the combination of several of these or all at the same time (figure 1), or can also produce what is known as "hyper-attenuated handle" that is present when the totality of the intestinal lumen is occupied by contrast dye (31).

Some authors use thresholds of attenuation of the contrast dye as a diagnostic criteria for acute bleeding (32,33), others compare CT of the same patient without contrast dye and immediately after administration of the same, to differentiate to pre-existing areas of high attenuation (31), given that small quantities of bleeding or laminar bleeding may not reach the threshold of 90 Hounsfield Units (HU) in the arterial phase (33).

Among the advantages of CT for the diagnosis and follow-up of patients with suspicion of gastrointestinal bleeding are high availability, speed, reproducibility and that is minimally invasive compared to the gold standard, which is conventional angiography with a catheter, in which complications such as inguinal hematoma, dissection and distal embolization are reported in 1.3 to 2.2 % of procedures (34,35).

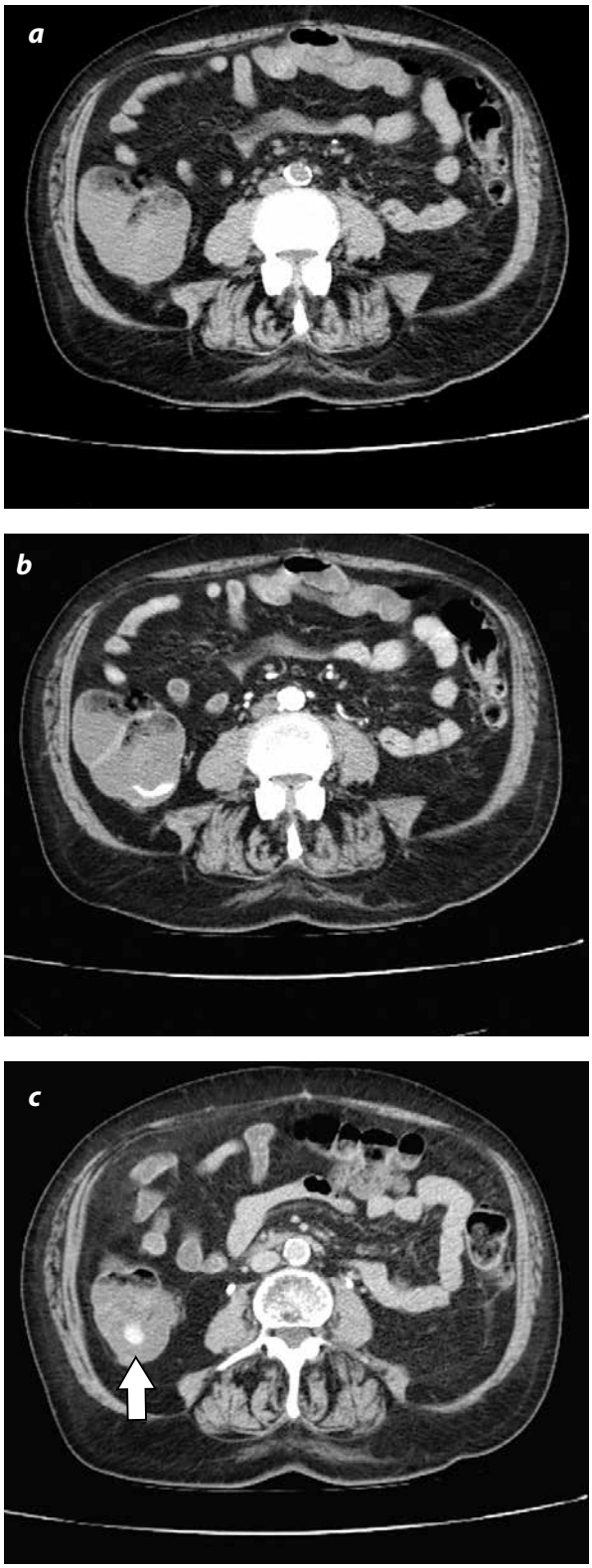

Figure 1. Lower digestive haemorrhage in 85 years old patient, with proctorrhagia. a) Abdominal CT without intravenous contrast dye. b) CT with intravenous contrast dye in the arterial phase that shows the active bleeding that affects the right colon. Note that in figure a) the absence of contrast dye does not allow its diagnosis. c) CT in the venous phase in which the change in the aspect of the foci of bleeding is observed (arrow).

Besides helping to detect the active gastrointestinal bleeding, CT allows the concurrent evaluation of the femoral and gastrointestinal vasculature, even identifying anatomical variation, which turns out to be very useful for pre-surgical or pre-intervention planning (31).

Another advantage of the use of CT in patients with gastrointestinal bleeding is the etiological identification of the bleeding source, especially in those stemming from the inferior gastrointestinal tract, for example, diverticular disease and colon angiodysplasia (36), in which a sensitivity of 70% and a specificity and positive predictive value of 100% has been reported (37).

On the other hand, abdominal CT can be performed immediately or during acute haemorrhagic episodes, which allows identification of the bleeding source. For example, in a not easily accessible anatomic region for endoscopy, such as the small intestine, which gives a significant advantage for a specific group of patients.

Nevertheless, in comparison with the upper digestive endoscopy, colonoscopy and angiography, the lack of therapeutic options is one of the main limitations of CT as well as the radiation dose and the risks derived from the use of contrast dyes.

In the last years, due to the technological renovation of health institutes and to the implementation of teleradiology, image diagnosis can be more easily obtained, especially for CT. This is of particular relevance in areas where there is a lack of human resources for the continual functioning of gastroenterological services, for which CT can become an attractive tool for the initiation of the diagnostic algorithm of patients with gastrointestinal bleeding; thus, the need to know whether this exam is as valid as endoscopic procedures for the diagnosis and localization of bleeding in patients with suspicion of gastrointestinal bleeding.

The objective of the present study is, through a systematic review of the literature, to make a meta-analysis for diagnostic studies with the highest methodological quality according to the *quality assessment tool for diagnostic accuracy studies* (QUADAS) (38).

Materials and methods

A literature search was performed to identify studies that evaluated the diagnostic value of CT in acute gastrointestinal bleeding. The database PubMed was used, limiting the search to studies published in English, in the last 15 years. The following terms were employed: MeSH *database gastrointestinal haemorrhage, gastrointestinal bleeding, CT angiography, X-ray computed, sensitivity, specificity, false-negative, false-positive, diagnosis, detection, accuracy*. The boolean connectors were AND/OR.

A search was also done in the National Guideline Clearinghouse, in the Canadian Medical Association Infobase, The Cochrane Library and in the Database of Abstracts of Reviews of Effectiveness (DARE).

The search strategy resulted in 49 articles through PubMed, of which the following were discarded: case reports, case series, studies that compared the different radiographical techniques of the CT, comparison of CT with techniques other than angiography, endoscopy, colonoscopy, medical follow-up, surgery or a combination of any of these methods, as well as articles in a language other than English. Articles with a low methodological quality according to QUADAS-1 (lower than a value of 6) were also discarded. Articles that reported patients classified as true positives, true negatives, false positives and

false negatives were included. Finally, 13 articles were selected for the data extraction for the meta-analysis (figure 2.)

To obtain the combined sensitivity and specificity, as well as the predictive values and the *Diagnostic Odds Ratio* (DOR), the data for each study were extracted and combined using a random effects estimation in the binary regression model frame for bivaried mixed effects through specification, estimation and prediction modeling, done with xtmelogit in Stata 13.0 (39-44).

The heterogeneity among studies was evaluated through the χ^2 and I^2 tests, where the statistical heterogeneity was considered when the χ^2 test reported a $p=< 0.10$ and the I^2 test were above 50% (45).

The possibility of a publication bias was also evaluated through the funnel graphic with Deek's test of asymmetry. Significant asymmetry was considered and thus with a bias with a $p< 0.10$ for the bias coefficient (46).

In tables 3 (28,32,33,47-56) and 4 (28,32,33,47-56) a summary is presented of the studies with an acceptable quality index (QUADAS above 6) with respect to the use of CT in patients with gastrointestinal bleeding.

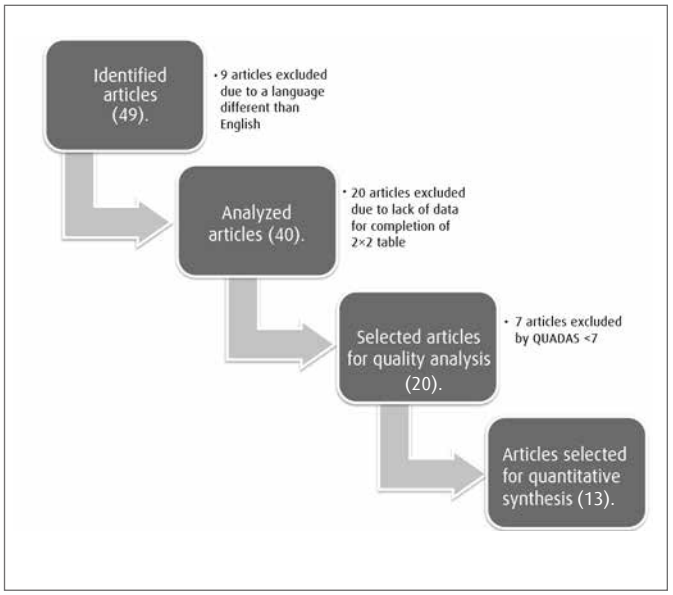

Figure 2. Search process and article selection.
Source: Elaborated by the authors.

Table 3. Comparative table with the average age of patients and main characteristics of the studies evaluated

Author	Year	N	Age	Study design	Gold standard	QUADAS
Ettorre, et al. (48)	1997	18	NA	Prospective	Conventional angiography or surgery	9
Ernst, et al. (28)	2003	24	59 (18-85)	Prospective	Colonoscopy, enteroscopy or surgery	10
Tew, et al. (32)	2004	13	NA	Retrospective	Conventional angiography, surgery or clinical follow	9
Miller, et al. (49)	2004	18	69 (43-83)	Prospective	Endoscopy, colonoscopy or conventional angiography	6
Sabharwal, et al. (50)	2006	7	69 (48-83)	Prospective	Conventional angiography or colonoscopy	10
Yoon, et al. (33)	2006	26	66 (18-89)	Prospective	Digital subtraction angiography	12
Jaeckle, et al. (51)	2008	36	51 (4-85)	Retrospective	Endoscopy or surgery	10
Zink, et al. (52)	2008	41	55 (21-92)	Prospective	Labeled RBC scintigraphy, or surgery	9
Lee, et al. (53)	2009	15	72 (42-90)	Retrospective	Conventional angiography, colonoscopy, video capsule enteroscopy, labeled RBC scintigraphy, or surgery	9
Kennedy, et al. (54)	2010	86	NA	Retrospective	Endoscopy, surgery, pathology report	9
Sun, et al. (55)	2012	113	48,7 (19-92)	Prospective	Digital subtraction angiography, endoscopy, surgery, pathology report	8
Marti, et al. (56)	2012	47	68	Prospective	Colonoscopy, angiography, surgery	11
Sun, et al. (47)	2013	58	54,2 (18-92)	Prospective	Angiography, endoscopy, surgery, pathology	12

Acronyms: N: Number of patients; NA: Data not available

Table 4. Results of the studies

Study	True positive	False positive	False negative	True negative	Sensitivity	Specificity
Ettorre, et al. (48)	13	0	3	2	0.81	1.00
Ernst, et al. (28)	15	0	4	5	0.79	1.00
Tew, et al. (32)	7	0	0	6	1.00	1.00
Miller, et al. (49)	14	0	2	2	0.88	1.00
Sabharwal, et al. (59)	5	0	0	2	1.00	1.00
Yoon, et al. (33)	20	1	2	3	0.91	0.75
Jaeckle, et al. (51)	26	0	0	10	1.00	1.00
Zink, et al. (52)	5	5	1	30	0.83	0.86
Lee, et al. (53)	7	5	2	1	0.78	0.17
Kennedy, et al. (54)	19	5	3	59	0.79	0.95
Sun, et al. (55)	80	0	13	20	0.86	1.00
Marti, et al. (56)	19	1	0	27	1.00	0.96
Sun, et al. (47)	39	0	5	14	0.89	1.00

Results

For the heterogeneity analysis, the DerSimonian and Laird tests show that there is statistical evidence of heterogeneity with a 95% confidence interval (*Chi-square):* LRT_Q = 6.926, df = 2,00, LRT_p = 0,016), as well as for the I^2 test (*Inconsistency [I-square]:* LRT_I2 = 71,95 % CI = [36-100]).

The combined average of the 13 studies with their confidence intervals are as follows: sensitivity 0.88 [0.84-0.92], specificity 0.96 [0.81-0.99], positive predictive value 22.5 [4.1-122.5], negative predictive value 0.12 [0.09-0.18], *Diagnostic Odds Ratio* 182 [28-1174].

The area under the curve, as demonstrated by figure 3 is of 0.91 with a 95% confidence interval of [0.17-1.00], which means a good diagnostic precision.

Figure 4 presents the "forest diagram" where the estimated effect for each study is shown along with its obtained value, combining the results of all investigation, accompanied by its respective confidence intervals and heterogeneity measurements, where it can be observed that the combined sensitivity presents low Q heterogeneity of 13.05 with p=0.370, in contrast to the specificity with a Q of 59.09 with a p=0.001. As far as publication bias it can be concluded that it is p=0.059, as shown in figure 5.

Discussion and conclusion

The precise diagnosis of gastrointestinal bleeding allows for selection of the appropriate treatment leading to a significant reduction in morbidity and mortality, along with improvement in quality of life of the patient and reduction in costs derived from directing attention to the pathology.

The definitive treatment of patients with gastrointestinal bleeding depends basically from the hemodynamic state, the type of lesion and bleeding site. The results from this meta-analysis prove that CT has a high sensitivity, specificity and predictive value, which coincide with published diagnostic studies in the literature.

Tew and collaborators, in the year 2004, described the use of CT with four multidetectors en the assessment of haematochezia in 13 consecutive patients, without false positive or false negative reports (32). Meanwhile, Yoon and collaborators studied 26 consecutive patients with significant gastrointestinal bleeding that lead to either systemic hypotension (systolic arterial pressure of 90 mm Hg) or the need for blood transfusion with at least four units of hematite concentrate within 24 hours, with which sensitivity, specificity, accuracy, positive and negative predictive values of CT in detection and localization of gastrointestinal bleeding were determined, with values of 91%, 75%, 97%, 95% and 98% respectively (33).

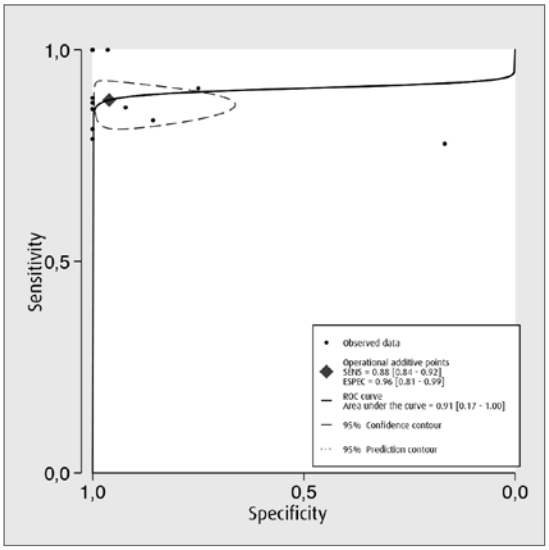

Figure 3. ROC curve (Receiver Operating Characteristic), which graphically represents sensitivity against (1-specificity) where it can be observed an area under the curve of 0.91, which classifies the Angio-CT as a very good test for the diagnosis of gastrointestinal bleeding.

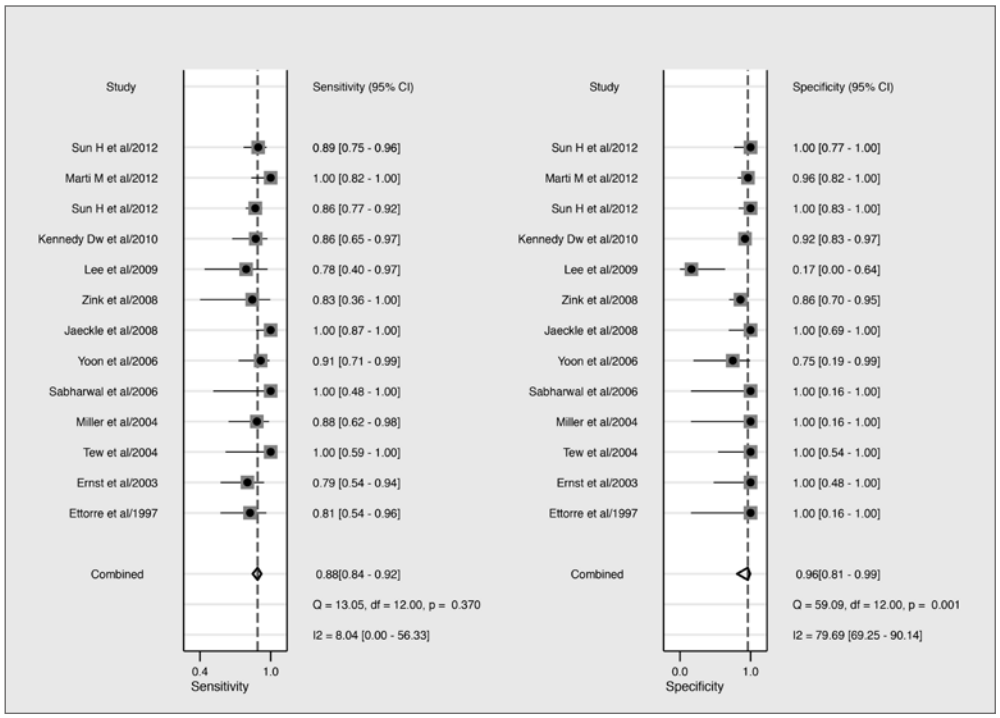

Figure 4. Tree diagram (sensitivity and specificity), which graphs the estimated effect for each study and its combined synthesis, along with its respective 95% confidence intervals, shows a global sensitivity with little heterogeneity () Q 13.905 - p = 0.370) and a specificity with higher heterogeneity (Q 59.09 - p = 0.001).

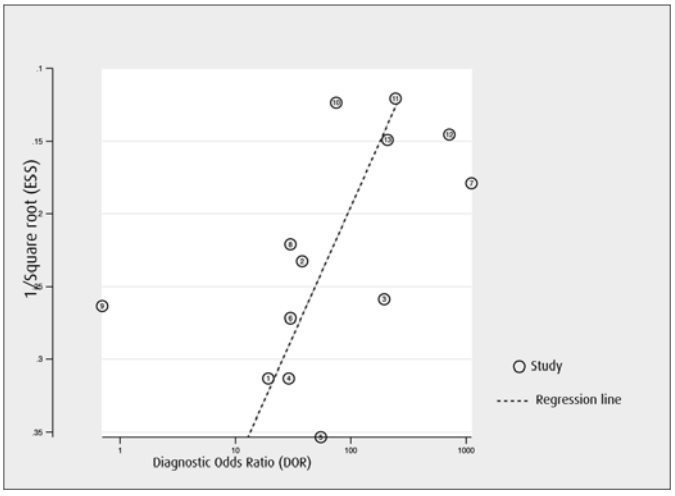

Figure 5. Publication bias figure that lists according to publication year (number within circle) each study with its corresponding Log Odds in the x axis and the inverse of the square root of the effective sample size (ESS) in the y axis; A linear regression is performed in which a significant asymmetry can be appreciated, which points to a publication bias (p = 0.06), reference value (p =< 0.10).

Different studies have shown the CT can diagnose the bleeding site when angiography has failed to localize it (48-51,53,57). For example, the Sabharwal and collaborators study, that reports through CT the bleeding site in three patients for whom conventional angiography had been negative and through subsequent emergency colonoscopy blood presence was confirmed in the lumen of the colon without identification of the exact site of bleeding (50). Jaeckle and collaborators, in their study for the diagnostic precision of CT for detection and localization of upper and lower gastrointestinal bleeding or intraperitoneal bleeding in 36 consecutive patients, with clinical signs of digestive bleeding, reported in 10 of the patients intraperitoneal bleeding and in 26 gastrointestinal bleeding. Likewise, they compared CT with endoscopy, angiography or surgery, for which they obtained confirmation of bleeding site in 24 of the 26 patients (51).

CT sensitivity can be even higher than reported in in these studies, since gastrointestinal bleeding, given its nature, is intermittent and the bleeding rate can vary from minute to minute (58). Patients can have active gastrointestinal bleeding that can cease at the moment of performing a colonoscopy or angiography. On this regard, Miller and collaborators presented five cases where the bleeding source was observed in the CT, but not with the other methods (51). All this leads us to suggest this diagnostic method as a new emerging tool for the assessment of these type of patients. Even though there were certain limitations in our analysis, such as heterogeneity, publication bias and the size of some the studies included in the meta-analysis, the results showed that CT present a good diagnostic accuracy, such that it can be concluded that it is a modality with a good diagnostic performance for gastrointestinal bleeding. However, random, multi-centric clinical trials with large sample size are required to establish with greater precision and reliability, the advantages of CT over conventional procedures for the diagnosis of gastrointestinal bleeding.

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Received for evaluation: October 9, 2014
Accepted for publication: March 4, 2015