Systematic Review and Meta-analysis comparing the diagnostic utility of Tc-99m tagged RBC scintigraphy with CT-angiography imaging studies in diagnosing Lower Gastrointestinal Bleeding

Jose Carlos T. Chanyungco, MD, Ruben V. Ogbac, MD

Division of Nuclear Medicine, University of the Philippines - Philippine General Hospital
E-mail address: jctc93@gmail.com , rvogbac@gmail.com

ABSTRACT

Background:

Lower Gastrointestinal bleeding (LGIB) is a serious and urgent condition which can be assessed using several different modalities. Tc-99m tagged RBC scintigraphy has been established as a diagnostic tool in Nuclear Medicine but several other modalities, including CT-based imaging (i.e. angiography) currently exist.

Objective:

The objective of this study is to compare Tc-99m tagged RBC scintigraphy with CT-based imaging studies in terms of clinical utility and diagnostic outcomes.

Methods:

A systematic review of available literature was done, with the goal of creating a meta-analysis focusing on the reported diagnostic outcomes - mainly sensitivity and specificity on the presence of a LGIB. Aside from this, a systematic review of the clinical utility and the differences of each test were discussed, including non-quantifiable advantages. The literature search was conducted following the guidelines of PRISMA, with searches from PubMed, Medline, and other pertinent databases. Quality assurance was done using the QUADAS tool. Statistical analyses of sensitivity, specificity, and a summary receiver operating characteristics plot were computed for the meta-analysis.

Results:

Pooled sensitivity and specificity for RBC scintigraphy were 0.886 and 0.119, respectively. Pooled sensitivity and specificity for CT-based imaging were 0.729 and 0.660, respectively. CT based imaging also showed higher localization and faster completion times. RBC scintigraphy had a longer acquisition window.

Conclusion:

Both Tc99m-tagged RBC scintigraphy and CT-based imaging have important clinical utility, with each modality having different advantages that the other test cannot provide.

Keywords*: Tc99m-tagged RBC scintigraphy, red blood cell tagging, gastrointestinal bleed scintigraphy, CT angiography, Multidetector CT, lower gastrointestinal bleed*

INTRODUCTION

Bleeding from the gastrointestinal tract is a serious condition which may lead to mortality in 8-14% of patients [1]. Bleeding within the gastrointestinal tract can be categorized by anatomy. The ligament of Trietz serves as the anatomic demarcation which separates bleeding into upper or lower gastrointestinal in origin. Lower gastrointestinal bleeding (LGIB) usually presents as painless hematochezia, accompanied by a drop in hematocrit values [2]. It accounts for around 20 - 33% of gastrointestinal hemorrhage [3]. According to one study in a tertiary hospital in Manila, LGIB is the most common indication for colonoscopies at around 34% [4].

Several causes of lower gastrointestinal bleeding are possible. According to the UCLA-Center for Ulcer Research and Education (CURE) database [2], the most common etiology is bleeding due to diverticulosis at 30%. This is followed by hemorrhoids and ischemic bowel disease at 14% and 12%, respectively. Management varies depending on the cause of bleeding and patients are usually seen by a multidisciplinary team of clinicians and diagnosticians.

Guidelines from the American College of Gastroenterology as well as the Philippine Society of Digestive Endoscopy recommend several diagnostic tools which a physician may use in evaluating LGIB [5,6].

Gastrointestinal bleeding has long been evaluated using scintigraphy with tagged RBC (also known as the gastrointestinal bleed scan) as one of the less invasive methods of diagnosis. The gastrointestinal bleed scan has proven its sensitivity in detecting a bleed, demonstrating effectiveness even for volumes less than 1 mL. Recently, several CT modalities have been introduced to evaluate GI bleeding. One of which is the CT angiography using a multidetector CT (MDCT). It uses iodinated contrast on the patient and allows for precise localization of any suspected hemorrhage. The CT-angiography imaging modality is currently not recommended as initial work-up for gastrointestinal bleeding, although its use is growing in popularity [7].

Several studies have been published comparing tagged RBC scintigraphy with CT-angiography, with varying results. A meta-analysis of these papers would be useful when considering the role of each modality for the assessment of patients with LGIB.

Objectives:

The primary objective of this study is to review the published literature on Tc-99m tagged RBC scintigraphy and CT-based diagnostics and come out with a conclusion commenting on the comparison between the two. This study also aims to have a set of recommendations for the use of both modalities, but with a focus on GI scintigraphy.

MATERIALS AND METHODS

Search Strategy

A comprehensive review of PubMed and Medline was done using a combination of the following search terms: “red blood cell tagging”, “scintigraphy”, “gastrointestinal bleed”, “CT angiography”, “Multidetector CT”. A manual review of references within pertinent studies was also done. The complete MeSH terms and search history are attached in the appendix.

Reporting of study results was done following the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses or PRISMA [8]. Two independent reviewers screened for the presence of duplicate results and for proper eligibility based on the title and abstract. The remaining studies were then assessed for eligibility.

Study Selection:

Studies from the initial search were carefully selected by setting several inclusion and exclusion criteria. These criteria were made to best answer the objectives of this paper.

The following are the inclusion criteria for the studies:

1. Studies must deal with patients who were worked up for acute lower gastrointestinal hemorrhage
2. Studies must have a direct comparison between RBC scintigraphy and CT-based imaging
3. Studies must report on either the clinical utility of each modality or at least one of the following diagnostic outcomes: sensitivity, specificity, localization
4. Studies must have actual patient populations who undergo each diagnostic test.

Below are the exclusion criteria for the studies:

1. Studies must not be a case-series, case report or a cohort study comparing different disease stages of LGIB.
2. Studies with less than 15 total patients will not be included
3. Studies must not be published earlier than 2005

Only the studies which fulfilled all of the inclusion criteria below were considered. Studies dealing with upper gastrointestinal hemorrhage were not in the inclusion criteria since RBC-tagging is not a usual diagnostic tool used for evaluation. In addition, studies that only examined one modality while just referencing the other modality were also not considered to avoid possible sources of bias.

Studies which possessed all the inclusion criteria were further filtered by the exclusion criteria. Cohort studies with diagnostics done at different disease stages were excluded in order to avoid testing for the presence of hemorrhage at different periods wherein the likelihood of a positive outcome is different. If the modalities were used at different time periods, an unacceptable amount of bias would be included, and this would disregard the evolution of the disease over time. An example of a study that would have been excluded was one where a certain modality was used as the initial work-up and the other modality used for a different purpose such as assessing efficacy of an intervention.

Case-series and case report studies were excluded since the designs of these studies cannot predict sensitivity and specificity based on the limited sample size

Study Quality Assessment and Data Extraction

Eligible studies were evaluated for their quality using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool to assess for bias and applicability. The QUADAS-2 tool was made to assess four pertinent aspects of a diagnostic study, which are: 1) patient selection, 2) index test, 3) reference standard and, 4) flow and timing [9]. The highest score a study can have is 14, with the lowest possible score of 0. Studies that scored 7 or less were not included in the review.

The specificity and sensitivity of each modality in diagnosing the presence of LGIB was extracted from the reported raw data and was also recomputed by the investigator. Separately, the rate of accurate localization was also extracted and the number of patients who were part of the study was also noted.

A study was considered positive if it was able to correctly identify the presence of bleeding, regardless of the findings on its localization. Only data from index tests which had a corresponding reference standard were included for the computation in the meta-analysis. However, studies which did not use an acceptable reference standard were still noted for the discussion. Clinical utility and other differences between the modalities which could not be statistically analyzed were also accounted for in the systematic review. Two independent reviewers discussed their respective assessments with a third reviewer available to resolve differences via consensus.

Statistical Analysis

A meta-analysis of studies which report the same clinical outcomes was done while studies which do not qualify for the meta-analysis were included in the discussion of the review. Data from the index tests, namely RBC scintigraphy and CT-based imaging, were extracted from each study. If available, this would be compared to the reference standard, which was catheter/conventional angiography. Also, surgical confirmation was also accepted as a reference standard. Sensitivity and specificity were recomputed for each study based on their presented raw data. Useable data was disaggregated from studies which only reported overall outcomes. Particularly, data disaggregation was done to separate the index tests that were evaluated against a reference standard from the index tests without proper comparison. Pooled sensitivity and specificity were then computed based on the extracted data. Accurate localization of a positive study was also extracted if available. Heterogeneity of the studies were analyzed during the pooling of sensitivity and specificity

To address the variabilities between the chosen studies, a summary receiver operating characteristic (SROC) curve was used. The SROC curve plots the 1-specificity and the sensitivity in the x- and y-axes using a regression model with a smooth curve as an outcome. From this, the area under the curve (AUC) may be computed with values between zero to one [10]. The AUC value is the probability for which a pair of a true positive and a true negative results is identified properly. An ideal test has an AUC of 1, while a test which randomly and equally assigns positive and negative results has an AUC of 0.5. The SROC analysis considers the different thresholds of positivity used in each study and the differences in population number, both of which are pitfalls when using pooled sensitivity, specificity, and averages [10]. The SROC curves and AUC values were generated using the MetaDisc 1.4 program.

Data on clinical utility and some other diagnostic outcomes were included in the systematic review and discussion, but not included in the SROC curve computation since these parameters can not be fairly compared quantitatively. Examples of these parameters in the discussion include the window period (possible acquisition time) for which bleeding can be seen.

RESULTS

Literature Search Outcome

A total of 182 studies were initially screened for eligibility based on the aforementioned search terms and combinations. Majority of the studies were excluded because they tackled a different subject matter. Six studies were deemed eligible to be included in the systematic review, based on the inclusion and exclusion criteria. However, two of the studies were not included in the meta-analysis due to differences in design and reported outcomes. The four studies included in the meta-analysis amounted to a total number of 374 patients. The diagram of the search flow following PRISMA is in the appendix. The list of the studies, alphabetically arranged by authors, may be seen in Table

1. Table 1 also indicates the study design and comments on how data was reported or used.

Characteristics of the studies

Among the selected studies, three (the studies by Awais, Kulkarni and Speir) compared the diagnostic outcomes of both index modalities using catheter angiography as the reference standard. All three were retrospective reviews of patients who underwent a catheter angiography (the reference standard) and had a CT-angiography and/or RBC scintigraphy. The study by Zink was a prospective evaluation of CT-angiography compared with RBC scintigraphy, however, not all patients were subject to catheter angiography or surgery. For this study, data was disaggregated and only the portion of the population which had an acceptable reference standard comparison was included in the meta-analysis.

Table 2 shows the total patient population and the number of procedures done for each index test for each study. Some patients underwent both tagged-RBC scintigraphy and CT-angiography, while other patients underwent work-up twice. The study by Kulkarni retrospectively looked at all patients who underwent CT-angiography, thus the entire population had the test done. The studies by Awais and Speir retrospectively went through all patients who were worked-up for LGIB, regardless of work-up done.

The study by Hsu only reported on the time for index test completion and time from the index test to catheter angiography. These diagnostic outcomes were not included in the meta-analysis by the investigator but included in the discussion. Data on the outcomes of the catheter angiography were not reported, thus sensitivity and specificity were not available. The study by Feuerstein reported diagnostic outcomes between both modalities, however the index tests served as its own reference standard, making the data on sensitivity and specificity incomparable with the other studies in the meta-analysis. However, Feuerstein also reported on the time for test completion, similar to the study by Hsu, thus making this portion of the study eligible for comparison in the systematic review.

TABLE 1. List of studies, alphabetically arranged by author, with study design and comments on their use in the paper

Study Title	Author and Year	Study Design	Comments
Accuracy of 99mTechnetium-labeled RBC Scintigraphy and MDCT With Gastrointestinal Bleed Protocol for Detection and Localization of Source of Acute Lower Gastrointestinal Bleeding	Muhammad Awais, MBBS et al (2015)	Retrospective	Included in meta-analysis
Localizing Acute Lower Gastrointestinal Hemorrhage: CT Angiography Versus Tagged RBC Scintigraphy	Joseph D. Feuerstein, et al (2015)	Retrospective	Used the index test as its own reference standard
Time to conventional angiography in gastrointestinal bleeding: CT angiography compared to tagged RBC scan	Michael J. Hsu, et al (2019)	Retrospective	Only reported on time
In the workup of patients with obscure gastrointestinal bleed, does 64-slice MDCT have a role?	Chinmay Kulkarni, et al (2012)	Retrospective	Included in meta-analysis
Correlation of CT Angiography and 99m Technetium - Labeled Red Blood Cell Scintigraphy to Catheter Angiography for Lower Gastrointestinal Bleeding: A Single -Institution Experience	Ethan J. Speir, et al (2019)	Retrospective	Included in meta-analysis
Noninvasive Evaluation of Active Lower Gastrointestinal Bleeding: Comparison Between Contrast- Enhanced MDCT and 99mTc-Labeled RBC Scintigraphy	Stephen I. Zink, et al (2008)	Prospective	Disaggregated data was included in meta-analysis

TABLE 2. Patient population and number of procedures for each index test done

	Total patient population	Number of RBC scintigraphy studies	Number of CT-angiography studies
Awais	76	56	25
Kulkarni	50	11	50
Speir	207	185	50
Zink	41	22*	22*
Total number	**374**	**274**	**147**

*Disaggregated data was used. The reported numbers are those wherein both the index test and the reference study were done.

The acquisition protocol of all modalities were reviewed. In all six studies, the tagged-RBC scintigraphy was performed using doses ranging from 555 MBq to 925 MBq of radiopharmaceutical. The RBCs were tagged with Tc-99m pertechnetate using the in-vitro technique. All acquisitions were made via planar imaging and none of the studies performed SPECT-CT fusion imaging. For the CT-angiography test, imaging using intravenous iodinated contrast at 300 mg I/mL was done in the arterial phase, with variable amounts of contrast used in each study. All studies used at least a 64-slice CT. Acquisition of the arterial phase was timed differently for each study, either after a few seconds after bolus or once the 150 HU-enhancement threshold was reached. Contrast-enhanced images were compared with non-contrast images taken prior. Each study followed the acceptable protocol for all modalities for their institution and all images were reviewed by experienced radiologists.

Quality of Selected studies

The selected studies were of moderate to good quality. Two studies scored twelve in the 14-point QUADAS tool for assessment of bias, while there was one study each scoring 11, 10, and 9 points. The study by Hsu, which only reported on completion times, scored 13 points. A detailed breakdown of the QUADAS scoring is in the appendix. These scores show that the studies selected had possible sources of bias in terms of the design. However, due to the nature of the disease which was being evaluated, as well as the protocols of the index tests and reference standard, the design of the studies were not expected to score full marks.

The studies consistently interpreted the results of the reference standard with prior knowledge of the index test. In some studies, the results of the index test determined clinical action and thus the reference standard was not always performed. Reviewing both tests together was part of the standard of care for patients. Images, from the CT-angiography and nuclear medicine, may easily be retroactively reviewed by investigators but it was difficult to do so with catheter angiography. A fully blinded, prospective, randomized control trial would have theoretically been able to create a better study design, but this would compromise patient care and is unethical. For retrospective studies, blinding was performed wherein the index tests were reviewed without knowledge of the results of the reference standard.

Another common source of potential bias is the ability of the reference standard (catheter angiography) to accurately diagnose the disease entity. This issue shall be further elaborated in the discussion portion of the study.

Results of Statistical Analysis

The results for the sensitivity and specificity values of RBC-tagging and CT-angiography may be seen in Tables 3 to 6. The pooled sensitivity of RBC-tagging is 0.886, higher than that of CT-angiography using MDCT which had a sensitivity of 0.729. Both tests show heterogeneity for sensitivity, although there was considerably less in the analysis of RBC-scintigraphy. Pooled specificity was significantly higher for CT-angiography at 0.660 while the RBC-tagging only had a pooled specificity of 0.119. Both tests for specificity had considerable heterogeneity, with the larger chi-squared value for RBC-tagging specificity attributable to vastly different population numbers. Issues with the reference standard, common to all

TABLE 3. Summary values and confidence intervals for Sensitivity of Tagged-RBC Scintigraphy

Summary Sensitivity: Tagged-RBC Scintigraphy

Study	Sen	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Awais	0.813	0.636 - 0.928	26/32	8/24
Kulkarni	0.700	0.348 - 0.933	7/10	1/1
Speir	0.944	0.846 - 0.988	51/54	8/131
Zink	0.944	0.727 - 0.999	17/18	2/3
Pooled Sen	**0.886**	**0.813 - 0.938**		

Heterogeneity chi-squared = 6.91 (d.f.= 3) p = 0.075

TABLE 4. Summary values and confidence intervals for Specificity of Tagged-RBC Scintigraphy

Summary Specificity: Tagged-RBC Scintigraphy

Study	Spe	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Awais	0.333	0.156 - 0.553	26/32	8/24
Kulkarni	1.000	0.025 - 1.000	7/10	1/1
Speir	0.061	0.027 - 0.117	51/54	8/131
Zink	0.667	0.094 - 0.992	17/18	2/3
Pooled Spe	**0.119**	**0.074 - 0.180**		

Heterogeneity chi-squared = 21.76 (d.f.= 3) p = 0.000

TABLE 5. Summary values and confidence intervals for Sensitivity of CT-angiography

Summary Sensitivity: CT-angiography

Study	Sen	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Awais	0.933	0.681 - 0.998	14/15	10/10
Kulkarni	0.722	0.548 - 0.858	26/36	8/14
Speir	0.852	0.663 - 0.958	23/27	12/23
Zink	0.389	0.173 - 0.643	7/18	3/3
Pooled Sen	**0.729**	**0.629 - 0.815**		

Heterogeneity chi-squared = 15.55 (d.f.= 3) p = 0.001

TABLE 6. Summary values and confidence intervals for Specificity of CT-angiography

Summary Specificity: CT-angiography

Study	Spe	[95% Conf. Iterval.]	TP/(TP+FN)	TN/(TN+FP)
Awais	1.000	0.692 - 1.000	14/15	10/10
Kulkarni	0.571	0.289 - 0.823	26/36	8/14
Speir	0.522	0.306 - 0.732	23/27	12/23
Zink	1.000	0.292 - 1.000	7/18	3/3
Pooled Spe	**0.660**	**0.512 - 0.788**		

Heterogeneity chi-squared = 13.14 (d.f.= 3) p = 0.004

studies, will be discussed further in the succeeding section. Aside from this, the low pooled specificity of RBC - tagging was likely skewed by the study of Speir which reported a specificity of 0.061. Individual specificities of 1.00 were also reported by Awais and Zink for CT-angiography and by Kulkarni for RBC-tagging. The presence of all these extreme values may be explained by the small patient pool used by the studies.

As mentioned earlier, an index test which correctly identified the presence of bleeding but incorrectly localized the bleeding site was still considered a positive result when computing for sensitivity and for the SROC curve. The data for correct localization was not present in all studies, thus if the condition of correct localization was applied to one study but not the others, an undue confounding factor will be introduced. This caused the need to separate the analysis on positive/negative diagnosis from the analysis on localization.

The summary receiver operating characteristic (SROC) curves are both seen in Figures 1 and 2, respectively. The area under the curve (AUC) of CT-angiography is higher at 0.81 compared to the 0.77 AUC of RBC-tagging. As seen on the figures, the confidence intervals for the SROC curve at 95% are both large thus this puts into question the clinical relevance of the rather small difference between the AUC of both modalities. As mentioned in the previous section, the SROC analysis takes into consideration the pitfalls of pooled sensitivity and specificity.

The Spearman's correlation coefficient was also derived, with RBC-tagging showing moderate positive correlation at 0.632 and with minimal negative correlation for CT-angiography of -0.2. The p-values were both high at 0.368 and 0.8 respectively, thus little clinically useable inferences can be derived.

Accurate localization was demonstrated in all CT-angiography tests from the study of Awais (14 of 14), and with only one (out of 17) misidentified source in the study by Feuerstein. On the other hand, RBC-tagging showed wrong localization in three (out of 26) tests from the study of Awais, in five (out of 34) from the study of Feuerstein, and one (out of 17) from the study of Zink. The remainder of the studies did not report on localization results. Further statistical analysis of the data was not done since there were inconsistencies between the studies on how localization was determined, however, the individual data sets showed that CT-angiography outperformed RBC-tagging.

Time from study order to completion showed a significantly faster completion time of CT-angiography on both studies which reported on it. The study by Hsu reported an average time to completion of 3 hours and 4 minutes for CT-angiography compared to 5 hours and 1 minute for RBC-tagging, while the study by Feuerstein showed an average time to completion of 1 hour and 41 minutes for CT angiography compared to 3 hours and 9 minutes for RBC-tagging. Significant differences between the averages of the same index

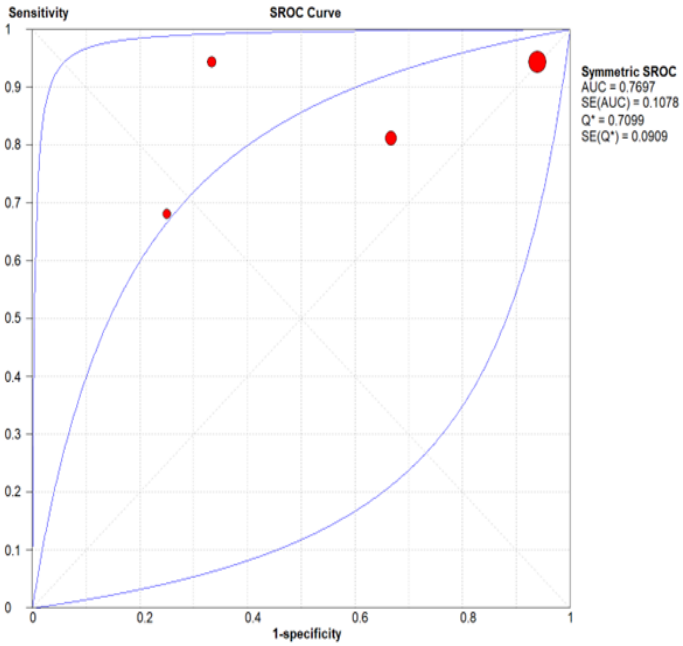

FIGURE 1. SROC curve for RBC-tagging scintigraphy

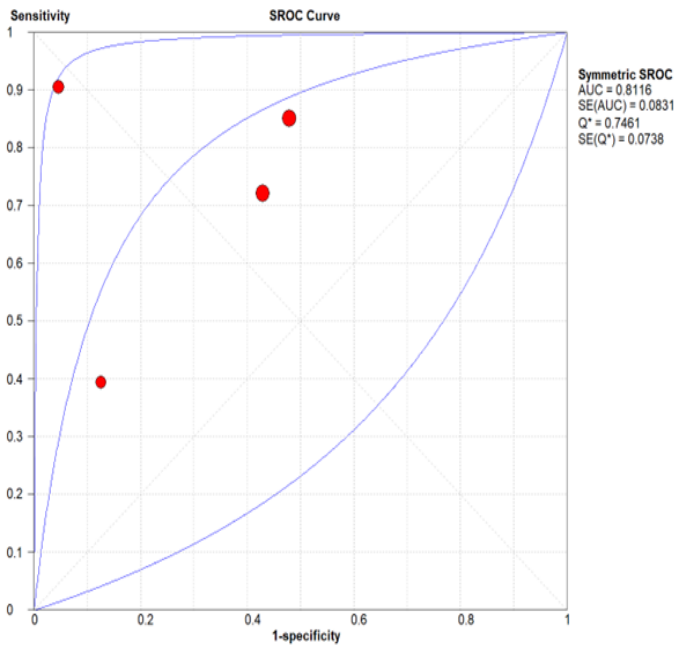

FIGURE 2. SROC curve for CT-angiography

test from the two studies may be attributed to the inter-hospital differences. A larger window for acquisition times for RBC-tagging was present, however, the complete data set was not reported in both studies.

DISCUSSION

Assessment and comparison of the two index tests is complex and should be done with careful discussion of the inherent differences each modality has. The AUC values of CT-angiography and tagged RBC scintigraphy were too close to be significant given the large confidence intervals. This implies the same likelihood that the two index tests will classify a pair of true positive and negative correctly. A number of the included studies discussed and concluded that CT-angiography demonstrates greater accuracy based on their sensitivity and specificity [13, 15], while others were not able to definitively conclude that there was statistically significant disagreement [17]. However, all studies agreed that both modalities were useful in evaluation of LGIB. Although different protocols for the sequence of which imaging modality for LGIB were used in the included institutions, a positive or negative finding in either of the index tests affected the management of the patient and both were clinically useful, regardless.

The derived sensitivity and specificities from the selected studies for RBC-tagging scintigraphy was lower than what is usually reported in other sources of literature. A sensitivity of higher than 90% is usually the accepted value with greater variance in the reported specificities, ranging from 30% to 90% [17]. Gastrointestinal bleeding as low as 0.1 mL/min can be detected by scintigraphy, with an imaging window of up to 24 hours from injection of the radiopharmaceutical [17, 23, 24] The small amount of bleeding needed as well as the large window of imaging contributes to the high reported sensitivity of scintigraphy in literature, with some even reporting values nearing 100% of active bleeding [20]. The pooled sensitivity at 0.866 may have been improved if a more thorough imaging protocol was done. Majority of the studies did not mention if delayed images were taken, considering the fact that the time of study order to completion only averaged at 5 hours in one study [15] and 3 hours in another [16].

The pooled specificity of RBC scintigraphy derived from the studies was 0.119, which is lower than what is reported in literature [17]. A possible explanation for this may come from the formula of specificity which is (true negatives) / (true negatives + false positives), focusing on the false positives. A study was deemed to be falsely positive if the index test (RBC-tagging scintigraphy) reported a positive result while the reference standard (catheter angiography) showed a negative result. Catheter angiography involves insertion of a catheter that delivers contrast which will extravasate into the gastrointestinal tract in the presence of active bleeding. This is the confirmatory sign of bleeding. Aside from this diagnostic utility, therapeutic embolization may also be done concurrently, making this a first-line imaging modality in gastrointestinal bleeding for some cases [18].

Despite being a reference standard, it is not uncommon that there are cases wherein a patient will test positively in RBC-tagging scintigraphy and negatively in catheter angiography. A 2013 study showed that out of 152 patients who were seen to have bleeding on gastrointestinal bleed scintigraphy, catheter angiography was not able to localize bleeding in 116 or around 76% [18]. The presence of an imperfect gold-standard may cause over- or underestimation of the parameters of the index test. The investigators believe that for majority of the studies, it has incorrectly increased the false positives, thus underestimating specificity. There is little, in terms of data processing, that can be done to rectify the values which come from an imperfect reference standard. A solution that can be offered to assess the presence of an actual condition, gastrointestinal bleeding in this case, is by using multiple tests [19]. In the study by Zink, there were cases where surgical confirmation of bleeding superseded the negative findings of catheter angiography, and thus classifying a patient who tested positive in RBC-scintigraphy as a true positive, despite being negative on catheter angiography [14]. However, only this one study offered data on other means of confirmation and so this method of using multiple tests to augment an imperfect reference standard was not done for all studies.

Similar to the values reported in RBC scintigraphy, CT-angiography also has a higher reported sensitivity and specificity in literature at 85% and 92% compared to the derived values from the included studies at 72.9% and 66% respectively [7]. Unlike gastrointestinal bleed scintigraphy, CT-angiography has a very short window of acquisition of 0.5 seconds [7]. This short acquisition window is likely the cause of a lower sensitivity since it eliminates the possibility of repeat acquisition in order to detect intermittent bleeding. Specificity and bleeding - site localization is also higher due to the inherent advantages of CT-based imaging in determining the anatomy of a patient. Accurate bleeding- site localization

is possible in all patients wherein active extravasation is identified; this was consistent with the findings from two of the studies which reported on site localization [11,16]. In addition, CT-angiography can also reliably identify other sources of bleeding, even if they are not active, such as tumors, AV malformations, or ulcerations [7]. This is a distinct advantage of CT-based imaging over gastrointestinal bleed scintigraphy and was discussed in the studies included in the meta-analysis

An in-depth discussion on tagged-RBC scintigraphy done with SPECT-CT acquisition was not present in all studies. Fused imaging of functional images from SPECT with anatomic imaging from CT drastically increased the ability to localize the source of bleeding. Studies show varying degrees of increased localization, with accuracy being 10-15% and up to 36% better than planar imaging [20, 21]. Addition of SPECT-CT fusion imaging does not compromise acquisition of planar imaging while offering the advantages of CT anatomic imaging [23]. The sensitivity in detecting a gastrointestinal bleed may still remain the same even with SPECT-CT fusion since interpretation of a positive scan still hinges on the interpretative criteria from scintigraphy [23, 24]. Comparing SPECT-CT gastrointestinal bleed scintigraphy with CT-angiography may be an interesting avenue to explore since no such paper was identified in the literature search.

The investigators believe that each patient must be evaluated individually with specific clinical scenarios calling for one index test over another. An example of this is RBC-tagging having distinct advantages for occult or intermittent bleeding while CT-angiography is better for localization with relatively larger bleeding volumes. The American College of Radiology (ACR) has released appropriate use criteria for both index tests, which can help guide the clinician as to when a test is appropriate [22]. Briefly, the ACR recommended both RBC scintigraphy and CT-angiography in a hemodynamically stable patient with active bleeding, meanwhile it only recommended CT-angiography in an unstable or transfusion-requiring patient.

CONCLUSION

To summarize, both tagged RBC scintigraphy and CT-angiography are clinically relevant and accurate tests to evaluate lower gastrointestinal bleeding. Sensitivity and AUC values derived from the SROC curves are comparable between both studies with tagged RBC scintigraphy showing a slight but not statistically significant advantage in sensitivity. CT-angiography showed greater specificity but issues with the reference standard likely compounded the results for tagged RBC scintigraphy causing lower values. Both index tests showed distinct advantages over the other such as a large window for acquisition for scintigraphy and accurate anatomic localization for CT angiography.

Limitations of the Study and Recommendations :

This paper is limited by the small number of studies which qualified given the inclusion and exclusion criteria. Furthermore, different methodologies between studies made direct comparison quite difficult. The small population for each individual study lessens the statistical significance which was inferred, as seen by the wide confidence intervals in the SROC.

Recommendations for further studies include reassessment of catheter angiography as a reference standard for other diagnostic modalities. More individual studies are also needed to create a robust data set where more definitive conclusions can be made. The roles of CT-angiography and tagged-RBC scintigraphy should be continuously reassessed when managing LGIB. The addition of SPECT-CT to tagged-RBC scintigraphy may be an interesting avenue to explore, given the added advantages it may give and lack of current literature.

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APPENDICES

Appendix 1. MESH terms and search history

Search Number	Query	Filter	Search Details	Results
3	((scintigraphy) OR (Red Blood Cell tagging)) AND (((MDCT) OR (CT angiography) OR (Multidetector CT) AND gastrointestinal))		(((((("radionuclide imaging"[MeSH Terms] OR ("radionuclide"[All Fields] AND "imaging"[All Fields])) OR "radionuclide imaging"[All Fields]) OR "scintigraphies"[All Fields]) OR "scintigraphy"[All Fields]) OR ((((("erythrocytes"[MeSH Terms] OR "erythrocytes"[All Fields]) OR (("red"[All Fields] AND "blood"[All Fields]) AND "cell"[All Fields])) OR "red blood cell"[All Fields]) AND ("tagged"[All Fields] OR "tagging"[All Fields]))) AND ((((((("multidetector computed tomography"[MeSH Terms] OR (("multidetector"[All Fields] AND "computed"[All Fields]) AND "tomography"[All Fields])) OR "multidetector computed tomography"[All Fields]) OR "mdct"[All Fields]) OR ((((("computed tomography angiography"[MeSH Terms] OR (("computed"[All Fields] AND "tomography"[All Fields]) AND "angiography"[All Fields])) OR "computed tomography angiography"[All Fields]) OR ("ct"[All Fields] AND "angiography"[All Fields])) OR "ct angiography"[All Fields])) OR ((((("multidetector computed tomography"[MeSH Terms] OR (("multidetector"[All Fields] AND "computed"[All Fields]) AND "tomography"[All Fields])) OR "multidetector computed tomography"[All Fields]) OR ("multidetector"[All Fields] AND "ct"[All Fields])) OR "multidetector ct"[All Fields])) AND (("gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields]) OR "gastrointestine"[All Fields]))	174
2	((scintigraphy) OR (Red Blood Cell tagging)) AND (((MDCT) OR (CT angiography)) AND gastrointestinal))		(((((("radionuclide imaging"[MeSH Terms] OR ("radionuclide"[All Fields] AND "imaging"[All Fields])) OR "radionuclide imaging"[All Fields]) OR "scintigraphies"[All Fields]) OR "scintigraphy"[All Fields]) OR ((((("erythrocytes"[MeSH Terms] OR "erythrocytes"[All Fields]) OR (("red"[All Fields] AND "blood"[All Fields]) AND "cell"[All Fields])) OR "red blood cell"[All Fields]) AND ("tagged"[All Fields] OR "tagging"[All Fields]))) AND (((((("multidetector computed tomography"[MeSH Terms] OR (("multidetector"[All Fields] AND "computed"[All Fields]) AND "tomography"[All Fields])) OR "multidetector computed tomography"[All Fields]) OR "mdct"[All Fields]) OR ((((("computed tomography angiography"[MeSH Terms] OR (("computed"[All Fields] AND "tomography"[All Fields]) AND "angiography"[All Fields])) OR "computed tomography angiography"[All Fields]) OR ("ct"[All Fields] AND "angiography"[All Fields])) OR "ct angiography"[All Fields])) AND (("gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields]) OR "gastrointestine"[All Fields]))	173
1	((scintigraphy) OR (Red Blood Cell tagging)) AND ((CT angiography) AND gastrointestinal))		(((((("radionuclide imaging"[MeSH Terms] OR ("radionuclide"[All Fields] AND "imaging"[All Fields])) OR "radionuclide imaging"[All Fields]) OR "scintigraphies"[All Fields]) OR "scintigraphy"[All Fields]) OR ((((("erythrocytes"[MeSH Terms] OR "erythrocytes"[All Fields]) OR (("red"[All Fields] AND "blood"[All Fields]) AND "cell"[All Fields])) OR "red blood cell"[All Fields]) AND ("tagged"[All Fields] OR "tagging"[All Fields]))) AND (((((("computed tomography angiography"[MeSH Terms] OR (("computed"[All Fields] AND "tomography"[All Fields]) AND "angiography"[All Fields])) OR "computed tomography angiography"[All Fields]) OR ("ct"[All Fields] AND "angiography"[All Fields])) OR "ct angiography"[All Fields]) AND (("gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields]) OR "gastrointestine"[All Fields]))	158

Appendix 2. PRISMA Diagram

QUADAS						
	Zink	**Feuerstein**	**Kulkarni**	**Speir**	**Awais**	**Hsu**
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes	Yes	Yes
Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Is the reference standard likely to correctly classify the target condition?	No	No	Yes	No	No	N/A
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes	Yes	Yes	Yes	Yes	Yes
Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	No	No	No	Yes	Yes	Yes
Did patients receive the same reference standard regardless of the index test result?	No	No	No	Yes	Yes	Yes
Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?	Yes	No	Yes	Yes	Yes	Yes
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes
Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	No	No	No	No	No	Yes
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Yes	Yes	Yes	Yes	Yes	Yes
Were uninterpretable/ intermediate test results reported?	Yes	Yes	Yes	Yes	Yes	Yes
Were withdrawals from the study explained?	Yes	Yes	Yes	Yes	Yes	Yes
TOTAL	**10**	**9**	**11**	**12**	**12**	**13**

APPENDICES

Appendix 3. PRISMA Diagram