Diagnostic accuracy of nuclear medicine imaging in protein losing enteropathy : systematic review and meta-analysis of the literature

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Abstract

Background and Aim : **Scintigraphy using Tc-99m or In-111 labeled proteins is an important diagnostic modality for diagnosis of protein losing enteropathy (PLE). We systematically reviewed the available literature regarding the accuracy of scintigraphy using Tc-99m or In-111 labeled proteins for diagnosis of PLE.**

Methods : **Medline and SCOPUS were searched using ((“protein losing”) AND (“scintigraphy” OR “Nuclear Medicine”)) as keywords without any language or date limit. All studies on the accuracy of scintigraphy using Tc-99m or In-111 labeled proteins in PLE were included in the systematic review.**

Results : **Overall 12 studies were included in our study. Pooled sensitivity and specificity were 87% [81-92%], and 62% [51-72%], respectively. Tc-99m labeled tracers had higher sensitivity but lower specificity compared to In-111 labeled ones. Delayed imaging could increase the sensitivity of imaging despite the lower specificity compared to the early images. Restriction of the analyses to larger studies (more than 10 patients) and to studies with the gold standard of fecal alpha1-antitrypsin did not change the pooled indices.**

Conclusion : **Scintigraphy using Tc-99m or In-111 labeled proteins has high sensitivity for diagnosis and localization of PLE. Using Tc-99m labeled tracers and delayed imaging can further increase the sensitivity. Despite the high sensitivity, specificity of scintigraphy is suboptimal and false positive abdominal activities can limit the usefulness of this imaging method.** (Acta gastroenterol. belg., **2013**, 76, **413-422**).

Key words : Protein losing enteropathy ; Scintigraphy ; Systematic review ; Meta-analysis ; Tc-99m Dextran ; Tc-99m-HSA ; In-111 Transferrin.

Introduction

Protein-losing enteropathy (PLE) is the term applied to a heterogeneous group of diseases which are associated with excessive loss of plasma proteins into the gastrointestinal tract (1). PLE is associated with more than 85 common diseases, including exudative conditions like gastroenteritis, colitis, gastrointestinal tract (GIT) malignancy, diverticular diseases, and diseases affecting the stomach and those resulting from increased intestinal hydrostatic pressure like cardiac disorders with increased central venous pressure and intestinal lymphangiectasia (2). Fecal alpha1-antitrypsin (AAT) is the main diagnostic marker for PLE ; this protein is a broad spectrum protease inhibitor that is synthesized in the liver and is resistant to proteolytic degradation within intestinal secretion and feces. However the assessment of this marker is cumbersome and needs fecal matter collection and manipulation. In addition this test cannot be used for diagnosis of PLE due to gastric pathologies (3,4).

Scintigraphy using Tc-99m or In-111 labeled proteins has been another widely used diagnostic tool for PLE since its introduction in 1986 (5). Previous studies suggested that this method is simple and sensitive not only to diagnose PLE, but also to localize the site of protein loss in the gastrointestinal tract (6). Usually Indium-111 (In-111) and Technetium-99m (Tc-99m) are used to tag the serum proteins (mostly transferrin and albumin). In-111-transferrin, Tc-99m-human serum albumin (HSA) or Tc-99m-dextran are the most widely used radiotracers. These radiotracers accumulate in the gastro-intestinal tract as protein loss occurs in the digestive system and this property can be exploited for imaging.

In the current study, we systematically searched the available literature on the accuracy of scintigraphy using Tc-99m or In-111 labeled proteins for the diagnosis and localization of PLE. We reported the results in a systematic review and meta-analysis format.

Materials and methods

Search strategy, selection criteria, data abstraction

Medline and SCOPUS were searched with the following search terms : ((“protein losing”) AND (“scintigraphy” OR “Nuclear Medicine”)) without any language or date limit.

Any study on the accuracy of scintigraphy using Tc-99m or In-111 labeled proteins in PLE was included if the following criteria were met :

1. Having at least 5 patients evaluated by radionuclide imaging.
2. Enough data to calculate sensitivity and/or specificity of the radionuclide imaging.

Reference lists of the relevant studies were evaluated for any possible missed citation. Citing articles of each

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relevant study were also reviewed (by citation tracking options of the SCOPUS and Google scholar) for any other possible relevant study. Corresponding authors were contacted if necessary.

Retrieved articles were evaluated blindly by two of the authors and in case of any disagreement ; the opinion of a third author was used. Possible duplicate publications were discussed and only the most recent studies were included.

The quality of the included studies was evaluated using the Oxford Center for Evidence Based Medicine Checklist of diagnostic studies (7).

Data on authors, publication year, type of the radiotracer, complementary diagnostic methods, characteristics of the patients, and information needed for sensitivity and/or specificity calculation were extracted by two authors independently.

Statistical analysis

The recommendations of Deville *et al*. for meta-analysis of diagnostic studies were followed (8). Due to considerable heterogeneity of the included studies regarding methods and patients, the random effects model was used for pooling the data (9). For heterogeneity evaluation, Cochrane Q test was used and significance level was set at $p = 0.05$. For quantifying the heterogeneity, I^2 index was used. For threshold effect evaluation, correlation between sensitivity and specificity of included studies was calculated (10). In addition, sensitivity and specifity of the individual studies were re-calculated for different thresholds of positivity (any activity in the abdomen vs. at least moderate activity in the abdomen) if possible. To explore the effect of radiotracer type and imaging time, subgroup analyses were used. To explore the effect of inclusion of studies with various gold standards and low sample size studies, sensitivity analyses were done.

Sensitivity, specificity, negative and positive likelihood ratios (LR-, LR+), and diagnostic odds ratio (DOR) were calculated for each study and overall results were calculated by pooling the data using random effects model (10). Summary receiver operating characteristics curve (sROC curve) fitting, area under the curve (AUC) calculation as well as Q^* value were also used for summarizing overall performance of the test (11).

Publication bias was addressed graphically using funnel plots. Funnel plots asymmetry was also statistically tested using Egger's regression intercept method (12). Duval-Tweedie's trim and fill method was used for quantifying possible publication bias effect (13).

Comprehensive Meta-analysis (version 2) and Meta-Disc (version 1.4) were used for statistical analyses (14).

Results

Figure 1 shows the search strategy of the study (PRISMA flowchart). In the first search, 143 studies seemed relevant but 71 were excluded by screening the abstracts and titles of the articles (irrelevant studies). The full texts of the remaining 72 studies were evaluated in detail and 60 studies were excluded being review articles, letter to editors or case reports. Finally 12 relevant studies were included in the meta-analysis (1,2,5,6,15-22). Table 1 shows characteristics summary of the included study in our systematic review.

Figure 2 and 3 show the forest plots of sensitivity and specificity pooling. For diagnosis of PLE the scintigraphy had pooled sensitivity of 87% [81-92%], specificity of 62% [51-72%], LR+ of 2.662 [1.304-5.434], LR- of 0.180 [0.075-0.433] and DOR of 25.820 [7.580-87.949].

Figure 4 and 5 show the funnel plots of sensitivity and specificity pooling. Egger's regression intercept for sensitivity and specificity pooling was 2.7 ($p = 0.00032$) and 2.45 ($p = 0.057$) respectively. Using Duval and Tweedie's trim and fill method, 6 studies for sensitivity pooling and 3 studies for specificity pooling were trimmed and adjusted pooled sensitivity and specificity were 14% and 17% lower than the observed ones, respectively.

sROC of the meta-analysis is shown in Figure 6 with AUC of 0.92 and Q* of 0.86.

Two studies (Simonsen *et al*. and Bhatnagar et al) reported their results according to the cut-off of positivity of the scintigraphy images. The pooled sensitivity and specificity were 100% [90-100] and 42.3% [23.4-63.1] if any abdominal activity is considered as a positive finding. The pooled sensitivity and specificity were 86.1% [70-95.3] and 92.6% [75.7-99.1] if only moderate abdominal activity is considered as a positive finding.

In seven studies (5,6,18-22) results were reported in early and delayed phases of imaging. In-111 was used for labeling in four studies (1,6,15,17) and Tc-99m in the remainder of the included studies.

Table 2 shows the subgroup analyses regarding type of the radiotracer, imaging time and threshold effect.

Discussion

Several techniques have been developed for the detection and quantification of protein loss in the gastrointestinal tract. Scintigraphy offers several advantages including simplicity, non-invasiveness, and low cost.

Another important advantage of scintigraphy in PLE is its ability to localize the diseased part of the GI tract which is almost impossible in certain cases with other imaging modalities. In addition scintigraphy using Tc-99m or In-111 labeled proteins does not require fecal matter handling which can be a limiting factor for fecal AAT test (20). It is worth mentioning that, fecal excretion of the radioactive material can also be used to quantify the amount and importance of protein loss. For example Dahlqvist *et al*. and Urita *et al*. quantified the GI protein loss by fecal collection and activity determination in the fecal matter using In-111-transferrin (15,23).

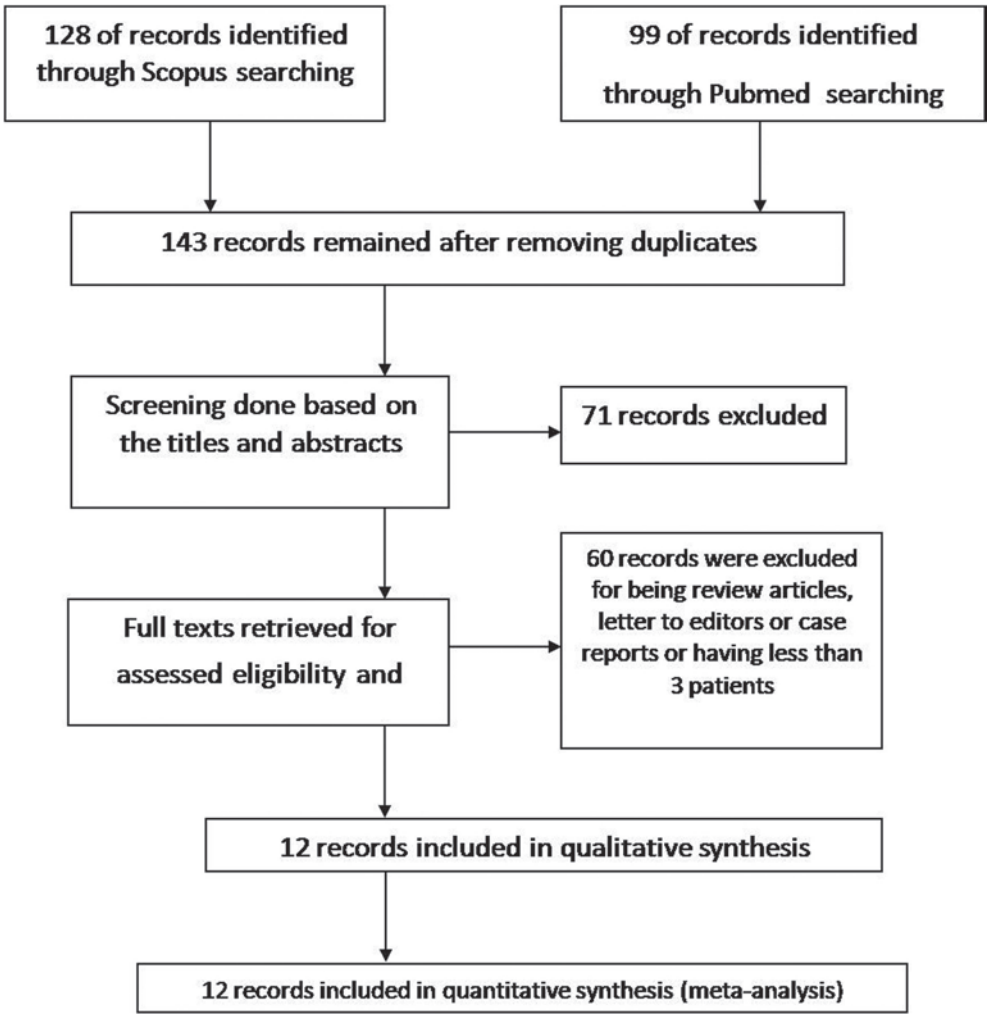

Fig. 1. — PRISMA flowchart of the study search strategy

In this systematic review, we have evaluated the sensitivity and specificity of the radiolabeled scintigraphy in the diagnosis of PLE.

Overall test accuracy

Overall the test works relatively well in the diagnosis of PLE (pooled DOR = 25.82, AUC of 0.92 and Q* of 0.86).

Pooled sensitivity was high (87%). This shows that the false negative results (no detection of the tracer in the gastrointestinal tract despite PLE) are relatively few. It is probable that these false negative results are secondary to protein-energy malnutrition or associated with hypertrophic gastritis rather than exudative causes (20). We should also consider the ability of abdominal scintigraphy to localize gastric causes of PLE. Diagnosis of this sub-set of PLE can be very hard and almost impossible with fecal AAT. In our systematic review, there were four Menetrier's patients and two hypertrophic gastropathic patients who were all diagnosed by scintigraphic imaging despite negative fecal AAT test (5,6,15-17).

On the other hand, the pooled specificity of the test was sub-optimal (62%). This means that false positive results (detection of tracer in the gastrointestinal tract despite no PLE) are the major shortcoming of the scintigraphy in the diagnosis of PLE. It is probable that these false positive results are due to simple physiological tracer activity in the bowel. Concomitant intestinal bleeding can be another reason of false positive results especially in patients with inflammatory bowel disease (2).

The included studies in the current systematic review were not homogenous and I^2 indices of sensitivity and specificity pooling were 71% and 86.3% respectively which are pretty high. In order to explore this heterogeneity, we evaluated the relation of several variables to the diagnostic performance of scintigraphy using Tc-99m or In-111 labeled proteins as shown in Table 2.

Type of the radiotracer

Scintigraphy with Tc-99m labeled tracers had higher pooled sensitivity as compared with In-111 (90.1% vs. 81.1%) but lower specificity (56.4% vs. 69.2%). This

Table 1. — **Summary of the 12 studies included in the review**

First author	Sample size (case/control)	Mean age Case/control	Sex, M/F Case vs. control	Cases group (number)	Control group (number)	Radiotracer	Sensitivity/ Specificity (%)	Consecutive recruitment of patients	Independent evaluation of the index test and reference standard	Gold standard
Takeda	5 (3/2)	NA	NA	IL (2), Hypertrophic Gastropathy (1)	NA	^{99m}TC-HSA	100/100	No	Yes	AAT&PGJ
Kashiwagi	9 (6/3)	NA	NA	NA	Patients with non-gastrointestinal tract disorder (3)	^{99m}TC-HSA	100/100	No	Yes	AAT
Okahara	15 (8/7)	NA	NA	NA	patients with ischemic heart disease (11)	^{99m}TC-HSA	88/0	No	Yes	AAT
Aburano	13 (7/6)	NA	NA	Menetrier's (2), Gastric ulcer (1), IL (1), Intestinal amyloidosis (1), Crohn's disease (1), Intestinal fistula (1)	Healthy volunteer (3), Hematologic disease (3)	^{111}In-T	100/100	No	Yes	AAT&PGJ
Simonsen	29 (14/15)	55.4/30.8	9/6 vs. 6/1	IBD (2), Enlarged liver (1), IL (3), Oedema (6), Menetrier's disease (1) DiGeorge syndrome (1)	Healthy volunteer (15)	^{111}In-T	100/21	Yes	Yes	Clinical: low serum albumin, oedema in patients without albuminuria, heart disease or ongoing intestinal inflammation
Halaby	18 (18/0)	54	11/7	PIL (15), Entrocolitis (1), Giardiosis (1),Unknown (1)	-	^{99m}TC-HSA	67/-	Yes	Yes	AAT
Chiu	38 (26/12)	45.9/51.2	11/5 vs. 6/6	SLE (13), Colon cancer (3), Intestinal lymphoma (3) IL (3), Enterocolitis (3), Infectious colitis (1)	Patients with no known gastrointestinal disease referred for cardiac blood-pool imaging (12)	^{99m}TC-HSA	96/100	No	Yes	Biopsy findings (12 patients and 12 control subjects), culture findings (one patient), or clinical follow-up (13 patients).
Chau	29 (10/19)	39/51	2/8 vs. 3/16	SLE (5), IL (2), Hypertrophic Gastropathy (1), Anorexia nervosa (1), Scleroderma (1)	SLE (6), IL (1), RA (3), bacterial overgrowth (1), Nasopharyngeal Carcinoma (1), Carcinoma of thyroid gland (1),Stomach carcinoma (1), Pancreas Carcinoma (2), Sjügren's syndrome (1) Tropical sprue (1), Hypertrophic gastropathy (1)	^{99m}TC-HSA	100/32	No	Yes	AAT, and Clinical: (i) clinical findings suggestive of an underlying disease known to be associated with PLE, (ii) the response to appropriate treatment, and (iii) the exclusion of alternative causes of hypoalbuminaemia
Bhatnagar	34 (22/12)	NA	NA	Ulcerative colitis (12), Enterocolitis (5), Worm infestation (2), IL (2), CHF (1)	Healthy volunteer (12)	^{99m}TC-D	100/67	Yes	Yes	AAT

De Kaski	23 (16/7)	9.7/6.1	NA	IL (4),Amyloid (2), Lymphoma (3), IBD (4), Cronkite-Canada syndrome (3),	Budd-Chiari syndrome (1), Alcoholic cirrhosis (2), Cardiomyopathy (1), Polyarteritis nodosa (1), Carcinoid syndrome (2)	^{111}In-T	75/86	No	Yes	Clinical: patients with hypoalbuminemia in whom urinary cause of loss was excluded.
Kapoor	8 (8/0)	5.18	5/3	Abdominal Tuberculosis (3), Tropical sprue (1), HW enteropathy (1), Marasmus (1), gastritis (1), Celiac disease (1)	-	^{99m}TC-D	75/-	Yes	Yes	Clinical: Hypoalbuminemia, oedema, and exclusion of non-GI causes of protein loss.
Urita	25 (12/13)	NA	NA	IL (2), IBD (2), Menetrier's disease (1), Cronkhite-Canada syndrome (1), postgastrectomy syndrome (1), severe atrophic gastritis (1), gastric cancer (1), gastroenteropathy of unknown origin (1)	healthy volunteer (4), patients with benign disease not accompanied by lesions in the digestive tract (9)	^{111}In-T	50/100	No	Yes	AAT

^{99m}TC-HSA: Technetium-99m human serum albumin, ^{111}In-T: Indium-111 transferrin, ^{99m}TC-D: Technetium-99m dextran, AAT: A1-antitrypsin of feces, PGJ: Protein content of gastric juice, SLE: Systematic lupus erythematous, IL: Intestinal lymphangiectasia, PIL: Primary Intestinal lymphangiectasia, IBD: Inflammatory bowel disease, RA: rheumatoid arthritis, CHF: congestive heart failure.

Table 2. — **Subgroup analyses of the studies regarding type of radiotracer, time of first activity and threshold effect**

	Sensitivity (%)	Specificity (%)	LR^+	LR^-	DOR
Type of radiotracer					
Indium-111	81.1 [68-90.6]	69.2 [52.4-83]	5.18 [0.40-66.68]	0.30 [0.12-0.73]	24.14 [5.44-107.11]
Technetium-99m	90.1 [82.5-95.1]	56.4 [42.3-69.7]	2.45 [0.93-6.46]	0.11 [0.038-0.31]	26.02 [3.28-206.01]
Time of first activity					
Early	63.2 [51.3-73.9]	100 [87.7-100]	9.60 [2.47-37.18]	0.36 [0.24-0.54]	29.82 [6.11-145.43]
Early or delayed	87 [81-92]	62 [51-72]	2.66 [1.30-5.43]	0.18 [0.075-0.43]	25.82 [7.58-87.94]
Threshold effect	86.1 [70.5-95.3]				
Moderate to severe activity	87 [81-92]	92.6 [75.7-99.1]	11.68 [3.06-44.54]	0.16 [0.07-0.37]	82.67 [13.62-501.70]
Any activity		62 [51-72]	2.66 [1.30-5.43]	0.18 [0.075-0.43]	25.82 [7.58-87.94]

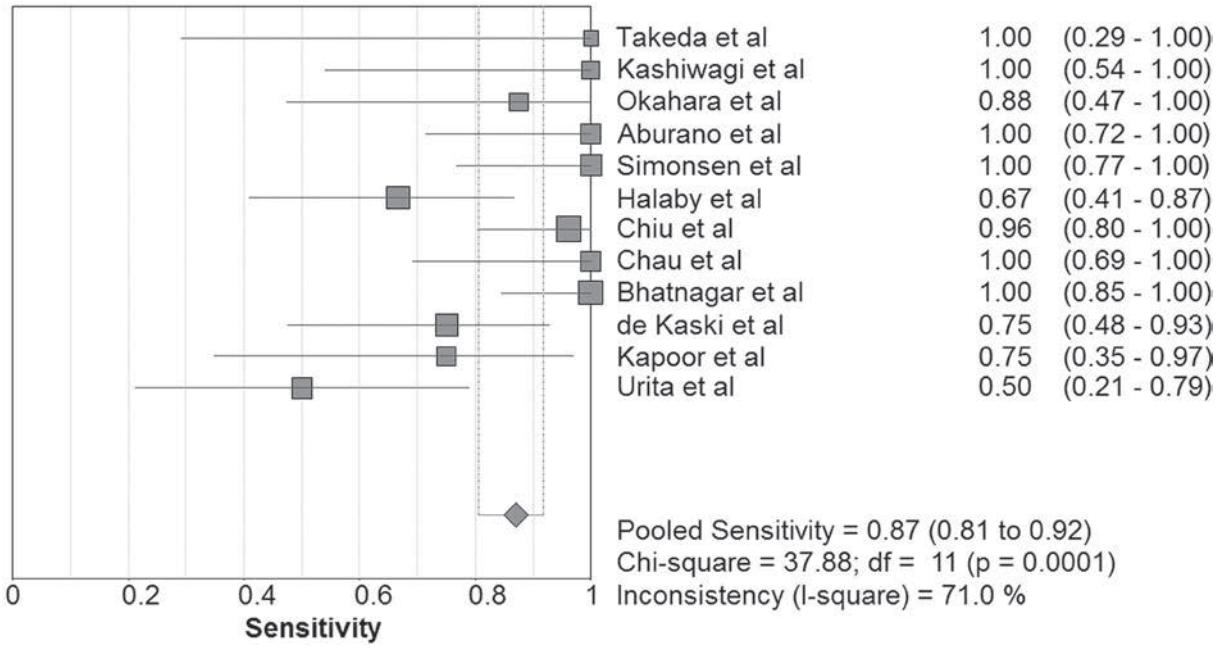

Fig. 2. — Forest plot of sensitivity pooling. The black squares are sensitivity of individual studies, and their sizes correspond to the sample size. Lines on each side of the squares represent 95% CI. The black diamond is the pooled sensitivity of the included studies, and the lines on each side represent 95% CI. I^2 index represents the proportion of between-study variance, which cannot be attributed to sampling error and is truly due to variations between studies.

lower specificity may be due to the appreciable activities in the kidneys and urinary bladder which are visible using Tc-99m HSA but not using In-111-transferrin (6). Another reason of lower pooled specificity with Tc-99m labeled tracer is in vivo breakdown of the labeled tracer yielding free pertechnetate (24). Some of the studies recommended Tc-99m as the tracer of choice for scanning patients with PLE because of availability and lower cost of this radioisotope (20, 21). On other hand, In-111 has prolonged physiologic half-life (2.8 days) and stable binding to transferrin, which makes it especially beneficial for delayed imaging and fecal quantification (1).

Time of imaging (early vs. delayed imaging)

If uptake at any time (either early or delayed images) is considered positive, the pooled sensitivity is relatively high (87%) and specificity is low (62%). On the other hand, if only early images are considered positive, pooled specificity increased to 100% and pooled sensitivity decreased to 63% (Table 2). This can be due to intermittent nature of protein loss from the gut in PLE (24). Hence it is important to include both early and delayed phases in the study especially when the clinical indication for scintigraphic imaging is localization of an otherwise proven PLE as delayed images increase the sensitivity up to 24%. However, abdominal activities on the delayed images may be due to the transit of the tracer along the bowel lumen which gives false positive results (17). This is the reason of 38% lower pooled specificity of the delayed images compared to the early ones.

Two studies showed concordance between presence of significant symptoms of PLE or high level of AAT (> 20 mg/day) and positive results at early scintigraphic images (5,6). In other words mild symptomatic PLE or low AAT levels can be associated with false negative

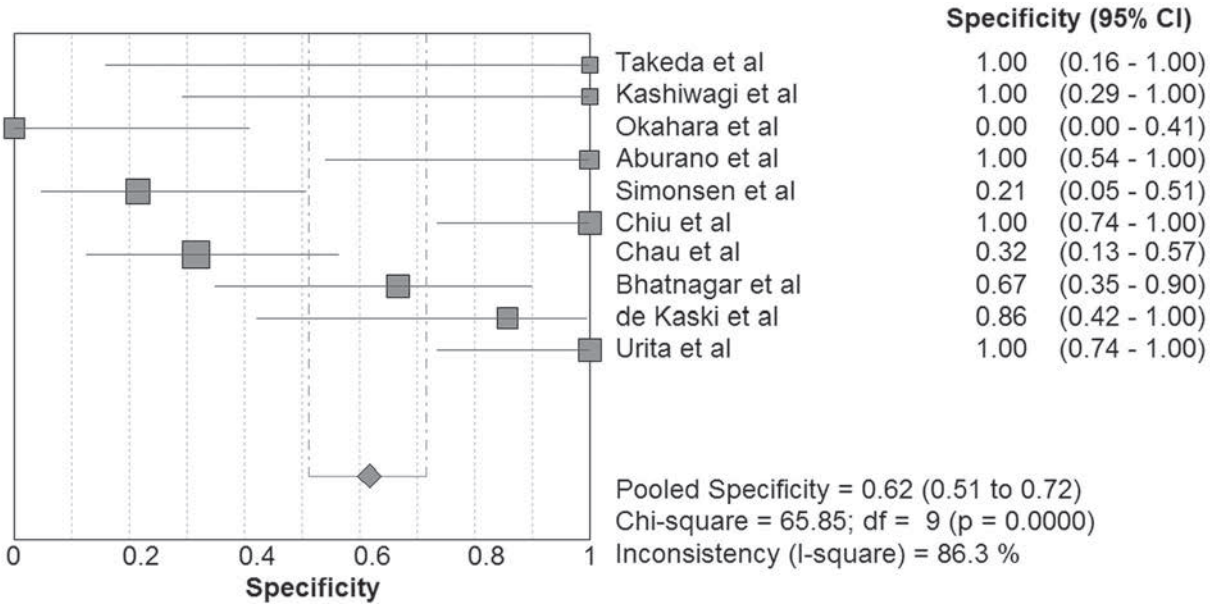

Fig. 3. — Forest plot of specificity pooling. Please refer to Figure 2 legend for description of the figure details

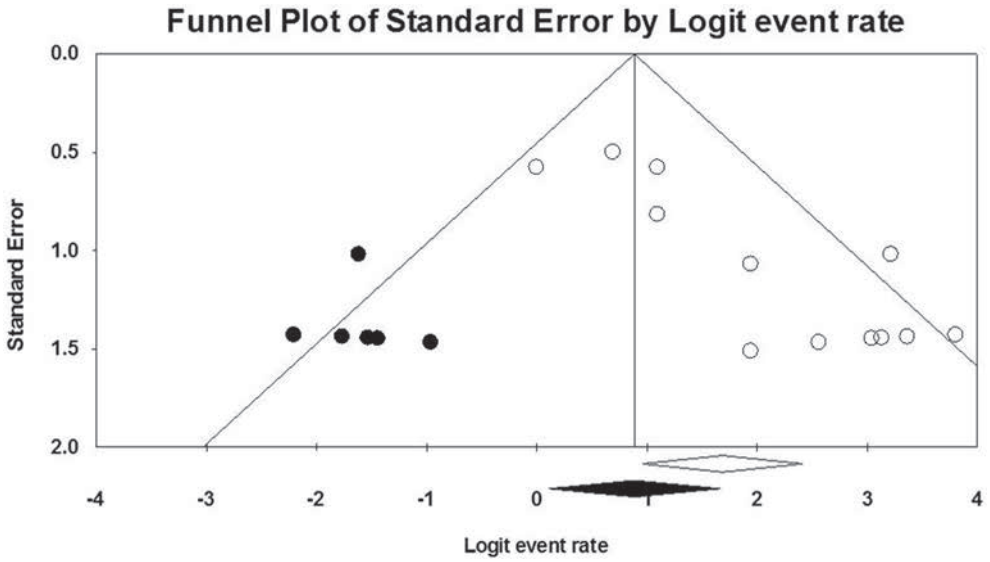

Fig. 4. — Funnel plot of sensitivity pooling. The black diamond is detection rate after adjustment for possible publication bias using trim and fill method. This is the plot of logit sensitivity against standard errors. Any asymmetry in the plot can be due to publication bias. The black diamond show trimmed pooled effect size after application of Tweedie's trim and fill method. This method represents the adjusted value of sensitivity after correction of possible publication bias. If the adjusted values show high deviation from the original ones, important publication bias can be implied.

early scintigraphic images. Delayed scintigraphic imaging can be of utmost importance in these patients considering its higher sensitivity.

Threshold effect

We evaluated the threshold effect on the sensitivity and specificity of the scintigraphic imaging. Although SROC showed minimal threshold effect, recalculation of the study results according to different thresholds (any abdominal activity or moderate abdominal activity as the thresholds of scan positivity) showed considerable threshold effect. If any activity in the abdomen is considered positive, the pooled sensitivity would be 100% despite 42.3% pooled specificity. By increasing the threshold of positivity to moderate abdominal activity the pooled sensitivity decreased to 86.1% but specificity increased to 92.6%. It seems that if localizing the site of PLE in previously diagnosed patients is the purpose of the scintigraphy, lower thresholds are more desirable considering the higher sensitivity.

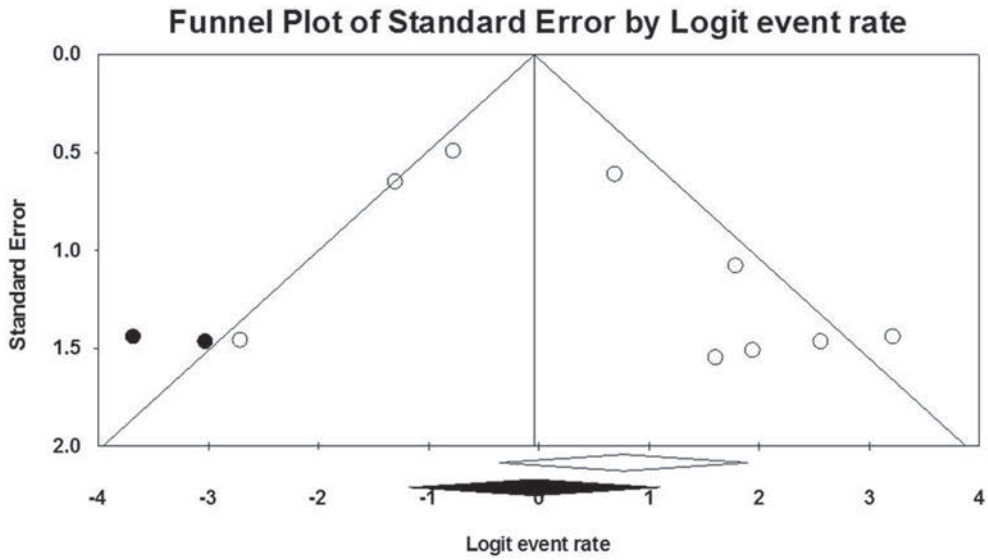

Fig. 5. — Funnel plot of specificity pooling. The black diamond is detection rate after adjustment for possible publication bias using trim and fill method. For more information regarding this method please refer to Figure 4 legend.

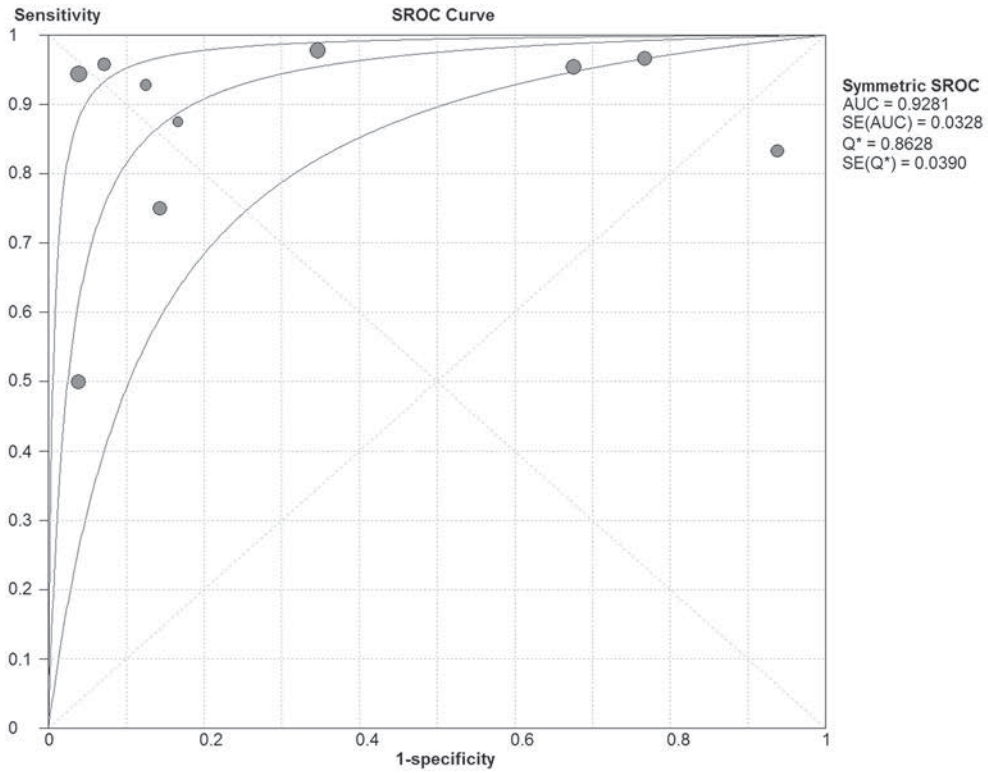

Fig. 6. — SROC of the meta-analysis. This is the plot of sensitivity against 1-specificity of each study for evaluating possible threshold effect in the included studies. The curves represent the SROC curve (middle) and 95% CI. The SROC curve represents overall performance of the test. AUC is the area under the SROC curve, and the higher values of AUC (closer to 1) mean better performance of the test. Q* is the point on the SROC curve at which the sensitivity and specificity are equal to each other. Again higher values of Q* (closer to 1) show better performance of the test.

Other important issues

Added value of SPECT imaging

The advantage of SPECT over planar imaging in nuclear medicine need not be underscored (25,26). Several case reports suggested that SPECT or SPECT/CT could improve the disease localization compared to the planar imaging (27,28). However, none of the included studies in the current systematic review evaluated the added value of SPECT or SPECT/CT. Future studies are needed in this regard.

Publication bias

We evaluated publication bias using funnel plots, and several statistical methods. Funnel plots of sensitivity and specificity pooling showed considerable asymmetry confirmed by statistically significant Egger's regression intercept method. This means that publication bias could affect the results of our meta-analysis.

To quantify possible publication bias, we used Duval and Tweedie's trim and fill method which showed 14% and 17% decrease in sensitivity and specificity after adjusting the observed results for possible publication bias.

Overall, publication bias ; if present, can be of concern in sensitivity and specificity pooling and this can be considered as a limitation of our study.

Quality of the included studies

Not all the included studies in the current meta-analysis had the same quality. As shown in Table 1, many of the included studies had non-consecutive recruitment or narrow spectrum of studied patients.

The included patients were also very heterogeneous as elucidated in Table 1. This can introduced a major bias into our systematic review.

The sample size of the included studies was also small (overall 246 patients were included in the current systematic review). To explore the effect of small studies, we performed a sensitivity analysis by limiting the meta-analysis on large studies (more than 10 patients). The results were not different from the original ones (sensitivity 87% [80-92], specificity 60% [49-70]). This shows that the results of our systematic review was robust to inclusion of small sample size studies.

However the most important limitation is the different gold standard test used in the included studies for diagnosis of PLE. Some studies even did not use AAT test as the gold standard and used a predefined clinical criteria instead (hypoalbuminemia, edema, ruling out of non-gastrointestinal causes of protein loss). We performed a sensitivity analysis by including only studies with AAT test as a part of the gold standard. Pooled diagnostic indices were not different from original ones (sensitivity 86% [77-92], specificity 61% [47-73]). Although the results of our study were robust to the variation in the gold standards, this variation can be considered as the major limitation of the current meta-analysis.

Conclusion

Scintigraphy using Tc-99m or In-111 labeled proteins has high sensitivity for diagnosis and localization of PLE. Using Tc-99m labeled tracers and delayed imaging can further increase the sensitivity. Despite high sensitivity, specificity of scintigraphy is suboptimal and false positive abdominal activities can limit the usefulness of this imaging method.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

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