Medicine®

OPEN

Scintigraphic peritoneography in the diagnosis of pleuroperitoneal leak complicating peritoneal dialysis

A comparison with conventional diagnostic methods

Lerwine Harry, MBCHB[a,*] iD, Nozipho Nyakale, BSc, MBChB, FCNP(SA), MMed[a], Partson Tinarwo, PhD[b]

Abstract

A pleuroperitoneal leak (PPL) is a relatively rare complication of peritoneal dialysis (PD) and early diagnosis is essential.

Patients suspected of a PPL usually present with dyspnea (marked during inflow of PD fluid) and tend to have transudative high glucose pleural effusions.

The PPL scintigraphy (PPLS) is one of the methods for objectively proving a PPL. The effectiveness of PPLS as a noninvasive method of evaluating a suspected PPL and its effectiveness in the exclusion of a leak in patients with similarly presenting comorbidities was assessed.

Patients suspected to have a PPL were considered for PPLS based on clinical presentation and pleural fluid analysis. Radiopharmaceutical was administered into the peritoneum via the dialysis port with the patient lying supine and immediate dynamic followed by delayed statics were acquired.

Of the 27 scans reviewed, 70% were found to be positive with majority detected within 12 minutes of radiopharmaceutical administration with a high predominance occurring in the right chest ($P < .001$). In PPLS-positive patients, when both chest X-rays and planar agreed on showing the right-sided chest predominance, the highest measurements of the pleural glucose:serum glucose ratio were recorded. A statistically significant correlation between the outcome of the scan and final decision on patient management was noted ($P < .01$).

The PPLS is an effective diagnostic tool for assessing PPLS. However, multicenter studies investigating its added value over other conventional methods are needed to establish it as a highly relevant diagnostic tool.

Abbreviations: CAPD = continuous ambulatory dialysis, CKD = chronic kidney disease, CV = coefficient of variation, CXR = chest X-ray, ESRD = end-stage renal disease, FSGS = focal segmental glomerulosclerosis, MAA = Tc-99m macroaggregated albumin, Max = maximum, Min = minimum, MR peritoneography = magnetic resonance peritoneography, n = number, PD = peritoneal dialysis, PPL = pleuroperitoneal leak, PPLS = pleuroperitoneal leak scintigraphy, Q1 = quartile 1, Q2 = quartile 2.

Keywords: peritoneal dialysis, pleuroperitoneal leak, pleuroperitoneal scintigraphy, technetium-99m-macroaggregated albumin scintigraphy, technetium-99m-nanocolloid

1. Introduction

Chronic ambulatory peritoneal dialysis or peritoneal dialysis (PD) is an effective method of renal replacement therapy in South Africa due to the high cost of other methods of renal replacement therapy such as hemodialysis and renal transplant. This method is not without complications.

Pleuroperitoneal leak (PPL) is a relatively rare complication of peritoneal dialysis and often leads to the suspension of peritoneal dialysis and a need to switch to the more expensive and less readily accessible haemodialysis.[1] As described in 1967 by Edward and Unger, hydrothorax resulting from a pleuro-peritoneal leak corresponds to the presence of peritoneal dialysis fluid in the pleural cavity due to the movement of dialysate under increased intra-abdominal pressure from the peritoneum to pleural cavity, through congenital or acquired defects in the dia-phragm.[2] Although uncommon, pleuroperitoneal leak consti-tutes a well-recognized complication of peritoneal dialysis. The mean incidence of hydrothorax is highly variable in the available literature, and based on a major series, it is estimated to range from 1.0% to 5.1%.[3,4]

The pleuroperitoneal leaks are usually suspected in peritoneal dialysis patients who present with signs and symptoms suggestive of a pleural effusion. These include those in respiratory distress with shortness of breath and pleuritic chest pain. In extreme conditions where treatment is delayed, some patients may even develop a lung collapse.[5] The diagnostic methods available for diagnosis of this complication are nonspecific and a more robust diagnostic method is important since misdiagnosis may lead to serious consequences. Pleural effusions are often diagnosed clinically and confirmed on chest X-ray (CXR). Pleural effusions associated with pleuroperitoneal leaks are typically transudative with a low cell and protein content, but glucose content that is higher than that of the serum blood glucose, often referred to as a "sweet hydrothorax."[6,7]

Available imaging methods of diagnosing pleuroperitoneal leaks include intraperitoneal infusion of contrast material through the catheter during plain abdominal radiography and computed tomography (CT). These are time consuming, require adequately trained personnel, and may be associated with complications related to intra-abdominal iodinated contrast media administration.[8] Other methods of diagnosing pleuroperitoneal leaks such as magnetic resonance peritoneography, methylene blue instillation into the peritoneal cavity, and videothoracoscopy are time consuming, expensive, and associated with risks of chemical peritonitis with methylene blue.[5,3,8]

The instillation of a radionuclide into the peritoneal cavity is a technique that was 1st described in 1985 by Pecoraro et al.[9] It involves injecting a nonabsorbable radionuclide via the peritoneal dialysis catheter port. The presence of this radioactivity in the pleural space and peritoneal cavity reflects a hydrothorax secondary to a communication between these 2 cavities. Radionuclide peritoneal scinitigraphy is a simple, safe and noninvasive, low radiation exposure and cost-effective method in the assessment of pleuroperitoneal leak in peritoneal dialysis patients.[10] The current diagnostic methods employed by the nephrology department at the Inkosi Albert Luthuli Central Hospital, Kwa-Zulu Natal, for evaluation of patients with suspected pleuroperitoneal leaks include clinical detection of a pleural effusion in peritoneal dialysis patients, confirmation of the pleural effusion with a chest X-ray and biochemical assessment of the pleural fluid to ascertain that a transudative "sweet" hydrothorax is present. Subsequently, these patients may be sent to the Nuclear Medicine department for pleuroperitoneal leak scintigraphy to confirm or exclude the diagnosis of a pleuroperitoneal leak. Pleuroperitoneal leaks scintigraphy are rarely life threatening.[5] However, early diagnosis of pleuroperitoneal leak is essential as continuation of peritoneal dialysis will result in respiratory embarrassment and membrane failure.

In this study, we assessed the effectiveness of pleuroperitoneal leak scintigraphy as a noninvasive method of evaluating a suspected pleuroperitoneal leak in comparison to the available conventional diagnostic methods generally used by the renal unit.

2. Materials and methods

The Biomedical Research Ethics Committee review board approved this retrospective study and waived the requirement for patient informed consent. The pleuroperitoneal leak scintigraphy were done in the period from January 1, 2008 to December 31, 2018 in the Nuclear Medicine department, Inkosi Albert Luthuli Hospital in Durban. Patients with end-stage renal disease (ESRD) on peritoneal dialysis who presented with clinical

Table 1

Aetiology of ESRD.

Causes of ESRD	n (%)
Hypertensive nephrosclerosis	9 (36)
Diabetic nephropathy	4 (16)
HIV-associated nephropathy	3 (12)
Chronic glomerulonephritis	3 (12)
Lupus nephritis	2 (8)
FSGS	1 (4)
Renal artery stenosis	1 (4)
Polycystic kidney disease	1 (4)
Unknown	1 (4)

ESRD = end-stage renal disease, FSGS = focal segmental glomerulosclerosis, HIV = human immunodeficiency virus, n = number.

or biochemical suspicion of a pleuroperitoneal leak and referred for pleuroperitoneal leak scintigraphy were included in the study. Overall, 24 out of 25 patients were studied. One of the patients was excluded due to inconclusive scan findings related to technical difficulties experienced during imaging. The 24 patients included 12 males and 12 females aged between 20 and 70 years, with a mean age of 46 ± 14 years. All the 24 patients had ESRD due to various causes (Table 1). The most common being hypertensive nephrosclerosis (n=9), respectively, followed by diabetic nephropathy (n=4), human immunodeficiency virus associated nephropathy (n=3), chronic glomerulonephritis (n=3), and other less common causes (Table 1). Peritoneal dialysis patients who were suspected to have a pleuroperitoneal leak were considered for pleuroperitoneal leak scintigraphy based on the clinical presentation which included shortness of breath, signs of fluid overload and decrease in ultrafiltration, a pleural effusion detected both clinically and on chest X-ray as well as and a peritoneal fluid chemistry suggestive of a transudative effusion. The symptomatic presentation was predominantly dyspnea occurring immediately at the initiation of a cycle of peritoneal dialysis. This presentation was noted in 52% of our population. Nine of the patients also presented with features of fluid overload and 3 had poor ultrafiltration. All the patients studied had signs and symptoms suggestive of a pleural effusion which was confirmed on chest X-ray. The time lapse from the commencement of peritoneal dialysis until the suspicion of a pleuroperitoneal leak was as early as 23 days after starting peritoneal dialysis and up to 5 years after initiating peritoneal dialysis, with a mean time duration of 590.6 days (Fig. 1).

The data collection included the patients' blood glucose, biochemical analysis, notably the glucose level of the pleural fluid, with records of the side of the chest where the pleural effusion was observed (clinically or radiologically) at the time of presentation. This information was extracted from the patient's electronic health records in the hospital.

An outline of the data collection procedure is briefly described. Patients suspected to have large leaks who were referred for pleuroperitoneal leak scintigraphy were capped off and peritoneal dialysis stopped prior to the time of imaging. Those suspected to have small slow leaks were only required to stop peritoneal dialysis overnight (for 12 hours) prior to having the study done. The patency of the peritoneal dialysis catheter was assessed for good flow prior to the start of the scan. Patients were scanned with no fluid in the abdomen ("dry abdomen") and if residual peritoneal fluid was found, it was drained via the peritoneal dialysis catheter before the administration of the radiopharmaceutical.
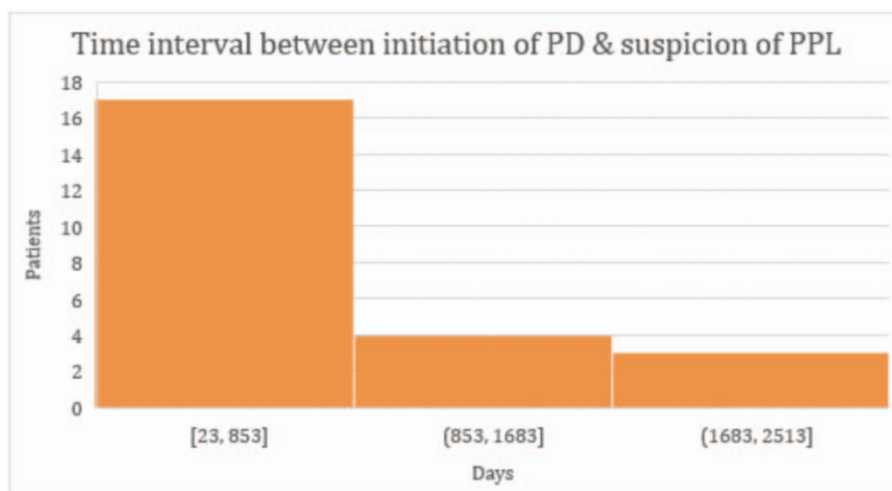
Figure 1. Time interval between initiation of peritoneal dialysis (PD) and suspicion of pleuroperitoneal leak (PPL).

All patients presented with the appropriate dialysate bags as per their peritoneal dialysis prescription with the necessary clamps and caps to facilitate the study. The standard in house protocol was employed using 4mCi Tc-99m macroaggregated albumin (MAA) or 5mCi Tc-99m nanocolloid. The choice of tracer was based on availability. Eighteen scans were positive for a pleuroperitoneal leak. Of these, 7 were scanned using Tc-99m nanocolloid and 11 were scanned used MAA. This was administered into the peritoneum via the dialysis port through the peritoneal dialysis catheter and flushed with dialysate fluid (as per usual patient dialysis script). This was done while patient was lying supine under the gamma camera and followed by an immediate dynamic image acquisition. Images were acquired using a dual head Siemens Intevo gamma camera equipped with a low energy high resolution collimator and a flood source on the posterior detector. The dynamic images were acquired immediately after the administration of the radiopharmaceutical for a period of 30 minutes, at 10 seconds per frame up to 180 frames using a matrix size of 64×64 and zoomed by a factor of 1. This was followed by multiple static image acquisitions using a matrix size of 256×256 and zoomed by a factor of 1 in the anterior, posterior, and lateral positions at 30 minutes, 90 minutes, 4 hours, and 24 hours postadministration.

A total of 27 scans were obtained from the 24 patients. Twenty-four scans were primary referrals, while the other 3 were done for recurrence postintervention.

2.1. Statistical analysis

The statistical analysis was conducted using the freely available Statistical Computing software called R, version 3.6.1. Since the main outcome was dichotomous, the variable distribution for continuous variables was tested using either a T test on normal distribution assumptions or the counterpart, the Wilcoxon signed rank test on nonparametric assumptions. In the case of categorical variables, the proportional distributions were tested by the application of the Chi-squared test or the Fisher exact test for expected values involving proportions $<5\%$. The distributional properties were also assessed with the aid of visual displays where box plots were instrumental for continuous variables, whereas mosaic and balloon plots applicable to the categorical variables of interest. Logistic regression was used to provide odds ratios for assessing the likelihood of the outcome between the levels of the categorical predictors. The post-hoc power analysis for the sample size was calculated using G-Power version 3.1.9.4.

3. Results

Of the 27 scans investigated, 70% were positive on pleuroperitoneal leak scintigraphy. Table 2 shows the distributional characteristics of the baseline and the covariates between patients diagnosed as pleuroperitoneal leak scintigraphy positive or negative. The majority of the positive scans were detected within 12 minutes of tracer administration and showed a high preponderance of occurring in the right chest ($P < .001$). Although the proportions of positive and negative pleuroperitoneal leak scintigraphy findings were similar between males and females ($P = .423$), the younger age group appeared to be associated with a higher likelihood of a positive pleuroperitoneal leak scintigraphy compared to the older age group in our population ($P = .034$). The visual displays further confirmed that those with positive pleuroperitoneal leak scintigraphy were significantly younger patients in their 40s compared to those that tested negative who tended to be around 50 years of age. Our data further showed a wider age variation among the younger group as compared to the older group (Table 2).

Most of the chest X-rays revealed a unilateral right pleural effusion, 74.1% on the right, 22.2% on the left, and 3.7% bilateral. We investigated the congruence in the results obtained from the initial chest X-rays and those from the pleuroperitoneal leak scintigraphy planar images. Generally, the proportional distributions across the initial chest X-rays sides and the pleuroperitoneal leak scintigraphy planar images sides were found to be significantly different ($P = .021$). Our data showed that most of the observations were on the right side of the chest on both the chest X-rays and pleuroperitoneal leak scintigraphy planar images (Fig. 2). Comparing the right side to the other sides, the results further revealed that an initial right chest X-ray finding was 14 times more likely to be on the right also on the pleuroperitoneal leak scintigraphy scans as compared to the other chest X-ray findings ($P = .026$). Considering how both the chest X-ray initial findings and the patient age could jointly predict the

Table 2

Univariate analysis of the relationship between pleuroperitoneal leak scintigraphy (PPLS) and the covariates.

| | PPLS | | | |
	Positive (n=18)	Negative (n=9)	Overall (n=27)	*P* value
Age, yrs[*]				.034
Mean (CV%)	41±14 (34.6)	53±11 (20.1)	46±14 (30.7)	
Median (Q1;Q2)	42 (31;49)	49 (49;55)	47 (36;54)	
Min–Max	20–67	36–70	20–70	
Gender[*]				.423
Male	7 (46.7%)	6 (66.7%)	13 (54.2%)	
Female	8 (53.3%)	3 (33.3%)	11 (45.8%)	
Initial CXR				.023
Right	16 (88.9%)	4 (44.4%)	20 (74.1%)	
Left	2 (11.1%)	4 (44.4%)	6 (22.2%)	
Bilateral	0 (0%)	1 (11.1%)	1 (3.7%)	
Pleural fluid glucose, mmol/L				.830
Mean (CV%)	14±13 (89.4)	11±8.2 (75.0)	13±11 (85.7)	
Median (Q1;Q2)	9.4 (6.5;14)	6.5 (5.8;15)	8.9 (6.2;15)	
Min–Max	2.9–49	3.3–26	2.9–49	
Serum glucose, mmol/L				.232
Mean (CV%)	5.9±3.6 (61.6)	7.5±4.8 (63.2)	6.5±4.0 (62.3)	
Median (Q1;Q2)	4.9 (4.2;6.0)	5.4 (4.6;7.8)	5.1 (4.5;6.2)	
Min–Max	3.9–19	4.5–18	3.9–19	
Pleural:serum glucose ratio				.530
Mean (CV%)	2.8±2.9 (105.8)	1.8±1.4 (78.1)	2.4±2.4 (101.8)	
Median (Q1;Q2)	2.0 (1.3;2.2)	1.4 (1.2;2.1)	1.6 (1.2;2.3)	
Min–Max	0.34–9.8	0.18–4.6	0.18–9.8	
Pleural fluid analysis[*]				1.00
Exudate	1 (6.2%)	0 (0%)	1 (4.2%)	
Transudate	15 (93.8%)	8 (100%)	23 (95.8%)	
Planar findings				<.001
Right	15 (83.3%)	0 (0%)	15 (55.6%)	
Left	3 (16.7%)	1 (11.1%)	4 (14.8%)	
Negative	0 (0%)	8 (88.9%)	8 (29.6%)	
Time to detection, min[*]				<.001
(+ve)0.5–12	13 (76.5%)	0 (0.0%)	13 (52%)	
(+ve)>30	4 (23.5%)	0 (0.0%)	4 (16%)	
(−ve)	0 (0.0%)	8 (100%)	8 (32%)	
Decision				<.001
Conservative	10 (55.6%)	0 (0%)	10 (37.0%)	
Surgery	5 (27.8%)	0 (0%)	5 (18.5%)	
Negative	3 (16.7%)	9 (100%)	12 (44.4%)	

CV=coefficient of variation, CXR=chest X-ray, Max=maximum, Min=minimum, n=number, PPLS=pleuroperitoneal leak scintigraphy, Q1=quartile 1, Q2=quartile 2, −ve=negative, +ve=positive.
[*] Based on valid records.

planar findings, our data indicated that age was not a factor (*P*=.144; Table 3).

Our data showed that both the unadjusted and age-adjusted chest X-ray initial findings had a significant predictive nature on the pleuroperitoneal leak scintigraphy planar imaging findings. As compared to the other chest X-ray side assessments (left or bilateral), the right-side assessment on the chest X-ray was at least 10 times more likely to result in pleuroperitoneal leak planar positive images. On the contrary, controlling for the chest X-ray, a 1-year increase in the patient's age was associated with a 10% less chance of being detected positive for the pleuroperitoneal leak (odds ratio=0.90 [0.80–0.99]; Table 4).

The median pleural fluid glucose was not significantly different between the positive and negative patients (*P*=.830) with notable similar distributions on the observations. The glucose of the pleural fluid relative to blood glucose, pleural:serum glucose ratio, was slightly lower than the patients who had a positive pleuroperitoneal leak. The negative patients' pleural glucose and the pleural:serum glucose ratio had a correlation of 0.89 (*P*=.007) indicating a linear relationship. A unit increase in the pleural glucose, increased the pleural:serum glucose ratio by 0.12 units (Fig. 3).

A further exploration into the behavioral patterns of pleural glucose and pleural:serum glucose ratio on the chest X-ray and pleuroperitoneal leak planar images congruence is given in Figure 4. The results indicated that when both the chest X-ray and pleuroperitoneal leak planar images agreed on showing the right-hand sided effusion, the highest measurements of the pleural glucose and pleural:serum glucose ratio were recorded. This phenomenon was observed among the pleuroperitoneal leak scintigraphy positive patients. A mismatch of chest X-ray left-side and pleuroperitoneal leak right-side planar images showed that the average measurements of both the pleural glucose and pleural:serum glucose ratio were common.

The results observed from the 2 radiopharmaceuticals (MAA and Tc-99m Nanocolloid) were not statistically different at 5%
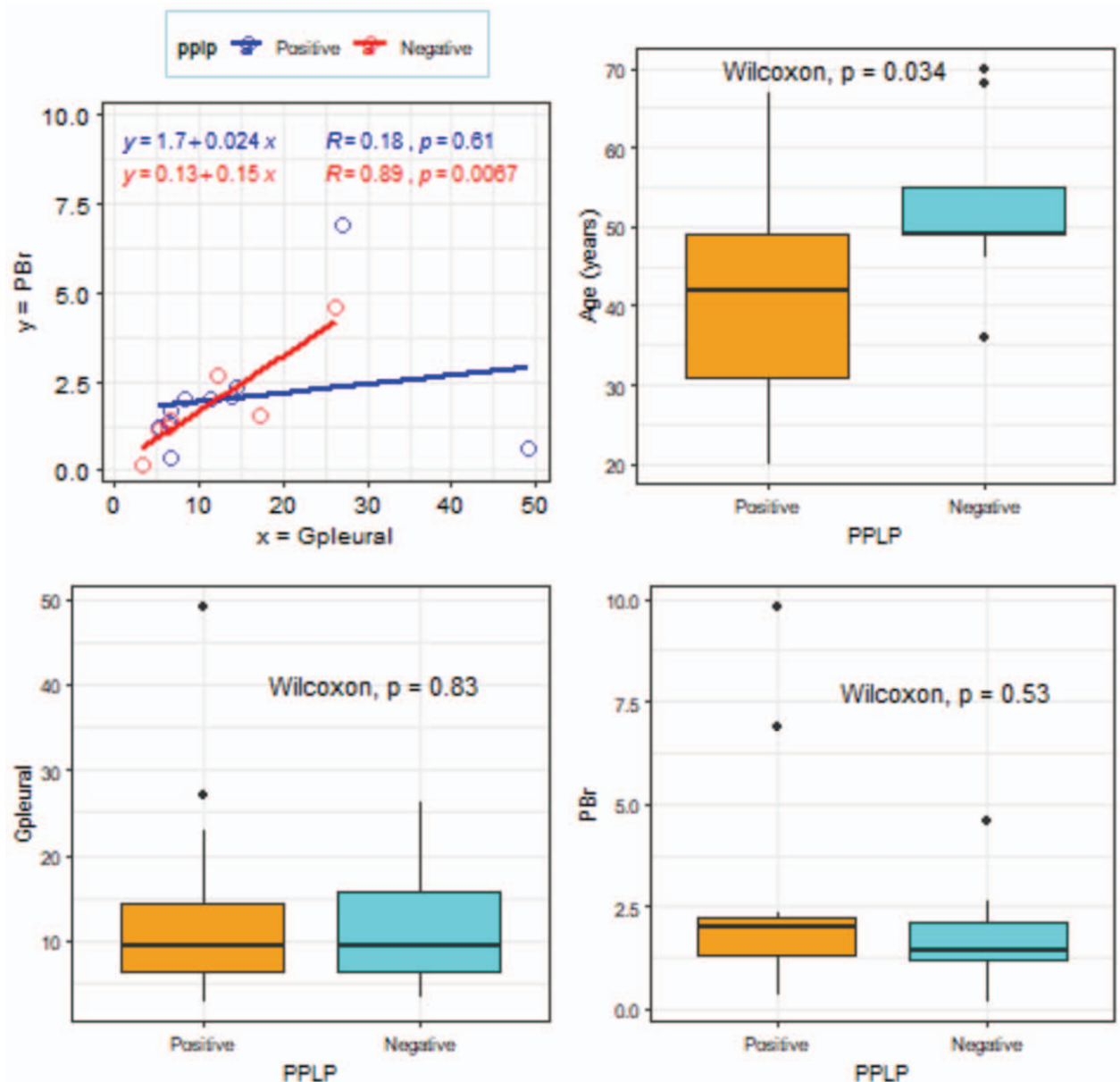
Figure 2. Correlation between the pleural : serum glucose ratio and the pleuroperitoneal leak scintigraphy findings.

level of significance (Table 5). Similarly, there was not enough evidence to conclude that the patient's baseline characteristics had different distribution between the radiopharmaceuticals. Further, the outcome pleuroperitoneal leak scintigraphy was fairly similar in both tracers ($P = .448$)

We looked at the treatment decision taken in our cohort in association with the study findings. There was a statistically significant association between the outcome of the scan and the final decision on patient management ($P < .01$). Patients with positive scans were either treated conservatively (stoppage of continuous ambulatory dialysis [CAPD] and conversion to hemodialysis) or surgically.

Table 3

**Contributing factors to the planar findings.**

Explanatory	OR (univariable)	OR (multivariable)
Age	0.95 (0.88–1.01, $P = .144$)	0.94 (0.86–1.01, $P = .137$)
CXR (right on CXR)	14.00 (1.85–296.61, **$P = .026$**)	13.13 (1.52–310.12, **$P = .041$**)

CXR = chest X-ray, OR = odds ratio. The P value is in the bold print.

Table 4

Contributing factors to the PPLP findings.

Explanatory	OR (univariable)	OR (multivariable)
Age	0.93 (0.85–1.00, $P = .065$)	0.90 (**0.80–0.99,** $P = .056$)
CXR (Right on CXR)	10.00 (1.56–91.85, **$P = .022$**)	15.14 (1.63–314.54, **$P = .034$**)

CXR = chest X-ray, OR = odds ratio, PPLP = pleuroperitoneal leak planar. The P value is in the bold print.
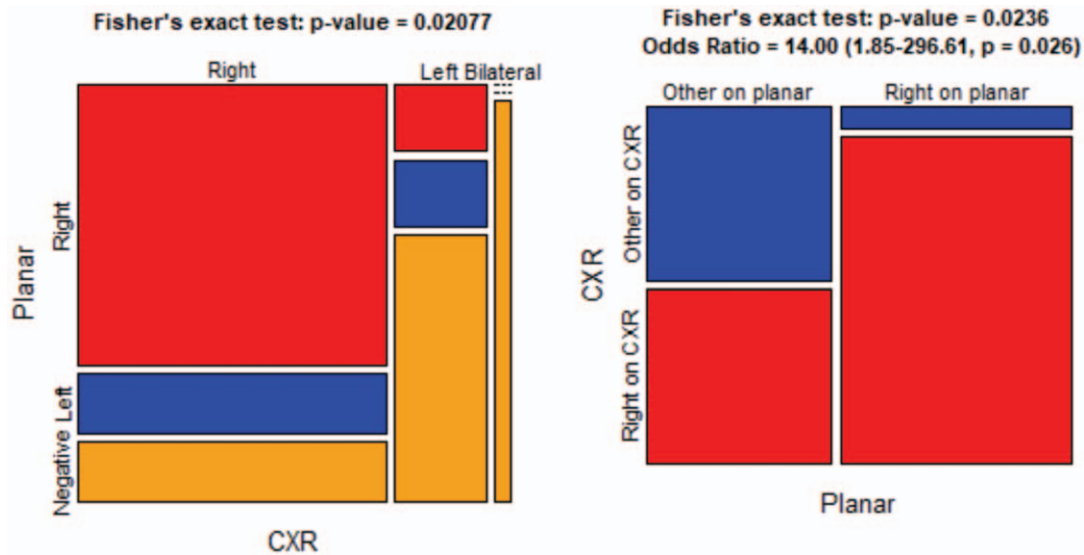
Figure 3. Data showing right sided congruency between observations on both the chest x-ray and planar imaging.

4. Discussion

Hypertension is a known leading cause of chronic kidney disease (CKD) in Sub-Saharan Africa and accounts for 45.6% of CKD cases in South Africa.[11] This was similarly the main cause of ESRD in our population. The time lapse from the commencement of peritoneal dialysis for these patients until the suspicion of a pleuroperitoneal leak was as early as 23 days up to 5 years of starting with peritoneal dialysis, with the majority occurring early. It is presumed that such early presentation may be related to congenital diaphragmatic defects while late presentation would likely be due to acquired diaphragmatic defects.[12–14] Pleural effusions result from imbalance in the relationship of the Frank–Starling forces hydrostatic pressure, osmotic pressure, and capillary permeability.[5] The elevated intra-abdominal pressure predisposes the patient to hernias or thinning of the diaphragm. Trauma frequently causes peritoneal dialysis fluid to appear in the thorax. A sudden increase in intra-abdominal pressure opens a communication between the abdomen and the thorax, thereby allowing fluid to leak into the thorax.[5,13,15]

In our population, the presenting complaints were similar those described in the existing literature in pleuroperitoneal leak patients, with most patients (n = 13) having shortness of breath and some with associated features of fluid overload and poor ultra-filtration thought to be related to the accumulation or sequestration of fluid into the pleural space.[5] No weight gain was reported in these patients despite the use of hypertonic dialysate as has been reported by some groups and none that were referred were asymptomatic at presentation.[5,12] A female predominance of pleuroperitoneal leak was not demonstrated as has been previously suggested by Promila et al, and no association could be found between gender and pleuroperitoneal leak scintigraphy findings.[10] An interesting finding in our study was that younger patients appeared to be associated with a higher likelihood of a positive pleuroperitoneal leak scan compared to those over 50 years of age. In the pediatric population, younger age is considered a risk factor for the development of a pleuroperitoneal leak but age as a risk factor is not clear in the adult population.[15]

In our cohort, 70% of the pleuroperitoneal leak scintigraphy scans done were positive for pleuroperitoneal leaks. The available reports in the literature describe the imaging time to range from the time of administration to 24 hours. The detection of pleuroperitoneal leak may vary and may be seen anytime within this time period. This is also likely related to the size of the leak as it is suspected due to limited camera resolution and counts detectable, small and slow leaks will likely be seen with time as the dialysate accumulates in the chest due to the limited counts that can be detected in the early stages.[16] Many of the leaks in our center were detected early, within 12 minutes of administration of the radiolabeled dialysate (Figs. 5–7). In a case report by Wu et al, rapid appearance (<30 minutes) of the radiotracer over right pleural cavity was associated with failure of oxytetracycline pleurodesis, suggesting a possible macroscopic diaphragmatic defect that required conversion to hemodialysis or surgery and hence may be related to the severity of the hydrothorax.[17]

The cause of a pleural effusion seen on the baseline chest X-rays is nonspecific and can be related to a multiple varying etiology making confirmation of a pleuroperitoneal leak important to ensure appropriate management.[18] All patients referred to us had demonstrating pleural effusion, 74.1% on the right, 22.2% on the left, and 3.7% had a bilateral effusion. We found that an initial right-sided chest X-ray effusion in these patients was 14 times more likely to reveal a positive right pleuroperitoneal leak scan compared to chest X-ray findings of a left or bilateral effusion (P = .026). Right-sided predominance of hydrothorax, as seen in our findings, is consistent with findings in the literature which suggest the higher likelihood of a presence of right hemi diaphragm abnormalities.[5,19,20] Gagnon and Daniels proposed that an embryonic remnant (the persisting pneumato-enteric recess and infracardiac bursa) provides a passage connecting the peritoneal cavity to the right pleural space.[14] Histologic findings from resected diaphragm include lack of common tissue, tendons, skeletal muscle tissues, and displacement by fibrous connective tissue on this side of the diaphragm.[14] It is also proposed that as the right diaphragm contracts, the relatively firm liver capsule acts as a piston, driving fluid through the porous defects on the right diaphragm unlike on
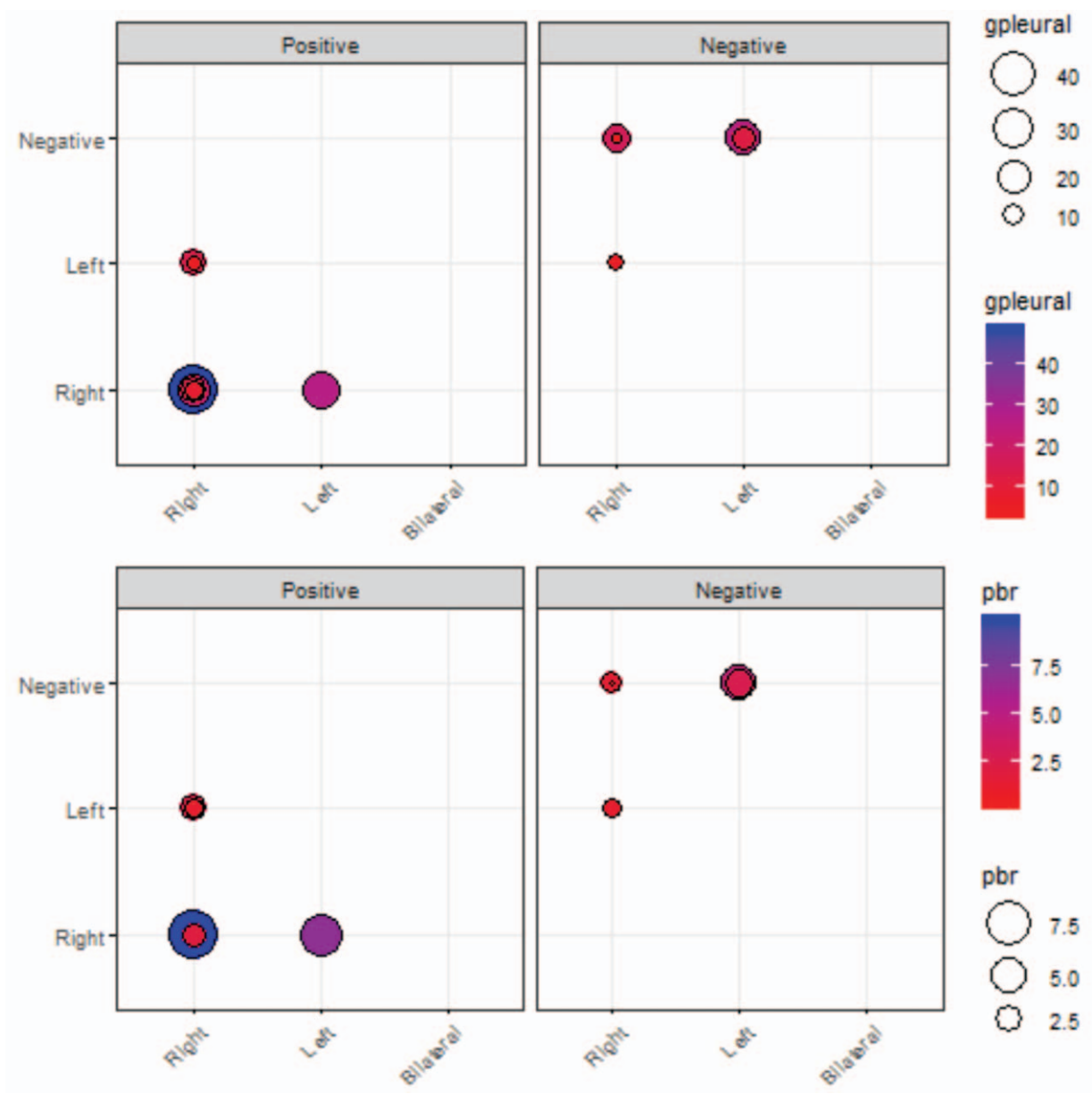
Figure 4. Behavioral patterns of pleural glucose and pleural serum ratio on the chest X-ray and pleuroperitoneal scans/planar. Gpleural = glucose of pleural fluid, PBr = pleural serum glucose ratio.

Table 5

The variable distribution within the radiopharmaceutical in the study.

	Radiopharmaceutical			
	MAA (n=15)	Nanocolloid (n=12)	Overall (n=27)	*P* value
Age, yrs				.910
Mean (CV%)	45±15 (33.9)	46±13 (28.7)	46±14 (30.7)	
Median (Q1;Q2)	47 (33;56)	47 (41;52)	47 (36;54)	
Min–Max	21–68	20–70	20–70	
Gender[*]				.682
Male	7 (58.3%)	6 (50.0%)	13 (54.2%)	
Female	5 (41.7%)	6 (50.0%)	11 (45.8%)	
Initial CXR				0.060
Right	13 (86.7%)	7 (58.3%)	20 (74.1%)	
Left	1 (6.7%)	5 (41.7%)	6 (22.2%)	
Bilateral	1 (6.7%)	0 (0%)	1 (3.7%)	
Pleural fluid glucose, mmol/L				.059

Table 5

(continued).

	Radiopharmaceutical			
	MAA (n=15)	Nanocolloid (n=12)	Overall (n=27)	*P* value
Mean (CV%)	11±14 (123.7)	15±8.1 (54.4)	13±11 (85.7)	
Median (Q1;Q2)	6.4 (5.4;9.2)	13 (7.8;22)	8.9 (6.2;15)	
Min–Max	2.9–49	5.3–27	2.9–49	
Serum glucose, mmol/L				.506
Mean (CV%)	7.4±5.3 (71.9)	5.5±1.9 (35.2)	6.5±4.0 (62.3)	
Median (Q1;Q2)	5.1 (4.5;6.7)	5.1 (4.4;5.8)	5.1 (4.5;6.2)	
Min–Max	4.1–19	3.9–11	3.9–19	
Pleural:serum glucose ratio				.102
Mean (CV%)	2.1±3.0 (142.5)	2.7±1.9 (69.7)	2.4±2.4 (101.8)	
Median (Q1;Q2)	1.2 (0.62;2.0)	2.0 (1.5;2.7)	1.6 (1.2;2.3)	
Min–Max	0.18–9.8	1.2–6.9	0.18–9.8	
Pleural fluid analysis[*]				1.00
Exudate	1 (7.7%)	0 (0%)	1 (4.2%)	
Transudate	12 (92.3%)	11 (100%)	23 (95.8%)	
PPLP				.448
Positive	11 (73.3%)	7 (58.3%)	18 (66.7%)	
Negative	4 (26.7%)	5 (41.7%)	9 (33.3%)	
Planar findings				.377
Right	10 (66.7%)	5 (41.7%)	15 (55.6%)	
Left	2 (13.3%)	2 (16.7%)	4 (14.8%)	
Negative	3 (20.0%)	5 (41.7%)	8 (29.6%)	
Time to detection, min[*]				.307
(+ve)0.5–12	9 (64.3%)	4 (36.4%)	13 (52.0%)	
(+ve)>30	1 (7.1%)	3 (27.3%)	4 (16.0%)	
(−ve)	4 (28.6%)	4 (36.4%)	8 (32.0%)	
Decision				.606
Conservative	5 (33.3%)	5 (41.7%)	10 (37.0%)	
Surgery	4 (26.7%)	1 (8.3%)	5 (18.5%)	
Negative	6 (40.0%)	6 (50.0%)	12 (44.4%)	

CV = coefficient of variation, CXR = chest X-ray, MAA = Tc-99m macroaggregated albumin, Max = maximum, Min = minimum, n = number, PPLP = pleuroperitoneal leak planar, PPLS = pleuroperitoneal leak scintigraphy, Q1 = quartile 1, Q2 = quartile 2, −ve = negative, +ve = positive.
[*] Based on valid records.
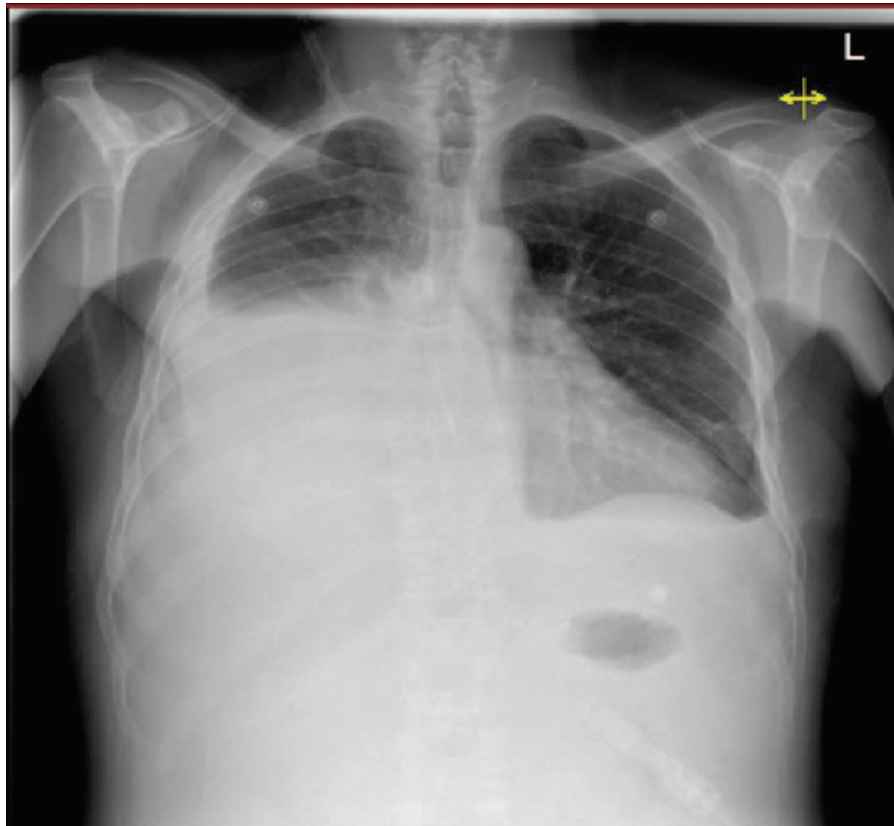
Figure 5. A 55-year-old male on continuous ambulatory dialysis for 2 years referred for a suspected pleuroperitoneal leak. Chest X-ray at presentation demonstrating a large right pleural effusion.

Figure 6. A 55-year-old male on continuous ambulatory dialysis for 2 years referred for a suspected pleuroperitoneal leak. (A, B) Pleuroperitoneal communication is demonstrated by the scintigraphy. Dynamic images show normal distribution of radionuclide within peritoneum followed by rapid accumulation of radionuclide into the right hemithorax. Anterior and posterior delayed static imaging of thorax and abdomen shows accumulation of radioactivity in the right hemithorax demonstrating a pleuroperitoneal communication.

the left where it is softer and more compliant thus not creating this piston-like force.[19] Furthermore, the presence of the heart on the left may be protective to the left diaphragm.[13]

All but one of the patients in our population were found to have transudative pleural effusions. Typically, transudative effusions correlate with pleuroperitoneal leaks, uremia, volume overload, and cirrhotic ascites.[5,14] Transudative effusions develop when the balance of hydrostatic and oncotic pressure across the pleura alters and the rate of pleural fluid formation exceeds that of reabsorption.[14,21] The patient with an exudative pleural effusion had a positive pleuroperitoneal leak study suggesting that this method of diagnosis may also be nonspecific.

Another commonly used parameter in the assessment of a pleuroperitoneal leak is the pleural fluid glucose. There is no consensus on the upper limit of the gradient between the pleural fluid glucose and serum glucose; however, a high index of suspicion of leakage of peritoneal dialysate exists when the gradient between the pleural fluid glucose and the serum glucose is >5.6 mmol/L (>100 mg/dL).[6] The lower glucose gradient does not preclude intraperitoneal dialysate leakage because the pleural mesothelial cells could metabolize the pleural fluid glucose.[7,13] The pleural to serum glucose ratio was not significantly different between the positive and negative patients, the negative patients tended to have the pleural to serum glucose ratios that were slightly lower than those in the positive patients and there was a

correlation of 0.89 (P = .0067) which indicated a linear relationship between the pleural glucose level and the pleural to serum glucose ratio. This demonstrates that there is a correlation between a positive scan on pleuroperitoneal leak scintigraphy with a higher pleural to serum glucose ratio and pleural glucose which is typical of a "sweet hydrothorax" described.[6,7,22] The cutoff value of 5.6 mmol/L also could not be confirmed in our study. It is important to note that when the leak is small the differences in concentration may be inconclusive and also, the equilibration of components via routes across the pleural membrane may alter the composition of the pleural fluid.[23] Other factors to consider include diameter of the defect causing the leakage, absorption rate of glucose from the pleural surface, glucose concentration of the dialysate, and the duration between the dialysate exchange and pleural fluid sample collection.[24] These factors may therefore render this method of diagnosis unreliable.

The choice of radiopharmaceutical used in the majority of the literature is not documented[25]; however, in a study by Bi-fang et al, the decision to use MAA was based on the fact that the diaphragmatic mesothelium contains many pores which are 4 to 12 μm in diameter which communicate with lymphatic vessels and are thus capable of the uptake of red blood cells and mesothelial cells.[26] MAA is believed to be well suited for this purpose as the particle size can be manipulated while generally
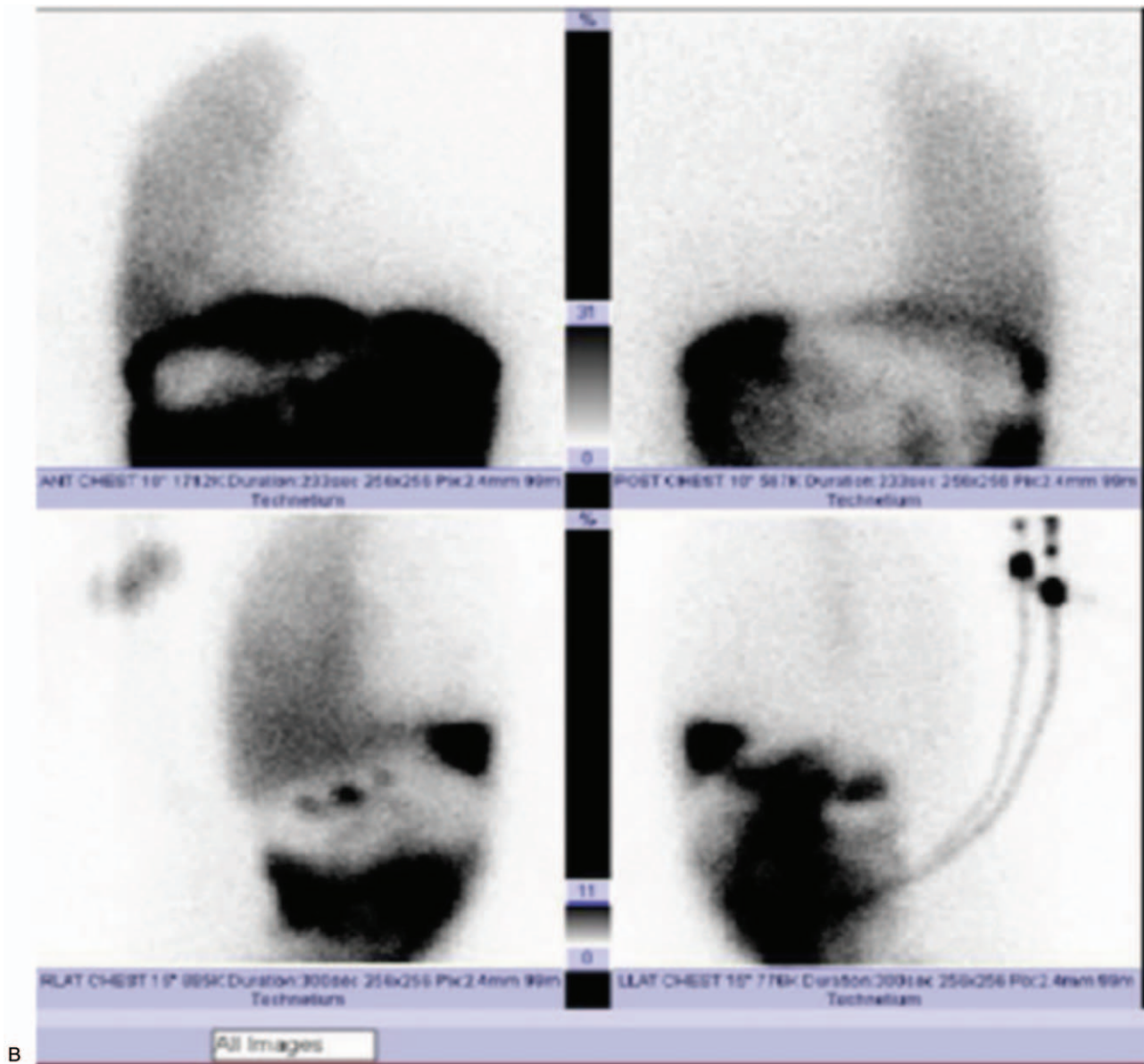
Figure 6. (Continued).

large particles may prevent passage of the radiopharmaceutical through the pores.[5,26,27] No significant difference in the observations made could be demonstrated when using MAA or Tc-99m nanocolloid nor was there evidence to suggest that the patients' baseline characteristics had varying distributions between these 2 tracers.

European Paediatric Dialysis Working Group reported the following risk factors of pleuroperitoneal leaks: young age, hernia, abdominal surgery, and peritonitis.[28] Other risk factors include trauma and polycystic kidney disease. The younger population are predisposed to leaks and hernias due to the relatively thinner and more fragile peritoneal wall.[29]

Hypothesis could be that the pleuroperitoneal leaks in younger patients are likely congenital in nature and thereby presentation is earlier.

Conservative management of pleuroperitoneal leak includes discontinuation of peritoneal dialysis for 4 to 6 weeks, the use of small volume exchanges or short dwell periods or "dry" days. This allows time for small diaphragmatic imperfections to heal themselves.[5] If the pleural membranes remain in intact and once the underlying problem resolves; the effusion is expected to reabsorb.[26] Recurrent pleural effusions may be treated with pleurodesis (method of obliterating the pleural space) and large recurrent pleural effusions may require treatment with video-thoracoscopy pleurodesis or surgical repair of the diaphragm via thoracotomy.

The general management method employed at our center was dependent on patient's clinical condition. If the patient is in a poor condition, talc chemical pleurodesis is the method of choice. If the patient is in a good condition, then thoracotomy is offered, and leak is identified then ligation with +/− pleurectomy is the method of choice to prevent further leaks. Most of the patients were treated conservatively with stoppage of the peritoneal dialysis and conversion to hemodialysis.
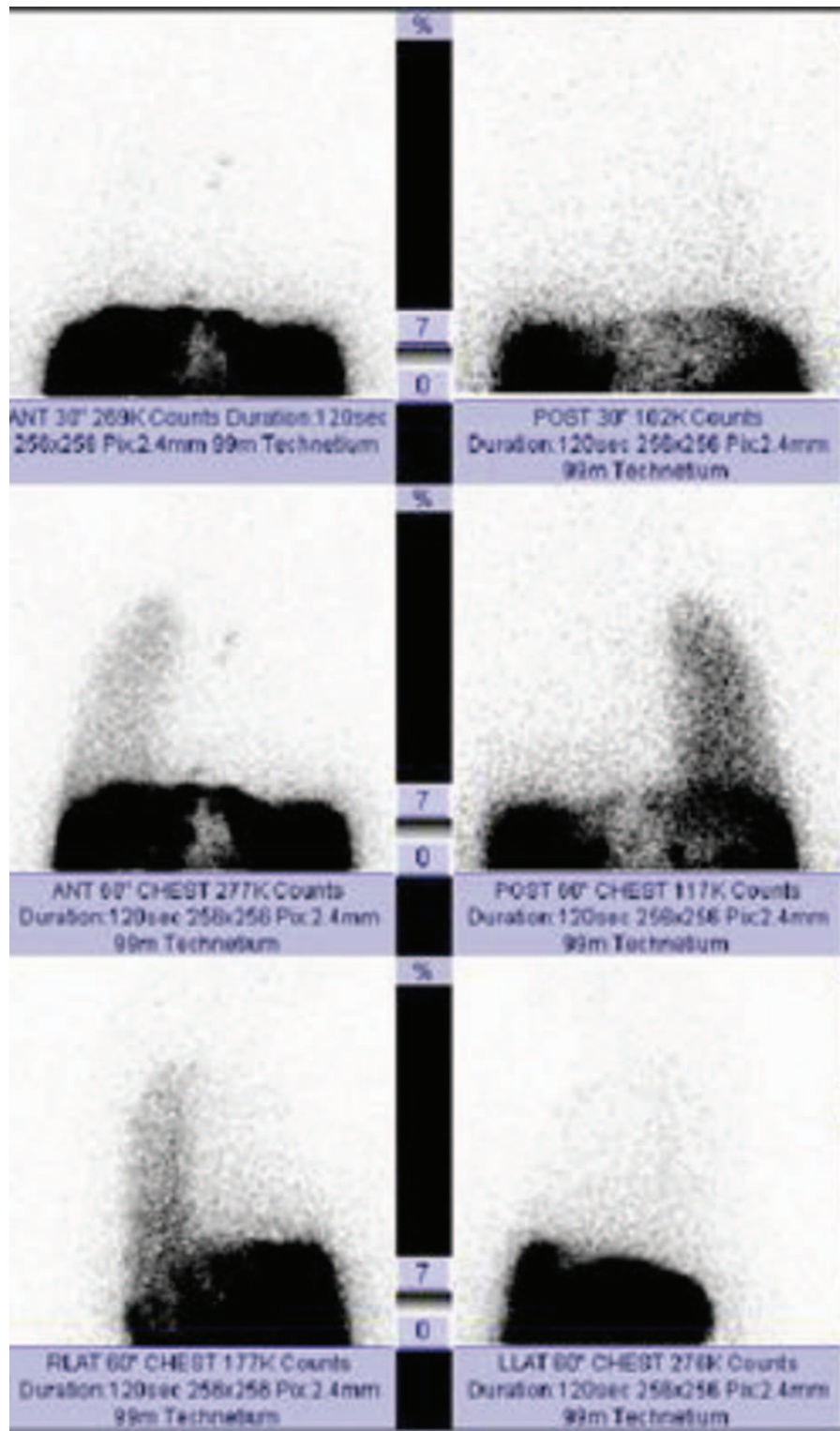
Figure 7. A 49-year-old female on continuous ambulatory dialysis referred for suspicion of pleuroperitoneal leak. Dynamic images were unremarkable with normal distribution of the radionuclide within the peritoneum, without passage to the pleural space. Delayed imaging demonstrated leakage of peritoneal fluid into the right pleural cavity confirming presence of a pleuroperitoneal leak.

Of the patients with positive pleuroperitoneal leak scans, 10 received conservative management and 3 received surgical intervention. Of these patients, all showed improvement posttreatment.

From our analysis, we found an association between our findings of a positive pleuroperitoneal leak with pleuroperitoneal leak scan and the treatment decision made. The patients with negative scans did not receive further treatment. These patients

went on to continue with their peritoneal dialysis with no recurrent suspicion of pleuroperitoneal leak. On follow-up of the patients with the negative pleuroperitoneal leak scans, it was found that 3 patients had pulmonary tuberculosis, 5 patients were found to have congestive cardiac failure while 1 patient failed CAPD due to recurrent peritonitis, resulting in removal of Tenckhoff catheter) and 1 patient demised due to septic shock secondary to sepsis.

Three patients with a positive pleuroperitoneal leak scans were initially capped off and converted to hemodialysis and evaluated by the cardiothoracic team who made the decision not to intervene as on repeated chest X-rays no pleural effusion was seen. Resumption of CAPD was then recommenced and resulted in recurrence of pleuroperitoneal leak which was confirmed by pleuroperitoneal leak scintigraphy.

The CT peritoneography is also a commonly used diagnostic technique for diagnosing pleuroperitoneal leaks. Although it is performed with slightly different methods in different centers, all methods involve drainage of the dialysate, followed by a repeat infusion of a mixture of 2 L dialysate with approximately 100 mL of a nonionic contrast medium containing 300 mg of iodine per milliliter. The infusion is performed with sterile technique by trained staff. Patient ambulation for 1 hour is then advised. Changes in position and maneuvers such as straining increase intra-abdominal pressure, ensuring good distribution of the contrast medium throughout the peritoneal cavity. Delayed 4-hour scanning may be repeated if 1-hour scan is negative. Lateral decubitus or prone position may be performed for questionable findings.

Kang and Kim reported that CT peritoneography can not only diagnose pleuroperitoneal leaks, but also locate the position of the leakage.[30] CT peritoneography is useful in cases of large pleuroperitoneal communication; however, it is not sensitive in detecting smaller defects.[31] It is associated with a 33% sensitivity for detection for pleuroperitoneal leaks.[32]

The main disadvantages of this method include exposure to ionizing radiation, possible anaphylaxis and nephrotoxicity associated with the contrast agent.

Peritoneal scintigraphy is associated with several advantages given that it is a noninvasive technique and important in assisting further patient management. The sensitivity of peritoneal scintigraphy is between 40% and 50%.[32] It can provide several images without increasing the radiation that the patient is exposed to. This capability is important because scintigrams that were initially negative often becomes positive after several hours of ambulation. It can detect slower leaks in view of acquiring a 24-hour image. Postdrainage images can also be helpful in confirming extraperitoneal leakage.

Peritoneal scintigraphy has the added advantage of determining if the free flow of fluid within the peritoneal cavity is in fact present and together with the addition of single photon-emission tomography or single photon-emission CT can assist with anatomic localization of pleuroperitoneal leaks and might help in patients with outflow failure by showing the distribution of the fluid to unexpected spaces in the abdomen.

Our study had a few limitations which were due to the small number of scans that were done. It is important to note that this is a rare complication of CAPD and thus the patient numbers for this indication are low. The lack of standardization with regard to the radiopharmaceutical used is also a potential limitation; however, no statistical difference could be demonstrated in the observations made by the radiopharmaceuticals used. Another

limitation is that being retrospective study, we had few missing data which was not captured on our local radiologic information system.

5. Conclusion

There is currently no standardized method of diagnosing pleuroperitoneal leaks; however, the conventional methods used are nonspecific with a lot of variable findings as demonstrated. pleuroperitoneal leak scintigraphy is a safe, noninvasive, and cost-effective method of visually detecting pleuroperitoneal leaks. In this study, it was shown to correlate with the conventional assessment of a right-sided pleural effusion on chest X-ray confirming the suggestion of a right-sided predominance of this condition, and the peritoneal glucose level which was more notably lower in the negative than in the positive scans. It also has got the advantage of delayed and multiplanar imaging with low radiation burden allowing for a long period of evaluation which would be necessary especially for the slow and small leaks. An interesting finding in our study was the correlation of a positive pleuroperitoneal leaks with patient's age and further studies need to be done to validate this finding. The use of this modality is particularly important in its potential role in determining the severity of the leak as well as choosing the appropriate choice of management.

Author contributions

Lerwine Harry conceived the idea, collected the data and wrote the manuscript. Nozipho Nyakale supervised the study. Partson Tinarwo did the statistical analysis.

References

[1] Del Peso G, Bajo M, Costero O, et al. Risk factors for abdominal wall complications in peritoneal dialysis patients. Perit Dial Int 2003;23: 249–54.

[2] Edwards S, Unger A. Acute hydrothorax - a new complication of peritoneal dialysis. JAMA 1967;199:853–5.

[3] Chow K, Szeto C, Li P, et al. Management options for hydrothorax complicating peritoneal dialysis. Semin Dial 2003;16:389–94.

[4] Martins A, Branco P, Goncalves M, et al. Pleuroperitoneal communication in peritoneal dialysis patients – presentation of four cases. Port Nephrol Hypert 2015;29:165–72.

[5] Lew S. Hydrothorax: pleural effusion associated with peritoneal dialysis. Perit Dial Int 2010;30:13–8.

[6] Momenin N, Colletti P, Kaptein E. Low pleural fluid-to-serum glucose gradient indicates pleuroperitoneal communication in peritoneal dialysis patients: presentation of two cases and a review of the literature. Nephrol Dial Transplant 2012;27:1212–9.

[7] Alraiyes A, Tunsupon P. Relapsing pleural effusion in a patient on automated peritoneal dialysis. Ochsner J 2017;17:136–7.

[8] Stuart S, Booth T, Cash C, et al. Complications of continuous ambulatory peritoneal dialysis. Radiographics 2009;29:441–60.

[9] Pecoraro J, Shea L, Tenora L, et al. Radioisotope assisted diagnosis of traumatic rupture of the diaphragm. Am Surg 1985;51:687–9.

[10] Promila P, Vivek P, Ishita S, et al. Use of radionuclide peritoneography in the diagnosis of pleuroperitoneal communication as a complication of continuous ambulatory peritoneal dialysis. Ind J Nucl Med 2005;20:1.

[11] Assounga A, Hariparshad S, Madala N. Kidney Diseases in an African Setting. Reach Publishers: Reach Publishers; 2012.

[12] Abraham G, Shokker A, Blake P, et al. Massive hydrothorax on patients on peritoneal dialysis: a literature review. Adv Perit Dial 1988.

[13] Kennedy C, McCarthy C, Alken S, et al. Pleuroperitoneal leak complicating peritoneal dialysis: a case series. Int J Nephrol 2011;2011: 526753.

[14] Gagnon RF, Daniels E. The persisting pneumatoenteric recess and infracardiac bursa: possible role in the pathogenesis of right hydrothorax complicating peritoneal dialysis. Adv Perit Dial 2004;20:132–6.

[15] Yoo S, Hwang J, Song J, et al. A rare case of unilateral pleural effusion in a pediatric patient on chronic peritoneal dialysis: is it a pleuroperitoneal leakage. Child Kidney Dis 2018;22:86–90.

[16] Bushberg J, Siebert J, Leidholdt E, et al. The Essentials Physics of Medical Imaging, 2nd ed., Lippincott Williams and Wilkins, Pg 696.

[17] Wu P, Lee B, Chiu N, et al. Peritoneal scintigraphy for the assessment of dialysate leakage in patients on continuous ambulatory peritoneal dialysis. Ann Nucl Med Sci 2001;14:11–8.

[18] Karkhanis V, Joshi J. Pleural effusion: diagnosis, treatment, and management. Open Access Emerg Med 2012;4:31–52.

[19] Guest S. The curious right-sided predominance of peritoneal dialysis-related hydrothorax. Clin Kidney J 2015;8:212–4.

[20] Light RW. Pleural Disease. 2nd ed. Philadelphia, PA: Lea & Febiger; 1990.

[21] Kinasewitz GT. Transudative effusions. Eur Respir J 1997;10:714–8.

[22] Chow KM, Szeto CC, Wong TY, et al. Hydrothorax complicating peritoneal dialysis: diagnostic value of glucose concentration in pleural fluid aspirate. Perit Dial Int 2002;22:525–8.

[23] Khanna R, Oreopoulos DG. Nolph KD. Complications of peritoneal dialysis other than peritonitis. Peritoneal Dialysis Boston: Martinus Nijhoff; 1985;441.

[24] Ustundag S, Ustun F, Yilmaz G, et al. Pleuroperitoneal leak complicating continuous ambulatory peritoneal dialysis: a case report. JMED Cases 2015;6:101–4.

[25] Ilhan K, Ilhan K, Gul A, et al. Scintigraphy as a reliable technique for the diagnosis and follow-up of pleuroperitoneal leakage in peritoneal dialysis patients. Turk Neph Dial Transpl 2016;25:139–41.

[26] Bi-fang L, Jer-ming C, Nan-Tsing C, et al. Peritoneoscintigraphy using Tc-99m MAA for diagnosis of diaphragmatic disruption in a peritoneal dialysis patient. Kaohsiung J Med Sci 1997;13:695–9.

[27] Hernandez A, Ferrer M, Poggio C, et al. Tc-99m MAA peritoneal scintigraphy in pleuroperitoneal communication in peritoneal dialysis patients. Rev Esp Med Nucl 2010;29:84–6.

[28] Dufek S, Holtta T, Fischbach M, et al. Pleuro-peritoneal or pericardio-peritoneal leak in children on chronic peritoneal dialysis - a survey from the European Paediatric Dialysis Working Group. Pediatr Nephrol 2015;30:2021–7.

[29] Alexander R. Pediatric Dialysis Case Studies: A Practical Guide to Patient Care. AG: Springer International; 2017.

[30] Kang TW, Kim CK. Pleuroperitoneal communication of peritoneal dialysis demonstrated by multidetector-row CT peritoneography. Abdom Imaging 2009;34:780–2.

[31] Alhasan K. Recurrent hydrothorax in a child on peritoneal dialysis: a case report and review of the literature. Clin Case Rep 2019;7:149–51.

[32] Tang S, Chui WH, Tang AW, et al. Video-assisted thoracoscopic talc pleurodesis in effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. Nephrol Dial Transplant 2003;18:804–8.