Original Research

Investigating the clinical utility of three protocols of hepatobiliary iminodiacetic acid scans in gallbladder dyskinesia

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ABSTRACT

Purpose: Stimulated hepatobiliary iminodiacetic acid (HIDA) scans assess gallbladder function by measuring gallbladder ejection fraction (GBEF) to help diagnose biliary dyskinesia, a functional disorder causing biliary-type pain with no structural abnormalities on ultrasound. Various HIDA protocols use different stimulants and imaging times, but their comparative clinical utility and impact on patient outcomes remain unclear. This study aimed to compare GBEF values, surgical intervention rates, pathology, and symptom resolution across three common HIDA protocols.

Methods: A retrospective review of 525 patients with abdominal pain, normal biliary ultrasound, and abnormal HIDA scans (GBEF ≤40% or radiologist opinion) from 2018–2022 was performed. Protocol 1 used intravenous sincalide with imaging at 30 minutes; Protocols 2 and 3 used oral stimulants (Ensure® and fatty meal, respectively) with imaging at 60 minutes. Demographic and clinical variables were compared using ANOVA, Welch's ANOVA, Chi-square, and Fisher's exact tests.

Results: Protocol 1 included 318 patients (60.6%), Protocol 2 had 175 (33.3%), and Protocol 3 had 32 (6.1%). Protocol 1 showed significantly lower mean GBEF values (60.7% ± 30.6) compared to Protocol 2 (74.9% ± 19.0; $p<0.001$), with greater variability. Cholecystectomy rates were higher in Protocol 1 (21.4%) versus Protocol 2 (9.7%; $p=0.004$). Symptom resolution post-surgery was similar across groups (63.6% for Protocol 1, 78.6% for Protocol 2; 80.0% for Protocol 3; $p=0.839$), as was final pathology ($p=0.485$).

Conclusion: Despite protocol differences affecting GBEF values and surgery rates, patient outcomes were comparable. Protocol 1 remains the gold standard, but Protocols 2 and 3 could serve as reasonable alternatives; prospective studies with standardized imaging times are needed to validate these findings.

Keywords: Hepatobiliary Iminodiacetic Acid Scan, Gallbladder Ejection Fraction, Biliary Dyskinesia, Cholecystectomy, Nuclear Medicine, Radiology.

Biliary dyskinesia is defined as a functional disorder of the gastrointestinal tract, presenting with a reduced gallbladder ejection fraction (GBEF) without another identified cause for biliary-type pain.[1] One diagnostic technique is the stimulated hepatobiliary iminodiacetic acid (HIDA) scan in nuclear medicine, often used when the first-line imaging modality - ultrasound - provides little diagnostic clarity.[2] Sequential images are captured with a gamma camera using radioactive tracers to evaluate bile flow through the hepatobiliary system into the small intestine, approximating the system's function.[3,4] The GBEF can then be calculated, which is often reduced in calculous and acalculous biliary diseases.[3] While the technique is well understood, there are inconsistencies in the literature regarding its clinical utility and the optimal imaging protocol.

Generally, the hepatobiliary system is first imaged for 60 minutes using a radiotracer.[5–8] The scan should be performed using either 99mTc-disofenin or 99mTc-mebrofenin as the radiotracer, which is injected intravenously. The radiotracer dose varies from 66.6 to 370 MBq, but most commonly ranges from 148 to 185 MBq of mebrofenin. In the gold-standard protocol (referred to as Protocol 1 in this study), sincalide, a cholecystokinin (CCK) synthetic, is given intravenously at 0.02 µg/kg and infused over 30-60 minutes (preferably 60 minutes) once the gallbladder is proven to be filled with radiotracer. A CCK synthetic is an ideal choice because it is a hormone responsible for gallbladder contraction.[9] The biliary system is then imaged with a gamma camera to track the flow of bile.[4,5,10] Some studies image for 20 minutes[10,11] or 30 minutes[12,13] post-infusion, while others image for up to 60 minutes or more.[4,6–8,13] Other studies[6,8] have concluded that Ensure ® (Regular formulation) or a fatty meal administered orally may be employed as alternatives for stimulating gallbladder contractions in HIDA scanning when sincalide is not available. Several studies have also explored the potential impact of adding morphine post-treatment if the gallbladder is unable to be visualized, or pre-treatment pre-emptively, which has shown promise.[14]

The values used for a normal GBEF vary throughout the literature. Some studies have used 38% as the lower limit of

normal when using a 60-minute sincalide infusion, as per the 2010 guidelines by the Society of Nuclear Medicine (SNM).[15] However, others have arbitrarily defined cut-off values for the normal range of GBEF, such as >40%.[16] Another study proposed a lower limit of normal of GBEF as high as 41% with a 60-minute sincalide infusion.[17] Others have accepted GBEF limits as low as 35% for the lower limit of normal.[4,7,10–12,18–20]

Many have suggested that GBEF is a useful tool in determining who will benefit from a cholecystectomy. One study found that the use of a HIDA scan in addition to an abdominal ultrasound significantly increased the sensitivity for diagnosing chronic cholecystitis.[2] It has been found that patients with an abnormally low GBEF have symptom improvement post-cholecystectomy.[16,19] A correlation has also been identified between low GBEF and histopathological changes in the gallbladder.[11,16] It has been reported that most patients with abnormal HIDA scans and abnormal pathologies had symptom resolution post-cholecystectomy.[11,20] Further, pain provocation during the sincalide infusion could be useful in determining which patients may have successful outcomes post-cholecystectomy.[21] Meanwhile, other studies have found no significant correlation between low GBEF, reproducible pain during the sincalide infusion, and resolution of symptoms post-surgical intervention.[4,7]

While the HIDA scan is a well-understood technique, there is still much controversy surrounding its utility and predictive value. Regardless, many authors agree that it is a useful tool for investigating chronic biliary dyskinesia and pain symptoms. The purpose of this study was to compare the diagnostic utility and clinical predictive value of each of the three protocols. Based on the current literature, it was hypothesized that all three protocols would likely produce equivalent findings regarding GBEF values and patient outcomes, which may help to inform clinicians' practice and choice of protocol.

METHODS

This study utilized data collected as part of a larger study (Kerr et al., unpublished data, 2024) exploring the value of HIDA scans in biliary dyskinesia. The study received full ethical approval by the local Health Research Ethics Board (file #20240629). This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This was a retrospective chart review including all patients who had undergone HIDA scans at a single institution from January 2018 to December 2022. The inclusion criteria included all patients with abdominal pain, normal biliary ultrasound findings, and abnormal HIDA scan findings as defined by GBEF ≤40% or radiologist opinion. The exclusion criteria specified patients with abnormal ultrasound findings (including cholelithiasis, pericholecystic fluid, gallbladder wall thickening, or sludge) and patients undergoing HIDA scans for indications other than abdominal pain in the context of normal biliary ultrasound findings. The local electronic medical records database, Meditech (Medical Information Technology Inc., Westwood, Massachusetts, USA), was used for the collection of relevant patient data, including age, sex, past medical and surgical history, date and indication for the HIDA scan, radiological impression and diagnosis, date of cholecystectomy, and final pathology report. Clinic notes were also searched to include data on preoperative symptoms and symptom resolution post-operatively.

Of note, at the institution during the study period, Protocol 1 imaging was conducted at the 30-minute mark post-sincalide infusion, reflecting historical practice at the time. Protocols 2 and 3, using oral gallbladder stimulants, employed imaging at the 60-minute mark, consistent with published protocols for these methods and allowing sufficient time for gallbladder contraction. This was a retrospective protocol which was the standard at the institution at the time of data collection. Since the completion of data collection, the institutional practice has become standardized for imaging to occur at 60 minutes across all protocols, reducing variability and improve comparability of GBEF measurements.

Statistical analysis of the final dataset was performed using R version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as means ± standard deviations, and categorical variables as frequencies and percentages. The distribution of patients across protocols was evaluated using a Chi-square goodness-of-fit test, with standardized residuals calculated to identify deviations from expected frequencies. Normality of residuals and homogeneity of variance for continuous variables were assessed using the Shapiro-Wilk test and Levene's test, respectively. One-way Analysis of Variance (ANOVA) was used for age comparisons, given that these assumptions were sufficiently met. Due to violations of these assumptions for GBEF, comparisons of GBEF across protocols were conducted using Welch's ANOVA to account for unequal variances, and post-hoc pairwise comparisons were performed using the Games-Howell test with adjustment for multiple comparisons. Categorical variables such as sex, comorbidities, surgical intervention rates, and pathology findings were analyzed using Chi-square tests of independence or Fisher's exact tests when expected cell counts were less than five. Significant results were followed by pairwise comparisons with Bonferroni correction to adjust for multiple tests. The threshold for statistical significance was set at a p-value of <0.05 for all analyses.

RESULTS

Of the 585 patients in the original sample, 60 were excluded (3 due to absence of gallbladder stimulation and 57 due to non-numeric GBEF values), leaving 525 patients for analysis.

Since data collection, the study's institution has changed Protocol 1 imaging to occur at the 60-minute mark; however, these data are not included, as this change occurred after the study period. Of these patients, 318 (60.6%) underwent Protocol 1, 175 (33.3%) Protocol 2, and 32 (6.1%) Protocol 3. This distribution differed significantly from equal distribution ($p<0.001$), with Protocol 1 overrepresented and Protocol 3 underrepresented (see Table 1).

Table 1. *Baseline patient demographics by protocol.*

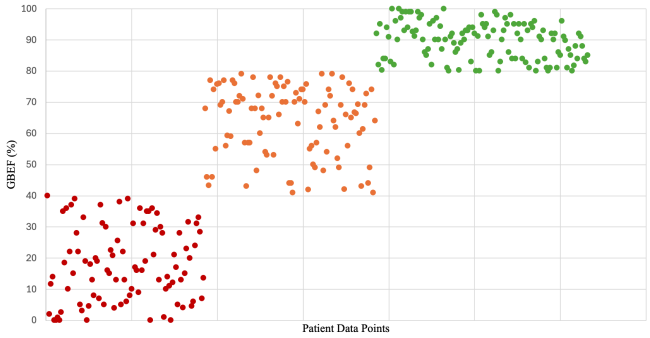
Patient Demographic	Protocol 1	Protocol 2	Protocol 3	p-value
Number of Patients (%)	318 (60.6%)	175 (33.3%)	32 (6.10%)	$<2.20 \times 10^{-16}$ (*)
Mean Age in Years (SD)	48.1 (16.5)	50.0 (15.7)	45.6 (15.2)	0.255
Female (%)	241 (75.8%)	126 (72.0%)	26 (81.3%)	0.449
Comorbidities (%)				
Dyslipidemia	15 (22.1%)	1 (20.0%)	0 (0%)	1.00
Type 2 diabetes mellitus	12 (17.6%)	1 (20.0%)	0 (0%)	1.00
Gastroesophageal reflux disease	31 (45.6%)	1 (20.0%)	1 (100.0%)	0.262
Hypertension	14 (20.6%)	2 (40.0%)	0 (0%)	0.452
Non-alcoholic steatohepatitis	2 (2.94%)	2 (40.0%)	0 (0%)	1.00
Chronic obstructive pulmonary disease	2 (2.94%)	0 (0%)	0 (0%)	1.00
Asthma	4 (5.88%)	1 (20.0%)	0 (0%)	0.353
Obstructive sleep apnea	2 (2.94%)	0 (0%)	0 (0%)	1.00
Alcohol Use (%)	15 (28.8%)	1 (33.3%)	0 (0%)	1.00
Smokers (%)	10 (19.2%)	1 (33.3%)	0 (0%)	0.594

Percentage proportions are based upon the total number of patients in each protocol with follow-up data available for the listed parameter. P-values are from Chi-square tests for categorical variables, Fisher's exact tests where appropriate, and one-way ANOVA for continuous variables. Follow-up data were available for N=74 patients (comorbidities), N=56 (alcohol/smoking). (*) indicates a statistically significant p-value.

There were no significant differences in baseline demographics, including age and sex, across protocols (all $p>0.05$; see Table 1). Data on comorbidities, alcohol use, and smoking were limited but similarly showed no significant differences between groups (all $p>0.05$; see Table 1). Common comorbidities included dyslipidemia (DLD), type 2 diabetes mellitus (T2DM), gastroesophageal reflux disease (GERD), hypertension (HTN), non-alcoholic steatohepatitis (NASH), chronic obstructive pulmonary disease (COPD), asthma, and obstructive sleep apnea (OSA). Eight patients (1.52%) had alternative diagnoses other than biliary dyskinesia documented, all in Protocol 1, including 4 diagnosed with irritable bowel syndrome (IBS), 1 diagnosed with Crohn's disease, 2 diagnosed with gastritis, and 1 diagnosed with abdominal pain not yet determined (NYD).

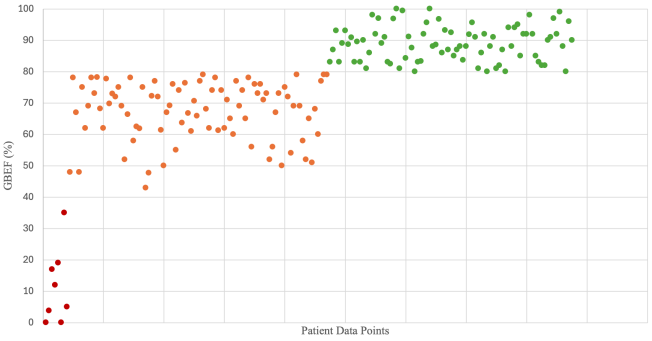
Mean GBEF differed significantly across protocols ($p<0.001$), with higher values observed in Protocol 2 compared to Protocol 1 (Welch's ANOVA; mean difference=14.2%, 95% CI 8.9–19.5). However, no significant differences were observed between Protocols 1 and 3 or Protocols 2 and 3 ($p=0.107$ and $p=0.116$, respectively).

The distribution of GBEF categories (hypokinetic [0–40%], dyskinetic [41–79%], hyperkinetic [80–100%]) also differed significantly across protocols (Chi-square test of independence, $p<0.001$). Protocol 1 demonstrated a higher proportion of hypokinetic values compared to Protocols 2 and 3. However, visual inspection of GBEF distributions suggested similar patterns of values below the abnormal threshold (≤40%) across protocols (see Figures 1-4).



Red indicates hypokinetic GBEF values (0-39%); orange indicates dyskinetic GBEF values (40-79%); green indicates hyperkinetic GBEF values (80-100%).

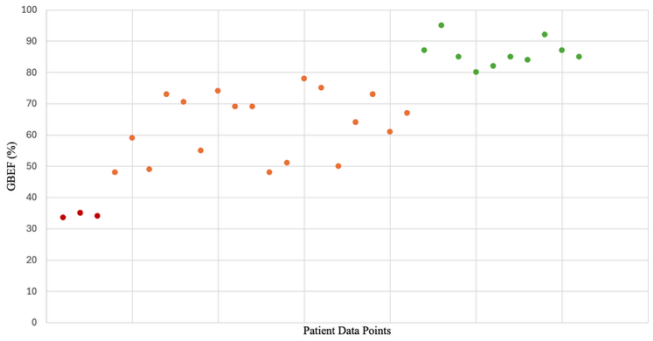
Figure 1. *Scatter plot showing individual gallbladder ejection fraction (GBEF) data points for Protocol 1.*



Red indicates hypokinetic GBEF values (0-39%); orange indicates dyskinetic GBEF values (40-79%); green indicates hyperkinetic GBEF values (80-100%).

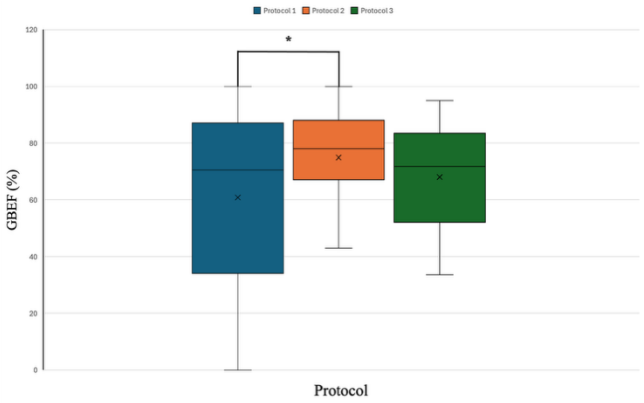
Figure 2. *Scatter plot showing individual gallbladder ejection fraction (GBEF) data points for Protocol 2.*

A total of 91 patients (17.3%) underwent surgical intervention via cholecystectomy. Surgical rates differed significantly across protocols, with higher rates observed in Protocol 1 compared to Protocol 2 (Chi-square test of independence, $p=0.00436$; see Table 2). Reasons for not undergoing surgery were documented for 44 patients (8.38%), and included clinical judgement (31.8%), loss to follow-up or no surgical assessment (22.7%), awaiting surgery (11.4%), and patient refusal (11.4%). Reasoning did not differ significantly between protocols (all $p>0.05$; see Table 2).



Red indicates hypokinetic GBEF values (0-39%); orange indicates dyskinetic GBEF values (40-79%); green indicates hyperkinetic GBEF values (80-100%).

Figure 3. *Scatter plot showing individual gallbladder ejection fraction (GBEF) data points for Protocol 3*



Significantly lower GBEF values were observed in Protocol 1 as compared to Protocol 2 (p=2.02x10-7; denoted by *).

Figure 4. *Box and whisker plot depicting the distribution and means of the gallbladder ejection fraction (GBEF) values in each protocol.*

Table 2. *Patient outcomes by protocol.*

Patient Outcome	Protocol 1	Protocol 2	Protocol 3	p-value
Surgical Intervention (%)	68 (21.4%)	17 (9.71%)	6 (18.8%)	0.00436 (*)
Pathology				
Chronic acalculous cholecystitis	41 (62.1%)	1 (50.0%)	0 (0%)	0.485
Other	25 (37.9%)	1 (50.0%)	1 (100%)	
Pain Resolution Post-Operatively (%)	42 (63.6%)	11 (78.6%)	4 (80.0%)	0.839
Reason for No Surgical Intervention (%)				
Patient declined	4 (10.3%)	1 (25.0%)	0 (0%)	1.00
Awaiting surgery	5 (12.8%)	0 (0%)	0 (0%)	
Surgeon clinical judgment	12 (30.8%)	1 (25.0%)	1 (100%)	
Lost to follow-up / no surgical assessment	8 (20.5%)	2 (50.0%)	0 (0%)	

Percentage proportions are based upon the total number of patients in each protocol with follow-up data available for the listed parameter. P-values are from Chi-square tests for categorical variables, Fisher's exact tests for small sample sizes, and post-hoc pairwise Fisher's exact tests

Among those who underwent surgery, pathology data were available for 69 patients, classified as chronic acalculous cholecystitis or other pathologies (e.g., chronic calculous cholecystitis, cholesterolosis, polyps, adenomyosis, benign cholelithiasis). No significant differences in pathology were found across protocols (Fisher's exact test, p=0.485; see Table 2).

Similarly, data on pain and/or symptom resolution were available for 85 patients (16.2%). The majority reported symptom resolution, with no significant differences between protocols (63.6% for Protocol 1, 78.6% for Protocol 2, 80.0% for Protocol 3; Fisher's exact test, p=0.839; see Table 2).

DISCUSSION

This study has addressed a clinically relevant issue, given that multiple protocols exist for HIDA scanning without clear data on whether clinical outcomes differ with each. The patients in this sample did not differ significantly on demographic characteristics such as age, sex, alcohol use, smoking rates, or presence of comorbidities. This indicates that significantly lower GBEF values observed in Protocol 1 are more likely attributable to the specific technique employed rather than demographic characteristics.

Despite this, the most relevant finding was that no significant differences were observed in clinical outcomes at follow-up appointments post-cholecystectomy, regardless of protocol used or GBEF values. Most patients fared very well, with approximately 60-80% of people across each protocol endorsing pain resolution post-operatively. Although significant differences were found in GBEF values across different protocols, this did not appear to have any clinical implications for patients in the long term.

While intravenous gallbladder stimulation is traditionally considered the gold standard, the present study's methodological limitations - including differing imaging time points, lack of within-subjects comparisons, and unequal sample sizes - warrant caution in interpreting direct comparisons between protocols. Our findings suggest that Protocols 2 and 3 may offer clinically comparable outcomes, but prospective, controlled studies are needed to confirm their equivalence. If the use of Ensure ® or a fatty meal administered orally were found in such future studies to produce relatively equal outcomes clinically, these may serve as equivalents to sincalide in scenarios such as shortages.[22] Therefore, intravenous gallbladder stimulation remains the recommended first-line method where available, with alternative protocols available for consideration when deemed appropriate.

The differences in GBEF values found in this study are conflicting findings as compared to the existing literature. In one retrospective study, no significant differences in GBEF

values were reported when using 60-minute protocols of sincalide versus Ensure ®.[23] Further, another study found no significant differences in mean GBEF values when using sincalide versus Ensure ®.[22] However, an important limitation of this study is the difference in imaging time points across protocols; imaging at 60 minutes generally yields higher and more stable GBEF values than earlier time points, such as 30 minutes, which can affect comparisons across protocols.[15] This variability is reflected in the current data, where Protocol 1 (imaged at 30 minutes) demonstrated a notably higher standard deviation in GBEF values (30.6%) compared to Protocols 2 and 3 (19.0% and 17.4%, respectively; see Table 2); meanwhile, some previously referenced studies imaged at 60 minutes when using intravenous gallbladder stimulation.[22] Existing literature posits that 60-minute imaging produces more consistent and diagnostically accurate values.[24–27] Given these findings and the variability observed, a 60-minute imaging time point may be the preferred default choice. This limitation should be considered when interpreting the results, as variability in GBEF measurements related to timing may affect the strength of conclusions regarding the equivalence of protocols. As well, given that the institutional technique for imaging time in Protocol 1 has been updated following data collection, future research may warrant a comparison between the prior and updated methods.

Significantly more surgical interventions were completed for patients in Protocol 1 versus Protocol 2. Overall, the most common reason cited for not pursuing surgical intervention was the clinical judgment of the attending physician, which is likely multifactorial and informed by individual opinions and experience.[28] As discussed, the Protocol 1 group contained significantly lower GBEF values than Protocol 2, which may be related to the use of intravenous gallbladder stimulation versus Ensure ®, and could have led clinicians and patients to decide with more objectivity that surgical intervention was warranted. After plotting all individual GBEF values for patients in each protocol, distinct categories of GBEF values were visualized (see Figures 1-3). Most patients had values clearly above or below the abnormal threshold of ≤40%; this supports the appropriateness of this cut-off in our population. Despite these findings, no significant differences were observed between the three protocols regarding pain and symptom resolution at follow-up appointments. This aligns with the findings of a study where post-cholecystectomy pain outcomes did not differ in patients with normal versus decreased GBEF values; thus, GBEF should be considered as one of many tools in decisions surrounding surgical management.[26]

All patients with alternative diagnoses had undergone Protocol 1. The majority of these were eventually diagnosed with IBS, with the remainder diagnosed with Crohn's disease, gastritis, or abdominal pain not yet determined. Each of the listed conditions displays much symptom overlap with diseases of the biliary tract and gallbladder dyskinesia, and HIDA scanning is generally expected to narrow the differential diagnosis.[29] As well, no significant differences were found regarding the final pathology between protocols, whether chronic acalculous cholecystitis or other. Therefore, differences in GBEF, number of cholecystectomies performed, and symptom resolution are less likely to be attributable to different underlying disease processes as a confounding factor and more likely due to implications surrounding the protocol itself.

This study utilized a retrospective, between-subjects design in which each patient underwent only one of the HIDA scan protocols. While this reflects real-world clinical practice, it limits the ability to directly compare protocols within the same individuals and control for inter-patient variability or the patient distribution across protocols. The uneven distribution of patients reflects real-world practice patterns during the study period but limits the statistical power and confidence in findings related to Protocol 3, increasing the risk of a type II error and decreasing generalizability. Accordingly, conclusions involving Protocol 3 should be interpreted with this consideration in mind, and future studies with larger and more balanced cohorts are warranted. Nevertheless, our findings contribute valuable comparable data from a large clinical cohort and highlight important considerations for protocol selection.

Finally, the follow-up data for parameters such as comorbidities, alcohol use, smoking rates, reasoning for no surgical intervention, and final pathology were limited. This incomplete data reduces the statistical power to detect potential differences between protocols in these areas and the generalizability of these results, and may introduce bias. Again, future studies would benefit from a more comprehensive prospective design.

CONCLUSION

This study reinforces the clinical relevance of HIDA scans in diagnosing and managing biliary dyskinesia. These findings suggest that, despite differences in GBEF values between protocols, patient outcomes were largely similar across all three protocols. While Protocol 1 remains the recommended first-line approach as the current gold standard, it is possible that Protocols 2 and 3 may serve as adequate alternatives when necessary. Imaging at the 60-minute mark appears to reduce variability in GBEF measurements compared to earlier imaging times, given the variability observed with 30-minute imaging. Due to the retrospective design of the study and limited follow-up data, future prospective studies with larger cohorts are warranted to validate these findings and better inform HIDA protocol selection in clinical practice.

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