Lung Sestamibi Uptake on Myocardial Perfusion Imaging and Outcomes in Chronic Kidney Disease

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Keywords

Stress testing · Coronary artery disease · End-stage kidney disease · Chronic kidney disease · Lung-heart-ratio · Outcomes · Myocardial perfusion imaging

Abstract

Background and Objectives: In patients with CKD and end-stage kidney disease (ESKD), cardiac stress testing has low sensitivity and specificity for coronary disease. Alternate markers that are derived during the stress testing may enhance the predictive characteristic of stress testing. The objective was to examine the predictive characteristic of lung-to-heart ratio (LHR) in patients with CKD and ESKD. **Design, Setting, Participants, and Measurements:** Retrospective parallel cohort of ESKD and CKD not on dialysis (CKD-ND) who underwent stress testing with nuclear myocardial perfusion imaging utilizing sestamibi tracer and regadenoson. Stress LHR was calculated by the processing software and reported. Patients were analyzed by tertile of LHR (≤ 0.28 ,

0.29–0.32, ≥ 0.33). The primary outcome was a composite of all-cause mortality, hospitalization for myocardial infarction or unstable angina, or revascularization. **Results:** There were 144 CKD-ND and 145 ESKD patients. Patients with ESKD had greater comorbidity burden than CKD-ND. Stress tests were more often performed for pre-operative risk assessment among ESKD versus CKD-ND (53.8 vs. 5.6%, $p < 0.001$). ESKD patients more likely had ischemia identified on stress testing (19.3 vs. 8.3%, $p = 0.001$). Mean LHR was 0.31 (Standard deviation – SD: 0.09) and was similar across CKD-ND stages and ESKD. Primary outcome in the lowest (23%) and highest (33.3%) LHR tertile was higher than the middle tertile (12.8%); $p = 0.005$. This finding was similar between CKD-ND and ESKD and persisted in multivariable analysis. **Conclusions:** LHR ≤ 0.28 and ≥ 0.33 are independently associated with higher risk for death in patients with CKD-ND and ESKD. Future studies are warranted to understand the association of extreme LHR values and outcomes in this high-risk population.

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Introduction

Cardiac stress testing, especially nuclear myocardial perfusion imaging (MPI), is commonly performed in patients with advanced CKD, including end-stage kidney disease (ESKD), to evaluate symptoms suggestive of cardiac ischemia and as part of routine workup prior to kidney transplantation [1, 2]. A number of factors have been shown to lower accuracy of stress testing in CKD patients, such as the prevalence of balanced ischemia in the presence of multivessel disease, left ventricular hypertrophy, and poor vascular reactivity to vasodilators that are used during non-invasive stress testing [3]. Despite these limitations, an abnormal stress test carries prognostic risk in the ESKD population [4–7]. In the recently completed ISCHEMIA-CKD trial, despite an overall null benefit for an initial invasive strategy in stable ischemic heart disease in advanced CKD and ESKD, subgroup analysis revealed a trend toward benefit from an initial invasive approach with the finding of severe ischemia on stress testing (hazard ratio for primary outcome – death or non-fatal myocardial infarction (MI) – with an initial invasive strategy in those with severe ischemia detected on stress testing: 0.70, 95% confidence interval 0.46–1.05) [8].

The myocardial tracer used in MPI has specificity for the myocardium but has non-cardiac uptake that has been found to be clinically relevant. Though not formally recommended as an ancillary marker of outcomes in cardiac stress testing, the lung uptake as compared to heart uptake during MPI, called the lung-to-heart ratio (LHR), has demonstrated associations with clinical outcomes. Lung uptake of thallium-201 (^{201}Tl) is a predictor of adverse cardiovascular outcomes [9, 10]. Novel synthetic tracers, specifically technetium ($^{99\text{m}}\text{Tc}$) sestamibi, provide higher quality imaging studies and have slower myocardial clearance than ^{201}Tl [11]. Despite a greater specificity for myocardium than thallium, Leslie et al. [12] recognized that elevated lung $^{99\text{m}}\text{Tc}$ -sestamibi uptake is an adjunctive prognostic measure in patients with known or suspected coronary artery disease (CAD), and others have similarly found associations [12–14]. The outcomes associated with an elevated LHR include mortality, number of diseased coronary vessels (typically multivessel disease associated with higher LHR [14, 15]), as well as markers of elevated left ventricular end diastolic filling pressure [15, 16]. In addition, severe critical disease such as left main trunk CAD has been associated with an elevated LHR independent of other stress parameters [17]. The exact reasons for these associations are not fully elu-

cidated. However, it is accepted that an increase in LHR is a marker of increased pulmonary capillary wedge pressure [18–20]. Thus, any activity that would induce an elevation in pulmonary capillary wedge pressure, such as acute myocardial dysfunction due to impaired coronary blood flow (especially diffuse impairment) would be associated with an increase in lung uptake of tracer and therefore the LHR. On the other hand, non-ischemic causes, such as mitral regurgitation, can also lead to elevation in LVEDP, and subsequently LHR; possibly explaining the multiple potential outcomes that LHR can be associated with. Nevertheless, the association, especially with multivessel disease, may prove useful in patients with CKD and ESKD given the frequent obfuscating nature of multivessel disease toward detection by standard ischemia assessment during MPI.

Other ancillary stress test markers (heart rate response during regadenoson stress MPI) have recently been demonstrated to have prognostic value in CKD and ESKD [21]. As no other study to our knowledge has examined the prognostic value of LHR from MPI in patients with CKD and ESKD, we hypothesized that an elevated LHR will predict a higher incidence of adverse outcomes (e.g., all-cause death, hospitalization for MIs/unstable angina (UA), or need for coronary revascularization) among patients with CKD not on dialysis (CKD-ND) and ESKD.

Methods

Cohort Creation

The institutional review board and research and development committee of the Columbia VA Health Care System approved this study. The study complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000511801) [22]. Figure 1 displays the cohort creation for the ESKD and CKD-ND groups. CKD stages were divided according to Kidney Disease: Improving Global Outcomes criteria: Stage 3a (eGFR 30–59); Stage 3b (eGFR 15–29); stages 4 and 5 (eGFR < 15) [23]. All veterans at the Columbia VA Health Care System who underwent pharmacologic stress nuclear single-photon emission computed tomography MPI and had an international classification of diseases 9 code of 585.6 (ESKD) in their problem list, between January 2010 and May 2019 were evaluated. Only the first stress test after starting dialysis was utilized for the primary analysis.

CKD-ND patients were identified using the same CPT codes, but excluding code 585.6. CKD-ND patients were selected by matching age to the mean $\pm$ 2 standard deviations age (48–80 years) of the ESKD study cohort. Patients were excluded if they did not fall in this age range, were identified as having ESKD at time of stress test on chart review or did not have a stress test performed.

Fig. 1. Study groups and cohort selection. eGFR, estimated glomerular filtration rate.

Given the large number of stress tests performed in CKD-ND population, only the first stress test in 2015 (midpoint of the ESKD screen time) was analyzed.

Clinical Data Points

Variables assessed included gender, race/ethnicity, BMI (3 months $\pm$ date of stress test), cardiac-specific medications (6 months prior to the stress test or 3 months after) (angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, aspirin, – clopidogrel, β -blocker, dihydropyridine calcium channel blockers, non-dihydropyridine calcium channel blockers, statins, mineralocorticoid receptor antagonists MRA), past medical history (history of CAD, stroke, heart failure [HF], hypertension, diabetes, and chronic obstructive pulmonary disease or emphysema), and outcomes (described below).

Local Stress Protocol and Imaging

Patients were instructed to avoid food and caffeine 8–12 h before the study. Patients underwent pharmacologic stress-rest studies with intravenously administered regadenoson, which was immediately followed with administration of ^{99m}Tc Sestamibi (first dose: 10.0 mCi for rest & 30 mCi for stress; if the patient is greater than 250 lbs: 15.0 and 40 mCi for rest and stress, respectively). Perfusion images were obtained within 90 min following radioactive tracer administration. Patients were instructed to hold β -blockers for at least 48 h prior to the procedure.

Image data were collected by commercial software (Phillips Jetstream, Milpitas, CA, USA) and automatically processed through IntelliSpace PACS (Philips, Milpitas, CA, USA). Images were interpreted by a Board-certified cardiologist or radiologist.

Stress Data Collection

All values were manually extracted from the VA EMR. The MPI results were recorded as “No ischemia,” “Ischemia present,”

“Peri-infarct ischemia,” “Fixed defect – scar,” or “Attenuation artifact.” Stress LHR (examples are shown in online suppl. Fig. 1a–c) was automatically calculated by the imaging software using the protocol described by Bacher-Stier et al. [24]. Machine calculated quantitative values of myocardial perfusion (summed stressed score [SSS], summed rest score [SRS], summed difference score [SDS]), transient ischemic dilatation, and ejection fraction (EF) were recorded. SSS is the sum of scores assigned to various segments of the myocardium on perfusion imaging during stress, SRS is the same during rest, and SDS is the difference between the 2 – the direct assessment of ischemia. For SSS and SRS, the higher the score, the greater the extent of ischemia. Transient ischemic dilatation is a measure of left ventricular cavity volume at stress and rest, and the greater the volume at stress in relation to rest, there is a correlation with multivessel coronary disease [25].

Outcomes

The primary outcome was a composite of all-cause death or first admission for MI/UA/urgent or planned coronary artery revascularization – percutaneous coronary intervention or coronary artery bypass grafting within 3 years of the MPI date. Secondary outcomes included the individual components of the primary composite outcome.

Statistical Analysis

All analyses were conducted utilizing R versus 3.6.1 (2019-07-05) (<https://cran.r-project.org/>). The packages utilized include *base*, *stats*, *survival*, *survminer*, *ggplot2*, *Publish*, and *TableOne*. Patients were evaluated according to the tertile of LHR (≤ 0.28 , $0.29–0.32$, ≥ 0.33). Descriptive statistics were performed to compare baseline demographic and stress characteristics. The primary analysis was performed with the groups separated by tertile of LHR. Kaplan-Meier curves were created to analyze univariate effects of each LHR tertile on the outcomes, with log-rank *p* values to assess

Table 1. Baseline characteristics

	LHR ≤ 0.28	LHR 0.29–0.32	LHR ≥ 0.33	<i>p</i> value
<i>N</i>	113	86	90	
Age (mean [SD]), years	63.36 (8.34)	66.12 (7.87)	64.98 (8.38)	0.06
Gender: males, <i>N</i> (%)	107 (94.7)	81 (94.2)	87 (96.7)	0.714
<i>Race, N (%)</i>				
African American	71 (65.7)	42 (50.6)	42 (47.2)	0.058
White American	36 (33.3)	40 (48.2)	44 (49.4)	
Other	1 (0.9)	1 (1.2)	3 (3.4)	
<i>CKD stage, N (%)</i>				
3a	39 (34.5)	30 (34.9)	29 (32.2)	0.772
3b	14 (12.4)	13 (15.1)	7 (7.8)	
4/5	4 (3.5)	4 (4.7)	4 (4.4)	
ESKD	56 (49.6)	39 (45.3)	50 (55.6)	
BMI	28.6 (4.91)	31 (5.7)	32.1 (5.8)	<0.001
<i>Comorbidities, N (%)</i>				
Hypertension	104 (92.0)	83 (96.5)	89 (98.9)	0.056
Diabetes mellitus	71 (62.8)	59 (68.6)	74 (82.2)	0.01
History of congestive HF	16 (14.2)	13 (15.1)	20 (22.2)	0.272
Prior CAD	27 (23.9)	29 (33.7)	28 (31.1)	0.279
History of stroke or transient ischemic attack	15 (13.3)	11 (12.8)	10 (11.1)	0.892
COPD or emphysema	26 (23.0)	21 (24.4)	18 (20.0)	0.771
<i>Medications at time of stress test, N (%)</i>				
Dihydropyridine CCB	41 (36.3)	32 (37.2)	37 (41.1)	0.766
Non-dihydropyridine CCB	2 (1.8)	3 (3.5)	2 (2.2)	0.729
ACEI	43 (38.1)	24 (27.9)	36 (40.0)	0.194
ARB	18 (15.9)	15 (17.4)	22 (24.4)	0.278
Mineralocorticoid receptor blocker	6 (5.3)	4 (4.7)	4 (4.4)	0.957
BB	64 (56.6)	55 (64.0)	60 (66.7)	0.309
Statins	84 (74.3)	61 (70.9)	73 (81.1)	0.275
Aspirin	62 (54.9)	42 (48.8)	50 (55.6)	0.612
Clopidogrel	5 (4.4)	7 (8.1)	4 (4.4)	0.452

COPD, chronic obstructive pulmonary disease; CCB, calcium channel blockers; LHR, lung-to-heart ratio; ESKD, end-stage kidney disease; CAD, coronary artery disease; HF, heart failure; BB, β blockers; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

unadjusted significance between groups; Kaplan-Meier curves confirmed that the assumption of proportionality of the groups was preserved. Univariate analysis was performed to assess for potentially significant predictors of outcomes, including the LHR tertile, age, gender, race/ethnicity, history of HF, diabetes mellitus, CKD stage, EF, medications, and qualitative and quantitative stress results; $p < 0.1$ was utilized to identify potential variables for multivariable analysis. Stress results were collapsed into 3 categories (No ischemia – no reversible ischemia and attenuation artifact; Ischemia – ischemia and peri-infarct ischemia; Scar – fixed defect/scar). Sensitivity analyses were performed: (a) LHR in patients who had a confirmed dialysis treatment ≤ 24 h before the stress test *v* those who had it > 24 h before to examine potential confounding of volume status that can be affected by dialysis treatment; (b) heterogeneity of the effects of the LHR values on outcomes based on CKD-ND and ESKD status; and (c) incremental value of high LHR

tertile with ischemia assessment from MPS on mortality using receiver operator curve with R package *pROC*. A $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Overall baseline demographic characteristics were similar between groups (Table 1). Notable differences included a higher proportion of patients with diabetes mellitus in the highest tertile of LHR (82.2 vs. 68.6% in 0.29–0.32 group and 62.8% in ≤ 0.28 ; $p = 0.01$ for trend); a significant increase in BMI from lowest to highest LHR

Table 2. Stress characteristics

	LHR ≤0.28	LHR 0.29–0.32	LHR ≥0.33	<i>p</i> value
<i>N</i>	113	86	90	
For dialysis patients – days from start of dialysis to stress test (mean [SD])	1,266.73 (1,581.69)	1,129.92 (1,415.11)	824.56 (951.67)	0.235
<i>For patients on hemodialysis – documented dialysis treatment <24 h prior to stress test, N (%)</i>				
No	7 (10.1)	5 (8.2)	4 (7.3)	0.343
Yes	5 (7.2)	9 (14.8)	11 (20.0)	
<i>Reason for stress test, N (%)</i>				
Atypical chest pain	39 (34.5)	28 (32.6)	22 (24.4)	0.699
Dyspnea on exertion	15 (13.3)	11 (12.8)	18 (20.0)	
No reason listed	1 (0.9)	2 (2.3)	4 (4.4)	
Other	22 (19.5)	18 (20.9)	18 (20.0)	
Preoperative risk stratification	35 (31.0)	25 (29.1)	26 (28.9)	
Typical chest pain	1 (0.9)	2 (2.3)	2 (2.2)	
<i>Qualitative result, N (%)</i>				
Attenuation artifact	15 (13.3)	8 (9.3)	10 (11.1)	0.567
Fixed defect/scar	13 (11.5)	15 (17.4)	19 (21.1)	
No reversible ischemia or infarct	69 (61.1)	47 (52.2)	47 (52.2)	
Peri-infarct reversible ischemia	2 (1.8)	5 (5.8)	3 (3.3)	
Reversible ischemia	14 (12.4)	11 (12.8)	11 (12.2)	
<i>Location of findings, N (%)</i>				
Anterior	4 (9.3)	4 (11.1)	6 (15.8)	0.274
Anterolateral	5 (11.6)	2 (5.3)	2 (5.6)	
Anteroseptal	1 (2.3)	2 (5.3)	6 (16.7)	
Apex	4 (9.3)	5 (13.2)	3 (8.3)	
Inferior	25 (58.1)	13 (34.2)	13 (36.1)	
Inferolateral	2 (4.7)	7 (18.4)	6 (16.7)	
Lateral	1 (2.3)	2 (5.3)	2 (5.6)	
Septal	1 (2.3)	1 (2.6)	0	
<i>Quantitative results (mean [SD])</i>				
SSS	4.48 (5.69)	5.22 (6.11)	6.69 (8.84)	0.077
SRS	2.29 (4.61)	2.51 (4.77)	4.29 (7.81)	0.037
SDS	2.04 (2.23)	2.53 (2.32)	1.96 (2.78)	0.234
Transient ischemic dilatation	0.99 (0.12)	0.97 (0.09)	0.98 (0.10)	0.499
EF	0.55 (0.11)	0.56 (0.12)	0.52 (0.14)	0.039
LHR	0.25 (0.04)	0.30 (0.01)	0.40 (0.10)	<0.001

EF, ejection fraction; LHR, lung-to-heart ratio; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.

Table 3. Outcomes by LHR tertile

	LHR ≤0.28	LHR 0.29–0.32	LHR ≥0.33	<i>p</i> value
<i>Events, N (%)</i>				
Primary Outcome	26 (23.0)	11 (12.8)	30 (33.3)	0.005
All-cause mortality	19 (16.8)	7 (8.1)	26 (28.9)	0.001
Hospitalization for MI/UA or revascularization	8 (7.1)	4 (4.7)	5 (5.6)	0.761

Primary outcome: all-cause mortality, hospitalization for MI/UA, revascularization (percutaneous coronary intervention/coronary artery bypass grafting). LHR, lung-to-heart ratio; MI, myocardial infarction; UA, unstable angina.

tertile ($p < 0.001$ for trend; BMI was also significantly higher in CKD-ND vs. ESKD – 31.4 vs. 29.4, $p = 0.002$, online suppl. Tables 2, 3). The distribution of LHR was similar between patients with normal renal function, CKD-ND and ESKD at this facility (shown in online suppl. Fig. 2).

Stress Test Characteristics (Table 2)

SRS was higher in the highest as compared to the middle and lowest tertiles (4.29 vs. 2.51 and 2.29; $p = 0.037$ for trend), and lower EF in the highest tertile (0.52 vs. 0.56 and 0.55; $p = 0.039$). Mean LHR in the highest, middle and lower tertiles were 0.4, 0.3, and 0.25, respectively; $p < 0.001$ for trend. Reason for stress test differed across CKD stage (online suppl. Table 3).

Outcomes

For the primary outcome, the highest (33.3%) and lowest (23%) tertiles had higher proportion than the middle group (12.8%), $p = 0.005$ for trend (shown in Table 3; Fig. 2a, c). This outcome was driven by mortality: p value for trend for the mortality outcome was 0.001 (Table 3).

Both lower tertile (HR 2.17 [95% CI, 1.06–4.43]) and highest tertile (HR 3.33 [95% CI, 1.66–6.69]) had significantly greater hazard for primary outcome than the middle tertile (Table 4) after multivariable adjustment. Similar trend was found for mortality, though the low LHR tertile demonstrated marginal significance ($p = 0.0495$) (Table 4). The qualitative stress result (Scar or Ischemia present vs. No Ischemia) was the only significant predictor associated with hospitalization for MI/UA or revascularization.

Table 4. Predictors of outcomes

Variable	Primary outcome				Mortality				MI/UA or revascularization			
	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value
		lower	upper			lower	upper			lower	upper	
Unadjusted												
LHR group												
≤0.28	1.89	0.94	3.83	0.077	2.16	0.91	5.14	0.08	1.53	0.46	5.09	0.487
0.29–0.32	Reference											
≥0.33	3.04	1.52	6.07	0.002	4.14	1.80	9.55	0.001	1.20	0.32	4.48	0.782
Adjusted												
LHR group												
≤0.28	2.17	1.06	4.43	0.034	2.41	1.00	5.78	<0.05	2.04	0.59	6.95	0.254
0.29–0.32	Reference for LHR groups											
≥0.33	3.33	1.66	6.69	0.001	4.47	1.92	10.43	<0.001	1.20	0.32	4.47	0.789
Clinical parameters												
Age	1.04	1.01	1.07	0.011	1.05	1.01	1.09	0.009	1.02	0.96	1.08	0.587
CHF	2.14	1.26	3.65	0.005	2.34	1.30	4.22	0.005	0.88	0.25	3.11	0.841
BMI	0.98	0.94	1.03	0.421	0.97	0.92	1.02	0.246	1.04	0.94	1.14	0.441
Stress result												
No ischemia	Reference for stress results											
Scar	1.79	0.98	3.27	0.058	1.34	0.68	2.62	0.401	4.50	1.25	16.28	0.022
Ischemia	2.50	1.38	4.53	0.003	1.46	0.69	3.08	0.320	6.65	2.10	21.06	0.001

MI, myocardial infarction; UA, unstable angina; CHF, congestive heart failure; LHR, lung-to-heart ratio.

Fig. 2. Kaplan-Meier time-to-event curves. **a** Demonstrates the higher rate of the primary outcome among the low (≤0.28) and high (≥0.33) LHR tertiles compared to the middle group (0.29–0.32); $p = 0.004$. **b** Demonstrates the higher rate of mortality in the low and high LHR tertiles compared to the middle group; $p <$

0.001. **c** Demonstrates the relationship of LHR tertile and outcome of MI/UA/coronary revascularization; no significant difference was found, $p = 0.8$. LHR, lung-to-heart ratio; MI, myocardial infarction; UA, unstable angina.

(For figure see next page.)

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Differences between Patients with CKD-ND and ESKD

Online suppl. Table 2 demonstrates baseline characteristics and online suppl. Table 3 demonstrates stress test characteristics between CKD-ND and ESKD. Majority of tests in ESKD group was for pre-operative assessment (53.8 vs. 5.6% in CKD-ND, $p < 0.001$), of which 74.4% were for pre-kidney transplant evaluation. Quantitative results were similar across stages except for EF, which was lowest among those with ESKD (0.52 vs. 0.56 for CKD-ND, $p = 0.013$). LHR was similar across CKD stages. All outcomes were similar between CKD-ND and ESKD (online suppl. Table 4).

Sensitivity Analyses

Among the 41 ESKD patients for whom proximate hemodialysis information was available, 25 had a treatment <24 h prior to the stress test and 16 had a treatment >24 h prior to the stress test; mean LHR was similar between these 2 groups (0.32 vs. 0.30, respectively, $p = 0.17$). Additionally, there was no significant correlation between dialysis vintage and LHR value (correlation -0.07 , $p = 0.37$).

An analysis of heterogeneity of association of LHR category with outcomes among CKD-ND and ESKD was conducted and demonstrated no significant differences (shown in online suppl. Fig. 3a, b). For the mortality outcome, the addition of an elevated LHR to the finding of Ischemia on stress testing increased the area under the receiver operating curve from 0.512 to 0.634 (an improvement of 24%). Low LHR demonstrated no improvement over ischemia assessment (data not shown).

Discussion

This is the first study to examine the prognostic value of LHR, determined from pharmacologic stress nuclear single-photon emission computed tomography MPI, in patients with CKD-ND and ESKD. There were two important findings from this analysis. First, LHR is independently associated with a higher risk of mortality in this patient population. Second, there is an increased risk with both lower and higher values, relative to a reference range of 0.29–0.32, which is a novel finding with the use of LHR as a predictive marker.

High LHR demonstrated a significant association with all-cause mortality. The hazard associated with death with a stress LHR on sestamibi regadenoson stress MPI in patients with CKD and ESKD was 2.73 (95% CI 1.62–

8.99). Similar findings were reported by Leslie et al. [12] who conducted an analysis of the prognostic indicator of stress and rest LHR from sestamibi MPI in patients with, presumably, normal renal function. An elevated sLHR (0.36 vs. 0.31, $p < 0.0001$) was significantly associated with the primary outcome. In their analysis, there were a total of 81 deaths of which at least 1/3 were cardiac related. The reasons for a lack of association with ischemia-related events in the current analysis are not clearly discernible. Among the MPI results evaluated for this analysis, there were a minority of MPI studies with evidence of ischemia or peri-infarct ischemia (16% of all studies), suggesting the majority of these patients had non-ischemic cardiac disease, though coronary angiography was not available to confirm these findings. On the other hand, Bangalore et al. [26] have previously demonstrated that different parameters on stress echocardiography may provide differential prognostic information. They demonstrated that while ischemic extent was the strongest stress parameter predictor ($\chi^2 = 13.8$, $p < 0.001$) associated with non-fatal myocardial infarction, EF was the strongest ($\chi^2 = 217.3$, $p < 0.001$) predictor of cardiac death. The current findings are consistent with these in that stress result was the only variable significantly associated with MI/UA/revascularization, whereas LHR was associated with death.

It has been accepted that elevated pulmonary uptake of radiotracer-associated moieties such as thallium and sestamibi represents a marker of elevated lung water content and slower lung transit time due to elevated pulmonary capillary wedge pressure [13]. Stress LHR from sestamibi MPI has been associated with LV function [15], EF [27], and pulmonary capillary wedge pressure and LV end diastolic pressure [16]. In the current analysis mean calculated EF was lower (52%) for the highest tertile of LHR as compared to the lowest tertile (55%), $p = 0.039$; though the mean values identified would not meet criteria for HF with reduced EF (<40%). It is well established that the intersection of HF and CKD represents a state of marked elevation in mortality [28–30]. On the contrary, an elevated LHR maintained independent prediction for mortality after correction for a history of HF. More detailed measures such as pulmonary capillary wedge pressures were not available for this analysis and may help better characterize the representation of LHR of cardiac function.

Additionally, low LHR was also associated with the primary outcome and mortality after adjustment for Leslie et al. [12] characterized their cohort into tertiles like the current analysis, but the lowest risk of outcomes was seen in the lowest tertile of LHR. The finding of a low LHR

or near absent lung uptake has been described in a case report of severe underlying emphysematous lung changes [31]. In the current cohort, there was no difference in history of chronic obstructive pulmonary disease or emphysema between the tertiles. Additional variables of cardiac and pulmonary function (e.g., echocardiographic data, right heart catheterization pressure information, and pulmonary function tests) were not available for this analysis. BMI was associated with LHR with low LHR having lowest BMI and vice versa. Low BMI is associated with mortality in advanced CKD and ESKD [30]. However, addition of BMI in multivariable analysis only partly attenuated low LHR association with mortality, but not eliminated. Mechanisms of the association between BMI and LHR are not known.

Limitations

This is a single center US Veteran's Affairs institution study with a typical US Veteran population (older and males), thus generalization is limited. Second, despite having dialysis information on a small subset to estimate the effect of volume status, no direct measure (such as natriuretic peptide level or physical exam) was available to accurately distinguish volume overloaded from euvolemic. Third, the findings from this analysis cannot be applied to patients with a kidney transplant as they were not included. Fourth, coronary angiography was not available in all patients to ascertain the performance of LHR in predicting CAD. Fifth, the total event rate (mortality and cardiac specific) was low. The low overall mortality rate is possibly related to the high proportion of African Americans in the ESKD cohort [30].

Despite these limitations the finding of association of an elevated and possibly low LHR with outcomes serves as a potential novel contribution as an ancillary marker in MPI in the CKD/ESKD population, with evidence of some diagnostic test improvement when considered along with traditional ischemia assessment. This is especially relevant given that the majority of tests in this cohort were essentially negative (no ischemia or attenuation artifact in over 60% in each LHR category).

Conclusion

The current analysis has demonstrated that LHR is significantly associated with mortality in patients with CKD-ND and ESKD (primarily on HD). This finding remained after multivariable risk assessment, including other standard parameters of ischemia derived from stress testing.

This is the first demonstration of the prognostic capability of LHR in the CKD-ND and ESKD population. In addition, for the first time, an association with mortality was identified for low LHR as well as a direct relationship between BMI and LHR. The reasons for these associations could not be determined from the current dataset and deserve specific evaluation in larger populations. Nevertheless, the findings highlight the importance of utilizing the multitude of data points derived from a complicated diagnostic test such as MPI.

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Statement of Ethics

This study was approved under expedited review through the Columbia VA HCS Institutional Review Board and Research and Development Committees.

Conflict of Interest Statement

The authors note no disclosures to report regarding this analysis.

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Author Contributions

Design and implementation of analysis: R.O.M., M.S.S., and S.B. Data acquisition, analysis, and initial draft composition: R.O.M. and J.B. Critical review and composition of revisions: R.O.M., J.B., J.A.S., J.R., R.W., C.A.H., M.S.S., A.A., and S.B. Final version review and acceptance: R.O.M., J.B., J.A.S., J.R., R.W., C.A.H., M.S.S., A.A., and S.B.

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