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Echocardiography to Screen for Pulmonary Hypertension in CKD

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Introduction: Pulmonary hypertension (PH) is a common yet incompletely understood complication of chronic kidney disease (CKD). Although transthoracic echocardiogram is commonly used to noninvasively estimate PH, it has not been validated in a CKD population. We investigated the utility of this diagnostic tool for CKD-associated PH in a large right heart catheterization (RHC) cohort.

Methods: We reviewed RHC and echocardiography data in 4036 patients (1714 with CKD) obtained between 2011 and 2014 at a single center. We used multivariate regression to determine the associations of echocardiography measurements with PH, and evaluated whether estimated glomerular filtration rate (eGFR) modified these associations. Using internal validation, we sequentially added measurements to predictive models and analyzed the incremental predictive performance using the change in the area under the receiver operating characteristic curve (ΔAUC) and net reclassification improvement.

Results: The echocardiography measurements most strongly associated with the diagnosis of PH included tricuspid regurgitant velocity (TRV), tricuspid annular plane systolic excursion (TAPSE), right atrial pressure, diastolic dysfunction, and right ventricular function. Among these measurements, eGFR significantly modified the associations of TAPSE and diastolic dysfunction with the diagnosis of PH. The model consisting of a combination of TRV, right atrial pressure, and TAPSE most accurately predicted the diagnosis of PH in a CKD population (AUC 0.82).

Conclusions: The optimal model to predict PH diagnosis included TRV, right atrial pressure, and TAPSE. Since TAPSE more strongly associated with PH in the CKD population, these findings support a CKD-specific approach to the development of noninvasive screening algorithms for PH.

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PH disproportionately affects persons with CKD and end-stage kidney disease: PH is present in approximately 20% to 25% of persons with CKD and up to half of those with end-stage kidney disease.[1–6] CKD-associated PH also substantially increases risks of cardiovascular events and mortality.[3,7,8] Unlike other states of chronic or episodic volume overload such as heart failure, CKD introduces additional factors which directly influence vascular biology and increase the risk of PH. These factors include increases in asymmetric dimethylarginine, serotonin, and endothelin-1, among others.[9–11] Hemodialysis further increases markers of endothelial cell injury.[12] Select retrospective analyses of RHC data suggest that the hemodynamic profile and survival of CKD-associated PH may differ from other populations, especially in regards to the prevalence of combined pre- and post-capillary PH.[13] The unique pathophysiology of CKD-associated PH warrants targeted evaluation of the diagnostic tools in a dedicated CKD cohort instead of assuming that results from other populations can be extrapolated to CKD.

Although RHC is the gold standard for the diagnosis of PH,[14,15] the invasive nature of this procedure limits its use for large-scale screening. Echocardiography is the most widely used noninvasive method to screen for PH, monitor disease progression, and track response to treatment. For example, nephrologists commonly rely on echocardiography to screen prospective kidney

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transplantation candidates for various cardiovascular complications, including PH, which may affect peri- and post-transplantation outcomes.[16] The performance of echocardiography in such cases is crucial because a poorly sensitive test precludes any effort to reduce cardiovascular risk pretransplantation; conversely, a nonspecific test may inappropriately subject patients to invasive procedures or disqualify them from a transplantation altogether. Despite the widespread use of echocardiography screening for CKD-associated PH, the performance of this diagnostic tool for PH has not been validated in a CKD population.

Whether alone or in combination with estimates of right atrial pressure,[17] TRV forms the backbone of echocardiography-based PH screening.[14,18] However, approximately 35% of echocardiograms cannot measure TRV due to technical limitations.[19] Furthermore, absence of TRV does not denote absence of PH: 47% of patients with missing TRV have PH on RHC.[19] Therefore, even if TRV performs well in persons with CKD, investigation into alternative echocardiography measurements may yield substantial benefit for persons with missing TRV.

To address these critical questions, we aimed to determine how well currently used echocardiography measurements predict the diagnosis of PH by RHC. We explored the performance of other commonly available echocardiography data, especially when TRV is absent, and we determined whether measurements perform differently in persons with versus without CKD. Finally, we analyzed how combinations of echocardiography measurements may improve correct detection of PH in CKD.

METHODS

Data Sources and Population

The study cohort included all adult patients (aged ≥18 years) who underwent RHC at Duke University Hospital from January 1, 2011, through December 31, 2014, as collected in the Duke Databank for Cardiovascular Disease. Exclusion criteria included the absence of hemodynamic data on RHC, echocardiography, or creatinine data within 6 months of catheterization; acute coronary syndrome at the time of catheterization; prior kidney transplantation; or catheterization performed for evaluation of heart or lung transplantation. The first qualifying RHC for each patient was included in this analysis; repeat RHCs were excluded. This study was approved by the Duke University Health Systems Institutional Review Board.

Echocardiography Measurements

All echocardiograms were obtained in the context of clinical care within 6 months of the RHC. We selected echocardiography measurements *a priori* based on known associations with PH or prognosis in other populations, including left ventricular ejection fraction, TRV, TAPSE, left atrial anteroposterior diameter, and mid–right ventricular diameter. Right atrial pressure was estimated from inferior vena cava size and respiratory variation; this estimate resulted in three categories: 3 mm Hg, 8 mm Hg, and 15 mm Hg. Diastolic dysfunction was classified into two groups: normal/grade 1 and ≥grade 2 dysfunction. Qualitative assessment of right ventricular function was organized into three groups: normal or mildly decreased, moderately decreased, and severely decreased. For comparison across severity of CKD, we categorized right ventricular function as normal or abnormal.

Kidney Function

Using the CKD Epidemiology Collaboration equation, we calculated the eGFR from the median of all creatinine data from the 6-month period before the RHC, as described previously.[7] Proteinuria data was insufficiently complete to contribute to CKD classification. The CKD cohort included all patients with an eGFR <60 ml/min per 1.73 m^2 or those receiving dialysis. For comparison of data across the spectrum of CKD, we grouped patients into the following categories: moderate/severe CKD (dialysis or eGFR <30 ml/min per 1.73 m^2), mild CKD (eGFR 30 to 59 ml/min per 1.73 m^2), or no CKD (eGFR ≥60 ml/min per 1.73 m^2).

Covariates

In addition to demographics (age, sex, and race), we collected covariates that have exhibited strong prior associations with PH diagnosis, prognosis, and/or mortality. These included body mass index and diagnosis of hypertension, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, obstructive sleep apnea, systemic lupus erythematosus, or scleroderma. We omitted chronic obstructive pulmonary disease from multivariate regression analyses because of the limited number of cases.

Outcomes

Based on the newly revised and currently accepted definition,[14,15] we defined PH as a mean pulmonary artery pressure of >20 mm Hg on RHC. We also performed sensitivity analyses for the univariate and multivariate logistic regression models with a mean pulmonary artery pressure cutoff of ≥25 mm Hg, consistent with the previous definition of PH. The results of these analyses did not significantly alter the findings of this study (Supplemental Material).

Table 1. Baseline characteristics stratified by PH diagnosis (revised criteria)[a]

Characteristic	Total cohort (N = 1714)	PH (n = 1489)	No PH (n = 225)	*P* value
Age, yr	69.1 ± 12.3	68.8 ± 12.3	70.7 ± 11.9	0.03
Female	795 (46)	700 (47)	95 (42)	0.20
Race				<0.001
White	1239 (73)	1052 (71)	187 (84)	
Black	412 (24)	380 (26)	32 (14)	
Native American	3 (0.2)	3 (0.1)	1 (0.5)	
Other	47 (3)	43 (3)	4 (2)	
eGFR, ml/min per 1.73 m^2	41.2 ± 13.3	40.6 ± 13.4	45.2 ± 11.7	<0.001
BMI, kg/m^2	29.7 ± 7.4	30.1 ± 7.6	27.2 ± 5.4	<0.001
HTN	1183 (69)	1022 (69)	160 (71)	0.50
Heart failure	1324 (77)	1187 (80)	137 (61)	<0.001
Diabetes	588 (34)	538 (36)	50 (22)	<0.001
COPD	9 (0.5)	8 (0.5)	1 (0.4)	0.55
OSA	182 (11)	168 (11)	14 (6)	0.03
SLE	25 (2)	20 (1)	5 (2)	0.47
Scleroderma	16 (0.9)	14 (0.9)	2 (0.9)	0.99
TAPSE, cm	1.7 ± 0.6	1.7 ± 0.5	2.0 ± 0.6	<0.001
TRV, m/s	3.1 ± 0.7	3.1 ± 0.7	2.5 ± 0.4	<0.001
LVEF (IQR)	50.0 (30.0, 55.0)	50.0 (30.0, 55.0)	55.0 (39.6, 55.0)	0.01
RAP, mm Hg				<0.001
3	687 (48)	558 (45)	129 (78)	
8	324 (23)	297 (24)	27 (16)	
15	409 (29)	400 (32)	9 (6)	
Left atrial dimension, cm	4.4 ± 0.8	4.5 ± 0.8	4.0 ± 0.8	<0.001
Diastolic dysfunction				<0.001
Normal	40 (5)	32 (5)	8 (6)	
Grade 1	396 (50)	296 (44)	100 (78)	
Grade 2	91 (11)	82 (12)	9 (7)	
Grades 3–4	273 (34)	261 (39)	12 (9)	
RV function				<0.001
Normal	875 (57)	719 (53)	156 (84)	
Mild decrease	312 (20)	295 (22)	17 (9)	
Moderate decrease	255 (17)	247 (18)	8 (4)	
Severe decrease	89 (6)	85 (6)	4 (2)	
RV dimension, mid, cm	3.2 ± 0.9	3.3 ± 0.9	2.6 ± 0.7	<0.001

BMI, body mass index; COPD; chronic obstructive pulmonary disease; HTN, hypertension; IQR, interquartile range; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; SLE, systemic lupus erythematosus; TAPSE; tricuspid annular systolic plane excursion; TRV, tricuspid regurgitant velocity.
[a]Values shown are n (%) unless otherwise stated.

Statistical Analyses

We used descriptive statistics to report baseline covariates and echocardiography parameters stratified by the presence or absence of PH by RHC. We expressed categorical data as number and percentage of patients, and continuous data as mean ± SD or median (interquartile range) for nonparametric data. We used unpaired Student *t* tests to compare normally distributed continuous variables, Wilcoxon rank sum tests to compare nonparametric continuous variables, and chi-square tests to compare proportions of categorical variables.

To determine the association of each echocardiography parameter with PH diagnosis, we constructed univariate and multivariate logistic regression models. We adjusted the multivariate models for the following covariates: age, sex, race, body mass index, hypertension, heart failure, diabetes mellitus, obstructive sleep apnea, systemic lupus erythematosus, and scleroderma. All patients had complete data for the outcome. Certain parameters were not reported in all echocardiograms either due to a provider request for a limited study or inability to measure the parameter. Also, select parameters (e.g., TAPSE) were not routinely reported until after the start of the study period. To account for these scenarios, regression models included only the patients with a reported value for the respective echocardiography measurement. In addition, we repeated all univariate and multivariate logistic regression models for each echocardiography measurement solely in persons with missing TRV data to determine if other measurements associate with PH in

absence of TRV. All covariates had <1% missingness; in these cases, we imputed the respective mean of the missing covariate. We assessed multicollinearity between covariates for each model using the variance inflation factor, which was <5 for each model, suggesting no significant multicollinearity.

To determine if echocardiography parameters associate differently across different severity of CKD, we repeated multivariate logistic regression after stratifying by CKD severity. We adjusted these models for age, sex, race, body mass index, diabetes, hypertension, and heart failure. We then tested for potential effect modification of eGFR on the association between each echocardiography measurement and the diagnosis of PH using tests for interaction.

We calculated the optimal binary cutpoint for each continuous echocardiography measurement which minimized the difference between sensitivity and specificity using the R package "cutpointr" (version 1.0.2). To evaluate the incremental diagnostic performance of each measurement, we first constructed a base model from the clinical covariates. To facilitate these analyses, we used multiple imputations by chained equations R package (version 3.11.0) to generate five imputed datasets using predictive mean matching (continuous variables), logistic regression (categorical variables), and proportional odds logistic regression (ordinal data). We then divided each imputed dataset into model derivation (70%) and verification (30%) cohorts. We used penalized Lasso regression to generate a parsimonious predictive model which restricted model error (lambda) to less than 1 standard error from the minimum. The covariates selected in >50% of imputed datasets were included in the final base model. Race, history of heart failure, and diagnosis of diabetes remained in the base model after penalized regression. We used two tests of model discrimination in the validation cohort: ΔAUC and continuous net reclassification index. The AUCs and ΔAUCs were calculated using the R package "pROC" (version 1.16.2). Given the absence of clinically applicable risk categories, we calculated the continuous net reclassification improvement (NRI) which provides a summary statistic which reflects the correct and incorrect changes in risk classification for cases (NRI+) and controls (NRI-); the maximum possible value for the continuous NRI is 2.0 (100% correct upward deflection of risk for cases and 100% downward risk deflection for controls). We used the R package "nricens" (version 1.6) to calculate continuous NRI. To account for multiple imputations, we combined model output using Rubin's rules and generated 95% confidence intervals using bootstrap resampling with 1000 bootstrap replicates. As a sensitivity analysis, we repeated the model discrimination analyses for the addition of each echocardiogram measurement to the base model after exclusion of all cases of isolated post-capillary pulmonary hypertension. All statistical analyses were conducted using R version 3.6.3.

RESULTS

Characteristics of the Study Population

Of a total of 4036 patients, 1714 patients had CKD. The median time between the echocardiogram and RHC is -2 days (interquartile range, -11 days to 0 days). The prevalence of PH was 72.7% for patients without CKD and 86.9% for patients with CKD. Table 1 presents the baseline characteristics and echocardiography data for the CKD cohort stratified by the diagnosis of PH. Patients with PH were younger than those without PH. PH was also overrepresented in patients of black race. The eGFR was significantly lower in persons with PH compared to those without PH. Heart failure and diabetes were more common in patients with PH. All echocardiography parameters differed significantly between patients with and without PH. Among the notable comparisons to patients without PH, patients with PH had a lower mean TAPSE (1.7 ± 0.5 cm vs. 2.0 ± 0.6 cm), higher mean TRV (3.1 ± 0.7 m/s vs. 2.5 ± 0.4 m/s), higher prevalence of elevated right atrial pressure, higher prevalence of abnormal right ventricular function, and larger mean mid-right ventricular diameter (3.3 ± 0.9 cm vs. 2.6 ± 0.7 cm). The median right atrial pressure by echocardiogram was 8 mm Hg (interquartile range, 3 to 15 mm Hg) compared to 10 mm Hg (interquartile range, 6 to 15 mm Hg) by right heart catherization ($r = 0.5$; $P < 0.001$).

Association of Echocardiography Measurements With PH in CKD

Table 2 presents the unadjusted and adjusted odds ratios for the association of echocardiography measurements with the diagnosis of PH in patients with CKD. Each 1-cm increase in TAPSE was associated with a greater than 60% reduction in the odds of PH. Each 1-m/s increase in TRV was associated with 6.7-fold increased odds of PH. Compared to a normal estimated right atrial pressure (3 mm Hg), severely elevated right atrial pressure (15 mm Hg) was associated with nearly 10-fold increased odds of PH. Each 1-cm increase in left atrial diameter was associated with increased odds of PH. Severe diastolic dysfunction and moderate-severely reduced ventricular function associated with more than 6-fold increased odds of PH. Each 1-cm increase in right ventricular diameter associated with nearly 3-fold increased odds of PH.

Table 2. Association of echocardiography parameters with PH diagnosis (revised criteria)

Parameter	N	Unadjusted OR (95% CI)	P	Adjusted[a] OR (95% CI)	P
TAPSE (per 1 cm increase)	1019	0.37 (0.26–0.51)	<0.001	0.39 (0.27–0.55)	<0.001
TRV (per 1 m/s increase)	1012	5.85 (3.80–9.28)	<0.001	6.74 (4.23–11.14)	<0.001
LVEF (per 10% increase)	1138	0.85 (0.75–0.96)	0.008	0.85 (0.74–0.97)	0.02
LVEF (<55% vs. ≥55%)	1138	1.45 (1.00–2.09)	0.05	1.37 (0.93–2.10)	0.11
RAP, mm Hg	1420				
3		1 (ref)		1 (ref)	
8		2.54 (1.67–4.01)	<0.001	2.51 (1.62–4.03)	<0.001
15		10.27 (5.47–21.98)	<0.001	9.95 (5.21–21.51)	<0.001
Left atrial dimension, (per 1 cm increase)	1360	2.02 (1.65–2.50)	<0.001	2.09 (1.66–2.66)	<0.001
Diastolic dysfunction	800				
Normal/grade 1		1 (ref)		1 (ref)	
≥Grade 2		5.38 (3.36–9.01)	<0.001	6.03 (3.53–10.69)	<0.001
RV function	1531				
Normal		1 (ref)		1 (ref)	
Mild decrease		3.77 (2.31–6.55)	<0.001	4.02 (2.42–7.11)	<0.001
Moderate/severe decrease		6.00 (3.43–11.5)	<0.001	6.38 (3.56–12.5)	<0.001
RV dimension, mid (per 1 cm increase)	830	2.93 (2.12–4.14)	<0.001	2.97 (2.11–4.28)	<0.001

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; TAPSE; tricuspid annular systolic plane excursion; TRV, tricuspid regurgitant velocity.
[a]Adjusted for age, sex, body mass index, hypertension, heart failure, diabetes, obstructive sleep apnea, systemic lupus erythematosus, and scleroderma.

To determine if the relationship of each factor with the diagnosis of PH differs in persons without reported TRV, we repeated the analysis after excluding patients with missing TRV (Table 3). Although the strength of the association with PH diminished for each measurement, most remained significantly associated with PH, including severe elevations in right atrial pressure, severe diastolic dysfunction, moderate-severely reduced right ventricular function, and right ventricular diameter. The association between TAPSE and PH no longer reached statistical significance.

Influence of CKD on the Association Between Echocardiography Measurements and PH

The eGFR significantly modified the association between TAPSE, left atrial diameter, and diastolic dysfunction with the diagnosis of PH (Figure 1). In each case, the association between the measurement and the diagnosis of PH was stronger in persons with CKD. Although the point estimates for mid-right ventricular diameter increased with the severity of CKD, the eGFR interaction term did not reach significance. The association of other measurements with PH was not modified by eGFR.

Table 3. Association of echocardiography parameters with PH diagnosis in persons without TRV reported

Parameter	N	Unadjusted OR (95% CI)	P	Adjusted[a] OR (95% CI)	P
TAPSE (per 1 cm increase)	295	0.64 (0.39–1.04)	0.07	0.63 (0.37–1.08)	0.09
LVEF (per 10% increase)	396	1.02 (0.86–1.20)	0.80	0.99 (0.81–1.20)	0.92
LVEF (<55% vs. ≥55%)	396	0.95 (0.57–1.58)	0.83	1.01 (0.57–1.79)	0.97
RAP, mm Hg	465				
3		1 (ref)		1 (ref)	
8		1.36 (0.74–2.66)	0.34	1.37 (0.71–2.80)	0.37
15		3.53 (1.50–10.40)	0.01	3.51 (1.44–10.57)	0.01
Left atrial dimension, (per 1 cm increase)	426	1.93 (1.39–2.73)	<0.001	1.79 (1.22–2.68)	0.004
Diastolic dysfunction	281				
Normal/grade 1		1 (ref)		1 (ref)	
≥Grade 2		3.42 (1.76–7.23)	<0.001	4.30 (2.02–9.85)	<0.001
RV function	522				
Normal		1 (ref)		1 (ref)	
Mild decrease		1.43 (0.76–2.89)	0.30	1.78 (0.89–3.78)	0.12
Moderate/severe decrease		3.05 (1.30–8.95)	0.02	3.68 (1.46–11.43)	0.01
RV dimension, mid (per 1 cm increase)	218	3.20 (1.84–5.97)	<0.001	2.95 (1.61–5.92)	0.001

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; TAPSE; tricuspid annular systolic plane excursion; TRV, tricuspid regurgitant velocity.
[a]Adjusted for age, sex, body mass index, hypertension, heart failure, diabetes, obstructive sleep apnea, systemic lupus erythematosus, and scleroderma.

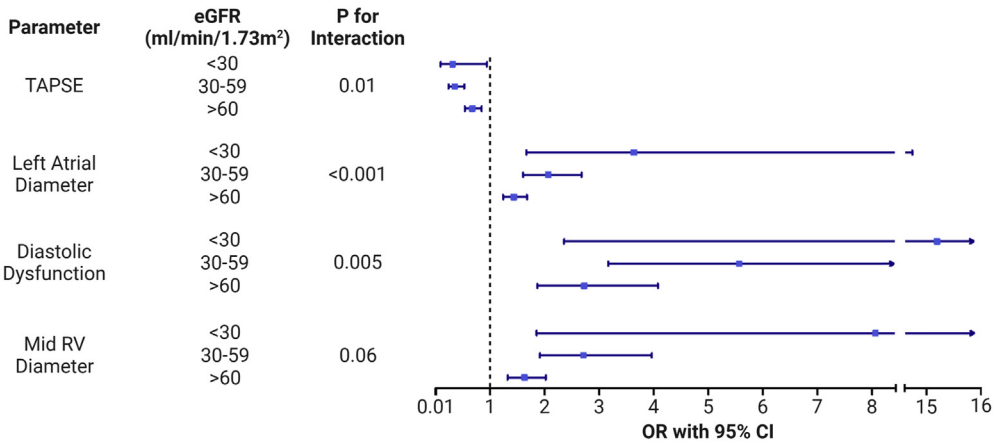

Figure 1. Effect modification of estimated glomerular filtration rate (eGFR) on the association between echocardiography parameters and pulmonary hypertension (PH) diagnosis stratified by severity of chronic kidney disease (CKD). For diastolic dysfunction, the combination of normal and grade 1 diastolic dysfunction served as the referent group. Odds ratios (ORs) for tricuspid annular systolic plane excursion (TAPSE), left atrial diameter, and mid–right ventricular (RV) diameter are per 1 cm increase. CI, confidence interval.

Performance of Echocardiography-Based Diagnostic Models for PH in CKD

After we derived the optimal cutpoint for each continuous measurement which minimized the difference between sensitivity and specificity for the diagnosis of PH (Supplemental Material), we analyzed the incremental changes in diagnostic performance above a base model of clinical factors for each echocardiography measurement in the subgroup of patients with CKD (Table 4). Among factors associated with PH on multivariate analyses, TRV showed the most substantial improvement in diagnostic accuracy above the base model of clinical predictors. The performance of each measurement was similar when we excluded cases of isolated pre-capillary pulmonary hypertension (Supplemental Material). When measurements were compared to a base model which contains TRV, the addition of left atrial diameter and right ventricular dimension no longer improved diagnostic accuracy; the addition of right atrial pressure provided the most

Table 4. Prediction of PH diagnosis

Model comparison	AUC base	AUC new	ΔAUC (95% CI)	NRI (95% CI)
Performance above BM				
BM[a] + TAPSE	0.66	0.72	0.05 (0.04–0.06)	0.74 (0.71–0.77)
BM + TRV	0.66	0.75	0.09 (0.07–0.10)	1.03 (0.96–1.12)
BM + RAP	0.66	0.76	0.09 (0.09–0.10)	0.62 (0.56–0.69)
BM + left atrial dimension	0.66	0.69	0.03 (0.03–0.03)	0.89 (0.87–0.91)
BM + diastolic dysfunction	0.66	0.69	0.03 (0.01–0.05)	0.52 (0.44–0.59)
BM + RV function	0.66	0.73	0.07 (0.06–0.07)	0.54 (0.50–0.57)
BM + RV dimension	0.66	0.71	0.05 (0.03–0.06)	0.79 (0.67–0.90)
Performance above TRV BM				
(BM + TRV) + TAPSE	0.75	0.78	0.03 (0.02–0.05)	1.13 (1.07–1.20)
(BM + TRV) + RAP	0.75	0.81	0.06 (0.04–0.08)	0.59 (0.54–0.65)
(BM + TRV) + Left atrial dimension	0.75	0.76	0.01 (-0.01 to 0.030)	1.12 (1.09–1.16)
(BM + TRV) + diastolic dysfunction	0.75	0.75	0.00 (-0.03 to 0.03)	0.55 (0.47–0.63)
(BM + TRV) + RV function	0.75	0.78	0.03 (0.02–0.05)	0.51 (0.47–0.56)
(BM + TRV) + RV dimension	0.75	0.78	0.02 (-0.004 to 0.05)	1.11 (0.97–1.26)
Performance above modified Bernoulli BM				
(BM + TRV + RAP) + TAPSE	0.81	0.82	0.01 (0.003–0.02)	1.03 (1.01–1.06)
(BM + TRV + RAP) + lLeft atrial dimension	0.81	0.81	0.00 (-0.01 to 0.01)	1.16 (1.07–1.26)
(BM + TRV + RAP) + diastolic dysfunction	0.81	0.79	-0.02 (-0.04 to 0.01)	0.63 (0.45–0.81)
(BM + TRV + RAP) +RV function	0.81	0.81	0.00 (-0.01 to 0.01)	0.29 (0.05–0.52)
(BM + TRV + RAP) +RV dimension	0.81	0.81	0.00 (-0.01 to 0.02)	1.08 (0.95–1.21)

AUC, area under the receiver operating characteristic curve; BM, base model; CI, confidence interval; NRI, net reclassification improvement; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitant velocity.
[a]Base model includes race, diagnosis of heart failure, and diagnosis of diabetes.

substantial increase in performance by ΔAUC. Based on the modified Bernoulli equation, we then compared the addition of each factor to a base model containing TRV and right atrial pressure in addition to clinical predictors. The addition of TAPSE further improved the predictive performance of this model.

DISCUSSION

The substantial burden of CKD-associated PH necessitates an improved diagnostic and therapeutic approach. A robust, noninvasive means to screen for PH would accelerate efforts to understand the scope, pathogenesis, and optimal treatment of PH in this population. In our study, the echocardiography measurements most strongly associated with the diagnosis of PH in persons with CKD included TRV, TAPSE, right atrial pressure, diastolic dysfunction, right ventricular function, and right ventricular diameter. Among these measurements, eGFR significantly modified the associations of TAPSE, left atrial diameter, and diastolic dysfunction with the diagnosis of PH. After establishing diagnostic cutoffs for continuous measurements, we showed that a model containing a combination TRV, right atrial pressure, and TAPSE most accurately predicted the diagnosis of PH in a CKD population.

Both the physiologic risk factors and sequelae of PH provide candidate measurements to estimate PH by echocardiography. We report both left-heart (diastolic dysfunction, left atrial diameter) and right-heart (TRV, TAPSE, right atrial pressure, right ventricular function, and right ventricular diameter) measurements which significantly associate with the diagnosis of PH in our CKD cohort. As expected, TRV most strongly associates with the diagnosis of PH. However, given the exclusion of TRV from nearly 35% of echocardiograms,[19] we separately analyzed the association of each measurement in persons with missing TRV. In such cases, we observed that most other measurements remained significantly associated with PH. Although this notable finding must be confirmed in other CKD cohorts, this suggests that alternative measurements or models may provide a successful alternative when TRV is not measurable.

This study is the first to our knowledge to investigate how these echocardiography measurements perform in a dedicated CKD population. As with many other facets of CKD care, extrapolation from other populations may yield incomplete or inaccurate information regarding the management of persons with CKD. We report that eGFR significantly modifies the association between multiple key measurements and the diagnosis of PH; in each case, the presence of CKD conveyed a stronger association between the measurement and PH in persons with CKD. Select observations may explain why the relationship between certain measurements and PH may differ in persons with CKD. We previously reported a unique hemodynamic subtype distribution and worse survival for persons with CKD and PH[13]; this finding suggests that the underlying pathophysiology of CKD-associated PH may differ from other chronic diseases. This unique pathophysiology may be driven by the combination of chronic volume overload and altered inflammatory markers, mineral metabolites, and endothelium-derived factors which promote left ventricular hypertrophy,[20–22] accelerate vascular calcification,[23,24] and adversely affect systemic and pulmonary vascular biology in CKD.[10,25] Further research is needed to confirm that the relationship between these measurements and PH also differs in other CKD cohorts; define which of these putative mechanisms contribute most to this altered relationship; and determine whether the prognostic information conveyed by these measurements also differs in CKD.

Given the potential overlap between select echocardiography measurements, even measurements which strongly associate with PH may not add incremental value to predict the diagnosis of PH above a model consisting of factors which convey similar predictive information. We used two assessments of this incremental predictive performance: ΔAUC and NRI. When added to a base model of clinical predictors, TRV produced the most substantial improvement in model performance. Consistent with prior studies in other populations, the addition of TRV and right atrial pressure to a base model of clinical predictors performed better than either measurement alone.[26] These measurements are often combined using the modified Bernoulli equation to estimate systolic pulmonary artery pressure.[26,27] Despite concerns regarding the accuracy of right atrial pressure by echocardiogram,[28] the estimated right atrial pressure aligned relatively well with the invasive measurement in our study cohort. TAPSE further improved the predictive performance above a base model inclusive of TRV and right atrial pressure. This finding is notable for several reasons. First, we show that measurements beyond TRV and right atrial pressure may improve the noninvasive estimation of PH diagnosis. In addition, because we showed that TAPSE more strongly associates with PH diagnosis in CKD, these data support the investigation of CKD-specific prediction models for the diagnosis of PH that include TAPSE.

We acknowledge several limitations to our current study. The patients included in this study were referred for RHC in the context of clinical care spanning the 5-year period between 2011 and 2014. Thus, some newer measurements which may further

influence the performance of echocardiography prediction of PH diagnosis were not available for this study. Additionally, data collection in the context of clinical care results in an enriched study population more likely to have both abnormal echocardiogram and RHC values. Whereas this bias may inflate the performance of select echocardiogram measurements, the nature of this population may also bias the ΔAUCs towards the null because detection of incremental performance between models is more difficult in homogenous populations.[29] Although indices of right ventricular size and function strongly associated with PH in our study, severe right ventricular dysfunction may paradoxically lower the pulmonary artery pressure and evade detection of PH in select patients.[30] Although TRV is difficult to measure in certain cases, select maneuvers, such as the use of contrast or agitated saline, may improve the ability to measure TRV[31]; we were not able to standardize or capture the use of these techniques in this study. We also could not control for reversible volume overload, especially regarding the timing of the echocardiogram or catheterization relative to hemodialysis in persons with end-stage kidney disease. Lastly, the classification of baseline kidney function was based on creatinine data from the 6 months before catheterization and may be inaccurate in some patients. These limitations affirm the need to verify our study findings in a prospective, asymptomatic cohort.

In conclusion, we report the first study of the use of echocardiography measurements to estimate the diagnosis of PH by RHC in a dedicated CKD population. For select measurements, including TAPSE, eGFR significantly modifies the association between the measurement and the diagnosis of PH. Through sequential addition of each measurement to predictive models, we determined that the optimal model to predict PH diagnosis included TRV, right atrial pressure, and TAPSE. Together, these findings not only identify effective estimates for PH in persons with CKD, but also support a CKD-specific approach to the development of noninvasive screening algorithms for PH.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Baseline characteristics stratified by previous PH diagnosis.

Table S2. Baseline characteristics stratified by training and validation datasets.

Table S3. Association of echocardiography parameters with prior PH diagnostic criteria.

Table S4. Optimal cutpoints for continuous echocardiography measurements.

Table S5. Distribution of pulmonary hypertension subtypes by cohort.

Table S6. Prediction of PH diagnosis after exclusion of isolated post-capillary PH.

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