

Original article

Study of left ventricular systolic dysfunction, left ventricular diastolic dysfunction and pulmonary hypertension in CKD 3b-5ND patients—A single centre cross-sectional study

Shivendra Singh^a, Vikas Aggarwal^b, Umesh Kumar Pandey^b, H.C. Sreenidhi^{a,*}

^a Department of Nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

^b Department of Cardiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

ARTICLE INFO

Article history:

Received 20 January 2022

Accepted 3 June 2022

Available online 22 June 2022

Keywords:

CKD

LVDD

LV systolic dysfunction

Pulmonary hypertension

ABSTRACT

Introduction: Cardiovascular diseases are associated with increased morbidity and mortality among CKD (chronic kidney disease) population. Recent studies have found increasing prevalence of PH (pulmonary hypertension) in CKD population. Present study was done to determine prevalence and predictors of LV (left ventricular) systolic dysfunction, LVDD (left ventricular diastolic dysfunction) and PH in CKD 3b-5ND (non-dialysis) patients. **Methods:** A cross sectional observational study was done from Jan/2020 to April/2021. CKD 3b-5ND patients aged ≥ 15 yrs were included. Transthoracic 2D (2 dimensional) echocardiography was done in all patients. PH was defined as if PASP (pulmonary artery systolic pressure) value above 35 mm Hg, LV systolic dysfunction was defined as LVEF (left ventricular ejection fraction) $\leq 50\%$ and LVDD as E/e' ratio >14 respectively. Multivariate logistic regression model was done to determine the predictors.

Results: A total of 378 patients were included in the study with 103 in stage 3b, 175 in stage 4 and 100 patients in stage 5ND. Prevalence of PH was 12.2%, LV systolic dysfunction was 15.6% and LVDD was 43.65%. Predictors of PH were duration of CKD, haemoglobin, serum 25-OH vitamin D, serum iPTH (intact parathyroid hormone) and serum albumin. Predictors of LVDD were duration of CKD and presence of arterial hypertension. Predictors of LV systolic dysfunction were eGFR (estimated glomerular filtration rate), duration of CKD, serum albumin and urine protein.

Conclusion: In our study of 378 CKD 3b-5ND patients prevalence of PH was 12.2%, LV systolic dysfunction was 15.6% and LVDD was 43.65%.

© 2022 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author.

E-mail address: sreenidhi1024@gmail.com (H.C. Sreenidhi).

<https://doi.org/10.1016/j.nefro.2022.06.001>

0211-6995/© 2022 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Estudio de la disfunción sistólica ventricular izquierda, disfunción diastólica ventricular izquierda e hipertensión pulmonar en pacientes con ERC 3b-5ND – un estudio transversal en un solo centro

RESUMEN

Palabras clave:

CKD
LVDD
Disfunción sistólica del VI
Hipertensión pulmonar

Introducción: Las enfermedades cardiovasculares se asocian a un aumento de la morbilidad y la mortalidad entre la población con enfermedad renal crónica (ERC). Estudios recientes han encontrado un aumento de la prevalencia de la hipertensión pulmonar (HP) en la población con ERC. El presente estudio se llevó a cabo para determinar la prevalencia y los predictores de la disfunción sistólica del ventrículo izquierdo (VI), la disfunción diastólica del VI y la hipertensión pulmonar en pacientes con ERC 3b -5ND (sin diálisis).

Métodos: Se realizó un estudio observacional transversal desde enero/2020 hasta abril/2021. Se incluyeron pacientes con ERC 3b -5ND de edad ≥ 15 años. Se realizó una ecocardiografía transtorácica 2D (bidimensional) a todos los pacientes. La HP se definió como un valor de presión sistólica de la arteria pulmonar superior a 35 mm Hg, la disfunción sistólica del VI se definió como una fracción de eyección del ventrículo izquierdo $\leq 50\%$ y la DVL como una relación $E/e' > 14$ respectivamente. Se realizó un modelo de regresión logística multivariante para determinar los predictores.

Resultados: Un total de 378 pacientes fueron incluidos en el estudio con 103 en estadio 3b, 175 en estadio 4 y 100 pacientes en estadio 5ND. La prevalencia de la HP fue del 12,2%, la disfunción sistólica del VI fue del 15,6% y la DVL fue del 43,65%. Los predictores de la HP fueron la duración de la ERC, la hemoglobina, la vitamina D 25-OH en suero, la iPTH en suero (hormona paratiroidea intacta) y la albúmina en suero. Los predictores de la EVL fueron la duración de la ERC y la presencia de hipertensión arterial. Los predictores de la disfunción sistólica del VI fueron la tasa de filtración glomerular estimada, la duración de la ERC, la albúmina sérica y las proteínas en orina.

Conclusión: En nuestro estudio de 378 pacientes con ERC 3b-5ND la prevalencia de la HP fue del 12,2%, la disfunción sistólica del VI fue del 15,6% y la DVL fue del 43,65%.

© 2022 Sociedad Española de Nefrología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

CKD is a major public health problem and prevalence is increasing in the recent years and is around 16%.^{1,2} Cardiovascular diseases are the most common cause of death in CKD population.^{3,4} Widespread utilization of 2D echocardiography helps in early identification of structural and functional abnormalities of heart.

Multiple factors in CKD population including hypervolemia, chronic inflammatory state and uraemia results in cardiac and vascular remodelling causing cardiac structural abnormalities and pulmonary hypertension. Recent studies have found increasing prevalence of PH in CKD population.⁵ Presence of LV systolic dysfunction, LVDD and PH is associated with increased morbidity and mortality among CKD patients.⁵⁻⁷

HD (Haemodialysis) is associated with high risk for LV systolic dysfunction, LVDD and PH. Most of the published studies on LV function and PH in CKD patients have included patients on HD. Data on prevalence and predictors of LV systolic dysfunction, LVDD and PH in non-dialysis dependent CKD patients in Indian population are sparse. Our study aims to determine prevalence and predictors of LV systolic dysfunction, LVDD and PH in CKD 3b-5ND patients.

Materials and methods

A cross sectional observational study was done from January 2020 to April 2021 in the Department of Nephrology and Cardiology IMS, BHU, Varanasi. CKD patients staged 3b to 5ND aged ≥ 15 years were included in the study. Following patients were excluded from study (1) Prior Cardiac diseases (ischaemic/valvular/congenital/cor-pulmonale), (2) Chronic pulmonary diseases, (3) Patients on RRT (Renal Replacement therapy)-HD/Peritoneal dialysis/Renal transplant, (4) Patients with upper limb AVF (Arterio-venous fistula), (5) HIV patients, (6) Primary pulmonary hypertension, (7) Chronic liver disease-cirrhosis, (8) Thyroid disorders-hyper/hypo thyroidism, (9) Pregnant females and pregnancy related kidney diseases, (10) Patients presented with AKI (Acute Kidney Injury) or underwent haemodialysis/peritoneal dialysis in prior 3 months, (11) Smokers (old/current) & patients not consenting for study. Patients with LVEF $< 50\%$ were excluded for PH. Institute ethics committee approval and consent from all study participants were taken.

Staging of CKD was done as per KDIGO (Kidney disease Improving Global Outcomes) 2012 guidelines considering eGFR & proteinuria.⁸ Proteinuria was quantified using 24 h urinary volume by Pyrogallol red method. eGFR was

calculated using CKD EPI(Chronic Kidney Disease Epidemiology Collaboration) equation using serum creatinine, age, sex & race. Serum haemoglobin, serum electrolytes, serum 25-OH vitamin D, serum iPTH & urine analysis was done in all patients.

Transthoracic 2D and Doppler Echocardiography was done at diagnosis of CKD in all patients

1. PASP was measured using modified Bernoulli equation as follows $PASP = 4 \times (TRV)^2 + RAP$, Where TRV is the maximum tricuspid regurgitation jet speed and RAP is the right atrium pressure which is estimated by inferior vena cava diameter. Pulmonary hypertension was defined as if PASP value above 35 mm Hg.⁹
2. LVEF was measured using Modified Simpson method. LV systolic dysfunction was defined as $LVEF \leq 50\%$. Mild, moderate and severe LV systolic dysfunction was defined if LVEF is 41–50%, LVEF 31–40% and $LVEF \leq 30\%$.¹⁰
3. LVDD was measured by the E/e' ratio, where E is the early mitral flow velocity on trans-mitral Doppler and e' is the early mitral annulus velocity obtained from tissue Doppler. An E/e' ratio of <8 is considered normal, while >14 was considered as LVDD. Grading of LVDD was done using peak E velocity and mitral E/A ratio, where A is late mitral flow velocity. Grade I LVDD was defined if E/A ratio ≤ 0.8 with a peak E velocity of ≤ 50 cm/s, grade 2 LVDD if E/A ratio of 0.9–1.9 and grade 3 LVDD if E/A ratio of ≥ 2 .¹¹

Statistical analysis

Statistical analysis was done using SPSS software (version 28.0). Continuous variables are expressed in mean \pm SD and compared using student's t test. Categorical variables are expressed as percentage and compared using Chi-square test. Variables which showed P value <0.1 on student's t test and Chi-square test were analyzed using multivariate logistic regression models. Correlation between quantitative variables was done using Pearson's or Spearman's correlations. P value <0.05 was considered statistical significant.

Results

A total of 378 patients were included in the study. Mean age of the study population was 51.56 ± 13.39 years. Male were 248 (65.6%) and female were 130(34.4%). There were 103 (27.2%) patients in stage 3b, 175 (46.3%) in stage 4 and 100 (26.5%) in stage 5-ND. Aetiology of CKD is shown in Fig. 1.

LV systolic dysfunction

Fifty nine patients had LV systolic dysfunction with prevalence of 15.6%. 17 patients (28.8%) had LVEF 41–50%, 40 patients (67.8%) had LVEF 31% to 40% and 2 patients (3.4%) had $LVEF \leq 30\%$. Patients were divided into 2 groups depending on presence or absence of LV systolic dysfunction. On comparing patients with and without systolic dysfunction (Table 1), significant variables were serum creatinine ($P < 0.001$), eGFR ($P < 0.001$), CKD stages ($P < 0.001$), duration of CKD ($P < 0.001$), 24 h urine protein ($P < 0.001$), presence of

ETIOLOGY OF CKD

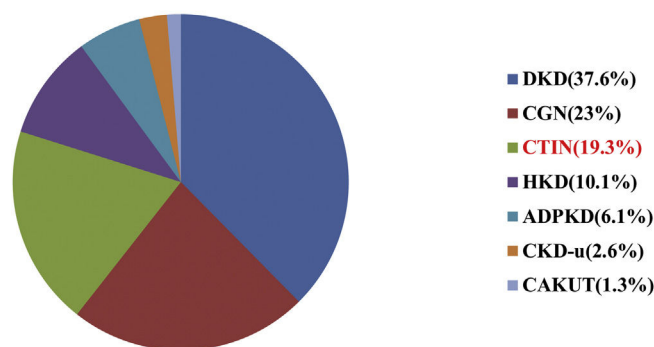


Fig. 1 – Frequency of distribution of aetiology of CKD (DKD–diabetic kidney disease, CGN–chronic glomerulonephritis, CTIN–chronic tubule-interstitial nephritis, HKD–hypertensive kidney disease, ADPKD–autosomal dominant polycystic kidney disease, CKD-u–CKD of unknown aetiology, CAKUT–congenital Anomalies of kidney & Urinary Tract).

arterial hypertension ($P < 0.001$), presence of diabetes mellitus ($P < 0.001$), Haemoglobin (Hb) ($P < 0.001$), serum calcium ($P = 0.02$), serum albumin ($P < 0.001$) and serum 25-OH Vitamin D ($P < 0.001$). On age and sex adjusted multivariate logistic regression analysis significant predictors of systolic dysfunction were eGFR (OR–0.828{0.711–0.965} $P = 0.02$), duration of CKD (OR–2.731{1.093–6.821} $P = 0.03$), serum albumin (OR–0.124{0.045–0.347} $P < 0.001$) and 24 h urine protein (OR–1.725{1.195–2.490} $P = 0.004$) (Table 2). In subgroup analysis of 59 patients with systolic dysfunction, severity of LV systolic dysfunction showed statistically significant negative correlation with serum albumin ($\rho = -0.268$, $P = 0.04$) (Table 3).

LVDD

One hundred and sixty five patients had LVDD with prevalence of 43.65%. 94 patients (56.96%) had grade I, 46 patients (27.88%) had grade II and 25 patients (15.16%) had grade III diastolic dysfunction. Twenty four patients (6.3%) had both LVDD and LV systolic dysfunction. Patients were divided into 2 groups depending on the presence or absence of LVDD. On comparing patients with and without diastolic dysfunction (Table 1), significant variables were age ($P < 0.001$), sex ($P = 0.01$), serum creatinine ($P < 0.001$), eGFR ($P < 0.001$), CKD stages ($P < 0.001$), duration of CKD ($P < 0.001$), presence of arterial hypertension ($P < 0.001$), Hb ($P < 0.001$), serum phosphorous ($P < 0.001$), $Ca \times P$ ($P < 0.001$), Serum uric acid ($P < 0.001$), Serum 25-OH VitD ($P < 0.001$) and Serum iPTH ($P < 0.001$). On age and sex adjusted multivariate logistic regression analysis significant predictors of diastolic dysfunction were duration of CKD (OR–1.807{1.072–3.047} $P = 0.03$) and presence of arterial hypertension (OR–4.692{2.464–8.933} $P < 0.001$) (Table 2). In subgroup analysis of 165 patients with diastolic dysfunction, severity of diastolic dysfunction (grade I/II/III) showed statistically significant positive correlation with serum creatinine ($\rho = 0.388$, $P < 0.001$), duration of CKD ($\rho = 0.450$, $P < 0.001$), serum iPTH

Table 1 – Comparison of variables in patients with and without, LV systolic dysfunction & LVDD.

Sr no	Variables	LV systolic dysfunction			LV diastolic dysfunction		
		Present (n=59)	Absent (n=319)	P value	Present (n=165)	Absent (n=213)	P value
1	Age (years)	50.73 ± 8.46	51.71 ± 14.12	0.47	54.39 ± 13.56	49.36 ± 12.86	<0.001
2	Sex (M:F)	36:23	212:107	0.46	119:46	129:84	0.01
3	Serum creatinine (mg/dl)	3.94 ± 1.47	3.16 ± 1.67	<0.001	3.71 ± 1.49	2.95 ± 1.73	<0.001
4	eGFR (ml/min)	17.27 ± 6.47	24.44 ± 10.17	<0.001	19.58 ± 8.88	26.21 ± 9.93	<0.001
5	CKD stages						
	Stage 3b (n=103)	0	32.3% (103/319)	<0.001	14.54% (24/165)	37.09% (79/213)	<0.001
	Stage 4 (n=175)	64.4% (38/59)	42.95% (137/319)		44.24% (73/165)	47.88% (102/213)	
	Stage 5 (n=100)	35.6% (21/59)	24.75% (79/319)		41.22% (68/165)	15.03% (32/213)	
6	Duration of CKD						
	≤ 1year (n=173)	20.34% (12/59)	50.47% (161/319)	<0.001	31.5% (52/165)	56.8% (121/213)	<0.001
	>1year (n=205)	79.66% (47/59)	49.53% (158/319)		68.5% (113/165)	43.2% (92/213)	
7	Systemic hypertension	6.78% (4/59)	26.02% (83/319)	<0.001	36.36% (60/165)	12.67% (27/213)	<0.001
8	Diabetes mellitus	74.57% (44/59)	30.72% (98/319)	<0.001	41.2% (68/165)	34.74% (74/213)	0.24
9	Urine protein (g/day)	2.85 ± 1.57	0.96 ± 0.94	<0.001	1.15 ± 1.1	1.33 ± 1.37	0.16
10	Haemoglobin (g/dl)	8.77 ± 0.77	9.97 ± 1.61	<0.001	9.44 ± 1.55	10.04 ± 1.53	<0.001
11	Serum calcium (mg/dl)	8.82 ± 0.75	9.08 ± 0.79	0.02	8.97 ± 0.86	9.09 ± 0.74	0.12
12	Serum phosphorous (mg/dl)	5.06 ± 1.26	4.74 ± 1.45	0.08	5.12 ± 1.57	4.53 ± 1.24	<0.001
13	Calcium × phosphorous	44.48 ± 10.95	42.66 ± 12.27	0.25	45.57 ± 13.44	40.91 ± 10.5	<0.001
14	Serum uric acid (mg/dl)	6.32 ± 1.48	6.26 ± 1.66	0.78	6.69 ± 1.53	5.94 ± 1.63	<0.001
15	Serum albumin (g/dl)	3.12 ± 0.52	3.81 ± 0.36	<0.001	3.69 ± 0.46	3.71 ± 0.47	0.78
16	Serum 25-OH vitamin D (ng/ml)	30.95 ± 12.62	37.94 ± 18.27	<0.001	33.21 ± 15.95	39.66 ± 18.46	<0.001
17	Serum iPTH (pg/nl)	186.72 ± 131.23	154.18 ± 124.4	0.08	175.19 ± 126.7	146.92 ± 124.17	0.03
18	Serum ALP (U/L)	246.4 ± 138.46	252.34 ± 145.66	0.58	250.62 ± 142.26	261.47 ± 156.28	0.42
19	BMI	23.96 ± 4.6	24.5 ± 3.94	0.72	24.84 ± 5.3	24.4 ± 4.3	0.61

(rho = 0.198, P = 0.01) and serum uric acid (rho = 0.188, P = 0.02). Severity of diastolic dysfunction (grade I/II/III) showed statistically significant negative correlation with eGFR (rho = -0.353, P < 0.001) and serum 25-OH vitamin D (rho = -0.194, P = 0.01) (Table 3).

PH

Forty six patients had PH with prevalence of 12.2%. Twenty five patients (6.6%) had both LVDD and PH. Patients were divided into 2 groups depending on the presence or absence of PH. On comparing patients with and without PH (Table 4), significant variables were age (P = 0.023), serum creatinine (P < 0.001), eGFR (P < 0.001), CKD stages (P < 0.001), duration of CKD (P < 0.001), 24 h urine protein (P = 0.005), Hb (P < 0.001), serum Calcium (P < 0.001), serum phosphorous (P < 0.001), Ca × P (P = 0.006), Serum albumin (P < 0.001), Serum 25-OH VitD (P < 0.001) and Serum iPTH (P < 0.001). On age and sex adjusted multivariate logistic regression analysis significant predictors of PH were duration of CKD (OR=3.838{1.276–11.547}P=0.02), Hb (OR=1.877{1.169–3.012}P=0.009), serum 25-OH vitamin D (OR=0.880 {0.827–0.936}P<0.001), serum iPTH (OR=0.995 {0.991–1}P=0.04)and serum albumin (OR=0.325{0.105–1.008}P=0.05 (Table 5). In subgroup analysis of 46 patients with PH, severity of pulmonary hypertension (PASP) showed statistically significant positive correlation with duration of CKD (r = 0.454, P = 0.002) and Ca × P (r = 0.306, P = 0.04) (Table 3). Fig. 2 shows prevalence of PH, LVDD and LV systolic dysfunction among different stage of CKD.

Discussion

This was a cross-sectional study to determine prevalence and predictors of LV systolic dysfunction, LVDD and PH in CKD

stage 3b-5ND patients using 2D M mode and Doppler echocardiography.

LV systolic dysfunction

In our study prevalence of LV systolic dysfunction (LVEF ≤ 50%) is 15.6%. Among these 28.8% had LVEF 41–50%, 67.8% had LVEF 31–40% and 3.4% had LVEF ≤ 30%. Gupta et al.¹² reported prevalence of LV systolic dysfunction of 11.8% among 3939 CRIC study participants. Chillo et al.¹³ reported a prevalence of LV systolic dysfunction of 16.2% among 191 CKD patients. In comparison with these 2 studies we have got a similar prevalence whereas Rao T et al.¹⁴ reported a prevalence of LV systolic dysfunction of 47.8% among 250 CKD patients. Since the latter study included only hospitalized patients could result in higher prevalence rate.

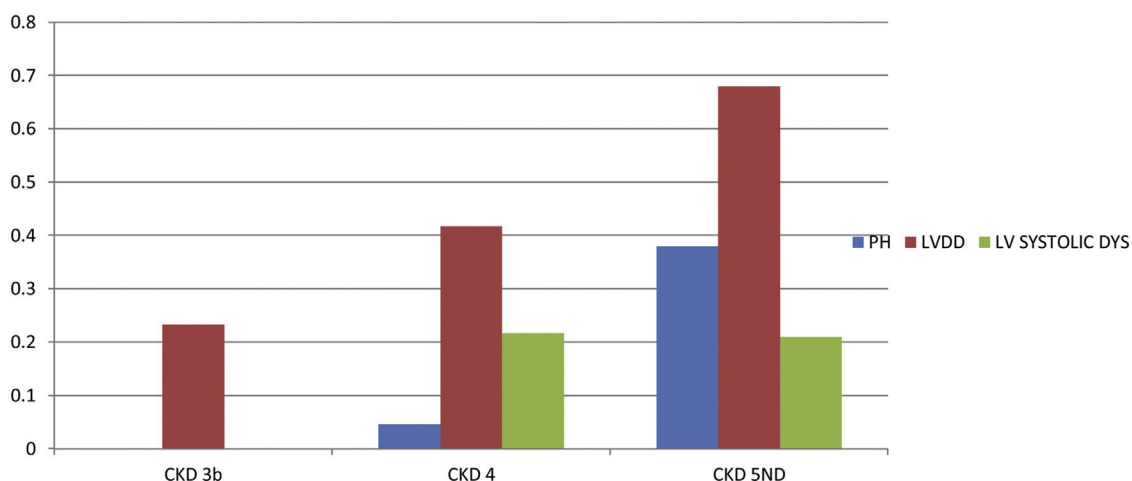
Park et al.¹⁵ reported no significant associations between different stages of eGFR and LVEF in 3487 patients as well as Chillo et al.¹³ Conversely we found eGFR as significant predictor of LV systolic dysfunction but prevalence of LV systolic dysfunction was similar in both stage4 & stage 5 CKD. Probably because of zero prevalence in stage 3 in comparison with stage 4&5 could have resulted in this.

Chen et al.¹⁶ in their cross-sectional study of 285 diabetic CKD 3–5 patients reported independent association between low serum albumin levels and decreased LVEF. Matsushita et al.¹⁷ reported higher albuminuria/ACR as consistent association with LV systolic dysfunction among 4175 ARIC (Atherosclerosis Risk in Communities) CKD participants. Similar to these findings in our study we found serum albumin and urine protein as significant predictors of LV systolic dysfunction, and negative correlation between severity of systolic dysfunction and serum albumin.

Table 2 – Age and sex adjusted multivariate logistic regression analysis for predictors of LV systolic dysfunction & LVDD.

Sr no	LV systolic dysfunction			LV diastolic dysfunction		
	Variables	OR (95%CI)	P value	Variables	OR (95%CI)	P value
1	Serum creatinine (mg/dl)	0.534 (0.257–1.110)	0.09	Serum creatinine (mg/dl)	0.905 (0.67–1.12)	0.51
2	eGFR (ml/min)	0.828 (0.711–0.965)	0.02	eGFR (ml/min)	0.945 (0.874–1.021)	0.15
3	CKD stage	0.354 (0.091–1.378)	0.13	CKD stage (years)	1.753 (0.729–4.212)	0.21
4	Duration of CKD	2.731 (1.093–6.821)	0.03	Duration of CKD	1.807 (1.072–3.047)	0.03
5	Systemic hypertension	1.001 (0.243–4.123)	0.99	Hypertension	4.692 (2.464–8.933)	<0.001
6	Serum haemoglobin (g/dl)	0.809 (0.509–1.286)	0.37	Serum haemoglobin (g/dl)	1.027 (0.807–1.306)	0.83
7	Serum albumin (g/dl)	0.124 (0.045–0.347)	<0.001	Serum uric acid (mg/dl)	1.169 (0.995–1.373)	0.06
8	Serum calcium (mg/dl)	1.159 (0.675–1.990)	0.59	Serum P (mg/dl)	0.827 (0.439–1.558)	0.56
9	Urine protein (g/day)	1.725 (1.195–2.490)	0.004	Ca × P	1.040 (0.968–1.117)	0.28
10	Serum 25-OH vitamin D (ng/ml)	1.015 (0.981–1.051)	0.38	Serum 25-OH vitaminD (ng/ml)	0.996 (0.972–1.021)	0.75
11	Diabetes mellitus	1.330 (0.465–3.802)	0.59	Serum iPTH (pg/ml)	1.000 (0.997–1.002)	0.76

OR, Odd's ratio; CI, confidence interval.

**Fig. 2 – Prevalence of PH, LVDD and LV systolic dysfunction among different stage of CKD.****LVDD**

In our study prevalence of LVDD is 43.65%. 94 patients (56.96%) had grade-I, 46 patients (27.88%) had grade-II and 25 patients

(15.16%) had grade-III diastolic dysfunction. Gupta et al.¹² reported prevalence of LVDD of 76.3% among 3939 CRIC study participants. Chillo et al.¹³ reported a prevalence of LVDD of 68.6% among 191 CKD patients. Rao T et al.¹⁴ reported

Table 3 – Spearman's 2-tailed correlation between LV systolic dysfunction, LVDD and quantitative variables, Pearson's 2-tailed correlation between PASP and quantitative variables.

Sr no		Systolic dysfunction (n = 59)		LVDD (n = 165)		PASP (mm Hg) (n = 46)	
		rho	P value (2-tailed)	rho	P value (2-tailed)	r	P value (2-tailed)
1	eGFR (ml/min)	rho	−0.064	rho	−0.353	r	−0.271
		P value (2-tailed)	0.63	P value (2-tailed)	<0.001	P value (2-tailed)	0.07
2	Serum creatinine (mg/dl)	rho	0.03	rho	0.388	r	0.249
		P value (2-tailed)	0.82	P value (2-tailed)	<0.001	P value (2-tailed)	0.09
3	Duration of CKD (months)	rho	0.135	rho	0.450	r	0.454
		P value (2-tailed)	0.31	P value (2-tailed)	<0.001	P value (2-tailed)	0.002
4	Urine protein (g/day)	rho	0.152	rho	0.061	r	0.109
		P value (2-tailed)	0.25	P value (2-tailed)	0.44	P value (2-tailed)	0.47
5	Hb(g/dl)	rho	−0.004	rho	−0.189	r	−0.189
		P value (2-tailed)	0.98	P value (2-tailed)	0.21	P value (2-tailed)	0.21
6	Serum Ca (mg/dl)	rho	0.091	rho	−0.064	r	0.136
		P value (2-tailed)	0.49	P value (2-tailed)	0.42	P value (2-tailed)	0.37
7	Serum P (mg/dl)	rho	0.114	rho	0.112	r	0.272
		P value (2-tailed)	0.39	P value (2-tailed)	0.153	P value (2-tailed)	0.07
8	Ca × P	rho	0.164	rho	0.09	r	0.306
		P value (2-tailed)	0.21	P value (2-tailed)	0.25	P value (2-tailed)	0.04
9	Serum albumin (g/dl)	rho	−0.268	rho	−0.093	r	0.031
		P value (2-tailed)	0.04	P value (2-tailed)	.233	P value (2-tailed)	0.84
10	Serum 25-OH VitD (ng/ml)	rho	0.109	rho	−0.194	r	−0.280
		P value (2-tailed)	0.41	P value (2-tailed)	0.01	P value (2-tailed)	0.06
11	Serum iPTH (pg/ml)	rho	−0.236	rho	0.198	r	0.155
		P value (2-tailed)	0.07	P value (2-tailed)	0.01	P value (2-tailed)	0.3
12	Serum uric acid (mg/dl)	rho	−0.092	rho	0.188	r	0.186
		P value (2-tailed)	0.48	P value (2-tailed)	0.02	P value (2-tailed)	0.23

rho, Spearman's coefficient; r, Pearson's coefficient.

Table 4 – Comparison of variables in patients with and without Pulmonary Hypertension.

Sr no	Variables	Pulmonary hypertension		P value
		Present (n = 46)	Absent (n = 332)	
1	Age	47.35 ± 14.18	52.14 ± 13.19	0.02
2	Sex(M:F)	29:17	219:113	0.49
3	Serum creatinine (mg/dl)	5.13 ± 1.17	3.03 ± 1.55	<0.001
4	eGFR(ml/min)	12.06 ± 4.09	24.87 ± 9.60	<0.001
5	CKD stages			
	Stage 3b(n = 103)	0% (0)	31.02% (103/332)	<0.001
	Stage 4(n = 175)	17.4% (8/46)	50.3% (167/332)	
	Stage 5(n = 100)	82.6% (38/46)	18.68% (62/332)	
6	Duration of CKD			
	≤ 1year(n = 173)	17.4% (8/46)	49.7% (165/332)	<0.001
	>1year(n = 205)	82.6% (38/46)	50.3% (167/332)	
7	Diabetes mellitus	45.65% (21/46)	36.45% (121/332)	0.25
8	Urine protein (g/day)	1.74 ± 1.3	1.19 ± 1.25	0.005
9	Haemoglobin (g/dl)	8.7 ± 1.04	9.93 ± 1.56	<0.001
10	Serum calcium (mg/dl)	8.54 ± 0.7	9.12 ± 0.78	<0.001
11	Serum phosphorous (mg/dl)	5.59 ± 1.64	4.67 ± 1.36	<0.001
12	Calcium × phosphorous	47.53 ± 14	42.31 ± 11.67	0.006
13	Serum uric acid (mg/dl)	6.42 ± 1.4	4.67 ± 1.36	0.506
14	Serum albumin (g/dl)	3.35 ± 0.55	3.75 ± 0.42	<0.001
15	Serum 25-OHvitaminD (ng/ml)	20.84 ± 9.24	39.06 ± 17.43	<0.001
16	Serum iPTH (pg/ml)	244.99 ± 142.94	147 ± 118.76	<0.001
17	Serum ALP (U/L)	264.62 ± 152.26	275.47 ± 170.24	0.68
18	BMI	23.84 ± 5.42	24.22 ± 4.14	0.58
19	Diastolic dysfunction	54.35% (25/46)	42.17% (140/332)	0.15
20	PASP (mm Hg)	48.69 ± 17.69	24.35 ± 4.86	<0.001

Table 5 – Age and sex adjusted multivariate logistic regression analysis for predictors of pulmonary hypertension.

Sr no	Variables	OR (95%CI)	P value
1	Serum creatinine (mg/dl)	1.025 (0.496–2.12)	0.95
2	eGFR (ml/min)	0.825 (0.652–1.044)	0.11
3	CKD stage (years)	1.635 (0.294–9.104)	0.58
4	Duration of CKD	3.838 (1.276–11.547)	0.02
5	Urine protein (g/day)	0.794 (0.51–1.23)	0.31
6	Hb (g/dl)	1.877 (1.169–3.012)	0.009
7	Serum Ca (mg/dl)	0.389 (0.055–2.73)	0.34
8	Serum P (mg/dl)	0.287 (0.012–6.943)	0.44
9	Ca × P	1.167 (0.809–1.683)	0.41
10	Serum vitD (ng/ml)	0.880 (0.827–0.936)	<0.001
11	Serum iPTH (pg/ml)	0.995 (0.991–1)	0.04
12	Serum albumin (g/dl)	0.325 (0.105–1.008)	0.05

OR, Odd's ratio, CI, confidence interval.

a prevalence of LVDD of 55.2% among 250 CKD patients. Comparing with these studies we have found a lower prevalence of LVDD. Probably different inclusion criteria, method of determining LVDD and different ethnicities may result in varied prevalence among different studies.

We found increased prevalence of LVDD with the stage of CKD. We found positive correlation between severity of LVDD and serum creatinine, and negative correlation between severity of LVDD and eGFR. This is consistent with previously published studies. Qi-Zhe Cai et al.¹⁸ reported prevalence of LVDD of 44.4% at baseline and 64.2% at 1 year, with significant change in prevalence and severity of LVDD in lower eGFR groups. Jain et al.⁷ (N=2056) reported greater degree of diastolic dysfunction and adverse clinical outcomes with worsening EGFR, and presence of LVDD was associated with increased morbidity and mortality.

Arterial hypertension is associated with increased prevalence of LVDD.^{19,20} Several potential mechanisms including haemodynamic, non-haemodynamic factors and myocardial ischaemia are implicated in development of LVDD in hypertensive patients. Pressure overload and stiffening of larger arteries strongly influence LVDD.²¹ Similar to these studies we found arterial hypertension as significant predictor of LVDD.

Pandit A et al.²² showed no significant association between vitamin D levels and LVDD (N=1011 patients). Banerjee et al.²³ in their RCT and meta-analysis reported that vitamin D supplementation has no beneficial effect on LV mass. We found a negative correlation between LVDD severity and serum 25-OH vitamin D. Since there were more number of grade III LVDD patients in stage 5 and low serum 25-OH vitamin D in stage 5 patients could result in this. With cross-sectional nature of our study it is hard to interpret this association.

Kim et al.²⁴ reported serum uric acid as an independent predictor of LVDD (N=1025 pre-dialysis CKD patients with preserved left ventricular systolic function). Pan et al.²⁵ reported that long-term Febuxostat therapy was associated with lower LVDD in patients with hypertensive LVH and asymptomatic hyperuricemia. Consistent with these findings we found serum uric acid as significant predictor of LVDD.

Disturbances of mineral metabolism including elevated PTH levels, hyperphosphatemia, and high values for serum Ca × P are associated with greater risk of cardiovascular

disease in CKD patients. Lishmanov et al.²⁶ (N=196 patients with CKD 3&4) reported iPTH level to be associated with increased incidence of cardiovascular events independent of calcium-phosphorous level. Similarly in our study iPTH was found to be significant predictor of LVDD.

Presence of LVDD in CKD is associated with higher mortality.^{27,28} Factors that have been implicated in the progression of LVDD include haemodynamic overload, alterations in mineral metabolism, circulating uraemic toxins, cardiotoxic steroids and increased aortic stiffness.^{29,30}

Pulmonary hypertension

In our study prevalence of PH is 12.2%, prevalence increased with the stage of CKD with zero prevalence in stage 3b, 4.57% in stage 4 and 38% in stage 5. Navaneethan et al.³¹ showed prevalence of pulmonary hypertension of 21% among 2959 non-dialysis dependent Chronic Renal Insufficiency Cohort(CRIC) study participants with higher rates in lower EGFR groups. Bolognani et al.³² (N=468 patients with CKD 2–4) found a prevalence of PH of 23%, with higher rates in stage 4. In Jackson heart study by Selvaraj et al.⁶ of 408 CKD patients with eGFR <60 mL/min per 1.73 m² reported prevalence of PH of 22% and was associated with a higher risk of heart failure admission and mortality. However compared with these studies we found a low prevalence of PH (12.2%). Probably inclusion of patients with lower LVEF or prior cardiac events, higher BMI, COPD, smokers, patients with AVF and different ethnicities among study groups, could have resulted in varied prevalence of PH. Tang et al.⁵ in their systematic review and meta-analysis on PH in CKD, which included 16 cohort studies with 7112 participants showed prevalence of PH of 26.6% and found dialysis as a risk for PH. Due to the fact we have excluded dialysis dependent CKD patients might result in lower prevalence of PH.

In our study significant predictors of PH were duration of CKD, haemoglobin, serum 25-OH vitamin, serum iPTH and serum albumin. Significant positive correlation between the severity of pulmonary hypertension, duration of CKD and Calcium × Phosphorous product was found in our study. Multiple predictors for PH in CKD have been reported in previous studies which includes age, eGFR, haemoglobin, low LVEF, presence of left ventricular hypertrophy, left atrial volume,

history of cardiovascular events, diabetes and presence of AVF.^{31–33} Study by Mehta et al.³⁴ reported positive correlation between PH and duration of CKD, duration of dialysis, BUN, serum creatinine, and calcium \times phosphorous product, and negative correlation between haemoglobin and PH. Suresh et al.³⁵ reported left-sided heart failure, anaemia, fluid retention, and increased calcium \times phosphorous product as risk factors for developing PH.

Studies have reported higher frequency of iron deficiency and anaemia in PH.^{36,37} Iron deficiency and anaemia are associated with chronic progressive remodelling of pulmonary vessels with accumulation of pulmonary arterial endothelial cells, pulmonary artery smooth muscle cells, myofibroblasts and pericytes.³⁸ CKD is associated with anaemia and functional iron deficiency which can cause remodelling in pulmonary vasculature and high risk for PH. Serum albumin levels are influenced by nutritional status, inflammatory state, liver function and renal loss in CKD population. Snipelisky et al.³⁹ reported serum albumin as an independent prognostic indicator and non-selective marker for severity in patients with PH. They found that lower serum albumin in patients with PH associated with more systemic comorbidities and represent a progressive clinical course. Thus in our study presence of low serum albumin in PH group may represent severe renal failure and associated co-morbidity.

Studies have reported higher prevalence of vitamin D deficiency in PH.^{40,41} Tanaka et al.⁴² in their experimental rat study reported improved right ventricular function after correction of vitamin D in vitamin D deficient rats. Similarly Mirdamadi et al.⁴³ reported improved right ventricular function and PASP in vitamin D deficient PH patients after restoration of serum vitamin D during a follow up period of 3 months. Studies have reported secondary hyperparathyroidism and associated CKD-MBD biochemical abnormalities are associated with increased risk of PH.^{34,35,44}

Multiple pathophysiological changes in CKD have been postulated for the development of PH. The presence of uraemic toxins in CKD impairs vasodilatory effect of nitric oxide and there is elevated endothelin-1 causing pulmonary vascular remodelling.⁴⁵ As CKD is chronic inflammatory state there is elevated levels of circulating pro-inflammatory cytokines which can modulate downstream signalling pathways that controls vascular structure and tone.^{45,46} Longer duration of CKD is associated with increased exposure to uraemic toxins and inflammatory cytokines results in increased risk for PH.

Strength of our study is to evaluate and determine predictors LV systolic dysfunction, LVDD and PH in CKD 3-5ND patients. Most of the studies done on LV systolic function, LVDD and PH in Indian CKD population have included dialysis dependent CKD patients, in contrast we have included non-dialysis dependent CKD 3-5ND patients.

Our study has following limitations. Since it is a cross-sectional observational study it precludes us from concluding causality or association. Furthermore we did not perform 2D echo or measure biochemical parameters at regular intervals to define more accurate association. We did not measure NT-Pro BNP and other inflammatory markers in our study participants. We haven't done right heart catheterization to determine the type of PH. As it is single centre study

heterogeneity between different races and ethnic groups could not be evaluated.

Conclusion

In our study the prevalence of PH is 12.2%, LV systolic dysfunction is 15.6% and LVDD is 43.65%. Predictors of PH were duration of CKD, haemoglobin, serum 25-OH vitamin-D, serum iPTH and serum albumin. Predictors of LVDD were duration of CKD and presence of arterial hypertension. Predictors of LV systolic dysfunction were eGFR, duration of CKD, serum albumin and 24 h urine protein. Routine screening of CKD population with 2D echocardiography is to be encouraged for early detection of LV dysfunction and PH. Prognostic implications and utility of these predictors requires prospective or randomized control studies for better validation.

Funding

Nil.

Conflicts of interest

Nil.

REFERENCES

1. Ingsathit A, Thakkinstian A, Chaiprasert A, Sangthawan P, Gojaseni P, Kiattisunthorn K, et al. Prevalence and risk factors of chronic kidney disease in the Thai adult population: Thai SEEK study. *Nephrol Dial Transplant*. 2010;25:1567–75, <http://dx.doi.org/10.1093/ndt/gfp669>.
2. Agarwal SK, Dash SC, Irshad M, Raju S, Singh R, Pandey RM. Prevalence of chronic renal failure in adults in Delhi. India. *Nephrol Dial Transplant*. 2005;20:1638–42, <http://dx.doi.org/10.1093/ndt/gfh855>.
3. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–81, [http://dx.doi.org/10.1016/S0140-6736\(10\)60674-5](http://dx.doi.org/10.1016/S0140-6736(10)60674-5).
4. Foster MC, Rawlings AM, Marrett E, Neff D, Willis K, Inker LA, et al. Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in the United States. *Am Heart J*. 2013;166:150–6, <http://dx.doi.org/10.1016/j.ahj.2013.03.016>.
5. Tang M, Batty JA, Lin C, Fan X, Chan KE, Kalim S. Pulmonary Hypertension, Mortality, and Cardiovascular Disease in CKD and ESRD Patients: A Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2018;72:75–83, <http://dx.doi.org/10.1053/j.ajkd.2017.11.018>.
6. Selvaraj S, Shah SJ, Ommerborn MJ, Clark CR, Hall ME, Mentz RJ, et al. Pulmonary Hypertension Is Associated With a Higher Risk of Heart Failure Hospitalization and Mortality in Patients With Chronic Kidney Disease: The Jackson Heart Study. *Circ Heart Fail*. 2017;10:e003940, <http://dx.doi.org/10.1161/CIRCHEARTFAILURE.116.003940>.
7. Jain A, Scott C, Chen HH. The renal-cardiac connection in subjects with preserved ejection fraction: a population based study. *ESC Heart Fail*. 2017;4:266–73, <http://dx.doi.org/10.1002/ehf2.12143>.

8. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report [published correction appears in *Kidney Int.* 2011 Nov;80(9):1000] [published correction appears in *Kidney Int.* 2011 Nov 1;80(9):1000]. *Kidney Int.* 2011;80:17–28, <http://dx.doi.org/10.1038/ki.2010.483>.
9. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37:67–119, <http://dx.doi.org/10.1093/eurheartj/ehv317>.
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [published correction appears in *Eur Heart J Cardiovasc Imaging.* 2016 Apr;17(4):412] [published correction appears in *Eur Heart J Cardiovasc Imaging.* 2016 Sep;17 (9):969]. *Eur Heart J Cardiovasc Imaging.* 2015;16:233–70, <http://dx.doi.org/10.1093/ehjci/jev014>.
11. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29:277–314, <http://dx.doi.org/10.1016/j.echo.2016.01.01>.
12. Gupta J, Dominic EA, Fink JC, Ojo AO, Barrows IR, Reilly MP, et al. Association between Inflammation and Cardiac Geometry in Chronic Kidney Disease: Findings from the CRIC Study. *PLoS One.* 2015;10:e0124772, <http://dx.doi.org/10.1371/journal.pone.0124772>. Published 2015 Apr 24.
13. Chillo P, Mujuni E. Prevalence and predictors of left ventricular dysfunction among patients with chronic kidney disease attending Muhimbili National Hospital in Tanzania - a cross-sectional study. *Research Reports in Clinical Cardiology.* 2018; 9:11-21 <https://doi.org/10.2147/RRCC.S159472><<https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.2147%2FRCC.S159472&data=05%7C01%7CS.Yadav%40elsevier.com%7C34f77e8c4dbb4ea5b1f608da5b1a41f3%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637922465572734078%7CUnknown%7CTWFpbGZsb3d8eyJWljiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6IjEhaWwiiLCJXVCi6Mn0%3D%7C3000%7C%7C%7C&sdata=LD1RIUsc4EDIglD0TRkguwHFe1keyruvffT6j7n22VI%3D&reserved=0>>.
14. Rao T, Karwa M, Wanjari A. Left ventricular dysfunction among chronic kidney disease patients: a cross sectional study. *International Journal of Advances in Medicine.* 2018;5:1093–9.
15. Park M, Hsu CY, Li Y, Keane M, Rosas SE, Dries D, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol.* 2012;23:1725–34, <http://dx.doi.org/10.1681/ASN.2012020145>.
16. Chen SC, Chang JM, Liu WC, Tsai YC, Tsai JC, Su HM, et al. Stepwise increases in left ventricular mass index and decreases in left ventricular ejection fraction correspond with the stages of chronic kidney disease in diabetes patients. *Exp Diabetes Res.* 2012;2012:789325, <http://dx.doi.org/10.1155/2012/789325>.
17. Matsushita K, Kwak L, Sang Y, Ballew SH, Skali H, Shah AM, et al. Kidney Disease Measures and Left Ventricular Structure and Function: The Atherosclerosis Risk in Communities Study. *J Am Heart Assoc.* 2017;6:e006259, <http://dx.doi.org/10.1161/JAHA.117.006259>. Published 2017 Sep 22.
18. Cai QZ, Lu XZ, Lu Y, Wang AY. Longitudinal changes of cardiac structure and function in CKD (CASCADE study). *J Am Soc Nephrol.* 2014;25:1599–608, <http://dx.doi.org/10.1681/ASN.2013080899>.
19. Santos AB, Gupta DK, Bello NA, Gori M, Claggett B, Fuchs FD, et al. Prehypertension is Associated With Abnormalities of Cardiac Structure and Function in the Atherosclerosis Risk in Communities Study. *Am J Hypertens.* 2016;29:568–74, <http://dx.doi.org/10.1093/ajh/hpv156>.
20. Dini FL, Galderisi M, Nistri S, Buralli S, Ballo P, Mele D, et al. Abnormal left ventricular longitudinal function assessed by echocardiographic and tissue Doppler imaging is a powerful predictor of diastolic dysfunction in hypertensive patients: the SPHERE study. *Int J Cardiol.* 2013;168:3351–8, <http://dx.doi.org/10.1016/j.ijcard.2013.04.122>.
21. Nadruz W, Shah AM, Solomon SD. Diastolic Dysfunction and Hypertension. *Med Clin North Am.* 2017;101:7–17, <http://dx.doi.org/10.1016/j.mcna.2016.08.01>.
22. Pandit A, Mookadam F, Boddu S, Pandit A, Tandar A, Chaliki H, et al. Vitamin D levels and left ventricular diastolic function. *Open Heart.* 2014;1:e000011, <http://dx.doi.org/10.1136/openhrt-2013-000011>. Published 2014 Feb 15.
23. Banerjee D, Chitalia N, Ster IC, Appelbaum E, Thadhani R, Kaski JC, et al. Impact of vitamin D on cardiac structure and function in chronic kidney disease patients with hypovitaminosis D: a randomized controlled trial and meta-analysis. *Eur Heart J Cardiovasc Pharmacother.* 2021;7:302–11, <http://dx.doi.org/10.1093/ehjcvp/pvz080>.
24. Kim IY, Ye BM, Kim MJ, Kim SR, Lee DW, Kim HJ, et al. Association between serum uric acid and left ventricular hypertrophy/left ventricular diastolic dysfunction in patients with chronic kidney disease. *PLoS One.* 2021;16:e0251333, <http://dx.doi.org/10.1371/journal.pone.0251333>. Published 2021 May 6.
25. Pan JA, Lin H, Wang CQ, Zhang JF, Gu J. Association between long-term prescription of febuxostat and the progression of heart failure with preserved ejection fraction in patients with hypertension and asymptomatic hyperuricemia. *Heart Vessels.* 2020;35:1446–53, <http://dx.doi.org/10.1007/s00380-020-01619-8>.
26. Lishmanov A, Dorairajan S, Pak Y, Chaudhary K, Chockalingam A. Elevated serum parathyroid hormone is a cardiovascular risk factor in moderate chronic kidney disease. *Int Urol Nephrol.* 2012;44:541–7, <http://dx.doi.org/10.1007/s11255-010-9897-2>.
27. Farshid A, Pathak R, Shadbolt B, Arnolda L, Talaulikar G. Diastolic function is a strong predictor of mortality in patients with chronic kidney disease. *BMC Nephrol.* 2013;14:280, <http://dx.doi.org/10.1186/1471-2369-14-280>. Published 2013 Dec 23.
28. Kim MK, Kim B, Lee JY, Kim JS, Han BG, Choi SO, et al. Tissue Doppler-derived E/e' ratio as a parameter for assessing diastolic heart failure and as a predictor of mortality in patients with chronic kidney disease. *Korean J Intern Med.* 2013;28:35–44, <http://dx.doi.org/10.3904/kjim.2013.28.1.35>.
29. Wang X, Shapiro JI. Evolving concepts in the pathogenesis of uraemic cardiomyopathy. *Nat Rev Nephrol.* 2019;15:159–75, <http://dx.doi.org/10.1038/s41581-018-0101-8>.
30. Nardi E, Cottone S, Mulè G, Palermo A, Cusimano P, Cerasola G. Influence of chronic renal insufficiency on left ventricular diastolic function in hypertensives without left ventricular hypertrophy. *J Nephrol.* 2007;20:320–8.
31. Navaneethan SD, Roy J, Tao K, Brecklin CS, Chen J, Deo R, et al. Prevalence, Predictors, and Outcomes of Pulmonary Hypertension in CKD. *J Am Soc Nephrol.* 2016;27:877–86, <http://dx.doi.org/10.1681/ASN.2014111111>.

32. Bolignano D, Lennartz S, Leonardis D, D'Arrigo G, Tripepi R, Emrich IE, et al. High estimated pulmonary artery systolic pressure predicts adverse cardiovascular outcomes in stage 2–4 chronic kidney disease. *Kidney Int.* 2015;88:130–6, <http://dx.doi.org/10.1038/ki.2015.2>.
33. Reque J, Garcia-Prieto A, Linares T, Vega A, Abad S, Panizo N, et al. Pulmonary Hypertension Is Associated with Mortality and Cardiovascular Events in Chronic Kidney Disease Patients. *Am J Nephrol.* 2017;45:107–14, <http://dx.doi.org/10.1159/000453047>.
34. Mehta KS, Shirkande AK, Bhurke SP, Pajai AE, Swami RS, Jadhav SN. Pulmonary Hypertension in Various Stages of Chronic Kidney Disease in Indian Patients. *Indian J Nephrol.* 2019;29:95–101, <http://dx.doi.org/10.4103/ijn.IJN.407-17>.
35. Suresh H, Arun BS, Moger V, Vijayalaxmi PB, Murali Mohan K. A prospective study of pulmonary hypertension in patients with chronic kidney disease: A new and pernicious complication. *Indian J Nephrol.* 2018;28:127–34.
36. Sonnweber T, Nairz M, Theurl I, Petzer V, Tymoszyk P, Haschka D, et al. The crucial impact of iron deficiency definition for the course of precapillary pulmonary hypertension. *PLoS One.* 2018;13:e0203396, <http://dx.doi.org/10.1371/journal.pone.0203396>. Published 2018 Aug 30.
37. Rhodes CJ, Howard LS, Busbridge M, Ashby D, Kondili E, Gibbs JS, et al. Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. *J Am Coll Cardiol.* 2011;58:300–9, <http://dx.doi.org/10.1016/j.jacc.2011.02.057>.
38. Sonnweber T, Pizzini A, Tancevski I, Löffler-Ragg J, Weiss G. Anaemia, iron homeostasis and pulmonary hypertension: a review. *Intern Emerg Med.* 2020;15:573–85, <http://dx.doi.org/10.1007/s11739-020-02288-1>.
39. Snipelisky D, Jentzer J, Batal O, Dardari Z, Mathier M. Serum albumin concentration as an independent prognostic indicator in patients with pulmonary arterial hypertension. *Clin Cardiol.* 2018;41:782–7, <http://dx.doi.org/10.1002/clc.22954>.
40. Callejo M, Mondejar-Parreño G, Esquivel-Ruiz S, Olivencia MA, Moreno L, Blanco I, et al. Total, Bioavailable, and Free Vitamin D Levels and Their Prognostic Value in Pulmonary Arterial Hypertension. *J Clin Med.* 2020;9:448, <http://dx.doi.org/10.3390/jcm9020448>. Published 2020 Feb 6.
41. Atamañuk AN, Litewka DF, Baratta SJ, Seropian IM, Prados GP, Payaslian MO, et al. Vitamin D deficiency among patients with pulmonary hypertension. *BMC Pulm Med.* 2019;19:258, <http://dx.doi.org/10.1186/s12890-019-1011-7>. Published 2019 Dec 21.
42. Tanaka H, Kataoka M, Isobe S, Yamamoto T, Shirakawa K, Endo J, et al. Therapeutic impact of dietary vitamin D supplementation for preventing right ventricular remodeling and improving survival in pulmonary hypertension. *PLoS One.* 2017;12:e0180615, <http://dx.doi.org/10.1371/journal.pone.0180615>. Published 2017 Jul 7.
43. Mirdamadi A, Moshkdar P. Benefits from the correction of vitamin D deficiency in patients with pulmonary hypertension. *Caspian J Intern Med.* 2016;7:253–9.
44. Genctoy G, Arikan S, Gedik O. Secondary hyperparathyroidism is associated with pulmonary hypertension in older patients with chronic kidney disease and proteinuria. *Int Urol Nephrol.* 2015;47:353–8, <http://dx.doi.org/10.1007/s11255-014-0889-5>.
45. Al-Qadi M, LeVarge B, Ford HJ. Epidemiology, Pathogenesis, and Clinical Approach in Group 5 Pulmonary Hypertension. *Front Med (Lausanne).* 2021;7:616720, <http://dx.doi.org/10.3389/fmed.2020.616720>. Published 2021 Mar 25.
46. Kwar B, Ellam T, Jackson C, Kiely DG. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. *Am J Nephrol.* 2013;37:281–90, <http://dx.doi.org/10.1159/000348804>.