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Coronary flow abnormalities in chronic kidney disease: A systematic review and meta-analysis

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Abstract

Background: Coronary vasomotion abnormalities have been described in small studies but not studied systematically. We aimed to review the present literature and analyze it to improve our understanding of chronic kidney disease (CKD) related-coronary microvascular dysfunction.

Objective: Coronary flow reserve (CFR) is a well-known measure of coronary vasomotion. We aimed to assess the difference in CFR among participants with and without CKD.

Methods: PubMed, Embase, and Cochrane CENTRAL were systematically reviewed to identify studies that compared CFR in participants with and without CKD. We estimated standardized mean differences in mean CFR reported in these studies. We performed subgroup analyses according to imaging modality, and the presence of significant epicardial coronary artery disease.

Results: In 14 observational studies with 5966 and 1410 patients with and without CKD, the mean estimated glomerular filtration rate (eGFR) was 29 ± 04 and 87 ± 25 ml/min/1.73 m², respectively. Mean CFR was consistently lower in patients with CKD in all studies and the cumulative mean difference was statistically significant ($2.1 \pm .3$ vs. $2.7 \pm .5$, standardized mean difference $-.8$, 95% CI $-1.1, -.6$, $p < .05$). The lower mean CFR was driven by both significantly higher mean resting flow velocity ($.58$ cm/s, 95% CI $.17, .98$) and lower mean stress flow velocity ($-.94$ cm/s, 95% CI $-1.75, -.13$) in studies with CKD. This difference remained significant across diagnostic modalities and even in absence of epicardial coronary artery disease. In meta-regression, there was a significant positive relationship between mean eGFR and mean CFR ($p < .05$).

Conclusion: Patients with CKD have a significantly lower CFR versus those without CKD, even in absence of epicardial coronary artery disease. There is a linear association

between eGFR and CFR. Future studies are required to understand the mechanisms and therapeutic implications of these findings.

KEYWORDS

chronic kidney disease, coronary flow reserve, coronary microvascular dysfunction

Key Points

1. In this meta-analysis of observational studies, there was a significant reduction in coronary flow reserve in studies with chronic kidney disease versus those without.
2. This difference was seen even in absence of epicardial coronary artery disease.
3. In meta-regression, a lower estimate glomerular filtration rate was a significant predictor of lower coronary flow reserve.
4. Coronary microvascular dysfunction, rather than atherosclerosis-related epicardial disease may underly increase cardiovascular risk in a patient with chronic kidney disease.

1 | INTRODUCTION

There is a high prevalence of chronic kidney disease (CKD) in the United States.¹ Cardiovascular (CV) disease is the most important cause of morbidity and mortality in these patients and the risk increases with a decrease in the estimated glomerular filtration rate (eGFR).^{2,3} Most CV morbidity and mortality in these patients are due to sudden cardiac death and heart failure-related death, and not due to type 1 myocardial infarction.³ Coronary microvascular dysfunction, assessed by coronary flow reserve (CFR, ratio of stress to resting flow), may underly this increased risk.^{4,5} CFR integrates the hemodynamic effects of coronary atherosclerosis, epicardial stenosis, and microvascular dysfunction,⁶ and the risk of CV mortality increase with a reduction in CFR.^{7,8} In this study, we explore the association between CFR and eGFR through a systematic review and metaanalysis.

2 | METHODS

This study was reported per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement (Table S1).⁹

2.1 | Study characteristics

We included studies (observation or randomized control trials) that reported CFR and eGFR in patients with and without CKD. We also included studies where patients were on hemodialysis or had renal transplants. For meta-regression, we also included studies that reported CFR and eGFR among patients with CKD only. We excluded studies where CFR was reported as a categorical variable (impaired

or preserved). In the case of multiple publications, we included data from studies with larger sample size. Two reviewers (V.J. and K.G.) screened the title and abstracts of the retrieved studies. Disagreements were resolved through a third reviewer (N.S.B.). Full texts of the included studies were then screened to extract data by two independent reviewers (V.J. and K.G.) on pre-specified forms.

2.2 | Search strategy

We queried PubMed, Embase, and Cochrane CENTRAL from inception to May 31, 2020, for studies with the terms “coronary flow reserve,” “CFR,” “myocardial blood flow,” “MBF,” “myocardial flow reserve,” “MFR,” “fractional flow reserve,” “FFR,” “microcirculation,” “chronic kidney disease,” “CKD,” and “impaired renal function.” The search strategy has been detailed in the supplement (**eSearch Strategy**).

We further queried the references of the included studies to look for any other studies that may have been missed in the initial search. The review was registered on PROSPERO (ID CRD42020192357). This was a review of already published literature, and institutional review board approval was not required.

2.3 | Study variables

The study provided definition of CKD was used. In the studies, CKD was defined using Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as an estimated eGFR < 60 ml/min/1.73 m² or markers of kidney damage, including albuminuria for >3 months.¹⁰ In studies where patients with CKD were divided into sub-groups based on CKD stage, the overall mean eGFR was calculated from each stage using formulas provided in Cochrane’s handbook.¹¹ Significant epicardial coronary artery disease (CAD) was defined using individual study definition or ≥50% obstruction in an epicardial coronary artery. All

patients with end-stage renal disease (ESRD) or on dialysis were considered to have a mean eGFR of 15 ml/min/1.73 m² unless the mean was specified. When not available, mean eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) equation using mean serum creatinine.¹²

2.4 | Outcome measure

The primary outcome was the standardized mean difference (SMD) of mean CFR in studies with and without CKD. Secondary outcomes were SMD of mean resting and stress coronary flow velocities and independent predictors of mean CFR.

2.5 | Statistical analysis

Random effects modeling was utilized given the heterogeneity between observational study populations for the outcomes of interest.¹³ Inverse variance weighting and DerSimonian-Laird estimator using random-effects models were used. We also performed a meta-regression and subgroup analysis to evaluate the effect of eGFR, age, sex, diabetes mellitus, hypertension, body mass index (BMI), and imaging modality used on CFR. These variables were used based on their known association with CFR.¹⁴⁻¹⁶

In cases where meta-regression models identified a significant association, we confirmed the finding using permutation analysis. Publication bias was assessed using the funnel plot method as well as Egger regression asymmetry testing.¹⁷ If there was a significant publication bias, we adjusted the pooled effect estimate with the Duval and Tweedie nonparametric *trim and fill* method of incorporating the estimates theoretically from the missing studies.¹⁸ All statistical analysis was performed using R statistical software V 3.6.0.

3 | RESULTS

There were 14 studies with 4560 and 1410 participants with and without CKD that met our inclusion criteria (Figure S1). The baseline characteristics and comorbidities in the included studies are given in Table 1. The sample size in the studies varied from 24 to 3946. The mean age in the two groups was comparable in almost all studies. The proportion of women ranged from 16% to 81%. Fourteen studies excluded patients with significant epicardial CAD (Table 1). The definition of CAD in these studies varied and is summarized in Table S2. CFR was measured using Doppler echocardiography in ten studies, positron emission tomography in eight studies, and invasive angiography in four studies (Table 2).

3.1 | CFR in studies with and without CKD

The mean eGFR in participants with and without CKD was 29 ± 04 and 87 ± 25 ml/min/1.73 m², respectively. Mean CFR was $2.1 \pm .3$ and $2.7 \pm .5$, respectively (SMD $-.8$, 95% CI -1.1 , $-.6$, Figure 1). There was

directional consistency in the results but there was high heterogeneity (I^2 83.0%, $p < .05$). There was a significant bias towards the publication of studies showing a statistically significant difference in CFR ($p = .02$, Figure S2). The effect estimate remained statistically significant after correction for publication bias (mean difference $-.7$, 95% CI $-.5$, -1.0 , I^2 52%, $p < .03$).

3.2 | Mean resting and stress coronary flow in studies with and without CKD

The lower mean CFR in studies with CKD was driven by both a significantly higher resting flow velocity (SMD .58 cm/s, 95% CI .17, .98, Figure S3A) and lower stress flow velocity (SMD $-.94$ cm/s, 95% CI -1.75 , $-.13$ Figure S3B).

3.3 | Sub-group analysis

Mean CFR was significantly lower in patients with CKD irrespective of significant epicardial CAD (Figure 1 and Table 3). Mean CFR was significantly lower in patients with CKD irrespective of imaging modality (p for sub-group difference $< .05$, Table 3).

3.4 | Dose-response relationship between eGFR and CFR

In addition to the 14 studies reporting CFR among participants with and without CKD, eight more studies reported CFR among patients with CKD only. In these 22 studies (5966 and 1410 patients with and without CKD, respectively), mean CFR had a significant positive association with mean eGFR such that mean CFR was reduced with a decrease in mean eGFR, suggesting a possible dose-response relationship (Figure 2).

In the multivariate analysis, besides mean eGFR, the presence of diabetes mellitus, and significant epicardial CAD were also significant predictors of mean eGFR, with a negative association. Table S3 summarizes the association of co-variables with CFR in the multivariate analysis.

4 | DISCUSSION

In this meta-analysis of observational studies, we found that mean CFR was lower among patients with CKD as compared to those with normal renal function. The lower mean CFR was driven by a higher mean resting flow but a lower mean stress flow. This difference was significant even in the absence of CAD and irrespective of the diagnostic modality. There appears to be a positive dose-response relation between mean eGFR and mean CFR in the studies.

CFR is the ratio of absolute myocardial blood flow during hyperemia (stress/exercise/maximal vasodilation) to rest.¹⁹ It provides an integrated assessment of coronary abnormalities in the epicardial

TABLE 1 Baseline laboratory, demographic, clinical and imaging characteristics in the included studies

Sr.no	Author	Year	Sample size	Mean age	Women (%)	Diabetes (%)	Hyper-tension (%)	Vessel	Modality	Epicardial CAD	Vasodilator	
Studies enrolling patients with and without CKD												
			No CKD	CKD	No CKD	CKD	No CKD	CKD				
1.	Ragosta ⁸	2004	43	21	52	52	25	100	CKD	No	Adenosine	
2.	Tok ²⁹	2005	14	10	56	57	43	40	0	100	Dipyridamole	
3.	Chade ³⁰	2006	481	124	47	59	57	81	6	32	Adenosine	
4.	Niizuma ³¹	2008	20	21	68	64	30	5	44	68	Adenosine	
5.	Caliskan ³²	2008	39	75	38	36	46	39	0	0	Dipyridamole	
6.	Bozbas ³³	2008	26	60	37	36	31	27	0	4	Dipyridamole	
7.	Koivuviita ³⁴	2009	10	22	59	54	30	41	0	0	Dipyridamole	
8.	Bezante ³⁵	2009	64	12	45	55	20	58	0	100	Adenosine	
9.	Charytan ¹⁴	2010	158	277	50	64	16	39	0	100	Adenosine	
10.	Sakamoto ³⁶	2012	60	13	61	68	57	62	7	15	Nitroglycerine	
11.	Charytan ²²	2017	198	3,748	49	70	66	47	28	29	Dipyridamole	
12.	Tsuda ³⁷	2017	46	46	74	77	59	61	28	72	Adenosine	
13.	Nelson ⁴³	2018	15	15	53	52	40	27	27	47	Acetylcholine	
14.	Bajaj ⁴	2020	236	116	62	73	64	61	31	39	Dipyridamole, Adenosine, Regadenoson	
Studies enrolling patients with CKD alone												
15.	Gorgulu ³⁹	2010	NA	83	NA	37	NA	39	NA	0	NA	Dipyridamole
16.	Nakanishi ⁴⁰	2011	NA	139	NA	73	NA	39	NA	29	NA	Adenosine
17.	Caliskan ⁴¹	2012	NA	37	NA	48	NA	59	NA	NA	NA	Dipyridamole
18.	Murthy ⁴²	2012	NA	866	NA	71	NA	50	NA	45	NA	Dipyridamole
19.	Shah ⁵	2017	NA	168	NA	61	NA	39	NA	61	NA	Dipyridamole, Adenosine, Regadenoson
20.	Wenning ⁴⁴	2020	NA	39	NA	49	NA	36	NA	23	NA	Adenosine
21.	Lakkas ⁴⁵	2020	NA	45	NA	50	NA	33	NA	16	NA	Dipyridamole
22.	Papamichail ³⁸	2020	NA	29	NA	63	NA	38	NA	17	NA	Dipyridamole

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; LAD, left anterior descending artery; LCX, left circumflex artery; NA, not available; PET, positron emission tomography.

TABLE 2 Renal function and coronary flow reserve in individual studies

Sr. no	Author	Year	Mean eGFR (ml/min/1.73 m ²)		Mean coronary flow reserve	
			No CKD	CKD	No CKD	CKD
1	Ragosta ⁸	2004	NA	15	2.7 ± .7	1.6 ± .5
2	Tok ²⁹	2005	87	12	2.6 ± .6	2.0 ± .3
3	Chade ³⁰	2006	76	53	3.0 ± .8	2.6 ± .6
4	Niizuma ³¹	2008	94	7	2.4 ± .5	2.0 ± .5
5	Caliskan ³²	2008	112	11	2.7 ± .7	1.7 ± .4
6	Bozbas ³³	2008	95	32	3.0 ± .6	2.3 ± .5
7	Koivuviita ³⁴	2009	76	22	2.9 ± 1.1	2.6 ± 1.1
8	Bezante ³⁵	2009	92	68 ^r	3.0 ± .7	2.5 ± .8
9	Gorgulu ³⁹	2010	NA	15	NA	1.7 ± .3
10	Charytan ¹⁴	2010	71	60*	2.8 ± 1.3	2.4 ± .9
11	Nakanishi ⁴⁰	2011	NA	46	NA	2.5 ± .7
12	Sakamoto ³⁶	2012	79	49	4.0 ± 1.1	3.1 ± .6
13	Caliskan ⁴¹	2012	NA	6	NA	1.8 ± .4
14	Murthy ⁴²	2012	NA	37	NA	1.5 ± .6
15	Charytan ²²	2017	119	42	2.0 ± .7	1.8 ± .6
16	Shah ⁵	2017	NA	15	NA	1.5 ± .4
17	Tsuda ³⁷	2017	72	44	2.2 ± .4	1.9 ± .4
18	Nelson ⁴³	2018	NA	7	3.1 ± .3	2.3 ± .4
19	Papamichail ³⁸	2020	NA	5	NA	1.6 ± .4
20	Wenning ⁴⁴	2020	NA	15	NA	2.9 ± 2.5
21	Lakkas ⁴⁵	2020	NA	51	NA	2.7 ± .8
22	Bajaj ⁴	2020	85	39	2.0 ± .7	1.6 ± .6

In studies where patients had eGFR > 60 ml/min/1.73 m², CKD was determined by increased albumin-creatinine ratio.

vessels and microvasculature.¹⁹ CFR < 2.0 is prognostic for future cardiovascular events.^{7,19} Its non-invasive assessment by transthoracic doppler, MRI, and PET is a class IIb (Level of Evidence: B) recommendation by the 2019 European Society of Cardiology guidelines for patients with chronic coronary syndromes suspected to have coronary microvascular dysfunction.⁷ CFR measurements correlate across diagnostic modalities, but the actual cut-off with the highest diagnostic accuracy for future CV events might differ.^{20,21} We could not find any study that has compared CFR across all available non-invasive modalities and reported modality-specific CFR cut-offs for future risk.

Increased risk of sudden cardiac death, rather than atherosclerosis-related myocardial infarction, in patients with CKD, led to the recognition that coronary microvascular dysfunction could be one of the underlying mechanisms.^{4,14,22} This microvascular dysfunction is seen in other arterial beds such as retinal and renal.^{23,24}

Our data suggest that lower mean CFR in studies among studies with CKD was due to a significantly higher rest flow and comparable (but statistically lower) stress flow. Low hemoglobin CKD can result in higher resting cardiac output and subsequently higher resting myocardial blood flow, with relatively less effect on peak stress flow. Data from individual studies suggest that in the early stages of CKD, rest flow is increased, and stress flow is comparable.¹⁴

Other pathophysiological mechanisms with a relatively larger impact on myocardial work at rest, such as hypertension and heart rate, may also explain higher rest flow in CKD. The impaired mean peak flow velocities could be due to both functional (smooth muscle dysfunction and inflammation) and structural (vascular calcification and capillary rarefaction) changes that constitute coronary microvascular dysfunction.^{25,26}

Our meta-regression results suggest a possible dose-response relationship such that mean CFR declines proportionately with a decline in mean eGFR. Data from individual studies suggest a stepwise decrease in CFR with increasing stages of CKD, such that there is a marked decline during the initial stages (2.06 and 1.91 in stages 1 and 2, respectively), with a plateau in later stages (1.54 and 1.66 in stages 4 and 5, respectively).²² Stepwise decrease in CFR seen with advancing CKD is likely multifactorial, with confounding from other known factors such as age, hypertension, and diabetes mellitus. Further studies should also explore the effect of renal replacement therapy and renal transplantation on CFR. Newer therapeutics, such as sodium-glucose transporter 2 inhibitors and non-steroidal mineralocorticoid receptor antagonists, are associated with improved CV and renal outcomes.^{27,28} It would be interesting to know if this CV benefit is mediated by any improvement in coronary microvascular dysfunction. Currently, it is unknown

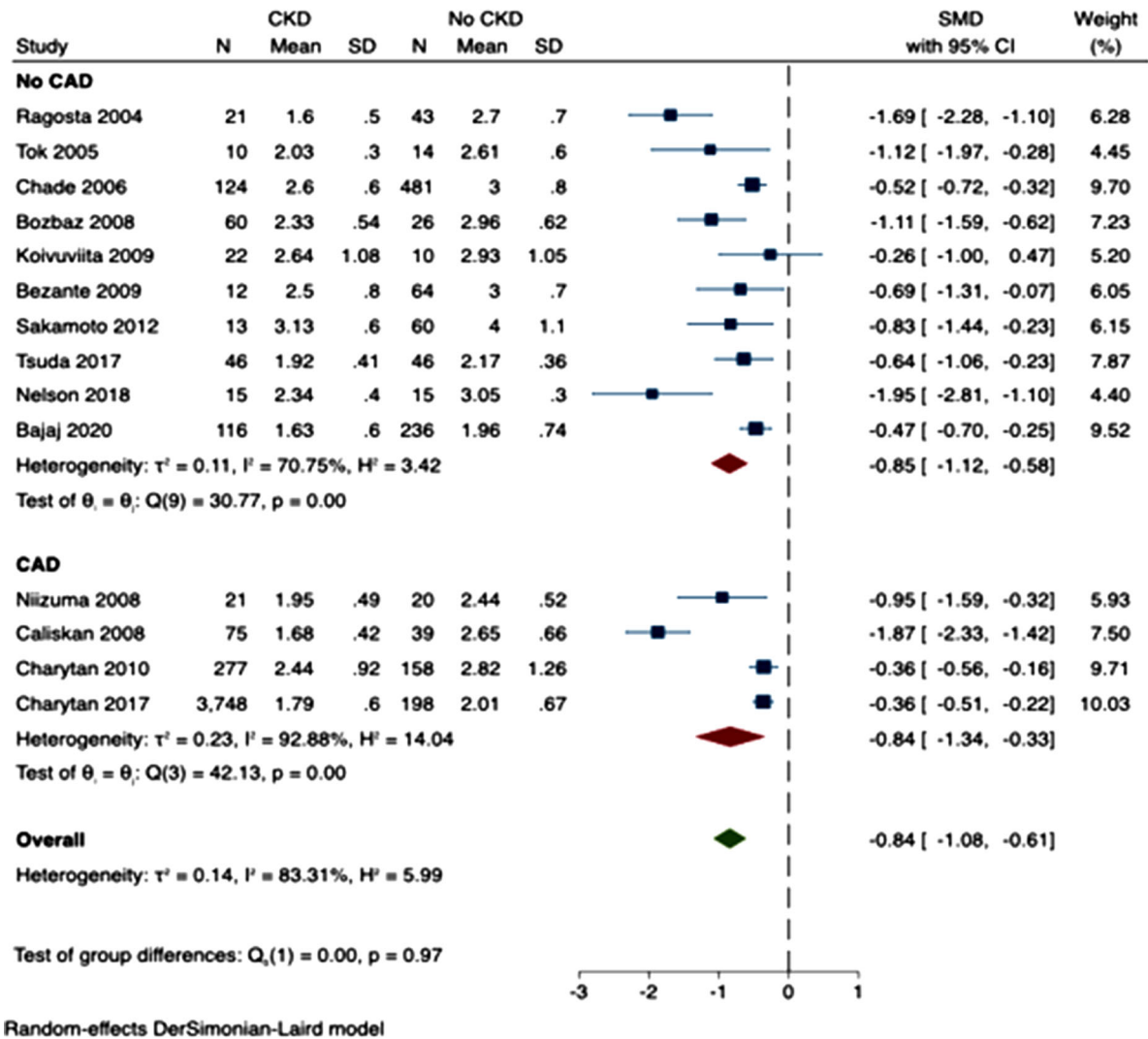


FIGURE 1 Forest plot showing the standardized mean difference for CFR between patients with and without CKD stratified by the presence or absence of epicardial coronary artery disease. The gray square boxes represent the mean difference reported in each study listed in the left column. Black solid diamond markers and associated solid lines represent the summary mean differences and 95% confidence interval (CI). The summary solid red diamond represents the effect estimate for the standardized mean difference using a random-effect meta-analysis. CKD denotes chronic kidney disease; CFR denotes coronary flow reserve; CAD denotes coronary artery disease.

TABLE 3 Summary of subgroup analysis based on imaging modality and epicardial CADR

Subgroup	Mean eGFR (ml/min/1.73 m ²)		Mean CFR		CFR mean difference
	No CKD	CKD	No CKD	CKD	
Imaging modality					
Invasive angiography	75 ± 5	30 ± 6	3.2 ± .4	2.4 ± .5	-.7 (-.9; -.5)
Doppler	96 ± 15	28 ± 4	2.7 ± .3	2.1 ± .4	-1.25 (-1.5; -1.0)
PET	85 ± 29	30 ± 4	2.3 ± .3	1.9 ± .3	-.40 (-.5; -.3)
Presence/absence of significant epicardial CAD					
Present	99 ± 29	20 ± 2	2.5 ± .4	2.0 ± .3	-.83(-1.3, -.3)
Absent	81 ± 7	35 ± 7	2.8 ± .6	2.3 ± .6	-.84 (-1.1, -.6)

Abbreviations: eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; CFR, coronary flow reserve; CKD, chronic kidney disease; PET, positron emission tomography.

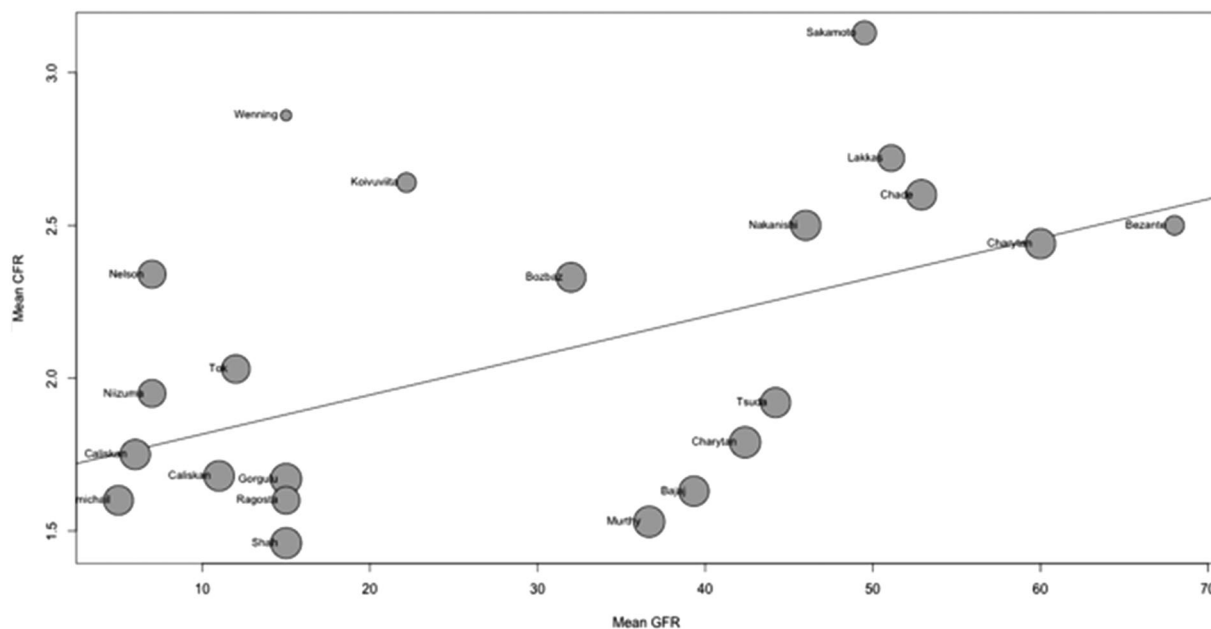


FIGURE 2 Bubble plot showing the meta-regression of the pooled mean eGFR as the independent variable and pooled mean CFR as the dependent variable in patients with CKD. Each bubble represents a study and the size of each bubble reflects the weight in the pooled effect. The slope of the regression line corresponds to the coefficient for eGFR (.01) and the y-intercept corresponds to the CFR when eGFR is zero (1.7). CFR denotes coronary flow reserve; GFR denotes glomerular filtration rate; CKD denotes chronic kidney disease.

if the assessment of coronary microvascular dysfunction improves prognostication in asymptomatic patients beyond already known risk factors.

To the best of our knowledge, this is the first quantitative synthesis of observational studies comparing CFR among patients with CKD and normal renal function. Despite directional consistency, there was significant heterogeneity in the reported results. This is likely due to varying baseline characteristics (such as age and comorbidities), etiology (such as diabetes and glomerulonephritis), and stage of CKD. Our study has important limitations. In studies where we computed mean eGFR from mean serum creatinine using the MDRD equation, patient-level factors such as race and BMI were not available for all studies. There was insufficient data on the etiology of CKD. Some etiologies, such as diabetes mellitus, may independently cause coronary microvascular dysfunction, and their prevalence is likely higher among patients with CKD. We used a random-effect meta-analysis; the results may be fundamentally skewed in a non-random fashion when comparing the two groups. Lastly, patients with renal transplants are a distinct group but were reported with patients without transplants if they had the same eGFR.

5 | CONCLUSION

In this meta-analysis of observational studies, we report that mean CFR is significantly lower in studies with CKD versus no CKD. The lower CFR is due to both higher resting flow and lower stress flow. This dif-

ference remains significant even in the absence of epicardial coronary artery disease.

CONFLICT OF INTEREST

The authors do not have conflicts of interest in relation to the content of this manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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