

## Research Article

# Preinterventional Cystatin C: A Highly Prognostic Marker for All-Cause Mortality after Coronarography

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**Purpose.** Glomerular filtration rate  $<60$  mL/min/1.73 m<sup>2</sup> is associated with increased all-cause mortality. Multiple studies have shown that serum cystatin C is more accurate than serum creatinine for detection of mild to moderate chronic kidney dysfunction. We examined the predictive value of the preinterventional cystatin C for all-cause mortality after contrast media exposition. **Methods.** The prognostic value of preinterventional cystatin C for all-cause mortality was retrospectively analysed in the prospective single-centre “Dialysis-versus-Diuresis” Trial (January 2001–July 2004). Associations during up to 1316 days of followup for all-cause mortality were assessed. The study population consisted of 373 patients (aged 35–89, mean 67 years, 16.4% female). **Results.** During followup, 65 deaths occurred. Multivariate cox regression confirmed the preinterventional CyC level to be an independent predictor of all-cause mortality (odds ratio 2.061, 95% confidence interval 1.054–4.031,  $P = 0.035$ ). Hazard rate ratio for all-cause mortality was increased in the third cystatin C quartile ( $>1.4$  mg/L) compared with the lowest quartile ( $<1.1$  mg/L), 4.12, 95% confidence interval 1.747–9.694 ( $P = 0.001$ ), in the fourth cystatin C quartile ( $>1.6$  mg/L) compared with the lowest quartile, 5.38, 95% confidence interval 2.329–12.427 ( $P < 0.001$ ). **Conclusions.** Cystatin C is significantly associated with all-cause mortality after coronarography, regardless of the age, gender, and glomerular filtration rate.

## 1. Introduction

Chronic kidney disease (CKD) is an important public health problem worldwide with a prevalence of 13% in the Western world [1, 2]. Chronic decreased glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m<sup>2</sup> is associated with an increased risk of developing cardiovascular disease (CVD) [2–6] and strongly associated with increased all-cause mortality [4]. Even mild to moderate renal impairment is associated with an increased risk of mortality [3, 4].

Cystatin C (CyC) and serum creatinine (SCr) are used as marker of renal function. A series of studies in the recent years have shown that serum CyC is superior to SCr for detection of mild to moderate renal impairment [7–9]. Comparably, CyC was also found to have a higher predictive value than SCr and GFR, based on Modification of Diet in Renal Disease equation for death so far only in selected cohorts such as elderly persons ( $>65$  years) [10–13].

However, the role of preinterventional CyC in predicting all-cause mortality after contrast media (CM) exposition is not revealed. Our aim was to examine if the preinterventional cystatin C predicts all-cause mortality after coronarography.

## 2. Patients and Methods

**2.1. Study Design and Methods.** Our report is a retrospective analysis of the cohort of the three hundred and seventy-three patients of the Dialysis-versus-Diuresis (DVD) trial by Reinecke et al. [14] to answer the question if the preinterventional CyC level has a predictive value according to the all-cause mortality of patients after contrast media (CM) exposition.

The DVD trial of Reinecke et al. was a randomized controlled, single-centre study from January 2001 to July 2007, to demonstrate the preventive value of a single haemodialysis, of hydration plus N-acetylcysteine and of hydration only

TABLE 1: Baseline characteristics depending on preinterventional CyC quartiles.

(mg/dL)	Total	CyC <1.06	CyC 1.07–1.26	CyC 1.27–1.58	CyC >1.59	<i>P</i>
Patients in group, <i>n</i> (% of total)	373 (100.0)	97 (26.0)	90 (24.1)	94 (25.2)	92 (25.2)	
CyC, mean ± s.d., (mg/dL)	1.39 ± 0.5	0.9 ± 0.14	1.17 ± 0.06	1.41 ± 0.09	2.09 ± 0.44	
Women, <i>n</i> (%)	61 (16.4)	11 (11.3)	12 (13.3)	17 (18.1)	21 (22.8)	0.144
Age, mean ± s.d., (years)	67.4 ± 10.1	62.3 ± 11.0	67.8 ± 9.7	69.4 ± 9.9	70.2 ± 7.9	<0.001
Adipositas, <i>n</i> (%)	91 (24.4)	16 (16.5)	27 (30.0)	26 (27.7)	22 (23.9)	0.147
History of smoking, <i>n</i> (%)	206 (55.2)	52 (53.6)	54 (60.0)	55 (58.5)	45 (48.9)	0.659
Diabetes, <i>n</i> (%)	109 (29.2)	15 (15.5)	27 (30.0)	33 (35.1)	34 (37.0)	0.004
Hypertension, <i>n</i> (%)	280 (75.1)	68 (70.1)	74 (82.2)	70 (78.7)	68 (73.9)	0.220
Hyperlipidemia, <i>n</i> (%)	240 (64.3)	62 (63.9)	63 (70.0)	61 (64.9)	54 (58.7)	0.618
Cardiovascular disease in family, <i>n</i> (%)	142 (38.1)	42 (43.3)	30 (33.3)	37 (39.4)	33 (35.9)	0.549
Coronary heart disease, total, <i>n</i> (%)	287 (76.9)	71 (73.2)	77 (85.6)	75 (79.8)	64 (69.6)	0.001
1-vessel disease	51 (13.7)	15 (15.5)	18 (20.0)	10 (10.6)	8 (8.7)	
2-vessel disease	90 (24.1)	34 (35.1)	19 (21.1)	21 (22.3)	16 (17.4)	
3-vessel disease	146 (39.1)	22 (22.7)	40 (44.4)	44 (46.8)	40 (43.5)	
Peripheral arterial occlusive disease, <i>n</i> (%)	66 (17.7)	9 (9.3)	15 (16.7)	24 (25.5)	18 (19.6)	0.030
Coronary heart disease and peripheral arterial occlusive disease, (%)	297 (76.9)	75 (77.3)	79 (87.8)	77 (81.9)	66 (71.7)	0.050
Ejection fraction ≤35%, <i>n</i> (%)	19 (5.1)	3 (3.1)	4 (4.4)	10 (10.6)	2 (2.2)	0.037
Previous myocardial infarction, <i>n</i> (%)	164 (44.0)	40 (41.2)	40 (44.4)	49 (52.1)	35 (38.0)	0.245
Haemoglobin, mean ± s.d., (mg/dL)	13.6 ± 1.7	14.3 ± 1.5	13.9 ± 1.5	13.5 ± 1.7	12.8 ± 1.7	<0.001
Baseline creatinine, mean ± s.d., (mg/dL)	1.35 ± 0.4	1.07 ± 0.1	1.2 ± 0.2	1.35 ± 0.3	1.77 ± 0.5	<0.001
Baseline GFR, mean ± s.d., (mL/min/1.73 m <sup>2</sup> )	58.5 ± 16.5	73.5 ± 11.9	63.7 ± 10.7	55.2 ± 11.9	41.0 ± 11.2	<0.001
Chronic kidney disease, total, <i>n</i> (%)						<0.001
Stage 1	8 (2.1)	8 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Stage 2	176 (47.2)	79 (81.4)	62 (68.9)	30 (31.9)	5 (5.4)	
Stage 3	175 (46.9)	10 (10.3)	27 (30.0)	64 (68.1)	74 (80.4)	
Stage 4	14 (3.8)	0 (0.0)	1 (1.1)	0 (0.0)	13 (14.1)	
Stage 5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Amount of contrast media, mean ± s.d., (mg/dL)	189 ± 79	186 ± 80	197 ± 89	193 ± 71	181 ± 75	0.521

Comparison of CyC quartiles. Differences were analysed by ANOVA-*F*-test for continuous variables and by chi-square test for dichotomous or categorical variables.

GFR: glomerular filtration rate; s.d.: standard deviation. The stages of CKD (chronic kidney disease) are mainly based on estimated GFR [MDRD formula]: stage 1 (≥90 mL/min/1.73 m<sup>2</sup>), stage 2 (60–89 mL/min/1.73 m<sup>2</sup>), stage 3 (30–59 mL/min/1.73 m<sup>2</sup>), stage 4 (15–29 mL/min/1.73 m<sup>2</sup>), and stage 5 (<15 mL/min/1.73 m<sup>2</sup> or dialysis). *n*: number of patients affected.

according to the frequency of contrast medium-induced acute kidney injury (CI-AKI).

**2.2. Patients.** The inclusion criteria of the DVD trial were an elective left heart catheterization between January 1, 2001 and July 6, 2004 and a SCr level between ≥1.3 mg/dL and ≤3.5 mg/dL, initially measured by the Jaffé-method.

Patients were excluded if they had an acute or recently suffered myocardial infarction (within 30 days), an advanced chronic heart failure (New York Heart Association class IV), a previous CM exposition within 7 days, or a monoclonal gammopathy.

**2.3. Measurement of Cystatin C Level, Determination of the Preinterventional Renal Function.** The baseline (preinterventional) serum CyC level was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) with a nephelometer (BNII, Dade Behring).

The baseline (preinterventional) SCr concentration was measured by the Jaffé-method.

The GFR was estimated based on the preinterventional SCr with the simplified Modification of Diet in Renal Disease equation [15].

TABLE 2: Baseline characteristics and all-cause mortality.

	Total	Died	Alive	<i>P</i>
Patients in group, <i>n</i> (% of total)	373 (100.0)	65 (17.4)	308 (82.6)	
Baseline cystatin C, mean $\pm$ s.d., (mg/dL)	1.39 $\pm$ 0.5	1.63 $\pm$ 0.6	1.34 $\pm$ 0.47	<0.001
Baseline creatinine, mean $\pm$ s.d., (mg/dL)	1.35 $\pm$ 0.4	1.5 $\pm$ 0.4	1.31 $\pm$ 0.4	0.001
Baseline GFR, [MDRD]				
Mean $\pm$ s.d., (mL/min/1.73 m <sup>2</sup> )	58.5 $\pm$ 16.5	50.8 $\pm$ 13.8	60.1 $\pm$ 16.6	<0.001
Chronic kidney disease, total, <i>n</i> (%)				0.004
Stage 1	8 (2.1)	0 (0.0)	8 (2.6)	
Stage 2	176 (47.2)	19 (29.2)	157 (51.0)	
Stage 3	175 (46.9)	43 (66.2)	132 (42.9)	
Stage 4	14 (3.8)	3 (4.6)	11 (3.6)	
Stage 5	0 (0.0)	0 (0.0)	0 (0.0)	
Women, <i>n</i> (%)	61 (16.4)	10 (15.4)	51 (16.6)	0.816
Age, mean $\pm$ s.d., (years)	67.4 $\pm$ 10.1	69.8 $\pm$ 9.9	66.8 $\pm$ 10.1	0.030
Haemoglobin, mean $\pm$ s.d., (mg/dL)	13.6 $\pm$ 1.7	13.1 $\pm$ 2.1	13.7 $\pm$ 1.6	0.008
Adipositas, <i>n</i> (%)	91 (24.4)	18 (27.7)	73 (23.7)	0.496
History of smoking, <i>n</i> (%)	206 (55.2)	37 (56.9)	169 (54.9)	0.765
Diabetes mellitus, <i>n</i> (%)	109 (29.2)	24 (36.9)	85 (27.6)	0.133
Hypertension, <i>n</i> (%)	280 (75.1)	40 (61.5)	240 (77.9)	0.003
Hyperlipidemia, <i>n</i> (%)	240 (64.3)	26 (40.0)	214 (69.5)	<0.001
Cardiovascular disease in family, <i>n</i> (%)	142 (38.1)	19 (30.7)	123 (39.6)	0.099
Coronary heart disease, total, <i>n</i> (%)	287 (76.9)	50 (76.9)	237 (77.0)	0.119
1-vessel disease	51 (13.7)	3 (4.6)	48 (15.6)	
2-vessel disease	90 (24.1)	17 (26.2)	73 (23.7)	
3-vessel disease	146 (39.1)	30 (46.2)	116 (37.7)	
Peripheral arterial occlusive disease, <i>n</i> (%)	66 (17.7)	13 (20.0)	53 (17.2)	0.594
Coronary heart disease and peripheral arterial occlusive disease, <i>n</i> (%)	297 (79.2)	51 (78.5)	246 (79.9)	0.865
Ejection fraction $\leq$ 35%, <i>n</i> (%)	19 (5.1)	8 (12.3)	11 (3.6)	0.004
Previous myocardial infarction, <i>n</i> (%)	164 (44.0)	29 (44.6)	135 (43.8)	0.908
Amount of contrast media, mean $\pm$ s.d., (mg/dL)	189 $\pm$ 79	191 $\pm$ 78	189 $\pm$ 79	0.831

Comparison of groups died during followup or not. Differences were analysed by ANOVA-*F*-test for continuous variables and by chi-square test for dichotomous or categorical variables.

GFR: glomerular filtration rate; s.d.: standard deviation. The stages of CKD (chronic kidney disease) are mainly based on estimated GFR [MDRD formula]: stage 1 ( $\geq$ 90 mL/min/1.73 m<sup>2</sup>), stage 2 (60–89 mL/min/1.73 m<sup>2</sup>), stage 3 (30–59 mL/min/1.73 m<sup>2</sup>), stage 4 (15–29 mL/min/1.73 m<sup>2</sup>), and stage 5 (<15 mL/min/1.73 m<sup>2</sup> or dialysis). *n*: number of patients affected.

**2.4. Angiography.** All patients underwent a heart angiography by using the isoosmolar, nonionic CM (Ultravist 370TM, Schering AG, Berlin, Germany). The intervention was performed by using arterial access from the femoral or brachial arteries. The number of diseased coronary arteries as well as the left ventricular ejection fraction were categorized by the classification of the American Heart Association and the American College of Cardiology [16].

**2.5. Long Term Followup.** An assessment for adverse events was sent once to all patients. If the patients assessment did not return (121 cases), a followup was made by telephone with the patient, a referring physician.

**2.6. Statistical Analysis.** We used for dichotomous or categorical variables the chi-square test and for continuous variables

the ANOVA-*F*-test. Each test was performed two-sided and was considered to be significant with *P* values less than 0.05.

Significant parameters in the univariate analyses, depending on the all-cause mortality, were chosen as covariates in the multivariate cox regression model. One univariate cox regression model was made to determine the predictive values of the CyC quartiles for the all-cause mortality. All statistical analyses were performed with SPSS 20.0 for Windows.

### 3. Results

For the DVD trial by Reinecke et al., a total of 8,653 patients were screened between January 2001 and July 2007, for inclusion. A total of 462 patients fulfilled inclusion criteria. A total of 424 were included in the trial [14]. During

the trial 12 patients dropped out, because the SCr levels within the planned followup were missing. Finally, for this retrospective report, 39 patients also dropped out because of missing preinterventional CyC levels. Consecutively, this retrospective analysis includes all 373 participants, whom preinterventional serum SCr and CyC levels were measured.

For analyses regarding the role of CyC for evaluating the risk of all-cause mortality the patients were divided into four groups: CyC quartiles 1–4.

Indications for invasive imaging of these patients were characterization of structural heart disease in patients with dilatative or ischaemic cardiomyopathy, valvular defects, tachyarrhythmias, or congenital heart disease.

**3.1. Baseline Characteristics.** In our cohort a total of 365 (97.9%) patients had a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m<sup>2</sup> (CKD stage ≥ 2). The mean age was 67.4 years (±10.1 s.d.) and a total of 297 (76.9%) patients suffered from a known CVD (287 (76.9%) patients from coronary heart disease (CHD) and 66 (17.7%) patients from peripheral arterial occlusive disease (PAD)). A total of 109 (29.2%) patients suffered from diabetes mellitus.

With regard to the CyC subgroups, patients with higher CyC levels were older ( $P < 0.001$ ), had higher baseline SCr levels ( $P < 0.001$ ), lower GFR ( $P < 0.001$ ), lower haemoglobin levels ( $P < 0.001$ ), and suffered more frequently from diabetes mellitus ( $P = 0.004$ ). There were no significant differences concerning adipositas ( $P = 0.147$ ), hyperlipidemia ( $P = 0.618$ ), and between genders ( $P = 0.144$ ). Baseline characteristics according to CyC quartiles are shown in Table 1.

**3.2. Preinterventional Cystatin C as a Predictor of All-Cause Mortality after Contrast Media Exposition.** The median duration of long-term followup was 553 days (range 63 to 1316 days).

A total of 65 (17.4%) patients died during followup. The preinterventional serum CyC concentration was significantly associated with all-cause mortality in the followup.

The hazard rate ratio for all-cause mortality was increased in the third CyC quartile (>1.4 mg/L) compared with the lowest quartile (<1.1 mg/L) 4.12, 95% confidence interval 1.747–9.694 ( $P = 0.001$ ), and in the fourth CyC quartile (>1.6 mg/L) compared with the lowest quartile 5.38, 95% confidence interval 2.329–12.427 ( $P < 0.001$ ) (Table 3).

All factors, which were found to be significant ( $P < 0.05$ ) associated with all-cause mortality in univariate analyses (Table 2), were entered into a multivariate cox regression model (Table 4). These were baseline CyC, baseline SCr, baseline GFR, age, hyperlipidemia, hypertension, ejection fraction ≤35%, and the haemoglobin level. Even after adjustment of these covariates, the baseline CyC turned out to be a significant independent predictor of all-cause mortality (odds ratio 2.061, 95% confidence interval 1.054–4.031,  $P = 0.035$ , Table 4). Hyperlipidemia, hypertension, and ejection fraction ≤35% also turned out to be independent predictors for all-cause mortality (Table 4). The cox regression model of long-term survival of the patients after contrast media exposure

TABLE 3: Univariate cox regression of CyC quartiles and all-cause mortality.

(mg/dL)	Odds ratio	95% CI		P
CyC <1.06				< <b>0.001</b>
CyC 1.07–1.26	1,909	0.739	4,929	0.181
CyC 1.27–1.58	<b>4,115</b>	1,747	9,694	<b>0.001</b>
CyC >1.59	<b>5,380</b>	2,329	12,427	< <b>0.001</b>

Univariate analysis by cox regression: preinterventional CyC quartiles and all-cause mortality; CI: confidence interval.

TABLE 4: Multivariate analysis by binary logistic regression of all-cause mortality.

	Odds ratio	95% CI		P
Baseline Cystatin C	<b>2.061</b>	<b>1.054</b>	<b>4.031</b>	<b>0.035</b>
Baseline Creatinine	0.731	0.212	2.524	0.621
Baseline GFR	0.977	0.942	1.013	0.206
Age	1.022	0.994	1.052	0.130
Hyperlipidemia	<b>0.510</b>	<b>0.303</b>	<b>0.857</b>	<b>0.011</b>
Hypertension	<b>0.562</b>	<b>0.331</b>	<b>0.955</b>	<b>0.033</b>
Ejection fraction ≤35%	<b>3.863</b>	<b>1.779</b>	<b>8.388</b>	<b>0.001</b>
Haemoglobin	0.917	0.777	1.081	0.303

Multivariate analysis by cox regression of all-cause mortality; CI: confidence interval.

depending on the preinterventional CyC quartiles is shown in Figure 1. The frequency of all-cause mortality depending on the CyC quartiles is shown in Figure 2 and demonstrates a stepwise and significant association.

## 4. Discussion

This study aimed to investigate whether the preinterventional cystatin C concentration in blood predicts an elevated risk of all-cause mortality. We found that the preinterventional CyC level in the blood flow is an independent predictor for all-cause mortality after CM exposition, with a higher predictive value than SCr and GFR, based on Modification of Diet in Renal Disease equation.

CyC is used as marker of renal function and also superior to SCr for detection of mild to moderate chronic kidney dysfunction [7–9]. CyC is produced at a constant rate by all nucleated cells [17], is not significantly bound to protein in the blood [18]. CyC is completely filtered by the glomeruli and undergoes complete tubular reabsorption and catabolism, without any secretion [19]. Hence it is not related to the muscle mass [20]. However, it seems that some factors like inflammation, thyroid dysfunction, and corticosteroids alter serum CyC levels independent of GFR [21].

The study population was divided into four groups according to their CyC concentrations. The risk of death was found to increase with increasing CyC level in the study group: mortality was the highest in the highest quartile of CyC concentrations (28%, with 7%, 12%, and 22% in the first, second, and third quartile, resp.).

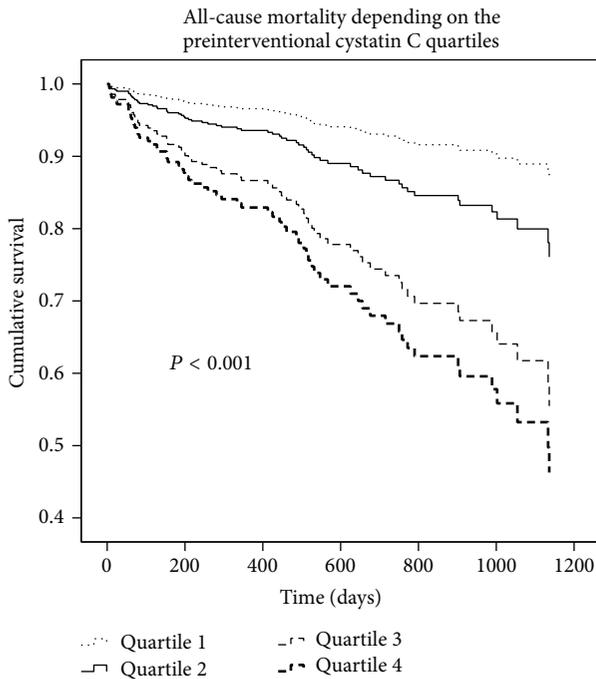


FIGURE 1: A cox regression model of long-term survival of the patients after contrast media exposure depending on the preinterventional cystatin C quartiles.

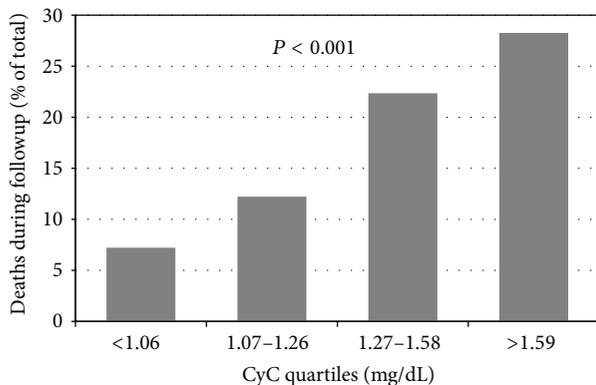


FIGURE 2: All-cause mortality depending on the preinterventional cystatin C quartiles. The figure demonstrates a stepwise and significant association between cystatin C and mortality.

In our study most patients had a mild or moderate renal impairment. In this area SCr tends to overestimate the GFR [22]. Consequently it is not surprising that in our cohort the SCr and the GFR, based on Modification of Diet in Renal Disease equation, appeared after adjustment to the other non- and biomarker baseline variables not to be independent predictors of all-cause mortality. This is in line with Shlipak et al., who reported 2006 that SCr was not associated with increased mortality. Their cohort had mainly a mild to moderate renal impairment [23]. In another study Shlipak et al. found that CyC had a much stronger association with mortality risk than SCr or creatinine-based estimates of GFR

[11]. Stevens and Levey even suggested that CyC is linked to mortality risk independently of kidney function in the elderly [24]. Similar assumptions have been anticipated by Shlipak et al. [10, 11].

So we can assume that CyC has a higher predictive value than SCr and the GFR for mortality in mild to moderate chronic kidney dysfunction.

We do not find any significant difference between men and women, whether related to the CyC levels or all-cause mortality. This is in line with previous CyC studies like Dharnidharka et al., 2002 [25].

Although we found across the CyC quartiles an association with older age, increasing frequency of diabetes mellitus, and decreasing haemoglobin levels in both men and women, which is in accordance with the well-known fact that renal function declines with age and higher frequency of diabetes [26, 27].

Contrary to former studies, we could not witness a significant association between CyC levels and adipositas, hyperlipidemia, and hypertension [28]. We found a significant independent association between hyperlipidemia, hypertension, ejection fraction  $\leq 35\%$ , and all-cause mortality. In this study we found no significant association between PAD or CHD and a higher risk of all-cause mortality.

Our study is limited by its retrospective, single-center design. Other important limitations are the fact that we cannot be certain whether the strong association of CyC with the all-cause mortality based due solely to its correlation with renal function. We cannot exclude the possibility of confounding due to potential associations between CyC with diseases that are independent of its correlation with renal function.

Shlipak et al. reported that CyC is an independent predictor of all-cause mortality in adults who were 65 years of age or older. We could expand these findings and conclude that CyC is a promising predictor of outcome in clinical patients after coronarography. CyC remained an independent predictor of death, regardless of the age, gender, and GFR.

### Abbreviations

- CyC: Cystatin C
- SCr: Serum creatinine
- GFR: Glomerular filtration rate
- CKD: Chronic kidney disease
- CM: Contrast media
- CI-AKI: Contrast medium-induced acute kidney injury
- CVD: Cardiovascular disease.

### Conflict of Interests

All authors have read and approved the paper. The authors do not have any conflict of interests to disclose.

### References

- [1] J. Coresh, E. Selvin, L. A. Stevens et al., "Prevalence of chronic kidney disease in the United States," *Journal of the American Medical Association*, vol. 298, no. 17, pp. 2038–2047, 2007.

- [2] National Kidney Foundation, "K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification," *The American Journal of Kidney Diseases*, vol. 39, supplement 1, no. 2, pp. S1-S266, 2002.
- [3] M. J. Sarnak, A. S. Levey, A. C. Schoolwerth et al., "Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention," *Circulation*, vol. 108, no. 17, pp. 2154-2169, 2003.
- [4] A. S. Go, G. M. Chertow, D. Fan, C. E. McCulloch, and C.-Y. Hsu, "Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization," *The New England Journal of Medicine*, vol. 351, no. 13, pp. 1296-1370, 2004.
- [5] N. S. Anavekar, J. J. V. McMurray, E. J. Velazquez et al., "Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction," *The New England Journal of Medicine*, vol. 351, no. 13, pp. 1285-1295, 2004.
- [6] T. Ninomiya, Y. Kiyohara, Y. Tokuda et al., "Impact of kidney disease and blood pressure on the development of cardiovascular disease: an overview from the Japan arteriosclerosis longitudinal study," *Circulation*, vol. 118, no. 25, pp. 2694-2701, 2008.
- [7] R. D. Perrone, N. E. Madias, and A. S. Levey, "Serum creatinine as an index of renal function: new insights into old concepts," *Clinical Chemistry*, vol. 38, no. 10, pp. 1933-1953, 1992.
- [8] O. F. Laterza, C. P. Price, and M. G. Scott, "Cystatin C: an improved estimator of glomerular filtration rate?" *Clinical Chemistry*, vol. 48, no. 5, pp. 699-707, 2002.
- [9] D. J. Newman, H. Thakkar, R. G. Edwards et al., "Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine," *Kidney International*, vol. 47, no. 1, pp. 312-318, 1995.
- [10] M. G. Shlipak, R. Katz, M. J. Sarnak et al., "Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease," *Annals of Internal Medicine*, vol. 145, no. 4, pp. 237-246, 2006.
- [11] M. G. Shlipak, M. J. Sarnak, R. Katz et al., "Cystatin C and the risk of death and cardiovascular events among elderly persons," *The New England Journal of Medicine*, vol. 352, no. 20, pp. 2049-2060, 2005.
- [12] T. Keller, C. M. Messow, E. Lubos et al., "Cystatin C and cardiovascular mortality in patients with coronary artery disease and normal or mildly reduced kidney function: results from the AtheroGene study," *European Heart Journal*, vol. 30, no. 3, pp. 314-320, 2009.
- [13] W. Koenig, D. Twardella, H. Brenner, and D. Rothenbacher, "Plasma concentrations of cystatin C in patients with coronary heart disease and risk for secondary cardiovascular events: more than simply a marker of glomerular filtration rate," *Clinical Chemistry*, vol. 51, no. 2, pp. 321-327, 2005.
- [14] H. Reinecke, M. Fobker, J. Wellmann et al., "A randomized controlled trial comparing hydration therapy to additional hemodialysis or N-acetylcysteine for the prevention of contrast medium-induced nephropathy: the Dialysis-versus-Diuresis (DVD) trial," *Clinical Research in Cardiology*, vol. 96, no. 3, pp. 130-139, 2007.
- [15] A. S. Levey, T. Greene, J. W. Kusek, and G. J. Beck, "MDRD Study Group: simplified equation to predict glomerular filtration rate from serum creatinine," *Journal of the American Society of Nephrology*, vol. 11, Article ID A0828, 2000.
- [16] S. C. Smith Jr., J. T. Dove, A. K. Jacobs et al., "ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines)—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary angioplasty) Endorsed by the society for Cardiac Angiography and Interventions," *Circulation*, vol. 103, no. 24, pp. 3019-3041, 2001.
- [17] M. Abrahamson, I. Olafsson, A. Palsdottir et al., "Structure and expression of the human cystatin C gene," *Biochemical Journal*, vol. 268, no. 2, pp. 287-294, 1990.
- [18] D. W. Cockcroft and M. H. Gault, "Prediction of creatinine clearance from serum creatinine," *Nephron*, vol. 16, no. 1, pp. 31-41, 1976.
- [19] S. Herget-Rosenthal, T. Feldkamp, L. Volbracht, and A. Kribben, "Measurement of urinary cystatin C by particle-enhanced nephelometric immunoassay: precision, interferences, stability and reference range," *Annals of Clinical Biochemistry*, vol. 41, no. 2, pp. 111-118, 2004.
- [20] M. Madero, M. J. Sarnak, and L. A. Stevens, "Serum cystatin C as a marker of glomerular filtration rate," *Current Opinion in Nephrology and Hypertension*, vol. 15, no. 6, pp. 610-616, 2006.
- [21] M. Pricker, P. Wiesli, M. Brändle, B. Schwegler, and C. Schmid, "Impact of thyroid dysfunction on serum cystatin C," *Kidney International*, vol. 63, no. 5, pp. 1944-1947, 2003.
- [22] A. S. Levey, R. L. Berg, J. J. Gassman, P. M. Hall, and W. G. Walker, "Creatinine filtration, secretion and excretion during progressive renal disease," *Kidney International*, vol. 36, no. 27, pp. S73-S80, 1989.
- [23] M. G. Shlipak, C. L. W. Fyr, G. M. Chertow et al., "Cystatin C and mortality risk in the elderly: the health, aging, and body composition study," *Journal of the American Society of Nephrology*, vol. 17, no. 1, pp. 254-261, 2006.
- [24] L. A. Stevens and A. S. Levey, "Chronic kidney disease in the elderly—how to assess risk," *The New England Journal of Medicine*, vol. 352, no. 20, pp. 2122-2124, 2005.
- [25] V. R. Dharnidharka, C. Kwon, and G. Stevens, "Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis," *The American Journal of Kidney Diseases*, vol. 40, no. 2, pp. 221-226, 2002.
- [26] R. D. Lindeman, J. Tobin, and N. W. Shock, "Longitudinal studies on the rate of decline in renal function with age," *Journal of the American Geriatrics Society*, vol. 33, no. 4, pp. 278-285, 1985.
- [27] R. A. DeFronzo, "Diabetic nephropathy: etiologic and therapeutic considerations," *Diabetes Reviews*, vol. 3, no. 3, pp. 510-564, 1995.
- [28] A. Servais, P. Giral, M. Bernard, E. Bruckert, G. Deray, and C. Isnard Bagnis, "Is serum cystatin-C a reliable marker for metabolic syndrome?" *The American Journal of Medicine*, vol. 121, no. 5, pp. 426-432, 2008.



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