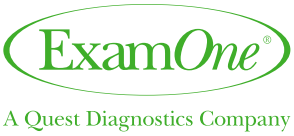
Cystatin C

Is it Ready for Underwriting “Prime Time”?

Hank George, FALU



Preface

Our paper, "Cystatin C: A Promising Test for Insurance Screening," was published in early 2009. At that time, most studies about this test were focused solely on its role as a novel kidney disease marker.

In the interim, several hundred new studies have greatly expanded our knowledge about cystatin C in a broad range of contexts. For this reason, a new comprehensive literature review is needed if we are to understand the true underwriting implications of this test.

This paper is meticulously documented on the basis of 273 studies, reports and commentaries, most of which were published after our first paper.

Thanks to the gracious support of our proactive cosponsors (whose logos adorn the cover of this report), we were able to do the research necessary to properly prepare it.

The purpose of this undertaking was to determine whether cystatin C has sufficient value to be embraced as a screening and reflexive test in life, disability, long term care and critical illness underwriting.

In our view, this question is unequivocally answered in the affirmative based on the weight of evidence revealed between 2009 and mid-2016.

Hank George, FALU

August 15, 2016

Table of Contents

"Cystatin C is a marker for kidney dysfunction and has a broad spectrum of roles in numerous cellular systems, ranging from anti-viral and antibacterial properties, bone resorption, tumor metastasis, modulation of inflammatory responses, and cell proliferation and growth."

Sebastien Gauthier
Nathan S. Kline Institute, Orangeburg, NY
Frontiers in Bioscience
3(2012):541

Background and Terminology

Cystatin C is a cysteine protease inhibitor found in all nucleated cells, produced by all tissues and present in all bodily fluids. [Akerblom-2, Levy-1]

It is freely filtered at the glomerulus and is almost entirely reabsorbed in the renal tubular system. [Chen-3, Lee-1]

Cystatin C is highly stable and unaffected by transport time. [Winsemius]

The process of globally standardizing cystatin C measurement is under way. [Lieske]

This does not affect us because we use the reference ranges reported in medical records on those (as yet uncommon) occasions when cystatin C is cited in an APS. The insurance laboratories use the Roche cystatin C assay.

Cystatin C levels have *"serious clinical implications rather than a mere reflection of kidney functions."* [Huerta, Xu]

As we reported in 2009, gender-based differences in cystatin C are minimal and do not impact its use in underwriting.

Cystatin C increases steeply at older ages: [Werner]

Age Range	Median Cystatin C (mg/L)
60-69	0.93
70-79	1.04
≥ 80	1.24

Note: hereafter all cystatin C values cited in this paper will be in mg/L (milligrams per liter).

Cystatin C is increased with obesity, but has a far more significant association with abdominal adiposity markers than with BMI. [Godreau, Panaich]

Cystatin C has negative associations with tobacco smoking, heavy alcohol intake and level of physical activity. [Akerblom-1, Powell, Riverol, Toft]

It also has a negative association with telomere length, a recognized mortality risk factor. [Zhang-6]

Cystatin C has a strong, independent and positive relationship with the following inflammation markers, in persons with and without chronic kidney disease (CKD):

- C-reactive protein (CRP, hs-CRP)
- Interleukin-6 (IL-6)
- Tumor necrosis factor alpha (TNF-a)
- Plasminogen activator inhibitor-1 1(PAI-1)
- Fibrinogen

[Deo-2, Keller-1, Qing, Sarnak. Tsuboi, Windhausen, Wu]

It is also positively linked to homocysteine, lipoprotein Lp(a), uric acid and insulin. [Lee-1, Mena, Sarnak, Sim]

Cystatin C is unaffected by statins. [Motovska]

Cystatin C and Creatinine as Blood Markers

"Serum creatinine testing should not be used as a stand-alone source for assessing kidney function."

Andrew S. Levy, MD
Tufts Medical Center
Journal of the American Medical Association
313(2015):837

Creatinine is currently the primary kidney disease blood marker in clinical medicine (and underwriting). [Woo]

Nevertheless, creatinine has major drawbacks.

- It is more likely than cystatin C to be significantly impacted by age, gender, race, limb amputation and anorexia.
- It reflects skeletal muscle trauma and increases with high levels of physical activity.
- It decreases with skeletal muscle mass loss (sarcopenia) in the elderly and is often false-negative in the presence of significant chronic kidney disease (CKD).
- It increases with heavy red meat intake.
- It is increased by creatine dietary supplements.
- It decreases in those following strict vegetarian diets.

[Baxman, Dupont, Levy-3, Polonsky, Taglieri]

Cystatin C and Creatinine in Specific Impairment Contexts

These are the findings in various contexts where cystatin C and creatinine were compared:

We found 12 studies published after our 2009 paper wherein cystatin C and serum creatinine were compared in terms of impact on significant clinical outcomes:

- Cystatin C was superior to creatinine as a marker for early onset chronic kidney disease (CKD). [Yashiro]
- In patients with type 2 diabetes, creatinine was inferior to cystatin C in detecting early renal impairment. [El-Shafey]
- After following 143 post-PCI patients for 9 months, cystatin C was an independent predictor of worsening renal function in those taking an ACE inhibitor. Creatinine was not. [Kanda]
- Cystatin C was more accurate than creatinine in gauging the extent of renal impairment in patients with gout. [Choe]
- Creatinine was elevated in patients treated with dronedarone for atrial fibrillation. Cystatin C was not, and elevated creatinine was deemed to be false positive. [Duncker]
- Cystatin C was an independent predictor of PAD in men. Creatinine was not. [Joosten]
- In 3,044 elderly subjects, creatinine was elevated in only 34% of those with high cystatin C readings, reflecting the adverse impact of sarcopenia on creatinine. [Deo-2]
- In the MESA study (6,653 CVD-free adults followed for 6 years), cystatin C was an independent predictor of incident cardiovascular disease (CVD) events when added to the Framingham Risk Score. Creatinine was not. [Ito]
- In 1,410 subjects, ≥ age 65 and followed for 10 years, cystatin C was superior to serum creatinine as a predictor of CV

events. [Beilby]

- Cystatin C was superior to creatinine as a marker for death or rehospitalization within 12 months in 247 patients with acute heart failure. [Campbell]
- Cystatin C was an independent predictor of post-liver transplantation mortality. Creatinine was not. [Allen]
- In 816 subjects followed for 17 years, cystatin C was an independent marker for all-cause mortality. Creatinine was not. [Tangri]

Bottom line: cystatin C has many advantages over creatinine as a prospective underwriting screening test, most notably at older ages.

Cystatin C and Circulatory Disease

"Cystatin C is associated with the presence of subclinical CVD and appears to be an independent predictor of death, cardiovascular events and heart failure among elderly individuals."

Hiroki Ito, MD, et al
Loyola University Medical Center
American Journal of Epidemiology
174(2011):949

We will review the impact of cystatin C in all domains of circulatory disease, demonstrating the broad range of its implications as a major CVD risk marker.

Blood Pressure/Hypertension

Tientcheu et al evaluated 3,027 subjects and found that 17.8% had masked hypertension (defined as normal clinical blood pressure readings but significantly elevated home BP levels). Cystatin C was an independent marker for undiagnosed masked HTN.

In 200 elderly patients with longstanding HTN, mean cystatin C levels were twice as high (1.84) in those with confirmed target organ damage as compared to those free of this complication (0.92). [Tan]

Prat and coworkers showed that > 70th percentile of cystatin C was a significant marker for LVH in hypertensive patients with normal serum creatinine and eGFR-Cr levels.

Mena and colleagues found that cystatin C was associated with a significant decrease in nocturnal diastolic BP, as well as wider diurnal and nocturnal pulse pressure.

Levin et al reported that cystatin C was a marker for greater likelihood of hypertension in type 2

diabetes (T2DM).

In elderly patients with hypertension and coronary disease, cystatin C was *"…closely related to the degree of blood pressure and coronary artery stenosis."* [Wang-2]

The risk of cardiac events and all-cause mortality in 142 hypertensive patients (mean age 64) was 5.7-fold greater in the 4th vs. 1st cystatin C quartile. The cut-off for higher risk was > 1 mg/L. [Garcia Gallego]

Atherosclerosis

Elevated monocyte count is both a marker for and a mediator of atherosclerotic plaque formation. Cystatin C in the 5th quintile was independently associated with 44-57% greater odds of monocytosis after risk factor adjustment. This is thought to be a potential mechanism linking cystatin C to greater risk of coronary disease. [Ganda]

In a twin study, there were *"shared genetic influences"* for having both CVD and high cystatin C. [Arpegard-1]

In 2,018 CKD patients, *"…kidney function as measured by cystatin C is an independent risk factor for CAC [coronary artery calcium]"* after multivariate risk factor adjustment. [He]

Asselbergs et al showed that the 2-D echocardiographic prevalence of multiple cardiac calcifications increased by cystatin C quartile in 3,929 community-dwelling subjects ≥ 65.

In 104 patients with stable chest pain, cystatin C was an independent predictor of a positive CAC score. [Ruiz-Salas]

Overall Relationship with Atherosclerotic Disease

Lee et al (UCLA) did a meta-analysis of 14 studies encompassing 22,509 subjects and reported that cystatin C was *"…strongly and independently associated with subsequent CVD risk."* [Lee-2]

Age Range	Hazard Ratio Highest vs. Lowest Cystatin C Levels
All CVD	2.62
CAD	1.72
Stroke	1.82
Heart failure	2.2
All-cause mortality	2.23

CVD risk per standard cystatin C deviation was 1.34-fold increased.

Coronary Artery Disease (CAD)

In a Norwegian study, each standard deviation of cystatin C increased the odds of CAD after risk factor adjustment. This assessment suggested that while cystatin C was not causally related to coronary disease, it is a biomarker for the disease process prior to detection of other routine clinical and laboratory evidence. [Svensson-Farcom-2]

In subjects free of CKD, the multivariate risk of CAD increased 65% with elevated cystatin C. [Zhao-1]

We reported this study in our first paper and are showing the findings here to emphasize the cystatin C/CAD connection. After following 990 ambulatory Californian CAD patients for 37 months, adjusted all-cause mortality increased progressively by cystatin C quartile. HR in the 4th vs. 1st quartile was 3.6, and results were similar for new CV events and heart failure. [Ix-1]

In a 2,162-subject CAD patient cohort followed for 3.7 years, those in the top quartile of cystatin C had an 86% increased risk of CV death, as compared to the pooled results in the three lower quartiles. Notably, there was no association

between creatinine and CV death. [Keller-2]

Angiographically Confirmed CAD

We found 11 studies addressing this question and will cite four of them:

In 936 patients free of renal impairment, cystatin C levels independently predicted for the presence and extent of CAD. The authors considered cystatin *"…a marker for CAD severity."* [Wang-3]

Negrusz-Kawecka and colleagues showed that cystatin C was a significant marker for extent of angiographic CAD, as well as being inverse to LVEF and predictive of ACS events.

Koc et al found that cystatin C correlated significantly for the presence and extent of angiographic CAD at a cutoff of 0.82 mg/L.

In 280 patients with proven CAD and hypertension, top quartile cystatin C was a marker for intima-media thickness and multivessel CAD. [Dzielinska]

Abid, Dandana, Doganer, Li, Niccoli, Shen and Zhang-2 provide corroborative evidence of the significant association between cystatin C and the extent of angiographic CAD.

Acute Coronary Syndrome (ACS)

Ferraro et al did a meta-analysis of 15 studies prior to 2011. The hazard ratio risk for all-cause mortality ranged from 2-fold to 3.6-fold increased when cystatin C was higher than their reference range. The odds of new events post-ACS were 1.7-fold to 9.6-fold higher.

Nead and associates tracked 470 patients with angiographically confirmed CAD for 5.6 years. CAD-specific mortality in the highest cystatin C subset was increased 79%, and all-cause mortality was 74% higher, after adjusting for all conventional risk factors.

In 423 post-menopausal females, the risk of CV death and/or MI was 5.6-fold greater, and the odds of all-cause mortality and/or MI increased 3.8-fold. [Patel-2]

Cavusoglu and coworkers followed 364 patients referred for angiography for 5 years. After accounting for medical history, usual risk factors and 8 other biomarkers (including NT-proBNP), mortality was 65% greater with elevated cystatin C.

A 2015 meta-analysis revealed that the the MI risk was 78% greater with elevated vs. normal cystatin C, with the magnitude of that excess risk being twice as high after vs. before 5-years' follow-up. [Bi]

In 1,128 Dutch NSTEMI (non-ST-elevated MI) patients, multivariate mortality was 2-fold higher in the 3rd vs. 1st cystatin C tertile. [Windhausen]

Ten additional investigations revealed similar outcomes. [Derzhko, Fu, Garcia Acuña, Ge, Kilic, Ristiniemi, Manzano-Fernandez, Tonkin, Wei]

In 277 post-PCI cases, cystatin C was an independent predictor of ACS and cerebrovascular events, with the risk 30% higher with each 0.1 mg/L increase. [Sai]

In a follow-up of 153 consecutive STEMI patients, the multivariate combined risk of reinfarction/death was 3.9-fold greater for elevated cystatin C, as compared to a 3.5-fold increase if the LVEF (left ventricular ejection fraction) was ≤ 40%. [Silva]

In another study, after observing 1,638 post-CABG patients for 3.5 years, the fully adjusted hazard ratios for all-cause mortality were 2.0 and 1.6 in the 5th and 4th cystatin C quartiles, respectively. Creatinine was not a multivariate risk predictor. [Dardashti]

Angeli et al tracked 2,757 post-PCI cases, mean age 63, for 2 years. Cystatin C significantly reclassified 15% of conventionally lower risk subjects into higher risk categories with substantial all-cause mortality.

In 108 anterior MI survivors who had a PCI, cystatin C at admission was a multivariate marker for impaired myocardial perfusion, poor cardiac functional recovery and onset of CHF. [Tang-2]

In non-ACS cases, cystatin C has been shown to be a significant predictor of left atrial and left ventricular size and function. [Liu-2, Patel-1]

Heart Failure

Cystatin C distinguished between heart failure patients with (LVEF ≥ 50%) and without (LVEF ≤ 40%) preserved systolic function. [Sanders-van Wijk]

Cystatin C increased significantly in elderly hypertensive patients with preserved LV function, increased E/E' ratio and elevated pulmonary wedge pressure. [Huerta]

Cystatin C was a multivariate marker for readmission in acute heart failure, with a 3-fold greater risk in the 3rd tertile, independent of creatinine and NT-proBNP. [Manzano-Fernandez-1]

After multivariate adjustment, cystatin C was a potent marker for cardiac death in heart failure. The risk is 7.2-fold and 19.5-fold greater in the 3rd and 4th quartiles, respectively, as compared to the 1st quartile. [Naruse]

Cerebrovascular Disease

Cystatin C was an independent predictor of carotid plaque in 1,477 subjects free of CKD at baseline. [Wen]

Subjects in the top tertile of cystatin C (> 1.04) had an independently greater risk of extra cranial carotid stenosis. One standard deviation increased this risk 3-fold. [Umemura]

In another study, cystatin C was the only renal marker significantly linked to ultrasonographic carotid plaque formation. [Zhu]

The hazard ratio for major acute cardiac events (MACE) was 2-fold greater in the 5th versus 1st cystatin C quintile in 1,004 patients with asymptomatic carotid artery disease. This was after adjustment for conventional risk factors, eGFR-Cr and serum creatinine (none of which significantly correlated with MACE risk). [Hoke]

Cystatin C was also a marker for cerebral small vessel disease. [Toyoda, Wada]

Cystatin C was independently linked to 1st-ever stroke, with the risk in the 4th and 5th quintiles being 2-fold and 2.9-fold higher, respectively, than in the 1st quintile. [Yang-1]

The prevalence of subacute brain infarction was independently associated with cystatin C but not with creatinine. [Seliger]

In 1,017 patients with a prior cerebral infarction, cystatin C was a multivariate significant predictor of recurrent CI and large vessel atherosclerosis. [Zeng]

Cerebral microbleeds are clinically silent, but are strongly linked to advanced microvascular ischemia and increased risk of future intracranial hemorrhagic events. Cystatin C was an independent predictor of these lesions, especially deep and infratentorial bleeds. [Oh, Zhang-5]

Peripheral Arterial Disease (PAD)

In the MESA study, elevated cystatin C was a univariate – but not multivariate – marker for progression to below-normal ankle:brachial index (ABI) after 10 years' follow-up of 6,814 subjects. [Garimella]

In a California study, there was a U-shaped relationship between cystatin C and ABI, with 27% and 21% greater risks of low (<0.9) and elevated (>1.4) results, respectively. [Ix-2]

Cooke et al showed that cystatin C had a superior correlation with abnormal ABI than all conventional markers, including diabetes and

smoking, in 540 high-risk patients.

In 272 T2 diabetics free of evidence of nephropathy, the risk of ABI ≤ 0.9 increased 1.7-fold per standard deviation of cystatin C. [Hug]

Cystatin C was an independent predictor of major circulatory events after 12 months in patients with angiographically proven PAD. [Yang-2]

In 240 patients with PAD, cystatin C was a marker for hard CV events and all-cause mortality. [Kim-2]

Cystatin C in Other Circulatory Risk Contexts

Reeve et al followed 210 chest pain patients for 6 months after discharge from a coronary care unit. Those with cystatin C in the 4th quartile, as contrasted to the 1st quartile, had 10.4-fold greater risk of cardiac events even after adjustment for GRACE score.

In 549 patients, only cigarette smoking and cystatin C were independent predictors of the presence of vasospastic angina following ergonovine challenge, and those in the top tertile of cystatin C had a 2.60-fold greater risk of multivessel spasm. [Lee-3]

Funayama and associates also showed that elevated cystatin C was an independent marker for vasospastic disease.

A University of Pennsylvania investigation revealed that patients with CAD in the top cystatin C quartile were 2-fold more likely to have inducible ischemia with stress echocardiography. This risk increased to 3-fold and to over 5-fold in patients without a prior CABG or not on beta-blockers, respectively. [Deo-1]

Age and cystatin C were the only independent markers for arterial stiffening in 206 Japanese patients. [Nakamura]

Cystatin C was a marker for rapidly growing abdominal aortic aneurysms. [Woloszko]

Fenster et al found that cystatin C was a predictor of right ventricular ejection fraction, mass (size), strain and diastolic dysfunction in patients with pulmonary arterial hypertension. This was independent of NT-proBNP.

In 20,572 subjects, mean age 59 and followed for 17 years, the risk of sick sinus syndrome increased 31% per 0.5 mg/L rise in cystatin C. [Jenssen]

Baseline and serial cystatin C readings were significantly associated with nonresponse to cardiac resynchronization therapy (CRT). [Chaterjee]

Among 3,044 septuagenarians followed for 6 years, cystatin C was an independent marker for adverse CV outcomes and for CV death. Cardiac mortality was 2-fold higher overall when cystatin C was > 1.18 vs. < 0.84, and 5-fold greater specifically in those having a prior CV event. [Deo-2]

Cystatin C and Renal Disease

> *"Cystatin C has been theorized to be involved in the progression of coronary artery disease as well as the composition and rupture of atherosclerotic plaque and may thus reflect the intersection between renal dysfunction and coronary artery disease."*
>
> Sergio Manzano-Fernandez, MD, et al
> *American Journal of Cardiology*
> 110(2012):1240

We will look at several studies showing the relationship between cystatin C and cardiac risks.

Muslimovic and colleagues showed that cystatin C is strongly correlated with cardiac biomarkers in patients with chronic kidney disease (CKD). Its associations with fibrinogen, serum albumin, D-dimer and antithrombin III were stronger, in relation to cardiovascular morbidity,

than those of creatinine.

These investigators called cystatin C *"…an important and strong predictor of cardiovascular risk in CKD patients stages 2 to 4 in comparison to serum creatinine and eGFR."*

Cystatin C is a marker for structural cardiac abnormalities in patients with early CKD. These include both concentric and eccentric LVH, as well as left atrial enlargement. [Sakuragi]

Meng at al found that cystatin C > 0.88 mg/L was an independent predictor of CV events in patients with eGFR > 60.

Cystatin C and microalbuminuria worked synergistically to determine CKD risk in 5,422 subjects, mean age 61 and followed for 5 years: [Shastri-1]

	Relative Risk
Microalbuminuria	1.4
Elevated Cystatin C	1.6
Both	2.1

Cystatin C and NT-proBNP

In the 2015 Life Underwriting Requirements Study, roughly 70% of participating insurers indicated they were using NT-proBNP. This remarkable test has also begun to replace more cumbersome and customer-unfriendly screening with ECG.

The potential for using NT-proBNP and cystatin C together at older ages depends in part on how they correlate in terms of mortality risk.

Therefore, we will look at studies where this question was addressed.

According to one cardiology researcher, "*CysC adds complementary information to the data provided by NT-proBNP.*" [Tang-1]
Swedish cardiologists followed 464 primary care patients, presenting with suspicious symptoms but no HF diagnosis, for 10 years. If cystatin C and NT-proBNP were both in the 4th quartile, all-cause mortality was 16-fold and 13-fold greater after 5 years and 10 years, respectively. When summarizing their findings, the authors stated that:

> *"Both cystatin C and NT-proBNP provided significant, independent prognostic information… when analyzed as continuous variables in a multivariate analysis and when they were adjusted for each other as well as for other background variables."*
>
> Urban Alehagen, MD, et al
> Department of Cardiology
> Linkoping University Medical School
> *European Journal of Heart Failure*
> 11(2009):354

Dupont reported the same association between the two tests after following 823 patients with stable HF for 3 years.

Akerblom-1 et al showed that NT-proBNP and cystatin C were independent and synergistic in terms of assessing 1-year post-ACS mortality.

Six additional investigations published since our 2009 paper further affirm the independent implications of NT-proBNP and cystatin C, consistent with the assumption that they would serve a complementary, rather than redundant, function in insurance screening and reflexive testing. [Arsenault, Bielecka-Dabrowa, Blok, Brouwers, Bjurman, Nilsson-1]

Bottom lines:

Studies between 2009 and 2016 document the wide range of substantial independent associations of cystatin CV and circulatory disease risk. Available evidence suggests that cystatin C and NT-proBNP are both independent and synergistic CV risk markers.

Based on these diverse data, cystatin C should

be a highly productive underwriting resource, alone or ideally in tandem with NT-proBNP for screening life, critical illness and long-term care applicants.

Cystatin C and Diabetes Mellitus

Cystatin C is a marker for increased risk of developing T2 diabetes and gestational diabetes. [Magnusson, Zhato-1]. However, it is only a univariate predictor for impaired fasting glucose (IFG). [Sim]

Nephropathy

Cystatin C was a superior indicator of incipient nephropathy in both T1 and T2 diabetes because it elevates prior to the onset of albuminuria and elevated creatinine. It was described as a *"useful, practical tool"* in this context. [Borges, Jeon, Papadopoulou-Marketou]

"Single cystatin C measurements carry important prognostic information on their own, even without prior context" and are independent of and additive to albuminuria in predicting all-cause and CV mortality in elderly T2 diabetics. [De Boer]

Retinopathy

In 1,119 diabetics, cystatin C was significantly associated with progressive changes from mild to moderate retinopathy, with a rising prevalence across quartiles. [Wong]

It was described as a *"promising marker"* for diagnosing and monitoring retinopathy in type 1 diabetics. [Domingueti-2]

Neuropathy

In 937 T2 diabetics, the odds ratio for peripheral neuropathy (PN) increased progressively across cystatin C quartiles, and was 5.9-fold higher in the 4th vs. 1st quartile.

After adjustment for all variables, including creatinine (which was not independently pre-

dictive), the risk of PN doubled when cystatin C was > 1.25 in men and > 1.05 in women. [Hu-1]

Another study showed that the odds ratio for cardiovascular autonomic neuropathy in T2 diabetics was 5.25-fold higher for each standard deviation increase in cystatin C, after multivariate analysis. [Chung]

Lower Extremity Disease

In 1,609 type 2 diabetics, mean cystatin C was 1.53 in those with lower limb ischemia (LLI) vs. 1.08 when LLI was absent. After full adjustment, the odds ratio was 3.40 in the 4th vs. 2nd quartile. [Liu-1]

The risk of *"incurable foot ulceration"* was 6-fold higher in the 4th vs. 1st cystatin C quartile. [Ai]

Additional Diabetes Considerations

The odds of developing hypertension in T2 diabetics increased 60% in the 4th cystatin C quartile after full adjustment, including DM duration. [Gao]

Okyay described cystatin C as a *"surrogate marker"* for multivessel vs. single vessel CAD in diabetics.

Petrica found that cystatin C is an independent predictor of cerebral vessel endothelial dysfunction, an atherosclerosis precursor in diabetics.

Uruska reported that cystatin C elevation is predictive of decreased insulin sensitivity.

Bottom line: cystatin C would make a considerable contribution in underwriting diabetes types 1 and 2.

Cystatin C and Metabolic Syndrome

Cystatin C was a significant predictor of metabolic syndrome diagnosis in middle-aged and elderly individuals. [Asefy, Liu-4, Tanindi]

In patients with metabolic syndrome, the odds of increased carotid intima-media thickness (CIMT) were 4-fold greater in the 4th vs. 1st cystatin C quartile. [Huang]

In 211 subjects, mean age 57 with normal eGFR, cystatin C was an independent predictor of asymptomatic CAD on angiography, and it increased proportionally with the number of affected vessels in those with metabolic syndrome. [Qing]

Additional Disorders Impacted by Cystatin

COPD

The risks of COPD and exacerbated COPD are both increased with elevated cystatin C, which was also significantly associated with the magnitude of airflow obstruction measured by FEV-1. The investigators describe cystatin C as *"…a potential biomarker for lung parenchymal destruction in COPD…"* [Zhang-3]

In 90 patients with exacerbated COPD, cystatin C was independently predictive of duration of post-exacerbation convalescence. [Zhang-4]

At a threshold of 1.59 mg/L, cystatin C increased the risk of in-hospital death due to exacerbation (relative risk: 5.49). [Hu-2]

Depression

In 3,075 community-dwelling elders, ages 70-79, 15% had a cystatin C reading > 1.25. Compared to subjects with lower readings, their risk of developing depression was 2.1-fold greater. [Miney]

Olson found that cystatin C significantly correlated with the risk of depression in both men and women, affecting multiple well-being and functional domains.

Rheumatoid Arthritis (RA) and Systemic Lupus (SLE)

Unlike creatinine, cystatin C correlated with the risk of developing RA, as well as with disease duration, Framingham Risk Score, elevated erythrocyte sedimentation rate and homocysteine levels. [Lertnawapan-1]

Tejera-Segura found that elevated cystatin C identified RA patients at high risk for subclinical atherosclerosis.

In another study, cystatin C was the only effective renal marker for monitoring RA disease activity. [Targonska-Stepniak]

In 76 RA patients age 50 and over, the risk of myelosuppression due to methotrexate Rx increased 2.3-fold per 0.1 mg/L over the upper limit of the cystatin C reference range. [Hayashi]

Cystatin C was the only renal marker linked to increased risk of SLE; it significantly correlated with 5 inflammatory markers, including ESR and IL-6. [Lertnawapan-2]

Peixoto found that cystatin C was superior to creatinine as a marker for nephropathy in SLE.

Cancer

Park reported that cystatin C was a powerful marker for invasive and metastatic potentials in breast cancer, considering it to be a key consideration in deciding between mastectomy and conservative management.

Bodnar showed that cystatin C was an independent predictor of all-cause mortality in patients with renal cell carcinoma.

Polycystic Ovary Syndrome (PCOS)

Cystatin C was an independent predictor of PCOS after adjusting for traditional risk factors; it was also a marker for developing metabolic syndrome in PCOS patients. [Cinar, Gozashti, Yildrim]

Age-related Macular Degeneration (AMD) of the Retina

In 4,926 subjects free of AMD at baseline and

followed for 15 years, cystatin C was an independent predictor of both early onset and exudative AMD, but not for disease progression. [Klein]

A second study of 5,874 patients revealed that those with cystatin C in the top decile had an 80% increased AMD risk compared to subjects in the 1st decile. [Chong]

Other conditions

Unlike creatinine, cystatin C levels declined substantially in obstructive sleep apnea patients shown to be compliant with continuous positive airway pressure (CPAP) therapy. [Zhang-4]

Cystatin C has been shown to be a strong predictor of Parkinson disease (PD), higher stage PD and the risk of mild cognitive impairment in PD patients. [Chen-2]

Cystatin C is effective in grading the severity of thyroid dysfunction in both subclinical and overt disease. [Simeoni]

In 30,239 subjects age 45 and older, cystatin C > 1.12 was independently associated with the risk of sepsis after adjusting for age, gender, demographics, health behaviors, chronic diseases, inflammation markers, albumin-creatinine ratio and eGFR. [Powell]

Bottom line: as with NT-proBNP and red blood cell distribution width (RDW), we are continuing to learn more each year about cystatin C and a growing list of chronic disease processes. This is not surprising when one considers that cystatin C is present in all nucleated cells and is also a marker for occult inflammation.

Cystatin C and Cognitive Dysfunction

The association between cystatin C and cognitive dysfunction is one of the most important aspects of this paper.

Most insurers currently require routine screening at ≥ age 70 with one or more labor-intensive cognitive tests. These tests are usually administered paramedically, by technicians with little or no formal training in this role.

Like ECGs, these tests are consummately customer-unfriendly, and we have been told many times by producers that cognitive screening is offensive to their clients.

Because of the emerging potential for cystatin C to replace conventional cognitive screening in underwriting, we are covering all studies related to this subject and frailty, including studies published prior to our first cystatin C paper.

> *"Serum cystatin C has an important role in predicting the transition from MCI to dementia, which indicates that the level of CysC plays an important part in the prediction of cognitive decline."*
>
> Wei Wei Chen, MD, et al
> *European Review for Medical and Pharmacological Sciences*
> 19(2015):2957

> *"Cystatin C is a therapeutic candidate that can potentially prevent brain damage and neurodegeneration."*
>
> Paul M Mathews, MD
> NYU School of Medicine
> *Ageing Research Reviews*
> E-published 6/19/16

It is well established that impaired renal function is a major risk factor for cognitive function decline. [Davey, Elias, Helmer, Jassel, Wang-4]

At least 6 investigations have proven that cystatin C localizes within beta-amyloid deposits in the brain. [Deng, Levy-2, Sastre, Selenica, Kaeser, Mi]

Both amyloid beta peptides and tau proteins measured in cerebrospinal fluid positively correlate with cystatin C and cognitive impairment, independent of age, gender and apolipoprotein E genotype. [Sundloff-2]

Plasma amyloid levels increase in familial and sporadic Alzheimer dementia (AD). Cystatin C was elevated in those who progressed to AD from MCI, as well as in those who progressed from normal cognition. [Lopez]

The Alzheimer Disease Conundrum

Numerous studies have been conducted to assess the relationship between cystatin C and AD.

While only elevated cystatin C is linked to developing AD at younger geriatric ages, several investigators have shown that both very low and, in most studies, elevated readings are markers for AD at age 75 and older. [Craig-Shapiro, Ghidoni, Slinin, Sundelof-1]

Cystatin C and Cognitive Impairment in Community-Dwelling Elders

Our first concern is identifying applicants with early cognitive decline, in part because those with overt dementia are unlikely to make it through the routine underwriting process undiscovered.

In 2,140 ostensibly healthy subjects, mean age 74, cystatin C correlated significantly with the percentage developing cognitive impairment over 4.3 years: [Sarnak]

Cystatin C Quartile	% Cognitive Impairment
1 (≤ 0.90)	4.5%
2 (0.91-1.01)	5.4%
3 (1.02-1.15)	5.3%
4 (≥ 1.16)	10.5%

In 6,184 healthy elders, cystatin C ≥ 1.24 was a significant risk factor for cognitive dysfunction after 11 years' follow-up. This study adjusted for inflammatory markers. Cystatin C's impact was equivalent to that of shorter telomere length. [Nettiksimmons]

In 1,332 dementia-free females, mean age 77 and followed for 10 years, the risk of cognitive impairment/dementia was modestly increased when cystatin C was > 1.25. The authors explained that their study was hampered by *"…insufficient power to determine the association because of the low prevalence of high cystatin C."* [Slinin]

In 1,320 UK subjects, ages 60-64, eGFR-cystatin C was strongly linked to verbal memory and reaction time impairment, consistent with asymptomatic early cognitive impairment. [Silverwood]

In 1,858 subjects from the NHANES study, mean age 70, Morris et al looked at the impact of creatinine and cystatin C on the DSST (Digit- Symbol Substitution Test). The DSST is a widely used cognitive screening test (the higher the score, the lower the risk). Cystatin C was a significant predictor of cognitive decline; creatinine was not:

	DSST Score	
Mean Reading	**< 34**	**≥ 34**
Cystatin C	1.02	0.97 (p = <0.001)
Creatinine [mmol/L]	77.0	76.0 (p = 0.426)

Riverol et al assessed 735 elders, mean age 73, and reported that cystatin C elevations were predictors of low scores on the DSST, Mini-Mental Status Exam and Benton Visual Retention Test.

In 3,030 elders enrolled in the Health ABC Study, those with high baseline cystatin C had worse scores on the Modified Mini-Mental Status Exam and DSST. After 7 years' follow-up, those with higher cystatin C showed *"…a more pronounced decline and higher incidence of cognitive impairment."* [Yaffe-1]

In the Cardiovascular Health Study involving 3,907 subjects ≥ age 65, eGFR-cystatin C < 60 was significantly correlated with lower scores on the Modified Mini-Mental Status Exam and the DSST. [Darsie]

Cystatin-based eGFR – but not creatinine-based eGFR – was independently associated with an abnormal Trail-Making Test. In this study, low eGFR-cystatin C (<60) was also linked to increased white matter brain hyperdensities, evidence of prior brain infarction, and ABI < 0.9. [Kim-3]

In 821 subjects ≥ 55, the top tertile of cystatin C correlated with poorer performance on the Trails A, Trails B and Boston Naming tests. [Yaffe-2]

In 447 Swedish elders with psychiatric diagnoses, high cystatin C was an independent marker for MCI and AD. [Nilsson-2]

Alosco et al found that cystatin C positively correlated with attention and executive dysfunction in bariatric surgery patients.

White matter hyperdense lesions and compromised microstructural integrity of normal-appearing white matter are associated with increased risk of cognitive impairment.

In the Rotterdam Study, diffusion MRI revealed that eGFR-cystatin C was a marker for impaired white matter integrity, whereas eGFR-creatinine was not. [Sedaghat]

Three studies have demonstrated that high cystatin C is a marker for the presence and severity of white matter lesions (even after adjusting for apolipoprotein E genotype in one investigation). [Galluzzi, Rajagopalan, Riverol]

Bottom line: cystatin C is an emerging marker for the presence and progression of cognitive impairment, based on significant correlations with AD-related proteins, MRI brain lesions, clinical diagnoses and unfavorable results on a variety of widely deployed cognitive function tests.

Cystatin C and Physical Frailty

Substantial decline in physical function (frailty) is an insidious and potent mortality risk factor in the elderly.

Many insurers screen for this during paramedical exams, using the Timed-Get-Up-and-Go (TUG) test or by measuring walking speed.

These tests have the same baggage as cognitive screening tests; it would be a major step forward if they could be replaced by cystatin C screening.

"Cystatin C was consistently associated with functional declines independent of other biomarkers."

Anne B. Newman, MD, et al
Graduate School of Public Health, University of Pittsburgh
International Journal of Epidemiology
E-published June 2016

Newman et al included cystatin C as one of 5 biomarkers for mobility limitation and ADL difficulties, accompanied by carotid intima-media thickness (CIMT), fasting glucose, pulmonary function testing and brain MRI.

The 1st assessment of the association between cystatin C and declining physical function was done in 2006 as part of the Health, Aging and Body Composition Study.

Fried et al discovered that subjects in the 4th cystatin C quartile (≥ 1.13) had a 40% greater risk than those in the 1st quartile of satisfying the Cardiovascular Health Study frailty criteria. This was after all adjustments, including gait speed and muscle strength.

In the Study of Osteoporotic Fractures, Ensrud et al followed 1,384 females, mean age 67, for 20 years. The odds of retaining good mobility were significantly higher in the 1st and 2nd vs. 4th cystatin C quartiles. The authors described cystatin C as *"…a promising marker for successful aging."* [Ensrud-2]

In 3,043 elders, mean age 74, the odds of combined impairment in multiple physical function parameters was 32% increased per standard deviation rise in cystatin C.

These parameters consisted of 300-meter walking time, grip strength, knee extension strength and overall lower extremity performance score. The cystatin C result was after adjustment for demographics, lifestyle variables, chronic health conditions, inflammation markers and level of physical activity. [Odden]

In 342 patients > age 65 with a prior ACS event, cystatin C was a multivariate marker for frailty. The odds ratio was 2.4 for readings > 1.2. Cystatin C was independent of NT-proBNP (which was not a significant indicator) and was the leading predictor among 19 screening biomarkers. [Sanchis]

In 538 females > age 75 followed for 4 years, cystatin C was positively and independently associated with severe sarcopenia. The odds ratio for an elevated cystatin C was 1.83. Creatinine was not significant. [Kim-1]

In 1,332 community-dwelling females, mean age 77, cystatin C had a positive correlation with the risk of multiple IADL impairments: [Slinin]

Cystatin C Quartile	% IADL Impairments
1	27.8%
2	34.5%
3	38.5%
4	45.6%

In the Osteoporotic Fracture in Men study (1,602 subjects, mean age 74), Hart et al reported on the association between cystatin C quartiles and 5 leading frailty criteria.

These odds ratios comparing the 4th versus 1st cystatin C quartiles were fully adjusted (including creatinine):

	Odds Ratio 4th vs. 1st Cystatin C Quartile
Shrinking	2.31
Weakness	1.32
Exhaustion	1.91
Slowness	1.65
Decreased Activity	1.89

They also compared cystatin C and creatinine odds ratios for pre-frailty and frailty. In each case, the risks are cited based on contrasting the 4th vs. 1st quartile:

	Pre-Frailty	Frailty
Cystatin C	2.07	4.17
Creatinine	1.11	1.21

Lastly, they reported on cystatin C quartiles and the risks of having either ≥ 3 IADL deficits or "fair/poor" self-rated health. Note that each risk doubles between the 3rd and 4th quartiles.

Cystatin C Quartile	% ≥ 3 IAD Deficits	% "Fair/Poor" Self-Rated Health
1	2.4%	10.2%
2	2.6%	12.7%
3	4.6%	12.5%
4	10.2%	24.2%

In the Cardiovascular Health Study of 3,459 frailty-free subjects followed for 4 years, lower eGFR-cystatin C was independently correlated with higher risk of incident and prevalent frailty. [Dalrymple]

In the Framingham Offspring Study following 1,226 subjects for 6.6 years, eGFR-cystatin C < 60 had a 55% fully adjusted increased risk of mobility disability. These subjects also had slower gait speed. Liu-3]

For the record, there is another enticing potential predictor of both premature physical decline and cognitive dysfunction in the elderly that could theoretically be added to risk histories taken on older age applicants.

Numerous studies document a powerful association between average nighttime sleep and both premature frailty and cognitive impairment:

- At ≥ 9 hours, the odds of a low MMSE score were 2.5 times greater than in those with 7-8 hours sleep per night.
- Another large study also showed a strong correlation with low MMSE, in this case limited to those getting 11+ hours sleep.
- The relative risk of a dementia diagnosis doubled at ≤ 5 and ≥ 9 hours.
- Similarly, the risk of mild cognitive dysfunction was increased 5 times at ≤ 5 hours and 3.7 times at ≥ 9 hours.
- Carefully measured sleep duration revealed that ≥ 9 hours' sleep accelerated patients' objective physical decline based on performance measures.
- > 9 hours was linked to over 2 times higher risk of IADL deficits.
- In females, > 9 hours was also shown to independently predict for poorer performance on the Timed Get-Up and Go (TUG) test we use in elder underwriting, as well as reduced muscle strength.
- In another investigation, ≤ 5.5 hours sleep reduced grip strength 97% and increased the odds of IADL deficits 93% in elderly women.

[Altena, Benito-Leon, Faubel, Fex, Potvin, Ramos, Spira, Stenholm, Tsubota-Utsugi]

By asking applicants how many hours of sleep, on average, they get per night, we would have

another marker for these issues, as well as for increased all-cause mortality.

At least one UK outsourced teleinterview service provider has included this question in their model questionnaire.

Cystatin C and Other Aging-Related Issues

In 2,140 subjects, mean age 74 and followed for 4.3 years, adjusted loss of successful aging increased 27% between the 1st and 4th cystatin C quartile. [Sarnak]

Cystatin C was a significant risk factor for falls in 2 studies. [Schwartz, Pelaez]

In 1,477 males ≥ 65, cystatin C was positively linked to decreased bone marrow density. [Fujita]

Osteoprotegerin is a marker for bone mineral density. Cystatin C is an independent predictor of osteoprotegerin levels in men ≥ age 50. [Kulcsar-Jakab]

Two studies revealed that cystatin C is an independent marker for hip fracture risk. [Barbour, Ensrud-1]

Cystatin C and Creatinine in eGFR

There have been many studies comparing conventional creatinine-based eGFR (eGFR-Cr) estimation methods with eGFR using cystatin C (eGFR-CysC).

Therefore, we have included a review of these studies to further underscore and emphasize the substantial advantages of cystatin C over creatinine as a blood test in underwriting.

> *"I find cystatin C a very useful tool for evaluating CKD patients. If the cystatin C eGFR is greater than the creatinine eGFR, this is usually reassuring. On the other hand, if the cystatin C eGFR is lower than the creatinine eGFR, such individuals appear to have a worse prognosis."*
>
> John C. Lieske, MD
> Medical Director
> Mayo Clinic Renal Testing Laboratory
> *Clinical Laboratory News*
> April, 2016:28

> *"eGFR-cystatin C below 60 mL/min/1.73m^2 confirms the presence of chronic kidney disease, whereas a value of 60 or higher refutes the diagnosis."*
>
> E. J. Lamb, et al
> NHS Foundation Trust
> *British Medical Journal*
> 350(2015):g7667

Current clinical guidelines recommend eGFR-Cr as the initial diagnostic test and to use eGFR-CysC as one method of confirmation for adult patients. [Levy-3]

Taglieri et al found that eGFR-Cr has a number of major limitations among CKD patients at older ages, and among those who are obese and/or have multiple comorbidities.

In contrast, eGFR-CysC avoids major dietary and muscle limitations, is more accurate than eGFR-Cr, is a better option for eGFR assessments in ostensibly healthy individuals and more strongly correlates with both CV events and all-cause mortality. [Ferguson, Woo]

Anders Grubb, the chair of the Working Group on Standardization of Cystatin C, opines that eGFR-CysC can replace more complex eGFR-Cr equations.

Presence and Extent of Chronic Kidney Disease (CKD)

> *"Cys-C is a more accurate surrogate marker of renal function compared with plasma creatinine."*
>
> Horng H. Chen, MB, MCH
> Mayo Clinic
> *Journal of the American College of Cardiology*
> 56(2010):1937[editorial]

In a literature review encompassing 13 studies with 5,352 subjects, eGFR-CysC was more accurate than eGFR-Cr due to lack of adverse impact from age, gender and race. The authors' conclusion was that *"it may be useful to consider more widespread use of GFR estimates based on cystatin C, either alone or in combination with [eGFR-Cr]."* [Inker-1]

The 2014 Kidney Disease Outcomes Quality Initiative advised that eGFR-CysC improves upon eGFR-Cr with respect to CKD risk classification. [Inker-2]

In addition, eGFR-CysC decreases the prevalence of stage 3 CKD by half and is superior to eGFR-Cr for distinguishing between eGFR 45-59 vs. 31-44. [Bloomfield, Delanaye, Korhonen, Levy-4, Peralta-1]

This has major insurability implications because those with eGFR 45-59 have significantly better mortality and morbidity prognoses than those with eGFR 31-44.

In the ARIC study, the risk of end-stage renal disease (ESRD) was only 2.6-fold elevated in patients with eGFR-Cr < 60 and normal cystatin C. In marked contrast, the ESRD risk was 23.8-fold elevated in cases where eGFR-CysC was also decreased. The added value of eGFR-CysC was independent of albuminuria. [Peralta-2]

Cardiovascular Disease

In a study of patients with CV disease, mean eGFR-Cr averaged 10 units higher than mean eGFR-CysC. [Akerlbloom-3]

Wang et al showed that eGFR-CysC is superior to eGFR-Cr as a renal marker in coronary artery bypass patients. [Wang-1]

In the Cardia Study, Bansal et al found that eGFR-CysC was a significant adjusted risk factor for > 5% increase in CAC (coronary artery calcium) scores over 5 years of follow-up in young adults. [Bansal-1]

In a 5-year study of young and middle-aged subjects with normal kidney function, eGFR-CysC between 60 and 75 was associated with a 5.6 g/m greater left ventricular mass index (LVMI) after risk factor adjustment, as compared to readings ≥ 90. [Bansel-2]

In 234 PAD patents undergoing endovascular therapy, eGFR-CysC was superior to eGFR-Cr for predicting future CV events and was recognized as more precise in stratifying PAD patients. [Otaki]

In 823 stable heart failure patients undergoing angiography at the Cleveland Clinic and followed for 3 years, eGFR-CysC was superior to eGFR-Cr in assessing the risk of new CV events. [Dupont]

Akoudad found that eGFR-CysC was a marker for a higher prevalence of cerebral small vessel atherosclerotic disease.

In patients with primary hyperparathyroidism, eGFR-CysC was superior to eGFR-Cr in determining the risk of future CV disease. [Ermetici]

Diabetes

Cystatin C-based eGFR *"has consistently provided a stronger association with outcomes than equations based on serum creatinine eGFR."* [Lopez-Giacoman]

In diabetes, eGFR-CysC was substantially superior to eGFR-Cr in a wide range of contexts:

- Risk of becoming diabetic [Heianza]
- Risk of acute renal insufficiency [Jarvela]
- Predicting ESRD [Krolewski]
- Predicting macroalbuminuria in T1DM [Domingueti-1]
- Risk of CV events in high-risk diabetics [Schottker]
- All-cause mortality – in one study, the hazard ratio was 3.8 (as compared to 2.6 with eGFR-Cr) [Ide]

eGFR-CysC was also superior to eGFR-Cr as a marker for PAD in diabetics and nondiabetics. [Selvin]

Elderly

When Schaeffner et al did a comparative analysis of eGFR methods in elderly (≥ age 70) subjects, they concluded that cystatin C is *"the preferred laboratory variable to be included in a GFR-estimating equation in an elderly population."*

Several additional studies support this statement. [Bevc, Patel-2, Shastri-2]

Fraser et al found that eGFR-CysC reclassified 24% of elderly subjects from stage 3a CKD by eGFR-Cr into not having CKD.

Colantonio et al showed that subjects who were ≥ age 80, with normal eGFR-Cr, but reduced eGFR-CysC, had higher prevalences of anemia, albuminuria and elevated hs-CRP, as well as increased all-cause mortality.

Daya found a graded association between eGFR-CysC and the risk of fracture hospitalization.

Cystatin C and Mortality

"[Cystatin C] is emerging as a strong risk marker for cardiovascular morbidity and mortality, as well as overall mortality."

Anna Köttgen, MD, MPH, et al
Johns Hopkins University Medical School
American Journal of Kidney Diseases
51(2008):385

After assessing the impact of cystatin C in NHANES study subjects, Wu and coworkers described this test as having *"…a unique prognostic potential regarding long-term mortality."*

Salminen reported on the hazard ratios for mortality per 0.1 unit increase in cystatin C in both genders:

	HR per 0.1 Unit Increase in Cystatin C	
	Men	**Women**
CV Mortality	1.18	1.14
Non-CV Mortality	1.12	1.14

These results were statistically significant on a univariate, as well as multivariate, basis.

In 11,402 Swedish twins free of cardiovascular disease at baseline, adjusted hazard ratios for MI, stroke and atherosclerotic disease mortality were significantly increased for cystatin C, but not for creatinine. [Arpegard-2]

Meinitzer et al looked at the impact of the asymmetrical dimethylarginine (ADMA) test as a marker for all-cause mortality. It was an independently significant risk indicators…and there was a robustly association between ADMA quartiles and cystatin C.

Luo et al conducted a meta-analysis of 9 studies encompassing 38,854 subjects. They were all general-population based and multivariate adjusted studies.

Eight of 9 showed that high cystatin C had significantly increased mortality in the highest vs. lowest category. They reported these aggregate fully adjusted hazard ratios:

	All-Cause Mortality HR
Overall	1.72
< 10 years	2.04
≥ 10 years	1.66
< Age 65	1.60
≥ Age 65	2.04

Astor et al looked at all-cause mortality in the ARIC study, following 9,888 subjects for 10 years. They reported these fully adjusted (including eGFR-Cr) hazard ratios. Note that they subdivided the 5th quintile into thirds in order to show where the impact of cystatin C was most substantial.

Cystatin C Quintile	**All-Cause Mortality HR**
1	1.00
2	1.21
3	1.29
4	1.46
5a	1.67
5b	1.77
5c	2.89

Shinkai et al followed 1,034 non-disabled persons ≥ age 65 for 7.9 years. Cystatin C in the top tertile conferred twice the mortality risk as in the 1st tertile and 70% greater death risk than in the 2nd tertile.

Wu et al looked at 13.7-year all-cause multivariate mortality in 2,990 subjects > age 40, free of known renal impairment.

Cystatin C Percentile	Mortality Hazard Ratio
< 10th	1.00
10th-90th	3.45
> 90th	4.36

Cardiac and noncardiac mortality at > 90th percentile were 7.44 and 3.15, respectively.

There was one outlier report, a 13-year follow-up of 6,500 Norwegians, mean age 60 and free of CVD and diabetes, in the Trømso Study. [Toft]

In this report, unadjusted mortality based on cystatin C was increased 23% in men and 36% in women in the 4th vs. 1st quartiles. However, after adjustment for all risk factors, most notably including hs-CRP, there was no increased mortality in men and only a 9% higher risk in females.

There was no univariate or multivariate excess mortality for serum creatinine. In addition, all interquartile eGFR-CysC levels were ≥ 60.

In a 13-year follow-up study, Swindell et al showed that cystatin C ≥ 1.3 was a fully adjusted mortality marker. At this threshold, mortality was 2.2-fold higher in both diabetics and nondiabetics. It was also 2.4-fold greater in smokers and 2.1-fold higher in nonsmokers. These results remained significant when deaths within the first 36 months were excluded.

In an investigation of 4,650 middle-aged individuals free of CV disease, both all-cause and CVD mortality was significantly elevated based on cystatin C. [Svensson-Farbom-1]

Sanders et al followed 2,737 elders age 70-79 for 9.3 years and found that cystatin C was 90% higher in subjects in the lowest tertile of their criteria for "healthiness." They also noted that cystatin C was *"…more strongly related with mortality than creatinine or the Modified Min-Mental Status Exam score."*

Lastly, in the French 3C Study, following 1,254 subjects from 3 communities for 8 years, cystatin C was the only one of 24 biomarkers significantly associated with plasma beta-amyloid levels. Mean cystatin C readings for survivors and decedents were 0:87 and 0.99, respectively (Spearman coefficient p <0.0001). [Gabelle]

All-Cause Mortality Based on eGFR

After comparing various creatinine-based eGFR equations, Meeusen (Mayo Clinic) added that *"…alternative models of care could be developed that include biomarkers (e.g., cystatin C) and clinical characteristics to estimate risk of end-stage renal disease and other key outcomes such as mortality…"*

Shlipak et al reported on their meta-analysis of 11 general population studies and 5 cohort studies: *"…using cystatin C alone or with creatinine strengthens the association between eGFR and risks of death and ESRD."*

Three additional studies support the argument that eGFR-CysC is the preferred approach when assessing all-cause mortality. [Barr, Helmersson-Karlqvist, Shastri-2]

Bottom line: cystatin C is a strong and independent predictor of excess mortality, especially at older ages.

Closing Observations

The studies reviewed in this paper show us the wide-ranging and substantial insurability implications of cystatin C.

Because of the burgeoning volume of investigations into all facets of cystatin C over the past 8 years, we now know that its value in our context far transcends that of merely being superior to creatinine as a kidney disease marker.

Elevated cystatin C has morbidity and mortality implications related to circulatory diseases, diabetes, COPD, etc., and most notably for cognitive status and physical functioning.

Taken together, this contemporary evidence argues for routine life insurance screening with cystatin C, ideally by age 55, and especially at ages 70 and over.

We are told that one major carrier has greatly expanded its use of cystatin C, and we encourage others to pursue the same course after doing their appropriate due diligence.

In addition, cystatin C clearly confers advantages for critical illness and long-term care risk assessment.

For some years now, senior life insurer management has made it clear that controlling acquisition cost, expediting the underwriting process and being both producer- and customer-centric must be major new business department priorities, along with maintaining favorable morbidity and mortality outcomes.

The continued use of paramedically-mediated cognitive and frailty screening, much like chest X-rays, treadmill tests and resting ECGs, is wholly incompatible with these mandates.

Current evidence suggests that cystatin C finally affords us the opportunity to go forward without these cognitive and frailty tests.

Furthermore, we believe that by combining cystatin C, NT-proBNP and hemoglobin to screen in the elder market, we can make the most efficient use of blood testing to sustain profitability with minimal inconvenience to prospective customers.

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