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REVIEW ARTICLE

Clinical Usefulness of Cystatin C to Assess the Prognosis of Acute Coronary Syndromes: A Systematic Review and Meta-Analysis

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Abstract

Cystatin C is used as a marker of renal function and has been shown to be promising for evaluating the prognosis of acute coronary syndromes (ACSs). To evaluate the prognostic value of cystatin C in patients with ACSs. The articles were searched using PubMed, Web of Science and Scielo databases. Observational cohort studies that evaluated the association between increased cystatin C and the development of cardiovascular events and mortality in patients with ACSs were included. Only studies that evaluated similar outcomes, studies that compared the highest with the lowest quartiles of cystatin C, and studies that performed multivariate analysis that included glomerular filtration rate or serum creatinine, were included in the meta-analysis. Methodological quality of the articles was assessed using the Newcastle-Ottawa Scale questionnaire for cohort studies. After applying the eligibility criteria, 17 studies were included in the systematic review. All included studies reported a significant association between higher levels of cystatin C and outcomes. The meta-analysis demonstrated that elevated levels of cystatin C are associated with increased risk of cardiovascular mortality or non-fatal myocardial infarction in patients with ACSs, and such association is independent of renal function [OR = 1.65 (1.464 – 1.861), $p < 0.001$]. Among the studies included, 4 have good quality and 13 have excellent methodological quality.The systematic review and meta-analysis demonstrated that there is a significant association between increased cystatin C levels and the development of cardiovascular events and mortality in patients with ACSs.

Keywords

Acute Coronary Syndrome / Physiopathology; Cystatin C; Prognosis, Biomarkers.

Introduction

Cystatin C is a protein belonging to cystatin superfamily of human cysteine protease inhibitors, which is composed of 12 proteins.[1] It is produced at a constant rate by nucleated cells. Due to its low molecular weight (13-kDa) and basic isoelectric point, cystatin C is removed from the bloodstream by glomerular filtration, reabsorbed and catabolized by tubular epithelial cells.[2] Serum cystatin C has been used as a marker of renal function, and suggested as a better endogenous marker of glomerular filtration rate (GFR) compared with serum creatinine.[2,3] The protein is able to detect small reductions in GFR, enabling the early diagnosis of renal dysfunction.[4]

Some studies have demonstrated that increased levels of cystatin C in patients with acute coronary syndrome (ACS) are associated with increased risk for cardiovascular events, cardiovascular death and overall mortality, indicating that cystatin C is a promising prognostic marker of ACSs.[5-7] However, due to lack of scientific evidence of its prognostic value, cystatin C has not been used in clinical practice.

Few systematic reviews[8] or meta-analysis[9-11] have been performed on the theme, and none of them has included exclusively ACS patients. Therefore, it is of great importance the development of a systematic review and a meta-analysis on this subject in order to compile and analyze the results of currently available

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studies. In light of this, this systematic review and meta-analysis aimed to assess the prognostic value of cystatin C in patients with ACS.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[12]

Search strategy

An electronic search was conducted in Medline via PubMed, Web of Science and Scielo databases. Descriptors were determined using the Medical Subject Headings (MeSH) for the search in PubMed and Web of Science, and the Health Sciences Descriptors for Scielo database. The search was conducted until 30 May, 2016.

The search strategy in Pubmed and Web of Science included the term "cystatin C" and its variations, combined with all variations of the term "acute coronary syndrome", using the connector word "AND". The search strategy in Scielo included the term "cystatin C" combined with all variations of the term "acute coronary syndrome", using the connector word "AND".

Eligibility criteria

Articles written in English, Portuguese or Spanish that met these eligibility criteria were included:

- Study design: observational cohort studies.
- Study population: patients with ACS - unstable angina, ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) - with increased baseline cystatin C levels.
- Exposure: increased cystatin C levels.
- Clinical outcome: cardiovascular events or mortality evaluated by odds ratio / relative risk and / or differences between the proportions of patients with higher and lower levels of cystatin C.

The following events were considered cardiovascular events: acute myocardial infarction, need for revascularization, stroke, recurrent angina, unstable angina, heart failure and cardiovascular death.

Article selection

After exclusion of duplicate articles, articles published until 30 May 2016 that met the eligibility criteria were selected. The articles were selected by two independent investigators in two steps: in the first step, analysis of the title and abstracts was performed; in the second step, the articles selected in the previous step were read in full.

Data extraction from the articles

The following information was extracted from each article: type of ACS, diagnostic method for ACS, number of patients, patients' age range; time of follow-up, outcome measures, method for cystatin C measurement, patients' kidney function (normal or not), GFR or serum creatinine, patients' classification by cystatin levels, variables included in the multivariate analysis, results (frequency of cardiovascular events, cardiovascular death or all-cause mortality and / or odds ratio).

Evaluation of the methodological quality of the articles

Methodological quality of the articles included in the systematic review was assessed by two reviewers. The Newcastle-Ottawa Scale (NOS)[13] for cohort studies was used, which also included the following evaluation categories - cohort selection, comparability of cohorts and outcome. A maximum of one star can be attributed to the categories selection of the cohorts and outcome, a maximum of two stars can be attributed to comparability of the cohorts, such that quality of the studies can be awarded up to nine stars. Articles awarded 5 or 6 stars were considered of good methodological quality, and those awarded 7 stars were considered of excellent methodological quality.

Meta-analysis

In this meta-analysis, we included only studies that analyzed similar outcomes, studies that compared the fourth quartile with the first quartile of cystatin C, and studies that performed multivariate analysis (which included, among other variables, GFR or serum creatinine). Odds ratio and 95% confidence interval adjusted by multivariate analysis and heterogeneity between studies were analyzed by the I2 test. The studies were considered homogeneous when I2 was greater than 50% and p-value was lower than 0.10. Odds ratio was calculated using the fixed or the random effect model in case of homogeneity or heterogeneity, respectively. The Comprehensive Meta-Analysis (CMA) software version 3 was used for statistical analysis.

Results

In the initial search, 640 articles were identified, and 17 were included in this systematic review (Figure 1).

The studies that met the eligibility criteria were published between 2004 and 2015; characteristics of these studies are described in Table 1. The studies included patients with ACS, 29.4% (n = 5) of them included STEMI patients only, 17.7% (n = 3) evaluated only patients with NSTEMI, 23.5% (n = 4) analyzed patients with unstable angina, STEMI and NSTEMI, and 17.7% (n = 3) examined patients with unstable angina and NSTEMI, and 11.7% (n = 2) evaluated patients with NSTEMI and STEMI. Among the studies evaluated, 35.3% (n = 6) used the recommended diagnostic criteria,[14] whereas 41.2% (n = 7) did not use these criteria; 23.5% (n = 4) did not report the criteria used.

Sample size of these studies varied from 71 to 16,401 patients; it was greater than 1,000 in 23.5% of the studies (n = 4);[2] between 200 and 1,000 in 52.9% (n = 8) of the studies, and lower than 200 in 29.4% (n = 5) of the studies. Age of the study groups ranged from 31 to 82 years. Mean follow-up period was 15 months, varying from 1 month to 5 years. Patients were followed for 1-6 months in 35.3% (n = 6) of the studies and for more than 6 months in 64.7% (n = 11).

In 52.9% (n = 9) of the studies, outcome measures were all-cause mortality and non-fatal cardiovascular events; 41.2% (n = 7) of them evaluated cardiovascular death and non-fatal cardiovascular events, and one study (5.9%)[3] analyzed all-cause mortality only.

The methods for cystatin C measurement were immunonephelometry (41.2% [n=7]), immunoturbidimetry (41.2% [n = 7]), immunofluorimetry (5.9% [n = 1]) and immunoenzymatic assay (5.9% [n = 1]), and one study (5.9%) did not report the method used.

In 88.2% (n = 15) of the studies, patients with normal and altered kidney function were included, whereas 11.8% (n = 2) of the studies included patients with normal kidney function only. Kidney function was assessed mostly by GFR (82.4% [n = 14]), followed by serum creatinine (17.6% [n = 3]).

Classification criteria of patients, the variables included in the multivariate analysis and results of each study are described in Table 2. In 14 (82.3%) studies, patients were classified by cystatin levels, in 7 (41.2%) by quartiles, in 3 (17.6%) by tertiles. Two studies (11.8%) adopted the cutoff point to prevent cardiovascular events, one (5.9%) study used the median values of cystatin C levels, another study used the reference value of the cystatin C measurement method (immunonephelometry), whereas 3 (17.6%) studies did not make this classification.

Most studies (88.2%, n = 15) performed multivariate analysis; 58.8% (n = 10) of them included, among other variables, GFR or serum creatinine in this analysis. On the other hand, five studies (29.4%) included other variables than GFR or serum creatinine.

All studies included in this systematic review assessed the association between increased cystatin C and outcome measures using odds ratio or relative risk and found a significant association between them. A significant association was found of increased cystatin C with cardiovascular events or all-cause mortality in 47.1% (n = 8) of the studies, with cardiovascular events or cardiovascular mortality in 17.6% (n = 3), with cardiovascular events in 17.6% (n = 3) and with cardiovascular death or all-cause mortality in 17.6% (n = 3).

In addition, 35.3% (n = 6) of the studies compared the proportion of patients with increased cystatin C levels who had outcomes with those who did not. This proportion was significantly greater for cardiovascular events in 2 (11.8%) studies, for cardiovascular events or all-cause mortality in two (11.8%), and for cardiovascular events or cardiovascular death in one study (5.9%). Only one (5.9%) study did not report a statistically significant difference between the proportions of patients with increased cystatin C levels who developed cardiovascular events or cardiovascular death in comparison with those with lower cystatin C levels who developed these outcomes.

Analysis of the methodological quality of the studies is described in Table 3, with the criteria for assignment of the stars described in detail in the legend. Four (23.5%) studies showed good methodological quality and 13 (76.5%) showed excellent methodological quality.

Only 5 studies compared the fourth and the first quartile of cystatin C and performed multivariate analysis, including GFR and serum creatinine in this analysis. Of these, only 2 evaluated similar outcomes (cardiovascular death, non-fatal myocardial death), and thereby were included in the meta-analysis (Figure 2). Since the studies were heterogeneous (I2 < 0,001 e p = 0,621), the odds ratio was calculated using the random effect model. Results of the meta-analysis (OR = 1.65 [1.464 – 1.861], p < 0.001) indicate a significant association between increased levels of cystatin C and the risk of cardiovascular death or non-fatal myocardial infarction in ACS patients.

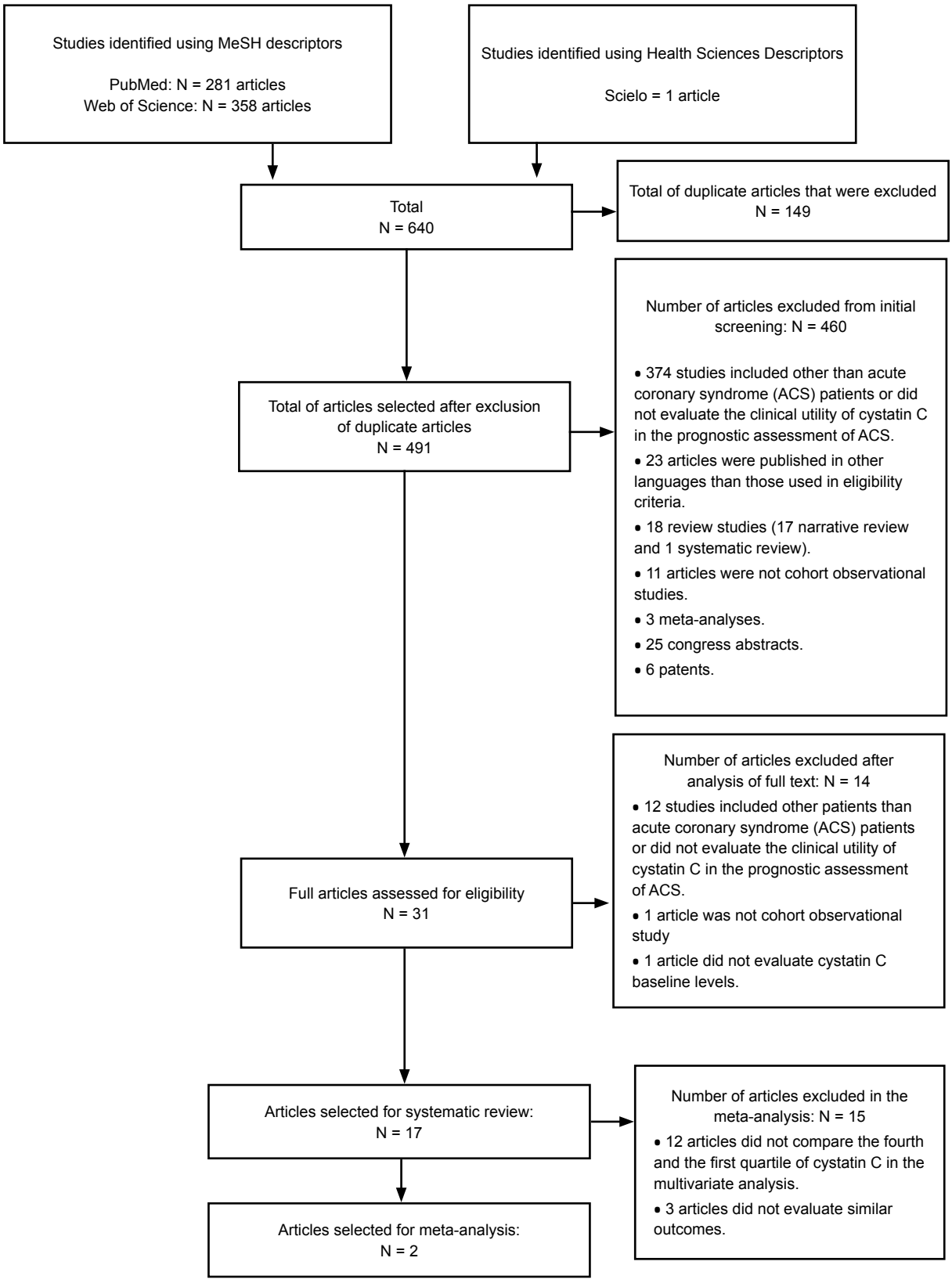

Figure 1 - Flowchart of the articles selected for systematic review and meta-analysis.

Table 1 - Characteristics of the selected studies

Author/ Year	Type of acute coronary syndrome	Diagnostic method for acute coronary syndrome	Number of patients / Age range (years)	Time of follow-up / Outcome measure	Method of cystatin C measurement	Inclusion of patients with normal kidney function only	GFR of patients (mL/ min/1,73m²) or serum creatinine
Studies included only in the systematic review and meta-analysis							
Tonkin et al., 2015[15]	Unstable angina, NSTEMI, STEMI	NI	9014 / 31-75	5 years / Cardiovascular death, non-fatal infarction	Immunoturbidimetry	Yes	GFR = 69 (60-80)
Akerblom et al., 2012[16]	NSTEMI, STEMI	NSTEMI: at least two of these criteria: change in ST segment; increase in cardiac marker levels; presence of one of the risk factors. STEMI: at least two of the following criteria: ST segment elevation in ECG; recent left bundle branch block; intention to perform primary PCI.	16401 / 57 (51-64) (1st quartile) 59 (52-67) (2nd quartile) 63 (56-71) (3rd quartile) 70 (61-76) (4th quartile)	12 months / Cardiovascular death, non-fatal infarction	Immunoturbidimetry	No	GFR = 82,6
Studies included only in the systematic review							
Tang et al., 2015[17]	STEMI	Chest pain > 30 min, ST segment elevation in ECG; recent left bundle branch block; increase in cardiac markers	108 / 58.8 ± 9.8 (cystatin C < 1.36 mg/L) 65.9 ± 11.3 (cystatin C ≥ 1.36 mg/L)	6 months / Cardiovascular death, non-fatal infarction, need of revascularization, stroke and CHF	Immunoturbidimetry	No	GFR = 81.6 ± 22.5 (cystatin C ≥ 1.36 mg/L) GFR = 99.5 ± 20.8 (cystatin C < 1.36 mg/L) p = 0.01
Fu et al., 2013[18]	Unstable angina, NSTEMI, STEMI	NI	660 / 81.74 ± 2.54 (group with diabetes) 81.99 ± 2.21 (group without diabetes)	28 months / All-cause mortality, myocardial infarction, need of revascularization	NI	No	GFR = 68.67 (55.97–82.14) (with DM) GFR = 72.55 (63.08-81.74) (without DM) p = 0.106
Akgul et al., 2013[19]	STEMI	Chest pain > 30 min, ST segment elevation in ECG	475 / 62.8 ± 13.1 (3rd quartile) 52.3 ± 10.5 (1st and 2nd quartiles)	1 month / Cardiovascular death, non-fatal infarction, need of revascularization	Immunoturbidimetry	No	GFR = 70.6 ± 24.3 (cystatin C > 1.12 mg/L) GFR = 98.1 ± 22.8 (cystatin C ≤ 1.12 mg/L) p < 0.001

Widera et al., 2013[20]	Unstable angina, NSTEMI	Unstable angina: increased levels of cardiac troponin. NSTEMI: increased levels or cardiac troponin, signs of ischemia in ECG, CAD, at least one 50% coronary stenosis	1146/ 74 (68-80) (with cardiac event) 69 (59-76) (without cardiac event)	6 months/ All-cause mortality, non-fatal infarction	Immunoturbidimetry	No	Serum creatinine (mg/dL) = 1.20(0.90-1.65) (with cardiac event) Serum creatinine (mg/dL) = 0.93 (0.79-1.13) (without cardiac event) p < 0.001
Manzano -Fernández et al., 2012[21]	Unstable angina, NSTEMI	Chest pain ≥ 10 min within 72 hours before hospital admission and/or ST segment deviation or increased cardiac markers	226/ 58 ± 11 (1st quartile) 64 ± 10 (2nd quartile) 71 ± 10 (3rd quartile) 76 ± 7 (4th quartile)	At least 12 months/ All-cause mortality	Immunonephelometry	No	GFR = 92.1 ± 25.7 (1st quartile) GFR = 85.9 ± 19.8 (2nd quartile) GFR = 77.8 ± 14.2 (3rd quartile) GFR = 54.8 ± 16.8 (4th quartile) p ≤ 0.001
Ristiniemi et al., 2012[22]	NSTEMI	NI	245/ 62 (10.9) (1st tertile) 69 (9.5) (2nd tertile) 76 (8.8) (3rd tertile)	12 months/ All-cause mortality non-fatal infarction	Immunofluorescence	No	GFR = 76 (17.4) (1st tertile) GFR = 62 (15.2) (2nd tertile) GFR = 44 (15.5) (3rd tertile) p < 0.0001
Silva et al., 2012[23]	STEMI	Chest pain at rest > 30 min, ST segment elevation in ECG or left bundle branch block	151/ 61 ± 12	12 months/ All-cause mortality, non-fatal infarction	Immunonephelometry	No	GFR = 96.9 ± 37.1 (no death or infarction) GFR = 80.9 ± 25.3 (death or infarction) p > 0.05
Sun et al., 2012[24]	Unstable angina, NSTEMI, STEMI	NI	660 patients/ 62.5 ± 10.5 (with cardiac event) 59.9 ± 10.6 (without cardiac event)	At least 12 months/ All-cause mortality, non-fatal infarction, need of revascularization, CHF, recurrent chest angina, stroke	Immunoturbidimetry	No	GFR = 96.00 (with cardiac event) GFR = 104.08 (without cardiac event) p = 0.057
Kaski et al., 2010[25]	Unstable angina, NSTEMI	Chest pain at rest > 5 min, and ≥ 1 of these criteria: signs of myocardial ischemia in ECG, CAD and/ or myocardial revascularization with PCI or bypass surgery; increased cardiac troponin	610/ 67.2 ± 10.9 (with cardiac event) 64.5 ± 11.3 (without cardiac event)	12 months/ All-cause mortality, non-fatal infarction	Immunonephelometry	No	GFR = 74 (58-87) (with cardiac event) GFR = 78 (64-94) (without cardiac event) p = 0.05

Cont. Table 1 - Characteristics of the selected studies

Author/ Year	Type of acute coronary syndrome	Diagnostic method for acute coronary syndrome	Number of patients / Age range (years)	Time of follow-up / Outcome measure	Method of cystatin C measurement	Inclusion of patients with normal kidney function only	GFR of patients (mL/ min/1,73m²) or serum creatinine
Taglieri et al., 2010[6]	NSTEMI	Chest pain and at least one of the following criteria: signs of myocardial ischemia in ECG; increased cardiac markers; history of CAD	525/ 58 (50-66) (1st quartile) 63 (53-70) (2nd quartile) 68 (59-74) (3rd quartile) 72 (67-67) (4th quartile)	12 months/ Cardiovascular death, non-fatal infarction, unstable angina	Immunonephelometry	No	GFR = 92.3 (80.2-107.4) (1st quartile) GFR = 84.0 (74.9-97.3) (2nd quartile) GFR = 75.1(62.6-89.8) (3rd quartile) GFR = 59.1(47.5-72.9) (4th quartile) p < 0.001 (4th quartile x 1st, 2nd and 3rd quartile)
Derzhko et al., 2009[26]	STEMI	Chest pain > 20 min, ST segment elevation in ECG, increased cardiac troponin	150/ 56.99 ± 11.3	6 months/ CHF, non-fatal infarction, unstable angina, all-cause mortality	Immunonephelometry	No	Serum creatinine (mg/dL) (general) = 1.02 ± 0.17
Ichimoto et al., 2009[7]	STEMI	Chest pain > 30 min, ST segment elevation in ECG, CK-MB levels twice greater than upper normal limit	71/ 61.9 ± 10.4 (cystatin C < 0.96 mg/L) 66.5 ± 12.6 (cystatin C ≥ 0.96 mg/L)	Approximately 6 months/ All-cause mortality, non-fatal infarction, need of revascularization, stroke, CHF	Immunoturbidimetry	No	Serum creatinine (mg/dL) = 0,93 ± 0,22 (cystatin C ≥ 0,96 mg/L) Serum creatinine (mg/dL) = 0,72 ± 0,14 (cystatin C < 0,96 mg/L) p < 0,01
Kilic et al., 2009[27]	Unstable angina, NSTEMI, STEMI	Increased cardiac markers and at least one of these criteria: chest pain; development of pathological Q waves in ECG; signs of ischemia in ECG; PCI; pathological findings of AMI	160/ 59 ± 10 (without cardiovascular events) 61 ± 10 (with cardiovascular events)	12 months/ Cardiovascular death, non-fatal infarction, recurrent angina	Immunoenzymatic assay	Yes	GFR = 80 ± 31 (with cardiac events) GFR = 92 ± 35 (without cardiac events) p = 0,03

García Acuña et al., 2009[28]	NSTEMI, STEMI	At least two of these criteria: chest pain: signs of ischemia in ECG; increased cardiac markers	203 / 59.21 ± 12.26 (cystatin C ≤ 0.95 mg/L) 72.49 ± 10.69 (cystatin C > 0.95 mg/L)	Approximately 6 months / Heart failure, no-fatal infarction, cardiovascular death	Immunonephelometry	No	Patients with cystatin C > 0.95 mg/L had a higher frequency of GFR < 60 and a lower frequency of GFR > 90 in comparison with patients with cystatin C levels ≤ 0,95 mg/L p = 0,001
Windhausen et al., 2009[5]	NSTEMI	Chest pain with increasing intensity or at rest, increased levels of cardiac troponin, and one of these criteria: signs of ischemia in ECG; CAD	1128 / 57 ± 10 (1st tertile) 62 ± 10 (2nd tertile) 67 ± 9 (3rd tertile)	3 years (infarction) and 4 years (death) / All-cause mortality, non-fatal infarction	Immunonephelometry	No	GFR = 102 (87-118) (1st tertile) GFR = 87 (75-103) (2nd tertile) GFR = 68 (56-82) (3rd tertile) p < 0,001

CK-MB: Creatine kinase isoenzyme MB; CAD: Coronary artery disease; ECG: Electrocardiogram; AMI: acute myocardial infarction; CHF: congestive heart failure; NI: not informed; NSTEMI: non-ST segment elevation myocardial infarction, PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; GFR: glomerular filtration rate.

Discussion

The current study aimed to assess the association between increased levels of cystatin C and the development of cardiovascular events and mortality in patients with ACS by a systematic review and meta-analysis. All studies included in the systematic review found a significant association between increased cystatin C levels and the outcome measures by odds ratio or relative risk, which was confirmed in the meta-analysis. Some studies also compared the proportion of patients with increased cystatin C levels who developed or not outcomes, and only one study showed no statistically significant difference. Therefore, results of the studies included in this systematic review and meta-analysis indicate a significant association between increased cystatin C levels and the development of cardiovascular events and mortality in ACS patients.

The mechanism responsible for this association has not been fully elucidated. However, a possible mechanism is based on the fact that cystatin C is a more sensitive marker for kidney dysfunction, capable to detect small reductions in GFR,[4] and a pre-clinical status of kidney dysfunction, which cannot be detected by serum creatinine or creatinine-based GFR.[29] Some studies have shown that the presence of mild-to-moderate kidney failure is an important risk factor for the development of cardiovascular events and mortality.[30-32] Thus, patients with increased cystatin C levels could have a mild kidney dysfunction, which could contribute to increased risk of cardiovascular events and worse prognosis.

Another possible mechanism is related to inflammation associated with the atherogenic process, since some studies have suggested that increased cystatin C levels are associated with inflammation and atherosclerosis.[32] Inflammatory cytokines and atherosclerosis stimulate the production of lysosomal cathepsins,[32] such as cathepsin S that seems to contribute to disruption of atherosclerotic plaque.[33] Since cystatin C is a cathepsin inhibitor,[32] increased cystatin C levels may be associated with inhibition of these cathepsins involved in atherosclerotic plaque disruption, contributing to the development of cardiovascular events.

Although all studies included in this review had good or excellent methodological quality, evaluated by the NOS,[13] they also showed some limitations. Only two studies (11.8%) included exclusively patients with normal kidney function. Nevertheless, most studies (88.2%, n = 15) performed a multivariate analysis, and more than half (58.8%, n = 10) included GFR or serum creatinine, which gives greater credibility to results. After adjustment for these and other risk factors, a

Table 2 - Classification of patients, variables included in the multivariate analysis and results of the selected studies

Author/ Year	Classification of patients according to cystatin C levels	Variables included in the multivariate analysis	Results
Studies included in the systematic review and meta-analysis			
Tonkin et al., 2015[15]	1st quartile (< 0.72 mg/L) 2nd quartile (0.72-0.81 mg/L) 3rd quartile (0.81-0.93 mg/L) 4th quartile (> 0.93 mg/L)	Age; sex; DM; current smoking; total cholesterol; triglycerides; fasting glycemia; acute coronary syndrome; hospitalization for unstable angina; History of coronary revascularization; systolic arterial pressure, history of hypertension; atrial fibrillation; GFR; BMI; level of dyspnea; level of angina; white blood cell count; peripheral arterial disease; use of aspirin; history of stroke.	Risk of cardiovascular events or death Univariate analysis: 2nd quartile x 1st quartile: OR = 1.30 (1.07-1.59) 3rd quartile x 1st quartile: OR = 1.33 (1.08-1.63) 4th quartile x 1st quartile: OR = 1.75 (1.41-2.18). p < 0.001 Multivariate analysis: 2nd quartile x 1st quartile: OR = 1.27 (1.05-1.54) 3rd quartile x 1st quartile: OR = 1.31 (1.08-1.58) 4th quartile x 1st quartile: OR = 1.64 (1.36-1.99). p < 0.001
Akerblom et al., 2012[16]	1st quartile (< 0.68 mg/L) 2nd quartile (0.68-0.83 mg/L) 3rd quartile (0.83-1.01 mg/L) 4th quartile (≥1.01 mg/L)	Age; female sex; weight; smoking; hypertension; DM; MI; CHF; non-hemorrhagic stroke; peripheral artery disease; CKD; acute coronary syndrome without ST segment elevation; acute coronary syndrome with ST segment elevation; use of aspirin; use of glycoprotein IIb/IIIa inhibitors; use of beta-blockers, use of ACE inhibitor, angiotensin receptor blockers, or both; use of statin; use of proton-pump inhibitors; coronary angiography; primary PCI for acute coronary syndrome with ST segment elevation; other PCIs before index event; myocardial revascularization; serum creatinine	Risk of cardiovascular events or cardiovascular death: Multivariate analysis of STEMI patients: 2nd quartile x 1st quartile: OR = 1.10 (0.86-1.42) 3rd quartile x 1st quartile: OR = 1.23 (0.96-1.58) 4th quartile x 1st quartile: OR = 1.81 (1.43-2.29) Multivariate analysis of NSTEMI patients: 2nd quartile x 1st quartile: OR = 0.94 (0.74-1.18) 3rd quartile x 1st quartile: OR = 1.19 (0.96-1.47) 4th quartile x 1st quartile: OR = 1.55(1.26-1.90)
Studies included in the systematic review			
Tang et al., 2015[17]	Cystatin C < median (< 1.36 mg/L) Cystatin C ≥ median (≥ 1.36 mg/L)	Angiography without reflux; ST segment resolution < 30%; IMR > 33.7 U after PCI; serum cystatin C ≥ median; peak CK-MB; baseline LVEF; left ventricular remodeling.	Proportion of patients who developed cardiovascular events or cardiovascular death: 18.5% (cystatin C ≥ median) x 13.0% (cystatin C < median). p = 0.43 Proportion of patients who developed CHF: 18.5% (cystatin C ≥ median) x 5.6% (cystatin C < median). p = 0.022 Risk for CHF: Univariate analysis: cystatin C ≥ median x cystatin C < median: OR = 4.54 (3.51 – 7.82). p < 0.001 Multivariate analysis: cystatin C ≥ median x cystatin C < median: OR = 3.85 (2.82 – 5.96). p = 0.005

Fu et al., 2013[18]	1st quartile (< 1.23 mg/L) 2nd quartile (1.23-1.43 mg/L) 3rd quartile (1.44-1.82 mg/L) 4th quartile (1.83-5.12 mg/L)	NA	Risk of all-cause mortality: Univariate analysis: 2nd quartile x 1st quartile: OR = 1.31 (1.23-1.43) 3rd quartile x 1st quartile: OR = 1.59 (1.44-1.82) 4th quartile x 1st quartile: OR = 2.23 (1.83-5.12) p = 0.0001
Akgul et al., 2013[19]	1st and 2nd tertile (≤ 1.12 mg/L) 3rd tertile (> 1.12 mg/L)	Age; female sex; DM; hypertension; current smoking; Killip class > 1; anemia at admission; KF; lesion in three cardiac vessels; unsuccessful PCI; LVEF < 40%; use of tirofiban; serum creatinine > 1.5 mg/dL.	Proportion of patients who developed cardiovascular events: 21.4% (3rd tertile) x 8.5% (1st and 2nd tertile). p < 0.001 Risk of cardiovascular death: Univariate analysis: 3rd tertile x 1st and 2nd tertiles: OR = 5.9 (2.6-13.3). p < 0.001 Multivariate analysis: 3rd tertile x 1st and 2nd tertiles: OR = 4.66 (1.3-16.6). p = 0.017
Widera et al., 2013[20]	Without classification	NA	Risk of cardiovascular event or all-cause mortality: Univariate analysis: Log (cystatin C): OR = 1.9 (1.6-2.3)
Manzano -Fernández et al., 2012[21]	1st quartile (< 0.79 mg/L) 2nd quartile (0.79-0.91 mg/L) 3rd quartile (0.92-1.13 mg/L) 4th quartile (1.14-2.55 mg/L)	BTP; serum cystatin C; serum creatinine; GFR; hemoglobin, anterior acute coronary syndrome without ST-segment elevation; GRACE risk score.	Risk of all-cause mortality Univariate analysis: 2nd quartile x 1st quartile: OR = 1.89 (0.35-10.3) 3rd quartile x 1st quartile: OR = 2.41 (0.47-12.4) 4th quartile x 1st quartile: OR = 7.87 (1.78-34.9) p = 0.004 Multivariate analysis: 2nd quartile x 1st quartile: OR = 1.85 (0.34-10.1) 3rd quartile x 1st quartile: OR = 1.98 (0.38-10.4) 4th quartile x 1st quartile: OR = 6.32 (1.40-28.6) p = 0.014
Ristiniemi et al., 2012[22]	1st tertile (< 0.96 mg/L) 2nd tertile (0.96-1.21mg/L) 3rd tertile (> 1.21 mg/L)	Age > 65 years; BMI (median > 27,1 kg/m²); sex; CHF; hypertension; previous MI; current smoking; DM; family history of CVD	All-cause mortality rate: 18% (3rd tertile) x 10% (2nd tertile) x 4% (1st tertile). p < 0.012 Proportion of cardiovascular events: 35% (3rd tertile) x 20% (2nd tertile) x 12% (1st tertile). p < 0.0012 (3rd tertile x 1st tertile) Risk of all-cause mortality: Univariate analysis: 3rd tertile x 1st tertile: OR = 2.19 (1.27-3.77). p = 0.0046 Multivariate analysis 3rd tertile x 1st tertile: OR = 2.19 (1.28-3.78). p = 0.0046 Risk of cardiovascular events: Univariate analysis: 3rd tertile x 1st tertile: OR= 1.86 (1.31-2.65). p = 0.0005 Multivariate analysis 3rd tertile x 1st tertile OR = 1.75 (1.22-2.51). p = 0.0024

Cont. Table 2 - Classification of patients, variables included in the multivariate analysis and results of the selected studies

Author/ Year	Classification of patients according to cystatin C levels	Variables included in the multivariate analysis	Results
Silva et al., 2012[23]	1st, 2nd and 3rd quartiles (< 0.84 mg/L) 4th quartile (≥ 0.84 mg/L)	Serum cystatin C ≥ 0,84 mg/L; creatinine ≥ 1,10 mg/dL; GFR ≤ 71,1 mL/min/1,73 m²; urea ≥ 52,25 mg/dL; uric acid ≥ 6,3 mg/dL; NT-proBNP ≥ 688,5 pg/mL; EF ≤ 40%.	Risk of all-cause mortality: Univariate analysis 4th quartile x 1st quartile: OR = 8.5 (1.71-42.15). p= 0.009 Risk of all-cause mortality or reinfarction: Univariate analysis: 4th quartile x 1st quartile: OR = 3.40 (1.23-9.39). p = 0.018 Multivariate analysis 4th quartile x 1st quartile: OR = 3.89 (1.23-12.31). p = 0.021
Sun et al., 2012[24]	1st quartile (< 1.02 mg/L) 2nd quartile (1.02-1.16 mg/L) 3rd quartile (1.17-1.34 mg/L) 4th quartile (≥1.35 mg/L)	Age; sex; DM; hypertension; serum creatinine; GFR; LVEF; serum troponin; number of arteries affected; implanted stents	Proportion of patient who developed cardiovascular events or all-cause mortality: 29.68% (4th quartile); 15.29% (3rd quartile); 9.10% (2nd quartile); 4.67% (1st quartile). p < 0.001 Risk of cardiovascular events or all-cause mortality: Multivariate analysis: 3rd quartile x 1st quartile: OR = 3.930 (1.306-11.829). p = 0.015 4th quartile x 1st quartile: OR = 6.380 (2.171-18.751). p = 0.001
Kaski et al., 2010[25]	Without classification	CHF; previous CVD; TIMI risk score	Risk of cardiovascular events or all-cause mortality: Multivariate analysis: OR = 2.15 (0.93-4.92)
Taglieri et al., 2010[6]	1st quartile (< 0.81 mg/L) 2nd quartile (0.81-0.92 mg/L) 3rd quartile (0.93-1.10 mg/L) 4th quartile (≥1.11 mg/L)	Age; sex; heart rate; BMI; hypertension; hypercholesterolemia; statin therapy; HDL cholesterol; hemoglobin; DM; smoking; myocardial revascularization; previous stroke ; TIMI risk score; troponin levels; CHD during hospitalization; RCP; PCI; administration of clopidogrel; creatinine levels at admission; GFR; serum cystatin C.	Proportion of patient who developed cardiovascular events or all-cause mortality 50% (4th quartile); 44% (3rd quartile); 37% (2nd quartile); 26 % (1st quartile). p < 0.044 Risk of cardiovascular events: Univariate analysis: 3rd quartile x 1st quartile: OR = 1.73 (1.08-2.81). p = 0.027 4th quartile x 1st quartile: OR = 1.88 (1.17-3.02). p = 0.009 Multivariate analysis: 3rd and 4th quartiles x 1st quartile: OR = 1.66 (1.07-2.57). p = 0.025
Derzhko et al., 2009[26]	Without classification	Age; sex; BMI; concomitant DM and hypertension; LDL cholesterol; HDL cholesterol; multivessel disease; left anterior descending artery infarction; mitral insufficiency; time of reperfusion; use of ACE inhibitor, use of ß-blocker and statin, baseline levels of the biomarkers CRP, cystatin C, NT-proBNP and troponin	Risk of cardiovascular events or all-cause mortality: Multivariate analysis: OR = 2.98 (1.21-7.40). p= 0.008

Ichimoto et al., 2009[7]	Cystatin C ≥ 0.96 mg/L Cystatin C < 0.96 mg/L	Killip class ≥ 2; time elapsed from hospital admission to angioplasty; cystatin C ≥ 0,96 mg/L; previous MI; increased creatinine; age.	Risk of cardiovascular events or all-cause mortality: Multivariate analysis: Cystatin C ≥ 0.96 mg/L: OR = 2.17 (1.07-6.98). p = 0.04
Kilic et al., 2009[27]	Patients with cystatin C > 1,051 ng/mL who developed fatal or non-fatal cardiovascular events Patients with cystatin C > 1,051 ng/mL who did not develop fatal or non-fatal cardiovascular events	Female sex; previous hypertension; previous DM; smoking; previous use of ACE inhibitor; previous use of diuretics; EF; creatinine clearance; fasting glycemia; log cystatin C; log BNP	Proportion of patients cystatin C > 1051 ng/mL who developed or not fatal and non-fatal cardiovascular events: 67% x 30% (developed cardiovascular events X did not develop cardiovascular events). p < 0.001 Risk of fatal and non-fatal cardiovascular events Univariate analysis: Log (Cystatin C): RR = 9.25 (3.94-21.6). p = < 0.001 Multivariate analysis: Log (Cystatin C): RR = 9.43 (4-21.8). p = < 0.001
García Acuña et al., 2009[28]	Cystatin C > 0.95 mg/L Cystatin C ≤ 0.95 mg/L	Age; EF; serum cystatin C; hs-CRP; TFG.	Risk of cardiovascular events or cardiovascular death: Multivariate analysis: RR = 1,91 (1,03-3,53), p = 0,03
Windhausen et al., 2009[5]	1st tertile (< 0.86 mg/L) 2nd tertile (0.86-1.01 mg/L) 3rd tertile (> 1.01 mg/L)	Age > 65 years; sex; hypertension; DM; smoking; hypercholesterolemia; history of CAD; history of MI; PCI or myocardial revascularization; use of aspirin; use of beta-blockers; use or ACE inhibitors before randomization; NT-proBNP ≥ 1170 ng/L in men and ≥ 2150 ng/L in women; CRP ≥ 10 mg/L; cardiac troponin ≥ 0,3 μg/L; ST segment deviation ≥ 0,1 mV in ECG ad admission.	Risk of mortality death: Univariate analysis: 2nd tertile x 1st tertile: OR = 1.81 (0.89-3.67) 3rd tertile x 1st tertile: OR = 4.07 (2.16-7.66). p < 0.001 Multivariate analysis: 2nd tertile x 1st tertile: OR = 1.41 (0.68-2.94) 3rd tertile x 1st tertile: OR = 2.04 (1.02-4.10). p = 0.004 Risk of cardiovascular event: Univariate analysis: 2nd tertile x 1st tertile: OR = 1.26 (0.67-2.35) 3rd tertile x 1st tertile: OR = 2.06 (1.17-3.63). p = 0.01 Multivariate analysis: 2nd tertile x 1st tertile: OR = 1.32 (0.70-2.50) 3rd tertile x 1st tertiile: OR = 1.95 (1.05-3.63). p = 0.04

BNP: B-type natriuretic peptide; CK-MB: Creatine kinase isoenzyme MB; CAD: Coronary artery disease; CVD: cardiovascular disease; DM: Diabetes mellitus; CKD: Chronic kidney disease; ECG: Electrocardiography; EF: ejection fraction; LVEF: left ventricular ejection fraction; HDL: high-density lipoprotein; CHF: congestive heart failure; PCI: percutaneous coronary intervention; ACE: angiotensin-converting-enzyme; MI: myocardial infarction; BMI: body mass index; IMR: Index of microcirculatory resistance; KF: kidney failure; LDL: low density lipoprotein; NA: not applicable; NT-proBNP: N-terminal pro–B-type natriuretic peptide; BTP: beta-trace protein; CRP: C reactive protein; GFR: glomerular filtration rate; hs-CRP: high-sensitivity C reactive protein. CKD: chronic kidney disease.

significant association was found between increased cystatin C levels and the development of cardiovascular events and mortality, suggesting that such association is independent of patients' kidney function. However, 7 studies did not include GFR or serum creatinine in the multivariate analysis or did not perform this analysis. Iin this case, a poor patient prognosis may result from kidney dysfunction rather from increased cystatin C levels, since several studies have demonstrated that kidney dysfunction is associated with cardiovascular events and mortality.

Only studies that performed multivariate analysis including GFR or serum creatinine were included in this meta-analysis. We found that the association between

Table 3 - Assessment of the studies' quality according to the Newcastle-Ottawa Scale

Author/Year	Selection				Comparability	Outcomes			Total points
	1	2	3	4	5	6	7	8	
Tonkin et al., 2015[15]	*	*	*	-	**	*	*	*	8
Akerblom et al., 2012[16]	*	*	*	-	**	*	*	*	8
Tang et al., 2015[17]	*	*	*	-	*	*	*	*	7
Fu et al., 2013[18]	*	*	-	-	-	*	*	*	5
Akgul et al., 2013[19]	*	*	*	-	**	*	-	*	7
Widera et al.,2013[20]	*	-	*	-	-	*	*	*	5
Manzano-Fernández et al., 2012[21]	*	*	*	-	**	*	*	*	8
Ristiniemi et al., 2012[22]	*	*	*	-	*	*	*	*	7
Silva et al., 2012[23]	*	*	*	-	**	*	*	*	8
Sun et al., 2012[24]	*	*	*	-	**	*	*	*	8
Kaski et al., 2010[25]	*	-	*	-	*	*	*	*	6
Taglieri et al., 2010[6]	*	*	*	-	**	*	*	*	8
Derzhko et al., 2009[26]	*	-	*	-	*	*	*	*	6
Ichimoto et al., 2009[7]	*	*	*	-	**	*	*	*	8
Kilic et al., 2009[27]	*	*	*	-	**	*	*	*	8
García Acuña et al., 2009[28]	*	*	*	-	**	*	*	*	8
Windhausen et al., 2009[5]	*	*	*	-	*	*	*	*	7

1- Representativeness of the exposed cohort: all studies were awarded one star, since the exposed cohort was somewhat representative of the average; 2 - Selection of the non-exposed cohort: in the studies that were awarded one star, the non-exposed cohort was drawn from the same community as the exposed cohort; in the studies that did not receive any star, no comparison was performed between patients exposed to high cystatin C levels and those who were not exposed; 3 - Ascertainment of exposure: studies that performed the measurement of cystatin C levels and informed which method was used were awarded one star, whereas no star was assigned if the study performed the measurements but did not inform the method used. 4- Demonstration that outcome of interest was not present at start of study: no study received a star, since patients had one of the outcome measures (acute coronary syndrome) in the beginning of the study; 5 - Comparability of cohorts on the basis of the design or analysis: studies that performed multivariate analysis, which included GFR or serum creatinine, among other variables, were awarded two stars; studies that performed multivariate analysis, which included variables other than GFR or serum creatinine, were awarded one star, whereas no star was awarded to studies that did not perform a multivariate analysis. 6 - Assessment of outcome; all studies were awarded one star, since assessment of outcome was performed independently, by the physicians. 7-Period of follow-up (long enough for outcomes to occur): studies in which patients were followed for at least 6 months were awarded one star, and studies in which patients were followed for less than 6 months received no star. 8 - Adequacy of follow up of cohorts: studies in which at least 90 of patients were followed until the end of the study or those with no description of significant losses were awarded one star.

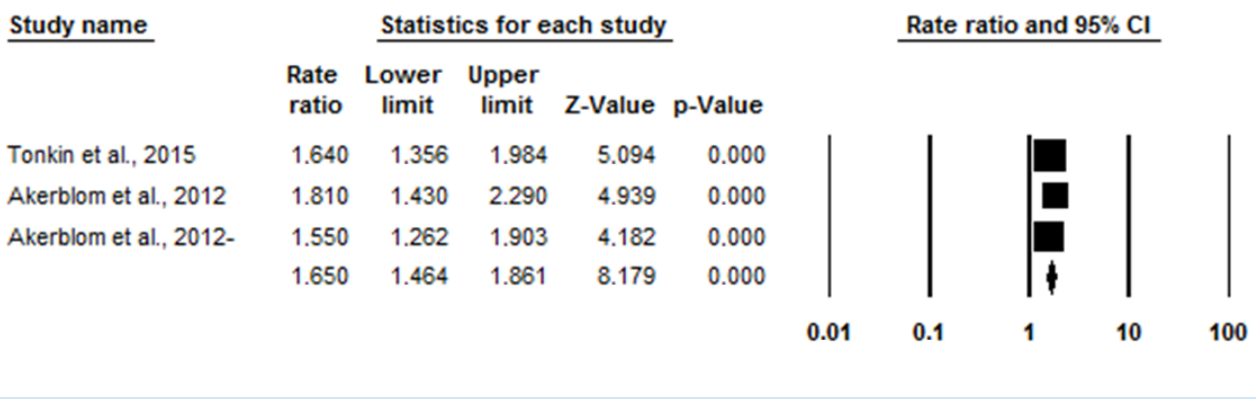

Figure 2 - Meta-analysis of the studies investigating the association between increased cystatin C levels and the development of cardiovascular death or non-fatal infarction by the comparison of the fourth and the first quartiles of cystatin C.

increased cystatin C levels and the risk for cardiovascular death or non-fatal myocardial infarction is independent of patient's kidney function.

Analysis of the studies that classified patients according to cystatin C tertiles or quartiles showed that patients with higher cystatin C levels were also older, which results from a progressive, physiological decrease in GFR associated with aging.[34] However, 58.8% (n = 10) of the studies included age in the multivariate analysis, including the two studies included in the meta-analysis, indicating that the association between increased cystatin C levels and worse cardiovascular prognosis is independent of age.

All studies assessed patients' kidney function, and most of them (82.4%, n = 14) (including the two studies included in the meta-analysis) used GFR, which is a better marker of kidney function than serum creatinine.[35] Serum creatinine levels may be affected by several factors like muscle mass, age, sex, and hence, it is not specific for assessment of kidney function.[32] Besides, increases in serum creatinine occur only when there is a decrease greater than 50% in glomerular ultrafiltration, and thereby is not considered a sensitive marker for assessment of kidney function.[36] Determination of GFR by calculation of creatinine clearance or equations based in serum creatinine levels may mitigate or eliminate these limitations.[36] The most common equations used to estimate GFR are the Cockcroft & Gault, MDRD and CKD-EPI equations, which include clinical and demographic variables in place of physiological factors known to affect creatinine serum concentrations.[37]

Classification of patients according to cystatin C levels was heterogeneous in the studies. A considerable number of these studies (58.8%) classified patients in quartiles or tertiles, which may have influenced the results. It is easier to obtain a correlation of increased cystatin C levels with poor prognosis when patients in the fourth quartile or third tertile (who have higher levels of cystatin C) are compared with patients in the first quartile or first tertile (whose cystatin C levels are decreased) than in comparison between patients with cystatin C levels above and below reference/median values. Nevertheless, classification of cystatin C levels in quartiles and tertiles is of greater clinical value, since it may be used in the determination of cutoff points above which the risk of cardiovascular events and mortality is significantly greater. Therefore, only studies in which patients were classified by cystatin C quartiles, and higher quartiles were compared with lower quartiles were included in the meta-analysis.

Immunonephelometry and immunoturbidimetry are the most used methods of cystatin C determination,[38] which has been confirmed in this systematic review, since 84.2% (n = 14) of the studies used these methods for cystatin C measurement, and only 3 studies used other methods or did not mention the method used. Immunonephelometry and immunoturbidimetry are the methods of choice for determination of cystatin C levels in body fluids due to their high accuracy, convenience, automation, in addition to being simple and fast for daily routine.[38] Besides, immunonephelometry has been suggested as a better method than immunoturbidimetry

for its high sensitivity in detecting smaller immune aggregates, and monitoring an increase in light intensity against a low background signal, which gives the method a theoretical edge.[38] Although a lack of standardization of the methods may affect the results reported in different studies, the fact that most studies used immunonephelometry and immunoturbidimetry may indicate high reliability of the results. In addition, all studies included in the meta-analysis used these methods for cystatin C measurement.

The predominant type of ACS was NSTEMI followed by STEMI and unstable angina. STEMI involves a total coronary obstruction and hence a more critical cardiovascular event than NSTEMI and unstable angina.[39] A well-established diagnosis of AMI should take into consideration all recommended criteria, that consist in increased levels of myocardial necrosis markers (preferably troponin or CK-MB mass) combined with at least one of the following parameters: symptoms suggestive of ischemia (chest pain), pathological Q-wave in ECG, significant changes in ST segment or T-wave inversion, new left bundle branch block, loss of viable myocardium, changes in segmental ventricular contractility in imaging tests, and intracoronary thrombus in angiography. Unstable angina is diagnosed by the same criteria, except for myocardial necrosis markers, which are not increased.[14] Some studies (23.5%) did not report the criteria used (i.e., it was not possible to determine whether these criteria were used or not), and 7 studies (41.2%) did not use these criteria, which may yield an incorrect diagnosis of ACS, and variations in the groups of patients included in these studies.

A study performed in 2009 demonstrated that STEMI is associated with increased short-term mortality risk, whereas NSTEMI is associated with increased long-term mortality risk.[40] All studies evaluated mortality, either alone or in combination with cardiovascular events, requiring a longer period of follow-up. Among the studies included in this systematic review, only one (5.9%) had a follow-up period shorter than six months; however, despite that, a significant association between increased levels of cystatin C and cardiovascular events or mortality was reported. Both studies included in the meta-analysis had a follow-up period longer than 12 months.

Four studies (23.5%) had a sample size greater than 1,000, which may increase their statistical power. Although 5 studies (29.4%) had a sample size smaller than 200, these studies also reported a significant association of cystatin C and the outcomes. The only study that did not find any significant difference between the frequencies of patients who developed cardiovascular events or cardiovascular death and of those who did not develop these outcomes, found a significant association between the proportion of patients with and without congestive heart failure. Sample size of this study was smaller than 200; patients were followed for 6 months and classified by median cystatin C, which may have contributed for the results of cardiovascular events and cardiovascular mortality.

Although this systematic review and meta-analysis has demonstrated a significant association between increased cystatin C levels and a worse prognosis of ACS, some limitations should be considered. First, the search was restricted to Medline via PubMed, Web of Science and Scielo databases; second, only articles published in English, Portuguese and Spanish were included in this study; finally the small number of articles included in the meta-analysis due to high variability of analyses between the studies.

Conclusion

Despite the limitations of the studies included in this systematic review, they demonstrated, using a prospective design, a significant association between increased cystatin C and the development of cardiovascular events and mortality in patients with ACSs. Such association was confirmed by the meta-analysis, and shown to be independent of renal function evaluated by serum creatinine or GFR. Therefore, cystatin C is a useful marker in the prognosis assessment of ACSs and can be used in combination with currently available markers.

Author contributions

Conception and design of the research: Martucheli KFC, Domingueti CP. Acquisition of data: Martucheli KFC, Domingueti CP. Analysis and interpretation of the data: Martucheli KFC, Domingueti CP. Statistical analysis: Martucheli KFC, Domingueti CP. Writing of the manuscript: Martucheli KFC. Critical revision of the manuscript for intellectual content: Domingueti CP. Supervision / as the major investigador: Domingueti CP.

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Ethics approval and consent to participate

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