

ORIGINAL ARTICLE

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Diagnostic and prognostic value of cystatin C in acute coronary syndrome: An up-to-date meta-analysis

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ABSTRACT

Background: The role of Cystatin C (CysC) in the diagnosis and prognosis of cardiovascular disease, particularly acute coronary syndrome (ACS), is increasingly significant. The goal of this meta-analysis was to assess the diagnostic and prognostic value of CysC in patients with ACS, as well as its association with major adverse cardiovascular events (MACE), defined as mortality, myocardial infarction, heart failure, and stroke.

Methods: The present study is a systematic review and meta-analysis. Using PubMed, Web of Science, Cochrane Library, and Embase, a literature review of cohort and case control studies reporting MACE and using the terms ACS and Cystatin C was conducted, excluding studies published after August 1st, 2024. The meta-analysis using a random effects model.

Results: CysC concentrations were significantly higher in patients with ACS compared to controls [mean difference (MD) = 0.36, p < 0.001], and in acute myocardial infarction (AMI) vs. unstable angina (MD = 0.18, p < 0.001). No significant differences were observed between ST elevation myocardial infarction (STEMI) and Non-ST elevation myocardial infarction (NSTEMI). Patients with MACE had higher CysC levels than those without (MD = 0.25, p < 0.001). Hospital survivors had lower CysC levels compared to those who died (MD = -0.25, p < 0.001). Higher CysC concentrations were associated with increased risks of MACE, cardiac death, overall mortality, myocardial reinfarction, and stroke, both during hospitalization and beyond.

Conclusions: *CysC is a promising biomarker for both diagnosis and prognosis in patients with ACS, especially in the context of predicting MACE, mortality and heart failure risk. The use of CysC may improve risk stratification and support therapeutic decision-making in clinical practice.* (Cardiol J 2025; 32, 2: 142–152) **Keywords: cystatin C, biomarker, prognosis, diagnosis, ACS, acute coronary syndrome, meta-analysis**

Introduction

Biomarkers play an increasingly vital role in medicine, aiding diagnostics, prognostics and treatment response prediction. Their integration into research and clinical practice enables early risk stratification, helping identify patients who benefit from timely interventions to prevent adverse outcomes [1–4]. As Robert M. Califf emphasizes [5], only validated biomarkers are useful in clinical trials as surrogate endpoints. Extensive research, including meta-analyses, is essential to distinguish promising biomarkers for clinical use from those deemed of lower priority for further development.

Historically Cystatin C (CysC) has been primarily recognized as a biomarker for estimating glomerular filtration rate (GFR). Its significance in nephrology is steadily increasing due to its advantages over traditional equations for estimating GFR [6]. Lees et al. [7] emphasized that further promotion of the routine use of CysC enables greater precision in the diagnosis of kidney diseases and reduces disparities among patients. CysC is useful not only in monitoring chronic kidney disease but also in identifying acute kidney injury among hospitalized patients [8].

Importantly, the utility of CysC, may extend beyond nephrology. Jung et al. [9], in their CysC meta-analysis that included 13 prospective cohort studies with a total of 57,214 participants. They demonstrated that an elevated CysC, an extracellular inhibitor of cysteine proteinases, is associated with an increased risk of all-cause and cardiovascular mortality in general populations [10]. Furthermore, research is ongoing as to the potential diagnostic properties of CysC in preeclampsia [11]. CysC is also a promising biomarker for cancerrelated fatigue (CRF), particularly as it belongs to the less-studied category of non-inflammatory biomarkers [12]. Ding et al. [13] highlighted CysC's potential prognostic role in oncology, particularly in renal cell carcinoma. Elevated CysC levels were linked to poorer prognosis, but it could not distinguish between localized and metastatic disease.

It is, therefore, not surprising that the use of CysC is being explored in the context of cardiovascular diseases. Fan et al. [14] identified CysC as a potentially useful biomarker for assessing the risk, progression, and even pathophysiology of cardiorenal syndrome type I (CRS I). This condition involves acute kidney injury resulting from worsening cardiac muscle dysfunction, and decompensated heart failure, and also occurs as the consequence of acute coronary syndrome (ACS). Early detection of acute cardiorenal syndrome allows for therapeutic interventions that can improve patient prognosis [14]. CysC may also allow for assessing cardiovascular risk among patients with chronic kidney disease, enabling stratification and confirming its prognostic utility in this patient cohort [15].

A meta-analysis conducted by Jin et al. [16] provided evidence of the prognostic value of CysC among patients with ACS. Patients with elevated concentrations of CysC, compared to those with lower concentrations, were at higher risk for major cardiovascular events (MACE) and all-cause mortality. Importantly, the statistical significance remained even after adjusting for renal function markers in the model. Einwoegerer et al. [17] showed that elevated CvsC levels increase the risk of cardiovascular events and mortality, even in patients with normal kidney function. These findings align with a meta-analysis by Sun et al. [18]. In addition, Yang et al. [19] demonstrated that elevated concentrations of CysC correlate with a higher risk of vascular events among patients with established coronary artery disease (CAD). While all these findings are promising regarding the role of CysC, as noted by Angelidis et al. [20], many areas require further research. The mechanism through which CvsC elevates cardiovascular risk remains unidentified; however, its robust prognostic capabilities in individuals with normal renal function imply that renal impairment alone is inadequate. The measurement methods for this biomarker require additional validation. The cost-effectiveness will influence adoption. Consequently, further comprehensive studies are required to validate its clinical applicability in standard environments.

Taking all of the above into consideration, the aim of this meta-analysis was to evaluate the diagnostic utility of CysC in patients with ACS. Additionally, the study assessed the predictive value of CysC in relation to major adverse cardiovascular events (MACEs), overall mortality, and other cardiovascular outcomes such as heart failure, myocardial infarction, and stroke, which were considered as potential endpoints. By synthesizing the available evidence, this meta-analysis aimed to clarify the diagnostic and prognostic role of CysC as an emerging biomarker in the management of patients with ACS.

Methods

Protocol and registration

This systematic review and meta-analysis were prospectively registered with PROSPERO International Prospective Register of Systematic Reviews (PROSPERO identifier CRD42024575092) and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21] (**Suppl. Table 1**).

Search strategy

A search of the PubMed, Web of Science, Cochrane Library, and Embase databases was conducted using the PRISMA guidelines. Retrieval time was limited from inception until August 1st. 2024. The literature search was limited to English and strategies were performed through a combination of Mesh terms and free words as follows: "cystatin C" OR "Cys-C" OR "CysC" AND "acute coronary syndrome" OR "ACS" or "ST Segment Elevation Myocardial Infarction" OR "ST Elevated Myocardial Infarction" OR "ST-elevation MI" OR "STEMI" OR "non-ST elevation myocardial infarction" OR "NSTEMI" OR "myocardial Infarction" OR "unstable angina". Additional studies were also identified by searching the reference lists of the included studies, previous relevant narrative reviews and systematic reviews.

Eligibility criteria

The inclusion criteria were: (1) patients aged \geq 18 years; (2) studies reporting sufficient information about CysC concentrations among ACS and healthy patients (at baseline); (3) outcomes: that included functional recovery, cognitive dysfunction, death, hemorrhagic transformation, vascular events, depression and recurrence; (4) cohort studies or case-control studies; and (5) studies published in English.

Studies meeting 1 of the following criteria were excluded: (1) duplicated publication; (2) study protocols; (3) cell or animal experiments; (4) incomplete or inaccessible data; (5) not matching the topic; (6) abstracts without full text; (7) no relevant outcomes; and (8) reviews or meta-analyses, conference abstracts, case reports and letters.

The references cited in identified publications were also searched to locate additional studies. Figure 1 (PRISMA Flow Diagram) depicts the publications identified during the search process.

Data extraction

After importing the searched articles into the reference management software Endnote X9, the title and abstract were read to rule out irrelevant studies after removing duplicates. Assessed data was independently extracted in duplicate, with discrepancies addressed through discussion or third-party consensus. Subsequently, the relevant information was extracted: (1) study details: the



Figure 1. PRISMA flow chart of the included studies

first author, publication year, country of origin, study type, inclusion criteria, exclusion criteria, primary outcomes, findings; (2) subject's information: study group, population number, age, sex; (3) main outcomes: CysC concentrations, adverse event occurrence [e.g., major cardiovascular event (MACE) (Suppl. Table 2), cardiac death, myocardial infarction and target vessel revascularization (TVR)]. In addition, when studies did not provide relevant data but gave bar charts or curve graphs, the corresponding results were extracted by the image digitization software, GetData Graph Digitizer 2.26. Two authors (MP and DS) performed these processes independently, with a third author (LS) participating in the discussion if there was a disagreement. When the continuous outcome was reported as median and interquartile range, means and standard deviations were estimated using the formula described by Hozo et al. [22].

Assessment of risk of bias

Two authors (MP and DS) independently assessed the risk of bias in each study using the Newcastle-Ottawa Scale (NOS). NOS consists of eight questions with three domains: selection, comparability, and exposure, and each question gives values in the form of stars [23]. When the number of stars reaches nine, it indicates a good methodological quality compared to the main biases of the case-control studies. Consensus resolved disagreements in risk of bias assessment.

Statistical analysis

A statistical analyses was performed using the STATA software version 14.0 (Stata Corp., College Station, TX) and the Review Manager software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Denmark). The significance of two-tailed p-values of 0.05 was set. The outcomes were reported as pooled odds ratios (ORs), risk ratios (RRs), standard differences (MDs), and the corresponding 95% confidence intervals (95% CIs). all meta-analyses were performed using a random-effects model, anticipating substantial heterogeneity between the study results. The random effects model tends to give a more conservative estimate with a wider 95% CI. The heterogeneity using the Cochrane Q test and the I² statistic was then evaluated. Low heterogeneity was defined as an I² value of less than 50%, intermediate heterogeneity as between 50% and 75%, and high heterogeneity as > 75%, respectively. The Egger's test and funnel plots to check for potential bias was used, and funnel plot tests for asymmetry were used to assess potential publication bias if there were more than ten trials in a single meta-analysis. Finally, a leave-one-out analysis was conducted during the sensitivity analyses.



Figure 2. A graphical representation of the origin of the studies included in the meta-analysis

Ethical approval statement

It was not necessary to obtain approval from the institutional review board. The ethical standards regulating this investigation conform to the recognized recommendations for systematic reviews and meta-analyses. A registered procedure was followed for the study and employed a transparent search and analysis method to prevent selective reporting.

Results

Summary of included trials

The search yielded 1,683 records, of which 1049 duplicates were removed. A total of 634 studies were excluded after a title and abstract sieve, with 122 studies selected for full text review. A final total of 59 studies, of 43,189 patients were included in this meta-analysis (S1–S59). A graphical representation of the origin of the studies included in the meta-analysis is shown in Figure 2. A summary of the articles included can be found in **Supplementary Table 3**.

Cystatin C concentrations meta-analysis

Pooled analysis of CysC concentrations varied between the following groups: ACS vs. controls (1.44 \pm 0.72 vs. 1.01 \pm 0.38, respectively; MD = 0.36; 95% CI: 0.25–0.48; p < 0.001; Fig. 3), acute myocardial infarction (AMI) vs. unstable angina pectoris (1.48 \pm 0.71 vs. 1.43 \pm 0.74; MD = 0.18; 95% CI: 0.08–0.29; $\begin{array}{l} p < 0.001; \mbox{ Fig. 4}), \mbox{ AMI vs. controls } (1.47 \pm 0.58 \mbox{ vs.} \\ 1.00 \pm 0.31; \mbox{ MD } = 0.42; \mbox{ 95\% CI: } 0.15-0.69; \mbox{ p } = \\ 0.002; \mbox{ Suppl. Fig. 1}), \mbox{ STEMI vs. controls } (1.19 \pm \\ 0.5 \mbox{ vs. } 0.99 \pm 0.28; \mbox{ MD } = 0.28; \mbox{ 95\% CI: } 0.06-0.49; \\ p = 0.01; \mbox{ Suppl. Fig. 2}), \mbox{ and NSTEMI vs. controls } \\ (1.07 \pm 0.47 \mbox{ vs. } 0.98 \pm 0.29; \mbox{ MD } = 0.48; \mbox{ 95\% CI: } 0.04-0.92; \\ p = 0.03; \mbox{ Suppl. Fig. 3}). \end{array}$

There were no significant differences in CysC concentrations between STEMI vs. NSTEMI (1.23 \pm 0.43 vs. 1.18 \pm 0.5; MD = 0.01; 95% CI: -0.08-0.10; p = 0.82; **Suppl. Fig. 4**).

Nineteen studies reported CysC concentrations in patients with and without MACE. Pooled CysC concentrations in the group with MACE were 1.26 (0.47) and were higher than in patients without MACE [0.98 (0.27; MD = 0.25; 95% CI: 0.19–0.31; p < 0.001 (Fig. 5)].

Pooled analysis of six studies showed that CysC concentrations were lower in patients who survived vs. those who died in the hospital [0.92 (0.23) vs. 1.38 (0.47); MD = -0.25; 95% CI: -0.26, -0.24; p < 0.001 (Fig. 6)].

Meta-analysis of low vs. high concentrations of Cystatin C

The results indicate significant clinical differences between groups with low and high CysC concentrations (Table 1). For MACE, the relative risk (RR) during hospitalization was 0.45 (0.31-0.66), p < 0.001 and was similar after 12 months, 0.43

		ACS		Mean Difference	Mean Difference				
Study or Subgroup	Mean SD Total Mean SD Tota		Total	Weight IV, Random, 95% CI		IV, Random, 95% CI			
Abed 2020	1.4	1	102	0.5	0.26	94	6.0%	0.90 [0.70, 1.10]	
de Hoog 2012	1.16	0.05	140	1.13	0.06	331	7.3%	0.03 [0.02, 0.04]	· · ·
Fu 2018	1.69	0.84	699	1.56	0.62	93	6.6%	0.13 [-0.01, 0.27]	
Ge 2009	2.08	0.95	126	1.51	0.41	34	5.8%	0.57 [0.35, 0.79]	
Huang 2019	1.42	0.46	184	1.24	0.3	46	6.9%	0.18 [0.07, 0.29]	-
Le 2023	1.02	0.23	104	0.82	0.21	35	7.1%	0.20 [0.12, 0.28]	-
Lodh 2013	1.47	0.94	150	0.9	0.17	150	6.5%	0.57 [0.42, 0.72]	
Ma 2020	1.28	0.22	96	0.9	0.21	20	6.9%	0.38 [0.28, 0.48]	-
Noto 2005	0.91	0.26	122	0.9	0.24	61	7.1%	0.01 [-0.07, 0.09]	+
Pan 2021	1.19	0.31	361	1.12	0.2	119	7.2%	0.07 [0.02, 0.12]	-
Shaker 2020	1.38	1	136	0.5	0.2	94	6.3%	0.88 [0.71, 1.05]	
Shen 2022	1.56	0.47	65	1.08	0.42	30	6.1%	0.48 [0.29, 0.67]	
Tayeh 2012	1.84	0.78	75	0.99	0.16	75	6.2%	0.85 [0.67, 1.03]	
Yan 2017	1.17	0.21	70	0.78	0.07	50	7.2%	0.39 [0.34, 0.44]	-
Zhang 2017	1.33	0.43	195	1.3	0.35	39	6.7%	0.03 [-0.10, 0.16]	+
Total (95% CI)			2625			1271	100.0%	0.36 [0.25, 0.48]	•
Heterogeneity: Tau ² :	= 0.05; 0	Chi ² =	547.83	3, df = 1	14 (P -	< 0.000	01); $I^2 =$	97%	
Test for overall effect	: Z = 6.1	10 (P <	< 0.000	01)					-2 -1 0 1 Favours [ACS] Favours [Control]

Figure 3. Forest pot demonstrating cystatin C concentrations among ACS and Control groups; ACS — acute coronary syndrome; CI — confidence interval; SD — standard deviation

		AMI			UAP			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Chen 2021	1.6	0.6	197	1.3	0.7	237	11.5%	0.30 [0.18, 0.42]	-
Fu 2018	1.96	0.81	135	1.62	0.84	564	10.6%	0.34 [0.19, 0.49]	-
Ge 2009	2.87	1.15	36	2.01	0.63	56	4.4%	0.86 [0.45, 1.27]	
Le 2023	1.12	0.22	37	1.03	0.22	36	12.1%	0.09 [-0.01, 0.19]	-
Ma 2020	1.32	0.21	71	1.18	0.21	25	12.2%	0.14 [0.04, 0.24]	-
Noto 2005	0.85	0.23	61	0.97	0.27	61	12.4%	-0.12 [-0.21, -0.03]	-
Shen 2022	1.71	0.35	35	1.38	0.53	30	8.5%	0.33 [0.11, 0.55]	
Tayeh 2012	1.89	0.71	56	1.63	0.99	19	3.5%	0.26 [-0.22, 0.74]	
Zhang 2017	1.38	0.51	112	1.26	0.27	83	11.8%	0.12 [0.01, 0.23]	
Zhang 2021	1.02	0.27	198	0.95	0.26	98	13.0%	0.07 [0.01, 0.13]	-
Total (95% CI)			938			1209	100.0%	0.18 [0.08, 0.29]	•
Heterogeneity: Tau ² =	0.02; 0	Chi ² =	62.51,	df = 9	(P < 0	.00001); $I^2 = 86!$	%	
Test for overall effect:	Z = 3.4	40 (P =	= 0.000	7)					Favours [AMI] Favours [UAP]

Figure 4. Forest pot demonstrating cystatin C concentrations among AMI and UAP groups; AMI — acute myocardial infarction; CI — confidence interval; SD — standard deviation; UAP — unstable angina

	MACE + MACE -				ACE -			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Abid 2016	1.19	0.4	32	1.01	0.35	95	4.4%	0.18 [0.02, 0.34]	
Ge 2009	2.36	0.89	26	1.47	0.57	22	1.4%	0.89 [0.47, 1.31]	
Grufman 2018	1.32	0.11	75	1	0.06	449	6.6%	0.32 [0.29, 0.35]	
Kallel 2012	0.94	0.07	66	0.79	0.03	1761	6.6%	0.15 [0.13, 0.17]	
Kaski 2010	1.01	0.22	54	0.94	0.05	556	6.2%	0.07 [0.01, 0.13]	~
Kilic 2009	1.53	0.39	42	0.94	0.09	118	5.1%	0.59 [0.47, 0.71]	-
López-Cuenca 2013	1.08	0.09	25	0.91	0.06	248	6.5%	0.17 [0.13, 0.21]	
Ma 2020	1.33	0.14	35	1.25	0.2	61	6.1%	0.08 [0.01, 0.15]	-
Mao 2019	1.05	0.21	50	0.9	0.05	372	6.2%	0.15 [0.09, 0.21]	-
Obeid 2020	1.21	0.49	192	0.98	0.37	1640	6.0%	0.23 [0.16, 0.30]	-
Shantsila 2015	1.04	0.22	16	0.99	0.08	32	5.3%	0.05 [-0.06, 0.16]	+-
Shlipak 2008	1.43	0.89	142	1.05	0.32	837	4.6%	0.38 [0.23, 0.53]	
Silva 2012	0.86	0.23	20	0.73	0.3	133	5.2%	0.13 [0.02, 0.24]	
Sun 2012	1.37	0.43	95	1.21	0.39	510	5.6%	0.16 [0.07, 0.25]	-
Vaduganathan 2019	1.28	0.24	621	1.14	0.21	4759	6.6%	0.14 [0.12, 0.16]	
von Jeinsen 2017	1	0.1	63	0.7	0.03	1741	6.6%	0.30 [0.28, 0.32]	
Wasyanto 2023	1.43	0.89	10	0.76	0.7	30	0.8%	0.67 [0.06, 1.28]	
Wei 2013	1.69	0.76	70	1	0.46	169	3.8%	0.69 [0.50, 0.88]	
Widera 2013	1.35	0.14	78	0.94	0.06	1068	6.5%	0.41 [0.38, 0.44]	•
Total (95% CI)			1712			14601	100.0%	0.25 [0.19, 0.30]	•
Heterogeneity: $Tau^2 =$	0.01; C	$hi^2 =$	511.64	, df = 1	8 (P <	0.0000	1); $I^2 = 96$	%	
Test for overall effect:	Z = 8.6	4 (P <	0.000	01)					

Figure 5. Forest pot demonstrating cystatin C concentrations among patients with and without MACE; CI — confidence interval; MACE — major advance cardiovascular event occurrence; SD — standard deviation

	Survive Dead					Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Abid 2016	0.96	0.27	121	1.21	0.36	6	9.8%	-0.25 [-0.54, 0.04]	
Bai 2021	1.2	0.1	420	1.65	0.25	69	21.2%	-0.45 [-0.51, -0.39]	•
Eggers 2010	1.14	0.04	353	1.47	0.08	92	22.2%	-0.33 [-0.35, -0.31]	
Flores-Blanco 2016	0.87	0.05	318	1.26	0.3	31	19.1%	-0.39 [-0.50, -0.28]	-
Keller 2009	0.79	0.03	1761	0.94	0.07	66	22.2%	-0.15 [-0.17, -0.13]	
Přeček 2018	0.97	0.38	633	1.65	1.17	26	5.5%	-0.68 [-1.13, -0.23]	
Total (95% CI)			3606			290	100.0%	-0.34 [-0.46, -0.22]	•
Heterogeneity: Tau ² = 0.02; Chi ² = 273.40, df = 5 (P < 0.00001); I ² = 98%								-2 -1 0 1 2	
rest for overall effect:	2 = 5.4	5 (P <	0.000	01)					Favours [Survive] Favours [Dead]

Figure 6. Forest pot demonstrating cystatin C concentrations among survived vs. decreased patients; CI — confidence interval; SD — standard deviation

Outcome	No. of	Events/partie	cipants	RR	Heterogene	P-value for differ-	
	studies	Low CysC	High CysC	(95% CI)	P-value	^s l ² statistic	ences across groups
MACE							
In-hospital	3	42/686	68/512	0.45	0.53	0%	< 0.001
		(6.12%)	(13.28%)	(0.31–0.66)			
1 month	2	68/573	92/427	0.55	0.04	76%	0.05
		(11.87%)	(21.55%)	(0.30–1.01)			
12 months	5	144/1332	318/1373	0.43	0.007	71%	< 0.001
		(10.81%)	(23.16%)	(0.30–0.61)			
> 12	3	417/4073	875/4029	0.39	< 0.001	93%	< 0.001
months		(10.24%)	(21.72%)	(0.24–0.64)			
Cardiac deat	h						
In-hospital	4	7/750	26/598	0.18	0.96	0%	< 0.001
		(0.93%)	(4.35%)	(0.08–0.41)			
1 month	2	7/573	29/427	0.15	0.66	0%	< 0.001
		(1.22%)	(6.79%)	(0.07–0.32)			
12 months	2	6/468	23/479	0.27	0.74	0%	0.004
		(1.28%)	(4.8%)	(0.11–0.65)			
> 12	3	78/3581	289/3200	0.25	0.44	0%	< 0.001
months		(2.18%)	(9.03%)	(0.19–0.32)			
Overall morta	ality						
In-hospital	6	69/4669	96/2065	0.27	0.04	57%	< 0.001
		(1.48%)	(4.65%)	(0.13–0.58)			
12 months	3	18/616	101/632	0.18	0.88	0%	< 0.001
		(2.92%)	(15.98%)	(0.11–0.29)			
> 12	7	209/5895	706/5512	0.25	< 0.001	82%	< 0.001
months		(3.55%)	(12.81%)	(0.16–0.38)			
MI reinfarctio	on						
In-hospital	4	26/750	24/598	0.76	0.62	0%	0.34
		(3.47%)	(4.01%)	(0.43–1.34)			
12 months	3	27/552	47/558	0.58	0.48	0%	0.02
		(4.89%)	(8.42%)	(0.36–0.91)			

Table 1. Pooled analysis of outcomes among low and high cystatin C concentration

Outcome	No. of	Events/parti	cipants	RR	Heterogene	P-value for differ- ences across	
	studies	Low CysC	High CysC	(95% CI)	tween trials		
					P-value	l ² statistic	groups
> 12	4	232/3661	323/3614	0.71	0.45	0%	< 0.001
months		(6.34%)	(8.94%)	(0.60–0.83)			
Heart failure							
In-hospital	2	18/455	36/297	0.29	0.40	0%	< 0.001
		(3.96%)	(12.12%)	(0.17–0.50)			
12 months	3	9/743	60/764	0.16	0.62	0%	< 0.001
		(1.21%)	(7.85%)	(0.08–0.33)			
> 12	3	69/4073	313/4029	0.22	< 0.001	86%	< 0.001
months		(6.34%)	(7.77%)	(0.09–0.50)			
Stroke							
In-hospital	3	3/493	2/330	0.85	0.18	44%	0.91
		(0.61%)	(0.61%)	(0.05–14.35)			
12 months	2	5/504	8/523	0.65	0.97	0%	0.45
		(0.99%)	(1.53%)	(0.21–1.97)			
> 12	2	58/3057	106/3008	0.54	0.83	0%	< 0.001
months		(1.89%)	(3.52%)	(0.39–0.74)			
TVR							
> 12	3	180/1159	203/1151	0.66	< 0.001	75%	0.14
months		(15.53%)	(17.64%)	(0.32–1.38)			

Table 1 (cont.). Pooled analysis of outcomes among low and high cystatin C concentration

CI — confidence interval; CysC — Cystatin C; MACE — major adverse cardiovascular events; MI — myocardial infarction; RR — relative risk; TVR — target vessel revascularization

(0.30–0.61), p < 0.001, and beyond, 0.39 (0.24–0.64), p < 0.001. For cardiac death, the RR during hospitalization was 0.18 (0.08–0.41), p < 0.001, and persisted beyond 12 months, 0.25 (0.19–0.32), p < 0.001. Regarding overall mortality, the RR during hospitalization was 0.27 [0.13–0.58], p < 0.001, and was similar beyond 12 months, 0.25 (0.16–0.38), p < 0.001. For myocardial reinfarction, the RR at 12 months was 0.58 (0.36–0.91), p = 0.02, and the risk of stroke beyond 12 months was also lower in the low CysC group [RR 0.54 (0.39–0.74), p < 0.001].

Discussion

This study demonstrated that patients with ACS had significantly higher CysC concentrations compared to healthy controls. Patients with AMI; either STEMI or NSTEMI exhibited significantly elevated CysC concentrations when compared to healthy individuals. A significant difference was also observed between patients with AMI and those with unstable angina (UAP). However, CysC concentrations did not significantly differentiate between patients with STEMI and NSTEMI. Overall, these findings suggest that elevated CysC concentrations may be associated with the occurrence of ACS and could be useful in differentiating between certain ACS subtypes, such as AMI and UAP but it cannot differentiate STEMI from NSTEMI.

In the context of clinically important findings, the meta-analysis further revealed that comparing low versus high CysC concentrations can be useful in predicting the potential occurrence of MACEs and cardiac death, both in hospital settings and beyond 12 months. High CysC concentrations were also associated with higher overall mortality, both in-hospital and exceeding 12 months. Additionally, the risk of myocardial reinfarction was higher among patients with elevated CysC concentrations at 12 months and beyond. Furthermore, higher CvsC was linked to an increased risk of heart failure, both in-hospital (RR = 0.29; p < 0.001) and over longer follow-up periods (RR = 0.22; p < 0.001). These findings indicate that CysC could be a valuable biomarker for risk stratification in ACS patients.

The findings of the meta-analysis align with the conclusions drawn by Einwoegerer et al. [17], who observed that elevated CysC concentrations in patients with normal renal function are associated with an increased risk of mortality and cardiovascular events. Similarly, Luo et al. [24] reached comparable conclusions. In a metaanalysis conducted by Lee et al., which included 22,509 subjects from the general population and 2,321 subjects with established cardiovascular history, it was demonstrated that elevated CysC is associated with an increased risk of cardiovascular events and coronary heart disease, even after accounting for other well-established cardiovascular risk factors [25].

Other meta-analyses lead to similar conclusions [16, 17]. However, the aforementioned metaanalyses were limited in the number of studies they included and were published a considerable time ago. Given the significantly larger number of studies included in the present analysis, there is a justified need for further research to more comprehensively explore the primary data. Finally, in the context of discussing the potential prognostic utility of CysC, it is important to highlight a 2022 meta-analysis, which showed that elevated CysC is linked to a higher risk of MACE and increased mortality among patients following AMI after undergoing percutaneous coronary intervention [10].

Moreover, the utility of CysC in cardiovascular medicine extends beyond ACS. Chen et al. [26] conducted a meta-analysis among patients with heart failure, demonstrating that elevated CysC is linked to an increased risk of all-cause mortality. Notably, unlike earlier meta-analyses, they found that higher CysC was directly associated with an increased risk of reaching a composite endpoint that included both mortality and rehospitalization. This observation is consistent with the current meta-analysis, which strongly emphasizes that elevated CvsC is associated with an increased risk of heart failure, both during hospitalization and in long-term follow-up. When interpreting the results of the meta-analysis by Chen et al. [26], it is important to consider that the study population exhibited significant heterogeneity due to the complex and varied potential causes of heart failure.

Ultimately, the present meta-analysis is consistent with the findings of Yang et al. [18], which found that, when comparing high versus low CysC, patients with the highest results concentrations have an increased risk of all-cause mortality, cardiovascular mortality, and total adverse vascular events. However, while Yang et al. [18] did not address time points in their analysis, the current study highlights that elevated CysC concentrations are associated with increased overall mortality specifically in hospital settings and beyond the 12-month index point. A similar timeframe is also observed for cardiac death.

It is pertinent to question whether CysC offers advantages over well-established diagnostic and prognostic biomarkers in ACS. Unfortunately, it is too early to answer this question definitively, partly due to the absence of a clear cut-off value. Clinical validation of a biomarker is a complex process that first requires the selection of a gold standard biomarker, which is not always straightforward, especially for prognostic markers. Additionally, more standardized protocols for conducting prospective studies are needed, which should not be guided solely by the feasibility of the research. There is also a need to effectively transition from retrospective observations to a prospective research approach. CysC may prove clinically useful at the intersection of nephrology and cardiology and could be valuable in cardiovascular risk stratification among patients with impaired renal function. This specific patient sub-population may represent a potential niche for the application of this biomarker.

The absence of significant differences in Cystatin C levels between STEMI and NSTEMI aligns with its role as a biomarker of cardiovascular risk and renal function rather than specific myocardial injury patterns. This limitation highlights the importance of integrating Cystatin C with other biomarkers and clinical tools, such as troponins, electrocardiographic findings, and imaging modalities, to achieve a more comprehensive diagnostic approach. Despite this limitation, the strong association of elevated CysC with increased risks of MACEs emphasizes its value in prognostication. This underscores its potential as a supportive biomarker in managing ACS patients broadly, aiding in risk stratification and therapeutic decision-making.

When interpreting the results of the current meta-analysis, several limitations should be considered. First, meta-analyses rely on literature searches, so biases related to search strategies, search processes and database access cannot be excluded [27]. Additionally, meta-analyses depend on data reported in published articles without access to individual patient data. The literature provides limited information on the cut-off concentrations used for risk stratification. Furthermore, although some studies have adjusted for known risk factors, the potential influence of variables such as age or certain behavioural habits, such as smoking, on elevated CysC results cannot be ruled out. This meta-analysis encompasses studies from the past 20 years, during which evolving definitions of myocardial infarction introduced changes in diagnostic thresholds and methods, likely contributing to result heterogeneity. Despite efforts to account for these variations, they may have influenced the interpretation of Cystatin C's clinical value. Future studies employing standardized definitions are essential to enable consistent comparisons.

This meta-analysis highlights the utility of CvsC as a key biomarker for risk stratification in ACS, showing strong associations with adverse outcomes like MACE, cardiac death, and myocardial reinfarction. Its prognostic value, extending beyond renal function and up to 12 months post-event, supports its role in both acute and long-term patient management. As one of the largest analyses to date, synthesizing data from over 43,000 patients, it reinforces Cystatin C's utility in general ACS risk profiling while clarifying its limitation in differentiating STEMI from NSTEMI. Its systemic nature, coupled with potential applications in patients with coexisting renal dysfunction, underscores its unique value in cardiovascular care and future multimodal diagnostic strategies.

Moreover, further research could focus on investigating the relationship between CvsC levels and high body mass index (BMI) or diabetes, wellknown cardiovascular risk factors. The relationship between elevated BMI and CysC levels remains ambiguous. Shankar and Teppala [28] found that individuals with higher BMI exhibited increased levels of CysC. Among adolescents aged 14–17, a similar pattern was noted in boys; however, in girls, the probability of obesity initially grew and subsequently diminished as CysC levels rose [28, 29]. Since obesity is linked to a heightened risk of pro-inflammatory processes, this may provide an explanation for the observed rise in CysC levels among obese individuals. Furthermore, there is a need for studies comparing CysC levels in diabetic patients with and without nephropathy or cardiovascular events to evaluate its prognostic value. Preliminary findings suggest that CvsC levels may, among other factors, correlate with the duration of diabetes [30].

Conclusions

Overall, this meta-analysis reveals that elevated CysC is strongly linked to a higher risk of MACE, cardiac death, all-cause mortality, myocardial reinfarction, and heart failure in patients with ACS. However, the utility of CysC as a predictive marker for stroke in the short term, and for TVR, appears to be limited. These findings highlight the significant potential of CysC as both a diagnostic and prognostic biomarker in the management of ACS, suggesting its incorporation could enhance risk stratification and inform therapeutic decisionmaking in clinical practice.

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Supplementary material: Suppl. Tables 1–4; Suppl. Figures 1–4.

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