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Review Article

The meta-analysis of the clinical significance of serum Cystatin C in the diagnosis of heart failure complicating acute myocardial infarction

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Abstract: Aim: This Meta-analysis aimed to explore the clinical significance of circulating Cystatin C (Cys-C) in the diagnosis of heart failure complicating acute myocardial infarction. Methods: In PubMed, EBSCO, Elsevier, Springer, Wiley, Cochrane, CNKI, and Wanfang Data databases, 'Heart failure', 'HF', 'serum Cyc-C', and 'acute myocardial infarction' were set as keywords to search for related prospective cohort studies between the period of January 1979 and 30th May 2020. The incidence rates of cardiovascular events, the all-cause mortality rates of patients, and the readmission rates were summarized and compared. Results: Finally, 6 prospective clinical cohort studies were included. When comparing the highest Cys-C level with the lowest, the combined hazard ratio of adverse cardiovascular events was found to be HR, 95% CI = 3.79 [2.38-6.04]; the combined hazard ratio of all-cause mortality was found to be HR, 95% CI = 3.09 [2.18-4.38]; the combined hazard ratio of readmission rates was found to be HR, 95% CI = 46.21 [23.03-92.74]. The results of subgroup analysis indicated that these correlations were not influenced by factors such as area, follow-up duration, or sample size. Conclusion: The increase in Cys-C level could be related to incidence rates of adverse cardiovascular events, all-cause mortality rates, and readmission rates in acute myocardial infarction patients.

Keywords: Serum Cystatin C, acute myocardial infarction, heart failure, incidence rates of adverse cardiovascular events, all-cause mortality rates, meta

Introduction

Currently, cardiovascular disease is the leading cause of death in non-communicable diseases, with acute myocardial infarction being one of the main causes of the disease [1-3]. Studies have shown that approximately 32.4% of acute myocardial infarction patients have heart failure complications, which further lead to an increase in mortality rate [2]. As a result, an earlier diagnosis of myocardial infarction is necessary for clinicians to adjust treatment plans in time.

Cystatin C (Cys-C) is a reversible competitive inhibitor of cysteine proteases and is highly concentrated in serum, saliva, semen, synovial fluid, and cerebrospinal fluid. It is filtered by the glomerulus and is an ideal endogenous marker for early prediction of renal function [4]. Cys-C is produced and secreted by cardiomyocytes, with its synthesis level increased during cardiac ischemia [5]. In heart failure (HF) patients, the increase in mortality rate of heart failure (HF) is correlated to the increase of Cys-C to an intermediate level above 1.3 mg/L [6]. In a cross-sectional study of 211 asymptomatic metabolic syndrome patients without histories of coronary artery disease (CAD), the serum Cys-C levels in asymptomatic CAD patients were significantly higher than that in patients without CAD [7]. The currently available studies are mainly focused on the evaluation of HF prognosis using Cys-C level, while there are few studies on the correlation between HF complicating AMI and Cys-C level. To our knowledge, this study is the first to perform a meta-analysis to measure the serum Cys-C level in HF complicating AMI patients as well as to evaluate the role of Cys-C in the prediction of HF complicating AMI. The study is as follows.

Material and methods

This study was conducted in accordance with protocols for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. Up until 30th May 2020, systematic searches were performed on electronic databases (PubMed, EBSCO, Elsevier, Springer, Wiley, Cochrane, CNKI, Wanfang Data) using 'serum Cystatin C', 'heart failure', 'HF", and 'acute myocardial infarction' as keywords without language preference. The studies that satisfied the following conditions were included: a. prospective studies; b. patients diagnosed with HF complicating AML; c. the result indicators including the incidence rates of cardiovascular events, the all-cause mortality rates of patients, or the readmission rates; d. monitoring of serum Cys-C level. The exclusion criteria were as follows: a. repeated research paper; b. reviews or case reports; c. unavailable results or complete research details; d. not Chinese or English paper.

Data extraction

Two researchers preliminarily examined the reference sections by strictly following the exclusion criteria and independently screened and excluded papers that did not meet the requirement. After a close inspection of po-tential studies, these two researchers had a full discussion regarding the different outcomes of these studies, or a third researcher was also invited to make the final decision.

The extracted data included: the name of the first author, year of publication, number of included cases, age (average), gender, number of samples, Cys-C level, and etc.

Quality evaluation

The methodological quality was assessed using the nine-star Newcastle-Ottawa Scale (NOS) [9]. The studies rated above 7 stars were classified into the high-quality group based on this scale.

Statistical analysis

We processed all the data with Review Manager 5.1.0, and a *P*-value < 0.05 was considered statistically significant. We aggregated the risk assessments after the multivariable adjustment based on the comparison of the highest and lowest Cys-C levels. The heterogeneity was measured using Cochran's Q test and I^2 statistic. The data related to non-significant heterogeneity were calculated by a fixed effects model (I^2 < 50%, P > 0.1). The heterogeneous data were calculated by a random effects model (I^2 > 50%, P < 0.1).

The funnel plot was used to assess the publication bias of the papers. Subgroup analysis was performed based on regions (Europe compared to other countries), follow-up durations (≥ 2 years vs < 2 years), and sample sizes (≥ 200 vs < 200). The reliability of aggregated risk assessments was assessed by sensitivity analysis of the deletion of each individual study in turn.

Results

After a comprehensive search of the database, a total of 172 articles were obtained. EndNote software is used to check duplicates and get 64 articles. By reading the title of the litera ture, we excluded 17 literature reviews and 10 case reports, and obtained 37 articles that met the requirements. By carefully studying the full text of the literature, we excluded 31 non-clinical randomized controlled studies, and finally determined that six of these studies were eligible [7, 10-14]. (**Figure 1**) indicated the search procedure for relevant papers.

Table 1 Summarised the characteristics of these 6 studies with a total number of 2453 patients. The follow-up period is 0.5-5 years. The geographical distribution of the studies is two each in Europe, the United States, and China. According to NOS, the overall quality score (range from 7-9) of included studies is good (**Table 1**).

Incidence rates of cardiovascular events

In the three studies by Carrasco F 2014 [10], Fu Z 2018 [11], and Silva D 2012 [13] respectively, the researchers all explored the correlation between serum Cys-C and incidence rates of cardiovascular events in HF complicating AMI patients. The result of heterogeneity measurement is chi-squared = 0.03, P = 0.98 and I^2 = 0%, thus a fixed effects model was adopted. The results showed that the incidence rates of cardiovascular events were higher in the patient group with high serum Cys-C level than that in the patient group with low serum Cys-C level (HR 3.79; 95% CI: 2.38-6.04, Z = 5.62, P < 0.0001) (**Figure 2**). The sensitivity analysis in-

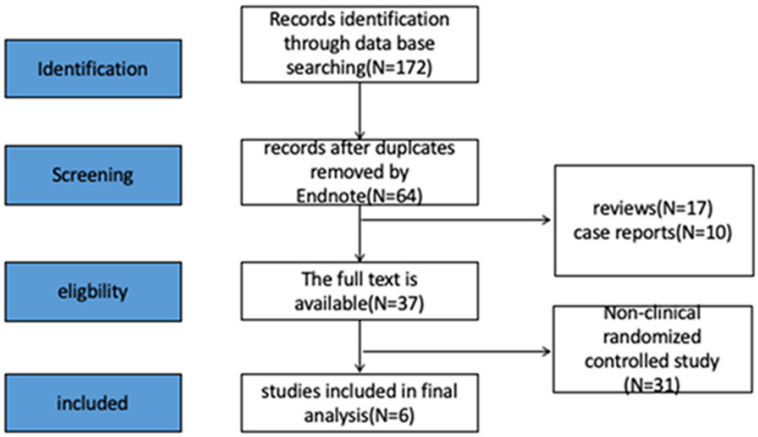

Figure 1. Search procedure for relevant papers. After a comprehensive search of the database, a total of 172 articles were obtained. EndNote software is used to check duplicates and get 64 articles. By reading the title of the literature, we excluded 17 literature reviews and 10 case reports, and obtained 37 articles that met the requirements. By carefully studying the full text of the literature, we excluded 31 non-clinical randomized controlled studies, and finally divided them into 6 eligible studies.

dicated that deletion of any individual study would not change this outcome.

All-cause mortality rate

These six studies included all that reported the value of serum Cys-C in predicting the risk of all-cause mortality. The result of heterogeneity measurement is chi-squared = 10.78, P = 0.06, and I^2 = 54%, thus a random effects model was adopted. In the random effects model, the all-cause mortality rate was higher in the patient group with high serum Cys-C level than that in the patient group with low serum Cys-C level (HR:3.45; 95%; CI: 2.37-5.03, Z = 6.45, P < 0.00001) (**Figure 3**). The results of the subgroup analysis indicated that these correlations were not influenced by factors such as area, follow-up duration or sample size (**Table 2**). The sensitivity analysis indicated that deletion of any individual study from the meta-analysis only led to minor changes in the aggregated risk assessments.

Readmission rate

In the three studies by Fu Z 3018 [11], Silva D 2012 [13] and Pérez J 2012 [12] respectively, the researchers all explored the correlation between serum Cys-C and readmission risk in HF complicating AMI patients. The result of heterogeneity measurement is chi-squared = 3.28, P = 0.19 and I^2 = 39%, thus a fixed effects model was adopted. The results showed that the readmission risk was higher in the patient group with high serum Cys-C level than that in patient group with low serum Cys-C level (HR 46.21; 95% CI: 23.03-92.74, Z = 10.79, P < 0.0001) (**Figure 4**). The sensitivity analysis indicated that the deletion of any individual study would not change this outcome.

Due to the relatively small number of papers, the results of publication bias were ignored [15].

Discussion

The meta-analysis showed that the increase in serum Cys-C levels could be related to the increase in incidence rates of adverse cardiovascular events, all-cause mortality rates, and readmission rates in HF complicating AMI patients. The meta-analysis results indicated that the increase of serum Cys-C level could be used as an independent predictor of poor prognosis in HF complicating AMI patients.

Previous studies showed that the early AMI would result in severe inflammatory reactions that involve the close participation of Cys-C and a strong correlation with the related prognosis of AMI [16-18]. A clinical study of patients with chronic heart failure (CHF) found that the Cys-C level significantly increased in CHF patients [19]. A prospective cohort study (PCS) of Cys-C level measurement in HF patients found that the incidence rates of adverse cardiovascular events significantly increased in the patient group with relatively higher Cys-C levels [20]. A prospective cohort study of 353 CHF patients indicated that there was a significant correlation between Cys-C level and overall incidence rates of cardiovascular events [21]. Furthermore, it has been reported that Cys-C levels were decreased in patients during the development of AMI and there was a significant correlation between Cys-C level and the recurrence rates of adverse cardiovascular events in patients [22]. The meta-analysis in this study indicates that Cys-C level is closely related

Table 1. General Information

study	country	Study design	Research time	Sample size	Cystatin c value	Incidence of vascular events	All-cause mortality	Risk of readmission	NOS
Breidthardt T 2017	England	PCS	2015-2017	153/54	2.0 mg/dL	/	58/6	/	8
Carrasco F 2014	England	PCS	2011-2013	163/32	1.30 mg/dL	115/12	46/4	/	7
Fu Z 2018	China	PCS	2016-2018	564/89	1.815 mg/L	205/12	267/6	69/1	8
Pérez J 2012	America	PCS	2010-2012	367/195	1.25 mg/dL	/	142/25	189/3	9
Silva D 2012	America	PCS	2010-2012	153/110	1.02 mg/L	15/3	31/4	7/5	9
Wu X 2020	China	PCS	2015-2020	418/137	1.35 mg/L	/	274/39	/	8

PCS: Prospective Cohort Study.

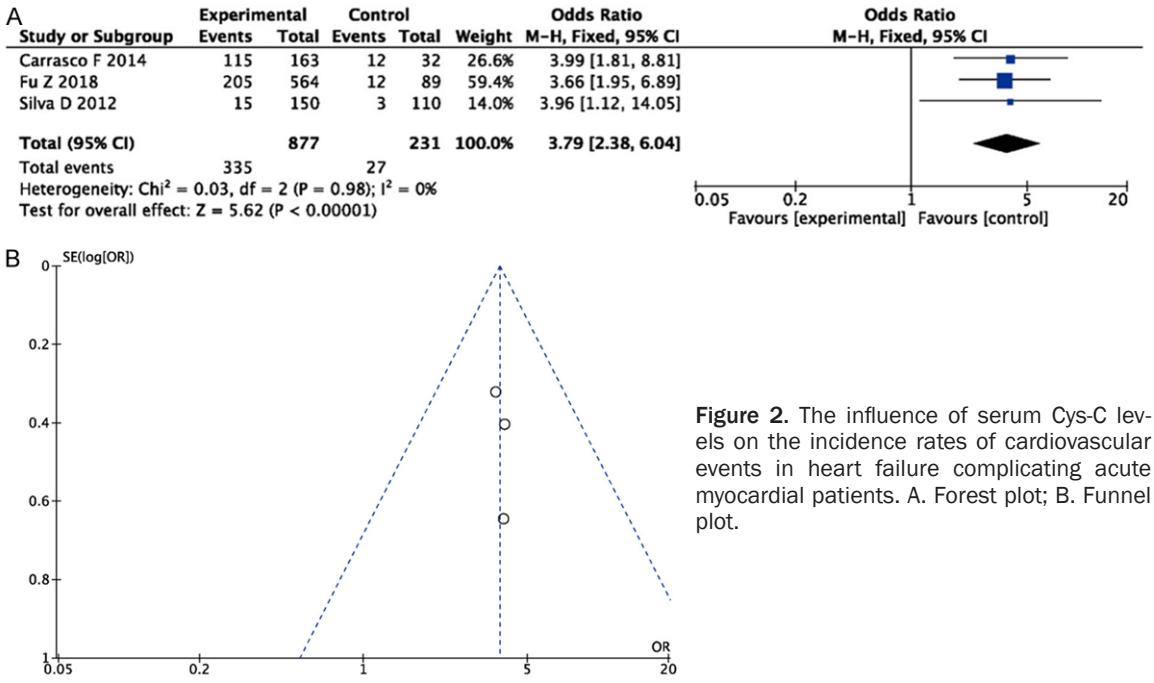

Figure 2. The influence of serum Cys-C levels on the incidence rates of cardiovascular events in heart failure complicating acute myocardial patients. A. Forest plot; B. Funnel plot.

to the incidence rates of adverse events in HF complicating AMI patients. This is consistent with the results above. The related mechanism may be that myocardial injury releases related inflammation, which promotes the production of cysteine proteases; the body compensates for the production of a large number of protease inhibitors and maintains the internal environment, and thus results in higher Cys-C levels [11].

In a clinical study, patients were divided into groups with high Cys-C levels and low Cys-C levels using 1.75 mg/L as the dividing point. The results indicated that the all-cause mortality rate in the high Cys-C level group was 39.4% which significantly increased compared to that in the low Cys-C level group [23]; In a PCS, the author analysed the Cys-C levels in AMI patients after the percutaneous coronary intervention (PCI) surgery and found that the all-cause mortality rates significantly increased in Cys-C high-level group compared to that in Cys-C low-level group [24]. The results of this study indicate that there is a significant correlation between Cys-C level and all-cause mortality rates in HF complicating AMI patients. The all-cause mortality rates increased with the increase in Cys-C levels, which is consistent with the results above. We performed subgroup analysis with the elimination of heterogeneity and found that these correlations were not influenced by factors such as area, follow-up duration, or sample size. When the serum Cys-C level decreases, the protease activity increases, and it is overexpressed in the vascular elastic layer of the arterial wall, causing pathological damage to the blood vessels. At the same

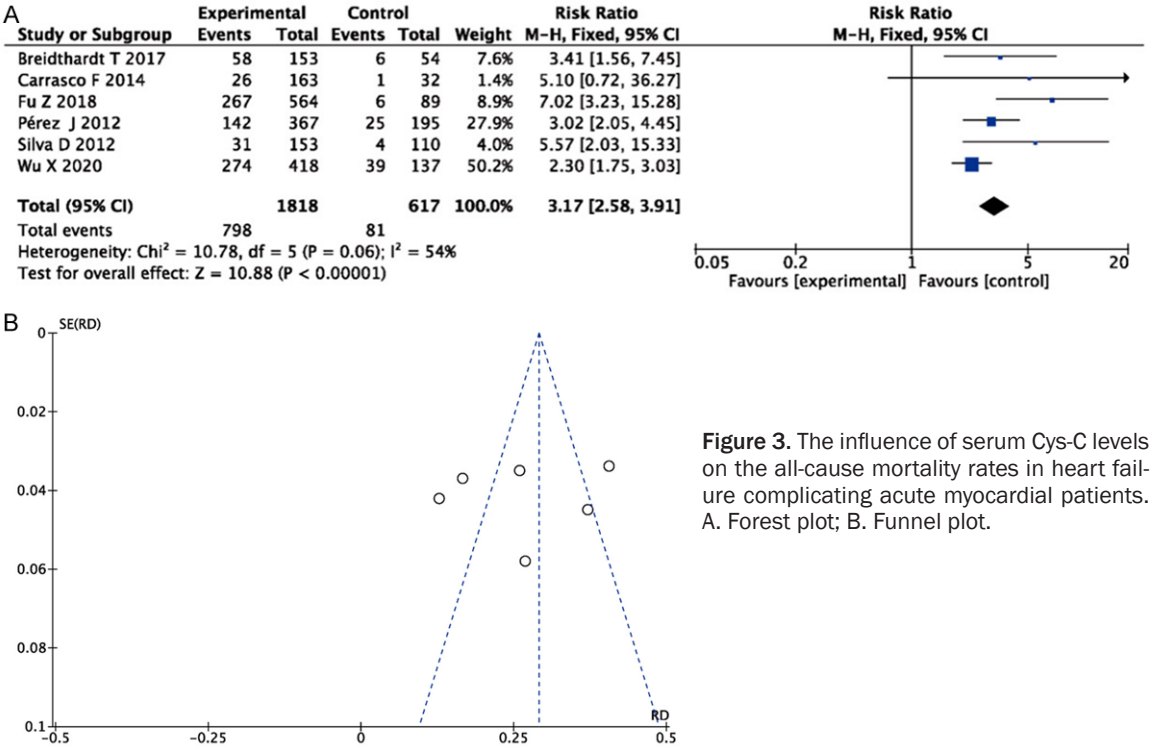

Figure 3. The influence of serum Cys-C levels on the all-cause mortality rates in heart failure complicating acute myocardial patients. A. Forest plot; B. Funnel plot.

Table 2. Subgroup analysis

Subgroup	Studies	Pooled HR	95% CIs	Heterogeneity across studies
Region				
Europe	2	3.09	2.18, 4.38	P = 0.78, I^2 = 0%
America	2	5.47	2.23, 13.45	P = 0.94, I^2 = 0%
China	2	3.81	1.18, 12.38	P = 0.004, I^2 = 88%
Follow-up duration				
< 3 years	4	4.37	2.62, 7.29	P = 0.19, I^2 = 37%
> 3 years	2	2.40	1.86, 3.11	P = 0.35, I^2 = 0%
Sample sizes				
< 200	3	3.14	2.23, 4.42	P = 0.85, I^2 = 0%
> 200	3	3.26	1.96, 5.42	P = 0.02, I^2 = 76%

time, Cys-C will increase compensatorily to restore the balance of proteases and inhibitors. Therefore, the increase of serum Cys-C level indicates that the vascular endothelial function of AMI patients may have been damaged. In addition, elevated serum Cys-C levels often indicate complicated multivessel disease [25]. Therefore, all-cause mortality in patients with elevated Cys-C levels increases.

In addition, relevant studies showed that readmission rates of AMI patients were higher in Cys-C high-level group than that in Cys-C low-level group. As a result, Cys-C level could be used to predict the prognosis of AMI patients [26]. However, another study found that there was no significant correlation between Cys-C levels and readmission rates of CHF patients [27]. The meta-analysis in this study indicates that the patients in Cys-C high-level group have increased readmission rates, which is consistent with the results above. The related mechanism may be that when the patient is in a pathological state of myocardial infarction, the contractile function of the myocardium in the diseased area is reduced or completely lost, and the amount of heartbeat bleeding is reduced. As an enzyme inhibitor of lysosomal

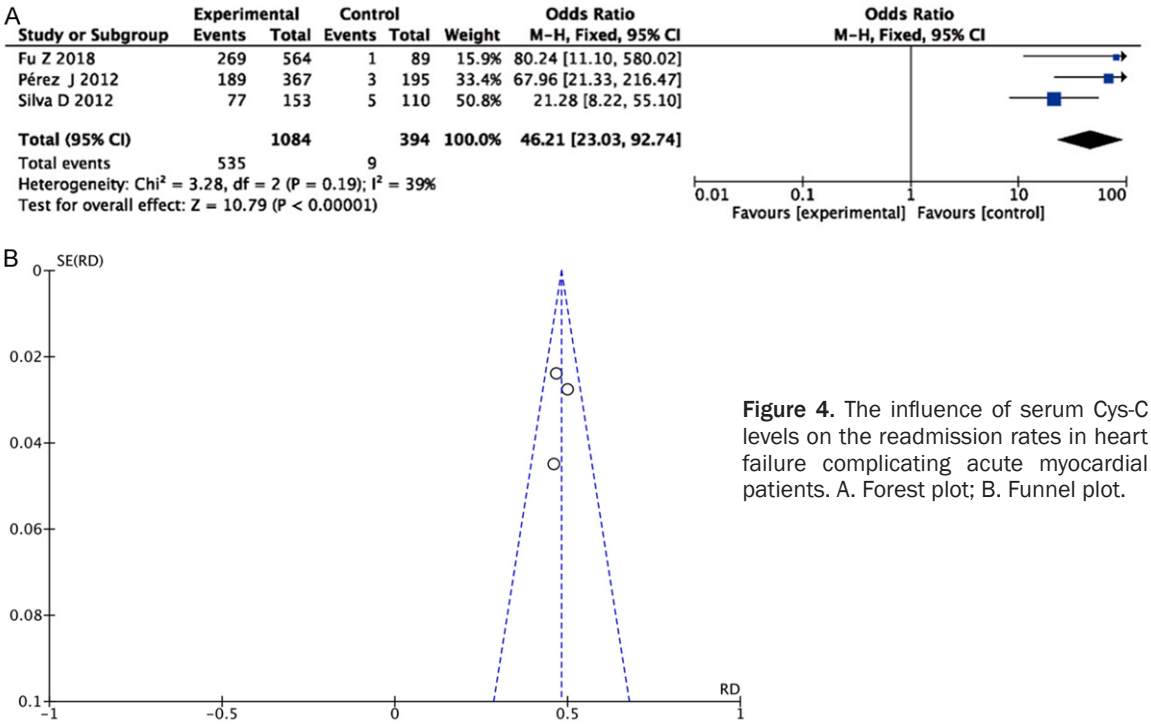

Figure 4. The influence of serum Cys-C levels on the readmission rates in heart failure complicating acute myocardial patients. A. Forest plot; B. Funnel plot.

proteases, Cys-C affects blood vessel walls. Gradually negative effects make the plaque more likely to rupture, leading to an increase in the incidence of readmissions [28].

Furthermore, this meta-analysis still has the following deficiencies: Firstly, there is an overestimation of the actual risk because the confounding factors that affect the Cys-C levels were not adjusted. Secondly, due to the varied thresholds of serum Cys-C in different studies, there could be deviations in meta-analysis results. Finally, due to the limited number of studies with relevant data, we did not use continuous data for evaluating the value of cys-C level in predicting prognosis.

In conclusion, the increase in circulating Cys-C levels could be related to the incidence rates of adverse cardiovascular events, the all-cause mortality rates of patients, and the readmission rates in HF complicating AMI patients. Serum Cys-C could be used as an independent predictor for the examination of HF complicating AMI patients. The determination of Cys-C levels could improve the classification of adverse outcomes in HF complicating AMI patients as well as aid clinicians in making treatment decisions.

Disclosure of conflict of interest

None.

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