Cardiac troponin and C-reactive protein for predicting all-cause and cardiovascular mortality in patients with chronic kidney disease: A meta-analysis

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Elevated serum levels of cardiac troponin and C-reactive protein are associated with all-cause and cardiovascular mortality in patients with end-stage renal disease. However, the relationship between these two biomarker levels and mortality in patients with chronic kidney disease remains unclear. We conducted a meta-analysis to quantify the association of cardiac troponin and C-reactive protein levels with all-cause and cardiovascular mortality in patients with chronic kidney disease. Relevant studies were identified by searching the MEDLINE database through November 2013. Studies were included in the meta-analysis if they reported the long-term all-cause or cardiovascular mortality of chronic kidney disease patients with abnormally elevated serum levels of cardiac troponin or C-reactive protein. Summary estimates of association were obtained using a random-effects model. Thirty-two studies met our inclusion criteria. From the pooled analysis, cardiac troponin and C-reactive protein were significantly associated with all-cause (HR 2.93, 95% CI 1.97-4.33 and HR 1.21, 95% CI 1.14-1.29, respectively) and cardiovascular (HR 3.27, 95% CI 1.67-6.41 and HR 1.19, 95% CI 1.10-1.28, respectively) mortality. In the subgroup analysis of cardiac troponin and C-reactive protein, significant heterogeneities were found among the subgroups of population for renal replacement therapy and for the proportion of smokers and the C-reactive protein analysis method. Elevated serum levels of cardiac troponin and C-reactive protein are significant associated with higher risks of all-cause and cardiovascular mortality in patients with chronic kidney disease. Further studies are warranted to explore the risk stratification in chronic kidney disease patients.

KEYWORDS: Renal insufficiency; Mortality; Troponin; C-reactive protein; Meta-analysis.

■ INTRODUCTION

The number of patients with chronic kidney disease (CKD), including end-stage renal disease (ESRD), has increased in recent years (1), and the mortality of these patients is much higher than that of the normal population. CKD is associated with an increased risk for cardiovascular mortality (2), and cardiovascular causes account for almost half of all deaths in patients with ESRD (3). Cardiovascular risk-factor control is urged for addressing the heavy burden of cardiovascular diseases and adverse events in patients with CKD (1). Studies have shown that diabetes, hypertension, smoking, age, and serum albumin, calcium, phosphorus, and parathyroid hormone levels are associated with all-cause and cardiovascular mortality in patients with CKD (4-10). Novel cardiovascular risk factors, including elevated serum C-reactive protein (CRP) and cardiac troponin (cTn) levels, are prevalent in these CKD patients (4). As a marker of inflammation that is critical to the pathogenesis of atherosclerosis (11), the serum level of CRP is elevated in more than 70% of patients with ESRD (12), and the serum level of cTn, a marker of myocardial infarction (13), may predict death in these patients (14).

Some studies have shown that elevated serum levels of CTn and CRP are associated with all-cause and cardiovascular mortality in patients with ESRD (14,15). However, the relationship between the serum levels of these two biomarkers and mortality in patients with CKD remains unclear. Some studies have shown that the serum levels of these two biomarkers were significantly associated with mortality in CKD patients (16-19), whereas different results were found in other studies (4,20,21). We conducted an up-to-date meta-analysis of published studies to quantify the association of these two biomarker levels with long-term mortality among CKD patients.

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■ METHODS

The meta-analysis was conducted according to the checklist of the Meta-Analysis of Observational Studies in Epidemiology group (22). We performed a systematic search of relevant studies published through November 2013 in the MEDLINE database.

Search strategy

Accessing the MEDLINE database, we performed a literature search for studies published until November 4, 2013 using the following search terms and key words: "C-reactive protein", "CRP", "troponin", "mortality" and "chronic kidney disease". We manually checked the reference list of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: 1) published in the English language; 2) had a randomized controlled trial or a prospective observational study design; 3) enrolled patients with CKD, which was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73 m^2 (23); 4) reported the long-term all-cause mortality or cardiovascular mortality of CKD patients who had abnormal elevated serum levels of CRP or cTn; and 5) presented estimates of risk ratios (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs) or reported the data necessary to calculate these values. Animal, autopsy, and phantom studies were excluded. If the studies excluded patients with a history of myocardial infarction, they were also excluded.

Data extraction

Two authors independently extracted the following data from each retrieved article: study characteristics (design, population, duration of follow-up, CRP analyzed as a continuous variable or elevated variable, cardiac troponin assays, and adjustment), patient characteristics (mean age, sex, proportion of cardiovascular death, renal replacement therapy, history of diabetes mellitus, history of cardiovascular disease, history of hypertension, history of tobacco use), and outcomes (all-cause and cardiovascular mortality).

Statistical analysis

We directly extracted or indirectly estimated hazard ratios (HRs) from each study and pooled HRs using a random-effects meta-analysis method. Subgroup analyses for all-cause and cardiovascular mortalities were conducted according to the following factors: the baseline population ($\geq$500 vs. <500); proportion of male patients ($\geq$50% vs. <50%); mean or average age ($\geq$60 years vs. <60 years); duration of follow-up ($\geq$2 years vs. <2 years); study design (prospective observational studies vs. randomized controlled trials); renal replacement therapy (hemodialysis vs. peritoneal dialysis vs. hemodialysis or peritoneal dialysis vs. receiving or not receiving renal replacement therapy vs. not receiving renal replacement therapy, or ESRD vs. not receiving renal replacement therapy); adjustment (no adjustment vs. appropriate adjustment vs. inappropriate adjustment; appropriate adjustment was defined as adjusting for age, history of diabetes mellitus, and history of cardiovascular diseases at the same time, whereas inappropriate adjustment was defined as not adjusting for age, history of

diabetes mellitus, and history of cardiovascular diseases at the same time); CRP analysis method (elevated variable vs. continuous variable); troponin assays (cardiac troponin T vs. cardiac troponin I); prevalence of diabetes mellitus ($\geq$30% vs. <30%); prevalence of cardiovascular diseases ($\geq$30% vs. <30%); prevalence of hypertension ($\geq$50% vs. <50% or $\geq$80% vs. <80%); proportion of smokers ($\geq$30% vs. <30%); and proportion of cardiovascular deaths ($\geq$50% vs. <50%).

To perform the quality assessment, two authors independently assessed the study quality using the Downs-Black criteria (24). The Downs-Black criteria is an instrument comprising 27 questions that evaluate reporting, external validity, internal validity (bias and confounding), and statistical power. All questions received a score of 0 or 1, with the exception of question 5, which received a score ranging from 0 to 2, depending on whether the statistical power of the survey was explicitly stated in the article as being at least 80%. Thus, the maximum score achievable by an article was 27 points. Disagreements were resolved by consensus.

Statistical heterogeneity between studies was evaluated with the I^2 statistic (25). Publication bias was assessed using the Egger asymmetry test ($p < 0.05$ indicating statistical significance) (26). P-values that were less than 0.05 were considered statistically significant. All statistical analyses were carried out with STATA, version 12.0 (Stata Corp, College Station, Texas).

■ RESULTS

Literature search

The details of the search steps are shown in Figure 1. We identified and screened 828 articles from our preliminary search, and 50 clinical trials were identified for title and
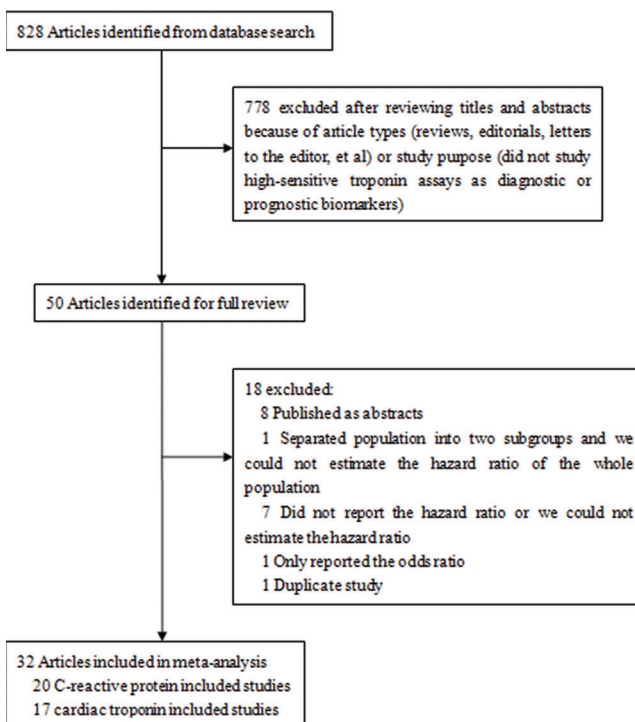

Figure 1 - Selection of included studies.

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abstract analysis. Eight articles were published as abstracts only and were excluded. Seven studies were excluded because they did not report the hazard ratio or we could not estimate the hazard ratio due to incomplete statistical data. One duplicate study and one study that only reported the odds ratio were also excluded. Among the included studies, 20 studies were included into the CRP analysis (4,16,17,27–43), and 17 studies were included into the cTn analysis (18–20,29,30,32,34,37,44–52).

Study characteristics

The characteristics of the included studies are shown in Table 1, and the patient characteristics are shown in Table 2. The total population of the included studies was 21,047, and most of the patients were male (53.93%). Most studies were prospective observational studies, and there were 3 randomized controlled studies, which studied CRP (16,17,38). Aside from the unavailable data, 2,321 cardiac deaths and 2,633 all-cause deaths were reported.

CRP predicting all-cause and cardiovascular mortality

The pooled HRs of all-cause and cardiovascular mortality in CKD patients are shown in Figures 2 and 3. Elevated serum levels of CRP were significantly associated with higher all-cause (HR 1.21, 95% CI 1.14-1.29) and cardiovascular (HR 1.19, 95% CI 1.10-1.28) mortality in CKD patients. There were heterogeneities among studies for both all-cause ($I^2 = 88.8\%$, $p < 0.001$) and cardiovascular ($I^2 = 75.9\%$, $p < 0.001$) mortality.

For all-cause mortality, significant heterogeneities were found among the subgroups of adjustment ($p = 0.003$) and CRP analysis method ($p < 0.001$). Studies with appropriate adjustment showed higher all-cause mortality (HR 1.52, 95% CI 1.16-1.99) compared with those with inappropriate adjustment (HR 1.07, 95% CI 1.02-1.11) and no adjustment (HR 1.39, 95% CI 1.13-1.71). When CRP was analyzed as an elevated variable, all-cause mortality was higher (HR 1.56, 95% CI 1.28-1.90) than when analyzed as a continuous variable (HR 1.10, 95% CI 1.03-1.17).

For cardiovascular mortality, significant heterogeneities were found among the population ($p = 0.033$), CRP analysis method ($p = 0.012$), and proportion of smokers ($p = 0.011$) subgroups. A larger population was linked to lower cardiovascular mortality (HR 1.10, 95% CI 1.04-1.17) compared with a smaller population (HR 1.52, 95% CI 1.14-2.04). Additionally, when CRP was analyzed as an elevated variable, cardiovascular mortality was higher (HR 1.44, 95% CI 1.17-1.77) than when analyzed as a continuous variable (HR 1.09, 95% CI 1.01-1.17). Compared with studies with a smaller proportion of smokers (HR 1.07, 95% CI 1.01-1.14), those with a larger proportion of smokers (HR 1.42, 95% CI 1.15-1.75) showed higher cardiovascular mortality.

Publication bias was found in the analysis of all-cause mortality ($p < 0.001$) and cardiovascular mortality ($p < 0.001$), indicating the presence of publication bias or other sources of bias. The funnel plots are shown in Figures 4A and 4B.

Sensitivity analysis

During the sensitivity analysis, excluding three studies (33,39,42) did not have a significant effect on the relationship between CRP serum levels and all-cause mortality. Excluding one study that enrolled patients without ESRD (16) also did not have a significant effect on the relationship between CRP serum levels and all-cause mortality. For cardiovascular mortality, one study was excluded (33), but this exclusion did not influence the statistical significance of the results. Excluding three studies that enrolled patients without ESRD (4,16,17) did not have a significant effect on the relationship between the serum levels of CRP and cardiovascular mortality.

Cardiac troponin for predicting all-cause and cardiovascular mortality

The pooled HRs of all-cause and cardiovascular mortality in CKD patients are shown in Figures 2 and 3. Elevated serum levels of cTn were significantly associated with higher all-cause (HR 2.93, 95% CI 1.97-4.33) and cardiovascular (HR 3.27, 95% CI 1.67-6.41) mortality in CKD patients. Additionally, there were heterogeneities among studies for both all-cause ($I^2 = 94.0\%$, $p < 0.001$) and cardiovascular ($I^2 = 96.4\%$, $p < 0.001$) mortality.

For all-cause mortality, significant heterogeneities were found among the population ($p = 0.015$) and renal replacement therapy ($p = 027$) subgroups. Studies with a smaller population showed higher all-cause mortality (HR 3.20, 95% CI 2.65-3.87) compared with a larger population (HR 1.54, 95% CI 0.88-2.70). Additionally, studies with a larger population did not show a significant association of the serum levels of cTn with increased all-cause mortality. Studies with different renal replacement therapies showed different associations of cTn with all-cause mortality. Studies with an ESRD population had higher all-cause mortality (HR 3.21, 95% CI 2.02-5.09) compared with those with a population that did not require renal replacement therapy (HR 1.75, 95% CI 1.33-2.30).

For cardiovascular mortality, significant heterogeneities were found in the subgroup of the proportion of cardiovascular deaths ($p = 0.043$). Studies with a higher proportion of cardiovascular deaths had higher cardiovascular mortality (HR 4.18, 95% CI 2.68-6.54) compared with those with a lower proportion of cardiovascular deaths (HR 1.88, 95% CI 1.00-3.53).

Publication bias was found in the analysis of all-cause mortality ($p < 0.001$) and cardiovascular mortality ($p = 0.014$), indicating the presence of publication bias or other sources of bias. The funnel plots are shown in Figures 4C and 4D.

Sensitivity analysis

Excluding two studies that enrolled patients without ESRD (18,19) did not have a significant effect on the relationship between cTn serum levels and all-cause mortality. For cardiovascular mortality, one study was excluded (41), but this exclusion did not influence the statistical significance of the results. Excluding one study that enrolled patients without ESRD (18) did not have a significant effect on the relationship between the serum levels of cTn and cardiovascular mortality.

Quality assessment

The quality assessment results for the included studies are shown in Table 1. Studies could reach a maximum of 27 points, divided into 5 different aspects – reporting, external validity, bias, confounding and power. The scores varied from 12 to 20, and the average score was 16. Because most of the included studies were not randomized controlled trials,

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Table 1 - Characteristics of the included articles

Studies	Study design	Total patients	Duration of follow-up (months)	Analyzed CRP as continuous variable/ elevated variable	Cardiac troponin assays (T or I)	Adjustment	Downs-Black criteria scores
Böger 2005, Germany (27)	Prospective observational study	445	46.8	Elevated variable	N/A	Age, hemodialysis duration, gender, smoking history, body mass index, medication, history of diabetes mellitus, history of coronary artery disease	19
Menon 2005, USA (16)	Randomized controlled study	697	125	Elevated variable	N/A	Age, gender, race, randomization to different protein diets and blood pressure strata, diabetes, current smoking, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, body mass index, systolic blood pressure, etiology of kidney disease	16
Tripepi 2005, Italy (28)	Randomized controlled study	217	41	Elevated variable	N/A	Cardiovascular death, namely age, gender, smoking, diabetes, systolic BP, previous cardiovascular events, asymmetric dimethylarginine	17
Hocher 2008, Germany (29)	Randomized controlled study	230	52	Elevated variable	T	No adjustment	15
Hocher 2003, Germany (30)	Randomized controlled study	245	25	Elevated variable	T	No adjustment	16
Panichi 2008, Italy (31)	Randomized controlled study	757	30	Elevated variable	N/A	No adjustment	14
Boulier 2004, France (32)	Randomized controlled study	191	13	Elevated variable	I	Age, sex, duration of dialysis, diabetes, smoking, hypertension, dialysis center, HD modality, total cholesterol, triglycerides	16
Shlipak 2005, USA (4)	Randomized controlled study	1249	103.2	Continuous variable	N/A	Age, sex, race, education, prevalent cardiovascular disease, elevated systolic blood pressure, diabetes, current smoking, HDL of 40 mg/dL or less, LDL of 130 mg/dL or more, triglycerides, alcohol use, obesity, physical activity, left ventricular hypertrophy, and diuretic use	18
Zoccali 2011, Italy (33)	Randomized controlled study	537	29	Elevated variable	N/A	Age, gender, cardiovascular comorbidities, Kt/V and dialysis duration	18
Paniagua 2010, Mexico (34)	Randomized controlled study	753	16	Continuous variable	T	No adjustment	15
Rao 2008, USA (35)	Randomized controlled study	182	78	Continuous variable	N/A	No adjustment	14
Kawaguchi 2011, International (36)	Randomized controlled study	2181	24	Continuous variable	N/A	Age, sex, vintage, BMI, spKt/V, hemoglobin, albumin, calcium, phosphorus, nPCR, BUN, creatinine, white blood cell count, total cholesterol, uric acid, ferritin, dialysis time, coronary artery disease, diabetes mellitus and other comorbidities	18
deFilippi 2003, USA (37)	Randomized controlled study	224	27	Elevated variable	T	Age, white race, sex, length of time receiving dialysis, history of smoking, coronary disease, or diabetes, levels of albumin, dialysis dose (Kt/V), BSA	20
McMurray 2011, International (17)	Randomized controlled study	4038	42.5	Elevated variable	N/A	Age, serum albumin, coronary heart disease, diabetes complications, arrhythmia, glycated hemoglobin, reticulocytes, BUN, cerebrovascular disease, gender, race, hemoglobin level, treatment, smoking status, heart rate, BMI, and other confounding factors	20

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Table 1. (*continued*)

Studies	Study design	Total patients	Duration of follow-up (months)	Analyzed CRP as continuous variable/ elevated variable	Cardiac troponin assays (T or I)	Adjustment	Downs-Black criteria scores
Schneider 2013, International (38)	Randomized controlled study	2776	38.4	Continuous variable	N/A	No adjustment	18
McMahon 2012, Australia (39)	Randomized controlled study	302	24	Continuous variable	N/A	Age, duration of dialysis, peripheral vascular disease, ESA dose, hemoglobin	17
Stenvinkel 2002, International (40)	Randomized controlled study	663	33 ± 1	Elevated variable	N/A	Age, body mass index, renal center, gender	15
Kalantar-Zadeh 2004, USA (41)	Randomized controlled study	378	12	Elevated variable	N/A	Age, gender, race, ethnicity, insurance status, diabetes mellitus, Charlson co-morbidity score, dialysis vintage, dialysis dose, BMI history of cardiovascular disease	18
Nascimento 2004, International (42)	Randomized controlled study	180	21	Continuous variable	N/A	Event-free times for age, SGA, CRP, S-Alb, fibrinogen, gender	17
Grootendorst 2007, International (43)	Randomized controlled study	840	36	Elevated variable	N/A	Age, gender, PKD, Khan comorbidity score, BMI, smoking habit, GFR	16
Acharji 2012, USA (18)	Randomized controlled study	2179	12	N/A	T and I	Differences in baseline clinical, ECG, laboratory findings	20
Dierkes 2000, Germany (44)	Randomized controlled study	102	24	N/A	T	Age, time on dialysis, baseline diabetes, cerebrovascular disease	18
Apple 2002, USA (45)	Randomized controlled study	733	36	N/A	T and I	Age, pre-draw history of coronary artery disease, time since initial hemodialysis	17
Hocher 2004, Germany (46)	Randomized controlled study	245	38	N/A	T	No adjustment	15
Ooi 1999, Canada (20)	Randomized controlled study	172	12	N/A	T	No adjustment	12
Ishii 2001, Japan (47)	Randomized controlled study	100	24	N/A	T	No adjustment	12
Deegan 2001, UK (48)	Randomized controlled study	73	15	N/A	T	No adjustment	12
Peetz 2003, Germany (49)	Randomized controlled study	104	6	N/A	T and I	No adjustment	12
Yakupoglu 2002, Turkey (50)	Randomized controlled study	38	48	N/A	I	No adjustment	13
Stolear 1999, Belgium (51)	Randomized controlled study	94	12	N/A	T	No adjustment	14
Löwbeer 2002, Sweden (52)	Randomized controlled study	26	48	N/A	T	No adjustment	13
Wood 2003, UK (19)	Randomized controlled study	96	24	N/A	T	Age, sex, diabetes mellitus, history of cardiovascular disease, serum creatinine	17

the questions about blinding and randomizing were scored 0 in most of the studies.

■ DISCUSSION

Elevated serum levels of cTn and CRP were found to be significantly associated with higher risks of all-cause and cardiovascular mortality in patients with CKD, according to our meta-analysis. Compared with CRP, cTn was more strongly associated with all-cause (HR 2.93 vs. 1.21) and cardiovascular (HR 3.27 vs. 1.19) mortality.

In our meta-analysis, CRP was significantly associated with increased all-cause and cardiovascular mortality, although the association was not as strong as that for cTn. In the subgroup analyses, significant heterogeneities were found in the subgroups of adjustment, CRP analysis method and population. These results indicated that a larger population might lead to lower cardiovascular

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Table 2 - Patient characteristics in included articles.

Studies	Average or median age (years old)	Male (%)	Cardiovascular death (%)	Renal replacement therapy	History of diabetes mellitus (%)	History of cardiovascular diseases (%)	History of hypertension (%)	History of tobacco use (%)
Böger 2005, Germany (27)	67.5 ± 8.2	54.83	38.69	Hemodialysis	100	57	N/A	44
Menon 2005, USA (16)	51 ± 12	58.11	51.45	Receiving or not receiving renal replacement therapy	4	N/A	N/A	10
Tripepi 2005, Italy (28)	60.7 ± 15.1	55	58.04	Hemodialysis or peritoneal dialysis	15	49	45	40
Hocher 2008, Germany (29)	65.6 ± 13.7	48.7	47.5	Hemodialysis	33	27	91.74	41
Hocher 2003, Germany (30)	65.6 ± 7.2	50.20	56.16	Hemodialysis	34	64	89.8	41
Panichi 2008, Italy (31)	66 ± 14	60.5	45.49	Hemodialysis	19	26	35	N/A
Boulier 2004, France (32)	66.7	50.8	44.83	Hemodialysis	20	33	22.5	27
Shlipak 2005, USA (4)	75 ± 6	47	N/A	Receiving or not receiving renal replacement therapy	17	N/A	N/A	10
Zoccali 2011, Italy (33)	63 ± 15	57.73	63.19	Hemodialysis	16	27	49	11
Paniagua 2010, Mexico (34)	48.64 ± 17.55	55.11	46.7	Hemodialysis or peritoneal dialysis	44	15.9	N/A	N/A
Rao 2008, USA (35)	62.2 ± 12.3	47	35.51	Hemodialysis	41	66	N/A	54
Kawaguchi 2011, International (36)	62.4 ± 12.6	58.6	N/A	Hemodialysis	33	29	72.08	18
deFilippi 2003, USA (37)	62	54	53	Hemodialysis	48	36	N/A	21
McMurray 2011, International (17)	67.5 ± 10.76	42.74	N/A	Not receiving renal replacement therapy	65.82	36.5	N/A	43.86
Schneider 2013, International (38)	64.2 ± 8.7	62.18	N/A	Hemodialysis	26.4	51.4	N/A	15.5
McMahon 2012, Australia (39)	60 ± 14	63.9	88.4	Hemodialysis or peritoneal dialysis	18.5	88.4	88.4	N/A
Stenvinkel 2002, International (40)	59.4 ± 1	56.41	N/A	Hemodialysis or peritoneal dialysis	0.243	N/A	N/A	N/A
Kalantar-Zadeh 2004, USA (41)	54.5 ± 14.7	53.2	51.28	Hemodialysis	55.1	50.8	N/A	N/A
Nascimento 2004, International (42)	49 ± 25	55	52	Hemodialysis	9	N/A	26	N/A
Grootendorst 2007, International (43)	59.1 ± 14.9	60.1	46.9	Hemodialysis or peritoneal dialysis	20.7	34.9	N/A	N/A
Acharji 2012, USA (18)	76 (troponin positive) 75 (troponin negative)	53.46	57.3	Not receiving renal replacement therapy	28.92	33.25	76.95	14.84
Dierkes 2000, Germany (44)	64 ± 13	49.02	39.29	Hemodialysis	40.2	21	N/A	44
Apple 2002, USA (45)	62	56	N/A	Hemodialysis	46	29	N/A	N/A
Hocher 2004, Germany (46)	63.5 ± 5.8	50.2	65.42	Hemodialysis	34.29	64.08	89.8	41.22
Ooi 1999, Canada (20)	61 (cTnT < 0.1 µg/L) 64.5 (0.1 µg/L ≤ cTnT ≤ 0.2 µg/L) 62.8 (cTnT > 0.2 µg/L)	64.47	38.71	Hemodialysis	29.07	31.4	43.6	N/A
Ishii 2001, Japan (47)	58	61	52.63	Hemodialysis or peritoneal dialysis	41	22	71	N/A
Deegan 2001, UK (48)	64 ± 18	57.53	57.14	Hemodialysis	16.44	24.66	N/A	N/A
Peetz 2003, Germany (49)	63 (male)65 (female)	60.58	85	Hemodialysis	26.92	37.5	70.19	N/A

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Table 2. (*continued*)

Studies	Average or median age (years old)	Male (%)	Cardiovascular death (%)	Renal replacement therapy	History of diabetes mellitus (%)	History of cardiovascular diseases (%)	History of hypertension (%)	History of tobacco use (%)
Yakupoglu 2002, Turkey (50)	55.9 ± 12.9	42.11	100	Hemodialysis	N/A	N/A	N/A	N/A
Stolear 1999, Belgium (51)	62.9 ± 1.4	58.51	58.33	Hemodialysis	18.09	30.85	N/A	N/A
Löwbeer 2002, Sweden (52)	58	50	73.33	Peritoneal dialysis	19	19	62	N/A
Wood 2003, UK (19)	52.4	66.67	90.48	Not receiving renal replacement therapy	14.6	24	N/A	N/A

mortality and that analyzing a large population as a continuous variable would lower the all-cause and cardiovascular mortality. More appropriate adjustments would lead to higher all-cause mortality. However, notably, there were heterogeneities in the subgroups of study design, mean or average age, renal replacement therapy, and the prevalence of hypertension for cardiovascular mortality, although the *p*-values were > 0.05. Randomized controlled trials, studies with younger patients and studies with fewer hypertension patients showed no significant results. In the subgroup of renal replacement therapy, the situation was similar. CRP is a biomarker of inflammation. CKD patients are subject to multiple nonvascular inflammatory stimuli, including chronic infection (53).
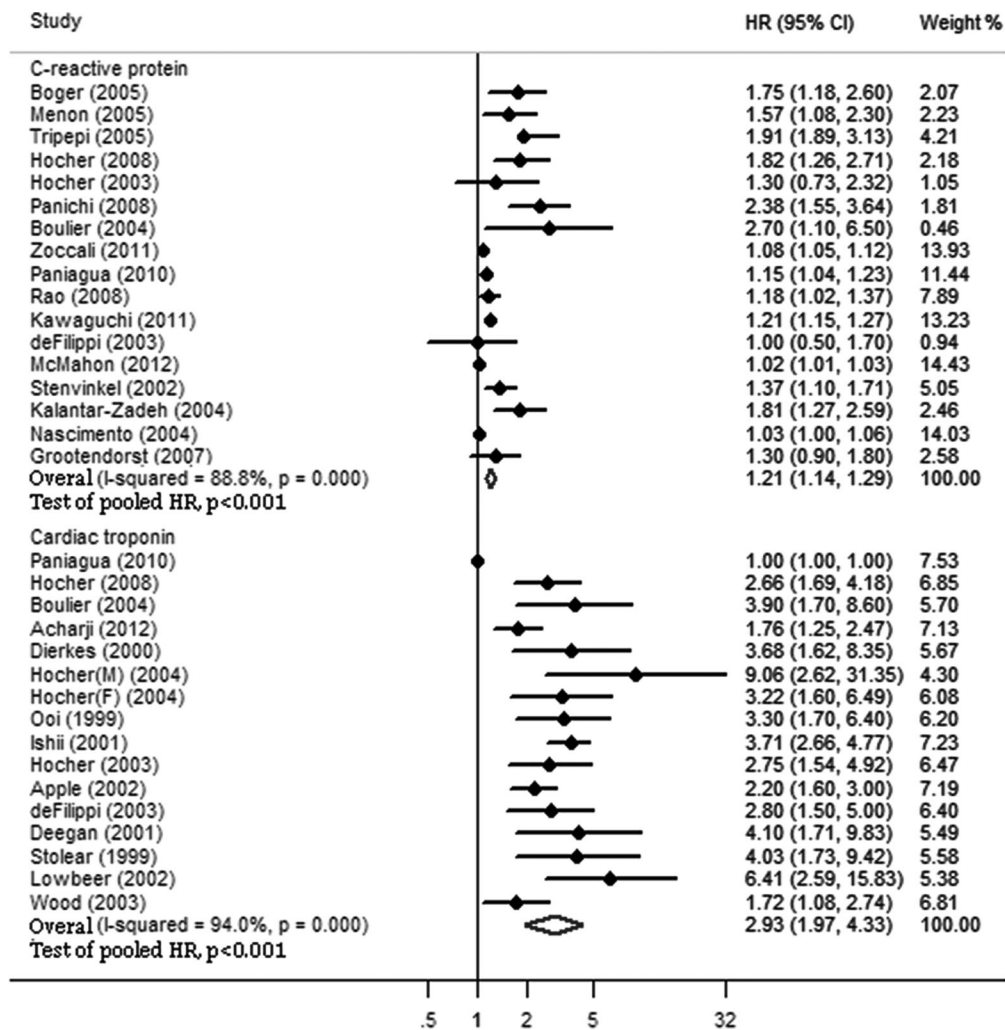

Figure 2 - C-reactive protein and cardiac troponin for predicting all-cause mortality. Elevated serum levels of C-reactive protein and cardiac troponin were significantly associated with all-cause mortality in patients with chronic kidney disease. However, the pooled HR of cardiac troponin was higher than that of C-reactive protein. HR, hazard ratio; CI, confidence interval.
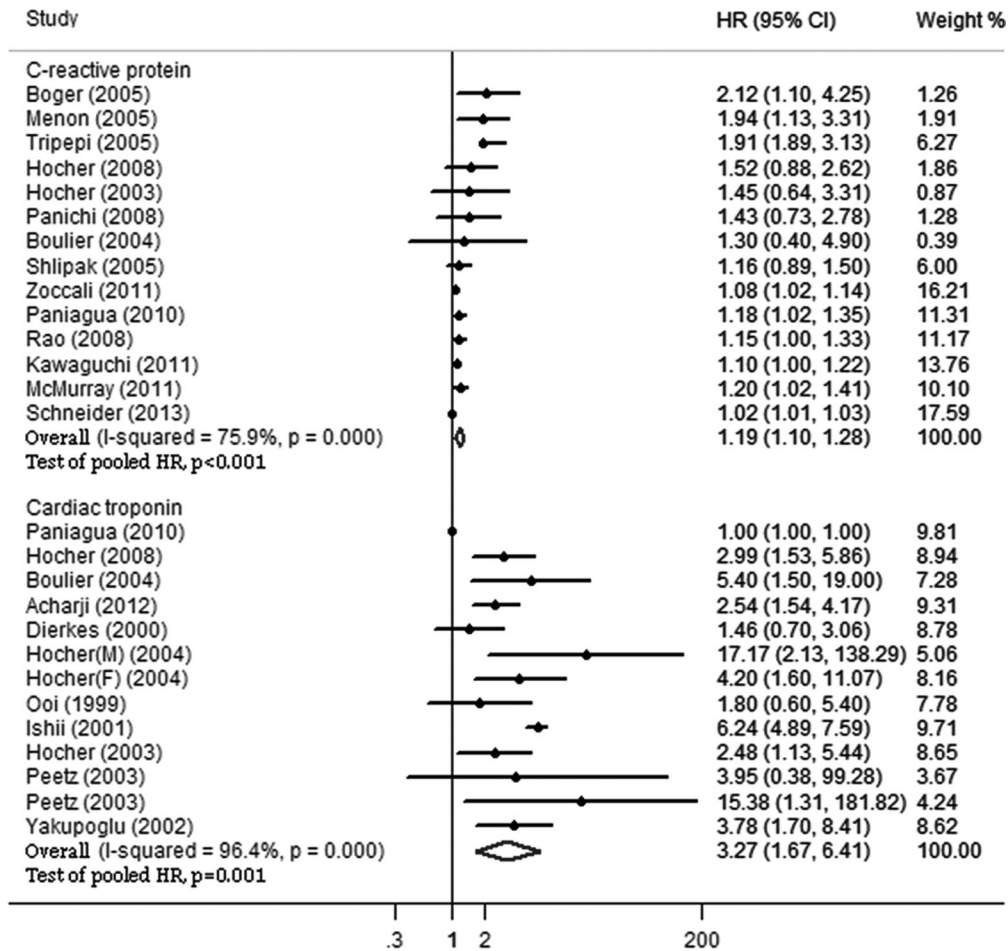
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Figure 3 - C-reactive protein and cardiac troponin for predicting cardiovascular mortality. Elevated serum levels of C-reactive protein and cardiac troponin were significantly associated with cardiovascular mortality in patients with chronic kidney disease. However, the pooled HR of cardiac troponin was higher than that of C-reactive protein. HR, hazard ratio; CI confidence interval.

Therefore, not surprisingly, elevated serum levels of CRP were found to be associated with higher all-cause and cardiovascular mortality due to inflammation. However, in the population with CKD, CRP elevation may also result from decreased renal clearance or degradation rather than increased production. This might explain the decreased statistical association of CRP with mortality (4). Thus, study characteristics, such as age, population, or renal replacement therapy, might affect the findings of the relationship between CRP and mortality, as we found in the subgroup analysis. This result suggests that screening CKD patients with elevated CRP for infectious or non-infectious inflammation and treating with proper interventions may improve patient outcomes.

We found that cTn was strongly associated with increased all-cause and cardiovascular mortality. However, patients who were not receiving renal replacement therapy showed significantly lower all-cause mortality compared with ESRD patients. Not surprisingly, ESRD patients were subject to infection, acute myocardial infarction, and death due to renal failure. Notably, in the subgroup analysis, the studies with a larger population showed no significant association of cTn with all-cause and cardiovascular mortality. Additionally, studies with younger patients, appropriate adjustment, a smaller prevalence of cardiovascular diseases, and a smaller proportion of cardiovascular deaths showed no significant association of cTn with cardiovascular mortality. cTn is specific for identifying myocardial cell injury. The elevation of cTn in CKD patients may result from microembolization (54), non-ischemic cardiomyopathy or left ventricular hypertrophy (55-57). Therefore, cTn elevation was found to be strongly associated with increased cardiovascular mortality in CKD patients. The association of cTn elevation with increased all-cause mortality might be the result of a large proportion of cardiovascular deaths in CKD patients. (3) In the population with fewer cardiovascular risk factors, as we found in the subgroup analysis, cTn elevation might not be a predictor. One possible explanation is the decreased renal clearance or degradation of cTn in CKD patients, but more mechanisms should be explored. According to the present results, screening for cardiovascular diseases and performing more active treatment may improve patient outcomes is suggested when serum levels of cTn are elevated in patients with CKD.

The strengths of this meta-analysis are the large number of patients analyzed and the robustness of the findings by sensitivity analyses. However, there were some limitations to this study. First, although we conducted an unrestricted
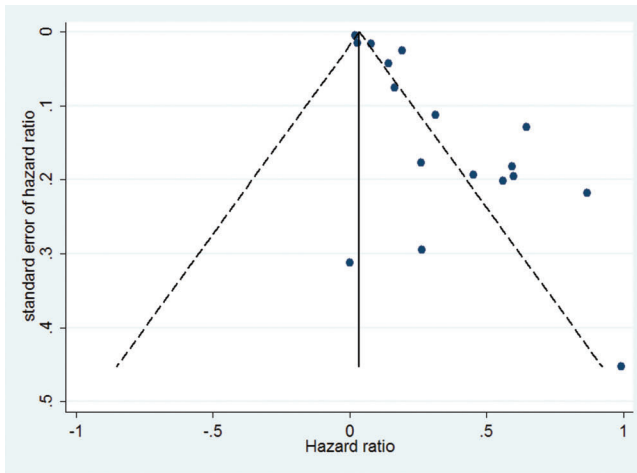
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Figure 4a Egger's funnel plots with 95% CI for CRP studies, for all cause mortality
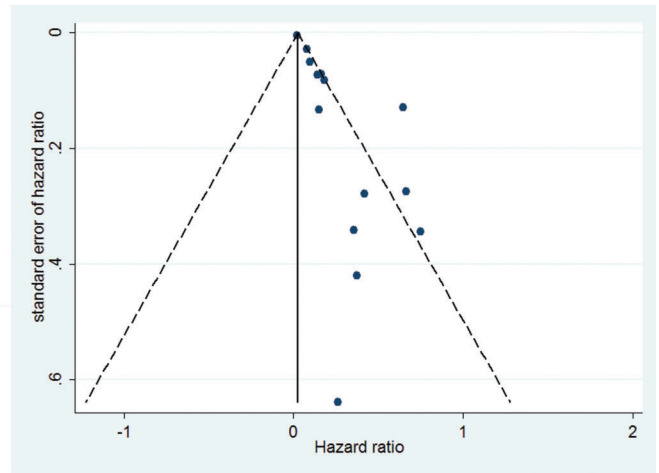
Figure 4b Egger's funnel plots with 95% CI for CRP studies, for cardiovascular mortality
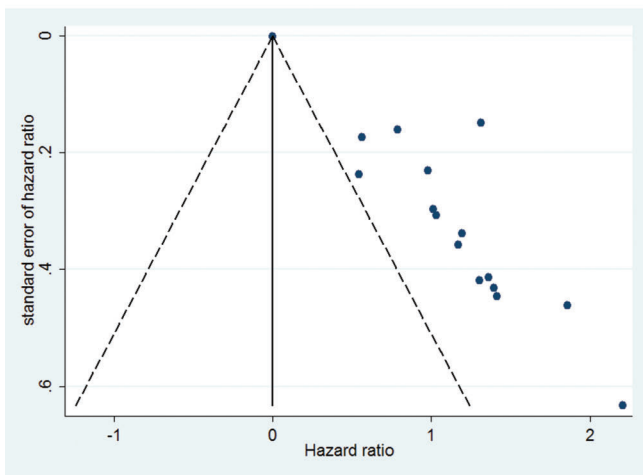
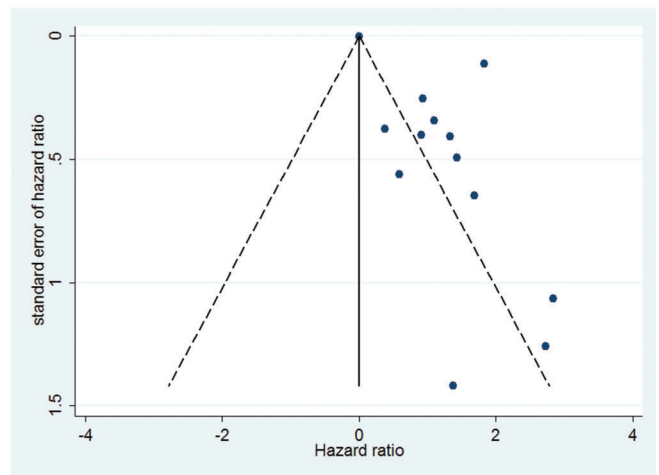**Figure 4c Egger's funnel plots with 95% CI for cardiac troponin studies, for all cause mortality**

Figure 4d Egger's funnel plots with 95% CI for cardiac troponin studies, for cardiovascular mortality

Figure 4 - Egger's funnel plots for C-reactive protein and cardiac troponin studies. Publication bias was found in this meta-analysis. CRP, C-reactive protein; CI confidence interval.

literature search, few studies were randomized controlled trials, few studies enrolled patients who did not need to receive renal replacement therapy, and few studies included a large population. Along with causing publication bias, these limitations would tend to overinflate the pooled estimate of HR. However, we did find a significant association of cTn and CRP with mortality in the sensitive analyses. Second, the studies included in our analysis used different cut-off points to define an elevation in the serum levels of cTn and CRP. This variation in cut-off point is at least in part related to the significant heterogeneity. Third, the inclusion criteria of included studies were not well balanced. Population differences might therefore influence our results.

In conclusion, the present meta-analysis shows that elevated serum levels of cTn and CRP are significantly associated with higher risks of all-cause and cardiovascular mortality in patients with CKD. Further studies with strict standardization, long-term follow up, rigorous design, and large and representative populations are warranted to explore the risk stratification in CKD patients.

■ AUTHOR CONTRIBUTIONS

Wu S conceived the study. Cheng I and Lin XL collected the data. Li WJ,[§] Chen XM,[§] Nie XY,[§] and Zhang J[§] drafted the manuscript and performed the data analysis. Li WJ and Cheng YJ performed the statistical analysis. [§] These authors contributed equally to this work.

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