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ORIGINAL RESEARCH

Prognostic role of copeptin with all-cause mortality after heart failure: a systematic review and meta-analysis

Peng Zhang
Xiaomei Wu
Guangxiao Li
Hao Sun
Jingpu Shi

Department of Clinical Epidemiology,
Center of Evidence-Based Medicine,
Institute of Cardiovascular Disease,
The First Hospital of China Medical
University, Shenyang, People's
Republic of China

Background: As the C-terminal section of vasopressin precursor, copeptin has been recently suggested as a new prognostic biomarker after heart failure (HF). Thus, the aim of this study was to evaluate the prognostic value of plasma copeptin level with all-cause mortality in patients with HF.

Methods: Comprehensive strategies were used to search relevant studies from electronic databases. Pooled hazard ratios (HRs) and standardized mean differences (SMDs) together with their 95% confidence intervals (CIs) were calculated. Subgroup analysis and sensitivity analysis were performed to find the potential sources of heterogeneity.

Results: A total of 5,989 participants from 17 prospective studies were included in this meta-analysis. A significant association was observed between circulating copeptin levels and risk of all-cause mortality in patients with HF (categorical copeptin: HR =1.69, 95% CI =1.42–2.01; per unit copeptin: HR =1.03, 95% CI =1.00–1.07; log unit copeptin: HR =3.26, 95% CI =0.95–11.25). Pooled SMD showed that copeptin levels were significantly higher in patients with HF who died during the follow-up period than in survivors (SMD =1.19, 95% CI =0.81–1.57). Subgroup analyses also confirmed this significant association, while sensitivity analyses indicated that the overall results were stable.

Conclusion: This study demonstrated that circulating copeptin seemed to be a novel biomarker to provide better prediction of all-cause mortality in patients with HF.

Keywords: heart failure, copeptin, all-cause mortality, meta-analysis

Introduction

As the terminal stage of all kinds of cardiovascular diseases, including hypertension, myocardial infarction (MI) and cardiomyopathy, heart failure (HF) is known as one of the leading burdens to the health care system not only for cost but also for morbidity and mortality all over the world.[1] According to the estimation of the US Centers for Disease Control and Prevention, the total cost of treatment for HF was up to $34 billion in 2010.[2] Furthermore, mortality rates in patients with HF were even similar to the 5-year mortality rates of some most severe cancers, which were up to 50%.[3]

Copeptin, which was first discovered in 1972, is located in the C-terminal section of the arginine vasopressin (AVP) precursor (pro-AVP) and consists of 39 amino acid glycopeptides.[4] Evidence demonstrated that copeptin is released from pro-AVP together and equivalent with AVP. AVP is widely known as a vital hormone with numerous effects in the human body, such as central nervous, hemodynamic, hemostatic and endocrinologic effects.[5] Plasma AVP levels increase apparently during the process of some acute and chronic diseases, and the measurement of AVP would be useful

Correspondence: Jingpu Shi
Department of Clinical Epidemiology,
Center of Evidence-Based Medicine,
Institute of Cardiovascular Disease,
The First Hospital of China Medical
University, No 155, North Nanjing
Street, Shenyang 110001, People's
Republic of China
Email sjp562013@126.com

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for the diagnosis of patients.[6] However, because of the pulse release mode and the short half-life of AVP, the clinical application of AVP is restricted.[7] Recently, as a result of the long-term stability and being easy to measure, copeptin has been used as an alternative marker of AVP and suggested as a biomarker for poor clinical outcome and mortality of some diseases, such as pneumonia,[8] MI,[9] diabetes,[10,11] HF,[12] stroke[13] and transient ischemic attack.[14,15]

In the current study, we performed a systematic review and meta-analysis aimed to assess the prognostic value of circulating copeptin levels for all-cause mortality in patients with HF.

Methods

We used comprehensive electronic literature databases to search for potential studies that estimated the prognostic value of copeptin in patients with HF. The current study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist.[16]

Electronic literature databases (PubMed, the Web of Science, EMBASE, Cochrane Collaboration Databases, Medline, Chinese National Knowledge Infrastructure, Wan Fang Database and Chong Qing VIP Database) were searched for relevant studies published up to October 2016 without restrictions of the type of document and language. The following search terms were used: ("heart failure" OR "HF" OR "cardiac dysfunction") and ("copeptin" OR "C-terminal provasopressin" OR "CT-pro-AVP"). Moreover, we also searched the references of the selected articles and textbooks manually as a source of related studies.

Two reviewers (PZ and GL) selected the relevant articles according to the inclusion criteria independently. Studies included in this meta-analysis should satisfy the following criteria: 1) adult patients with HF; 2) prospective studies that estimated the association between copeptin and all-cause mortality risk in patients with HF and 3) studies that reported the description of risk estimation of the relative risks (RRs) or hazard ratios (HRs) together with their corresponding 95% confidence intervals (CIs) or provided mean differences of copeptin in survivors and non-survivors. For studies on the same population or overlapping data, only the one with the largest number of subjects was included.

Information of all involved studies was carefully extracted by two reviewers (PZ and XW) independently, and any disagreement was settled by other reviewers (GL and HS). The following information was extracted from all the eligible studies: first author's name, publication year, country, number of centers, type of patients, follow-up period, sample size (including number of survivors and non-survivors), mean age, baseline copeptin levels, type of copeptin measurement, RRs or HRs together with their 95% CIs and mean copeptin levels with standard deviations (SDs); if not reported, median copeptin levels with interquartile ranges (IQRs) were used.

According to the Newcastle–Ottawa Quality Assessment Scale (NOS),[17] two reviewers (PZ and HS) assessed the methodological quality of each eligible study independently. Disagreements were resolved from discussion with other reviewers (GL and XW). The following three aspects were used to assess the quality of cohort studies: the selection of participants, the comparability of the exposed and unexposed cohort and the assessment of the outcome. The total scores of each study ranged between 0 and 9, and studies achieving scores >6 were regarded as high quality.

According to the different reporting forms of copeptin, we separately performed three meta-analyses for the risk estimation between copeptin and all-cause mortality in patients with HF based on unit copeptin, logarithm of copeptin, and copeptin categories, respectively. For the studies that reported the categorical data, we used the RRs (or HRs) between highest and lowest categories of copeptin. When both multivariate and univariate results were available, the former was preferred in the current analysis. Furthermore, for the studies that reported RRs, the RRs were regarded as HRs directly, as pooled HRs were used for all the risk estimations.

Based on the strength of association between copeptin and all-cause mortality in patients with HF, pooled standardized mean differences (SMDs) were estimated according to the mean copeptin levels ± SDs reported in the studies. For studies in which the mean copeptin levels ± SDs were unavailable, medians were treated as mean values directly and IQRs were used to estimate the SDs using the following formula: $SD = IQR/1.35$.[18]

I^2 test was used for testing the heterogeneity among different studies.[19] $I^2 > 50\%$ was considered as a sign of high heterogeneity using random-effects model. Otherwise, the fixed-effects model was used.[20] Subgroup analyses were performed to find the potential sources of heterogeneity, on the basis of sample size, age, female percentage, baseline copeptin, number of centers, type of HF (acute or chronic), measurement methods of copeptin, quality of studies and follow-up period.

Test for funnel plot asymmetry was conducted when at least 10 studies were included. Only six studies were included in our analyses for HR estimation by copeptin categories and unit copeptin, therefore the potential publication

bias was not assessed. Sensitivity analysis was conducted by removing one study each time. $P<0.05$ was regarded as statistically significant, and all statistical analyses were performed using the STATA 12.0 (Stata, College Station, TX, USA).

Results

A detailed description of the process of study selection is shown in Figure 1. At first, 254 potential articles were identified from the databases searching, and only 161 articles remained after removing the duplicate studies. After assessing based on the title and abstract, 109 irrelevant studies were excluded. Finally, a total of 52 articles were fully reviewed, and 17 prospective studies providing data for 5,989 participants met the inclusion criteria and were included in the current meta-analysis.

The main characteristics of the included studies are listed in Table 1. The mean follow-up period ranged from 14 days to 13 years, while the sample size ranged from 40 to 1,237. The detailed scores of included studies are listed in Table 2. A total of 14 studies reported RRs or HRs with 95% CIs for the risk estimation between baseline copeptin level and all-cause mortality in patients with HF, 11 out of these 14 studies reported results from multivariate regression analyses and the other three studies reported results from univariate regression analyses only. As for the evaluation of the strength, three out of nine studies provided the mean copeptin levels with SDs, while the remaining six studies provided median copeptin levels with IQRs only.
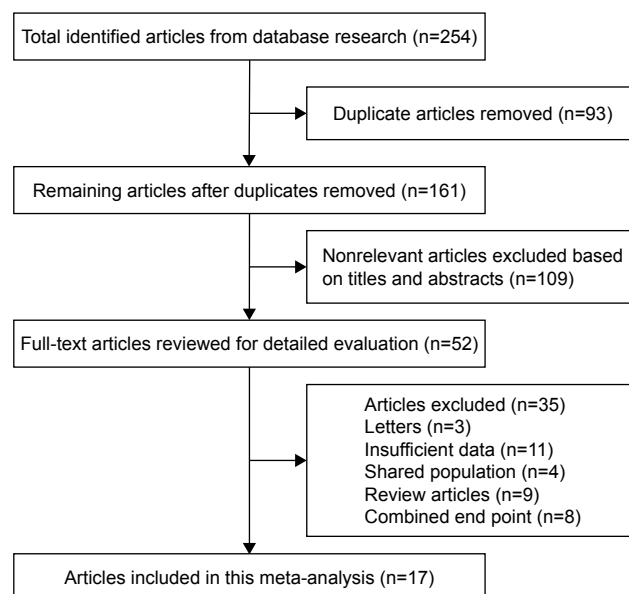
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Total identified articles from database research (n=254)
                    │
                    ├──────▶ Duplicate articles removed (n=93)
                    ▼
Remaining articles after duplicates removed (n=161)
                    │
                    ├──────▶ Nonrelevant articles excluded based
                    │         on titles and abstracts (n=109)
                    ▼
Full-text articles reviewed for detailed evaluation (n=52)
                    │
                    ├──────▶ Articles excluded (n=35)
                    │         Letters (n=3)
                    │         Insufficient data (n=11)
                    │         Shared population (n=4)
                    │         Review articles (n=9)
                    │         Combined end point (n=8)
                    ▼
Articles included in this meta-analysis (n=17)
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Figure 1 Flowchart of study selection and exclusion process.

Table 1 Main characteristics of included studies

Author, year	Country	No of centers	Sample size	Age (years)	Baseline copeptin (pmol/L)	Measurement methods of copeptin	Female (%)	Death (%)	HF type	NYHA functional class	Follow-up period	Quality
Stoiser et al, 2006[34]	Austria	6	268	71.0	24.90	ILMA	33.00	30.97	CHF	III or IV	2 years	7
Gegenhuber et al, 2007[35]	Austria	1	137	76.2	21.00	ILMA	6.57	29.93	AHF	II–IV	1 year	8
Neuhold et al, 2008[36]	Austria	3	786	57.0	18.90	CLIA	19.00	29.64	CHF	I–IV	2 years	8
Miller et al, 2009[37]	America	1	40	68.0	43.90	ILMA	32.50	40.00	CHF	III or IV	22 months	6
Voors et al, 2009[28]	Norway	6	224	68.0	14.00	CLIA	30.00	14.29	HF	NA	33 months	7
Masson et al, 2010[29]	Italy	51	1,237	67.0	13.80	CLIA	19.60	26.84	CHF	II–IV	5.7 years	7
Neuhold et al, 2010[38]	Austria	3	181	70.0	23.48	CLIA	35.00	19.89	CHF	II–IV	2 years	7
Potocki et al, 2010[39]	Switzerland	1	154	78.0	34.00	CLIA	49.00	13.64	AHF	II–IV	30 days	8
Alehagen et al, 2011[40]	Sweden	1	470	73.0	NA	ILMA	47.87	48.09	HF	I–III	13 years	8
Maisel et al, 2011[41]	International	15	557	NA	38.50	ILMA	37.70	11.49	AHF	NA	90 days	6
Peacock et al, 2011[42]	International	15	466	70.8	26.00	ILMA	41.40	4.08	AHF	NA	14 days	7
Tentzeris et al, 2011[30]	Austria	1	172	65.9	NA	ILMA	24.30	20.93	CHF	I–III	1,301 days	7
Balling et al, 2012[43]	Denmark	1	340	NA	15.15	ILMA	27.07	48.53	HF	I–IV	55 months	8
Bosselmann et al, 2013[44]	Denmark	1	424	72.0	15.13	CLIA	29.00	59.43	HF	I–IV	4.5 years	8
Holmstrom et al, 2013[45]	Sweden	1	179	70.8	15.40	ILMA	33.00	24.58	HF	NA	30 months	7
Pozsonyi et al, 2015[46]	Hungary	1	195	69.5	16.10	ILMA	26.00	56.00	CHF	I–IV	5 years	9
Long-hai et al, 2015[47]	People's Republic of China	1	159	NA	23.30	ELISA	52.20	11.32	HF	I–IV	490 days	7

Abbreviations: AHF, acute HF; CHF, chronic HF; CLIA, chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; HF, heart failure; ILMA, immunoluminometric assay; NA, not available; NYHA, New York Heart Association.

Table 2 The scores of included studies assessed by NOS

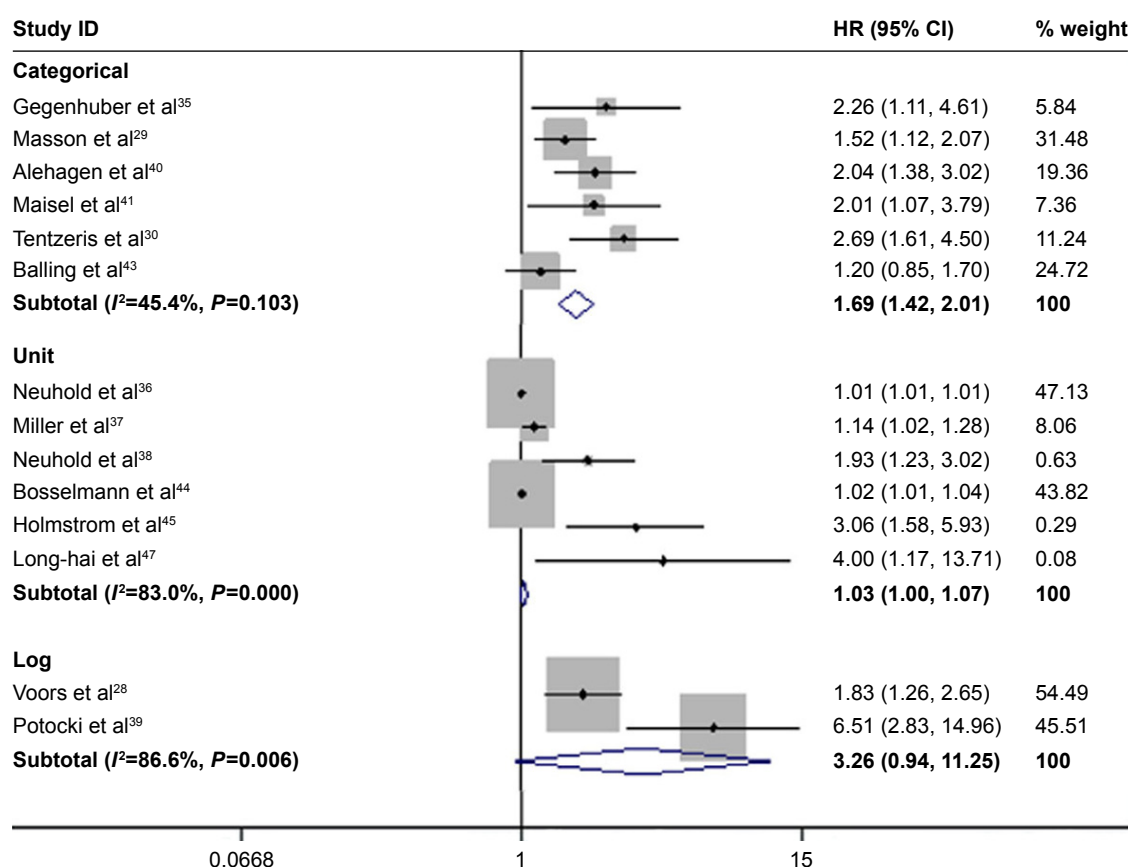| Author	Year	Selection	Comparability	Outcome	Quality
Stoiser et al[34]	2006	***	*	***	7
Gegenhuber et al[35]	2007	***	**	***	8
Neuhold et al[36]	2008	****	*	***	8
Miller et al[37]	2009	***	*	**	6
Voors et al[28]	2009	***	**	**	7
Masson et al[29]	2010	***	**	**	7
Neuhold et al[38]	2010	***	*	***	7
Potocki et al[39]	2010	***	**	***	8
Alehagen et al[40]	2011	***	**	***	8
Maisel et al[41]	2011	***	*	**	6
Peacock et al[42]	2011	***	*	***	7
Tentzeris et al[30]	2011	***	*	***	7
Balling et al[43]	2012	****	*	***	8
Bosselmann et al[44]	2013	***	**	***	8
Holmstrom et al[45]	2013	***	*	***	7
Pozsonyi et al[46]	2015	****	**	***	9
Long-hai et al[47]	2015	****	*	**	7

Note: *, **, *** and **** means 1 point, 2 points, 3 points and 4 points, respectively.
Abbreviation: NOS, Newcastle–Ottawa Quality Assessment Scale.

Six studies including 2,913 patients with HF reported the risk estimation according to copeptin categories. No evidence of heterogeneity was observed (I^2=45.4%, P=0.103), and the fixed-effects model was used in this meta-analysis. The pooled HR was 1.69 (95% CI =1.42–2.01; Figure 2). Table 3 shows the detailed information of subgroup analyses

by copeptin categories, and the significant association between copeptin and all-cause mortality in patients with HF was also confirmed in each subgroup.

Six studies reported the RRs or HRs with 95% CIs for the risk estimation of all-cause mortality in patients with HF by unit copeptin. A total of 1,769 participants were included

Study ID	HR (95% CI)	% weight
Categorical		
Gegenhuber et al[35]	2.26 (1.11, 4.61)	5.84
Masson et al[29]	1.52 (1.12, 2.07)	31.48
Alehagen et al[40]	2.04 (1.38, 3.02)	19.36
Maisel et al[41]	2.01 (1.07, 3.79)	7.36
Tentzeris et al[30]	2.69 (1.61, 4.50)	11.24
Balling et al[43]	1.20 (0.85, 1.70)	24.72
Subtotal (I^2=45.4%, P=0.103)	**1.69 (1.42, 2.01)**	**100**
Unit		
Neuhold et al[36]	1.01 (1.01, 1.01)	47.13
Miller et al[37]	1.14 (1.02, 1.28)	8.06
Neuhold et al[38]	1.93 (1.23, 3.02)	0.63
Bosselmann et al[44]	1.02 (1.01, 1.04)	43.82
Holmstrom et al[45]	3.06 (1.58, 5.93)	0.29
Long-hai et al[47]	4.00 (1.17, 13.71)	0.08
Subtotal (I^2=83.0%, P=0.000)	**1.03 (1.00, 1.07)**	**100**
Log		
Voors et al[28]	1.83 (1.26, 2.65)	54.49
Potocki et al[39]	6.51 (2.83, 14.96)	45.51
Subtotal (I^2=86.6%, P=0.006)	**3.26 (0.94, 11.25)**	**100**

0.0668   1   15

Figure 2 Pooled estimate of HR of all-cause mortality with copeptin in patients with HF.
Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.

Table 3 Pooled HRs of all-cause mortality by copeptin levels in subgroup analyses

	Categorical copeptin					Per unit copeptin				
	N	HR (95% CI)	*P*-value	I^2 (%)	P_h-value	N	HR (95% CI)	*P*-value	I^2 (%)	P_h-value
Overall	6	1.69 (1.42–2.01)	0.000	45.4	0.103	6	1.03 (1.00–1.07)	0.074	83.0	0.000
Sample size										
<200	2	2.53 (1.67–3.85)	0.000	0.0	0.698	4	1.97 (1.12–3.47)	0.018	81.7	0.001
≥200	4	1.56 (1.29–1.88)	0.000	35.4	0.200	2	1.01 (1.00–1.02)	0.003	38.6	0.202
Age (years)										
<70	2	1.77 (1.36–2.30)	0.000	71.4	0.062	2	1.06 (0.94–1.19)	0.337	76.7	0.038
≥70	2	2.09 (1.48–2.94)	0.000	0.0	0.805	3	1.71 (0.88–3.32)	0.111	89.1	0.000
Percentage of females										
<30%	4	1.58 (1.29–1.93)	0.000	60.4	0.056	2	1.01 (1.00–1.02)	0.003	38.6	0.202
≥30%	2	2.03 (1.46–2.84)	0.000	0.0	0.969	4	1.97 (1.12–3.47)	0.018	81.7	0.001
Baseline copeptin										
<20	2	1.37 (1.09–1.72)	0.007	0.1	0.317	3	1.02 (0.99–1.04)	0.209	83.9	0.002
≥20	2	2.12 (1.32–3.40)	0.002	0.0	0.810	3	1.67 (0.95–2.91)	0.074	77.1	0.013
No of centers										
1	4	1.75 (1.40–2.18)	0.000	64.0	0.040	4	1.23 (0.99–1.52)	0.068	84.1	0.000
>1	2	1.60 (1.22–2.11)	0.001	0.0	0.437	2	1.34 (0.72–2.52)	0.361	87.6	0.005
Mortality										
<30%	4	1.84 (1.46–2.32)	0.000	24.6	0.264	4	1.95 (1.02–3.74)	0.044	87.3	0.000
≥30%	2	1.52 (1.17–1.96)	0.002	74.7	0.047	2	1.06 (0.96–1.18)	0.260	71.9	0.059
HF type										
AHF	2	2.12 (1.32–3.40)	0.002	0.0	0.810	0	–	–	–	–
CHF	2	1.77 (1.36–2.30)	0.000	71.4	0.062	3	1.14 (0.96–1.36)	0.134	83.8	0.002
Inclusion of NYHA class I										
Yes	3	1.70 (1.35–2.15)	0.000	74.3	0.020	3	1.01 (1.00–1.03)	0.101	68.9	0.040
No	2	1.62 (1.22–2.14)	0.001	0.3	0.317	2	1.42 (0.85–2.35)	0.179	80.0	0.025
Measurement methods										
ILMA	5	1.78 (1.44–2.19)	0.000	52.9	0.075	2	1.77 (0.68–4.62)	0.246	87.9	0.004
CLIA	1	1.52 (1.12–2.07)	0.008	–	–	3	1.02 (0.99–1.04)	0.153	79.3	0.008
Quality according to NOS										
>6	5	1.67 (1.39–2.00)	0.000	54.8	0.065	5	1.02 (0.99–1.06)	0.202	84.1	0.000
Follow-up time										
≤2 years	2	2.12 (1.32–3.40)	0.002	0.0	0.810	4	1.20 (0.98–1.46)	0.076	82.5	0.001
>2 years	4	1.63 (1.36–1.97)	0.000	63.0	0.044	2	1.68 (0.57–4.90)	0.344	90.5	0.001
Analysis										
Univariate	1	2.69 (1.61–4.50)	0.000	–	–	3	1.71 (0.88–3.34)	0.117	89.4	0.000
Multivariate	5	1.59 (1.33–1.91)	0.000	28.9	0.229	3	1.09 (0.94–1.27)	0.260	75.8	0.016
Adjusted for age										
Yes	3	1.52 (1.24–1.85)	0.000	49.4	0.138	3	1.64 (0.86–3.14)	0.136	84.0	0.002
No	3	2.36 (1.67–3.35)	0.000	0.0	0.775	3	1.16 (0.95–1.42)	0.150	86.7	0.001

Notes: N, number of studies; *P*, *P*-value for HR =1; P_h, *P*-value for heterogeneity test.
Abbreviations: AHF, acute HF; CHF, chronic HF; 95% CI, 95% confidence interval; CLIA, chemiluminescent immunoassay; HF, heart failure; HR, hazard ratio; ILMA, immunoluminometric assay; NOS, Newcastle–Ottawa Quality Assessment Scale; NYHA, New York Heart Association.

in this meta-analysis, and a significant heterogeneity among studies was observed (I^2=83.0%, *P*<0.001). Using the random-effects model, the pooled HR of all-cause mortality was 1.03 (95% CI =1.00–1.07; Figure 2). As presented in Table 3, a few subgroups by unit copeptin corroborated this association between copeptin and all-cause mortality in patients with HF, even though other subgroups showed a borderline association, such as the higher mortality group (≥30%) and the younger age group (<70).

The other two studies reported the risk estimation by log copeptin, and the pooled HR was 3.26 (95% CI =0.95–11.25;

Figure 2) using a random-effects model (I^2=86.6%, *P*<0.001). Subgroup analyses according to log copeptin were not conducted, as the number of original studies was relatively small.

Based on the pooled SMD, nine studies provided data for 630 deaths and 2,152 survivors were included in this meta-analysis. Obvious heterogeneity between studies was observed (I^2=92.1%, *P*<0.001), and the random-effects model was chosen. The result of the pooled SMD (1.19, 95% CI =0.81–1.57; Figure 3) showed that baseline copeptin levels were significantly higher in patients who died during
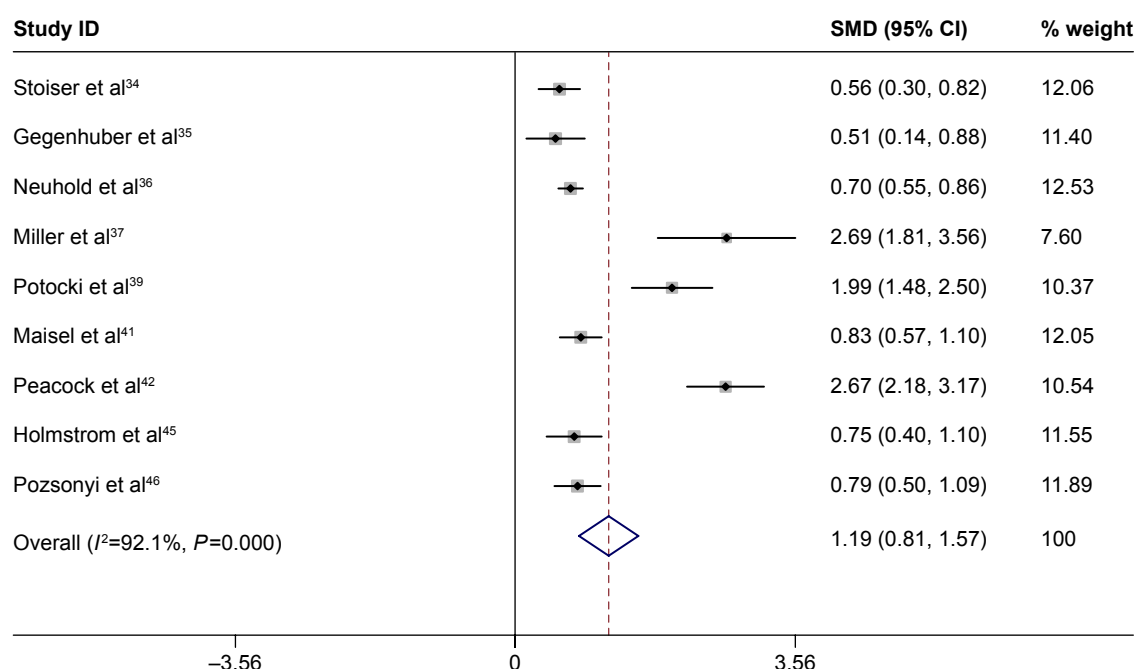
Study ID		SMD (95% CI)	% weight
Stoiser et al[34]		0.56 (0.30, 0.82)	12.06
Gegenhuber et al[35]		0.51 (0.14, 0.88)	11.40
Neuhold et al[36]		0.70 (0.55, 0.86)	12.53
Miller et al[37]		2.69 (1.81, 3.56)	7.60
Potocki et al[39]		1.99 (1.48, 2.50)	10.37
Maisel et al[41]		0.83 (0.57, 1.10)	12.05
Peacock et al[42]		2.67 (2.18, 3.17)	10.54
Holmstrom et al[45]		0.75 (0.40, 1.10)	11.55
Pozsonyi et al[46]		0.79 (0.50, 1.09)	11.89
Overall (*I²*=92.1%, *P*=0.000)		1.19 (0.81, 1.57)	100

−3.56   0   3.56

Figure 3 Pooled estimate of standardized mean copeptin value with all-cause mortality in patients with HF.
Abbreviations: CI, confidence interval; HF, heart failure; SMD, standardized mean difference.

the follow-up period than survivors, indicating that higher circulating copeptin levels were positively associated with the risk of all-cause mortality in patients with HF. The results of subgroup analyses are presented in Table 4, and the significant association was also observed in each subgroup.

Sensitivity analyses were conducted by removing one study at a time to observe the influence of each included study on the overall pooled estimates. As shown in Figure 4, no single study was observed to significantly influence the overall pooled estimates, which indicated that our overall results were statistically stable.

Discussion

AVP, also called antidiuretic hormone, was produced by the hypothalamus and secreted from the neurohypophysis in reaction to osmotic and hemodynamic stimuli.[21] When released into the blood flow, AVP began to take different peripheral effects through three different receptors, namely V_{1a}, V_{1b}, and V_2, respectively. In patients with HF, increased AVP contributed to the process of left ventricular dysfunction, by activating V_{1a} and V_2 receptors and making further effects such as leading to water retention, peripheral vasoconstriction, and myocardial remodeling.[22] Generally, plasma AVP level increased sharply in patients with HF and was relevant to the severity of disease.[23] Thus, knowledge of circulating AVP levels would be of vital importance to the diagnosis and assessment of therapeutic intervention with HF. However,

due to the shortages of the half-time of 24 minutes, unstability in frozen plasma and difficult measurement method, the clinical use of AVP for HF was restricted.[24,25]

Copeptin, also named the AVP-associated glycopeptides, was derived from pro-AVP together with AVP, neurophysin II and a signal peptide.[26] Different from AVP, copeptin was discovered to be stable even at room temperature and easily measured by sandwich immunoassay, with results stable in 20–60 minutes.[27] In recent years, despite the exact mechanism connecting copeptin with the severity of HF not clear, the clinical use of copeptin as a surrogate marker of AVP was proposed. Early studies had indicated that a higher circulating copeptin level was an independent prognostic factor not only for mortality but also for poor functional outcome in patients with HF.[28,29] These multiple studies in different clinical settings showed that circulating copeptin levels were necessary for risk stratification in patients with HF.[30,31]

A previous research conducted by Sun et al[32] suggested that copeptin was a prognostic biomarker for all-cause mortality in patients with cardio-cerebrovascular disease. However, comprehensive study about the prognostic role of copeptin in patients with HF was not reported. To our best knowledge, this was the first systematic review and meta-analysis attempting to evaluate the prognostic value of copeptin and all-cause mortality in patients with HF. Through this collaborative meta-analysis, our study provided new and powerful evidence to the suggestion of using copeptin as an

Table 4 Pooled SMDs in subgroup analyses

	N	SMD (95% CI)	*P*-value	*I²* (%)	*P*ₕ-value
Overall	9	1.19 (0.81–1.57)	0.000	92.1	0.000
Sample size					
<200	5	1.25 (0.67–1.84)	0.000	95.1	0.000
≥200	4	1.15 (0.56–1.73)	0.000	89.7	0.000
Age (years)					
<70	3	1.17 (0.58–1.78)	0.000	89.6	0.000
≥70	5	1.28 (0.53–2.02)	0.001	94.9	0.000
Percentage of female					
<30%	3	0.70 (0.57–0.83)	0.000	0.0	0.502
≥30%	6	1.52 (0.87–2.18)	0.000	94.3	0.000
No of centers					
1	5	1.25 (0.67–1.84)	0.000	95.1	0.000
>1	4	1.15 (0.56–1.73)	0.000	89.7	0.000
Mortality					
<30%	6	1.21 (0.70–1.72)	0.001	93.7	0.000
≥30%	3	1.18 (0.46–1.89)	0.000	90.4	0.000
HF type					
AHF	4	1.49 (0.58–2.39)	0.001	95.3	0.000
CHF	4	0.94 (0.54–1.33)	0.000	85.8	0.000
Inclusion of NYHA class I					
Yes	2	0.72 (0.59–0.86)	0.000	0.0	0.602
No	4	1.36 (0.53–2.19)	0.001	93.2	0.000
Measurement methods					
ILMA	7	1.18 (0.69–1.66)	0.000	92.3	0.000
CLIA	2	1.32 (0.06–2.59)	0.040	95.5	0.000
Quality according to NOS					
>6	7	1.10 (0.67–1.53)	0.000	92.8	0.000
Follow-up time					
≤2 years	7	1.34 (0.84–1.84)	0.000	94.0	0.000
>2 years	2	1.19 (0.81–1.57)	0.000	0.0	0.854
Estimating method of mean and SD					
Described	3	1.07 (0.49–1.65)	0.000	90.4	0.000
Estimated	6	1.23 (0.70–1.79)	0.000	93.0	0.000

Notes: N, number of studies; *P*, *P*-value for SMD =0; *P*ₕ, *P*-value for heterogeneity test.
Abbreviations: AHF, acute HF; CHF, chronic HF; 95% CI, 95% confidence interval; CLIA, chemiluminescent immunoassay; HF, heart failure; ILMA, immunoluminometric assay; NOS, Newcastle–Ottawa Quality Assessment Scale; NYHA, New York Heart Association; SD, standard deviation; SMD, standardized mean difference.

independent prognostic biomarker for risk stratification in patients with HF.

Our results showed that higher circulating copeptin levels at baseline were significantly associated with the increased risk of all-cause death in patients with HF, with a pooled SMD (difference of mean copeptin level between death group and survival group/pooled SD) of 1.19. Overall, the risk of death from all causes in patients with HF increased 3% for per unit (1 pmol/L) increase in baseline copeptin level and >200% for 10-fold copeptin increase. Meanwhile, compared to the group with lower copeptin level, the patients with HF with higher circulating copeptin levels were at a 1.69 times higher risk from all-cause death. Subgroup analyses also presented several important findings. In the subgroup analysis based on mortality and female percentage, the lower mortality group (<30%) revealed a more prominent association as well as

the higher female proportion group (≥30%). Furthermore, when analyzing according to the sample size, a more extrusive association was found in studies with subjects <200 compared to studies with subjects ≥200. As small studies with limited sample sizes were more likely to report larger beneficial effects,[33] multicenter studies with large sample size were desired to evaluate a more accurate estimate about the association between copeptin and all-cause mortality in patients with HF.

Although some credible findings have been achieved, some limitations of our meta-analysis should be declared in this article. First, we restricted our study to all-cause mortality rather than HF related morbidity or mortality, which might show different relationship with copeptin. Second, we did not extract the original data from the eligible studies, which restricts further statistical estimate of circulating copeptin
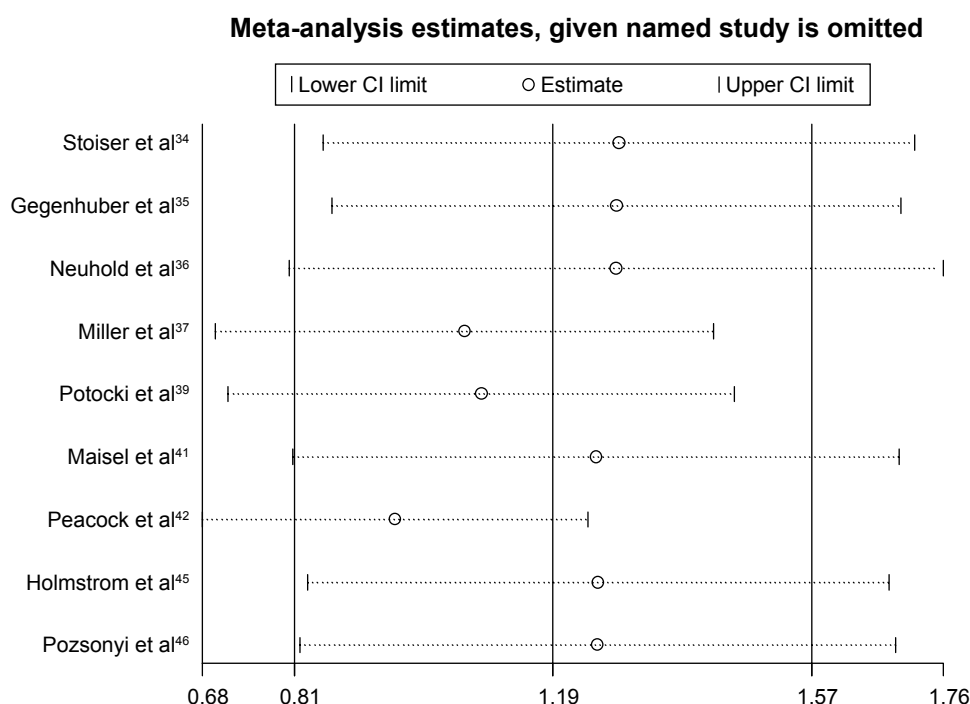
Meta-analysis estimates, given named study is omitted

Figure 4 Sensitivity analysis of included studies (on SMD).
Abbreviations: CI, confidence interval; SMD, standardized mean difference.

levels in the evaluation of the prognostic accuracy in the receiver operating characteristic curve after HF. Third, merely crude RR (HR) could be achieved from some included studies. Therefore, the confounding factors of the different studies could not be adequately accounted for in the current analysis. Finally, publication bias might be a key element, for negative studies seemed to be more difficult to publish and have less impact; thus, the insufficiency of negative studies might influence the results of our meta-analyses.[13]

Conclusion

The results of our study indicated a prognostic role of copeptin that higher circulating copeptin levels were positively associated with the risk of all-cause mortality in patients with HF. Thus, in patients with HF, we recommended using copeptin as a new prognostic biomarker to provide better information not only in decision making for treatment but also in the prediction of clinical outcome. Since the exact mechanism of this association between copeptin and mortality in patients with HF is not fully understood, future well-designed studies with large sample size are required.

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Disclosure

The authors report no conflicts of interest in this work.

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