

Plasma endothelin-1-related peptides as the prognostic biomarkers for heart failure

A PRISMA-compliant meta-analysis

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Abstract

Background: Most studies reported that high plasma endothelin-1 (ET-1), big ET-1, and C-terminal proET-1 (CT-proET-1) were correlated with poor prognosis of heart failure (HF). However, available evidence remains controversial. To help solve the debate, we collected all the available studies and performed a meta-analysis.

Methods: We searched the databases covering Embase, PubMed, Ovid, and Web of Science on June 28, 2017. The hazard ratio (HR) or risk ratio (RR) and its 95% confidence intervals (CIs) were collected and calculated by use of a random-effect model. Heterogeneity was assessed by Cochran's Q test, and publication bias was assessed by funnel plots with Egger's and Begg's linear regression test.

Results: Thirty-two studies with 18,497 patients were included in the analysis. Results showed that circulating ET-1, big ET-1, and CT-proET-1 were positively correlated with high risk of adverse outcomes, with pooled RRs (95% CIs) of 2.22 (1.82–2.71, $P < .001$), 2.47 (1.93–3.17, $P < .001$), and 2.27 (1.57–3.29, $P < .001$), respectively. In the subgroup of death as primary outcome, the pooled RRs (95% CIs) were 2.13 (1.68–2.70, $P < .001$), 2.55 (1.82–3.57, $P < .001$), and 2.02 (1.39–2.92, $P < .001$) for ET-1, big ET-1, and CT-proET-1, respectively. No significant publication bias was observed in this study.

Conclusion: Our meta-analysis provided evidence that increased plasma levels of ET-1, big ET-1, and CT-proET-1 were associated with poor prognosis or mortality for HF populations.

Abbreviations: AHF = acute heart failure, BNP = B-type natriuretic peptide, CHF = chronic heart failure, CI = confidence intervals, EIA = enzyme immunoassay, ET-1 = endothelin-1, HF = heart failure, HR = hazard ratio, NA = not available, NOS = Newcastle–Ottawa Scale, NYHA = New York Heart Association, RCT = randomized controlled trial, RIA = radioimmunoassay, RR = risk ratio, SMC = single molecule counting technology.

Keywords: endothelin-1, heart failure, meta-analysis, prognostic factor

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1. Introduction

Heart failure (HF) is the major cause of mortality in patients with cardiovascular diseases. Over 30 million people suffered from HF globally, and the cost for HF in USA is over 30 billion US dollars each year.^[1] Early identification of HF patients with higher risk can lead to earlier intervention, which may potentially improve outcomes.^[2] Studies that investigate prognostic biomarkers for HF have been bursting over the last decades; however, short- and long-term prediction of outcomes are still challenging. Previous studies have revealed several biomarkers with prognostic value for HF, such as B-type natriuretic peptide (BNP),^[3] N-terminal proBNP (NT-proBNP),^[3] mid-regional proatrial natriuretic peptide,^[4] high sensitivity C-reactive protein,^[3] and endothelin-1 (ET-1).^[5] Among them, only BNP and NT-proBNP have been recommended by current guidelines.^[6]

ET family includes 3 isoforms, namely ET-1, ET-2, and ET-3, which are encoded by 3 different genes.^[7] ET-1, a 21 amino acid peptide, is predominantly generated by endothelial cells and cleared by binding to its receptors in the pulmonary vascular bed.^[8] ET-1 is described as the most potent endogenous vasoconstrictor discovered to date.^[9] ET-2 and ET-3 are mainly involved in neonatal growth, intestinal functions, and central nervous system.^[7] The initial product of the human ET-1 gene consists of 212 amino acid peptides, which is called propro-ET-1.

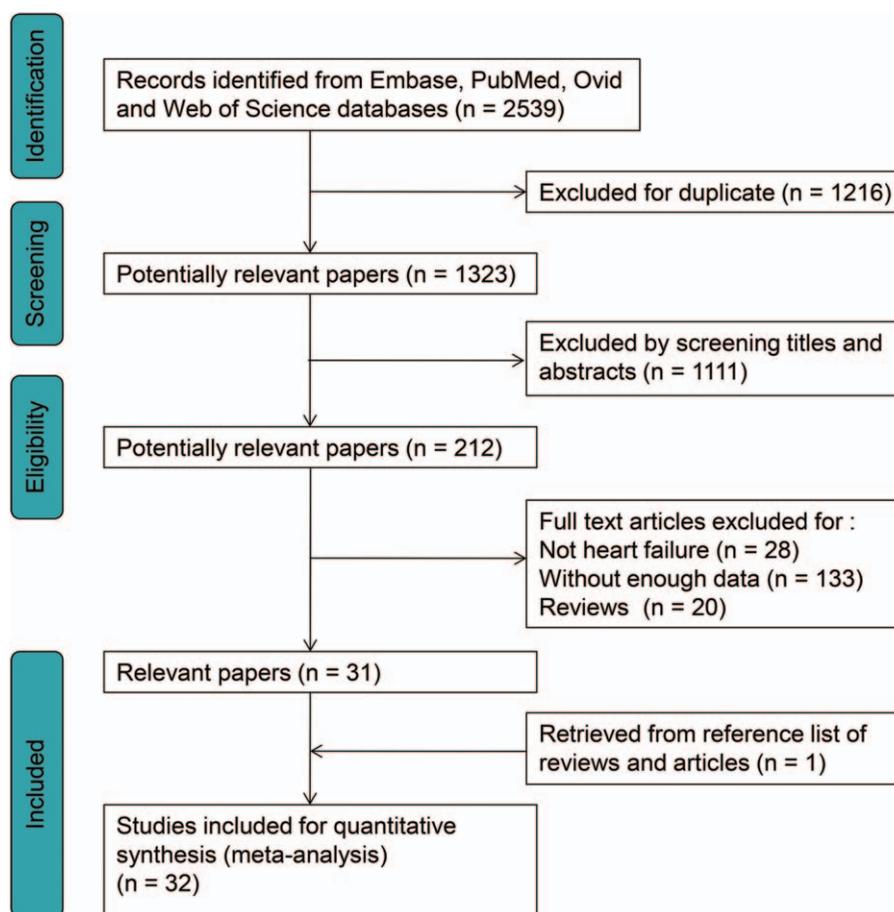


Figure 1. Flow diagram of literature retrieval for this study.

After removal of a short secretory signal sequence, prepro-ET-1 is converted into pro-ET-1. Pro-ET-1 is then cleaved by furin to generate a biologically inactive 38 amino acid precursor named big ET-1, and a 44 amino acid peptide named C-terminal pro-ET-1 (CT-proET-1). Mature and active ET-1 is finally excised from big ET-1 by the action of endothelin-converting enzyme.^[7] Plasma level of ET-1 can be altered by stimuli such as hypoxia, shear stress, lipoproteins, free radicals, and endotoxin.^[7] In 1995, Tsutamoto et al^[10] indicated that HF patients with higher level of ET-1 had elevated risk of cardiac death. Since then, many studies have investigated the predictive role of ET-1 related peptides in both acute HF (AHF) and chronic HF (CHF). Even though most of the studies have reported the relationship between higher ET-1 related peptides and clinical adverse outcomes of HF patients,^[5,11,12] there were still several studies holding the opposite opinion.^[13,14] To address this issue, we performed a meta-analysis to assess the values of ET-1, big ET-1, and CT-proET-1 in predicting prognosis in HF patients.

2. Methods

The study was performed according to Meta-analysis of Observational Studies in Epidemiology.^[15]

2.1. Search strategy

Two investigators (Zhang and Xie) independently carried out a comprehensive literature search for original articles up until June

28, 2017. Both Medical Subject Heading terms and free text words were used to acquire relevant studies by searching databases covering Embase, PubMed, Ovid, and Web of Science. The terms searched were: “heart failure,” “endothelin,” “endothelins,” “endothelin-1,” “ET-1,” “ET,” “edn1,” “big endothelin-1,” “big ET-1,” “C-terminal proendothelin-1,” “CT-proET-1,” “prognosis,” “prognostic,” “predict,” “prediction,” “outcome,” “mortality,” and “death”. The search was limited in English language articles. Retrieved articles were screened according to the titles and abstracts, and irrelevant papers were dropped out. References of the related articles were screened to find missed papers by literature retrieval. All relevant papers were then assessed according to the inclusion and exclusion criteria as described below.

2.2. Inclusion and exclusion criteria

The inclusion criteria were set as follows: the included patients were diagnosed with CHF or AHF; plasma ET-1, big ET-1, or CT-proET-1 were detected in recruited participants; the endpoints were death, heart transplant, or other adverse outcomes; only prospective studies were included; results were evaluated by survival curve, HR or risk ratio (RR) with its 95% confidence interval (CI); when 2 publications reported data from overlapping samples, the study containing the larger dataset was included. Reviews, case reports, and meta-analyses were excluded. For studies without

Table 1
Characteristics of the studies included in the meta-analysis.

| First author, year | Study design | Country | No. of cases, % male | HF type | NYHA III-IV, % | Follow-up time, mo | Peptides assayed | Method | Cutoff value pmol/L | NOS score |
|--|-------------------------------|---------------------------------|----------------------|---------|----------------|-------------------------------|------------------|--------|---------------------|-----------|
| Tsutamoto (1995) ^[10] | Cohort study | Japan | 102 (59) | CHF | 70.6 | 22.0 [*] | ET-1 | RIA | 0.96 | 7 |
| Galatius-Jensen (1996) ^[32] | Cohort study | Denmark | 44 (75) | CHF | 45.4 | 17.0 [*] | ET-1 | RIA | 1.2 | 6 |
| Pousset (1997) ^[29] | Cohort study | France | 120 (83) | CHF | 53.3 | 12.0 ± 11.2 [‡] | ET-1 | RIA | 2.0 | 6 |
| Pousset (2000) ^[28] | Cohort study | France | 117 (79) | CHF | 30.8 | 7.9 ± 4.5 [‡] | ET-1 | RIA | 1.8 | 7 |
| Aronson (2003) ^[33] | Cohort study | Israel, USA | 88 (61) | CHF | 100 | 10.2 ± 5.1 | ET-1 | NA | 3.4 | 6 |
| Latini (2004) ^[31] | RCT | USA | 1934 (NA) | CHF | NA | 23 | ET-1 | RIA | 1.5 | 7 |
| Ketelslegers (2005) ^[3] | Cohort study | Multi-center | 476 (74) | AHF | NA | 16.0 [*] | ET-1 | NA | 0.5 | 7 |
| Gardner (2005) ^[14] | Cohort study | UK | 150 (83) | CHF | 86 | 22.2 [‡] | ET-1 | EIA | 1.5 | 7 |
| Tang (2010) ^[27] | Cohort study | New Zealand | 154 (75) | CHF | 36 | 39.0 [‡] | ET-1 | NA | 2.3 | 8 |
| Rousseau (2011) ^[34] | Cohort study | Belgium | 345 (NA) | CHF | NA | 36.1 [‡] | ET-1 | RIA | NA | 8 |
| Perez (2015) ^[30] | Cohort study | USA | 872 (NA) | AHF | NA | 6 | ET-1 | SMC | 3.0 | 8 |
| Friedman (2015) ^[26] | Cohort study | USA | 200 (NA) | CHF | NA | 37.2 [‡] | ET-1 | SMC | NA | 7 |
| Metra ^a (2015) ^[5] | Cohort study | Israel, UK, Germany, USA | 638 (69) | AHF | NA | 3 | ET-1 | EIA | 0.88 | 8 |
| Metra ^b (2015) ^[5] | Cohort study | Israel, UK, Germany, USA | 709 (50) | AHF | NA | 3 | ET-1 | EIA | 0.88 | 8 |
| Miyamoto (2016) ^[36] | Cohort study | Japan | 103 (45) | CHF | 9 | 96 | ET-1 | RIA | 1.2 | 7 |
| Gaggin (2017) ^[35] | Cohort study | USA | 99 (85) | CHF | 52.5 | 10 | ET-1 | SMC | 2.4 | 7 |
| Pacher (1996) ^[38] | Cohort study | Austria | 113 (86) | CHF | 55.7 | 12 | Big ET-1 | RIA | 4.3 | 6 |
| Hulsmann (1998) ^[41] | Cohort study | Austria | 218 (88) | CHF | 46 | 12 | Big ET-1 | RIA | 4.3 | 7 |
| Stanek (1999) ^[37] | RCT | Austria | 59 (81) | CHF | 100 | 12 | Big ET-1 | RIA | 4.3 | 6 |
| Frey (2000) ^[42] | Cohort study | Austria | 32 (94) | CHF | 100 | 7 | Big ET-1 | RIA | 4.3 | 6 |
| Masson (2006) ^[39] | RCT | Europe, Australia, South Africa | 2359 (82) | CHF | 33.6 | 23 | Big ET-1 | EIA | 0.83 | 7 |
| Frantz (2007) ^[51] | Cohort study | USA | 206 (80) | CHF | 100 | 12 | Big ET-1 | RIA | 2.4 | 8 |
| Zhang (2009) ^[11] | Cohort study | Austria | 1233 (59) | HF | 23.7 | 24 | ET-1 | RIA | 2.7 | 8 |
| Li (2014) ^[40] | Cohort study | China | 622 (74) | DCM | 75.9 | (31.2 ± 19.2) [†] | Big ET-1 | NA | 0.3 | 8 |
| Olivier (2017) ^[43] | Cohort study | Multi-center | 463 (74) | AHF | NA | 12.6 | Big ET-1 | EIA | 0.95 | 8 |
| Gergei (2017) ^[44] | Cohort study | German | 2829 (71) | CHF | NA | 112 | Big ET-1 | RIA | >1.9 vs. ≤1.4 | 7 |
| Dieplinger (2009) ^[48] | Cohort study | Austria | 137 (93) | AHF | 56.9 | 12 | Big ET-1 | EIA | >0.98 vs. ≤0.66 | 7 |
| Adlbrecht (2009) ^[50] | Random trial and Cohort study | Multi-center | 786 (81) | CHF | 63 | 24 | CT-proET-1 | EIA | 79 | 8 |
| Gombos (2010) ^[47] | Cohort study | Hungary | 194 (75) | CHF | NA | 12 | CT-proET-1 | EIA | 77.4 | 7 |
| Neuhold (2010) ^[45] | Cohort study | Austria | 181 (65) | CHF | 98 | 24 | CT-proET-1 | EIA | NA | 7 |
| Jankowska (2011) ^[46] | Cohort study | UK, Italy, Poland, Greece | 491 (91) | CHF | 46 | 12 | CT-proET-1 | EIA | 85.6 | 8 |
| Cleland (2012) ^[49] | Cohort study | UK | 2289 (65) | CHF | NA | 58.8 (39.6–84.0) [§] | CT-proET-1 | NA | 87.1 | 8 |
| Gottlieb (2015) ^[12] | Cohort study | USA | 134 (76) | CHF | 44.8 | 28.8 ± 12.0 [†] | CT-proET-1 | EIA | >108 vs. ≤61 | 8 |
| | | | | | | | ET-1 | SMC | 80 | 8 |
| | | | | | | | | | 1.76 | |

ET-1, 1 pmol/L = 2.496 pg/mL; big ET-1, 1 pmol/L = 4.287 pg/mL; ^aage <72 year; ^bage ≥72 year.

AHF = acute heart failure, CHF = chronic heart failure, DCM = dilated cardiomyopathy, EIA = enzyme immunoassay, NA = not available, NOS = Newcastle–Ottawa Scale, RCT = randomized controlled trial, RIA = radioimmunoassay, SMC = single molecule counting technology.

^{*} Mean.

[†] Mean ± SD.

[‡] Median.

[§] Median (IQR).

enough data to obtain RRs, the corresponding authors were contacted by email.

2.3. Outcomes

The endpoint evaluated in this study was adverse outcomes, which included death (all cause death, sudden death, and cardiac death) and advanced therapies (heart transplantation and HF hospitalization).^[16]

2.4. Data extraction

All the data were extracted independently by 3 authors (Cheng-Lin Zhang, Shang Xie, and Xue Qiao). We extracted information

from each study with the following criteria: first author, publication year, research design, country of origin, number of cases, HF type, percentage of patients in New York Heart Association (NYHA) class III-IV, follow-up period, peptides assayed, assessing methods, and cutoff value. If there was any disagreement among the 3 investigators, it was resolved by discussion with other authors until consensus was reached among them.

2.5. Quality assessment

The Newcastle–Ottawa Scale (NOS) was performed to evaluate the methodological quality of included studies.^[17] A high-quality

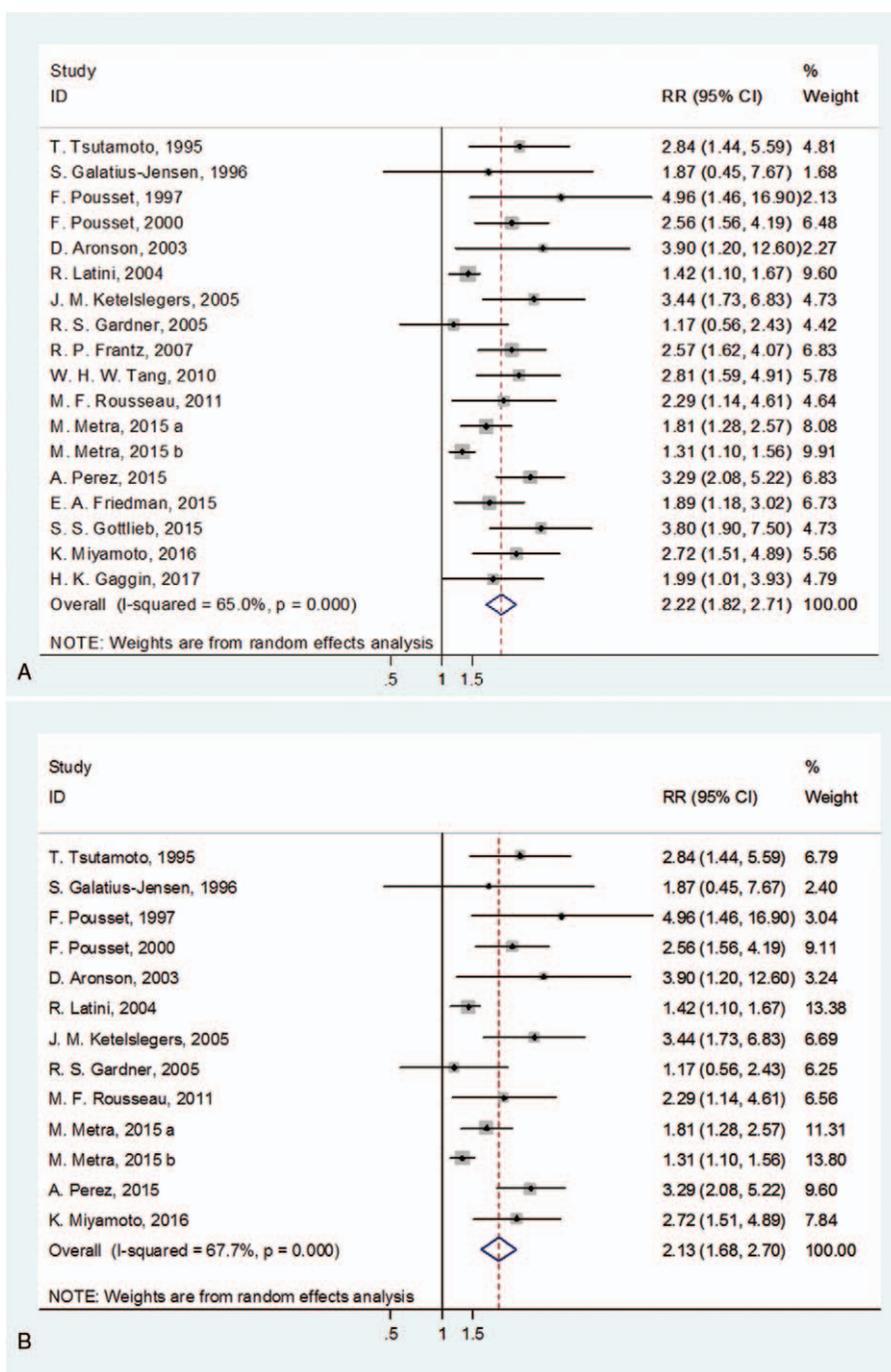


Figure 2. Forest plots evaluating the prognostic value of ET-1 for adverse outcomes (A) or death (B). CI = confidence intervals, RR = risk ratio; a, age <72 year; b, age ≥72 year.

study was defined if 1 with greater than or equal to 7 points. The assessments were performed by 2 authors (Cheng-Lin Zhang and Yuan-Ming An) independently, and discrepancies were resolved by discussion with other authors until consensus was reached.

2.6. Statistical analysis

All the data management and analysis were performed with STATA 11.0 software (Stata Corporation, College Station, TX). If HRs, RRs, and 95% CIs were given, data were directly

extracted from the original articles. For studies with Kaplan-Meier survival curves, whereas without HRs or RRs, survival curves were read and calculated by Engauge Digitizer version 4.1 according to Parmar et al^[18] and Tierney et al^[19]. Then, RRs were estimated by STATA 11.0 software (Stata Corporation). RRs were used as the universal effect sizes across studies, and HRs were directly used as RRs.^[20] RRs and corresponding 95% CIs were transformed to their natural logarithms (lnRR, the logarithm of RR) to stabilize variance and normalize the distribution, which were subsequently converted back to linear measures for data presentation.^[21]

Table 2
Subgroup analyses of ET-1 for adverse outcomes.

| Covariates | Subgroup | No. of studies | RR, 95% CI | P | Heterogeneity | |
|-----------------------|----------|----------------|------------------|--------|---------------|--------------------|
| | | | | | P | I ² , % |
| HF type | AHF | 3 | 2.14 (1.34–3.44) | 0.010 | < 0.001 | 84.8 |
| | CHF | 14 | 2.27 (1.82–2.82) | <0.001 | 0.025 | 47.5 |
| NYHA class III-IV (%) | ≥50 | 6 | 2.36 (1.69–3.30) | <0.001 | 0.275 | 21.0 |
| | <50 | 5 | 2.80 (2.12–3.71) | <0.001 | 0.876 | 0.0 |
| | NA | 6 | 1.90 (1.46–2.46) | <0.001 | 0.001 | 73.1 |
| NYHA class III-IV (%) | ≥80 | 3 | 2.14 (1.15–3.96) | 0.016 | 0.121 | 56.2 |
| | <80 | 8 | 2.75 (2.17–3.49) | <0.001 | 0.885 | 0.0 |
| | NA | 6 | 1.90 (1.46–2.46) | <0.001 | 0.001 | 73.1 |
| Follow-up (mo) | ≥24 | 5 | 2.51 (1.93–3.26) | <0.001 | 0.542 | 0.0 |
| | 12 to 24 | 7 | 2.17 (1.48–3.17) | <0.001 | 0.013 | 62.8 |
| | <12 | 5 | 2.12 (1.47–3.05) | <0.001 | 0.001 | 76.2 |
| Detecting methods | EIA | 2 | 1.43 (1.14–1.79) | <0.001 | 0.239 | 30.0 |
| | RIA | 8 | 2.29 (1.69–3.11) | <0.001 | 0.027 | 55.8 |
| | SMC | 4 | 2.59 (1.84–3.65) | <0.001 | 0.209 | 33.9 |
| | NA | 3 | 3.14 (2.09–4.73) | <0.001 | 0.841 | 0.0 |
| Cutoff value (pmol/L) | ≥1.76* | 8 | 2.87 (2.32–3.54) | <0.001 | 0.829 | 0.0 |
| | <1.76* | 7 | 1.75 (1.39–2.22) | <0.001 | 0.016 | 59.3 |
| | NA | 2 | 2.01 (1.36–2.96) | <0.001 | 0.655 | 0.0 |
| Number of cases | ≥200 | 7 | 1.97 (1.54–2.53) | <0.001 | 0.000 | 73.6 |
| | <200 | 10 | 2.57 (2.06–3.21) | <0.001 | 0.508 | 0.0 |

AHF = acute heart failure, CHF = chronic heart failure, CI = confidence intervals, EIA = enzyme immunoassay, HF = heart failure; NA = not available, NYHA = New York Heart Association, RIA = radioimmunoassay, RR = risk ratio, SMC = single molecule counting technology.

* Median.

Heterogeneity was assessed by Cochran's Q test, and the significance was set at *P* value less than 0.1.^[22] In this case, the random-effect model was used to estimate the pooled RRs. Otherwise, the pooled RRs were estimated by the fixed-effect model.^[23] The inconsistency index (*I*²) was calculated to assess the variation caused by heterogeneity. The value of *I*² between 0 and 25% represents insignificant heterogeneity, 26 and 50% as low heterogeneity, 51 and 75% as moderate heterogeneity, and more than 75% as high heterogeneity.^[24] Subgroup analysis was performed to explore the sources of heterogeneity. Evidence of publication bias was assessed with funnel plots by Egger's and Begg's linear regression. Significance was set at *P* value less than .05.^[25] Sensitivity analysis was performed by excluding each study to assess its influence on the combined RR.

3. Results

3.1. Literatures retrieval and study description

A total of 2539 records were identified through literatures retrieval and 1323 articles were left after excluding duplicates. Among them, 1111 records were dropped out for unconformity with our issues by reading titles and abstracts. The remaining 212 were considered potentially eligible and their full-text articles were screened. One study was retrieved from the reference.^[26] After serious scrutiny for eligibility, a total of 32 articles consisting of 18,497 individuals met our criteria and were included in this study (Fig. 1). Among them, 15 studies provided relevant data about ET-1 with 6151 participants,^[3,5,10,14,26–36] 9 studies for big ET-1 with 7928 participants,^[11,37–44] and 6 studies for CT-proET-1 with 4078 participants,^[45–50] 1 study included both ET-1 and big ET-1 with 206 participants,^[51] and 1 study included both ET-1 and CT-proET-1 with 134 participants.^[12] Diagnosis of HF was conducted according to symptom, echocardiography or New York Heart Association

(NYHA) classes. Twenty-five studies were designed for CHF,^[3,10,12,14,26–29,31–39,41,42,44–47,49–51] 5 studies for AHF,^[3,5,30,43,48] 1 for dilated cardiomyopathy,^[40] and 1 study did not report HF classifications.^[11] The follow-up time ranged from 3 to 112 months, with the median time of 16 month (interquartile range from 12 to 24 months). Among the 32 studies, 3 are randomized controlled trails (RCT),^[31,37,39] 28 are cohort studies, and 1 study composes of both RCT and cohort study.^[50] 22 studies reported HR or RR, HR of 1 study was acquired from the author,^[14] HRs or RRs of 9 studies were estimated by methods mentioned above.^[10,29,31,32,37,38,40–42] HRs of 5 studies were multivariate analysis or adjusted by other confounders.^[5,26,34,44,47] Since 1 article only provided the subgroup data according to age of the patients, we designated the group of age less than 72 as "M. Metra (2015)^a", and the group of age ≥72 as "M. Metra (2015)^b".^[5]

3.2. Quality assessment

The NOS (range 0–9 points) was performed to evaluate the quality of included studies.^[17] In our meta-analysis, 26 studies have quality scores of 7 to 8, others with quality scores of 6. Results of quality assessment were shown in Table 1.

3.3. Circulating ET-1 is correlated with adverse outcomes and death in HF patients

In this part, 17 studies related to ET-1 were included. Moderate heterogeneity was seen cross all included studies (*I*² = 65.0%, *P*_[Q-test] < .001). Thus, random-effect model was used to combine the HRs or RRs and 95% CIs. Results showed that high plasma level of ET-1 was significantly correlated with adverse outcomes in patients with HF (RR = 2.22, 95% CI 1.82–2.71; *P* < .001; Fig. 2A). Three methods were involved in the measurement of ET-1. Heterogeneities were reduced after subgroup analysis by

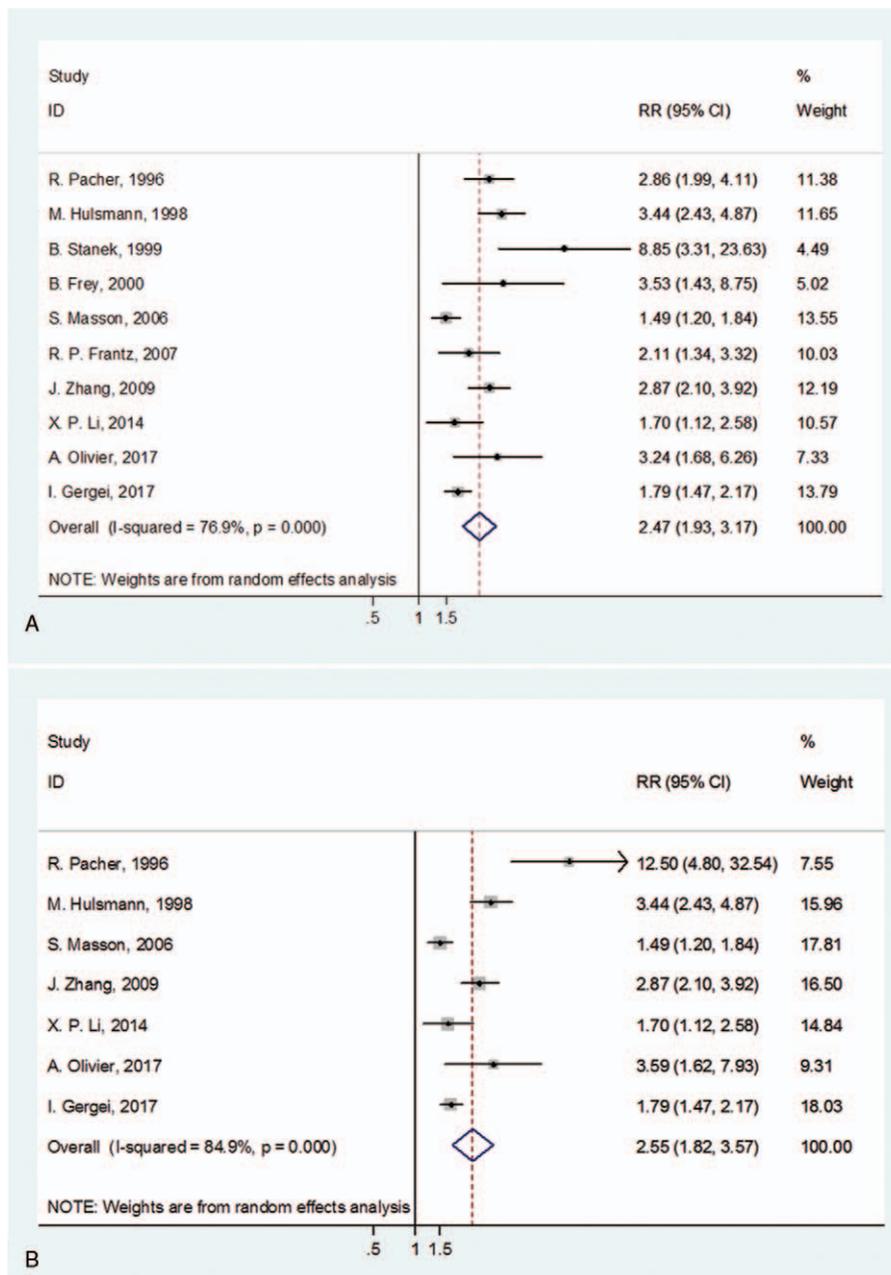


Figure 3. Forest plots evaluating the prognostic value of big ET-1 for adverse outcomes (A) or death (B). CI = confidence intervals, RR = risk ratio.

detecting methods ($I^2=30.0\%$ for enzyme immunoassay [EIA], $I^2=55.8\%$ for radioimmunoassay [RIA], $I^2=33.9\%$ for single molecule counting technology), indicating that the difference between methods may partly contribute to the heterogeneity for ET-1. After subgroup analysis by HF type, the pooled RRs for CHF and AHF were 2.27 (95% CI 1.82–2.82) and 2.14 (95% CI 1.34–3.44), respectively. For studies concerning severe HF (more than 80% patients were in NYHA class III-IV), the pooled RR was 2.14 (95% CI 1.15–3.96). The combined RRs were significant in follow-up time more than or equal to 24 months (RR=2.51, 95% CI 1.93–3.26; $P<.001$), less than 12 months (RR=2.12, 95% CI 1.47–3.05; $P<.001$), or in between (RR=2.17, 95% CI 1.48–3.17; $P<.001$). For the 16 cohort studies, the pooled RR was 2.34 (95% CI 1.88–2.92; $P<.001$). In the

12 studies that regarded death as primary outcome, the combined RR was 2.13 (95% CI 1.68–2.70; $P<.001$; Fig. 2B). Detailed subgroup analysis results were shown in Table 2.

3.4. Circulating big ET-1 is correlated with adverse outcomes and death in HF patients

Big ET-1 is the biologically inactive precursor of ET-1. We further detected whether big ET-1 was valuable in predicting poor prognosis in HF patients. Considerable heterogeneity existed among the 10 available studies ($I^2=76.9\%$, $P_{[Q-test]}<.001$). Random-effect model was applied to combine the HRs or RRs and 95% CIs. Results showed that high level of big ET-1 was capable of indicating the adverse outcomes of HF (RR=2.47,

Table 3**Subgroup analyses of big ET-1 for adverse outcomes.**

| Covariates | Subgroup | No. of studies | RR, 95% CI | P | Heterogeneity | |
|-----------------------|--------------|----------------|------------------|--------|---------------|--------------------|
| | | | | | P | I ² , % |
| HF type | CHF | 8 | 2.36 (1.78–3.13) | <0.001 | <0.001 | 78.5 |
| | Unclassified | 1 | 2.87 (2.10–3.92) | <0.001 | – | – |
| | AHF | 1 | 3.24 (1.68–6.25) | <0.001 | – | – |
| NYHA class III-IV (%) | ≥50 | 5 | 2.73 (1.81–4.11) | <0.001 | 0.024 | 64.4 |
| | <50 | 3 | 2.42 (1.40–4.17) | 0.001 | <0.001 | 90.7 |
| | NA | 2 | 2.21 (1.27–3.85) | <0.001 | 0.090 | 65.2 |
| NYHA class III-IV (%) | ≥80 | 3 | 3.70 (1.62–8.49) | 0.002 | 0.030 | 71.4 |
| | <80 | 5 | 2.34 (1.63–3.34) | <0.001 | <0.001 | 84.2 |
| | NA | 2 | 2.21 (1.27–3.85) | <0.001 | 0.090 | 65.2 |
| Follow up (mo) | ≥24 | 3 | 2.06 (1.49–2.85) | <0.001 | 0.030 | 71.4 |
| | 12 to 24 | 6 | 2.79 (1.84–4.23) | <0.001 | <0.001 | 83.4 |
| | <12 | 1 | 3.53 (1.43–8.74) | 0.006 | – | – |
| Detecting method | EIA | 3 | 1.65 (1.44–1.89) | <0.001 | 0.457 | 0.0 |
| | RIA | 6 | 3.14 (2.40–4.10) | <0.001 | 0.170 | 35.6 |
| | NA | 1 | 2.87 (2.10–3.92) | <0.001 | – | – |
| Cutoff value (pmol/L) | ≥4.3* | 4 | 3.51 (2.54–4.86) | <0.001 | 0.211 | 33.5 |
| | <4.3* | 6 | 2.00 (1.59–2.51) | <0.001 | 0.011 | 66.6 |
| Number of cases | ≥200 | 7 | 2.19 (1.70–2.82) | <0.001 | <0.001 | 76.7 |
| | <200 | 3 | 3.97 (2.12–7.45) | <0.001 | 0.106 | 55.4 |

AHF = acute heart failure, CHF = chronic heart failure, CI = confidence intervals, EIA = enzyme immunoassay, HF = heart failure, NA = not available, NYHA = New York Heart Association, RIA = radioimmunoassay, RR = risk ratio.

* Median.

95% CI 1.93–3.17; $P < .001$; Fig. 3A). Two methods were involved in the measurement of big ET-1. Heterogeneities were reduced and became acceptable in both subgroups ($I^2 = 0.0\%$ for EIA, $I^2 = 35.6\%$ for RIA). In the subgroup of studies that included only CHF patients, the pooled RR was 2.36 (95% CI 1.78–3.13). In the 3 studies that concerns severe HF (more than 80% patients were in NYHA class III-IV), the combined RR for adverse outcomes was 3.70 (95% CI 1.62–8.49). In the subgroup analysis of follow-up time, the prognostic effect of big ET-1 was significant in follow-up more than or equal to 24 months (RR = 2.06, 95% CI 1.49–2.85; $P < .001$) or between 12 and 24 months (RR = 2.79, 95% CI 1.84–4.23; $P < .001$). Among the 8 non-RCT cohort studies, the pooled RR was 2.48 (95% CI 1.98–3.11, $P < .001$). In the 7 studies with death as primary outcome, the pooled RR was 2.55 (95% CI 1.82–3.57; Fig. 3B). A detailed subgroup analysis results were shown in Table 3.

3.5. Circulating CT-proET-1 is correlated with adverse outcomes and death in HF patients

CT-proET-1 is a stable ET-1 precursor metabolite. We further detected whether CT-proET-1 was valuable for the poor prognosis of HF. Among the 7 relevant studies, a significant heterogeneity was found ($I^2 = 93.3\%$, $P_{[Q-test]} < .001$). Random-effect model was performed to combine the HRs or RRs and 95% CIs. Results showed that CT-proET-1 was also correlated with adverse outcomes of HF (RR = 2.27, 95% CI 1.57–3.29; $P < .001$; Fig. 4A). Combining the 6 studies that involved with only CHF yielded an RR of 2.24 (95% CI 1.50–3.34). In the subgroup analysis of follow-up period, the combined RRs of CT-proET-1 were 2.44 (95% CI 1.37–4.33) for longer than or equal to 24 months and 2.11 (95% CI 1.59–2.80) for 12 to 24 months. In the 6 studies with death as primary outcome, the pooled RR was 2.02 (95% CI 1.39–2.92; Fig. 4B). Detailed subgroup analysis results were shown in Table 4.

3.6. Publication bias and sensitive analyses

Publication bias was assessed by performing funnel plot. No significant publication bias was found in the analyses of ET-1 (Egger's test $P = .294$; Begg's test $P = .224$), big ET-1 (Egger's test $P = .597$; Begg's test $P = .592$), and CT-proET-1 (Egger's test $P = .813$; Begg's test $P = .548$). Sensitivity analyses results demonstrated that all the estimates were changed between the lower CIs limits and the upper CIs limits, suggesting that the RR estimated were not significantly influenced by excluding each article successively (Fig. 5).

4. Discussion

In this study, we performed a meta-analysis and systematically reviewed the prognostic value of ET-1-related peptides in HF. Our results indicated that high circulating ET-1, big-ET-1, and CT-proET-1 were correlated with increased risk of death or adverse outcomes in HF populations.

Apart from endothelium, ET-1 is also produced by smooth muscle cells, cardiomyocytes, and cardiac fibroblasts.^[7] Circulating ET-1 is increased in pulmonary arterial hypertension, systemic hypertension, aging, diabetes, and myocardial infarction.^[7,52] This meta-analysis showed that high plasma level of ET-1 was significantly correlated with mortality or adverse outcomes in patients with HF. In the subgroup analysis, the pooled RR of ET-1 is significant in both AHF and CHF. The pooled RR of ET-1 is also significant for studies with follow-up time more than or equal to 24 months, less than 12 months, or in between. This suggests that ET-1 may have a wide range of application value in predicting outcomes of HF. Plasma ET-1 is increased with severities of HF according to the NYHA functional class.^[10,27,29] Notably, the heterogeneity of ET-1 was obviously reduced after subgroup analysis by the percentage of patients in NYHA class III-IV, suggesting that the severity of HF may affect the prognostic value of ET-1.

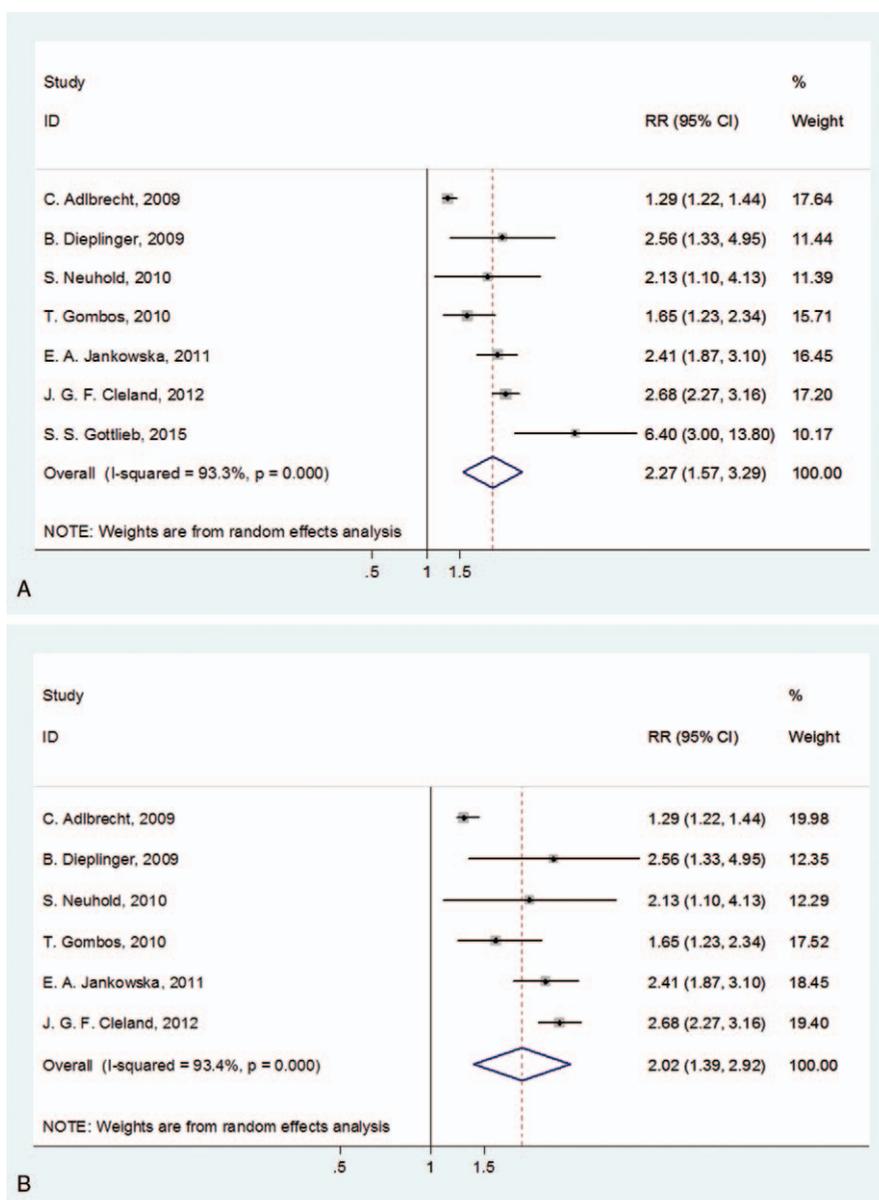


Figure 4. Forest plots evaluating the prognostic value of CT-proET-1 for adverse outcomes (A) or death (B). CI = confidence intervals, RR = risk ratio.

Table 4

Subgroup analyses of CT-proET-1 for adverse outcomes.

| Covariates | Subgroup | No. of studies | RR, 95% CI | P | Heterogeneity | |
|-----------------------|-----------------------|----------------|------------------|------------------|---------------|--------------------|
| | | | | | P | I ² , % |
| HF type | CHF | 6 | 2.24 (1.50–3.34) | <0.001 | <0.001 | 94.2 |
| | AHF | 1 | 2.56 (1.33–4.94) | 0.005 | – | – |
| NYHA class III-IV (%) | ≥50 | 3 | 1.75 (1.08–2.83) | 0.023 | 0.045 | 67.7 |
| | <50 | 2 | 3.67 (1.42–9.45) | 0.007 | 0.017 | 82.4 |
| | NA | 2 | 2.15 (1.34–3.45) | 0.002 | 0.008 | 85.6 |
| | NYHA class III-IV (%) | ≥80 | 1 | 2.13 (1.10–4.13) | 0.025 | – |
| NYHA class III-IV (%) | <80 | 4 | 2.45 (1.39–4.30) | 0.002 | <0.001 | 92.5 |
| | NA | 2 | 2.15 (1.34–3.45) | 0.002 | 0.008 | 85.6 |
| | Follow-up (mo) | ≥24 | 4 | 2.44 (1.37–4.33) | 0.002 | <0.001 |
| Detecting methods | 12 to 24 | 3 | 2.11 (1.59–2.80) | <0.001 | 0.162 | 45.0 |
| | EIA | 6 | 2.18 (1.48–3.20) | <0.001 | <0.001 | 88.2 |
| Number of cases | NA | 1 | 2.68 (2.27–3.17) | <0.001 | – | – |
| | ≥200 | 3 | 2.02 (1.17–3.48) | 0.012 | <0.001 | 97.3 |
| | <200 | 4 | 2.59 (1.50–4.46) | 0.001 | 0.013 | 72.0 |

AHF=acute heart failure, CHF=chronic heart failure, CI=confidence intervals, EIA=enzyme immunoassay, HF=heart failure, NA=not available, NYHA=New York Heart Association, RR=risk ratio.

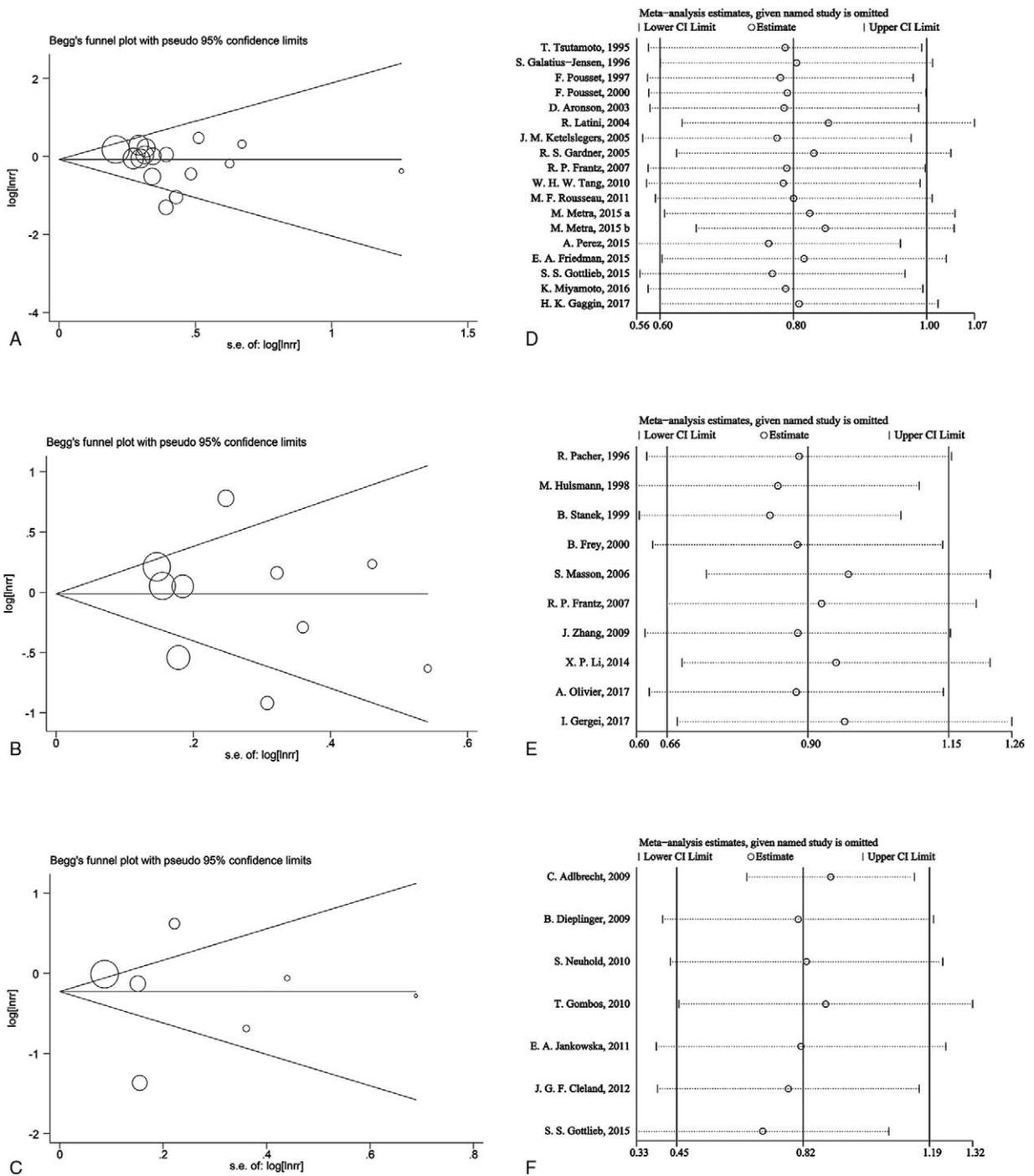


Figure 5. Funnel plots for ET-1 (A), big ET-1 (B), and CT-proET-1 (C); Sensitivity analyses for ET-1 (D), big ET-1 (E), and CT-proET-1 (F). ET-1 = endothelin-1.

However, if it is to be a biomarker, 2 intrinsic deficiencies of ET-1 should not be ignored, that is its low plasma concentration and short half life. The average or median concentration of ET-1 in the included studies ranges from 0.5 to 3.4pmol/L (Table 1), which requests high sensitive detecting methods to measure it. Moreover, circulating ET-1 can be quickly cleared by endothelium cells in pulmonary vascular, resulting in its half life less than 1 minute.^[8] These characters of ET-1 determine a higher risk of deviations between the measured ET-1 concentration in vitro and the real concentration in vivo. Therefore, it is preferable to find an

alternative molecule, which can reflect the content of ET-1 more stably.

Big ET-1 is the inactive precursor of ET-1. The half life of big ET-1 in vivo is much longer than ET-1, which is about 23 minutes.^[53] This character may makes big ET-1 more advantageous than ET-1 to be a prognostic biomarker. However, the amino sequences between ET-1 and big ET-1 are highly similar, which makes it easier to cross-react with each other for unspecific antibodies. Meanwhile, plasma concentration of big ET-1 is very low (Table 1), which also requests a sensitive detecting method.

Beneden et al^[5,4] reported that RIA was more precise than EIA in measuring big ET-1 in severe congestive HF. Consistently, our study suggests that studies using RIA tended to have higher pooled RR than studies using EIA (Table 3). Meanwhile, the heterogeneity of big ET-1 was reduced obviously after subgroup analysis by detecting method. These characters of big ET-1 may also greatly reduce its application prospects to be an independent prognostic biomarker for HF.

CT-proET-1 is derived from proET-1 and in equal molar amounts to ET-1. In contrast to ET-1 and big ET-1, circulating CT-proET-1 level is higher (~80 pmol/L) and less cross-react with other ET-1 peptides.^[12,50] CT-proET-1 is stable and more resistant to rapid turnover both *in vivo* and *in vitro*, which makes it easier to obtain reliable results.^[50] BNP and NT-proBNP are regarded as the pivotal markers for the diagnosis and prognosis of HF. Therefore, we summarized studies that both assayed CT-proET-1 and BNP-related peptides, allowing head-to-head comparison of the prognostic accuracy of these peptides. Notably, among the 5 studies involved,^[12,45,46,48,50] 4 of them showed that the RR of CT-proET-1 was more robust.^[12,45,48,50] Therefore, it may be more prospective to use plasma CT-proET-1 as a potential prognostic biomarker in HF. However, only limited studies were carried out to this area, and more clinical trials are required to certify this hypothesis.

Background diseases and therapies should be considered when using ET-1-related peptides as prognostic markers. Plasma ET-1 concentration is correlate with clinical and hemodynamic severity under pathological conditions.^[55] Big ET-1 is mainly cleared in liver and kidney, as a consequence, plasma level of big ET-1 can be influenced by hepatic or renal dysfunction.^[53] Plasma CT-proET-1 level is correlated with renal function, age, left atrial size, and diastolic blood pressure.^[56] Whether an adjustment of these factors should be made in the determination of the prognostic value of ET-1-related peptides still needs further exploration.

There are several limitations in this study. First, the criteria of HF, background diseases and therapies were different among the included studies. These might be important sources of clinical heterogeneity of this study. Meanwhile, the quality assessment of RCTs by NOS scale may also cause some bias. Second, the primary outcome in our study was adverse outcomes, which might be varied among the studies. Third, 5 of 32 studies reported only with the multivariate or adjusted HR,^[5,26,34,44,47] which might also cause some bias for the prognostic value of ET-1-related peptides.

In summary, there is a close relationship between circulating ET-1-related peptides and the prognosis HF patients. Our study provided the meta-analysis evidence for the prognostic value of ET-1, big ET-1, and CT-proET-1 in predicting mortality or adverse outcomes in HF patients.

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