A meta-analysis of proinflammatory cytokines in chronic heart failure

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ABSTRACT

Background Previous studies suggested that inflammation was involved in chronic heart failure (CHF), but their sample sizes were small.

Objective To summarise the clinical cytokine data systematically and emphasise the importance of proinflammatory cytokines in the pathogenesis of CHF, we conducted a meta-analysis of relevant literatures.

Methods Articles about cytokines and CHF were searched in Pubmed, EMBASE, Cochrane Library, Chinese National Knowledge Infrastructure and Chinese Wanfang Database. The pooled effects were measured by weighted mean difference (MD) and 95% CI, which were calculated by RevMan 5.1 software.

Results Finally, a total of 28 studies were included. Compared with normal control subjects, concentrations of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β and C reactive protein (CRP) in the peripheral blood in CHF patients are significantly increased. The overall MDs with 95% CIs for TNF-α, IL-6, CRP and IL-1β were 2.59 pg/ml (2.14~3.05, p<0.00001), 5.49 pg/mL (4.68~6.29, p<0.00001), 11.45 mg/dL (7.68~15.23, p<0.00001) and 0.11 pg/mL (0.09~0.14, p<0.00001). The mortality of elevated IL-6 group was significantly higher than control group (OR=6.73, 95% CI 2.39~18.93, p=0.0003).

Conclusions Concentrations of TNF-α, IL-6, IL-1β and CRP are significantly higher in CHF patients than in control subjects. Proinflammatory cytokines play an import role in the pathogenesis of CHF.

INTRODUCTION

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. The lifetime risk of developing heart failure is 20% for Americans ≥40 years old. Over 650,000 new cases are diagnosed every year in America.[1 2] Disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels may all lead to heart failure.[2] In the past few years, researchers have realised that immune-inflammatory activation may play an important role in the pathogenesis of chronic heart failure (CHF).[3] Several studies have reported that levels of proinflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β and C reactive protein (CRP) are increased in CHF patients.[4–8] They may also be good predictors for improvement and readmission in CHF.[4 9] However, the sample sizes of these studies are rather small. Moreover, no systematic review with a quantitative synthesis of the cytokines of CHF patients compared to controls has been reported yet. Consequently, in the present study, we systematically reviewed available data and conducted a meta-analysis to enhance the importance of proinflammatory cytokines in the disease process of CHF.

METHODS

Search methods

Two investigators (JC and JK) independently performed electronic searches on cytokines and CHF in Pubmed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database from their inception to November 2nd 2013 with the following terms: TNF-α, IL-6, IL-1β, CRP, cytokine, inflammatory factor, heart failure and cardiac insufficiency. The reference lists of relevant studies were also searched for any additional trials. The language was restricted to English and Chinese.

Inclusion criteria

The inclusion criteria for eligible studies were as follows: (1) studies should be published in a peer reviewed journal; (2) study type should be case control study or cohort study; (3) comparison should be made between CHF patients and normal controls. As for the predictive value of cytokines, CHF patients should be divided into two groups (elevated cytokine group vs control group) and followed-up for at least 12 months; (4) provided sufficient data of cytokine concentrations; (5) sample size should be more than 20. Patients with acute myocardial infarction, chronic inflammatory diseases, autoimmune disease, acute infection, cancer and severe renal failure were excluded. Meeting abstracts, case reports, editorials and reviews were excluded.

Data extraction and quality assessment

In the data extraction process, we collected study type, the first author's name, year of publication, country in which the study was performed, population characteristics, sample size (CHF patients and controls), mean age, gender, sample source, cytokines and measure techniques of each study. Newcastle-Ottawa quality assessment scale (NOS)[10 11] was used to assess the quality of these included studies. A case control study can be awarded a highest score of nine. Data extraction and quality assessment was completed by two investigators (ML and JC) independently. Disagreements were resolved by discussion.

Statistical analysis

In this article, Cochrane Q test and I^2 were used to investigate the heterogeneity. The p value for heterogeneity tests was set at 0.10, others were 0.05. All the p values were 2-tailed. If I^2 >50%, a random-effect model was chosen. Accordingly, we

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ran a fixed-effect model if I^2 <50%. Funnel plot was used to evaluate the publication bias. Weighted mean differences (MD) and 95% CIs were calculated for the concentrations of TNF-α, IL-6 and IL-1β. As for mortality, an OR with 95% CI was selected. All statistical tests were performed with Review Manager 5.1 for Windows available from the Cochrane Collaboration.

RESULTS

Literature search

A total of 1815 citations were found in the initial search. Animal experimental studies were excluded. After removing duplicates and reading the titles, 86 articles were entered into the full text review process. Among them, 38 studies were excluded for improper control groups (not CHF patients vs normal subjects). Double publications were found in 15 studies, which were all from China. Finally, 30 relevant articles[5–8 12–37] met the selection criteria and were included for analysis in this review. In all the eligible studies, samples (serum or plasma) were collected from peripheral blood. TNF-α, IL-6 and IL-1β concentrations were compared in picogram per millilitre (pg/mL). CRP concentration was milligram per decilitre (mg/dL). Three studies [18 36 37] reported the predictive value of IL-6 for the mortality in CHF patients. The mean duration of follow-up was 12–18 months. Flow diagram and main characteristics of included studies were shown in figure 1 and table 1, respectively.

Comparison of TNF-α concentration between CHF patients and control subjects

As shown in figure 2, 19 studies[5–8 16 18–31] incorporating 1852 participants were included in the comparison of TNF-α concentration between CHF patients and control subjects. We selected a random-effect model because of a statistical heterogeneity found in this analysis. To assess the publication bias, a funnel plot was made and shown in figure 3. The results indicated that concentration of TNF-α was significantly higher in CHF patients than control subjects. The overall MD for TNF-α was 2.59 pg/ml (95% CI (2.14 to 3.05), p<0.00001).

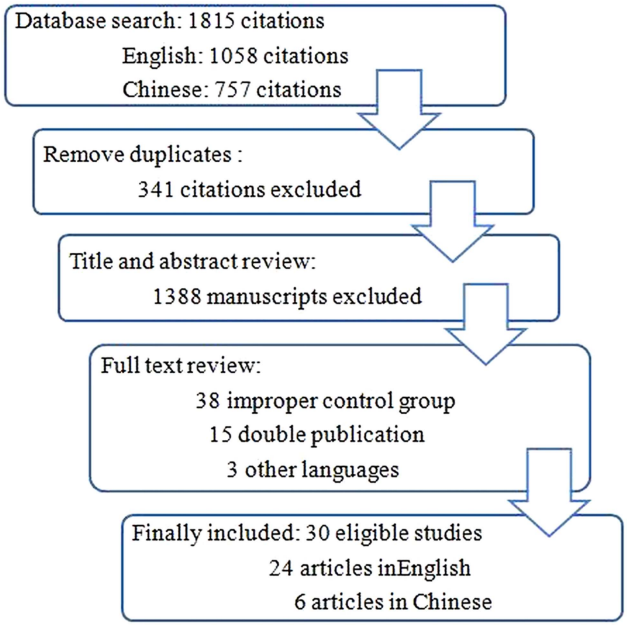

Figure 1 Flow diagram of the literature search process.

Comparison of IL-6 concentration between CHF patients and control subjects

Data of IL-6 concentrations were collected in 733 CHF patients and 688 control subjects from 15 studies.[5 7 8 17–23 26 30 32–34] Cochrane Q test indicated a significant heterogeneity among these studies (p<0.001), I^2 >50%. Accordingly, a random-effect model was selected (figure 4). Compared with normal control subjects, concentration of IL-6 was higher in CHF patients. The overall MD for IL-6 was 5.49 pg/mL (95% CI (4.68 to 6.29), p<0.00001).

Comparisons of CRP and IL-1β concentrations between CHF patients and control subjects

CRP and IL-1β concentrations in CHF patients and normal control subjects were detected in 1167 participants from 10 studies[8 12–15 17 22 31 34 35] and 233 participants from three eligible studies,[5 18 21] respectively. We chose a random-effect model in the pooled analysis for CRP (I^2=99%) and a fixed-effect model in the pooled analysis for IL-1β (I^2=34%). From the results displayed in figure 5, CHF patients had a higher level of CRP concentration. The overall MD for CRP was 11.45 mg/dL (95% CI (7.68 to 15.23), p<0.00001). The concentration of IL-1β was also statistically higher in CHF patients than control subjects (MD 0.11 pg/mL, 95% CI (0.09 to 0.14), p<0.00001; figure 6).

Predictive value of IL-6 for the mortality in CHF patients

There were three studies[18 36 37] that reported the predictive value of IL-6 vis-a-vis mortality. CHF patients were divided into elevated IL-6 group and control group (concentrations of IL-6 <cut-off points). No statistical heterogeneity was found in this analysis (I^2=36%), and a fixed-effect model was selected (figure 7). The mortality of elevated IL-6 group was significantly higher than control group (OR=6.73, 95% CI (2.39 to 18.93), p=0.0003).

DISCUSSION

The findings from our meta-analysis suggest that concentrations of TNF-α, IL-6, IL-1β and CRP in the peripheral blood of CHF patients were significantly higher than in the control subject. The serum level of IL-6 may be a useful marker to predict the mortality in patients with CHF.

Early in 1990, Levine *et al*[38] were the first to report a possible role of proinflammatory cytokines in CHF. They found that circulating levels of TNF were increased in cachectic patients with CHF. Subsequently, more studies concerning the role of proinflammatory cytokines in CHF were published. Kinugawa *et al*[19] measured the serum IL-6 and TNF-α concentration in 84 CHF patients and 34 controls. Results indicated that significantly elevated serum IL-6 and TNF- α levels were found in CHF patients. Increase of IL-1β and CRP in CHF were also reported.[5 15] The Framingham Heart Study[39] included 732 elderly subjects free of prior myocardial infarction and CHF. During the follow-up (mean 5.2 years), 56 subjects developed CHF. A serum CRP level > or =5 mg/dL was associated with a 2.8-fold increased risk of CHF. There was a 60% (TNF- α) to 68% (IL-6) increase in risk of CHF per tertile increment in cytokine concentration. The results indicated that serum proinflammatory cytokines were associated with increased risk of CHF.

In the present study, we have conducted the first meta-analysis of published literatures to emphasise the importance of proinflammatory cytokines in the pathogenesis of CHF. We pooled

Table 1 Main characteristic of included studies

Study	Year	Country	Population	Patient/control	Age (years)	Sample	Cytokines	Technique	NOS
Wu	2008	China	CHF	246/107	57.2/56.9	Serum	CRP	Olympus AU600 automatic biochemical analyser (Japan)	8
Lubrano	2010	Italy	CHF, EF<40%	166/48	64/48	Plasma	IL-6, TNF-α, CRP	ELISA, Immulite System (DPC, Los Angeles, USA)	7
Rodriguez–Reyna	2005	Mexico	Stable CHF	128/35	59/NA	Serum	TNF-α	ELISA	6
Kinugawa	2012	Japan	CHF, EF<45%	106/39	59.2/55.1	Serum	IL-6, TNF-α	CLEIA, Quantikine HS (R&D Systems, Minneapolis, Minnesota, USA)	7
Emdin	2004	Italy	CHF, NYHA I–IV	105/94	66.7/58.9	Plasma	IL-6, TNF-α	Immulite Automated Analyser (DPC, Los Angeles, USA)	7
Kinugawa	2003	Japan	CHF, EF<45%	84/34	59.4/56.7	Serum	IL-6, TNF-α	CLEIA, Quantikine HS (R&D Systems, Minneapolis, Minnesota, USA)	8
Wang	2009	China	CHF, NYHA I–IV	65/32	50.6/51.5	Plasma	IL-6	Immunoradiometric assay	6
Rauchhaus	2000	Germany	CHF	58/19	60/59	Serum	TNF-α	ELISA	8
Haugen	2008	Sweden	CHF, NYHA II–III	54/70	80.1/75.2	Serum	IL-1β, IL-6, CRP, TNF-α	Evidence analyser (Randox Laboratories, UK)	8
Stumpf	2003	Germany	CHF, NYHA II–IV	50/25	66.9/63.6	Serum	CRP, TNF-α	ELISA	8
Wang	2001	China	CHF, NYHA II–IV	48/30	72.8/69.8	Serum	IL-6	ELISA	7
Greig	2008	Spain	CHF, EF<40%	42/15	56/NA	Serum	IL-6, CRP	ELISA	6
Pan	2004	China	CHF, NYHA III–IV	37/44	62/63	Serum	IL-6, TNF-α	ELISA, Quantikine HS (R&D Systems, Minneapolis, Minnesota, USA)	7
Anker	1999	UK	CHF without cachectic	36/15	58.9/57.9	Plasma	IL-1β, IL-6, TNF-α	ELISA, Immunometric enzyme immunoassay (R&D Systems, Minneapolis, Minnesota, USA)	7
Sirera	2003	Spain	CHF, NYHA III–IV	30/30	67/NA	Plasma	IL-6, NF-α	ELISA	6
Milani	1996	Germany	CHF without cachectic	29/25	56/41	Serum	TNF-α	ELISA	8
White	2006	Canada	CHF, NYHA III–IV	29/15	61.9/54.1	Serum	CRP, IL-6	ELISA, Dade Behring N Highly Sensitivity CRP assay (Dade Behring Diagnostics)	6
Liu	2008	China	CHF, NYHA III–IV	46/45	62.2/61.7	Serum	CRP	LETIA (Beckman LX20 automatic biochemical analyser)	7
Kosar	2006	Turkey	CHF, NYHA III–IV	25/33	61.4/60.8	Serum	IL-1β, IL-6, TNF-α, CRP	ELISA	8
Parissis	1999	Greece	Cachectic CHF, NYHA III–IV	25/15	64/57	Plasma	TNF-α	ELISA	7
Zhang	2010	China	CHF, NYHA I–IV	87/35	58.6/57.6	Serum	CRP	HITACHI 7600 automatic biochemical analyser (Japan)	6
Mayer	2005	Germany	CHF, EF<40% NYHA II–III	21/20	57.6/NA	Serum	IL-6, TNF-α	Immunometric enzyme immunoassay (R&D Systems, Minneapolis, Minnesota, USA)	6
Nishigaki	1997	Japan	CHF, NYHA II	20/62	66/62	Serum	IL-6, TNF-α	ELISA	8
Niethammer	2008	Germany	CHF, EF<40%	17/20	70/56	Serum	TNF-α	Quantikine HS (R&D Systems, Minneapolis, Minnesota, USA)	7
Genth–Zotz	2002	UK	CHF, EF≤40%	15/7	65/59	Serum	TNF-α	Quantiglo and Quantikine (R&D Systems, Minnesota, USA)	6
Toth	2006	USA	CHF, NYHA II–IV	10/11	63/70	Serum	CRP, IL-6, TNF-α	ELISA	6
Chen	2011	China	CHF, NYHA II–IV	60/20	62.7/60.5	Serum	CRP	Radioimmunoassay (Dade Behring Diagnostics)	8
Liao	2010	China	CHF, NYHA III	60/50	54–57/ 52–67	Serum	CRP	CL8000 automatic biochemical analyser (Japan)	6
Orus	2000	Spain	CHF, NYHA I–IV	87/-	57/-	Plasma	IL-6	Immunoenzyme assay kits (Medgenix, Belgium)	6
Roig	1998	Italy	CHF, EF<40%	40/-	57/-	Serum	IL-6	Immunoenzyme assay kits (Medgenix, Belgium)	6

CHF, chronic heart failure; CLEIA, chemiluminescence enzyme immunoassay; CRP, C reactive protein; DPC, Diagnostic Products Corporation; EF, ejection fraction; IL, interleukin; LETIA, latex enhanced turbidimetric immunoassay; MN, Minnesota; NA, not available; NOS, Newcastle Ottawa Quality Assessment Scale; NYHA, New York Heart Association; TNF, tumour necrosis factor.

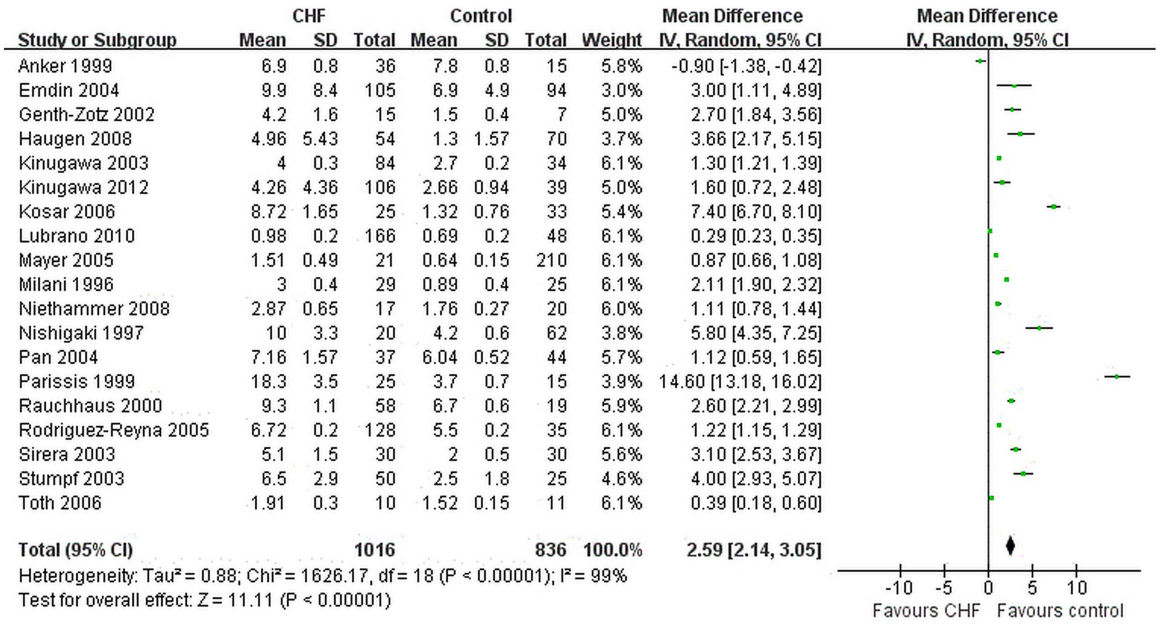

Figure 2 Forest plot displaying random-effect meta-analysis results of difference in TNF-α concentration between chronic heart failure (CHF) patients and control subjects.

and analysed the previous studies together systematically. For each cytokine in the included studies, the measurement unit was the same. However, significant heterogeneity was found in most comparisons. Accordingly, we chose a random-effect model. We thought that the variety of cytokines' measurement techniques in different studies may contribute to this heterogeneity. From the assessment of funnel plot, the publication bias was acceptable. Finally, the pooled results of our study indicated significantly higher proinflammatory cytokines in CHF patients compared with control subjects, which enhanced the importance of the role of proinflammatory cytokines played in the pathogenesis of CHF.

Proinflammatory cytokines are able to modulate cardiac function and ventricular remodelling by a variety of mechanisms. Studies have shown that TNF-α may mediate both negative inotropic effects on the myocardium through direct effects on calcium-dependent processes and impairment of β-adrenergic responsiveness.[3 40] TNF-α may also increase baseline catabolism by stimulating apoptosis and induce myocyte necrosis via a cytotoxic mechanism.[41] IL-6 promotes myocardial hypertrophy, lymphocyte proliferation, and the synthesis of caspases. It can also induce muscle proteolysis *in vitro*, which will lead to wasting and weight loss.[41] IL-1β and TNF-α may also increase the activity of total matrix metalloproteinase, and contribute to ventricular dilation and myocardial failure by promoting the remodelling of interstitial collagen.[42]

Furthermore, proinflammatory cytokines are also reported to be independent predictors of cardiovascular events in older persons. In a cohort study[9] including 2225 participants, blood levels of IL-6, CRP and TNF- α were assessed. After an average follow-up of 3.6 years, IL-6 was significantly associated with all outcomes (incident coronary heart disease, stroke, and congestive heart failure) and CRP was significantly associated with congestive heart failure events. Another study, which enrolled 118

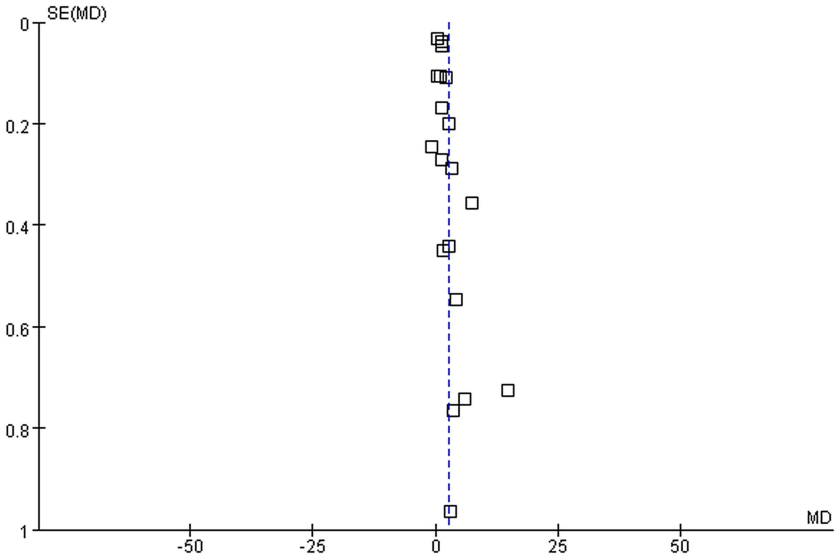

Figure 3 Funnel plot of included studies in the meta-analysis of TNF-α concentration.

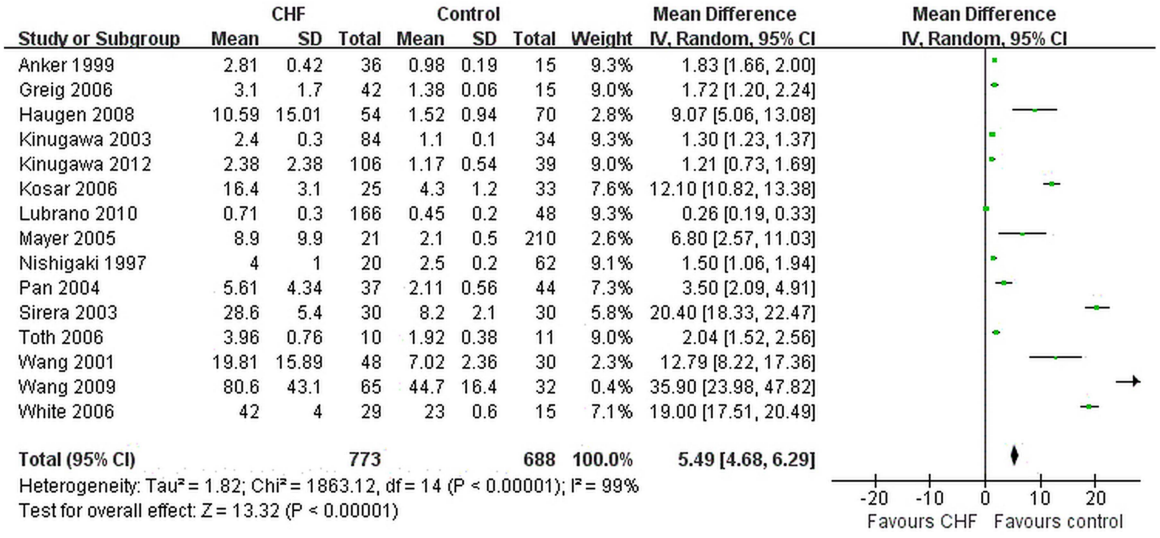

Figure 4 Forest plot displaying random-effect meta-analysis results of difference in IL-6 concentration between chronic heart failure (CHF) patients and control subjects.

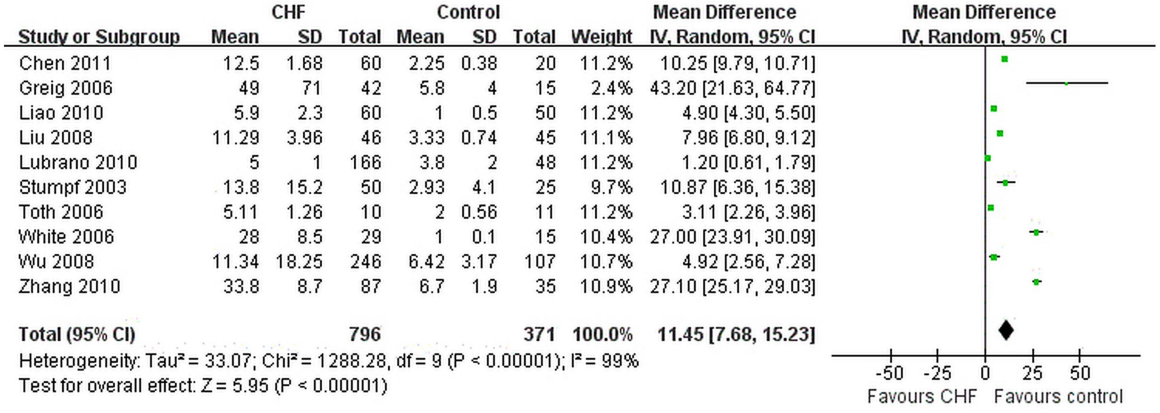

Figure 5 Forest plot displaying random-effect meta-analysis results of difference in C reactive protein concentration between chronic heart failure (CHF) patients and control subjects.

CHF patients, also indicated that the plasma levels of IL-6 and TNF-α and especially the former, were useful markers to gauge the progression of severity and late cardiac death in patients with CHF.[26] Our meta-analysis also indicated that the risk of death was significantly increased in patients with elevated IL-6 concentrations. Summarily, elevated proinflammatory cytokines are associated with the development and prognosis of CHF.

Our study has several limitations. First, there was marked heterogeneity across studies. We have to choose random-effect models, which produce wider CIs. Second, only publications in English and Chinese were considered in our search process. Studies in other languages were lost inevitably. Moreover, the number of eligible studies for meta-analysis of IL-1β was relatively small. Further, only TNF-α, IL-6, IL-1β and CRP levels were scrutinised in the current meta-analysis and other species of proinflammatory cytokines (IL-18) and anti-inflammatory cytokines (IL-10, TGF-β) were not included. Last, throughout the included studies, the cytokines' measurement techniques

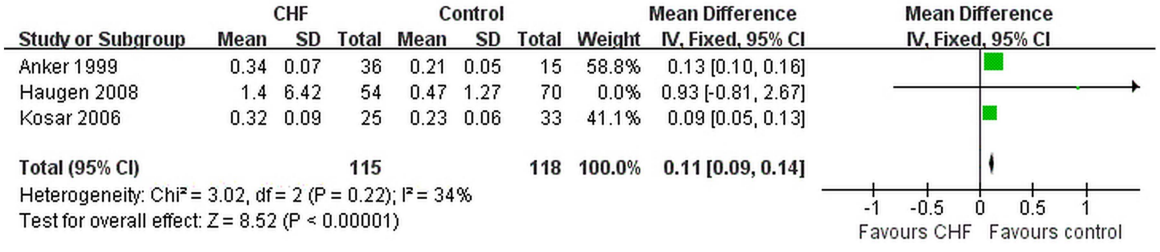

Figure 6 Forest plot displaying fixed-effect meta-analysis results of difference in IL-1β concentration between chronic heart failure (CHF) patients and control subjects.

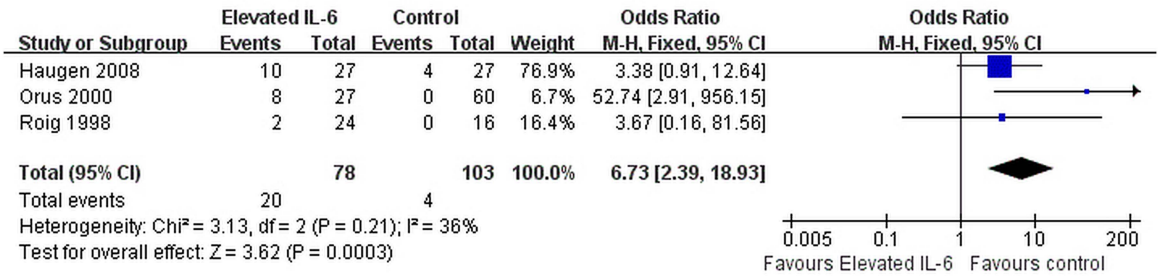

Figure 7 Forest plot comparing mortalities in chronic heart failure (CHF) between the elevated IL-6 group and the control group.

were not the same. As a result, a detection bias cannot be completely excluded in our analysis.

CONCLUSIONS

In summary, the meta-analysis of available evidence indicates that concentrations of TNF-α, IL-6, IL-1β and CRP in CHF patients were significantly higher than in control subjects. Proinflammatory cytokines play an import role in the pathogenesis of CHF, and can be used as outcome predictors in CHF patients.

Contributors Conceived and designed the study: JC, ML and WW. Data searching and extraction: JC, JK and ML. Data analysis: JC, DH. Data interpretation: ML and DH. Writing of paper: ML, JC and WW. Equal contributions were made by ML and JC to this article. The authors did not report any conflict of interest regarding this work and agreed to the final version.

Competing interests None.

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