Growth differentiation factor–15 predicts the prognoses of patients with acute coronary syndrome: a meta-analysis

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Abstract

Background: Recent studies have shown Growth differentiation factor–15 (GDF-15) that is a member of the transforming growth factor β (TGF-β) superfamily might be a potential predictive cytokine for the prognosis of Acute coronary syndrome (ACS). However, there are discrepancies in these studies.

Methods: Publication searches of the PubMed/Medline and EMBASE databases were performed without any time or ethnicity restrictions. The inclusion and exclusion criteria, when clear, were addressed. Random effects models were used for all analyses. Publication bias was tested using funnel plots and the Egger test.

Results: We identified eight eligible studies that provided mortality data. Five of these studies provided recurrent myocardial infarction (MI) data. The maximal duration of follow-up ranged from 6 months to 6 years. A significant association was found between the patients with the highest and lowest GDF-15 levels (overall analyses) in terms of mortality (p < 0.00001; RR = 6.08; 95% CI = 4.79–7.71) and recurrent MI (p < 0.00001; RR = 1.76; 95% CI = 1.49–2.07). We also found significant associations between the subgroup analyses stratified by ACS types, cutoff points and follow-up durations (p < 0.001). The combined hazard ratio was high for GDF-15 to ACS (HR = 1.656, 95% CI = 1.467–1.871).

Conclusion: High plasma GDF-15 levels are associated with an increased risk of mortality and recurrent MI in patients with ACS.

Background

Acute coronary syndrome (ACS), including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP), result from the rupture or erosion of vulnerable atherosclerotic plaque [1], and death and recurrent myocardial infarction (MI) can occur at any time after the first attack episode. Currently, even with medication and coronary intervention, the prognosis for ACS patients is still not good [2]. Therefore, the early evaluation of ACS and its timely treatment are particularly important.

Growth differentiation factor–15 (GDF-15) is a member of the transforming growth factor β (TGF-β) superfamily. GDF-15 primarily regulates multiple cellular functions, as well as the biological processes underlying the growth of multiple organs and the differentiation and renovation of tissues [3]. Researchers have verified that GDF-15 exerts a suppressive function in the progress, invasiveness, and metastasis of tumors by facilitating the apoptosis of tumor cells [4]. In addition, GDF-15 is also related to cardiovascular diseases, such as heart failure [5], cardiac hypertrophy [6], and coronary heart disease (CHD) [7]. Recent studies have shown that GDF-15 might be a potential predictive cytokine for the prognosis of ACS and, therefore, might assist physicians in evaluating the prognoses of ACS patients [8]. Studies examining the association between GDF-15 and ACS prognosis have included research on patient mortality [7, 9–15] and recurrent MI [9–12, 15]. However, there have been discrepancies in these studies, including the target participants, follow-up period, and patient ethnicity. Hence, this meta-analysis was performed to investigate the role of GDF-15 in predicting the prognosis of ACS patients.
Methods

Inclusion criteria
We performed a meta-analysis to determine whether GDF-15 could predict the prognoses of ACS patients. Studies that had a follow-up duration of at least 6 months and that examined the correlation between plasma GDF-15 levels and the prognoses of ACS patients were collected. The quality of each included study has been tested under the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [16]. The MOOSE systemic assessments included the following criteria: 1) a clear explanation of the inclusion and exclusion criteria, 2) the attrition rate of the samples during the follow-up period, 3) a clear explanation of the outcomes and outcome assessments, 4) a sufficient follow-up period, 5) appropriate statistical analyses, and 6) identification of the important confounding and prognostic factors. All items had the following answer options: yes/no/unclear information to answer the question. When a criterion was fulfilled, a score of 1 was given; a score of 0 was given if a criterion was unclear, and –1 was given if a criterion was not achieved. The MOOSE assessment of each study was discussed and carefully evaluated by all authors.

Study selection
The study selection was based on an online search of the PubMed/MEDLINE and EMBASE databases, without any language restrictions; studies published before November 14, 2014 were included. The following medical subject headings were used for the publication search: “ST-segment elevation myocardial infarction, STEMI, Non-ST-segment elevation myocardial infarction, NSTEMI, Unstable angina pectoris, UAP, Acute coronary syndrome, ACS, growth differentiation factor-15, GDF-15, Placental growth factor, PGF, macrophage inhibitory cytokine-1, MIC-1”. The terms were then combined using Boolean operators “OR, AND”. We extracted the data from individual studies that included the first author’s name, year of publication, ethnicity, participants, outcome data (mortality and recurrent MI), and maximal follow-up years, as well as methods that stratified the GDP-15 levels. The extraction was performed by two independent reviewers (SZ and DD).

Statistical analysis
Review Manager 5.3 and STATA 11.0 statistical software were used for the meta-analysis [17]. Statistical heterogeneity was tested using Cochran’s Q statistic and I² tests [18]. The random effects model was used for all meta-analyses. The calculated GDF-15 concentration data were extracted from the initial follow-up, and \( p < 0.05 \) was considered to be statistically significant.

Results

Study selection
We retrieved 73 studies from PubMed/MEDLINE and 186 studies from EMBASE (Fig. 1). After removing duplicates, 158 of 194 studies were excluded based on title and abstract reviews. In the remaining 36 studies, there were seven reviews, nine studies based on animals, nine studies with different participants, and three studies with inadequate data. Finally, eight articles were included in our meta-analysis, including 4 NSTEMI studies, 2 STEMI studies and 2 other studies that did not clearly provide the types of ACS. No unstable angina pectoris data were found.
Characteristics of the individual studies are shown in Table 1. Eight studies, including 8903 participants, investigated the association between GDF-15 and mortality. Five of these studies, including 7193 participants, investigated the association between GDF-15 and recurrent MI. The maximal follow-up duration ranged from 6 months to 6 years.

Association between GDF-15 and the ACS prognosis
In addition to comparing the prognoses of the ACS patients with the highest and lowest GDF-15 levels (overall analyses), we also performed subgroup analyses based on the ACS types and a stratification of the GDF-15 values: <1200 ng/L, 1200–1800 ng/L, and >1800 ng/L. Moreover, based on the included studies, we stratified the follow-up duration into “>1 years” and “≤1 years”. Patient mortality and recurrent MI data were analyzed (Table 2, Additional file 1: Figure S1 and Additional file 2: Figure S2).

For the mortality analyses, a significant association was found in the overall analyses (p < 0.00001, RR = 6.08, 95 % CI = 4.79–7.71) and subgroup analyses of ACS (p < 0.00001, RR = 6.03, 95 % CI = 3.66–9.93), NSTEMI (P < 0.00001, RR = 5.94, 95 % CI = 4.38–8.05) and STEMI (p < 0.00001, RR = 8.24, 95 % CI = 3.35–20.25).

Positive results were also revealed in the subgroup analyses stratified by GDF-15 Cutoff Point (<1200 ng/L vs. 1200–1800 ng/L: p < 0.00001, RR = 2.23, 95 % CI = 1.66–2.99; 1200–1800 ng/L vs. >1800 ng/L: p < 0.00001, RR = 2.76, 95 % CI = 2.28–3.34; and >1800 ng/L vs. <1200 ng/L: p < 0.00001, RR = 6.22, 95 % CI = 4.77–8.10).

As for subgroup analyses stratified by follow-up duration, positive results were also obtained for the ≤1 year (p < 0.00001, RR = 8.83, 95 % CI = 5.32–14.66) and >1 year subgroups (p < 0.00001, RR = 5.47, 95 % CI = 4.18–7.16).

For the recurrent MI analyses, a significant association was observed in the overall analyses (p < 0.00001, RR = 1.76, 95 % CI = 1.49–2.07) and in the subgroup analyses of NSTEMI (p < 0.00001, RR = 1.66, 95 % CI = 1.35–2.03) and ACS (p < 0.00001, RR = 2.02, 95 % CI = 1.56–2.61). A significant association was also found when comparing the following GDF-15 cutoff points: 1200–1800 ng/L vs. >1800 ng/L (p < 0.00001, RR = 1.49, 95 % CI = 1.17–1.89) and >1800 ng/L vs. <1200 ng/L (p < 0.00001, RR = 1.66, 95 % CI = 1.35–2.03). As for the subgroup analyses stratified by the follow-up durations, a positive result was found only in the >1 year follow-up duration (p < 0.00001, RR = 1.84, 95 % CI = 1.54–2.19); we did not find a significant result for follow-up periods ≤1 year (P = 0.08, RR = 1.42, 95 % CI = 0.96–2.08).

Heterogeneity of the current study
High heterogeneity was found in the comparison of the recurrent MI between the GDF-15 levels of <1200 ng/L and 1200 to 1800 ng/L. (I² = 65 %). Heterogeneity was low for all the above mentioned analyses (I² < 27 %).

The combined prognostic data of hazard ratio
Hazard ratio (HR) was obtained in seven studies [7, 9, 10, 12–15], which was on the association of the GDF-15 and mortality or recurrent of MI. However, after sensitivity analysis, we excluded a study [15] that could lead to high heterogeneity to the overall meta-analysis. Our results showed a significant high HR (HR = 1.656, 95 % CI = 1.467–1.871, I² = 0 %) for GDF-15 to the ACS (Fig. 2).

Discussion
Our meta-analysis identified eight studies, including 8903 participants, and attempted to evaluate the predictive value of plasma GDF-15 levels in the prognosis of ACS patients by calculating the risk of mortality and

Table 1 The characteristics of the studies included in the meta-analysis

| Author/year/ethnicity | Participants | Outcomes | Follow-up* | Comparisons (ng/L) | RR [95 %CI]a | MOOSE |
|-----------------------|-------------|----------|------------|-------------------|--------------|--------|
| Kempf T/2009/Europeans [7] | ACS (n = 877) | M | 6 | <1200, 1200–1800, >1800 | 8.5 [3.81, 18.99] | 6 |
| Bonaca MP/2011/Europeans [9] | ACS (n = 3501) | M, R | 2 | <1362 | 4.99 [2.82, 8.83] | 5 |
| Wollert KC/2007(1)/Europeans [10] | NSTEMI (n = 2079) | M, R | 2 | <1200, 1200–1800, >1800 | 6.11 [3.35, 11.16] | 6 |
| Damman P/2014/Europeans [11] | NSTEMI (n = 1115) | M, R | 5 | <1200, 1200–1800, >1800 | 5.54 [3.18, 9.64] | 6 |
| Wollert KC/2007(2)/Europeans [12] | NSTEMI (n = 2081) | M, R | 1 | <1200, 1200–1800, >1800 | 9.12 [4.93, 16.85] | 4 |
| Eggers KM/2010/Europeans [13] | NSTEMI (n = 950) | M | 5 | <1200, 1200–1800, >1800 | 4.3 [2.44, 7.58] | 6 |
| Kempf T/2007/Europeans [14] | STEMI (n = 741) | M | 1 | <1200, 1200–1800, >1800 | 6.66 [2.43, 18.23] | 6 |
| Eitel I/2011/Europeans [15] | STEMI (n = 238) | M, R | 0.5 | <1319 | 19 [2.58, 139.66] | 4 |

SAP stable angina pectoris, ACS acute coronary syndrome, NSTEMI non-ST-elevation myocardial infarction, STEMI ST-elevation myocardial infarction, M mortality, R recurrent MI, *the maximum follow up year, †the calculated risk ratio based on the mortality, MOOSE meta-analysis of observational studies in epidemiology.
Table 2 The association between GDF-15 concentration and ACS prognosis

| Comparison                        | Participants | RR [95 %CI]   | p value   | I²  |
|-----------------------------------|--------------|---------------|-----------|-----|
| **Mortality**                     |              |               |           |     |
| ACS type                          |              |               |           |     |
| Overall                           | 8903         | 6.08 [4.79, 7.71] | <0.00001  | 0 % |
| ACS                               | 4123         | 6.03 [3.66, 9.93] | <0.00001  | 11 %|
| NSTEMI                            | 4038         | 5.94 [4.38, 8.06] | <0.00001  | 8 % |
| STEMI                             | 742          | 8.24 [3.35, 20.25] | <0.00001  | 0 % |
| Cutoff Point                      |              |               |           |     |
| <1200 VS 1200–1800                | 5551         | 2.23 [1.66, 2.99] | <0.00001  | 0 % |
| 1200–1800 VS >1800                | 4985         | 2.76 [2.28, 3.34] | <0.00001  | 0 % |
| <1200 VS >1800                    | 5164         | 6.22 [4.77, 8.10] | <0.00001  | 0 % |
| Follow up duration                |              |               |           |     |
| >1 years                          | 6744         | 5.47 [4.18, 7.16] | <0.00001  | 0 % |
| ≤1 years                          | 2159         | 8.83 [5.32, 14.66] | <0.00001  | 0 % |
| **Recurrence of MI**              |              |               |           |     |
| ACS type                          |              |               |           |     |
| Overall                           | 7193         | 1.76 [1.49, 2.07] | <0.00001  | 5 % |
| ACS                               | 3501         | 2.02 [1.56, 2.61] | <0.00001  | NA  |
| NSTEMI                            | 3454         | 1.66 [1.35, 2.03] | <0.00001  | 0 % |
| STEMI                             | 238          | 1.00 [0.39, 2.58] | 1.00       | NA  |
| Cutoff Point                      |              |               |           |     |
| <1200 VS 1200–1800                | 3766         | 1.10 [0.75, 1.59] | 0.64      | 65 %|
| 1200–1800 VS >1800                | 3402         | 1.49 [1.17, 1.89] | 0.0010    | 27 %|
| <1200 VS >1800                    | 3454         | 1.66 [1.35, 2.03] | <0.00001  | 0 % |
| Follow up duration                |              |               |           |     |
| >1 years                          | 5538         | 1.84 [1.54, 2.19] | <0.00001  | 5 % |
| ≤1 years                          | 1655         | 1.42 [0.96, 2.08] | 0.08      | 0 % |

NA not applicable, the units of GDF-15 concentration is ng/L.

Fig. 2 Funnel plots of GDF-15 with mortality and recurrent MI
recurrent MI after the ACS events. We found that higher GDF-15 levels indicated a higher risk for ACS mortality and recurrent MI. This association also remained when the GDF-15 levels were stratified by the cutoff point, which might be valuable in terms of the risk stratification of ACS prognoses because it has been previously reported that 1800 ng/L GDF-15 levels may be an ideal cutoff value for several disease states [19]. Moreover, we also found significant associations between GDF-15 levels and subsequent ACS events. Furthermore, we found high HR for GDF-15 to ACS. These findings might assist with monitoring the prognoses of ACS patients.

GDF-15 has been described as a promising cardioprotective agent [20]. Previous studies have reported that higher expression levels of GDF-15 could predict deteriorating conditions for heart disease patients, particularly ACS patients, independent of troponin or BNP levels [7, 9–15]. It has also been reported that GDF-15 plays a protective role in heart disease, which may be attributed to the anti-apoptotic, anti-inflammatory, or anti-hypertrophic effects demonstrated in animal models [21, 22]. Moreover, GDF-15 might induce angiogenesis, which plays an essential role in the recovery of damaged myocardium [23]. A prolonged increase in GDF-15 levels after episodes of ischemia and reperfusion may be associated with increased levels of oxidative stress, inflammation, and infarct healing, and the increase of GDF-15 requires for enhanced oxidative metabolism and tissue repair [9]. Accordingly, one feasible explanation for the predictive role of GDF-15 is that higher levels of GDF-15 indicate a greater extent of myocardium damage and the risk of adverse remodeling. GDF-15 is also strongly induced in other cardiovascular conditions, such as heart failure [21], Takotsubo cardiomyopathy [24], and atherosclerosis [25].

In this meta-analysis, clear inclusion and exclusion criteria were required for study inclusion. The quality of the current study was well assessed using the MOOSE system. There was no publication bias, according to the funnel plots (Fig. 3). Heterogeneity was high among the “<1200 ng/L vs. 1200–1800 ng/L” subgroup of recurrent MI patients. The following sensitive test showed that this heterogeneity disappeared ($I^2 = 0\%$) when we removed an included study from the Netherlands [11], thus indicating that the heterogeneity might have resulted from ethnicity differences, as the remaining two studies included samples from Sweden. The other comparisons showed low or no heterogeneity ($I^2 < 27\%$), suggesting that our study results were reliable.

There are ethnic differences in GDF-15 levels. In Europeans, the median GDF-15 concentration ranged from 1244 to 1635 ng/L, whereas it was much lower in Asians (650 ng/L) [26]. However, the Asian study cohort was limited in number, and future well-designed studies with different ethnicities are warranted.

**Limitations**

Although individual patient data from eight eligible studies were included in our meta-analysis, this study had some limitations. First, the definitions of all-cause mortality and cardiovascular mortality were not confirmed. Among the studies included, only two studies provided detailed information [7, 9]. For the recurrent MI patients without causes of death, we only performed subgroup analyses for “recurrent MI”. Second, although the revealed heterogeneity was low for most of the comparisons, GDF-15 levels might be influenced by many factors, including age, male gender, current smoking, symptomatic heart failure, reduced kidney function, and diabetes mellitus, among others [27]. Third, the ACS patients were treated with different treatment strategies, which might alter the GDF-15 levels. Fourth, the
obtained blood samples were extracted at different times, therefore the GDF-15 levels may change by different time after ACS events, however, evidence found that GDF-15 levels showed small alterations several months after ACS events [28], hence, we could not give a judgment if the different time of the tests of the GDF-15 would influence our findings. Fifth, the follow-up durations differed in each study. In addition, one study [13] recorded the initial mortality rate 6 months after the ACS occurred, which might slightly alter our study results. Sixthly, the HR of different studies were obtained at different time after the ACS happened, which may slightly influence the results, however, the combined data showed no heterogeneity ($I^2 = 0\%$).

**Conclusion**

The present study suggests that GDF-15 is a strong predictor of mortality and recurrent MI in ACS prognosis. Thus, it has the potential to become a clinically useful novel biomarker that can provide independent prognostic information and also help to direct optimal treatment strategies. Current ongoing clinical trials are needed to further clarify the benefits of GDF-15 in predicting the prognoses of patients with acute coronary syndrome.

**Ethics**

This study is not involved in any ethical issues.

**Additional files**

***Additional file 1: Figure S1.*** Forest plots of GDF-15 with mortality. (TIF 28 kb)

***Additional file 2: Figure S2.*** Forest plots of GDF-15 with recurrent of MI. (TIF 25 kb)

**Abbreviations**

GDF-15: growth differentiation factor–15; ACS: acute coronary artery syndrome; MI: myocardial infarction; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; UAP: unstable angina pectoris; CHD: coronary heart disease; MOOSE: meta-analysis of observational studies in epidemiology.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

HC, SZ, DD and XW designed this meta-analysis. DO, HZ, HJ, RJ collected and extracted the data of this meta-analysis. LJ and QL, FY and XW calculated the data. HC, SZ, DD and XW written this meta-analysis. All authors read and approved the final manuscript.

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**Financial competing interests or non-financial competing interests**

This study is not involved in any conflicts of financial competing interests or non-financial competing interests.

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