Review

Growth-differentiation factor-15 predicts adverse cardiac events in patients with acute coronary syndrome: A meta-analysis

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A B S T R A C T

Background: We aimed to analyse the association between high-level growth-differentiation factor-15 (GDF-15) and mortality, recurrent MI and heart failure compared to low-level GDF-15 in patients with acute coronary syndrome (ACS).

Methods: PubMed and EMBASE were searched from their commencement to December 2017 for qualified studies that evaluated the associations between GDF-15 and ACS. Risk ratios were synthesized with random effect meta-analysis. Publication bias and sensitivity analyses were also conducted.

Results: A total of thirteen studies and 43,547 participants were analyzed systematically in our meta-analysis. Our study showed a significant association between GDF-15 values and mortality (p = 0.000; RR = 6.75; 95% CI = 5.81–7.84) and recurrent MI (p = 0.000; RR = 1.95; 95% CI = 1.72–2.21) in the overall analyses. Subgroup analyses revealed similar results. However, there was evidence of heterogeneity in the study of heart failure, whose overall RR was 6.66, with an I² of 87.3%.

Conclusion: There was a significant association between high-level GDF-15 and mortality, recurrent MI in patients with ACS. We need more data to research the risk stratification of heart failure in ACS patients in the future.

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1. Introduction

Plaque rupture or erosion with overlying thrombosis in coronary artery was considered to be the main initiating mechanism of ACS [1]. Despite we have made remarkable advances in early reperfusion of ischemic coronary artery, patients who admitted with ACS were still at high risk of death and recurrent MI. It was necessary to identify urgent condition and adopt effective measures or health care. Several risk scores rely on clinical characteristics and physiological parameters have therefore been developed to improve risk stratification [2–5], at the same time, some biochemical markers were also used to further optimize treatment strategies [6–9].

N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), cardiac troponin I (cTnI), creatinine kinase-MB isoenzyme (CK-MB) were common biochemical markers for early diagnostic assessment in patients with ACS. However, there were limited data to support the predictive value of CRP and recent study showed CRP was weak to predict future cardiovascular risk [10–13]. On the other hand, NT-proBNP was effected by age, gender, body weight, and renal function, it seemed not suitable for lower-risk chest pain patients [14,15]. What’s more, cTnI and CK-MB were not elevated within the first few (≤6) hours, they were not suitable for early evaluation of patients suspected of having ACS. It gave us the impression that traditional biochemical markers worked inferior to novel GDF-15.

GDF-15 was a member of the transforming growth factor-b cytokine superfamily [16–18], which was strongly induced in the heart for cellular protection during the process of ischemia and reperfusion injury [19]. Several studies have reported associations between the circulating levels of GDF-15 and mortality · recurrent MI or heart failure in patients with ACS [20–32]. However, its prognostic value was disorganized concerning follow-up time · types of ACS or GDF-15 levels. Therefore, in this meta-analysis, we aimed to combine data from above large-scale articles to provide an adequate method for risk stratification and offer insight into prognosis in patients with ACS.

Abbreviations: GDF-15, growth-differentiation factor-15; ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRP, C-reactive protein; cTnI, cardiac troponin I; CK-MB, creatinine kinase-MB isoenzyme; RR, risk ratio; CI, confidence intervals; OR, odds ratio; NOS, Newcastle-Ottawa Scale; AR, a third reviewer; CAD, coronary artery disease; CVD, cardiovascular disease; PTE3K, phosphoino- sride 3-0H kinase; F, heart failure; M, mortality; R, recurrent myocardial infarction; Q, quarter.

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2. Methods

2.1. Literature search

Study quality was evaluated by Newcastle-Ottawa Scale criteria. We identified relevant studies in PubMed, EMBASE from their commencement to December 2017 using the following search strategy with the terms (“st elevation myocardial infarction” or “st elevated myocardial infarction” or “stemi” or “non-st elevated myocardial infarction” or “nstemi” or “non-st-elevation myocardial infarction” or “non-st-segment elevation myocardial infarction” or “unstable angina” or “uap” or “acute coronary syndrome” or “acs” and (“growth differentiation factor 1” or “macrophage inhibitory cytokine 1” or “prostate differentiation factor” or “differentiation factor, prostate” or “gdf-15” or “placental growth factor” or “pgf” or “mic-1”). The references of recent review articles and related meta analyses were searched for additional studies.

2.2. Study selection and quality assessment

The eligibility criteria were as follows: [1] the included studies were written in English, [2] Patients were eligible if admitted with chest pain suggestive of an ACS including NSTEMI, UA [33], STEMI [34], [3] studies comparing the risk of mortality, recurrent MI or heart failure in patients with ACS depending on the circulating levels of GDF-15, [4] the studies provided original data such as the number of mortality, recurrent MI or heart failure in different levels of GDF-15, the odds ratio (OR) or risk ratio (RR), 95% confidence intervals (CIs), or enough raw data to allow calculation of the risk estimates. The observational studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) criteria. The concrete content consists of the following items: patient selection, comparability, and ascertainment of outcome, with a score ranging from zero to nine. Any disagreements in abstracted data were adjudicated by a third reviewer (AR).

2.3. Data extraction and quality evaluation

Standard information was extracted independently by 2 reviewers according to the inclusion criteria and placed into a spreadsheet. The data extracted from each paper included first author, year of publication, country, follow-up period, number of patients in different levels of GDF-15, and adverse events.

2.4. Statistical analysis

We used the STATA 14.0 statistics software (StataCorp LP, College Station, TX) to calculate the available data from each study. The random effect model was used to calculate the summary RR and its 95% CI in all meta-analyses. We assessed heterogeneity using I² statistics. Subgroup analysis was performed to explore the differences across ACS categories, follow-up time and the levels of GDF-15. We used graphical examination of funnel plots and Begg’s test to appraise the publication bias. A two-tailed p-value <0.05 was considered indicative for statistical significance except in the presence of heterogeneity.

3. Results

We identified 255 potentially relevant articles (89 articles from PubMed, 166 articles from EMBASE) with regard to the association between GDF-15 and ACS after the initial literature search. After 80 duplicate articles, 8 animal/in vitro studies, 1 meta, 11 meeting abstracts, 30 reviews were excluded based on titles or abstracts, we had 125 articles for further evaluation by reading full text. Finally, 13 articles were deemed eligible in our meta-analysis, others were excluded for lacking sufficient data or no relevant exposure. The details of the search and literature review process were shown in Fig. 1. Among the included articles, 5 were from Germany [25-27,29,30], 5 were from the Sweden [20,22-24,28], 2 were from U.S. [21,31], 1 was from Netherland [32].
The quality of the included studies was assessed by Newcastle-Ottawa Scale (NOS) criteria, and all studies scored equal to or greater than five in NOS.

3.1. GDF-15 values and the ACS prognosis

After comprehensively analyzing the included studies, we decided to compare the prognostic value of GDF-15 in patients with ACS by the highest and lowest GDF-15 levels, because they were divided into three groups or quadrisected in different articles. When overall analyses were accomplished, including mortality, recurrent MI and heart failure, we performed subgroup analyses as follow: 1) GDF-15 values: <1200 ng/L, 1200–1800 ng/L, >1800 ng/L or Q1, Q2, Q3, Q4; 2) follow-up time: “≤1 years”, “<1 years”; 3) ACS categories: STEMI, NSTEMI, ACS (no specific differentiates) (Table 1, Fig. 2, Fig. 3, Fig. 4).

First, we conducted meta-analyses to evaluate the association between GDF-15 values and mortality in ACS patients, pooled results revealed a RR of 1.91, (p = 0.000, 95% CI: 1.22–2.95), indicating that high GDF-15 values were correlated with elevated risk of recurrent MI in ACS patients. Then we conducted the subgroup analyses by different GDF-15 cutoff point values, follow-up time and ACS categories (detailed groups were described above), the pooled results were also shown in Table 2. In general, there was no obvious different risk of recurrent MI when ACS patients with GDF-15 valued 1200–1800 ng/L compared to those with GDF-15 valued <1200 ng/L (p = 0.072). However, patients with GDF-15 valued >1800 ng/L had a higher risk of recurrent MI compared to those with GDF-15 valued 1200–1800 ng/L (p = 0.000), the same results were found when group of more than1800 ng/L compared to group of <1200 ng/L (p = 0.000), Q2 compared to Q1 (p = 0.000), Q3 compared to Q1 (p = 0.000), Q4 compared to Q1 (p = 0.000), Q4 compared to Q1 (p = 0.001), Q4 compared to Q2 (p = 0.000), as well as Q4 compared to Q3 (p = 0.000). Statistically significant results in subgroup analyses conducted by ACS categories and follow-up time, indicating an association between high GDF-15 values and increased risk of recurrent MI both in NSTEMI patients (p = 0.000) and STEMI patients (p = 0.000), as well as in ACS patients without specific differentiates (p = 0.000), and no matter the follow-up time was less than or equal to 1 year (p = 0.000) or more than1 year (p = 0.000).

Second, we conducted meta-analyses to evaluate the association between GDF-15 values and recurrent MI in ACS patients, pooled results revealed a RR of 1.95, (p = 0.000, 95% CI: 1.72–2.21), indicating that high GDF-15 values were correlated with elevated risk of recurrent MI in ACS patients. Then we conducted the subgroup analyses by different GDF-15 cutoff point values, follow-up time and ACS categories (detailed groups were described above), the pooled results were also shown in Table 2. In general, there was no obvious different risk of recurrent MI when ACS patients with GDF-15 valued 1200–1800 ng/L compared to those with GDF-15 valued <1200 ng/L (p = 0.072). However, patients with GDF-15 valued >1800 ng/L had a higher risk of recurrent MI compared to those with GDF-15 valued 1200–1800 ng/L (p = 0.000), the same results were found when group of more than1800 ng/L compared to group of <1200 ng/L (p = 0.000), Q2 compared to Q1 (p = 0.000), Q3 compared to Q1 (p = 0.000), Q4 compared to Q1 (p = 0.000), Q4 compared to Q1 (p = 0.001), Q4 compared to Q2 (p = 0.000), as well as Q4 compared to Q3 (p = 0.000). Statistically significant results in subgroup analyses conducted by ACS categories and follow-up time, indicating an association between high GDF-15 values and increased risk of recurrent MI both in NSTEMI patients (p = 0.000) and in ACS patients without specific differentiates (p = 0.000), no matter the follow-up time was less than or equal to 1 year (p = 0.000) or more than1 year (p = 0.000), but this relationship was not showed in STEMI patients (p = 0.232).

Finally, we conducted meta-analyses to evaluate the association between GDF-15 values and heart failure in ACS patients, pooled results revealed a RR of 6.66, (p = 0.000, 95% CI: 2.94–15.1), indicating that high GDF-15 values were correlated with elevated risk of heart failure in ACS patients.

4. About heterogeneity

High heterogeneity was found during the comparison of GDF-15 values for recurrent MI in the overall analyses (I² = 45.8%), subgroup analyses of ACS (I² = 64.4%) and ≤1 year (I² = 59.6%), after we omitted one study (Hagström E/2016/Sweden) by conducting both sensitive
**Fig. 2.** Forest plot showing the RR and 95% CI for mortality for studies comparing the highest and lowest GDF-15 levels.

**Fig. 3.** Forest plot showing the RR and 95% CI for recurrent MI for studies comparing the highest and lowest GDF-15 levels.
analysis and Galbraith plot, we got lower $I^2$ value of overall analyses ($I^2 = 0\%$), ACS ($I^2 = 12.6\%$) and ≤ 1 year ($I^2 = 33.3\%$). About the relationship between GDF-15 values and heart failure, $I^2$ was 87.3\%, the probable reasons may be only two articles were involved, and they had different follow-up time (2 years VS 1 year) and inclusion criteria (NSTEMI vs ACS).

Figure 4. Forest plot showing the RR and 95% CI for heart failure for studies comparing the highest and lowest GDF-15 levels.

Table 2
GDF-15 concentration and adverse cardiac events

<table>
<thead>
<tr>
<th>Adverse cardiac events</th>
<th>Stratification group (ng/L)</th>
<th>No. of studies (study size)</th>
<th>RR (95%CI)</th>
<th>p-value</th>
<th>$I^2$(%)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Overall</td>
<td>13(1057,1068/108,1406)</td>
<td>6.75[5.81–7.84]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.840</td>
</tr>
<tr>
<td>Cutoff Point</td>
<td>1200–1800 VS 1200</td>
<td>8(184,3633/112,5439)</td>
<td>2.46[1.95–3.11]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.687</td>
</tr>
<tr>
<td></td>
<td>&gt;1800 VS 1200–1800</td>
<td>8(420,2611/184,3633)</td>
<td>2.80[2.36–3.32]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.977</td>
</tr>
<tr>
<td></td>
<td>Q2 VS Q1</td>
<td>3(121,6741/81,6772)</td>
<td>1.49[1.13–1.97]</td>
<td>0.005</td>
<td>0.0</td>
<td>0.857</td>
</tr>
<tr>
<td></td>
<td>Q3 VS Q1</td>
<td>3(221,6642/81,6772)</td>
<td>2.70[2.10–3.48]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.379</td>
</tr>
<tr>
<td></td>
<td>Q4 VS Q1</td>
<td>3(566,6291/81,6772)</td>
<td>6.98[5.54–8.79]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.955</td>
</tr>
<tr>
<td></td>
<td>Q2 VS Q2</td>
<td>3(221,6642/121,6741)</td>
<td>1.82[1.46–2.27]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.519</td>
</tr>
<tr>
<td></td>
<td>Q4 VS Q2</td>
<td>3(566,6291/121,6741)</td>
<td>4.68[3.85–5.67]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.519</td>
</tr>
<tr>
<td></td>
<td>Q4 VS Q3</td>
<td>3(566,6291/221,6642)</td>
<td>2.53[1.98–3.22]</td>
<td>0.000</td>
<td>46.3</td>
<td>0.155</td>
</tr>
<tr>
<td>ACS type</td>
<td>NSTEMI</td>
<td>5(292,2773/56,3503)</td>
<td>6.15[4.63–8.18]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.470</td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
<td>3(181,1601/23,1644)</td>
<td>6.97[4.53–10.72]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.592</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>5(584,6307/129,8920)</td>
<td>7.33[5.14–8.75]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.953</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>≤ 1 year</td>
<td>8(822,7886/150,1041)</td>
<td>7.33[5.14–8.75]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.953</td>
</tr>
<tr>
<td></td>
<td>Q2 VS Q1</td>
<td>3(238,6624/158,6695)</td>
<td>1.50[1.23–1.83]</td>
<td>0.000</td>
<td>44.5</td>
<td>0.179</td>
</tr>
<tr>
<td></td>
<td>Q3 VS Q1</td>
<td>3(318,6545/158,6695)</td>
<td>2.01[1.66–2.42]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.911</td>
</tr>
<tr>
<td></td>
<td>Q4 VS Q1</td>
<td>3(423,6434/158,6695)</td>
<td>2.66[2.22–3.19]</td>
<td>0.000</td>
<td>1.0</td>
<td>0.364</td>
</tr>
<tr>
<td></td>
<td>Q2 VS Q2</td>
<td>3(318,6545/238,6624)</td>
<td>1.34[1.13–1.57]</td>
<td>0.001</td>
<td>0.0</td>
<td>0.490</td>
</tr>
<tr>
<td></td>
<td>Q4 VS Q3</td>
<td>3(423,6434/238,6624)</td>
<td>4.68[3.85–5.67]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.441</td>
</tr>
<tr>
<td></td>
<td>Q3 VS Q2</td>
<td>3(423,6434/318,6545)</td>
<td>1.33[1.16–1.53]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.480</td>
</tr>
<tr>
<td>ACS type</td>
<td>NSTEMI</td>
<td>4(251,2587/165,3037)</td>
<td>1.85[1.53–2.23]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.745</td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
<td>2(70,1395/31,1434)</td>
<td>1.79[0.69–4.67]</td>
<td>0.232</td>
<td>70.5</td>
<td>0.066</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>3(249,2211/233,4713)</td>
<td>2.02[1.64–2.48]</td>
<td>0.000</td>
<td>12.6</td>
<td>0.318</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>≤ 1 year</td>
<td>6(270,3904/272,5873)</td>
<td>1.96[1.54–2.49]</td>
<td>0.000</td>
<td>33.3</td>
<td>0.186</td>
</tr>
<tr>
<td></td>
<td>Q2 VS Q1</td>
<td>3(291,2299/177,2771)</td>
<td>1.95[1.63–2.34]</td>
<td>0.000</td>
<td>0.0</td>
<td>0.917</td>
</tr>
<tr>
<td></td>
<td>Q3 VS Q2</td>
<td>3(218,2105/61,4216)</td>
<td>6.66[2.94–15.1]</td>
<td>0.000</td>
<td>87.3</td>
<td>0.005</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CI, confidence interval; GDF-15, growth-differentiation factor-15; NSTEMI, non-set-segment elevation myocardial infarction; MI, myocardial infarction; RR, risk ratio; STEMI, set-segment elevation myocardial infarction; Q, quartern; Number of adverse events with high GDF-15 value, Number of no adverse events with high GDF-15 value/Number of adverse events with low GDF-15 value, Number of no adverse events with low GDF-15 value; p-valuea reflects the heterogeneity, p-valueb < 0.10 was considered statistically significant; p-value < 0.05 was considered statistically significant.
5. Discussion

This meta-analysis covered 13 studies with 43,547 participants, and the results suggested that there was a significant association between GDF-15 values and mortality and recurrent MI in the overall analyses. Subgroup analyses revealed similar results. GDF-15 predicts adverse cardiac events in patients with ACS and may guide further optimize treatment strategies.

Currently, analysis of the highly sensitive troponin testing was usually used for an accurate diagnosis of ACS patients in the emergency department. However, with the early and accurate diagnosis of ACS, its high sensitivity usually led to a misattribution of the severity of the disease, which may result in a more aggressive therapeutic approach, such as an increased rate of percutaneous coronary intervention, longer hospitalization time or higher drug dosages. To provide incremental prognostic information, the application of the TIMI and GRACE score was gradually promoted in the clinical practice, but they were based only on clinical characteristics [35-40]. The angiographic extent of coronary artery disease (CAD) was confirmed as a predictor of cardiovascular disease (CVD) [39,40], and similarly, other admission biomarkers can help to improve risk stratification in comparison to clinical characteristics alone. For Better triage and therapeutic decision making provided better patient outcome and lower health-care costs, we choose the independent predictive biomarker - GDF-15, but not the common elevated levels of NT-proBNP, CK-MB, which possibly resulted in a final diagnosis of non-cardiac disease or influenced by other factors [14,15,41].

The level of GDF-15 provides independent prognostic information on the risk of adverse event in patients with ACS [31], GDF-15 on admission is an objective tool to aid the physician in the early recognition of high-risk patients in the emergency department. As our study showed, high GDF-15 values predicted high risk of mortality, recurrent MI and heart failure in patients after the ACS events, that meant patients with ACS presenting with an elevated GDF-15 level would benefit from aggressive treatment, for example an intensified preventive therapy and early revascularization [25]. What’s more, a validated ELISA had been established for determining the concentration of GDF-15 [42], simple and quick operation would make it more convenient to carry out in the emergency department.

GDF-15 was a distant member of the transforming growth factor-β superfamily [43] maintaining tissue homeostasis and adaptation. When ischemia and reperfusion injury happened, the expression of it was significantly upregulated via phosphoinosito-3-OH kinase (PI3K) and Akt-dependent signaling pathways, GDF-15 protected cardiomyocytes from apoptotic [44], thus, as our meta-analysis revealed, GDF-15 value predicted the degree of stress response and the risk of serve cardiovascular events.

However, our conclusions were tempered for some reasons. First of all, during the comparison of GDF-15 values and the risk of recurrent MI, the overall link was moderate with a global RR of 1.95, but for the prognosis of mortality, the link was stronger (6.75), although they were all statistically significant. Empirically, a strong prognostic factor might be defined as one that has at least a twofold increased RR [45]. Second, Among the studies included, only two article involved heart failure from apopotic [44], thus, as our meta-analysis revealed, GDF-15 value and time of heart failure to assess the incidence of it, and GDF-15 enlighten us to collect more cases with ACS involving GDF-15 value and time of heart failure to assess the incidence of it, the result of coronary angiography and type of ACS would be preferable. Lastly, all included case-control studies in this meta-analysis were satisfactory and met our inclusion criterion.

6. Study limitations

Our meta-analysis has several limitations. First, all included studies were performed in European population, influenced by body type, living habit, the results may be circumscribed. Second, Studies may have differed in the baseline characteristics included (age, male gender, medical history, coronary angiography, therapeutic options), GDF-15 levels might be influenced [26-28,31,46]. Third, there was no consistent standard for cut-off values, our subgroup analysis was performed according to the values (GDF-15 values: <1200 ng/L, 1200–1800 ng/L, >1800 ng/L or Q1, Q2, Q3, Q4). Though our results showed high GDF-15 value predict high risk of adverse cardiac events, we were unable to determine the optimized cutoff value for predicting prognoses. Lastly, even though a funnel plot and Begg’s test showed no publication bias in our meta-analysis, the possibility of publication bias may still exist since only fully published studies and studies in English were included.

7. Conclusion

In conclusion, we have showed that there was a significant association between GDF-15 and mortality and recurrent MI in patients with ACS. GDF-15 was valuable for early risk stratification and therapeutic decision making, its impact on resource utilization, health-care costs, and patient outcome may have far-reaching meaning for emergency medicine development. We need more data to research the risk stratification of heart failure in ACS patients in the future.

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Statement of competing interests

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