



Review

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

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ARTICLE INFO

Article history:

Received 28 November 2018

Received in revised form 20 March 2019

Accepted 18 April 2019

Keywords:

STEMI

Unstable angina

Acute coronary syndrome

Growth-differentiation factor-15

Meta-analysis

ABSTRACT

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 I^2 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].

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; CIs, confidence intervals; OR, odds ratio; NOS, Newcastle-Ottawa Scale; AR, a third reviewer; CAD, coronary artery disease; CVD, cardiovascular disease; PI3K, phosphoinositide 3-OH kinase; F, heart failure; M, mortality; R, recurrent myocardial infarction; Q, quarter.

☆ No funding.

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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- β 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.

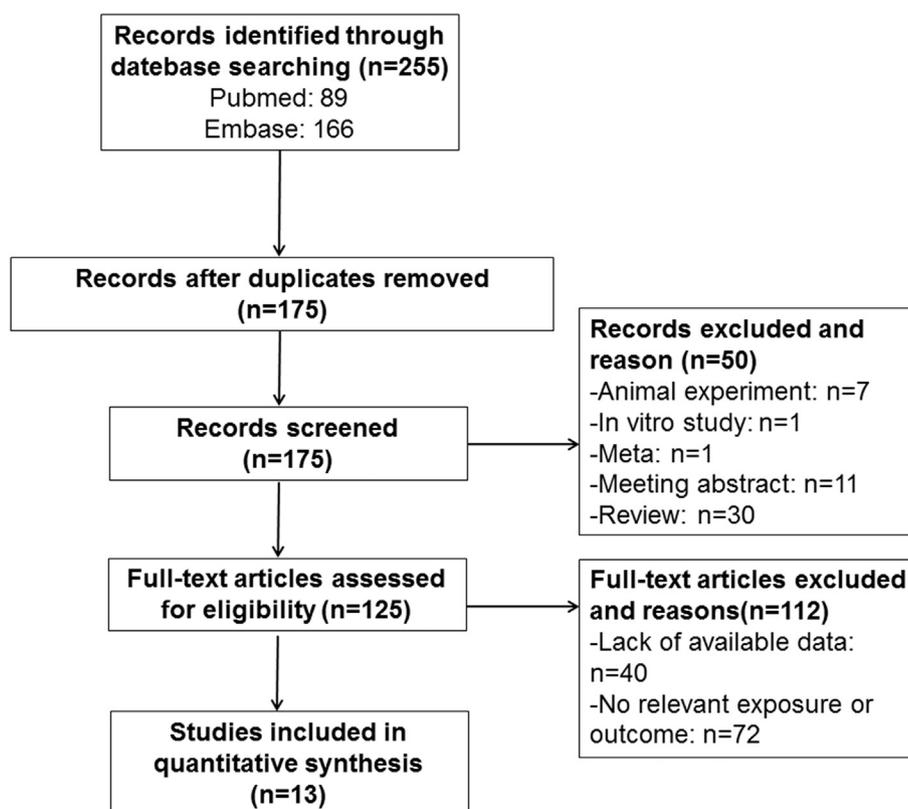


Fig. 1. Flowchart showing selection of studies.

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 pectoris” 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 I^2 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].

Table 1
Characteristics of studies included in the meta-analysis

Author/Year/Country	Participants	GDF-15 (ng/L)	Follow-up ^a (years)	Adverse event	Sample		RR (95%CI)
					Lowest (m ₁ , r ₁ , f ₁ /n ₁)	Highest (m ₂ , r ₂ , f ₂ /n ₂)	
Wollet KC [2]/2007/Germany	NSTEMI (n = 2061)	<1200, 1200–1800, >1800	1	M, R	11,34/713	99,51/704	9.12 (4.93,16.85) 1.52 (1.00,2.32)*
Wollet KC [1]/2007/Germany	NSTEMI (n = 2079)	<1200, 1200–1800, >1800	2	M, R	13,66/816	48,76/493	6.11 (3.35,11.16) 1.91 (1.40,2.60)*
Kempf T [1]/2007/Germany	STEMI (n = 741)	<1200, 1200–1800, >1800	1	M	4/202	44/317	7.01 (2.56,19.21)
Eggers KM [1]/2009/Sweden	NSTEMI (n = 950)	<1200, 1200–1800, >1800	5	M	15/357	41/227	4.30 (2.44,7.58)
Kempf T [2]/2009/Germany	ACS (n = 877)	<1200, 1200–1800, >1800	6.9	M	7/409	31/213	8.50 (3.81,18.99)
Bonaca MP/2011/U.S.	ACS (n = 3501)	<1362, ≥1362	2	M, R, F	14,82,23/1752	70,166,101/1749	5.01 (2.83,8.86) 2.03 (1.57,2.62)* 4.40 (2.81,6.68) [#]
Eitel I/2011/Germany	STEMI (n = 238)	<1319, ≥1319	0.5	M, R	1,8/119	19,8/119	19.00 (2.58,139.66) 1.00 (0.39,2.58)*
Damman P/2014/Netherland	NSTEMI (n = 1151)	<1200, 1200–1800, >1800	5	M, R	9,29/380	45,49/348	5.54 (3.18,9.64) 1.85 (1.19,2.85)*
Eggers KM [2]/2008/Sweden	ACS (n = 479)	<1200, 1200–1800, >1800	0.5	M, R	0,2/149	11,14/174	19.71 (1.17,331.74) 5.99 (1.38,25.95)*
May EAB/2014/U.S.	ACS (n = 4035)	<1200, 1200–1800, >1800	1	M, R, F	53,169,38/2525	83,69,80/537	7.36 (5.28,10.26) 1.92 (1.47,2.50)* 9.90 (6.81,14.40) [#]
Velders MA/2015/Sweden	STEMI (n = 5385)	<1116, 1116–1492, 1492–2120, >2120	1	M, R	18,23/1346	118,62/1346	6.56 (4.02,10.70) 2.70 (1.68,4.32)*
Hagström E/2016/Sweden	ACS (n = 16,876)	<1145, 1145–1550, 1550–2219, >2219	1	M, R	55,99/4214	389,286/4218	7.07 (5.35,9.34) 2.89 (2.31,3.61)*
Lindholm D/2017/Sweden	NSTEMI (n = 5174)	<1107, 1107–1472, 1472–2052, >2052	1	M, R	8,36/1393	59,75/1293	7.38 (3.54,15.37) 2.08 (1.41,3.08)*

ACS, acute coronary syndrome; CI, confidence interval; F, heart failure; GDF-15, growth-differentiation factor-15; M, mortality; NSTEMI, non-st-segment elevation myocardial infarction; R, recurrent myocardial infarction; RR, risk ratio; STEMI, st-segment elevation myocardial infarction * recurrent MI group, [#] heart failure group, ^a maximum follow-up time.

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 quadrised 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 6.75 ($p = 0.000$, 95% CI: 5.81–7.84), indicating that high GDF-15 values were correlated with elevated mortality 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 shown in Table 2. In general, ACS patients with GDF-15 valued 1200–1800 ng/L had a higher mortality compared to those with GDF-15 valued <1200 ng/L ($p = 0.000$). Likewise, patients with GDF-15 valued >1800 ng/L had a higher mortality compared to those with GDF-15 valued 1200–1800 ng/L ($p = 0.000$), the same results were found when group of more than 1800 ng/L compared to group of <1200 ng/L ($p = 0.000$), Q2 compared to Q1 ($p = 0.005$), Q3 compared to Q1 ($p = 0.000$), Q4 compared to Q1 ($p = 0.000$), Q3 compared to Q2 ($p = 0.000$), 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 mortality 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 than 1 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 >1800 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 than 1800 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 ($p = 0.000$), Q3 compared to Q2 ($p = 0.001$), 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 than 1 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 ($I^2 = 45.8\%$), subgroup analyses of ACS ($I^2 = 64.4\%$) and ≤ 1 year ($I^2 = 59.6\%$), after we omitted one study (Hagström E/2016/Sweden) by conducting both sensitive

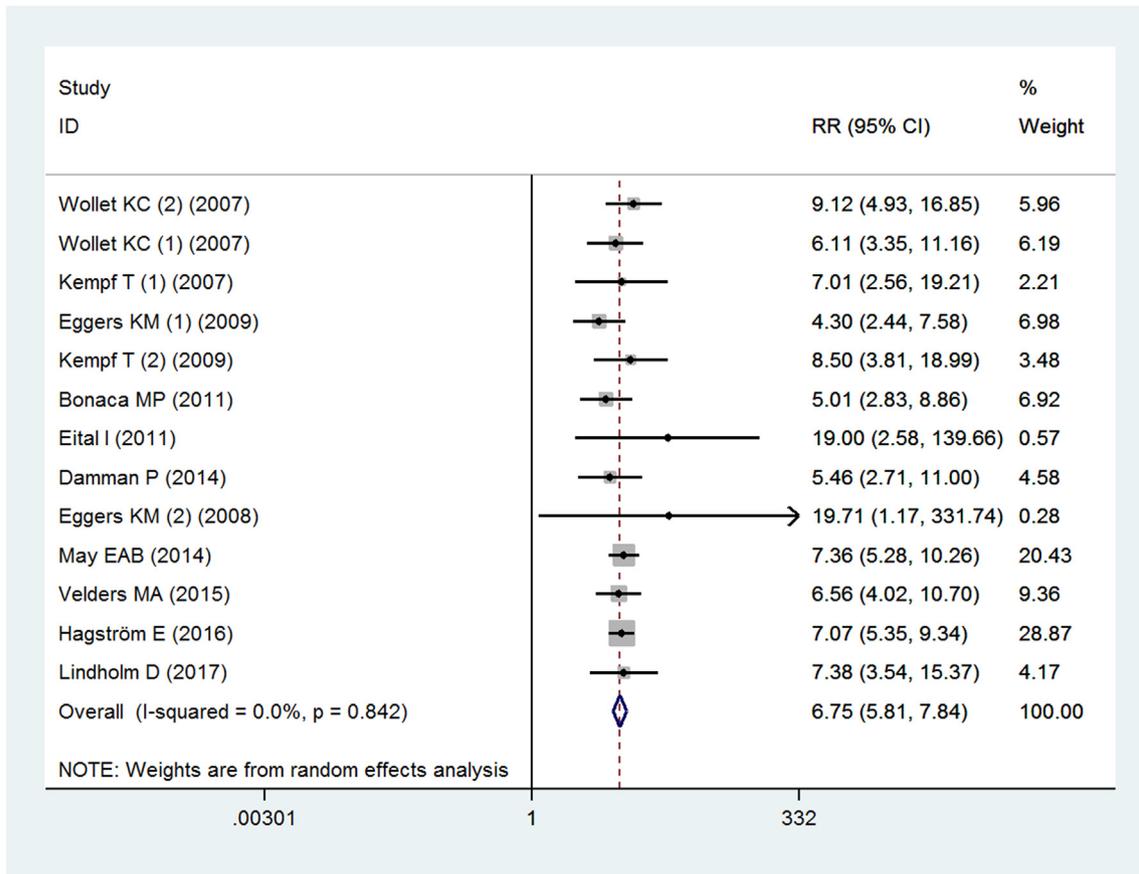


Fig. 2. Forest plot showing the RR and 95% CI for mortality for studies comparing the highest and lowest GDF-15 levels.

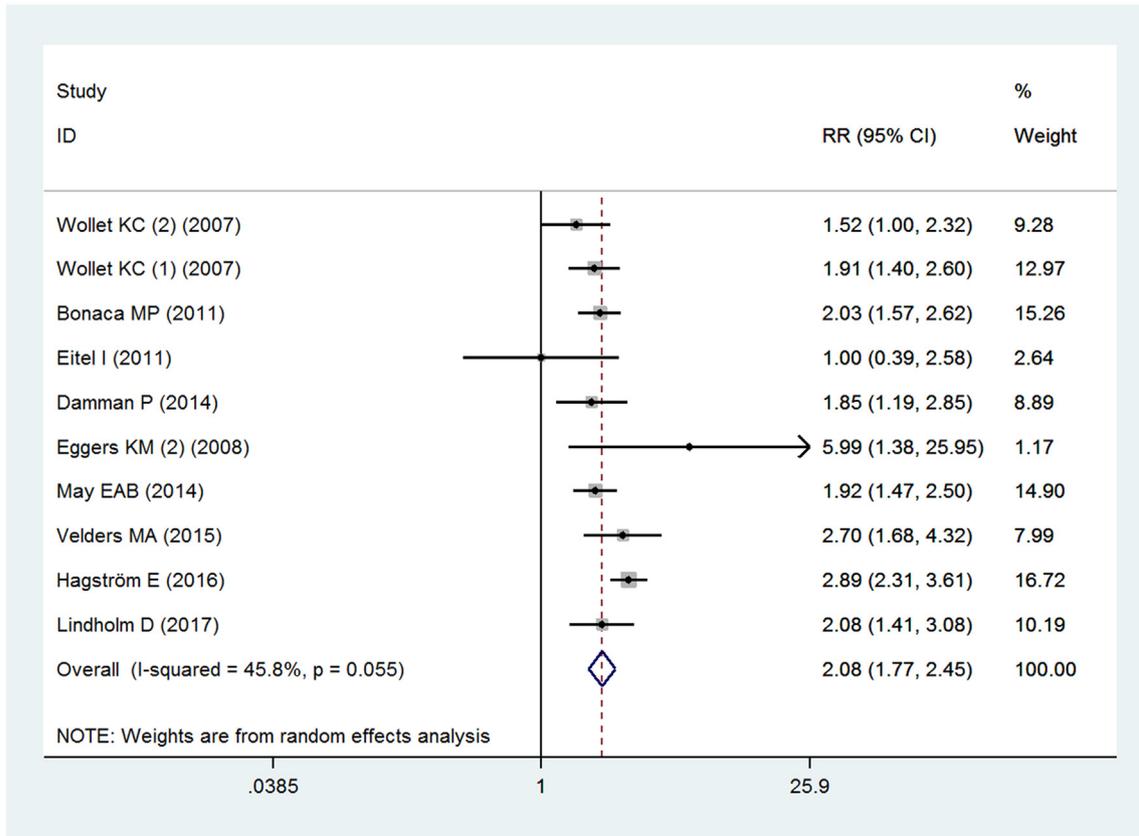


Fig. 3. Forest plot showing the RR and 95% CI for recurrent MI for studies comparing the highest and lowest GDF-15 levels.

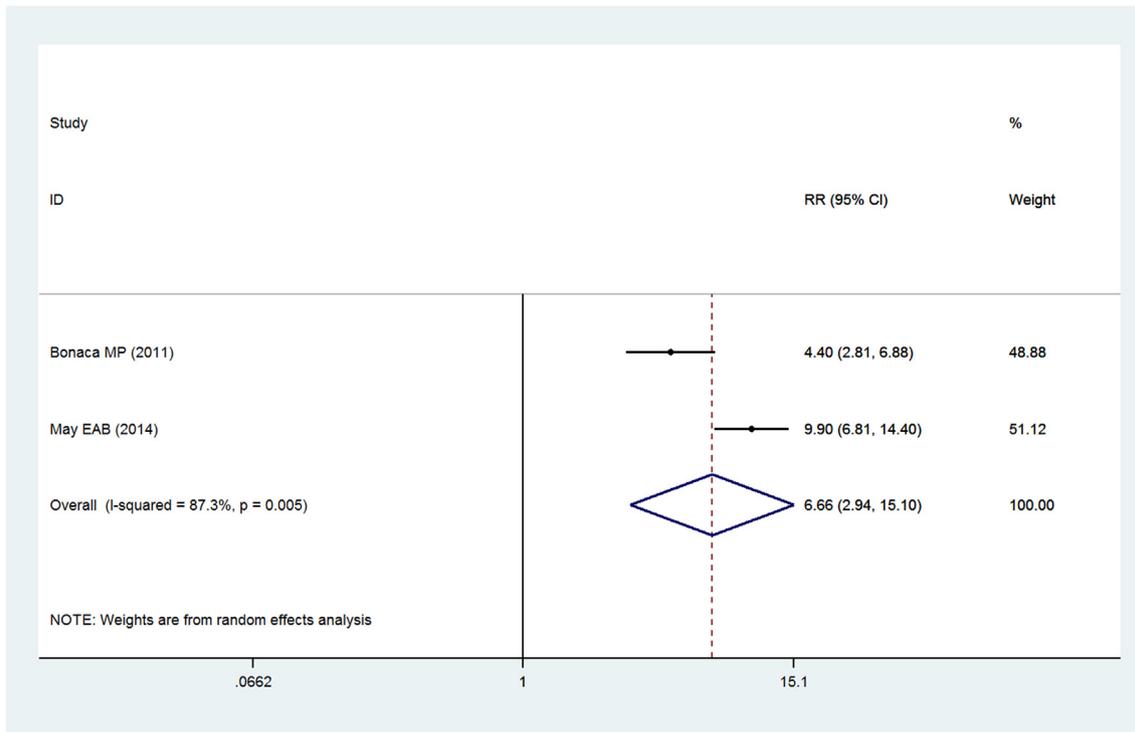


Fig. 4. Forest plot showing the RR and 95% CI for heart failure for studies comparing the highest and lowest GDF-15 levels.

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).

Table 2
GDF-15 concentration and adverse cardiac events

Adverse cardiac events	Stratification group (ng/L)	No. of studies (study size ^a)	RR [95%CI]	p-value	I^2 (%)	p-value ^b	
Mortality	Overall	13(1057,10681/208,14067)	6.75[5.81–7.84]	0.000	0.0	0.840	
	Cutoff Point	1200–1800 VS <1200	8(184,3633/112,5439)	2.46[1.95–3.11]	0.000	0.0	0.687
		>1800 VS 1200–1800	8(402,2611/184,3633)	2.80[2.36–3.32]	0.000	0.0	0.977
		>1800 VS <1200	8(402,2611/112,5439)	6.75[5.46–8.35]	0.000	0.0	0.664
	Q2 VS Q1	3(121,6741/81,6772)	1.49[1.13–1.97]	0.005	0.0	0.857	
	Q3 VS Q1	3(221,6642/81,6772)	2.70[2.10–3.48]	0.000	0.0	0.379	
	Q4 VS Q1	3(566,6291/81,6772)	6.98[5.54–8.79]	0.000	0.0	0.955	
	Q3 VS Q2	3(221,6642/121,6741)	1.82[1.46–2.27]	0.000	0.0	0.519	
	Q4 VS Q2	3(566,6291/121,6741)	4.68[3.85–5.67]	0.000	0.0	0.519	
	Q4 VS Q3	3(566,6291/221,6642)	2.53[1.98–3.22]	0.000	46.3	0.155	
	ACS type	NSTEMI	5(292,2773/56,3503)	6.15[4.63–8.18]	0.000	0.0	0.470
		STEMI	3(181,1601/23,1644)	6.97[4.53–10.72]	0.000	0.0	0.592
		ACS	5(584,6307/129,8920)	7.00[5.76–8.49]	0.000	0.0	0.706
	Follow-up time	≤ 1 year	8(822,7886/150,10411)	7.33[6.14–8.75]	0.000	0.0	0.953
>1 year		5(235,2795/58,3656)	5.46[4.11–7.24]	0.000	0.0	0.722	
Recurrent MI	Overall	9(570,6193/449,8644)	1.95[1.72–2.21]	0.000	0.0	0.469	
	Cutoff Point	1200–1800 VS <1200	5(243,2743/300,4283)	1.24[0.98–1.57]	0.072	36.3	0.179
		>1800 VS 1200–1800	5(259,1997/243/2743)	1.53[1.23–1.89]	0.000	29.9	0.222
		>1800 VS <1200	5(259,1997/300,4283)	1.86[1.58–2.20]	0.000	0.0	0.490
	Q2 VS Q1	3(238,6624/158,6695)	1.50[1.23–1.83]	0.000	0.0	0.445	
	Q3 VS Q1	3(318,6545/158,6695)	2.01[1.66–2.42]	0.000	0.0	0.911	
	Q4 VS Q1	3(423,6434/158,6695)	2.66[2.22–3.19]	0.000	1.0	0.364	
	Q3 VS Q2	3(318,6545/238,6624)	1.34[1.13–1.57]	0.001	0.0	0.490	
	Q4 VS Q2	3(423,6434/238,6624)	4.68[3.85–5.67]	0.000	0.0	0.441	
	Q4 VS Q3	3(423,6434/318,6545)	1.33[1.16–1.53]	0.000	0.0	0.480	
	ACS type	NSTEMI	4(251,2587/165,3037)	1.85[1.53–2.23]	0.000	0.0	0.745
		STEMI	2(70,1395/31,1434)	1.79[0.69–4.67]	0.232	70.5	0.066
		ACS	3(249,2211/253,4173)	2.02[1.64–2.48]	0.000	12.6	0.318
	Follow-up time	≤ 1 year	6(279,3894/272,5873)	1.96[1.54–2.49]	0.000	33.3	0.186
>1 year		3(291,2299/177,2771)	1.95[1.63–2.34]	0.000	0.0	0.917	
Heart failure	Overall	2(181,2105/61,4216)	6.66[2.94–15.1]	0.000	87.3	0.005	

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, quarter; ^a 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; ^b p-value^b reflects the heterogeneity, p-value^b < 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 two 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 phosphoinositide 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 severe 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, whose overall RR was 6.66, with an I^2 of 87.3%. The follow-up time may contribute to this heterogeneity. Anymore, the results indicate a significant positive association between elevated levels of GDF-15 and heart failure. Given the limited number of studies included in the analysis, the findings from our meta-analysis should be confirmed in future research.

Our meta-analysis had several advantages: First, our meta-analysis involved a total of thirteen studies and 43,547 participants, the huge sample size increased the accurateness and theoretical stringency of this article. Second, sufficient date was extracted from well-selected studies, which could provide stable and robust power. Further, we performed subgroup analyses by GDF-15

values (divided into three or four groups), follow-up time, ACS categories in adverse events including mortality, recurrent MI or heart failure to reveal different relationships of GDF-15 and unfavorable prognosis, the lack of insight on the relationship of heart failure 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 shown 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

Acknowledgements

It took months to accomplish this study, thanks for my family and all people who helped me.

Statement of competing interests

None declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37(3):267–315.
- [2] Antman EM, Cohen M, Bernini PJ, McCabe CH, Horace T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284(7):835–42.
- [3] Eagle KA, Lim MJ, Dabboo's OH, Pieper KS, Goldberg RJ, Van de Warf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; 291(22):2727–33.
- [4] Lagerkvist B, Dadahol E, Lindahl B, Husted S, Konni F, Stale E, et al. FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. *Heart* 2005;91(8):1047–52.

- [5] Fox KA, Clayton TC, Damman P, Pocock SJ, de Winter RJ, Tijssen JGP, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J Am Coll Cardiol* 2010;55(22):2435–45.
- [6] Harb TS, Zareba W, Moss AJ, Ridker PM, Marder VJ, Rifai N, et al. Association of C-reactive protein and serum amyloid A with recurrent coronary events in stable patients after healing of acute myocardial infarction. *Am J Cardiol* 2002;89(2):216–20.
- [7] Morrow DA, de Lemos JA, Blazing MA, Sabatine MS, Murphy SA, Jarolim P, et al. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. *JAMA* 2005;294(22):2866–71.
- [8] Lindahl B, Lindbäck J, Jernberg T, Johnston N, Stridsberg M, Venge P, et al. Serial analyses of N-terminal pro-B-type natriuretic peptide in patients with non-ST-segment elevation acute coronary syndromes: a Fragmin and fast revascularisation during in stability in coronary artery disease (FRISC)-II substudy. *J Am Coll Cardiol* 2005;45(4):533–41.
- [9] Eggers KM, Lagerkvist B, Venge P, Wallentin L, Lindahl B. Prognostic value of biomarkers during and after non-ST segment elevation acute coronary syndrome. *J Am Coll Cardiol* 2009;54(4):357–64.
- [10] Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European concerted action on thrombosis and disabilities angina pectoris study group. *Lancet* 1997;349(9050):462–6.
- [11] Danesh J, Wheeler JG, Hirschfeld GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350(14):1387–97.
- [12] Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004;351(25):2599–610.
- [13] Wilson PW, Nam BH, Pencina M, D'Agostino RB Sr, Benjamin EJ, O'Donnell CJ. C-reactive protein and risk of cardiovascular disease in men and women from the Framingham heart study. *Arch Intern Med* 2005; 165 (21): 2473–8.
- [14] Khan SQ, Narayan H, Ng KH, Dhillon OS, Kelly D, Quinn P, et al. N-terminal pro B type natriuretic peptide complements the GRACE risk score in predicting early and late mortality following acute coronary syndromes. *Clin Sci (Lond)* 2009;117(1):31–9.
- [15] Lorgis L, Zeller M, Dentan G, Sicard P, Buffet P, L'Huillier I, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in elderly people with acute myocardial infarction: prospective observational study. *BMJ* 2009;338(7704):1195.
- [16] Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. *Proc Natl Acad Sci U S A* 1997;94(21):11514–9.
- [17] Bottner M, Laaff M, Schechinger B, Rappold G, Unsicker K, SuterCrazzolara C. Characterization of growth-differentiation factor 15, a transforming growth factor beta superfamily member induced following liver injury. *Mol Cell Biol* 2000;20(10):3742–51.
- [18] Hsiao EC, Koniaris LG, Zimmers-Koniaris T, Sebald SM, Huynh TV, Lee SJ. Characterization of growth-differentiation factor 15, a transforming growth factor beta superfamily member induced following liver injury. *Mol Cell Biol* 2000;20(10):3742–51.
- [19] Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia reperfusion injury. *Circ Res* 2006;98(3):351–60.
- [20] Eggers KM, Kempf T, Allhoff T, Lindahl B, Wallentin L, Wollert KC. Growth-differentiation factor-15 for early risk stratification in patients with acute chest pain. *Eur Heart J* 2008;29(19):2327–35.
- [21] May EAB, Bonaca M, Scirica B, Kuder J, Murphy S, Jarolim P, et al. Growth differentiation Factor-15 level predicts recurrent cardiovascular events in patients with an acute coronary syndrome in MERLIN-TIMI 36. *J Am Coll Cardiol* 2014;63(12):A20.
- [22] Velders MA, Wallentin L, Becker RC, van Boven AJ, Himmelmann A, Husted S, et al. Biomarkers for risk stratification of patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention: insights from the platelet inhibition and patient outcomes trial. *Am Heart J* 2015;169(6):879–89.
- [23] Hagström E, James SK, Bertilsson M, Becker RC, Himmelmann A, Husted S, et al. Growth differentiation factor-15 level predicts major bleeding and cardiovascular events in patients with acute coronary syndromes: results from the PLATO study. *Eur Heart J* 2016;37(16):1325–33.
- [24] Lindholm D, James SK, Bertilsson M, Becker RC, Cannon CP, Giannitsis E, et al. Biomarkers and coronary lesions predict outcomes after revascularization in non-ST-elevation acute coronary syndrome. *Clin Chem* 2017;63(2):573–84.
- [25] Wollert KC, Kempf T, Lagerkvist B, Lindahl B, Olofsson S, Allhoff T, et al. Growth differentiation factor 15 for risk stratification and selection of an invasive treatment strategy in non-ST-elevation acute coronary syndrome. *Circulation* 2007;116(14):1540–8.
- [26] Wollert KC, Kempf T, Peter T, Olofsson S, James S, Johnston N, et al. Prognostic value of growth-differentiation Factor-15 in patients with non-ST-elevation acute coronary syndrome. *Circulation* 2007;115(8):962–71.
- [27] Kempf T, Björklund E, Olofsson S, Lindahl B, Allhoff T, Peter T, et al. Growth-differentiation factor-15 improves risk stratification in ST-segment elevation myocardial infarction. *Eur Heart J* 2007;28(23):2858–65.
- [28] Eggers KM, Kempf T, Lagerkvist B, Lindahl B, Olofsson S, Jantzen F, et al. Growth-differentiation factor-15 for long-term risk prediction in patients stabilized after an episode of non-ST-segment-elevation acute coronary syndrome. *Circ Cardiovasc Genet* 2010;3(1):88–96.
- [29] Kempf T, Sinning JM, Quint A, Bickel C, Sinning C, Wild PS, et al. Growth-differentiation factor-15 for risk stratification in patients with stable and unstable coronary heart disease: results from the AtheroGene study. *Circ Cardiovasc Genet* 2009;2(3):286–92.
- [30] Eitel I, Blase P, Adams V, Hildebrand L, Desch S, Schuler G, et al. Growth-differentiation factor 15 as predictor of mortality in acute reperfused ST-elevation myocardial infarction: insights from cardiovascular magnetic resonance. *Heart* 2011;97(8):632–40.
- [31] Bonaca MP, Morrow DA, Braunwald E, Cannon CP, Jiang S, Breher S, et al. Growth differentiation factor-15 and risk of recurrent events in patients stabilized after acute coronary syndrome: observations from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol* 2011;31(1):203–10.
- [32] Damman P, Kempf T, Windhausen F, van Straalen JP, Guba-Quint A, Fischer J, et al. Growth-differentiation factor 15 for long-term prognostication in patients with non-ST-elevation acute coronary syndrome: an invasive versus conservative treatment in unstable coronary syndromes (ICTUS) substudy. *Int J Cardiol* 2014;172(2):356–63.
- [33] Wright, R.S., Anderson, J. L., Adams, C. D., Bridges, C.R., Jr, D. E. C., & Ettinger, S. M., et al. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; 123 (18): 2022–60.
- [34] Borja I, Stefan J, Stefan A, Manuel J Antunes, Chiara Bucciarelli-Ducci, Héctor Bueno, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39(2): 119–77.
- [35] Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;333(7578):1091–4.
- [36] Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;102(17):2031–7.
- [37] Chang WC, Kaul P, Fu Y, Westerhout CM, Granger CB, Mahaffey KW, et al. Forecasting mortality: dynamic assessment of risk in ST-segment elevation acute myocardial infarction. *Eur Heart J* 2006;27(4):419–26.
- [38] Stebbins A, Mehta RH, Armstrong PW, Lee KL, Hamm C, Van de Werf F, et al. A model for predicting mortality in acute ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: results from the assessment of Pexelizumab in acute myocardial infarction trial. *Circ Cardiovasc Interv* 2010;3(5):414–22.
- [39] De Luca G, Suryapranata H, van 't Hof AW, de Boer MJ, Hoorntje JC, Dambrink JH, et al. Prognostic assessment of patients with acute myocardial infarction treated with primary angioplasty: implications for early discharge. *Circulation* 2004; 109(22):2737–43.
- [40] Halkin A, Singh M, Nikolsky E, Grines CL, Tchong JE, Garcia E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction: the CADILLAC risk score. *J Am Coll Cardiol* 2005;45(9):1397–405.
- [41] Eggers KM, Oldgren J, Nordenskjöld A, Lindahl B. Risk prediction in patients with chest pain: early assessment by the combination of troponin I results and electrocardiographic findings. *Coron Artery Dis* 2005;16(3):181–9.
- [42] Kempf T, Rüdiger HW, Brabant G, Peter T, Allhoff T, Klein G, et al. Circulating concentrations of growth differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immunoradiometric sandwich assay. *Clin Chem* 2007;53(2):284–91.
- [43] Ago T, Sadoshima J. GDF15, a cardioprotective TGF-beta superfamily protein. *Circ Res* 2006;98(3):294–7.
- [44] Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. *Circ Res* 2006;98(3):351–60.
- [45] Hayes DF, Isaacs C, Stearns V. Prognostic factors in breast cancer: current and new predictors of metastasis. *J Mammary Gland Biol Neoplasia* 2001;6(4):375–92.
- [46] Lin DY, Wei LJ, Ying Z. Model-checking techniques based on cumulative residuals. *Biometrics* 2002;58(1):1–12.