Impaired renal function and abnormal level of ferritin are independent risk factors of left ventricular aneurysm after acute myocardial infarction

A hospital-based case–control study

Yunfei Feng, MD$, Qiqi Wang, PhD®, Guoping Chen, PhD®, Dan Ye, MD$, Weiwei Xu, PhD®∗

Abstract
This study was performed to determine the prognostic value of glomerular filtration rate (GFR) and ferritin compromised in left ventricular aneurysm (LVA) patients who suffered acute myocardial infarction (AMI) beforehand.

A hospital-based case–control study was conducted in the Department of Cardiology, First Affiliated Hospital, Zhejiang University in 2013 and 2014. Patients were divided into 3 groups according to kidney function and ferritin level. Observation outcomes include age, sex, C-reactive protein (CRP), medical history including major risk factors for CAD, ferritin and GFR, previous angina, time between MI and coronary angiography or time to rescue (TTR), and prior treatment.

Around 60 patients were included in the case group (AMI with LVA) and 133 matched patients (AMI without LVA) in the control group. The prevalence of single-vessel disease (odd ratio [OR]=2.490; 95% confident interval [95% CI]=1.376–4.506; P=.002), total LAD occlusion (OR=1.897; 95% CI=1.024–3.515; P=.041), absence of previous angina (OR=1.930; 95% CI=1.035–3.600; P=.037), time between myocardial infarction (MI) and coronary angiography more than 12 h (OR=1.970; 95% CI=1.044–3.719; P=.035), GFR less than 60 mL/min (OR=2.933; 95% CI=1.564–5.503; P=.001), and ferritin levels (P=.0003) were all higher in the aneurysm group compared with those in the control group. After adjustments for other variables, single-vessel disease (OR=1.211; 95% CI=1.080–1.342; P=.02), GFR lower than 60 mL/min (OR=1.651; 95% CI=1.250–2.172; P=.013), and high or low levels of ferritin (OR=1.151; 95% CI=1.050–1.252; P=.042) remained the independent determinants of LVA formation after AMI.

Decreased GFR and abnormal ferritin levels are independent risk factors of LVA formation after AMI.

Abbreviations: 95% CI = 95% confidential interval, AMI = acute myocardial infarction, BMI = body mass index, CAD = coronary heart disease, CKD = chronic kidney disease, FBG = fasting blood glucose, GFR = glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LVA = left ventricular aneurysm, LVEF = left ventricular ejection fraction, OR = odd ratio, TC = total cholesterol, TG = triglyceride, TTR = time to rescue.

Keywords: acute myocardial infarction, kidney function, left ventricular aneurysm, serum ferritin

1. Introduction
Left ventricular aneurysm (LVA), defined as the expansion of the dykinetic area of the left ventricular wall,[1] is one of the most fatal complications of acute myocardial infarction (AMI). Angiographically defined LVA were previously reported in 7.6% of coronary artery disease (CAD) patients referred for coronary angiography.[1] Aneurysms usually develop from a portion of weakened tissue in the ventricular wall, usually lead to left ventricular ejection fraction (LVEF) reduction and cardiac death.[2] After suffering AMI, LVA patients have increased risk of complications, such as arrhythmias,[3] thromboembolic phenomena,[4] and congestive heart failure.[1] Therefore, searching for the prognostic factors contributing to LVA formation after AMI and preventing them for morbidity and mortality reduction are necessary.

Many authors investigated the risk factors of LVA formation after AMI. However, disagreements regarding factors involved in LVA pathogenesis remain.[1,2,3,4] The traditional determinant factors of LVA after AMI include age, lesion of myocardial infarction, single vessel lesion, and ischemic heart disease before acute MI or not.[2,3,5,6] However, whether ferritin and kidney function could be predictive factors for LVA formation after AMI remains unknown.

Ferritin is a globular protein complex which consists of 24 protein subunits forming a nanocage comprising multiple metal–protein interactions.[8,9] Ferritin is widely found in the liver, spleen, skeletal muscles, and bone marrow. Most of the iron stored in the body is bound to ferritin, which acts as a buffer against iron deficiency and iron overload.[8,9] Serum ferritin is
directly proportional to that stored in the tissues and the circulation so that it reflects the total amount of stored iron. Levels decrease very early during the development of iron deficiency anemia; hence, ferritin is a useful biomarker for early detection of iron deficiency.[8,9]

Iron is essential for many physiological processes; whereas, iron overload has been known as a risk factor in progression of atherosclerosis.[10] Another clinical study has established that serum ferritin is an independent factor in coronary artery stenosis among hemodialysis patients.[11] Furthermore, it was confirmed that serum ferritin is weakly positively associated with CAD risk.[12] Yet the association between ferritin and prevalence of LVA after AMI has not been studied so far.

The correlation between renal function and complications after AMI has been proven by many studies. Chronic kidney disease (CKD) is associated with worse outcomes among patients with acute coronary syndrome (ACS).[13] Meanwhile, AKI has detrimental effect on patients prognosis, raising mortality two- to threefold not only during the 30 first days but also during the first year after the acute event.[14] But whether kidney function is associated with the prevalence of LVA after AMI has not been reported yet.

Ferritin, GFR, and LVA share not only the same risk factors and complications for the decrease in coronary heart disease (CAD) and chronic kidney disease (CKD) incidence as age advances[15] but also the same pathophysiological conditions, such as inflammation and anemia-induced hypoxia[16] as a retrospective study has reported that anemia as a progression factor with cardiovascular disease.[17] Whether kidney function and ferritin are involved in LVA formation after AMI still requires clinical evidence and further investigation.

In this study, determining whether kidney function and ferritin are involved in the pathogenesis of LVA formation after AMI was attempted in a large Chinese patient population. The clinical data and the coronary angiograms of 60 patients with AMI and LVA were reviewed and compared with matched 133 patients with previous AMI but without LVA. The patients with AMI and LVA underwent coronary angiography in a one-month period.

2. Methods

2.1. Study population and study design

A hospital-based case-control study was conducted. Subjects were patients from the Department of Cardiology, First Affiliated Hospital of Zhejiang University from 2012 to 2013. A total of 1857 patients were enrolled. Patients without evidence of previous AMI for more than 1 year and significant coronary artery disease (defined as 50% or greater narrowing of luminal diameter of a major coronary artery segment more than 1 month), and those having technically inadequate coronary angiograms for interpretation were excluded from the study. The controls were hospitalized AMI patients without LVA during the same period, and they were matched 2:1 with LVA cases for the variables of age, gender, and admission date. Some of the matched cases were excluded according to the exclusion criteria (Fig. 1). All of the patients involved in this study signed informed consent forms. This study was approved by the Research Ethics Board of Zhejiang University.

2.2. Definitions

AMI is defined according to the third universal definition of myocardial infarction (2012).[18] AMI was considered to be present if any of the following criteria meets the diagnosis for MI: Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: symptoms of ischemia, new or presumed significant ST-segment-T wave (ST-T) changes or a new left bundle branch block (LBBB), and development of pathological Q waves in the ECG.[19]

LVA was diagnosed ultrasonographically according to the coronary artery surgery study (CASS) protocol.[19] Aneurysm was diagnosed when all the following criteria were found: protuberance of the involved segment, displaying either akinetic or dykinetic motion, absence of trabeculation in the involved segment, and well-defined demarcation of the lesion.[19] The diagnosis of LVA was then adjusted by left ventricular angiogram.

GFR was used to determine the stage of kidney disease. An MDRD formula using age, race, gender, and serum creatinine were used to calculate GFR.[20] Stage 1 has normal or high GFR (GFR > 90 mL/min); Stage 2, mild CKD (GFR = 60–89 mL/min); Stage 3, moderate CKD (GFR = 30–59 mL/min); Stage 4, severe CKD (GFR = 15–29 mL/min); and Stage 5, end-stage CKD (GFR < 15 mL/min).

Serum ferritin was obtained from fasting patients and analyzed through chemiluminescent immunoassay. The normal range was within 7.0 to 323.0 ng/mL. The patients were then divided into 3 groups according to ferritin level. Patients in Group 1 have ferritins levels under the normal range; those in Group 2, within normal range; and those in Group 3, above normal range.

2.3. Data extraction

Observation outcomes include age, sex, C-reaction protein (CRP), thyroid function, medical history including major risk factors for CAD (hypertension, diabetes mellitus, current cigarette smoking, dyslipidemia, and family history of MI at younger than 50 years), ferritin and GFR, fasting blood glucose (FBG), HbA1c, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), previous angina, time between MI and coronary angiography or time to rescue (TTR), ECG localization of MI, and prior treatment (beta blockers, calcium channel blockers, and angiotensin-converting enzyme blockers). All data were obtained from the charts of the patients.

2.4. Statistical analysis

Continuous variable data are expressed as the mean±S.D. Unpaired Student t-test was performed to evaluate the continuous variables, and chi-square tests were used to compare the means of proportions. Kappa statistic was used to assess intraobserver variability. All the observation variables were selected for univariate analysis. A P of .05 was considered significant. Variables below P of .10 were selected for further multivariate modeling, which was performed through logistic regression analysis. A P of .05 was considered significant. PASW program (version 19.0) was used to perform all the statistical calculations.

3. Results

Around 60 patients were then compared with 134 consecutive patients with previous AMI but without LVA. The patients were
enrolled by scanning through 1857 patients with AMI in the Department of Cardiology and Emergency, First Affiliated Hospital, Zhejiang University. According to the scan results, 22.2% of patients were female and had a mean age of 64.62 years. LVA incidence was 3.2%, while those of hypertension, diabetes mellitus, and dyslipidemia were 31.6%, 45.22%, and 46.63%, respectively (see Table 1).

Analysis results revealed that single-vessel disease, absence of previous angina, total LAD occlusion, number of patients with CKD stage higher than stage 3, and ferritin levels were all higher in the aneurysm group compared with those in the control group. single-vessel disease (OR = 2.490; 95% CI = 1.376–4.506; P = .002), total LAD occlusion (OR = 1.897; 95% CI = 1.024–3.515; P = .041), absence of previous angina (OR = 1.930; 95% CI = 1.035–3.600; P = .037), TTR of >12 hours (OR = 1.970; 95% CI = 1.044–3.719; P = .035), GFR of <60 mL/min (OR = 2.933; 95% CI = 1.564–5.503; P = .001), and ferritin levels (P = .0003). No difference was observed between the baseline clinical characteristics, such as weight, hypertension, diabetes mellitus, dyslipidemia, smoking, and family history of CAD, of the case and control groups. Furthermore, no significant difference was observed between the groups with regard to mean lesion stenosis in the LAD artery, such as circumflex (Cx) and right coronary artery (RCA) and coronary collateral score (see Table 2).

The patients were divided into groups according to GFR. One group had GFRs of ≥60 mL/min and the other group had GFRs of <60 mL/min. After age, sex, smoking history, and previous medical history were adjusted, LVA proportion increased as the CKD stage advanced (OR = 1.651; CI = 1.250–2.172; P = .013). The patients were divided into 3 groups according to ferritin levels. One group has below normal range (ferritin <7.0 ng/mL) and within normal range (7.0–323.0 ng/mL), above normal range (ferritin >323.0 ng/mL). Significant results were obtained after the adjustment of age, sex, smoking history, and previous medical history. The proportion of LVA patients are different among the 3 groups (P = .042). Moreover, after the other clinical and angiographic variables were adjusted, single-vessel disease (OR = 1.211; 95% CI = 1.080–1.342; P = .020) remained the independent determinants of LVA formation after acute MI (see Table 2).

4. Discussion
This cross-sectional study revealed that the prevalence of LVA after AMI is associated with single-vessel disease, total LAD occlusion, absence of previous angina, TTR of >12 hours, GFR of <60 mL/min, and high or low levels of ferritin. Multiple variant analysis results showed that patients with single-vessel diseases, GFR of <60 mL/min, and high or low ferritin levels are independent predictive factor of LVA after AMI.
Table 1
Baseline characteristics of case (AMI with LVA) and control (AMI without LVA) group.

| Clinical factor                  | AMI with LVA (n=60) | AMI without LVA (n=134) | P-value |
|----------------------------------|---------------------|-------------------------|---------|
| Age, years                       | 67.3 ± 11.8         | 66.03 ± 12.83           | .476    |
| BMI, kg/m²                       | 25.32 ± 6.23        | 23.32 ± 4.82            | .784    |
| Sex (Male/Female)                | 49/11               | 101/33                  | .376    |
| Previous medical history (%)     | 32.60               | 35.20                   | .158    |
| Smoking                          | 37.90               | 34.80                   | .078    |
| Hypertension                     | 42.10               | 49.30                   | .353    |
| Diabetes mellitus                | 29.50               | 33.60                   | .511    |
| Thrombolytic therapy             | 18.50               | 21.50                   | .663    |
| Previous medication (%)          | 28.30               | 26.20                   | .871    |
| Calcium channel blocker          | 17.30               | 21.70                   | .478    |
| ACE inhibitors                   | 19.00               | 16.80                   | .76     |
| D-dimer, µg/L                    | 177.19 ± 137.74     | 198 ± 168.61            | .415    |
| C reactive protein, mg/L         | 56.53 ± 58.3        | 44.59 ± 53.1            | .326    |
| Percent of C reactive protein ≥ 10 mg/L (%) | 16.67 | 14.9 | .903 |
| Hemoglobin, g/L                  | 14.5 ± 3.24         | 13.7 ± 2.35             | .576    |

Unpaired Student t-test was performed to evaluate the continuous variables, and chi-square tests were used to compare the means of proportions. A P of .05 was considered significant. PASW program (version 18.0) was used to perform all the statistical calculations.

BMI = body mass index.

Previous studies reported the traditional risk factors of LVA. Tikiz et al. revealed that single-vessel disease, absence of previous angina, total LAD occlusion, and female gender were independent risk factors of LVA formation after AMI. Traditionally risk factors of coronary artery disease, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, and family history of CAD, were not found to be important determinants in the aneurysm formation. Meanwhile, the comparison of these 2 groups on the basis of LVA formation can lead to erroneous results during the identification of the contributing factors. Gender was not found to play an important role in LVA formation maybe due to limited sample size and ethnics. Large clinical studies should be conducted to investigate the underlying mechanism.

Several studies have shown that LVA is mostly associated with the single-vessel disease; others had suggested that the multivessel disease was an independent predictor in the development of LVA. Our finding is consistent with the findings that single-vessel disease is the most prevalent angiographic finding in patients that developed an aneurysm after anterior MI. In patients with the multivessel disease, the occurrence of less aneurysm formation may be related to the diffusely impaired LV function, so the demarcation of the infarct area from the noninfarct area may not have been well defined. Furthermore, it can be easily imagined that MI in patients with the single-vessel disease could impose the greatest regional distortion on LV function with the most extreme strain occurring at the junction of the infarcted and noninfarcted zones.

The association between renal function and LVA can be partially explained by the cardiorenal syndrome (CRS). The pathophysiology of CRS can be caused by 2 broad categories of factors. One is hemodynamic factors, such as reduction of cardiac

Table 2
Risk factors of LVA after AMI.

| Location of MI | AMI with LVA (n = 60) | AMI without LVA (n = 134) | Odd ratio, 95% confidential interval | P-value (single-variant model) | P-value (multiple-variant model) |
|---------------|-----------------------|---------------------------|-------------------------------------|-------------------------------|----------------------------------|
| Anterior      | 27                    | 34                        | —                                   | <.001                         | —                               |
| A/S           | 30                    | 28                        | —                                   | —                             | —                               |
| A/L           | 1                     | 22                        | —                                   | —                             | —                               |
| Thrombolytic therapy | 30 73 | 0.836 (0.454,1.537) | .334 | — |
| Single vessel disease | 42 50 | 2.490 (1.376,4.506) | .002 | .02 |
| Total occlusion LAD | 32 50 | 1.897 (1.024,3.515) | .041 | — |
| TTR ≥ 24 hours | 40 67 | 1.970 (1.044,3.719) | .035 | — |
| OXD stage ≥ 3 (GFR<60 mL/min) | 36 45 | 2.933 (1.546,5.503) | .001 | .013 |
| Serum ferritin | Group 1 (<3.0 ng/mL) | 15 4                       | —                                   | .000                          | 0.042                           |
|               | Group 2 (3.0–323.0 ng/mL) | 35 99                  | —                                   |                              |                                  |
|               | Group 3 (>323.0 ng/mL) | 10 21                    | —                                   |                              |                                  |

Continuous variable data are expressed as the mean ± S.D. Unpaired Student t-test was performed to evaluate the continuous variables, and chi-square tests were used to compare the means of proportions. Kappa statistic was used to assess intraobserver variability. Variables below P of .10 were selected for further multivariate modeling which was performed through logistic regression analysis. A/L = anterolateral, A/S = anteroseptal, AMI = acute myocardial infarction, OXD = chronic kidney disease, LAD = left anterior descending coronary artery, LVA = left ventricular aneurysm, LVEF = left ventricular ejection fraction, LVMI = left ventricular interior diameter, TTR = time between MI and coronary angiography.
output, elevation of intra-abdominal, and central venous pressures. The others are so-called nonhemodynamic factors or “cardiorenal connectors,” such as neurohormonal and inflammatory activation. Several studies have shown similar phenomenon. Those patients with more severe acute myocardial infarction are more likely to have acute heart failure, which results in more life-threatening events including acute kidney failure. Acute kidney failure, in turn, can cause water-sodium retention and aggravate LVA after AMI. In addition, those patients with chronic kidney disease are in poorer health and more fragile to a strike of AMI. Furthermore, according to clinical study, lower levels of kidney function were associated with higher rates of death, AMI hospitalization, and major bleeding among patients after hospitalization for ACS due to clinical pharmacokinetics. This study presented that decreased renal function is an independent risk factor of LVA after AMI. The underlying mechanism still needs further research.

Low serum ferritin is one of the most specific lab tests for iron-deficiency anemia and can contribute to the pathogenesis of myocardial fibrosis and LVA after an ischemic attack. Low ferritin may also indicate hypothyroidism and vitamin C deficiency and can accelerate LVA formation. Meanwhile, anemia could be complications of CKD, which is another risk factor of LVA because it leads to hypoxia. The prognostic value of low ferritin is independent of hemoglobin and CKD stage, indicating that lack of ferritin may act in another particular way. The underlying mechanism still requires further investigation.

At high ferritin levels, iron is in excess or else an acute inflammatory reaction occurs in which ferritin is mobilized without iron excess, including coronary arterial atherosclerosis. A normal C-reactive protein (CRP) can be used to exclude elevated ferritin caused by acute phase inflammatory reactions. After normalizing with CRP, ferritin is a risk factor of LVA after AMI because of its chronic inflammation rather than acute bacterial infection. Furthermore, studies have reported higher level of ferritin indicates larger area of necrosis myocardial cell and predicts poorer prognosis after AMI. Iron-mediated damage to cardiomyocytes and myocardial scarring are more likely due to cytosolic iron excess.

The current study still has some limitations. First, the primary diagnosis of LVA was based on ultrasonographic examination, which is not the “golden criteria” for LVA detection, especially for tiny lesion detection. However, this method is widely used in clinical practice and epidemiological studies for LVA detection because it is widely available and noninvasive. Meanwhile, whether decreased GFR and abnormal ferritin are bystanders, causal factors or consequences of LVA formation cannot be concluded from the results of this case-control study. The fact that size of match control was higher than that of the case studies may overestimate the results. Their precise interrelationship should be enclosed by well-designed prospective studies.

In summary, results demonstrated a significant correlation between GFR and ferritin level and LVA. Further studies on the involvement of kidney function and ferritin in LVA will not only expand the authors’ understanding of the mechanism of LVA but also assist in the eventual development of new prevention and treatment strategies for the disease.

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Author contributions

Conceptualization: Qiqi Wang, Weiwei Xu.
Data curation: Yunfei Feng, Qiqi Wang.
Formal analysis: Weiwei Xu.
Funding acquisition: Dan Ye, Weiwei Xu.
Methodology: Guoping Chen.
Software: Weiwei Xu.
Writing – original draft: Guoping Chen, Weiwei Xu.
Writing – review & editing: Dan Ye.

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