Elevated serum FGF21 predicts the major adverse cardiovascular events in STEMI patients after emergency percutaneous coronary intervention

Lingyun Gu [1] , **Wenlong Jiang** [1] , **Huidong Qian** [1] , **Ruolong Zheng** [1] , **Weizhang Li** [Corresp. 1]

[1] Department of Cardiology, Jiangyin hospital affiliated to Southeast University, Jiangyin, Jiangsu, China

Corresponding Author: Weizhang Li
Email address: liwz@jyrmyy.com

Background. Although there have been several studies related to serum fibroblast growth factor 21 (FGF21) levels and acute myocardial infarction, the value of serum FGF21 levels in ST-segment elevation myocardial infarction (STEMI) patients after emergency percutaneous coronary intervention (PCI) has not been previously investigated. **Methods.** A total of 348 STEMI patients who underwent emergency PCI were enrolled from January 2016 to December 2018. The primary endpoint was the occurrence of major adverse cardiovascular events (MACEs), with a median follow-up of 24 months. Eighty patients with stable angina (SA) who underwent selective PCI served as the control group. Serum FGF21 levels were measured by ELISA. **Results.** Serum FGF21 levels were significantly higher in the STEMI group than in the SA group (225.03±37.98 vs. 135.51±34.48, P<0.001). Multiple linear regression analysis revealed that serum FGF21 levels were correlated with NT-proBNP (P<0.001). According to receiver operating characteristic (ROC) analysis, the areas under the ROC curve (AUCs) of FGF21 and NT-proBNP were 0.812 and 0.865, respectively. The Kaplan-Meier curves showed that STEMI patients with lower FGF21 levels had an increased MACE-free survival rate. Cox analysis revealed that high FGF21 levels (HR: 2.011, 95% CI: 1.160-3.489) proved to be a powerful tool in predicting the risk of MACEs among STEMI patients after emergency PCI. **Conclusion.** Elevated FGF21 levels on admission have been shown to be a powerful predictor of MACEs for STEMI patients after emergency PCI.

1 **Elevated serum FGF21 predicts the major adverse cardiovascular events in**
2 **STEMI patients after emergency percutaneous coronary intervention**

4 Lingyun Gu, Wenlong Jiang, Huidong Qian, Ruolong Zheng, Weizhang Li

6 Department of Cardiology, Jiangyin hospital affiliated to Southeast University, Jiangyin, Jiangsu,
7 China

9 Corresponding Author: Weizhang Li
10 Email address: liwz@jyrmyy.com

12 **Abstract**
13 **Background.** Although there have been several studies related to serum fibroblast growth factor
14 21 (FGF21) levels and acute myocardial infarction, the value of serum FGF21 levels in ST-
15 segment elevation myocardial infarction (STEMI) patients after emergency percutaneous
16 coronary intervention (PCI) has not been previously investigated.
17 **Methods.** A total of 348 STEMI patients who underwent emergency PCI were enrolled from
18 January 2016 to December 2018. The primary endpoint was the occurrence of major adverse
19 cardiovascular events (MACEs), with a median follow-up of 24 months. Eighty patients with
20 stable angina (SA) who underwent selective PCI served as the control group. Serum FGF21
21 levels were measured by ELISA.
22 **Results.** Serum FGF21 levels were significantly higher in the STEMI group than in the SA
23 group (225.03±37.98 vs. 135.51±34.48, P<0.001). Multiple linear regression analysis revealed
24 that serum FGF21 levels were correlated with NT-proBNP (P<0.001). According to receiver
25 operating characteristic (ROC) analysis, the areas under the ROC curve (AUCs) of FGF21 and
26 NT-proBNP were 0.812 and 0.865, respectively. The Kaplan-Meier curves showed that STEMI
27 patients with lower FGF21 levels had an increased MACE-free survival rate. Cox analysis
28 revealed that high FGF21 levels (HR: 2.011, 95% CI: 1.160-3.489) proved to be a powerful tool
29 in predicting the risk of MACEs among STEMI patients after emergency PCI.
30 **Conclusion.** Elevated FGF21 levels on admission have been shown to be a powerful predictor of
31 MACEs for STEMI patients after emergency PCI.
32 **Keywords:** Fibroblast growth factor 21, ST-segment elevation myocardial infarction, Major
33 adverse cardiovascular events
34

Introduction

36 Acute myocardial infarction (AMI) is one of the most common cardiovascular emergencies, with

37 a high mortality and disability rate. An increasing number of studies have found that the

38 inflammatory response following AMI plays a significant role in determining the infarct area and

39 subsequent adverse left ventricular (LV) remodeling (Ong S B, et al. *2018*). As the understanding

40 of inflammatory mechanisms following AMI has increased, many liver-derived biomarkers with

41 excellent prognostic value, such as C-reactive protein and interleukin-6, have been discovered

42 (Groot H E, et al. *2015;* Ziakas A, et al. *2006*).

43   Another liver-secreted cytokine with anti-inflammatory effects, fibroblast growth factor 21

44 (FGF21), has gained increasing interest in recent cardiovascular research. Previous studies have

45 found that FGF21, in addition to its anti-inflammatory effects, has an antioxidative stress effect

46 and regulates glycolipid metabolism (Fisher F M, et al. *2016;* Luo Y, et al. *2017*). Previous

47 studies have found that inflammation, oxidative stress, and disturbances in glycolipid

48 metabolism play an important role in the pathogenesis of AMI (Neri M, et al. *2017;* Tao L, et al.

49 *2015;* Zhang Q, et al. *2018*). Therefore, we speculate that FGF21 is correlated with the prognosis

50 of AMI.

51   Previous studies have found that serum FGF21 levels were higher in patients with AMI than

52 in patients with stable angina (SA), and correlated with the occurrence of major adverse

53 cardiovascular events (MACEs) (Chen H, et al. *2018;* Sunaga H, et al. *2019;* Zhang W, et al.

54 *2015*). However, these studies did not distinguish between STEMI patients and NSTEMI

55 patients. Therefore, the relationship between serum FGF21 levels and the prognosis of STEMI

56 patients, who account for 45.8% of AMI patients (Kuch B, et al. *2007*), remains unclear. The

57 goal of this study was to evaluate whether serum FGF21 levels on admission could predict

58 MACEs in STEMI patients after emergency percutaneous coronary intervention (PCI).

59

Methods

Study population

62 A total of 348 patients with STEMI admitted to Jiangyin People's Hospital were enrolled from

63 January 2016 to December 2018. They all underwent emergency coronary angiography and PCI

64 within 12 hours after the onset of ischemic symptoms. The STEMI patients received medication

65 according to the American College of Cardiology Foundation/American Heart Association

66 (ACCF/AHA) guidelines (O'Gara P T, et al. *2013*). To exclude the influence of PCI on the

67 experimental results, 80 patients with SA who underwent selective coronary angiography and

68 PCI during the same period were selected as the control group.

69 The research was approved by the Ethics Committee of Jiangyin People's Hospital

70 (approval number: 2015ER035), and written informed consent was obtained from all enrolled

71 patients before participation. STEMI is a clinical syndrome defined by characteristic symptoms

72 of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation

73 and the subsequent release of biomarkers of myocardial necrosis (O'Gara P T, et al. *2013*).

74 Patients will be excluded if they present with the following diseases: cardiac shock, primary

75 valvular heart disease, congenital heart disease, tachycardia-induced cardiomyopathy, pericardial

76 disease, chronic liver insufficiency, acute renal failure, rheumatic disease, pulmonary embolism,

77 neoplasm, inflammatory or infectious disorders, and excess alcohol consumption.

78 **Clinical and Laboratory Assessments**

79 The baseline characteristics of the participants and history of hypertension, diabetes mellitus and

80 atrial fibrillation were recorded by experienced physicians. All patients underwent physical

81 examination on admission, and elbow venous blood was drawn with a separation gel vacuum

82 tube on an empty stomach early the next morning. A portion of the blood samples were sent to

83 the central laboratory for troponin I testing by a Beckman DXI800 and for triglyceride, total

84 cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol

85 (HDL-C), uric acid, N-terminal proBNP (NT-proBNP) and creatinine assessment by Roche e602

86 and c701 modules, respectively. The other part of each blood sample was centrifuged to obtain

87 serum and stored at -80°C in a refrigerator, and serum FGF21 levels were measured every 3

88 months, as in our previous study (Gu L, et al. *2021*).

89 **Echocardiography**

90 All patients underwent echocardiography on 7-10 days after primary PCI (P-PCI).

91 Echocardiogram was performed by experienced operators with an ultrasound machine (Philips iE

92 33 xMatrix).

93 The mitral regurgitation was examined and evaluated for severity using the flow

94 convergence (PISA) method according to the guidelines of the American Society of

95 echocardiography (Zoghbi W A, et al. *2003*). Pulmonary artery pressure was assessed by the

96 tricuspid regurgitation method. The left atrial diameter (LAD), interventricular septum thickness

97 (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic diameter

98 (LVEDD), left ventricular end-systolic diameter (LVESD) and left ventricular ejection fraction

99 (LVEF) were measured in the parasternal long-axis view in the M-mode images. left ventricular

100 end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were

101 measured by the Simpson method. Left ventricular mass (LVM) was calculated using the

102   formula $0.8 \times 1.04 \times [(IVST + LVPWT + LVEDD)^3 - (LVEDD)^3] + 0.6$ (Lang R M, et al.

103   *2015*).

104   **Follow-up**

105   Follow-up, which was initiated at enrollment and ended in April 2020, was conducted for

106   STEMI patients only. The median follow-up time was 24 months (interquartile range, 16-36.25

107   months). The primary endpoint of the study was the first MACE, defined as all-cause mortality

108   or readmission for angina, heart failure, or recurrent AMI. The follow-up was conducted through

109   periodic outpatient interviews and scripted telephone interviews with the patients or their

110   families every month. Due to the high mobility of migrant workers and changes in phone

111   numbers, 30 of the STEMI patients were lost to follow-up. Among all STEMI patients, 106

112   recorded MACEs, including 6 deaths and 100 readmissions (Fig. 1).

113   **Statistical analysis**

114   Statistical analysis was conducted using the SPSS 22.0 statistical package. The quantitative

115   variables are expressed as the means ± standard deviations and compared using Student's t test.

116   Categorical variables were expressed as absolute numbers (percentages) and compared using the

117   chi-square test and Mann-Whitney-Wilcoxon test. Multiple linear regression analysis was

118   performed on the STEMI groups to evaluate the association between serum FGF21 concentration

119   and other clinical covariates. Receiver operating characteristic (ROC) analysis was used to

120   determine the accuracy of the best cutoff value of variables for predicting the occurrence of

121   MACEs. MACE-free survival analysis was performed with Kaplan-Meier survival curves and

122   compared using the log-rank test. Univariate and multivariate Cox proportional hazards models

123   were used to analyze the relationships between FGF21 levels and MACEs by calculating hazard

124   ratios (HRs) and 95% CIs. Multivariate Cox analysis was performed on all variables that reached

125   statistical significance in univariate Cox analysis. A p value< 0.05 was considered statistically

126   significant (two-tailed).

127

128   **Results**

129   The demographic and baseline clinical characteristics of the subjects are summarized in Table 1.

130   No differences were observed in sex, age, incidence of atrial fibrillation, levels of triglycerides,

131   total cholesterol, uric acid, creatinine, pulmonary pressure, mitral regurgitation, IVST, LVPWT

132   and LVEDV between the STEMI and SA groups. Compared with the SA group, the STEMI

133   group had a higher incidence of hypertension and diabetes. LDL-C and NT-proBNP levels were

134   markedly higher in the STEMI group than in the SA group, while the HDL-C levels were lower

135   in the STEMI group than in the SA group (all P<0.05). The LAD, LVEDD, LVESD, LVESV,

136   LVM and LVEF were also markedly different between the groups. There were significant

137   differences between the two groups in the culprit artery and lesion site (P<0.05). The levels of

138   serum FGF21 were significantly higher in the STEMI group than in the SA group (225.03±37.98

139   vs. 135.51±34.48, P<0.001) (Table 1). Multiple linear regression analysis revealed that serum

140   FGF21 levels were correlated with NT-proBNP levels (P<0.001).

141   During the median follow-up of 24 months, 30 patients (8.62%) were lost to follow-up.106

142   patients (30.46%) experienced MACEs in the study: 6 patients died, and 100 patients were

143   rehospitalized due to angina, heart failure or recurrent AMI. According to the ROC analysis,

144   both FGF21 and NT-proBNP levels were significant indicators of MACEs in STEMI patients

145   (Fig. 2). The area under the ROC curve (AUC) of NT-proBNP was 0.865 (95% CI: 0.822-0.909),

146   which was greater than that of FGF21 (AUC, 0.812; 95% CI: 0.765-0.860). The difference

147   between the two AUCs was statistically significant (Z=2.230, P=0.026).

148   According to the optimal cutoff value determined by ROC analysis and Youden index,

149   FGF21 was divided into high FGF21 level group and low FGF21 level group for Kaplan-Meier

150   analysis. The optimal cutoff value of FGF21 was 229.77 pg/ml, with a corresponding sensitivity

151   of 84.00% and a specificity of 65.10%.

152   In the Kaplan-Meier analysis, a significant difference was observed between the high serum

153   FGF21 level group and the low serum FGF21 level group (Fig. 3). The Mace-free probability

154   among STEMI patients with high serum FGF21 levels was significantly lower than that of

155   STEMI patients with low serum FGF21 levels.

156   The results of univariate and multivariate Cox proportional hazards models are shown in

157   Table 2. Univariate Cox analysis showed that a high FGF21 level was a predictor for MACEs in

158   STEMI patients, in addition to age, creatinine, troponin I, NT-proBNP, pulmonary pressure,

159   mitral regurgitation, LAD, LVESD, LVESV and LVEF. In the multivariate Cox analysis, high

160   FGF21 levels (HR: 2.224, 95% CI: 1.122-4.407) also proved to be a powerful tool in predicting

161   the risk of MACEs. We also found that troponin I (HR: 6.842, 95% CI: 3.870-12.094), NT-

162   proBNP levels (HR:3.452, 95% CI: 1.765-6.750), and mitral regurgitation (HR: 2.011, 95% CI:

163   1.160-3.489) increased the risk of MACEs.

164

165   **Discussion**

166   In this study, we demonstrated that serum FGF21 levels were significantly elevated in STEMI

167   patients and correlated with NT-proBNP. At a median follow-up of 24 months, MACE-free

168   survival was reduced in STEMI patients with elevated FGF21 levels, and elevated FGF21 levels

169   were shown to be a strong predictor of MACEs in STEMI patients.

170   Recent studies have found that the heart is not only a target organ for FGF21 but also one of

171   its sources (Planavila A, Redondo-Angulo I, Ribas F, et al. *2015*). The expression of FGF21

172   increases due to stimulation by inflammation, oxidative stress, lipid toxicity and endoplasmic

173   reticulum stress, which plays an important role in cardiovascular disease (Brahma M K, et al.

174   *2014;* Planavila A, Redondo-Angulo I, Ribas F, et al. *2015;* Steven S, et al. *2019*). Then, FGF21

175   is synthesized by cardiomyocytes and secreted in an autocrine manner (Planavila A, et al. *2013;*

176   Planavila A, Redondo-Angulo I, & Villarroya F *2015*). In target cells, FGF21 binds to FGF

177   receptors and β Klotho, which are widely expressed in cardiomyocytes (Domouzoglou E M, et

178   al. *2015*). Increased cardiac FGF21 expression protects cardiomyocytes from inflammation,

179   oxidative stress and dysfunction after myocardial I/R injury (Hu S, et al. *2018;* Zhang J, et al.

180   *2016*).

181   Accumulating evidence indicates that elevated FGF21 concentrations are associated with a

182   higher incidence of diabetes, chronic kidney disease, hypertension, and cardiovascular diseases,

183   including coronary artery disease, heart failure, atrial fibrillation and AMI (Gu L, et al. *2020;*

184   Shen Y, et al. *2017;* Shen Y, et al. *2018;* Wang R, et al. *2015;* Wu C H, et al. *2018;* Zhang W, et

185   al. *2015*). Moreover, FGF21 significantly predicts the incidence of coronary artery disease and

186   all-cause and cardiovascular mortality (Lakhani I, et al. *2018*). This is consistent with the results

187   of our study.

188   However, the increase in FGF21 levels, which has a cardioprotective effect, is negatively

189   correlated with the prognosis of cardiovascular disease. Previous research reveals that the

190   elevation of FGF21 levels in pathological conditions may be part of a compensatory response to

191   the underlying metabolic stress or may be caused by FGF21 resistance as a result of impaired

192   FGF21 signaling (Lewis J E, et al. *2019;* Woo Y C, et al. *2013*). Therefore, more FGF21 is

193   secreted to compensate for its reduced metabolic regulation caused by FGF21 resistance.

194   Moreover, additional supplementation with FGF21 has been shown to have a therapeutic effect

195   in in vitro trials (Zhu W, et al. *2014*). Furthermore, some companies, such as Eli Lilly and Pfizer,

196   have now developed FGF21 analogs and demonstrated their therapeutic potential in clinical trials

197   for the treatment of metabolic diseases (BonDurant L D, et al. *2018*).

198   Inconsistent with previous studies, the Multi-Ethnic Study of Atherosclerosis (MESA)

199   recently found that FGF21 levels were not associated with incident cardiovascular disease after

200   multiple adjustments (Ong K L, et al. *2019*); however, this study enrolled only patients without

201   cardiovascular disease. In contrast to MESA, the patients enrolled in our study were STEMI

202   patients, and we found that FGF21 was associated with the occurrence of MACEs. In MESA,

203   481 patients underwent PCI because of cardiac ischemia, mainly acute coronary syndrome

204   (ACS). Subgroup analysis showed that the higher the FGF21 level was, the sooner the ACS
205   occurred and the higher the incidence of PCI. These studies suggested that for patients with
206   cardiovascular disease, elevated FGF21 levels indicated a poor prognosis. Similarly, serum
207   FGF21 levels were an independent predictor of incident coronary heart disease (CHD) in
208   diabetic patients (Lee C H, et al. *2017*). In general, for patients with cardiovascular disease or
209   diabetes, FGF21 is likely to be a powerful biomarker for predicting MACEs. However, for
210   healthy people, a large number of studies are still needed to validate this conclusion.
211   Although several studies have focused on the association of FGF21 with AMI, we found for
212   the first time that FGF21 was related to the prognosis of STEMI patients after treatment with
213   emergency PCI. Sunaga et al found that serum FGF21 levels were significantly higher in patients
214   with AMI after PCI than in patients with SA, but this study was not followed up (Sunaga H, et al.
215   *2019*). Another study that included a sample of 55 STEMI and NSTEMI patients found that
216   FGF21 was associated with AMI and with the incidence of reinfarction within 30 days after
217   onset (Zhang W, et al. *2015*). Similar to our study, Chen et al. found that FGF21 was associated
218   with MACEs in patients with AMI (Chen H, et al. *2018*). However, unlike our study, the study
219   did not distinguish between STEMI patients and NSTEMI patients, although STEMI patients
220   were enrolled in the study. Overall, FGF21 was first identified as a MACE-related biomarker in
221   our follow-up study of STEMI patients treated with emergency PCI.
222   The study had several limitations. Our study was conducted at a single hospital and
223   included only Chinese people. Although our sample size meets the needs of the study, our
224   follow-up time was too short, and the number of endpoints was not large enough. The absence of
225   height, weight, ECG and peak troponin I data made it impossible to assess other factors
226   associated with MACEs. Unfortunately, we did not follow up the SA group and therefore could
227   not compare it to the STEMI group. In addition, serum FGF21 levels were measured only at
228   admission instead of including a repeated measurement at the time of readmission. Therefore,
229   large-scale and long-term clinical studies are needed to confirm the role of FGF21 and its
230   relationship to STEMI.
231   Moreover, early echocardiography was used to assess the prognosis of STEMI patients who
232   underwent emergency PCI. Although early echocardiography is not the best method to predict
233   outcomes, some studies show that early echocardiography has a predictive value for the
234   prognosis of AMI (Awad E M L, et al. *2020;* Cetin M, et al. *2021;* Reindl M, et al. *2019*).
235   However, a better approach would be to perform an echocardiography at the follow-up visit with
236   a before-and-after comparison.
237

Conclusions

In conclusion, we observed that serum FGF21 levels were significantly elevated in STEMI patients who had undergone emergency PCI. Moreover, elevated FGF21 levels on admission have been shown to be a powerful predictor of MACEs. Therefore, FGF21 can be used as a novel biomarker for STEMI after emergency PCI.

Acknowledgements

The author thanks Professor Yao Yuyu for his assistance in this manuscript.

References

1   Awad, EML, Mahmoud, AH, Maghrby, KS, Taha, NM,Ibrahim, AM. 2020. Short-term prognostic value of TAPSE, RVFAC and Tricuspid S' wave peak systolic velocity after first acute myocardial infarction. *BMC Res Notes*, 13: 196. DOI 10.1186/s13104-020-05040-2.

2   BonDurant, LD,Potthoff, MJ. 2018. Fibroblast Growth Factor 21: A Versatile Regulator of Metabolic Homeostasis. *Annu Rev Nutr*, 38: 173-96. DOI 10.1146/annurev-nutr-071816-064800.

3   Brahma, MK, Adam, RC, Pollak, NM, Jaeger, D, Zierler, KA, Pocher, N, Schreiber, R, Romauch, M, Moustafa, T, Eder, S, Ruelicke, T, Preiss-Landl, K, Lass, A, Zechner, R, Haemmerle, G. 2014. Fibroblast growth factor 21 is induced upon cardiac stress and alters cardiac lipid homeostasis. *J Lipid Res*, 55: 2229-41. DOI 10.1194/jlr.M044784.

4   Cetin, M, Ozer, S, Cinier, G, Yilmaz, AS, Erdogan, T,Satiroglu, O. 2021. Left atrial volume index and pulmonary arterial pressure predicted MACE among patients with STEMI during 8-year follow-up: experience from a tertiary center. *Herz*, 46: 367-74. DOI 10.1007/s00059-020-04966-4.

5   Chen, H, Lu, N,Zheng, M. 2018. A high circulating FGF21 level as a prognostic marker in patients with acute myocardial infarction. *Am J Transl Res*, 10: 2958-66. DOI.

6   Domouzoglou, EM, Naka, KK, Vlahos, AP, Papafaklis, MI, Michalis, LK, Tsatsoulis, A, Maratos-Flier, E. 2015. Fibroblast growth factors in cardiovascular disease: The emerging role of FGF21. *Am J Physiol Heart Circ Physiol*, 309: H1029-38. DOI 10.1152/ajpheart.00527.2015.

7   Fisher, FM,Maratos-Flier, E. 2016. Understanding the Physiology of FGF21. *Annu Rev Physiol*, 78: 223-41. DOI 10.1146/annurev-physiol-021115-105339.

8   Groot, HE, Hartman, MH, Gu, YL, de Smet, BJ, van den Heuvel, AF, Lipsic, E, van der Harst, P. 2015. Soluble interleukin 6 receptor levels are associated with reduced myocardial reperfusion after percutaneous coronary intervention for acute myocardial infarction. *Cytokine*, 73: 207-12. DOI 10.1016/j.cyto.2015.02.004.

9   Gu, L, Jiang, W, Zheng, R, Yao, Y,Ma, G. 2020. Fibroblast Growth Factor 21 Correlates with the Prognosis of Dilated Cardiomyopathy. *Cardiology*, 1-7. DOI 10.1159/000509239.

276 10 Gu, L, Jiang, W, Zheng, R, Yao, Y,Ma, G. 2021. Fibroblast Growth Factor 21 Correlates with
277   the Prognosis of Dilated Cardiomyopathy. *Cardiology*, 146: 27-33. DOI 10.1159/000509239.

278 11 Hu, S, Cao, S, Tong, Z,Liu, J. 2018. FGF21 protects myocardial ischemia-reperfusion injury
279   through reduction of miR-145-mediated autophagy. *Am J Transl Res*, 10: 3677-88. DOI.

280 12 Kuch, B, von Scheidt, W, Kling, B, Heier, M, Hoermann, A,Meisinger, C. 2007.
281   Characteristics and outcome of patients with acute myocardial infarction according to
282   presenting electrocardiogram (from the MONICA/KORA Augsburg Myocardial Infarction--
283   Registry). *Am J Cardiol*, 100: 1056-60. DOI 10.1016/j.amjcard.2007.04.054.

284 13 Lakhani, I, Gong, M, Wong, WT, Bazoukis, G, Lampropoulos, K, Wong, SH, Wu, WKK,
285   Wong, MCS, Ong, KL, Liu, T, Tse, G, International Health Informatics Study, N. 2018.
286   Fibroblast growth factor 21 in cardio-metabolic disorders: a systematic review and meta-
287   analysis. *Metabolism*, 83: 11-17. DOI 10.1016/j.metabol.2018.01.017.

288 14 Lang, RM, Badano, LP, Mor-Avi, V, Afilalo, J, Armstrong, A, Ernande, L, Flachskampf, FA,
289   Foster, E, Goldstein, SA, Kuznetsova, T, Lancellotti, P, Muraru, D, Picard, MH, Rietzschel,
290   ER, Rudski, L, Spencer, KT, Tsang, W, Voigt, JU. 2015. Recommendations for cardiac
291   chamber quantification by echocardiography in adults: an update from the American Society
292   of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J*
293   *Cardiovasc Imaging*, 16: 233-70. DOI 10.1093/ehjci/jev014.

294 15 Lee, CH, Woo, YC, Chow, WS, Cheung, CYY, Fong, CHY, Yuen, MMA, Xu, A, Tse, HF,
295   Lam, KSL. 2017. Role of Circulating Fibroblast Growth Factor 21 Measurement in Primary
296   Prevention of Coronary Heart Disease Among Chinese Patients With Type 2 Diabetes
297   Mellitus. *J Am Heart Assoc*, 6. DOI 10.1161/JAHA.116.005344.

298 16 Lewis, JE, Ebling, FJP, Samms, RJ,Tsintzas, K. 2019. Going Back to the Biology of FGF21:
299   New Insights. *Trends Endocrinol Metab*, 30: 491-504. DOI 10.1016/j.tem.2019.05.007.

300 17 Luo, Y, Ye, S, Chen, X, Gong, F, Lu, W,Li, X. 2017. Rush to the fire: FGF21 extinguishes
301   metabolic stress, metaflammation and tissue damage. *Cytokine Growth Factor Rev*, 38: 59-
302   65. DOI 10.1016/j.cytogfr.2017.08.001.

303 18 Neri, M, Riezzo, I, Pascale, N, Pomara, C,Turillazzi, E. 2017. Ischemia/Reperfusion Injury
304   following Acute Myocardial Infarction: A Critical Issue for Clinicians and Forensic
305   Pathologists. *Mediators Inflamm*, 2017: 7018393. DOI 10.1155/2017/7018393.

306 19 O'Gara, PT, Kushner, FG, Ascheim, DD, Casey, DE, Jr., Chung, MK, de Lemos, JA, Ettinger,
307   SM, Fang, JC, Fesmire, FM, Franklin, BA, Granger, CB, Krumholz, HM, Linderbaum, JA,
308   Morrow, DA, Newby, LK, Ornato, JP, Ou, N, Radford, MJ, Tamis-Holland, JE, Tommaso,
309   CL, Tracy, CM, Woo, YJ, Zhao, DX. 2013. 2013 ACCF/AHA guideline for the management
310   of ST-elevation myocardial infarction: a report of the American College of Cardiology
311   Foundation/American Heart Association Task Force on Practice Guidelines. *Journal of the*
312   *American College of Cardiology*, 61: e78-e140. DOI 10.1016/j.jacc.2012.11.019.

313 20 Ong, KL, Campbell, S, Wu, BJ, McClelland, RL, Kokkinos, J, Szklo, M, Polak, JF, Allison,
314   MA, Rye, KA. 2019. Relationship of fibroblast growth factor 21 with subclinical

315 atherosclerosis and cardiovascular events: Multi-Ethnic Study of Atherosclerosis.
316 *Atherosclerosis*, 287: 46-53. DOI 10.1016/j.atherosclerosis.2019.06.898.

317 21 Ong, SB, Hernandez-Resendiz, S, Crespo-Avilan, GE, Mukhametshina, RT, Kwek, XY,
318 Cabrera-Fuentes, HA, Hausenloy, DJ. 2018. Inflammation following acute myocardial
319 infarction: Multiple players, dynamic roles, and novel therapeutic opportunities. *Pharmacol*
320 *Ther*, 186: 73-87. DOI 10.1016/j.pharmthera.2018.01.001.

321 22 Planavila, A, Redondo, I, Hondares, E, Vinciguerra, M, Munts, C, Iglesias, R, Gabrielli, LA,
322 Sitges, M, Giralt, M, van Bilsen, M, Villarroya, F. 2013. Fibroblast growth factor 21 protects
323 against cardiac hypertrophy in mice. *Nature Communications*, 4: 2019. DOI
324 10.1038/ncomms3019.

325 23 Planavila, A, Redondo-Angulo, I, Ribas, F, Garrabou, G, Casademont, J, Giralt, M,
326 Villarroya, F. 2015. Fibroblast growth factor 21 protects the heart from oxidative stress.
327 *Cardiovascular Research*, 106: 19-31. DOI 10.1093/cvr/cvu263.

328 24 Planavila, A, Redondo-Angulo, I,Villarroya, F. 2015. FGF21 and Cardiac Physiopathology.
329 *Front Endocrinol (Lausanne)*, 6: 133. DOI 10.3389/fendo.2015.00133.

330 25 Reindl, M, Reinstadler, SJ, Tiller, C, Feistritzer, HJ, Kofler, M, Brix, A, Mayr, A, Klug, G,
331 Metzler, B. 2019. Prognosis-based definition of left ventricular remodeling after ST-elevation
332 myocardial infarction. *Eur Radiol*, 29: 2330-39. DOI 10.1007/s00330-018-5875-3.

333 26 Shen, Y, Zhang, X, Pan, X, Xu, Y, Xiong, Q, Lu, Z, Ma, X, Bao, Y, Jia, W. 2017.
334 Contribution of serum FGF21 level to the identification of left ventricular systolic
335 dysfunction and cardiac death. *Cardiovasc Diabetol*, 16: 106. DOI 10.1186/s12933-017-
336 0588-5.

337 27 Shen, Y, Zhang, X, Xu, Y, Xiong, Q, Lu, Z, Ma, X, Bao, Y, Jia, W. 2018. Serum FGF21 Is
338 Associated with Future Cardiovascular Events in Patients with Coronary Artery Disease.
339 *Cardiology*, 139: 212-18. DOI 10.1159/000486127.

340 28 Steven, S, Frenis, K, Oelze, M, Kalinovic, S, Kuntic, M, Bayo Jimenez, MT, Vujacic-Mirski,
341 K, Helmstadter, J, Kroller-Schon, S, Munzel, T, Daiber, A. 2019. Vascular Inflammation and
342 Oxidative Stress: Major Triggers for Cardiovascular Disease. *Oxid Med Cell Longev*, 2019:
343 7092151. DOI 10.1155/2019/7092151.

344 29 Sunaga, H, Koitabashi, N, Iso, T, Matsui, H, Obokata, M, Kawakami, R, Murakami, M,
345 Yokoyama, T, Kurabayashi, M. 2019. Activation of cardiac AMPK-FGF21 feed-forward
346 loop in acute myocardial infarction: Role of adrenergic overdrive and lipolysis byproducts.
347 *Sci Rep*, 9: 11841. DOI 10.1038/s41598-019-48356-1.

348 30 Tao, L, Bei, Y, Lin, S, Zhang, H, Zhou, Y, Jiang, J, Chen, P, Shen, S, Xiao, J, Li, X. 2015.
349 Exercise Training Protects Against Acute Myocardial Infarction via Improving Myocardial
350 Energy Metabolism and Mitochondrial Biogenesis. *Cell Physiol Biochem*, 37: 162-75. DOI
351 10.1159/000430342.

352 31 Wang, R, Yi, X, Li, X,Jiang, X. 2015. Fibroblast growth factor-21 is positively associated
353 with atrial fibrosis in atrial fibrillation patients with rheumatic heart disease. *Int J Clin Exp*

354   *Pathol*, 8: 14901-8. DOI.

355   32   Woo, YC, Xu, A, Wang, Y,Lam, KS. 2013. Fibroblast growth factor 21 as an emerging
356   metabolic regulator: clinical perspectives. *Clin Endocrinol (Oxf)*, 78: 489-96. DOI
357   10.1111/cen.12095.

358   33   Wu, CH, Chou, RH, Kuo, CS, Huang, PH, Chang, CC, Leu, HB, Huang, CC, Chen, JW, Lin,
359   SJ. 2018. Circulating Fibroblast Growth Factor 21 is Associated with Subsequent Renal
360   Injury Events in Patients Undergoing Coronary Angiography. *Sci Rep*, 8: 12425. DOI
361   10.1038/s41598-018-30744-8.

362   34   Zhang, J, Cheng, Y, Gu, J, Wang, S, Zhou, S, Wang, Y, Tan, Y, Feng, W, Fu, Y, Mellen, N,
363   Cheng, R, Ma, J, Zhang, C, Li, Z, Cai, L. 2016. Fenofibrate increases cardiac autophagy via
364   FGF21/SIRT1 and prevents fibrosis and inflammation in the hearts of Type 1 diabetic mice.
365   *Clin Sci (Lond)*, 130: 625-41. DOI 10.1042/CS20150623.

366   35   Zhang, Q, Shao, M, Zhang, X, Wang, Q, Guo, D, Yang, X, Li, C, Wang, Y. 2018. The Effect
367   of Chinese Medicine on Lipid and Glucose Metabolism in Acute Myocardial Infarction
368   Through PPARgamma Pathway. *Front Pharmacol*, 9: 1209. DOI 10.3389/fphar.2018.01209.

369   36   Zhang, W, Chu, S, Ding, W,Wang, F. 2015. Serum Level of Fibroblast Growth Factor 21 Is
370   Independently Associated with Acute Myocardial Infarction. *PLoS One*, 10: e0129791. DOI
371   10.1371/journal.pone.0129791.

372   37   Zhu, W, Wang, C, Liu, L, Li, Y, Li, X, Cai, J, Wang, H. 2014. Effects of fibroblast growth
373   factor 21 on cell damage in vitro and atherosclerosis in vivo. *Can J Physiol Pharmacol*, 92:
374   927-35. DOI 10.1139/cjpp-2014-0227.

375   38   Ziakas, A, Gavrilidis, S, Giannoglou, G, Souliou, E, Gemitzis, K, Kalampalika, D, Vayona,
376   MA, Pidonia, I, Parharidis, G, Louridas, G. 2006. In-hospital and long-term prognostic value
377   of fibrinogen, CRP, and IL-6 levels in patients with acute myocardial infarction treated with
378   thrombolysis. *Angiology*, 57: 283-93. DOI 10.1177/000331970605700304.

379   39   Zoghbi, WA, Enriquez-Sarano, M, Foster, E, Grayburn, PA, Kraft, CD, Levine, RA,
380   Nihoyannopoulos, P, Otto, CM, Quinones, MA, Rakowski, H, Stewart, WJ, Waggoner, A,
381   Weissman, NJ, American Society of, E. 2003. Recommendations for evaluation of the
382   severity of native valvular regurgitation with two-dimensional and Doppler
383   echocardiography. *J Am Soc Echocardiogr*, 16: 777-802. DOI 10.1016/S0894-
384   7317(03)00335-3.

385

Figure 1

Flow chart of this study

A total of 348 patients with STEMI were enrolled from January 2016 to December 2018. They all underwent emergency coronary angiography and PCI within 12 hours after the onset of ischemic symptoms. 80 patients with stable angina who underwent selective coronary angiography and PCI were selected as the control group. Follow-up, which was initiated at enrollment and ended in April 2020, was conducted for STEMI patients only. The median follow-up time was 24 months (interquartile range, 16-36.25 months). The primary endpoint of the study was the first MACE, defined as all-cause mortality or readmission for angina, heart failure, or recurrent AMI. Eventually, 30 of the STEMI patients were lost to follow-up and 106 recorded MACEs, including 6 deaths and 100 readmissions. PCI: percutaneous coronary intervention; STEMI: st-segment elevation myocardial infarction; MACEs: major adverse cardiovascular events; AMI: acute myocardial infarction.

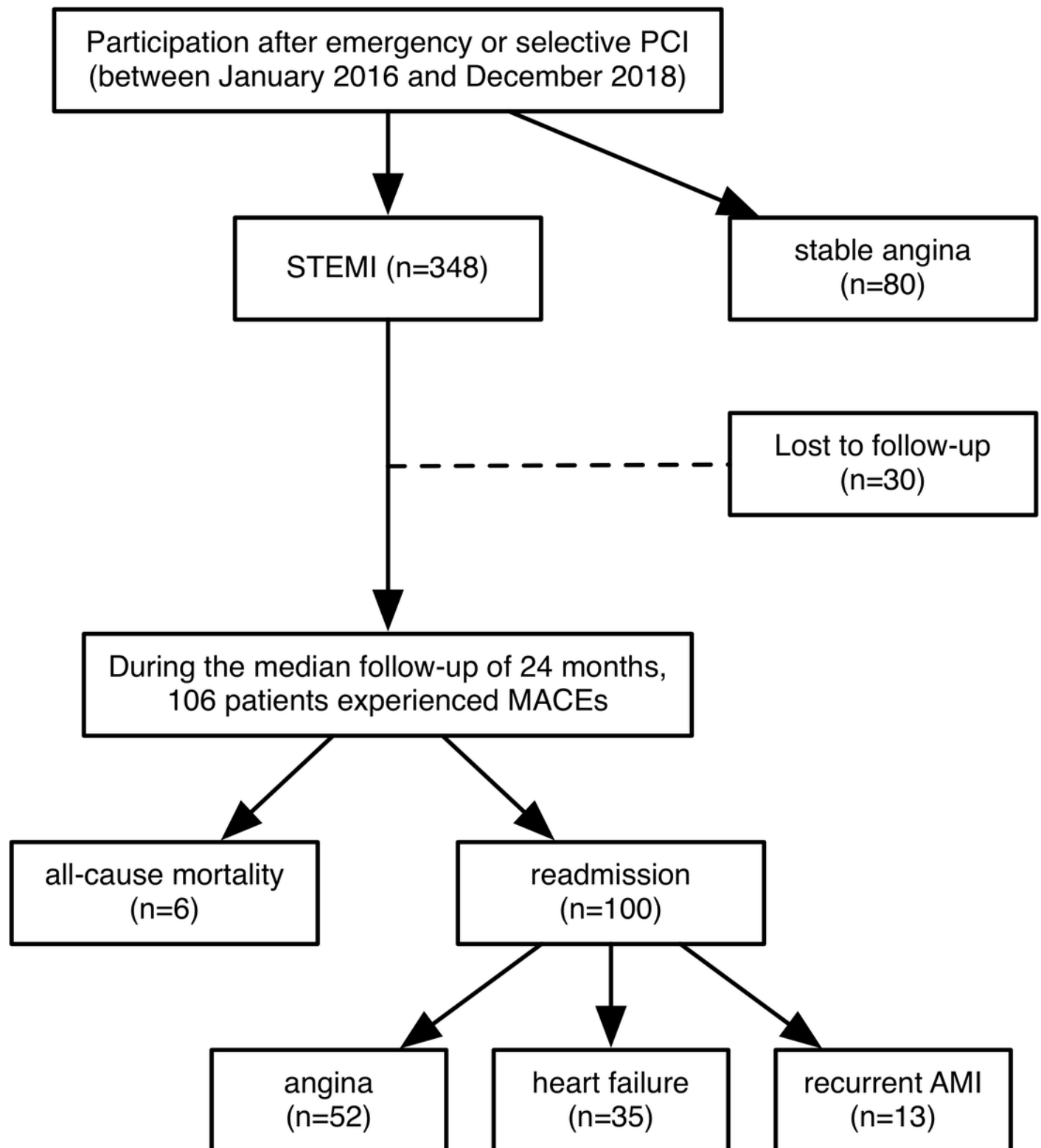



Figure 2

Receiver operating characteristic curve for predicting prognosis in STEMI patients after emergency PCI

During the median follow-up of 24 months, 106 patients experienced MACEs in the study: 6 patients died, and 100 patients were rehospitalized due to angina, heart failure or recurrent AMI. According to the ROC analysis, both FGF21 and NT-proBNP levels were significant indicators of MACEs in STEMI patients. The area under the ROC curve (AUC) of NT-proBNP was 0.865 (95% CI: 0.822-0.909), which was greater than that of FGF21 (AUC, 0.812; 95% CI: 0.765-0.860). The difference between the two AUCs was statistically significant (Z=2.230, P=0.026). NT-proBNP, N-terminal proB-type natriuretic peptide; FGF21, fibroblast growth factor 21.

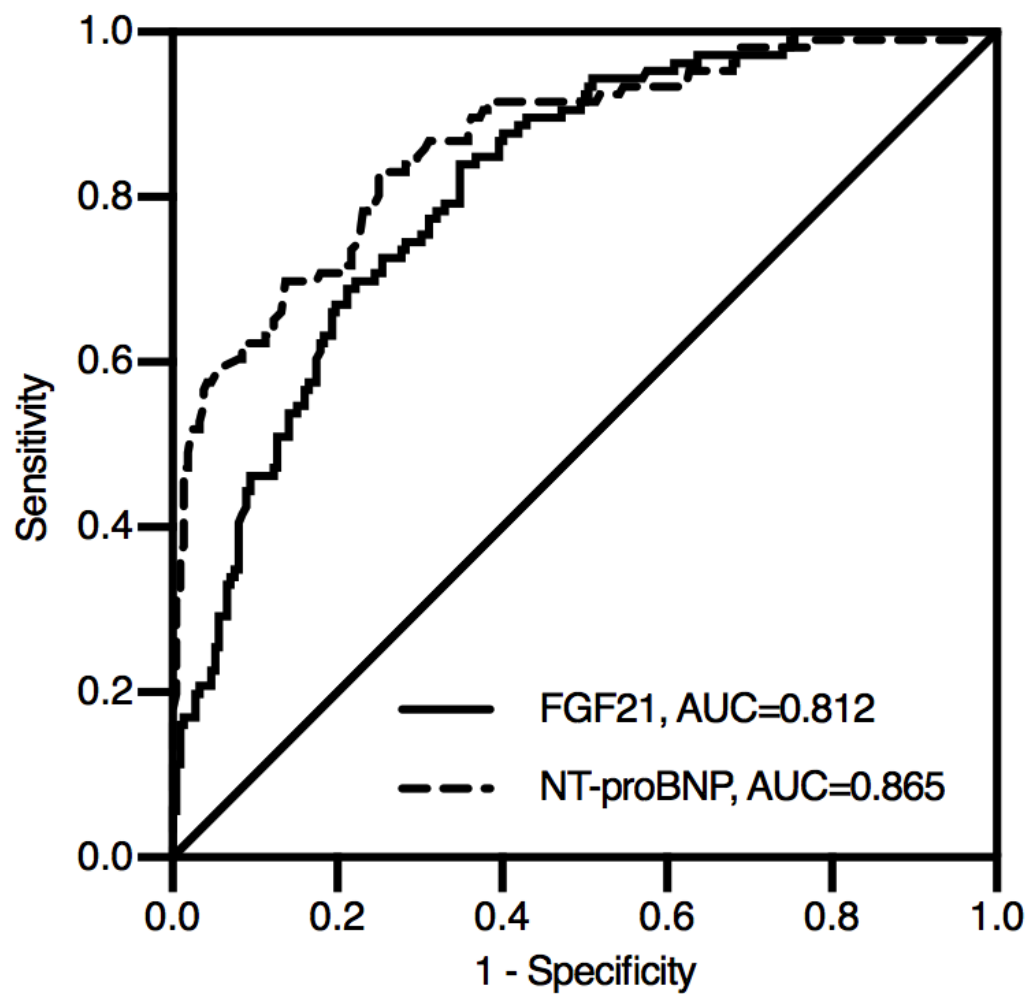
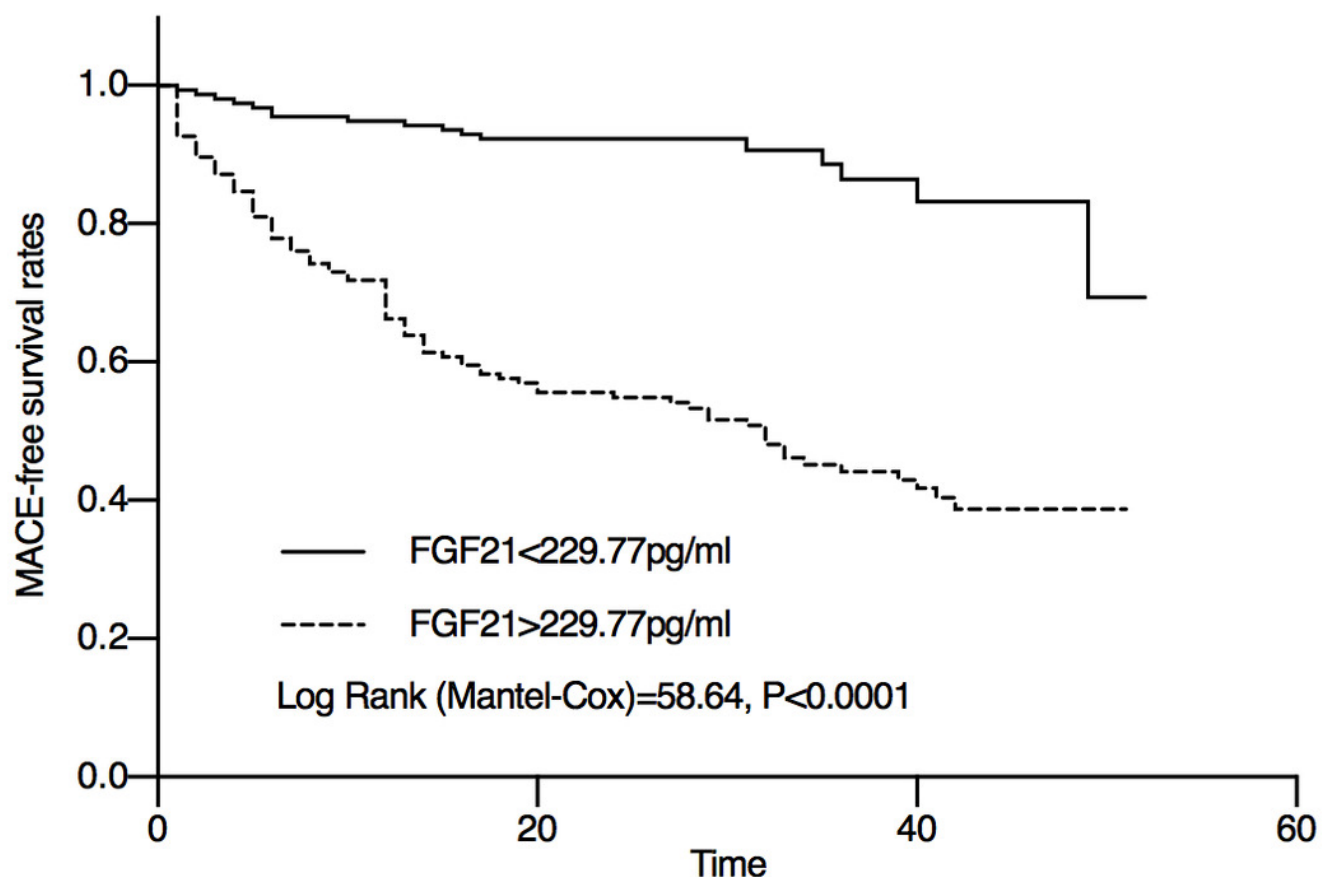



Figure 3

Kaplan-Meier curve showing the Mace-free probability of STEMI patients after emergency PCI with different FGF21 levels.

According to the optimal cutoff value determined by ROC analysis and Youden index, FGF21 was divided into high FGF21 level group and low FGF21 level group. The optimal cutoff value of FGF21 was 229.77 pg/ml. The Mace-free probability among STEMI patients with high serum FGF21 levels was significantly lower than that of STEMI patients with low serum FGF21 levels.

The Demographic and Baseline Clinical Characteristics of the Patients

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NT-proBNP, N-terminal proB-type natriuretic peptide; FGF21, fibroblast growth factor 21; IVST, interventricular septal wall thickness; LVPWT, left ventricular posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LCX, left circumflex artery; RCA, right coronary artery.

1 **Table 1:**

2 **The Demographic and Baseline Clinical Characteristics of the Patients**

Variables	STEMI group (n=348)	SA group (n=80)	P value
Demographic data			
Male, n (%)	280 (80.46%)	57 (71.25%)	0.069
Age (years)	62.05±13.05	59.70±12.56	0.144
Hypertension, n (%)	185(53.16%)	17 (21.25%)	0.020
Diabetes mellitus, n (%)	64 (18.39%)	7 (8.75%)	0.037
Atrial fibrillation, n (%)	27 (7.76%)	4 (5.00%)	0.391
Laboratory data			
Total cholesterol (mmol/L)	4.33±1.11	4.50±1.29	0.271
Triglyceride (mmol/L)	1.83±1.44	2.04±1.57	0.245
LDL-C (mmol/L)	3.26±1.01	2.49±0.72	0.000
HDL-C (mmol/L)	1.14±0.44	1.29±0.42	0.008
Uric acid (μmol/L)	340.16±98.12	332.52±59.90	0.370
Creatinin (μmol/L)	80.88±59.96	72.18±20.05	0.219
Troponin I (ng/ml)	44.07±20.76	-	-
NT-proBNP (pg/ml)	593.17±584.25	164.03±100.25	0.000
FGF21 (pg/ml)	225.03±37.98	135.51±34.48	0.000
Echocardiographic data			
Pulmonary pressure (mmHg)	32.30±8.34	32.00±6.16	0.762
Mitral regurgitation	49 (14.08%)	11 (13.75%)	0.818
LAD (mm)	41.26±4.74	39.68±4.05	0.006
IVST (mm)	9.75±1.69	9.63±1.33	0.548
LVPWT (mm)	9.86±1.35	9.65±1.25	0.203
LVEDD (mm)	52.42±4.45	50.33±3.96	0.000
LVESD (mm)	37.75±4.83	33.18±4.07	0.000
LVEDV (ml)	127.18±38.03	121.08±21.89	0.057
LVESV (ml)	59.63±23.52	45.76±14.58	0.000
LVM (g)	193.21±42.47	177.35±40.14	0.003
LVEF (%)	53.66±7.99	62.36±6.32	0.000
Angiographic data			
Culprit artery			0.003
LAD, n (%)	207 (59.48%)	61 (76.25%)	
LCX, n (%)	32 (9.20%)	7 (8.75)	

RCA, n (%)	109 (31.32%)	12 (15.00%)	
Culprit lesion site			0.038
Proximal segment, n (%)	195 (56.03%)	32 (40.00%)	
Middle segment, n (%)	121 (34.77%)	43 (53.75%)	
Distal segment, n (%)	32 (9.20%)	5 (6.25)	
Number of diseased vessels			0.194
One vessels, n (%)	248 (71.26%)	62 (77.50%)	
Two vessels, n (%)	67 (19.25%)	15 (18.75%)	
Three vessels, n (%)	33 (9.48%)	3 (3.75%)	

3 LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NT-proBNP, N-

4 terminal proB-type natriuretic peptide; FGF21, fibroblast growth factor 21; IVST, interventricular septal wall

5 thickness; LVPWT, left ventricular posterior wall thickness; LVEDD, left ventricular end-diastolic diameter;

6 LVESD, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left

7 ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAD,

8 left atrial dimension; LCX, left circumflex artery; RCA, right coronary artery.

Univariate and Multivariate COX Analysis for Prognosis in STEMI Patients

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NT-proBNP, N-terminal proB-type natriuretic peptide; FGF21, fibroblast growth factor 21; IVST, interventricular septal wall thickness; LVPWT, left ventricular posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; LCX, left circumflex artery; RCA, right coronary artery.

1 **Table 2:**

2 **Univariate and Multivariate COX Analysis for Prognosis in STEMI Patients**

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Sex (male)	0.744	0.474-1.166	0.197	-	-	-
Age (years)	1.766	1.188-2.626	0.005	-	-	-
Hypertension	1.102	0.752-1.616	0.619	-	-	-
Diabetes mellitus	1.398	0.874-2.236	0.162	-	-	-
Atrial fibrillation	1.317	0.705-2.461	0.388			
Total cholesterol	0.872	0.728-1.045	0.139	-	-	-
Triglyceride	0.850	0.718-1.006	0.059	-	-	-
LDL-C	1.168	0.965-1.414	0.111	-	-	-
HDL-C	0.773	0.479-1.245	0.289	-	-	-
Uric acid	1.000	0.998-1.001	0.676	-	-	-
Creatinine	1.002	1.000-1.004	0.016	-	-	-
Troponin I	8.143	4.834-14.716	0.000	6.842	3.870-12.094	0.000
NT-proBNP	7.496	4.508-12.462	0.000	3.452	1.765-6.750	0.000
FGF21	5.901	3.509-9.922	0.000	2.224	1.122-4.407	0.022
Pulmonary pressure	1.510	1.015-2.247	0.042			
Mitral regurgitation	1.745	1.071-2.844	0.025	2.011	1.160-3.489	0.013
LAD	1.732	1.178-2.547	0.005			
IVST	1.381	0.671-2.842	0.381			
LVPWT	0.987	0.662-1.471	0.948			
LVEDD	1.359	0.924-1.998	0.119			
LVESD	1.749	1.170-2.614	0.006			
LVEDV	1.359	0.924-1.998	0.119			
LVESV	1.749	1.170-2.614	0.006			
LVM	1.334	0.882-2.016	0.172			
LVEF	1.999	1.339-2.985	0.001			
Culprit artery						
LAD			0.077			
LCX	0.487	0.212-1.120	0.091			
RCA	0.671	0.426-1.0574	0.085			
Culprit lesion site						
Proximal segment	4.095	1.287-13.028	0.017			
Middle segment	3.660	1.127-11.892	0.031			

Distal segment			0.056
Number of diseased vessels			
One vessels			0.186
Two vessels	1.144	0.921-2.262	0.109
Three vessels	0.794	0.383-1.649	0.794

3 LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NT-proBNP, N-

4 terminal proB-type natriuretic peptide; FGF21, fibroblast growth factor 21; IVST, interventricular septal wall

5 thickness; LVPWT, left ventricular posterior wall thickness; LVEDD, left ventricular end-diastolic diameter;

6 LVESD, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left

7 ventricular end-systolic volume; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; LAD,

8 left atrial dimension; LCX, left circumflex artery; RCA, right coronary artery.