Prognostic Value of Combined C-Reactive Protein, Body Mass Index, and Left Ventricular Ejection Fraction in Predicting Cardiovascular Events in Patients ≥80 Years of Age With Acute Myocardial Infarction

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Elevated high-sensitivity C-reactive protein (hsCRP) and low body mass index (BMI) are linked to increased mortality in the elderly population. However, the combined value for predicting adverse cardiovascular events in the oldest-old (≥80 years old) with acute myocardial infarction (AMI) remains undetermined. A total of 463 AMI patients, who were ≥80 years old, were enrolled in this study between January 2012 and June 2017. A nested case-control study was implemented in 106 deaths and 212 controls, who were matched for age, gender, time of inclusion, and myocardial infarction type. Furthermore, the individual and additive values of hsCRP, BMI, and left ventricular ejection fraction (LVEF) were assessed using adjusted hazard ratio, unadjusted Kaplan-Meier analysis, and receiver-operating characteristic curve models. The median follow-up time was 19.15 months, and there were 106 deaths (33.3%). Furthermore, HsCRP, BMI, and LVEF were significantly associated with all-cause mortality (p <0.05, respectively). In addition, a negative correlation between BMI and LVEF, and the positive association of hsCRP with all-cause mortality in the fully adjusted Cox proportional hazards model were detected. The combination of hsCRP, BMI, and LVEF was found to exhibit an enhanced predictive value for all-cause mortality (0.733 in jointly vs 0.623 in cardiovascular risk factors, p = 0.0007) in these oldest-old AMI patients. HsCRP, BMI, and LVEF are the independent risk factors for all-cause mortality for the oldest-old patients with AMI, and this combination offers more appreciable and reliable predictive value for all-cause mortality. **(Am J Cardiol 2019;123:544−548)**

In China, like the rest of the world, the population is dramatically ageing, with the oldest-old (i.e., ≥80 years of age) expanding most rapidly, which is usually accompanied by an increased risk of coronary artery disease (CAD) including acute coronary syndrome (ACS) and all-cause mortality.[1−3] Thus, it is imperative to perform an earlier and more accurate risk estimation of outcomes in the oldest-old experiencing ACS to prevent recurrent attacks of coronary ischemia or infarction.[3] High-sensitivity C-reactive protein (hsCRP), a low body mass index (BMI), and left ventricular ejection fraction (LVEF) have been reported to be independent predictors of ACS patients.[4−8] Although the predictive value of individual cardiovascular (CV) risk factors is appreciable in the determination of risks and adverse CV events in both patients with CV disease and the general population,[9,10] the prognostic value of combined biomarkers in predicting the outcomes has been of particular interest in CV medicine, especially for extremely high-risk patients. However, few studies have been performed to examine the combined value of several available biomarkers in predicting mortality in the oldest-old with ACS. The present study sought to examine the correlation between low BMI, elevated hsCRP, and the combined value with LVEF and traditional CV risk factors for predicting all-cause mortality among the oldest-old with acute myocardial infarction (AMI).

Methods

A total of 60,012 consecutive patients with CAD, who were hospitalized in Fuwai Hospital, National Center for Cardiovascular Diseases, between January 2012 and June 2017, were collected for the present study. Patients were excluded from the present study according to our study purpose (Figure 1). Finally, a total of 463 patients with AMI, who were >80 years old, were included in the present study. Among these patients, 106 all-cause mortality cases

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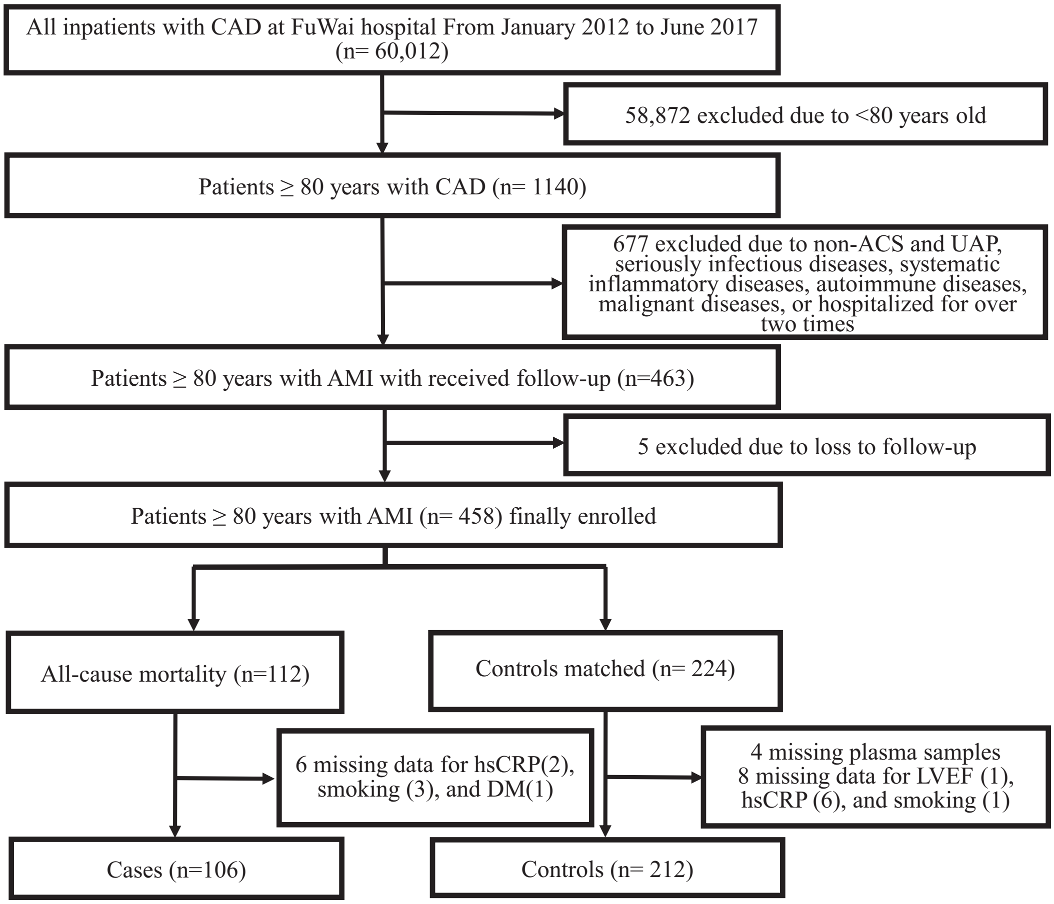

Figure 1. Flow chart of the study design. The diagram outlines how the matched sample of the case−control cohort was obtained. CAD = coronary artery disease; ACS = acute coronary syndrome; UAP = unstable angina pectoris; AMI = acute myocardial infarction; MI = myocardial infarction.

(death group) were matched with 212 survival control participants (control group) with regard to the same age range (±5 years), gender, myocardial infarction type, and time of participation in the baseline examination (±3 months) and finally enrolled as shown in Figure 1.

Baseline demographic and clinical characteristics were obtained from clinical examination and self-administered questionnaires (Supplementary Tables 1 and 2). Smoking statuses were classified as never, former smokers (who quit smoking at least 1 year before the examination), or current smokers. AMI was diagnosed according to the "Third Universal Definition of Myocardial Infarction."[11] Unstable angina, hypertension, hyperlipidemia, and diabetes mellitus were defined based on the guidelines of American Heart Association and American Diabetes Association, respectively. Revascularization included percutaneous coronary intervention and coronary artery bypass graft.

Blood samples were collected from each fasting participant within the first 48 hours after admission. The concentrations of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured using an automatic biochemistry analyzer (Hitachi 7150, Japan), whereas the concentration of hsCRP was measured by immunoturbidimetry (Beckmann Assay360, Bera, California).

Patients were followed up by clinic revisit or telephone conducted by trained nurses or doctors, who were blinded to the information of patients until death occurred or up to the last day of the follow-up period. The clinical end point was all-cause mortality, which was defined as death caused by a cardiac origin. For the patients that died, the follow-up information was obtained from their family members. The median follow-up period from baseline to the event of death was 19.15 months (interquartile range 7.89 to 33.68 months).

Continuous variables are described as medians with 25th and 75th percentiles, or mean ± standard deviation, when appropriate. Categorical variables are described as percentages and frequencies, respectively. Student's *t* test was used for comparing normally distributed continuous variables. Mann-Whitney *U* test was used for comparing skewed distributed continuous variables. Fisher's exact test or chi-square test was used to compare categorical variables, as appropriate. Log-rank test and unadjusted Kaplan-Meier analysis were carried out to assess the correlation between risk factors and all-cause mortality. Cox proportional hazards analysis was used to evaluate the association of risk factors with all-cause mortality in a multivariate setting. Covariates were traditional CV risk factors, including age, gender, smoking status, hypertension, dyslipidemia, and diabetes mellitus, and all variables were had a p value of <0.05 in the univariate analysis. The area under the receiver-operating characteristic curve (ROC_{AUC}) was conducted for the evaluation and comparison of predictive models. Statistical analyses were performed using IBM SPSS Statistics v. 20 (IBM Corp) and MedCalc v. 18 (MedCalc software bvba). A 2-tailed *P*-value <0.05 was considered statistically significant. The study was complied with the principles of the Declaration of Helsinki and was approved by the Research Ethics Board of Fuwai Hospital. All participants acknowledged the study and provided a signed informed consent.

Results

The baseline demographic and clinical characteristics of patients with AMI are presented in Supplementary Tables 1 and 2. The mean age of participants was 82.96 ± 2.66 years old, in which 58.50% were male. The most MI type identified in participants was ST-segment elevation MI. A univariate analysis was initially performed to identify potential risk factors for all-cause mortality shown in Supplementary Tables 1 and 2. The death group had a lower percentage of participants with hyperlipidemia history, lower LVEF, and BMI, but had higher plasma hsCRP, creatinine, and uric acid levels, compared with the control group. In addition, a lower percentage of participants in the death group received ACE inhibitor medication and revascularization therapy at baseline. However, these 2 groups had no significant differences in MI type and subtype.

The Kaplan-Meier curve of event-free survival is shown in Figure 2. Patients with higher levels of hsCRP (i.e., hsCRP >median of hsCRP) had lower event-free survival rates. Conversely, patients with lower BMI (i.e., less than the mean of BMI) and LVEF (less than the mean of LVEF) had a lower event-free survival rate. Also, as shown in Table 1, after adjusting for traditional risk factors and variables, hsCRP had a positive and significant association, and BMI had a negative and significant association with all-cause mortality in the oldest-old with AMI. In addition, ACE Inhibitor medication and experiencing revascularization had a significant negative association with all-cause mortality.

Next, the investigators sought to investigate the combined value of hsCRP, BMI, and LVEF in predicting all-cause mortality in oldest-old AMI patients with ROC_{AUC}. As shown in Table 2 and Supplementary Figure 1, LVEF combined with CV risk factors, but neither hsCRP nor BMI combined with CV risk factors, provided a stronger estimate, compared with the model that only included CV risk factors. However, when the sum of hsCRP, BMI, and LVEF was added into the predictive model, together with traditional CV risk factors, the diagnostic accuracy for predicting all-cause mortality significantly increased.

Table 1
Determination of the associations of factors with all-cause mortality by multivariate Cox proportional regression analysis

Variable	HR	95% confidence interval	p value
Body mass index	**0.935**	**0.884-0.988**	**0.018**
Hypertension	1.254	0.764-2.06	0.371
Hyperlipidemia	0.842	0.532-1.334	0.465
Diabetes mellitus	1.456	0.944-2.245	0.089
Smoke	1.011	0.667-1.533	0.959
Left ventricular ejection fraction	**0.973**	**0.954-0.993**	**0.007**
Revascularization	**0.552**	**0.347-0.877**	**0.012**
Creatinine	1.004	0.999-1.008	0.097
Uric acid	1.000	1-1.001	0.260
High sensitive C-reactive protein	**1.043**	**1.002-1.087**	**0.041**
Angiotensin-converting enzyme inhibitors	**0.576**	**0.367-0.904**	**0.017**

Revascularization indicates coronary artery bypass grafting or percutaneous coronary intervention.

Discussion

In this nested case-control study, we found that HsCRP, BMI, and LVEF were independent risk factors for all-cause mortality for the oldest-old with AMI. Moreover, the combined use of these indexes with traditional CV risk factors significantly improved the detective value of risks for all-cause mortality compared with traditional CV risk factors alone. Therefore, the outcome of the present study may provide important evidence with regard to predicting the all-cause mortality of AMI in patients >80 years old.

It has been reported that the levels of inflammatory markers such as hsCRP can markedly improve the risk

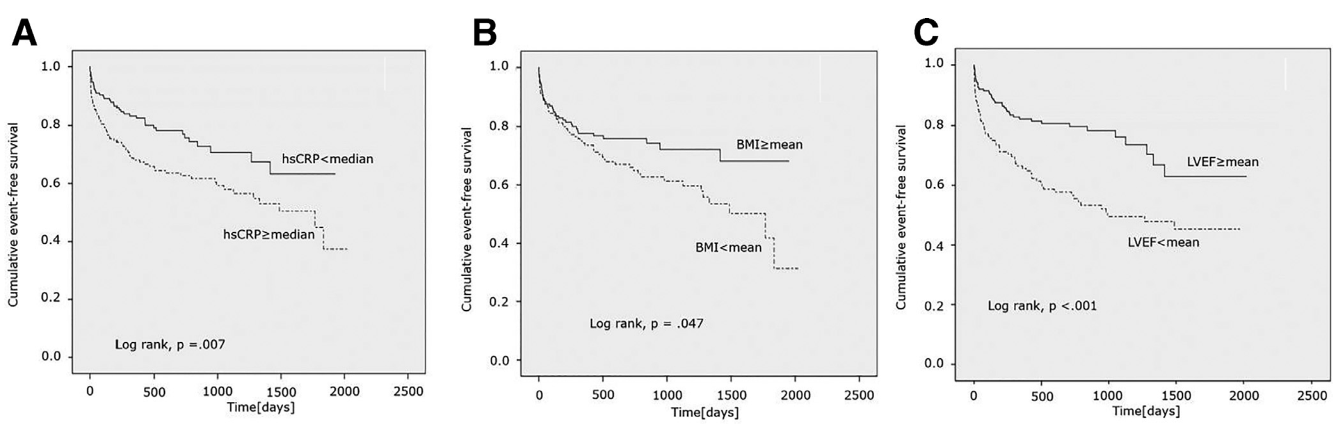

Figure 2. Kaplan-Meier curve for long-term survival according to the hsCRP *(A)*, BMI *(B)*, and LVEF *(C)* groups is shown. Cumulative event-free survival was defined as freedom from death. BMI = body mass index; hsCRP = high-sensitivity C-reactive protein; LVEF = left ventricular ejection fraction.

Table 2
Determination of the combined value of high-sensitivity C-reactive protein, body mass index, and left ventricular ejection fraction in predicting all-cause mortality with area under the curve

Variable	AUC	95% CI	p value	p value
Model A CV risk factors	0.623	0.555-0.691	0.001	Reference
Model B LVEF and CV risk factors	**0.701**	**0.637-0.765**	**<0.001**	**0.0081**
Model C hsCRP and CV risk factors	0.658	0.591-0.725	<0.001	0.1899
Model D hsCRP, LVEF, and CV risk factors	**0.712**	**0.652-0.771**	**<0.001**	**0.0033**
Model E BMI and CV risk factors	0.650	0.585-0.716	<0.001	0.1744
Model F hsCRP, BMI, and CV risk factors	**0.679**	**0.616-0.741**	**<0.001**	**0.0465**
Model G BMI, LVEF, and CV risk factors	**0.714**	**0.652-0.776**	**<0.001**	**0.0045**
Model H hsCRP, BMI, LVEF, and CV risk factors	**0.733**	**0.675-0.791**	**<0.001**	**0.0007**

The CV risk factors indicate age, gender, smoking, HTN, HL, and DM.
BMI = body mass index; DM = diabetes mellitus; HL = hyperlipidemia; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; LVEF = left ventricular ejection fraction.

prediction for CAD.[12,13] Two decades earlier, the "Fragmin during Instability in Coronary Artery Disease" (FRISC) study revealed that older patients with high CRP levels had a higher risk of death from cardiac causes.[14] In recent years, the circulating hsCRP concentration in ACS patients has been shown to provide prognostic information for short- or long-term mortality independent of classic risk factors.[15−18] Consistent with these observations, in the present study, it was also found that oldest-old AMI patients with higher hsCRP levels had more adverse CV events, compared with those having normal or low hsCRP levels.

Recently, a new phenomenon "the obesity paradox" has been reported in CAD patients,[19] in which overweight and obese patients with CAD had reduced all-cause mortality compared with normal or underweight BMI patients.[6,19−22] Unfortunately, few patients >80 years old were included in these studies. In the present study, the data further delineated the relationship between BMI and post-AMI mortality in oldest-old patients. We found a significant correlation between BMI and mortality in oldest-old AMI patients. Thus, the present study suggested an important information that BMI might be as an independent predicator for clinical outcomes in AMI patients with oldest-old. Therefore, the present findings provide novel insights into the predictive value of BMI and mortality in oldest-old Chinese AMI patients.

The important finding of the present study was the ability of the combined information of hsCRP, BMI, and LVEF to improve the prognostic value of traditional CV risk factors. The addition of hsCRP to established risk scoring systems or conventional risk factors has already been studied in ACS patients,[16,17,23] but none of these studies have assessed the combination of CRP and/or BMI with LVEF and other traditional risk factors in these patients. LVEF has already been proved to be an important predictor for mortality after MI, as evidenced by the findings that most deaths after MI occurred in patients with impaired LVEF, including those with moderately reduced LVEF (LVEF 36% to 50%).[24] In line with previous findings, the present ROC analysis revealed that the diagnostic accuracy of traditional CV risk factors for post-MI mortality significantly increased when LVEF was included. More importantly, the combined usefulness of hsCRP and BMI further increased the predictive capacity of LVEF and other traditional risk factors for MI-linked deaths, which was not examined in previous studies. In addition, our results also indicated that oldest-old people with concomitantly high hsCRP and low BMI had a high risk of long-term mortality after AMI, regardless of LVEF and other traditional risks. Although the definitive mechanisms remain unclear, future studies will be needed to confirm our findings.

Correct risk prediction significantly contributes to disease prevention and management. Novel biomarkers may be included in existing risk prediction models to generate new models. However, there is a critical question on how much improvement in prediction accuracy can these new models achieve. In large prospective cohort studies, a standard full-cohort design requires marker measurements in the entire cohort, which may not be practical due to expense and the low rate of clinical condition of interest. The present study was performed using a nested case-control model, which was considered to be generally more efficient than a case-cohort design with the same number of selected controls, and provides a valid and precise estimate of the prediction ability of new markers.[25−27] In addition, the present death cases and controls were directly matched in terms of age, gender, infarction type, and time of participation in the baseline examination, which may maximally eliminate the influences of strong risk predictors on post-MI mortality.

Although the present study has added some novel information into the geriatric medicine regarding the prognosis of AMI in old populations, there were also several limitations. First, the present study was single-center manner, which might have led to recruitment bias, thereby compromising external validity. Second, the present study had a relatively limited sample size and short follow-up period. Therefore, these findings should be validated through studies with a larger cohort and longer follow-up periods in the future.

In conclusion, in this study with a moderate sample size and follow-up duration, we demonstrated that hsCRP, BMI, and LVEF are independent predictors of all-cause mortality in oldest-old patients with AMI. More importantly, to the best of our knowledge, the present study is the first study to demonstrate that the combination of those 3 indexes can significantly improve the predictive value of traditional CV risk factors for all-cause mortality after AMI.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.025.

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