

Prognostic value of atherogenic index of plasma in patients with type 2 diabetes and acute coronary syndrome

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Abstract

Background: Atherogenic index of plasma (AIP) has been identified as a risk factor for cardiovascular disease (CVD) and an independent predictor of mortality. However, it remains unknown whether AIP level may predict mortality in patients with diabetes and acute coronary syndrome (ACS).

Methods: A total of 2531 consecutive patients with type 2 diabetes who underwent coronary angiography for ACS were enrolled in the study. Patients were divided into tertiles according to admission AIP level. The AIP was calculated as the base 10 logarithm of the ratio of the fasting concentration of triglyceride (TG) to high-density lipoprotein-cholesterol (HDL-C). The primary endpoints were all-cause death and cardiovascular death. Multivariate cox hazard regression analysis were performed to calculate the hazard ratio(HR)and 95% confidence interval(CI) C-statistics, continuous net reclassification improvement(NRI) and integrated discrimination improvement(IDI) were calculated to evaluate the added prognostic value of AIP beyond the established mode for prediction of death

Results: During 3-year follow-up, all-cause death events occurred in 142 cases and cardiovascular death events occurred in 120 cases, respectively. The risk of all-cause death and cardiovascular death increased with AIP tertiles at a 3-year follow-up. The Kaplan-Meier curves showed that significant differences in event-free survival rates among AIP tertiles(all-cause mortality: $p=0.006$; cardiovascular mortality: $p=0.003$).Multivariate cox hazard regression analysis revealed that AIP was independently associated with all-cause death (HR: 3.859, 95% CI:1.926-7.734; $p<0.001$) and cardiovascular death (HR:4.723, 95% CI: 2.243-9.946; $p<0.001$). Addition of AIP to the established mode for mortality prediction was not associated with a significant improvement in the C-statistics value but there were significant improvements in reclassification for all-cause death (NRI: 0.198, $p=0.022$; IDI: 0.008, $p=0.016$) and cardiovascular death (NRI: 0.260, $p=0.006$; IDI: 0.010, $p=0.021$).

Conclusions: Admission AIP was independently correlated with long-term mortality in patients with type 2 diabetes and ACS. These findings suggest that AIP may optimize the mortality prediction among patients with diabetes and ACS.

Background

Diabetes mellitus is the most important independent predictor of death in acute coronary syndrome (ACS). ACS is the leading cause of death among patients with diabetes mellitus [1]. In China, more than 30% of patients presenting with ACS suffered from diabetes mellitus [2]. Despite optimal medical treatment, patients with diabetes and ACS remain at higher risk of mortality than their nondiabetic peers [3]. There is evidence demonstrating that abnormal lipoprotein metabolism characterized by elevated triglyceride (TG) level, low high-density lipoprotein cholesterol (HDL-C) level and high small-dense low-density lipoprotein cholesterol (LDL-C) level significantly contributes to poor prognosis in patients with diabetes with ACS [4]. Therefore, it is essential to discover novel biomarkers reflecting atherogenic dyslipidemia of diabetes to identify high-risk patients who may benefit from more aggressive treatment strategies.

The atherogenic index of plasma (AIP), which is the logarithmic transformation of the TG to HDL-C ratio, has been recognized as a marker of plasma atherogenicity and a comprehensive index of specific dyslipidemia in diabetic patients[5, 6].Previous studies have found a positive association between AIP and cardiovascular

disease, including carotid atherosclerosis[7–10], arterial stiffness[11],coronary artery calcification[12], and coronary artery disease (CAD) [13–16]. Moreover, recent evidence indicated that AIP could provide significant prognostic information in patients with ACS after coronary revascularization [17]. The AIP is associated with not only CVD risk but also the development of diabetes [18]. These findings suggest that AIP may play an important role in predicting prognosis in patients with diabetes and ACS.

A recent study demonstrated that AIP was a useful marker for predicting adverse cardiovascular events in type 2 diabetic patients undergoing percutaneous coronary intervention (PCI) [6]. However, the association between AIP and survival among patients with type 2 diabetes and ACS remains undetermined. To define the association between AIP and prognosis in patients with type 2 diabetes and ACS, the present study was designed to investigate whether AIP level may predict death and improve the discrimination of mortality prediction in patients with type 2 diabetes and ACS.

Methods

Study population

This study was a single-center, retrospective, observational cohort study. From January 2016 to December 2016, 3428 consecutive patients with T2DM and ACS who were admitted to Tianjin Chest Hospital for coronary angiography were enrolled in this study. We included patients with a history of T2DM who were currently using insulin or hypoglycemic medications, or those with a fasting blood glucose (FBG) ≥ 7.0 mmol/L or a 2-h plasma glucose level on their oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L. Patients with diabetic symptoms underwent the OGTT test during this hospitalization. ACS was defined as including either unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI). Those with severe valvular disease or congenital heart disease requiring cardiac surgery (n = 42), acute infection (n = 76), malignancy (n = 14), severe hepatic dysfunction (n = 18), severe kidney dysfunction (n = 172), nutritional derangements (n = 8), or other severe medical illnesses, or those lacking complete clinical data (n = 285) were excluded. A total of 2815 patients participated in the research. Patients were followed up from January 2019 to December 2019 by telephone or outpatient clinical visit, and 2531 (89.9%) patients completed the 3-year clinical follow-up. The patients were divided into tertiles according to the admission AIP: tertile 1 (n = 844, AIP ≤ 0.066), tertile 2 (n = 843, $0.067 \leq \text{AIP} \leq 0.278$) and tertile 3 (n = 844, AIP ≥ 0.279). This study was approved by the local research ethics committee and strictly adhered to the Declaration of Helsinki. Given the retrospective nature of the present research, no informed consent was required.

Data collection and definition

Clinical data were collected from all of the medical records by trained clinicians who were blinded to the purpose of the study. The data included age, gender, duration of diabetes, whether diabetes had been newly diagnosed, smoking history, history of hypertension, family history of CAD, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), previous stroke, height, weight, left ventricle ejection fraction (LVEF) and medication at discharge. Peripheral venous blood samples were collected early in the morning after an overnight fast on admission and analyzed shortly after sampling. FBG, hemoglobin A1c (HbA1c), total cholesterol (TC), TG, LDL-C, HDL-C, serum creatinine, serum uric acid, high-sensitivity C-reactive protein (hs-CRP) and N-terminal proB-type natriuretic peptide (NT-

proBNP) levels were analyzed. Renal function was assessed using the baseline estimated glomerular filtration rate (eGFR). Body mass index (BMI) was defined as weight (kg)/height (m²). All of the patients underwent coronary angiography during this hospitalization. Significant stenosis was defined as $\geq 50\%$ diameter stenosis in at least one major coronary artery and multivessel disease was defined as ≥ 2 vessels with significant stenosis as observed during angiography. AIP was calculated as $\log(\text{TG}/\text{HDL-C})$.

Study endpoints

The endpoints were all-cause death and cardiovascular death. All-cause death referred to death attributed to cardiovascular or non-cardiovascular causes. Cardiovascular death was defined as death caused by acute MI, congestive heart failure, malignant arrhythmia, structural or functional cardiac diseases, or stroke.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation when normally distributed, and as medians with interquartile ranges for results not normally distributed. Categorical variables were presented as frequencies. Baseline demographic characteristics, clinical presentation, laboratory findings, extent of CAD, revascularization, and medication data were compared between groups using analysis of variance or Kruskal-Wallis tests for continuous variables, and with chi-square test or Fisher's exact test for categorical variables. The association of AIP with all-cause and cardiovascular death was evaluated by multivariate Cox proportional hazard models. Hazard ratios (HRs) and 95% confidence interval (CI) were calculated for AIP as a group variable with the lowest AIP tertiles as reference category. Four adjusted models were used. Model 1 was adjusted for age, male, duration of diabetes, newly diagnosed diabetes, smoker, hypertension, family history of CAD, previous MI, previous PCI, previous CABG, previous stroke, BMI. Model 2 was adjusted for model 1 covariates plus LVEF, AMI, left main disease, multi-vessel disease, revascularization. Model 3 was adjusted for model 2 covariates plus FBG, HbA1c, TC, LDL, Uric acid, hs-CRP, NT-proBNP, eGFR. Model 4 was adjusted for model 3 covariates plus aspirin, clopidogrel/ticagrelor, β -blocker, ACEI/ARB, statin, insulin. Survival analysis was performed by using the Kaplan-Meier method and the log-rank test. Possible factors associated with all-cause death or cardiovascular death were determined by using univariate Cox regression analysis. Then, variables with significant association (P values < 0.10) with all-cause death or cardiovascular death were included in multivariate Cox proportional hazards regression analysis. To evaluate whether an increased AIP had incremental predictive value for mortality, C-statistics, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were compared between models. A 2-sided analysis with a P value < 0.05 was considered significant. All analyses were performed using SPSS version 20.0 (IBM Corp, Armonk, New York) and SAS version 9.1.3 (Cary, NC, USA).

Results

Patient's Baseline Characteristics

Baseline clinical characteristics and clinical events data were fully recorded for 2531 patients (89.9%). Patients characteristics are listed in Table 1. The study patients had an average age of 66.3 ± 6.8 and 1415 (55.9%) patients were male. Patients were divided into 3 tertiles according to the admission AIP levels (tertile 1: $n = 844$, $\text{AIP} \leq 0.066$; tertile 2: $n = 843$, $0.067 \leq \text{AIP} \leq 0.278$; and tertile 3: $n = 844$, $\text{AIP} \geq 0.279$). The mean levels of AIP of the 3 groups were -0.079 ± 0.117 , 0.167 ± 0.059 , and 0.450 ± 0.150 , respectively. There were

significant differences ($P < 0.05$) among the 3 groups in terms of previous PCI, BMI, clinical presentation, HbA1c, TC, TG, LDL-C, HDL-C, Uric acid, hs-CRP and eGFR, and no significant difference was found in the other indicators.

AIP levels and mortality

During 3-year follow-up, 142 (5.61%) all-cause deaths and 120 (4.74%) cardiovascular death were recorded. All-cause mortality across AIP tertile groups were 4.03%, 5.22%, 7.58%, respectively. Cardiovascular mortality across AIP tertile groups were 3.08%, 4.51%, 6.64%, respectively. As shown in Fig. 1A and Fig. 1B, the cumulative all-cause mortality and cardiovascular mortality increased significantly with higher AIP, demonstrating that elevated AIP level is associated with poorer prognosis (log-rank test $P = 0.006$ and 0.003 , respectively).

Table 2 shows the Cox proportional hazard analysis for all-cause death and cardiovascular death. Setting AIP tertile1 as reference, patients with AIP in the tertile3 showed significantly higher all-cause mortality and cardiovascular mortality while no difference was observed for those with AIP tertile2 in the unadjusted model. Adjusted for potential covariates in four models with gradual expansion did not change this association. Univariate and multivariate Cox proportional hazards regression analyses and predictors for all-cause death and cardiovascular death are presented in Table 3 and Table 4. Multivariate cox hazard regression analysis revealed that AIP was an independent predictor for all-cause death (HR: 3.859, 95% CI: 1.926–7.734; $P < 0.001$) and cardiovascular death (HR: 4.723, 95% CI: 2.243–9.946; $P < 0.001$).

Model Discrimination

As shown in Table 5, when AIP was combined with the established model for mortality prediction, there was no significant improvement in C-statistics value for prediction of all-cause or cardiovascular death. However, adding AIP to the model of established risk factors has incremental prognostic value for predicting all-cause mortality in terms of NRI (19.8% improvement, 95%CI: 0.029–0.367, $P = 0.022$) and IDI (0.8% improvement, 95%CI: 0.002–0.015, $P = 0.016$), especially when comparing the baseline model with established risk factors. In addition, adding AIP to the model of established risk factors also has incremental prognostic value for predicting cardiovascular mortality in terms of NRI (26.0% improvement, 95%CI: 0.077–0.442, $P = 0.006$) and IDI (1.0% improvement, 95%CI: 0.002–0.019, $P = 0.021$), especially when comparing the baseline model with established risk factors.

Discussion

In the present study, we made several important findings that provided insight into the association between AIP and survival in patients with type 2 diabetes and ACS. First, we found that admission AIP level was positively associated with increased risks of all-cause and cardiovascular death in patients with type 2 diabetes and ACS during follow-up. Second, after adjustment for established risk factors affecting prognosis, AIP remained an independent predictor for all-cause and cardiovascular mortality. Third, adding AIP to the established mode may improve the reclassification for mortality prediction in patients with type 2 diabetes and ACS. To the best of our knowledge, this is the first study showing that admission AIP levels may predict mortality risk in patients with type 2 diabetes and ACS.

It has been demonstrated that each of typical dyslipidemic features of diabetes is associated with adverse cardiovascular events in patients with diabetes and established CAD, independent of conventional risk factors [19–21]. Recent studies revealed that the combination of high TG and low HDL-C in the form of a ratio has greater predictive value for detecting the risk of CVD compared with individual lipid marker alone [22, 23]. The AIP, as a quantitative indicator used to evaluate the TG to HDL ratio and a comprehensive index of specific dyslipidemia in diabetic patients, has shown its positive association risks of CVD and diabetes. Recent evidence suggested that AIP may be stronger predictors of mortality than individual lipoproteins cholesterol concentrations alone among older adult population [24]. In a 10-year prospective observational study, AIP was positively associated with the risk of all-cause mortality in elderly women with hypertension [25]. In incident dialysis patients, the highest and the lowest quintiles groups independently predicted all-cause mortality [26]. It is well established that AIP is a useful independent predictor of all-cause death and cardiovascular events in the context of CAD [6, 27]. CVD accounts for nearly 70% death casualty of patients with diabetes mellitus [28]. Even if receiving standard treatment, diabetic patients with ACS remain have high mortality risk. Hence, finding the prognostic value of AIP in patients with diabetes with ACS will helpful for better risk stratification such kind of patients.

However, whether AIP may predict cardiovascular outcomes in patients with type 2 diabetes is controversial. Giacomo et al. reported that, in 3084 type 2 diabetic outpatients without cardiovascular disease, higher AIP predicted all-cause and CVD mortality during a mean follow-up period of 4.9 years after adjustment for traditional risk factors, BMI, HbA1c and medication use. However, the association vanished after adjustment for renal function [29]. These results suggested that AIP was not an independent predictor of all-cause and CVD death in patients with type 2 diabetes and the prognostic value of AIP in type 2 diabetes might be largely mediated by kidney function. On the contrary, in a Chinese cohort of 1,447 type 2 diabetic patients with angiographic-proven stable CAD with an average of 20.3 months follow-up, Yang et al. found that AIP was a significant predictor of cardiovascular events defined as the composite of cardiac death, stroke, nonfatal MI and post-discharge revascularization in patients with diabetes and stable CAD after adjustment for multiple traditional risk factors of CVD[30]. Besides, in the study by Qin et al, with 2356 type 2 diabetic patients who underwent PCI during a median of 47.50 months of follow-up, higher AIP level was associated with increased risk of all-cause and cardiac death after adjusting for age, BMI, sex, medical history and medical treatment [6]. However, the association between AIP and mortality was not adjusted for cholesterol levels. One of the possible reasons for these different results was that differences in participant selection, event definition or follow-up time. Obviously, the association of AIP and survival in patients with diabetes and ACS with different treatment strategies was not well evaluated.

In the present study, we found that the risk for all-cause and cardiovascular mortality progressively increased with raising levels of AIP in patients with diabetes hospitalized with angiography-proven ACS. Moreover, after adjusting for risk factors of cardiovascular disease, extent of CAD, treatment methods, cholesterol levels and medication use, the association did not change. Therefore, our study further extended the positive association between AIP levels and cardiovascular risk to patients with diabetes and ACS who received different treatments. In addition, we found that AIP was the most powerful and independent predictor for all-cause mortality and cardiovascular mortality, even after adjusting for TG and HDL-C, suggesting that the predictive value of AIP for mortality is superior to traditional lipid parameters including TG and HDL. Also, we found that adding AIP to the model of established risk factors improved all-cause and cardiovascular mortality risk

prediction in terms of NRI and IDI, which strongly support the use of AIP for reclassification of mortality risk. To the best of our knowledge, we proved for the first time that AIP can provide incremental prognostic value in patients with diabetes and ACS. Therefore, our findings strongly suggest that AIP may be an important addition to risk stratification in patients with diabetes and ACS. All these results support the unique clinical value of AIP and indicate the clinical importance of AIP calculation in patients with type 2 diabetes with ACS.

Currently, both European Society of Cardiology/European Atherosclerosis Society and American College of Cardiology/American Heart Association guidelines recommend intensive LDL-C lowering treatment for patients with diabetes and CVD [31, 32]. There is also evidence that residual cardiovascular risk caused by the coexistence of elevated TG level and low HDL-C level in patients with diabetes can be safely and effectively reduced [33, 34]. However, routine lipid measures may not fully reflect the compositional changes of lipid metabolism in patients with diabetes. AIP, as a comprehensive index of dyslipidemia in diabetic patients may be improved through managements, such as dietary modifications [35], aerobic exercise [36] and supplementation with eicosapentaenoic acid [37]. Therefore, AIP may be a potential therapeutic target and a clinically convenient index for monitoring patients during follow-up. Future studies are needed to explore whether decreasing AIP would be associated with reduced risk of mortality in patients with diabetes and ACS.

The underlying mechanisms behind the association of AIP and mortality have not been definitively established. AIP, as a composite of TG and HDL-C, reflects the interaction between atherogenic and protective lipoprotein. The proatherogenic effect may partly account for the association between AIP and mortality. Moreover, AIP is a surrogate for concentration of atherogenic small dense of LDL particles which may predict all-cause mortality and adverse cardiovascular events [38]. In addition, AIP is associated with the degree of insulin resistance [39]. AIP has been found to be linked with CVD risk factors such as hypertension [40], metabolic syndrome [40], obesity [41] and non-alcoholic fatty liver disease [42]. AIP has also been correlated with microvascular damage, such as diabetic neuropathy. In the present study, we observed that patients with elevated AIP levels were more likely to have higher levels of HbA1c, Uric acid, hs-CRP and reduced eGFR, these conditions are known to increase the risk of death. However, the exact mechanism of the association between AIP and mortality risk need to be further explored.

Several limitations should be considered when interpreting these results. First, as the present study was a single-center retrospective study, it is difficult to exclude influence from unmeasured and residual confounding factors. Due to the relatively small number of events, we could not perform subgroup analysis. Therefore, a larger prospective study with longer follow-up would be necessary. Second, TG and HDL-C levels were only measured at the baseline. Thus, longitudinal monitoring with these lipids would be needed to explore the impact of change of AIP on mortality. Third, the study was based on Chinese patients, which may limit the generalization of these results. Despite these limitations, the present study has important clinical significance because it is the first study to investigate the association between AIP and survival in patients with type 2 diabetes and ACS who received different treatments.

Conclusions

Our study for the first time indicated that AIP was an independent predictor for all-cause and cardiovascular death in patients with diabetes and ACS, suggesting that AIP may be a potential marker for risk stratification

and prognosis in patients with diabetes and ACS.

Abbreviations

CVD: Cardiovascular disease; AIP: Atherogenic index of plasma; CAD: Coronary artery disease; ACS: Acute coronary syndrome; T2DM: Type 2 diabetes mellitus; FBG: Fasting blood glucose; UAP: Unstable angina pectoris; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; LVEF: Left ventricle ejection fraction; HbA1c: Hemoglobin A1c; TC: Total cholesterol; TG: Triglyceride; LDL-C: Low density lipoprotein-C; HDL-C: High density lipoprotein-C; hs-CRP: High-sensitivity C-reactive protein; NT-proBNP: N-terminal proB-type natriuretic peptide; eGFR: Estimated glomerular filtration rate; BMI: Body mass index; MACE: Major adverse cardiovascular event; NRI: Net reclassification improvement; IDI: Integrated discrimination improvement; ROC: Receiver operating characteristic; AUCs: Area under the receiver operating characteristic curves; SYNTAX: The Synergy Between PCI With Taxus and Cardiac Surgery.

Declarations

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Authors' contributions

LW, HLC and JXZ participated in the study design. LW, YCH, AW, YYZ, HY, LBR, WQ, WYL and CWL participated in data collection. LW, HY and LBR performed the statistical analysis. LW drafted the article. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by our local ethical committee. No informed consent was required.

Consent for publication

All the authors and participants have approved the manuscript for publication.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, tables 1-5 are only available as downloads in the supplemental files section.

Figures

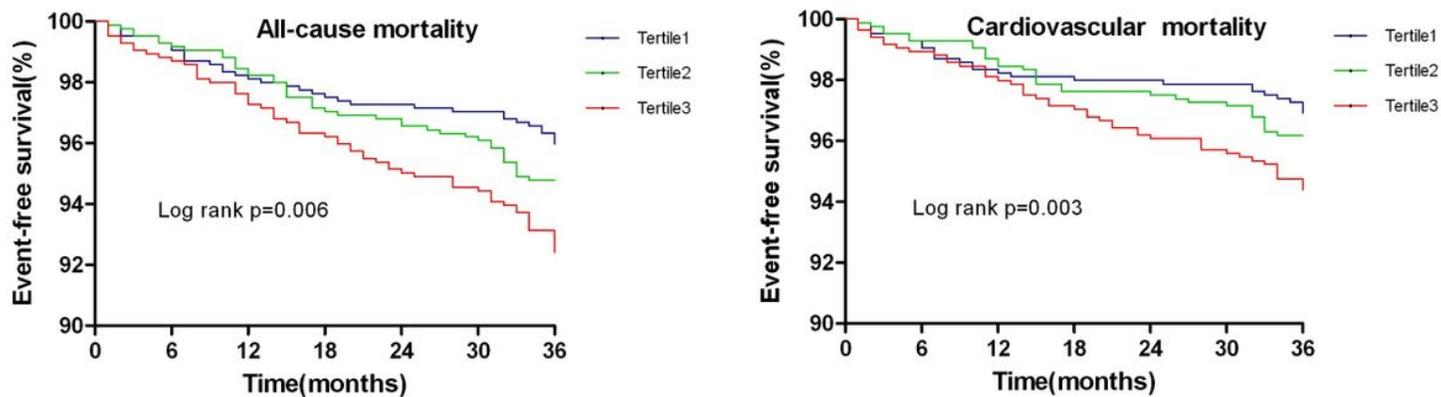


Figure 1

Figure 1A: Kaplan-Meier survival curve for all-cause mortality across AIP tertiles. Figure 1B: Kaplan-Meier survival curve for cardiovascular mortality across AIP tertiles.

Supplementary Files

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