

Monocyte-to-serum albumin Ratio as a Novel Predictor of Long-Term Adverse Outcomes in Patients after Undergoing Percutaneous Coronary Intervention: A Retrospective Cohort Study

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Research

Keywords: monocyte-to-serum-albumin ratio, percutaneous coronary intervention, mortality, prognosis.

Posted Date: November 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-109729/v1>

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Abstract

Background: Inflammation plays a significant role in the initiation and progression of atherosclerosis. Monocyte and serum albumin have been proved to be involved in the process of systemic inflammation. Therefore, we investigated the prognostic value of monocyte-to-serum albumin ratio (MAR) in patients who underwent percutaneous coronary intervention (PCI).

Methods: A total of 3,561 patients enrolled in this study from January 2013 to December 2017, who were divided into two groups according to the cut-off value of MAR (MAR<0.014, n=2220 and MAR≥0.014, n=1119). The average follow-up time was 37.59±22.24 months.

Results: There were significant differences between the two groups in the incidences of all-cause mortality (ACM) ($P<0.001$), cardiac mortality (CM) ($P<0.001$), major adverse cardiovascular events (MACEs, $P=0.038$) and major adverse cardiovascular and cerebrovascular events (MACCEs, $P=0.037$). Kaplan–Meier survival analysis suggested that patients with higher MAR value tended to have an increased accumulated risk of ACM and CM (Log rank $P<0.001$ and Log rank $P<0.001$, respectively). And multivariate Cox regression analyses showed MAR was an independent predictor for ACM (hazard ratio [HR]=1.461, 95% confidence interval [CI]:1.009–2.115, $P=0.045$) and CM (HR=1.695, 95% CI:1.056-2.721, $P=0.029$).

Conclusion: The present study suggests that MAR is a novel independent predictor of long-term mortality in patients who underwent PCI.

Trial registration: ChiCTR, ChiCTR1800019699. Registered 24 November 2018, <http://www.chictr.org.cn/showproj.aspx?proj=33249>

1. Background

Over the past few decades, percutaneous coronary intervention (PCI) has revolutionized the management of coronary heart disease (CHD), with a significant mortality reduction [1]. However, the long-term mortality benefit of PCI has not been shown in these patients and the prognostic benefits still remain uncertain [2]. Consequently, a long-term risk stratification in patients treated with primary PCI is very important to help guide management decisions in these patients.

The role of inflammation in the pathogenesis and prognosis of CHD has gained wide attention [3]. Recently, inflammation based indexes, such as monocyte to high-density lipoprotein cholesterol ratio, platelet-to-lymphocyte ratio (PLR) and C-reactive protein-to-albumin ratio, have been reported as useful prognostic indicators in patients with CHD [4–6].

A large number of evidences implicate that monocyte plays an important role in the progression of atherosclerosis, by interacting with platelets and leading to chronic activation of pro-inflammatory leukocyte subpopulations [7, 8]. Berg et.al showed that the percentage and number of classical

monocytes could predict cardiovascular events [9]. As a negative acute phase protein, serum albumin is considered as the intensity of the infection-triggered inflammatory response [10]. Population-base studies have shown that the lower serum albumin is associated with the development of atherosclerosis, and the initiation of myocardial infarction [11, 12].

Considerably, the monocyte and serum albumin are associated with the progression of CHD. However, the value of monocyte to albumin ratio (MAR) in CHD patients after PCI has not been investigated. Therefore, we investigated the prognostic value of MAR in patients who underwent PCI.

2. Methods

2.1 Participants

A total of 3,561 patients with CHD who underwent PCI at the First Affiliated Hospital of Zhengzhou University between January 2013 to December 2017 were enrolled. The inclusion criteria were CHD patients who were confirmed by coronary angiography, including non-ST-segment elevation acute coronary syndrome (ACS), ST-segment elevation ACS and stable angina and implanted at least one stent. Exclusion criteria included severe valvular heart disease, decompensated heart failure, pulmonary heart disease, rheumatic heart disease, serious renal or hepatic disease, pernicious anemia, infective diseases and malignancy. This study complies with the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University.

2.2 Follow Up

Two hundred and twenty-two patients were excluded for the monocyte or albumin data not being available or the presence of renal failure, infective disease and malignancies. Finally, 3,339 patients were evaluated and categorized into two groups by MAR value ($MAR < 0.014$, $n = 2220$ and $MAR \geq 0.014$, $n = 1119$). The cut-off value of MAR (0.014) was according to the analysis of the ROC curve for the baseline monocyte-to-serum albumin ratio of the study population. The flowchart of the participants' enrollment is shown in Fig. 1. In our center, all patients undergoing PCI received a regular follow up conducted by telephone interview. During the duration of follow up, all events were carefully checked and verified by an independent group of clinical physicians.

2.3 Outcome

The primary endpoints included all-cause mortality (ACM) and cardiac mortality (CM). The secondary endpoints were stroke, bleeding, rehospitalization, major adverse cardiovascular events (MACEs) and major adverse cardiac and cerebrovascular events (MACCEs). MACEs were defined as the composite of cardiac death, recurrent myocardial infarction (MI), or target-vessel revascularization. And MACCEs were defined as MACEs plus stroke [13, 14].

2.5 Statistical Analysis

All data was analyzed by the SPSS 22.0 for Windows statistical software (SPSS Inc, Chicago, Illinois, United States). The enrolled patients were grouped into 2 categories based on the value of MAR (MAR < 0.014 and MAR \geq 0.014). Continuous data were given as the mean \pm standard deviation, and categorical variables were presented as numbers and percentages. To compare the difference of parametric continuous variables, Student's *t* tests were used; and Mann-Whitney U tests were used when compared the difference of nonparametric continuous variables. Chi-squared (χ^2) tests were used for the comparison of categorical variables. Kaplan–Meier analysis was used for cumulative incidence rates of long-term outcomes and the log-rank test was employed to compare between groups. Multivariate Cox regression analysis was performed to examine the predictive value of the MAR for outcomes during and up to the 6-year follow-up. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The *P* values were 2-sided, considered being significant difference when *P* < 0.05.

3. Result

3.1 Baseline characteristics

In the study, 3,339 patients who underwent PCI were enrolled. The median follow-up time is 37.59 \pm 22.24 months. The participants were categorized into two groups according to the cut-off value of MAR: the lower MAR group (MAR < 0.014, n = 2220) and the higher MAR group (MAR \geq 0.014, n = 1119). All the baseline data were shown in Table 1. The variables in regards to age, gender, smoking, heart rate, creatinine (Cr), uric acid (UA) and high-density lipoprotein (HDL-C) showed significant differences between the two groups (all *P* < 0.05).

Table 1
Baseline characteristics

Variables	MAR < 0.014 (n = 2220)	MAR ≥ 0.014 (n = 1119)	χ ² or t	P-value
Age, years	62.74 ± 10.47	64.37 ± 10.92	-4.189	< 0.001
Gender (male), n (%)	1441 (64.9)	858 (76.7)	48.024	< 0.001
Family history of CAD, n (%)	425 (19.3)	202 (18.2)	0.575	0.448
Smoking, n (%)	620 (27.9)	397 (35.5)	20.023	< 0.001
Alcohol drinking, n (%)	340 (15.3)	200 (17.9)	3.590	0.058
Diabetes, n (%)	514 (23.2)	273 (24.4)	0.639	0.424
Hypertension, n (%)	1242 (55.9)	614 (54.9)	0.349	0.555
Heart rate, rpm	74.10 ± 20.38	75.55 ± 11.92	-2.150	0.032
Cr, umol/L	70.39 ± 24.69	77.69 ± 51.08	-5.547	< 0.001
UA, mmol/L	294.81 ± 82.33	307.50 ± 91.96	-4.017	< 0.001
TG, mmol/L	1.69 ± 1.17	1.62 ± 1.02	1.778	0.075
TC, mmol/L	3.92 ± 1.03	3.86 ± 1.01	1.608	0.108
LDL-C, mmol/L	2.40 ± 0.84	2.40 ± 0.85	0.184	0.854
HDL-C, mmol/L	1.06 ± 0.30	1.00 ± 0.27	4.621	< 0.001

3.2 Comparison Of Clinical Outcomes

We showed the clinical outcomes in Table 2. For the primary endpoints, the incidence of ACM was 2.9% in the lower MAR group and 5.5% in the higher MAR group ($P < 0.001$). And the incidence of CM was a significant difference between the two groups (1.7% vs. 3.8%, $P < 0.001$). For the secondary endpoints, the incidence of MACEs and MACCEs between the two groups showed significant differences (10.5% vs. 13.0%, $P = 0.038$ and 13.8% vs. 16.5%, $P = 0.037$, respectively). However, there were no significant differences between the two groups in regards to the incidence of stroke, bleeding events and readmission. As Kaplan–Meier survival analysis suggested that CHD patients with higher MAR tended to have an increased accumulated risk of ACM and CM (Log rank $P < 0.001$ and Log rank $P < 0.001$, respectively) (Fig. 2 and Fig. 3).

Table 2
Outcomes comparison between two groups

Variables	MAR < 0.014 (n = 2220)	MAR ≥ 0.014 (n = 1119)	χ ² or t	P-value
Primary endpoints				
ACM, n (%)	65 (2.9)	62 (5.5)	13.881	< 0.001
CM, n (%)	37 (1.7)	42 (3.8)	14.024	< 0.001
secondary endpoints				
MACEs, n (%)	234 (10.5)	145 (13.0)	4.321	0.038
MACCEs, n (%)	307 (13.8)	185 (16.5)	4.329	0.037

3.3 Prognostic significance of MAR in patients who underwent PCI

Baseline variables, which showed significant differences ($P < 0.05$) between two groups in univariate models entered into multivariate Cox regression analysis. In the multivariate Cox regression analysis, compared with the lower MAR group, the risk of ACM, CM in the higher group were increased by 46.1% (HR = 1.461, 95% CI: 1.009–2.115, $P = 0.045$), 69.5% (HR = 1.695, 95% CI: 1.056–2.721, $P = 0.029$) respectively (Tables 3 and 4). We did not find significant difference in the MACEs (HR = 1.147, 95% CI: 0.921–1.428, $P = 0.220$) and MACCEs (HR = 1.154, 95% CI: 0.952–1.399, $P = 0.144$) between the two groups.

Table 3
Cox regression analysis results for ACM

Variables	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>P</i>	<i>HR (95%CI)</i>
Age [years]	0.069	0.010	51.355	< 0.001	1.072 (1.052–1.092)
Gender (male)	-0.176	0.239	0.544	0.461	0.838 (0.525–1.340)
Smoking	0.056	0.218	0.066	0.797	1.058 (0.690–1.622)
Heart rate	0.002	0.002	1.130	0.288	1.002 (0.998–1.007)
Cr	0.007	0.001	53.038	< 0.001	1.007 (1.005–1.008)
HDL-C	-0.530	0.370	2.048	0.152	0.589 (0.285–1.216)
UA	0.001	0.001	0.317	0.573	1.001 (0.999–1.003)
MAR	0.379	0.189	4.023	0.045	1.461 (1.009–2.115)

Table 4
Cox regression analysis results for CM

Variables	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>P</i>	<i>HR (95%CI)</i>
Age [years]	0.064	0.012	28.382	< 0.001	1.066 (1.041–1.091)
Gender (male)	-0.531	0.340	2.444	0.118	0.588 (0.302–1.144)
Smoking	0.110	0.263	0.174	0.676	1.116 (0.667–1.868)
Heart rate	0.002	0.003	0.282	0.596	1.002 (0.996–1.007)
Cr	0.006	0.001	22.125	< 0.001	1.006 (1.003–1.008)
HDL-C	-0.874	0.489	3.199	0.074	0.417 (0.160–1.087)
UA	0.002	0.001	2.253	0.133	1.002 (0.999–1.004)
MAR	0.528	0.241	4.780	0.029	1.695 (1.056–2.721)

4. Discussion

In the present study, we found the prognostic value of MAR in patients who underwent PCI and demonstrated higher MAR value was independently associated with adverse outcomes of patients who underwent PCI.

Considering the high prevalence and poor prognosis of CHD, the early diagnostic biomarkers for patients with CHD are in need. Vascular inflammation plays a crucial role in the progression of CHD, and inflammation-based biomarkers have been shown previously [15–17], such as monocyte [18], high-sensitivity C-reactive protein and serum albumin [19]. However, it is still elusive which cell plays a role in initiation of the cascade processes.

Atherosclerosis has long been associated with chronic inflammation, and monocytes and monocyte-derived macrophages account for the coronary plaque progression [20]. Circulating monocytes populate plaques and adhere to the dysfunctional endothelial surface via binding to leukocyte adhesion molecules only expressed by abnormal endothelial cells [21, 22]. Cao et al have reported that all stages of atherogenesis, from the earliest lesions (fatty strips) to the formation of complex plaque, are associated with macrophages which are considered as a driving force [23]. In another recent study, efficient degradation of CCR2 mRNA in monocytes attenuated the number of monocytes in atherosclerotic plaques, reduced the infarct size following coronary artery occlusion [24], which may be a novel therapeutic strategy for CHD patients undergoing PCI. Serum albumin is considered as a negative acute-phase protein in the progression of inflammation [25]. As previous studies demonstrated, low serum albumin concentration can predict the clinical outcome of acute myocardial infarction [12]. As shown in Table 1, age, gender, smoking, Cr and UA have significant differences between the 2 groups. Aging, gender

and smoking are often characterized by a number of dysfunctional conditions including: myocardial sarcopenia, hypertrophy, vascular hyperpermeability, hypertension, inflammation, and functional impairment [26–30]. Increasing evidence demonstrates that age is a major risk factor in cardiac-related morbidity and mortality resulting from the decrease of the self-renewal of yolk sac-derived resident macrophages that play a key role in the post-MI repair and maintaining the cardiac homeostasis with age [31]. Ovaries removed or natural menopausal women exhibit systematic inflammation [32]. CHD has been considered to be male disease [28] because men are at a greater risk of CVD than women [29], who may decrease significantly the secretion of pro-inflammatory markers interleukin-6 (IL-6), IL-1, TNF- α via the estrogen [33]. Smoking has been known as an independent risk factor of atherosclerosis via promoting inflammation, thrombosis, and oxidative stress [30]. There are no doubts that age, gender, smoking, etc are confounding factors in our study, while after including these confounding factors in the multivariate Cox regression analysis, we still obtained positive results which demonstrated that the high MAR is an independent risk factor for ACM and CM in patients who underwent PCI.

To the best of our knowledge, it is the first time to demonstrate the MAR, which is a novel, powerful, inexpensive and effective predictor for outcomes of CHD after PCI. There are some limitations in our study. Firstly, we did not monitor the dynamic change of their variables. Secondly, our study is a single retrospective cohort design. Thirdly, we failed to collect inflammatory markers such as high sensitive C reaction protein (hsCRP) and erythrocyte sedimentation rate (ESR). Besides, to demonstrate the association between MAR and the outcomes of CHD after PCI, our study needs to be further verified by a multi-center, prospective study. And we expect more researches about the mechanism of MAR will be explored.

5. Conclusion

In conclusion, our findings suggest that the MAR is a sensitive, reliable and effective predictor of adverse outcomes in CHD patients undergoing PCI.

Abbreviations

PCI: percutaneous coronary intervention

MAR: monocyte-to-serum albumin ratio

ACM: all-cause mortality

CHD coronary heart disease

MACEs major adverse cardiovascular events

MACCEs major adverse cardiac and cerebrovascular events

Declarations

Acknowledgements

Not applicable.

Authors' contributions

All of the authors were actively involved in the study. JY Zhang and YY Zheng conceived the study and participated in the design. ZL Zhang, YY Zheng and JN Tang participated in the design, XT Yue, QQ Guo, JC Zhang, MD Cheng, FH Song, ZY Liu, K Wang, LZ J, XM Yang, L Fan, Y Bai, XY Dai and RJ Zheng collected the data, ZL Zhang and YY Zheng performed statistical analyses and drafted the manuscript. JY Zhang and YY Zheng critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This research was funded by the National Natural Science Foundation of China (81870328, 81760043 and 81800267).

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

This study complies with the Declaration of Helsinki and was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

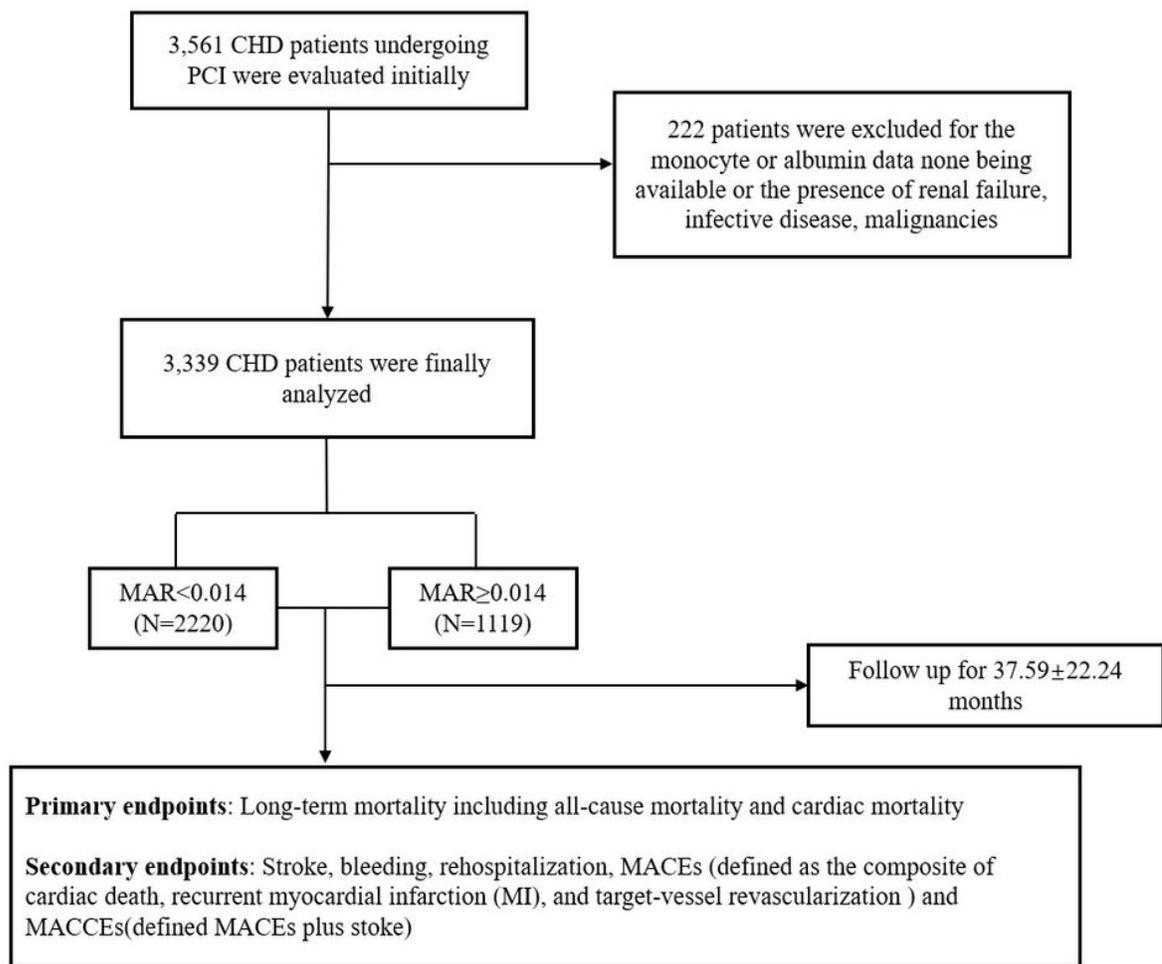


Figure 1

The flowchart of patients' enrollment

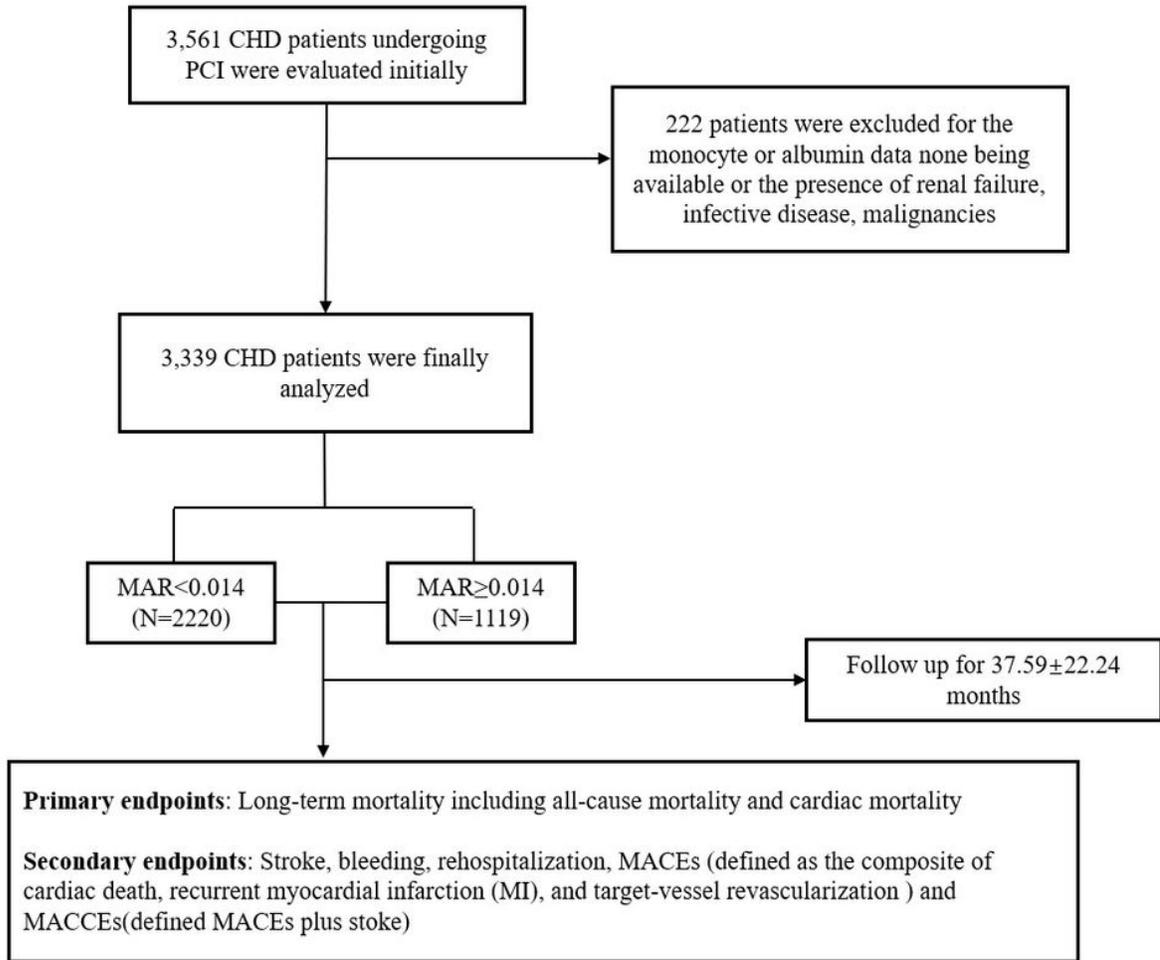


Figure 1

The flowchart of patients' enrollment

ACM

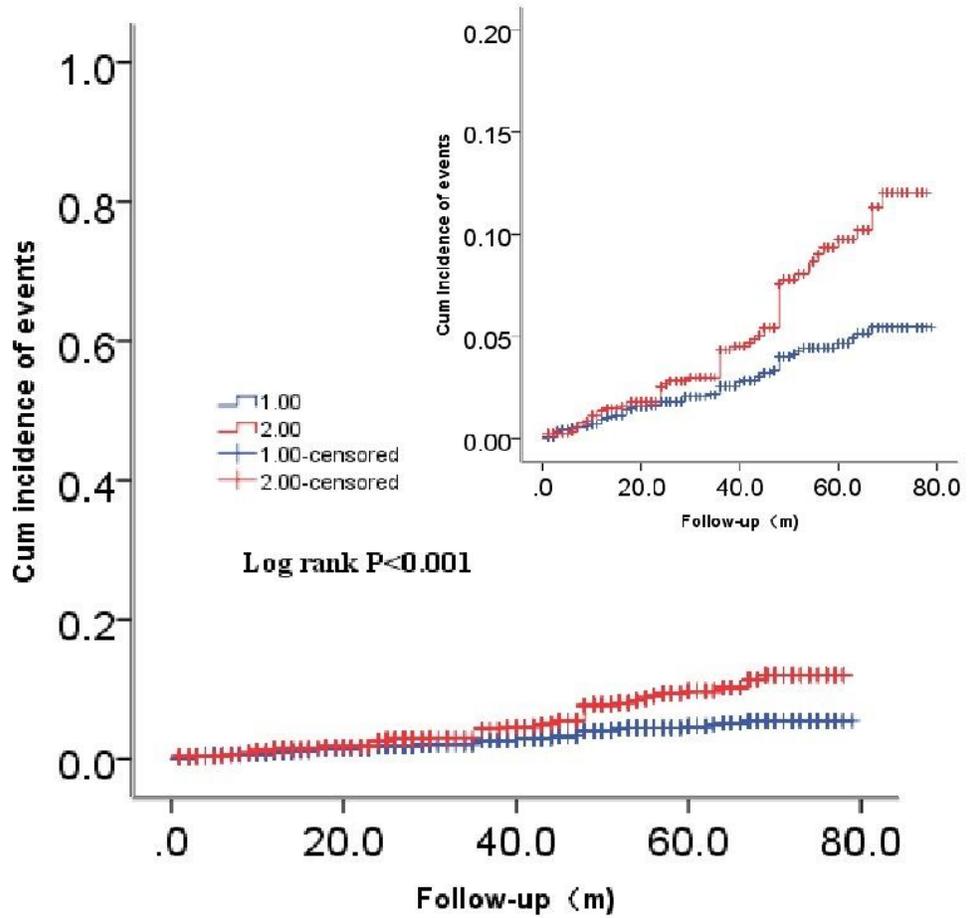


Figure 2

Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of ACM

ACM

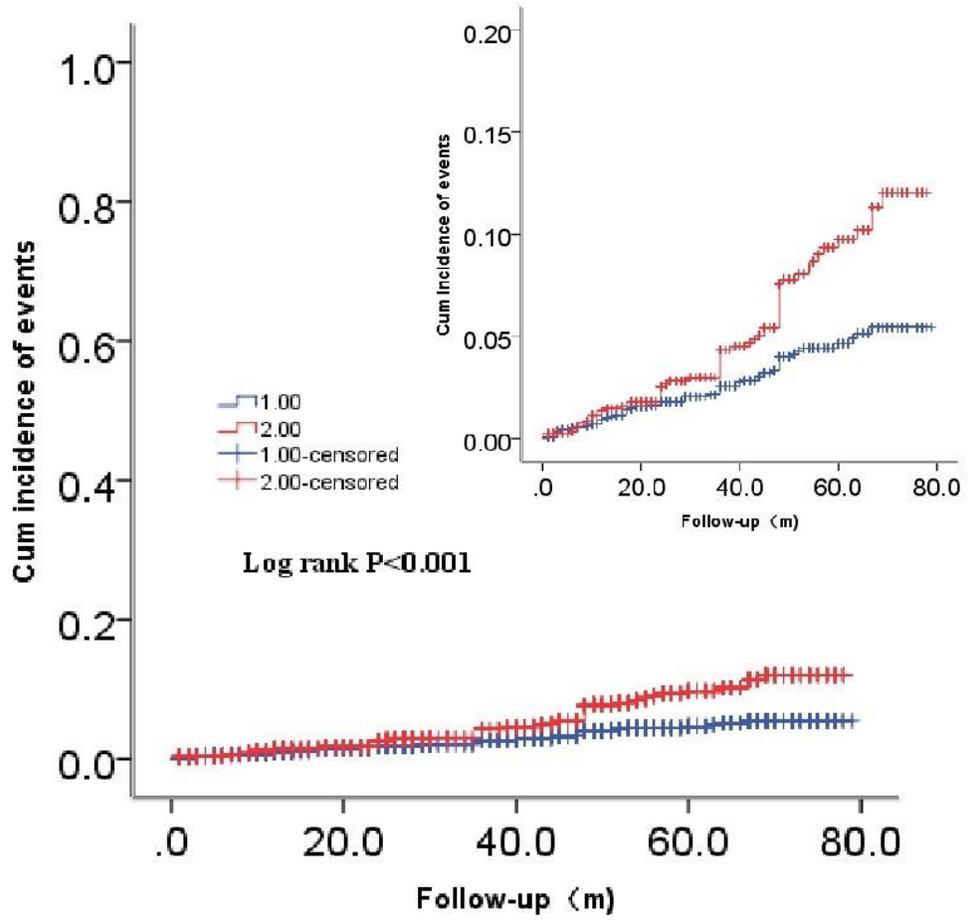


Figure 2

Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of ACM

CM

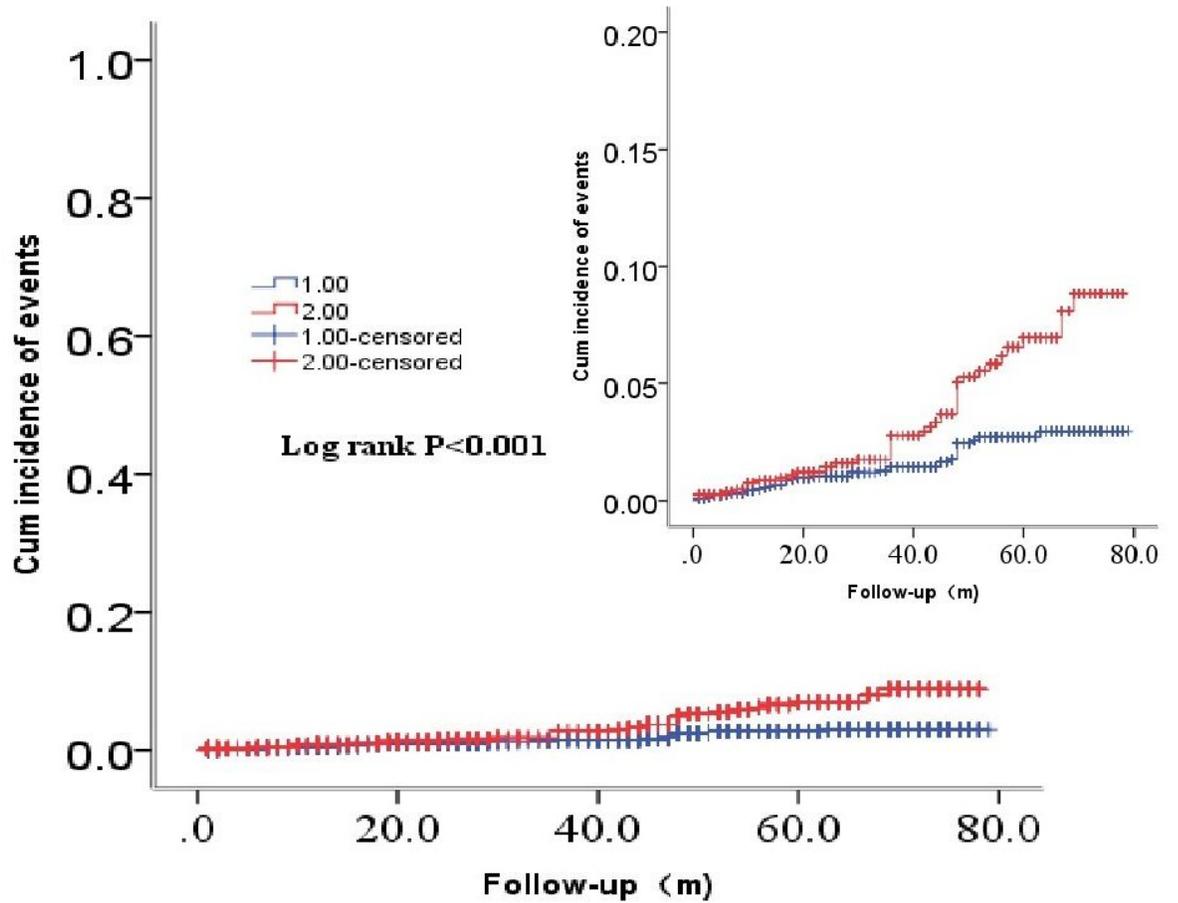


Figure 3

Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of CM In figure 2 and figure 3, the red line indicates the higher MAR, and blue line indicates the lower MAR.

CM

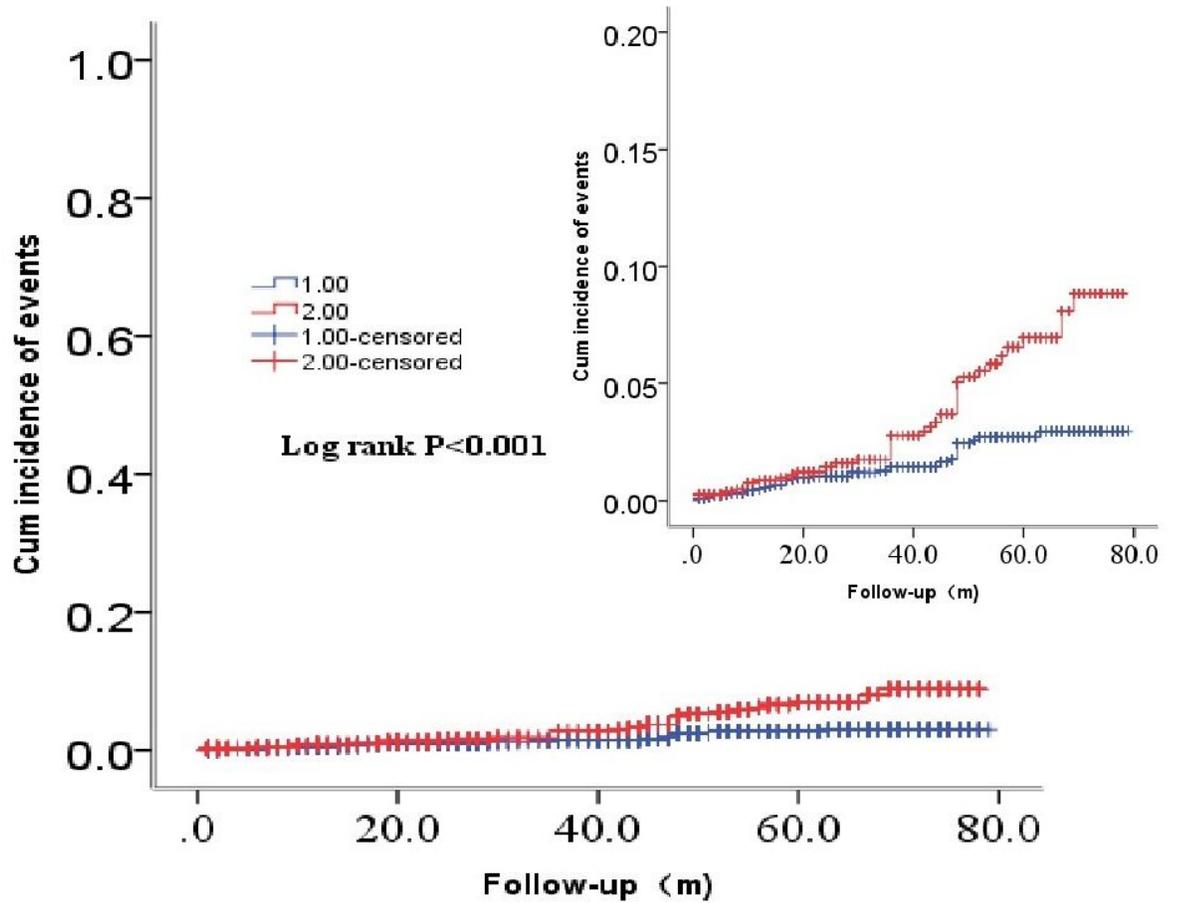


Figure 3

Cumulative Kaplan-Meier estimates of the time to the first adjudicated occurrence of CM In figure 2 and figure 3, the red line indicates the higher MAR, and blue line indicates the lower MAR.