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Mean Corpuscular Volume Predicts In-Stent Restenosis Risk for Stable Coronary Artery Disease Patients Receiving Elective Percutaneous Coronary Intervention

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Manuscript Preparation E
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Background: The purpose of this study was to analyze predictive performance of MCV in midterm ischemic events among SCAD patients undergoing elective PCI.

Material/Methods: We retrospectively included 226 consecutive patients with SCAD who received elective PCI. The patients were grouped based on MCV quartile values. The prognostic significance of MCV was assessed using univariate and multivariate Cox proportional hazard regression analyses.

Results: According to MCV quartile points (87.5 fL, 89.7 fL, and 92.4 fL, respectively), the included patients were divided into 4 groups, with an average follow-up of 34.2 months. There were 28 (48.3%) patients with stent thrombosis in the 1st quartile, 24 (29.1%) in the 2nd quartile, 18 (31.6%) in the 3rd quartile, and 15 (27.8%) in the 4th quartile (log-rank test, *P*=0.027). Multivariate analysis confirmed that MCV 1st quartile (HRadj=2.047, 95% CI 1.041–4.026; *P*=0.038), ALT (HRadj=1.013, 95% CI 1.004–1.023; *P*=0.004) and number of PCI vessels (HRadj=1.198 95% CI 1.013–1.415; *P*=0.034) were risk factors for ischemic events. The restenosis rate in patients belonging to the MCV 1st quartile was 2 times higher than that in MCV 2nd, 3rd, and 4th quartile groups (*P*=0.007).

Conclusions: MCV value may be independently correlated with restenosis in SCAD patients undergoing PCI. Low MCV predicts high risk of in-stent restenosis.

MeSH Keywords: **Coronary Artery Disease • Erythrocyte Indices • Percutaneous Coronary Intervention • Prognosis**

Abbreviations: **PCI** – percutaneous coronary intervention; **MCV** – mean corpuscular volume; **SCAD** – stable coronary artery disease; **LVEF** – left ventricular ejection fraction; **RBC** – red blood cell; **HB** – hemoglobin; **HCT** – hematocrit; **RDW CV** – red blood cell distribution width CV; **WBC** – white blood cell; **N** – neutrophil; **L** – lymphocyte; **PLT** – platelet; **FIB** – fibrinogen; **T3** – triiodothyronine 3; **T4** – triiodothyronine 4; **FT3** – free triiodothyronine 3; **FT4** – free triiodothyronine 4; **TSH** – thyroid stimulating hormone; **TBIL** – total bilirubin; **ALT** – alanine transaminase; **TC** – total cholesterol; **LDL** – low-density lipoprotein; **HDL** – high-density lipoprotein; **Lp(a)** – lipoprotein(a)

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Background

Mean corpuscular volume (MCV), a routine index of whole blood count, refers to the mean volume of red blood cells, and can be detected easily with low cost [1–3]. MCV was first used as a diagnostic biomarker for anemia. Recently, several studies have demonstrated that MCV can predict the mortality and morbidity of some diseases, including coronary artery disease [4–6]. Macrocytosis predicts adverse outcomes for cases receiving percutaneous coronary intervention, or those with acute decompensated heart failure [6].

Coronary artery disease (CAD) is a prevalent disease, greatly threatening human health worldwide. Percutaneous coronary intervention (PCI) is a common revascularization strategy in the management of CAD due to its safety profile, low complication rates, symptom relief, and survival benefits [7–9]. MCV and RDW can influence CAD progression, and could be employed as prognostic biomarkers for CAD patients undergoing PCI [10,11]. However, the correlation of MCV with adverse outcomes in patients with stable CAD (SCAD) was rarely discussed in previously published articles.

In this study, we estimated the predictive significance of MCV in midterm ischemic events among SCAD patients undergoing elective PCI.

Material and Methods

Study population and data collection

The present study was carried out in Zhongshan Hospital Fudan University from January 2008 to December 2017, and assessed 16 099 adults undergoing PCI, of which 9269 were SCAD patients. Among them, 1031 patients underwent elective PCI and 698 participants were recruited in the follow-up investigation.

Medical information of the patients, including demographics, concomitant diseases, drug prescriptions, lesion characteristics, and procedures, was retrospectively extracted by an experienced cardiologist. Preoperative whole blood samples were processed to ascertain results on RBC (red blood cell), hemoglobin, hematocrit, MCV, red cell distribution width (RDW), WBC, Neutrophil%, Lymphocyte%, and platelets using an automated blood counter (Sysmex XN-2000 Hematology System; Sysmex Corp., Kobe, Japan). Sysmex CS-5100 automated coagulation analyzers measured fibrinogen and d-dimer levels. Serum TSH, T3, T4, FT3, FT4, total bilirubin (TBIL), ALT (alanine transaminase), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and lipoprotein (a) were determined using a Roche Cobas 8000 automatic biochemical-immune analyzer (Roche Diagnostics, Mannheim, Germany).

Endpoint

Cardiovascular events among the patients were clinically monitored. Cardiovascular events such as cardiac death and in-stent restenosis were considered as endpoints and were retrospectively reviewed in November 2017. Once in-stent restenosis occurred, the patients would receive individualized treatments after comprehensively considering the severity of symptoms, co-morbidities, vascular bed, length of restenotic lesion, and plaque burden. Main treatment strategies included drug eluting stents, stent-grafts, and balloon angioplasty. In addition, the patients also received antiplatelet drugs, beta-blockers, or statins treatments according to the status of their complicated diseases. Follow-up information was recorded at 30 days, 6 months, 1 year, 2 years, and 4 years through telephone calls and follow-ups at a clinic. Survival time referred to the duration between first PCI and first event or final date.

Statistical analysis

Continuous variables are expressed as average ± standard deviation (SD) or median (interquartile range), and their differences between groups were analyzed using the *t* test (for 2 groups) or Mann-Whitney U test (for more than 2 groups). Normal data distribution was detected using the Shapiro-Wilk test. Patients were grouped according to their quartile points of MCV values. One-way ANOVA or Kruskal-Wallis H was used for comparisons among subgroups. Differences in categorical variables were estimated using the chi-square test or Fisher exact test. Kaplan-Meier method with log-rank test was used for survival analysis. Cox analysis covered clinically important parameters (age, sex, LVEF, hypertension, diabetes, smoke, number of PCI vessels, number of stents, stent length, medication, laboratory results). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated using multiple analysis to identify independent biomarkers for 2-year cardiac mortality. All calculations were accomplished using SPSS 22.0 (IBM Corp, Chicago, IL). Tests were 2-tailed, and $P<0.05$ suggested statistical significance for results.

Results

Baseline characteristics stratified by MCV quartiles

Patients with malignant tumors (n=85), undergoing reoperation procedures (n=312), or with advanced valve diseases (n=23) were excluded. Unfortunately, 52 patients were further lost in the investigation. Finally, a total of 226 eligible patients were included in our study.

The included patients were grouped according to their quartiles of MCV values. The first quartile was defined as the middle

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Table 1. Baseline clinical characteristics by quartiles of MCV.

	Group I	Group II	Group III	Group IV	*P* value
	59	55	57	55	
Age (years)	62±9	61±10	62±11	67±9	**0.017**
Sex no. (%)					0.734
Male	40 (67.8)	37 (67.3)	43 (75.4)	40 (72.7)	
Female	19 (32.2)	18 (32.7)	14 (24.6)	15 (27.3)	
LVEF (%)	62.0±9.6	63.3±6.6	62.3±8.0	62.0±8.2	0.812
Hypertension no. (%)	43 (72.9)	28 (50.9)	34 (59.6)	34 (61.8)	0.116
Diabetes no. (%)	11 (39.0)	12 (29.1)	10 (17.5)	10 (18.2)	0.942
Smoke no. (%)	22 (37.3)	27 (49.1)	19 (33.3)	20 (36.4)	0.340
Drug application history					
Antiplatelet	9 (15.3)	15 (27.3)	10 (17.5)	11 (20.0)	0.412
Beta blockers	4 (6.8)	7 (12.7)	7 (12.3)	5 (9.1)	0.686
Statins	4 (6.8)	8 (14.5)	6 (10.5)	5 (9.1)	0.578

LVEF – left ventricular ejection fraction; Beta blockers – referring to the β1-selective agents; Statins – including atorvastatin, Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

value between the smallest value and the median of the data set (MCV: 87.5fL). The second quartile referred to the median value of MCV (89.7 fL). The third quartile was the middle value between the median and the highest values of MCV (92.4 fL). The patients were divided into 4 groups based on these 3 quartile points of MCV value. In statistical application, the quartiles of a ranked set of data values formed 4 subsets whose boundaries were the 3 quartile points. Thus, individual item might be described as "on the upper quartile". The quartile method is helpful in analyzing the trends of a dataset.

Baseline information stratified by the quartile of MCV is demonstrated in Table 1. Age showed significant differences among the 4 groups, and patients with higher MCV were older (P=0.017). Other clinical characteristics, including underlying disease and medication history, did not exhibit obvious differences among groups. Laboratory data were also compared among groups, and the results are summarized in Table 2. RBC appeared to be lower in patients with higher MCV levels (P<0.001). RDW in group I was remarkably higher than in other groups (P=0.002). Patients with high MCV were more likely to have high TBIL (P=0.031). Table 3 shows endovascular treatment procedure and the medication at discharge for patients. The stent lengths ranged from 14 to 110 mm, and the average number of placed stents was 1.7±0.8, 1.7±0.8, 1.8±0.7, and 1.6±0.7 in group 1, 2, 3, and 4, respectively (P=0.678). The number of PCI vessels in group 4 was less than in other groups, but without a significant difference (P>0.05). No obvious differences were observed in drugs used, such as antiplatelet drugs, beta-blockers (β1-selective agents), or statins (including atorvastatin, Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin) among groups (P>0.05).

Survival analysis and predictors for outcome

The average duration of follow-up was 34.2 months. During this course, 79 patients presented in-stent restenosis. In Kaplan-Meier analysis, the cumulative restenosis rate at 48 months was 35.0%. The incidence of restenosis showed the highest value in the 1st quartile (48.3%) compared with other groups (log-rank test, P=0.027). However, the incidence exhibited no significant differences among the 2nd quartile, 3rd quartile, and 4th quartile groups (29.1% *vs.* 31.6% *vs.* 27.8%, P>0.05) (Figure 1).

Cox regression analyses were performed to identify indicators for ischemic events. Univariate analysis demonstrated that LVEF (left ventricular ejection fraction), MCV quartiles, ALT, HDL, number of PCI vessels, and stent length were significantly associated with ischemic events. Summarized hazard ratios (HRs) for LVEF, MCV 1st quartile *vs.* 2nd quartile, ALT, HDL, number of PCI vessels, and stents length were 0.972 (95% CI 0.950–0.996; P=0.020), 2.037 (95% CI 1.106–3.753; P=0.022), 1.011 (95% CI 1.002–1.020; P=0.014), 0.333 (95% CI 0.146–0.757; P=0.009), 1.219 (95% CI 1.052–1.413; P=0.009), and 1.012 (95% CI 1.002–1.023; P=0.019), respectively (Table 4). The restenosis rate for MCV 1st quartile was

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Table 2. Laboratory findings by quartiles of MCV.

	Group I	Group II	Group III	Group IV	*P* value
	59	55	57	55	
RBC (mln/mm³)	4.7±0.5	4.5±0.4	4.4±0.5	4.2±0.4	**<0.001**
HB (mmol/L)	135.6±19.8	137.2±14.4	137.4±15.9	136.7±14.1	0.931
HCT (%)	39.9±5.7	40.0±3.9	40.2±4.4	40.3±3.9	0.971
RDW CV (%)	13.4±1.2	13.0±0.7	12.7±0.6	13.1±1.0	**0.002**
WBC (tys/mm³)	7.1±1.8	7.6±2.4	6.8±1.8	6.9±2.3	0.278
N (%)	64.8±9.1	60.0±14.9	61.2±11.5	61.3±9.9	0.144
L (%)	26.0±9.0	27.9±10.6	28.1±9.0	28.4±9.4	0.532
PLT	217.3±63.3	221.7±45.1	200.8±56.0	199.3±59.3	0.081
FIB	307.4±95.0	288.4±94.9	292.9±83.7	293.7±68.8	0.683
D Dimer	0.5±0.7	0.3±0.4	0.4±0.5	0.4±0.5	0.716
T3	1.5±0.3	1.6±0.3	1.5±0.3	1.5±0.3	0.773
T4	98.8±23.2	100.2±19.1	94.2±18.4	94.7±19.9	0.563
FT3	4.2±0.7	4.3±0.7	4.3±0.7	4.3±0.8	0.737
FT4	18.4±18.1	15.8±2.3	16.1±2.2	15.1±2.6	0.286
TSH	2.9±4.4	1.88±1.5	2.5±1.7	2.8±2.4	0.241
TBIL	8.8±3.6	8.5±3.3	10.4±4.8	10.3±4.3	**0.031**
ALT	26.2±15.1	33.7±22.7	27.9±23.9	26.3±19.1	0.185
TC	4.2±1.1	4.3±1.3	3.8±1.0	4.2±1.0	0.076
LDL	2.2±0.9	2.4±1.0	2.0±0.9	2.3±0.8	0.113
HDL	1.0±0.4	1.0±0.3	1.1±0.3	1.1±0.4	0.293
Lp(a)	392.6±463.4	315.6±351.0	350.7±372.6	315.0±390.6	0.698

RBC – red blood cell; HB – hemoglobin; HCT – hematocrit; RDW CV – red blood cell distribution width CV; WBC – white blood cell; N – neutrophil; L – lymphocyte; PLT – platelet; FIB – fibrinogen; T3 – triiodothyronine 3; T4 – triiodothyronine 4; FT3 – free triiodothyronine 3; FT4 – free triiodothyronine 4; TSH – thyroid stimulating hormone; TBIL – total bilirubin; ALT – alanine transaminase; TC – total cholesterol; LDL – low-density lipoprotein; HDL – high density lipoprotein; Lp(a) – lipoprotein(a).

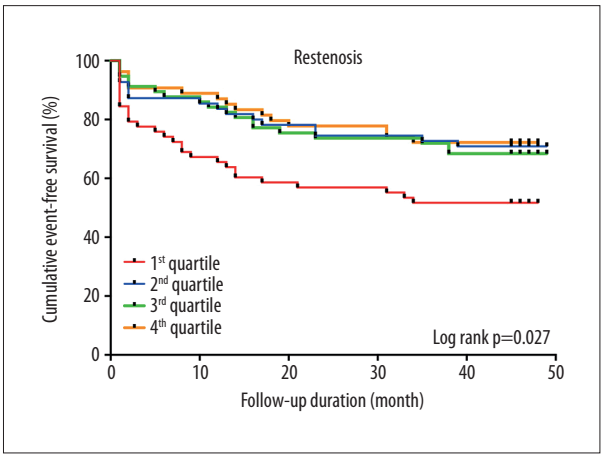

Figure 1. Kaplan-Meier curve for primary vessel patency during follow-up stratified by MCV quartile (n=226). Patients in the 1st quartile had lower survival rate than those of 2nd quartile, 3rd quartile, and 4th quartile (*P*=0.027, log-rank test), but there was no significant difference in survival among patients of the 2nd quartile, 3rd quartile, and 4th quartile (*P*>0.05).

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Table 3. Clinical characteristics by quartiles of MCV.

	Group I	Group II	Group III	Group IV	*P* value
	59	55	57	55	
No. of PCI vessel	2.7±1.4	2.8±1.5	2.6±1.5	2.2±1.2	0.164
No. of stents	1.7±0.8	1.7±0.8	1.8±0.7	1.6±0.7	0.678
Stent length	44.6±24.0	46.5±21.9	47.5±22.1	39.9±17.8	0.369
Discharge medication no.					
Antiplatelet	59 (100)	55 (100)	57 (100)	55 (100)	–
Beta blockers	59 (100)	55 (100)	55 (96.5)	55 (100)	0.396
Statins	54 (91.5)	50 (90.1)	53 (93.0)	55 (100)	0.319

PCI – percutaneous coronary intervention; Beta blockers – referring to the β1-selective agents; Statins – including atorvastatin, Fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Table 4. Univariable comparison of factors associated with re-infarction event.

	HR	95% CI	*P* value
Age (years)	1.000	0.978–1.022	0.993
Sex No. (%)	1.470	0.869–2.487	0.151
LEVF (%)	0.972	0.950–0.996	**0.020**
Hypertension no. (%)	1.097	0.700–1.719	0.687
Diabetes no. (%)	0.755	0.468–1.220	0.252
Smoke no. (%)	0.903	0.576–1.415	0.655
Antiplatelet	1.391	0.768–2.522	0.276
Beta blocker	1.558	0.678–3.583	0.296
Statin	0.927	0.463–1.855	0.829
MCV			**0.036**
Quartile 1	Ref.		
Quartile 3	1.002	0.501–2.004	0.995
Quartile 4	1.089	0.555–2.135	0.804
RBC (mln/mm^3)	1.213	0.767–1.919	0.410
HB (mmol/L)	0.997	0.983–1.011	0.636
HCT (%)	0.998	0.949–1.050	0.946
RDW CV (%)	1.136	0.909–1.420	0.262
WBC (tys/mm^3)	1.024	0.923–1.135	0.658
N (%)	1.003	0.983–1.023	0.789
L (%)	0.993	0.969–1.017	0.567
FIB	1.002	1.000–1.004	0.082
D Dimer	1.028	0.675–1.566	0.897
T3	0.483	0.163–1.176	0.101
T4	0.990	0.976–1.005	0.196
FT3	0.854	0.621–1.175	0.333
FT4	1.012	0.996–1.029	0.136
TSH	0.990	0.913–1.074	0.810
TBIL	0.978	0.923–1.035	0.442
ALT	1.011	1.002–1.020	**0.014**
TC	1.081	0.888–1.316	0.436
LDL	1.042	0.819–1.325	0.740
HDL	0.333	0.146–0.757	**0.009**
LP(a)	1.000	0.999–1.000	0.315
No. of PCI vessel	1.219	1.052–1.413	**0.009**
No. of stents	1.188	0.867–1.627	0.284
Stents length	1.012	1.002–1.023	**0.019**

LVEF – left ventricular ejection fraction; MCV – mean corpuscular volume; RBC – red blood cell; HB – Hemoglobin; HCT – hematocrit; RDW CV – red blood cell distribution width CV; WBC – white blood cell; N – Neutrophil; L – lymphocyte; FIB – fibrinogen; T3 – triiodothyronine 3; T4 – triiodothyronine 4; FT3 – free triiodothyronine 3; FT4 – free triiodothyronine 4; TSH – thyroid stimulating hormone; TBIL – total bilirubin; ALT – alanine transaminase; TC – total cholesterol; LDL – low-density lipoprotein; HDL – high density lipoprotein; LP(a) – lipoprotein(a); PCI – percutaneous coronary intervention.

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Table 5. Predictors for re-infarction event by multivariate Cox regression.

	HR	95% CI	*P* value
LVEF (%)	0.976	0.953–1.000	**0.054**
MCV			**0.007**
Quartile 1	Ref.		
Quartile 2	2.047	1.041–4.026	**0.038**
Quartile 3	0.706	0.321–1.551	0.385
Quartile 4	0.936	0.445–1.967	0.861
ALT	1.013	1.004–1.023	**0.004**
HDL			
No. of PCI vessel	1.198	1.013–1.415	**0.034**
Stents length	1.010	0.999–1.022	0.079

LVEF – left ventricular ejection fraction; MCV – mean corpuscular volume; ALT – alanine transaminase; HDL – high density lipoprotein; PCI – percutaneous coronary intervention.

approximately 2 times higher than that for MCV 2nd, 3rd, and 4th quartiles, with a baseline hazard ratio of 2.037. After adjustments for confounding factors, the risk of developing ischemic events was still associated with MCV 1st quartile *vs.* 2nd quartile (HRadj=2.047, 95% CI 1.041–4.026; *P*=0.038), ALT (HRadj=1.013, 95% CI 1.004–1.023; *P*=0.004) and number of PCI vessels (HRadj=1.198 95% CI 1.013–1.415; *P*=0.034), but was not associated with LVEF, HDL, or stent length (Table 5).

Discussion

We estimated the influences of MCV on the prognosis of CAD patients undergoing PCI surgery. We found that patients with decreased MCV were more likely to undergo in-stent restenosis among the entire population. Moreover, multivariate analysis demonstrated that MCV was significantly correlated with stent thrombosis after adjusting for confounding factors, such as ALT, HDL, number of PCI vessels, and stent length. The patients in the 1st quartile, who had the lowest MCV values, exhibited high risk of restenosis.

The first generation of bare metal stents (BMS) significantly reduced the morbidity of restenosis (to roughly 16–44%) [12]. The first generation of DES reduced the incidence of restenosis to about 20% within 5 years. Newer DES has reduced this even further, to about 5–7% in 5 years [13–15]. Among our selected patients, the morbidity of restenosis (35%) was similar to that reported in earlier published studies. Kaplan-Meier survival analyses showed MCV could predict the occurrence of restenosis. Patients with lowest MCV values exhibited high risk of restenosis. Furthermore, multivariate regression analyses showed that MCV quartiles independently affect in-stent restenosis. Patients with MCV values lower than 87.5 fL exhibited high risk of in-stent restenosis. Myojo et al. reported that macrocytosis obviously increased mortality, as well as main adverse cardiovascular and cerebrovascular events (MACCE), among patients receiving PCI [6]. Our study population consisted of SCAD cases undergoing PCI, which might have influenced our results. Osadnik et al. reported that higher RDW values yielded higher comorbidity rates and mortality rates [10]. Furthermore, RDW can be used as an indicator for mortality among SCAD patients. Our analysis showed no obvious difference in RDW between restenosis and patency groups. The divergences might be attributed to different study populations, relatively small sample size, and genetic heterogeneity. Further investigations are required to address this issue.

The normal size of RBCs ranges from 82 to 100 fL. Gamaldo et al. observed significant, linear, age-related increases in MCV among white people, even after controlling additional blood indices [16]. The results obtained in our study were in accordance with previously published articles. Age was significantly different among the various MCV quartile groups. Bilirubin is an endogenous inhibitor of atherosclerosis, and total bilirubin level possibly influences the risk of cardiovascular diseases [17,18]. Patients with higher MCV values may also have higher TBIL levels. According to our results, patients with higher MCV value had lower susceptibility to restenosis, and the correlation between MCV and TBIL agrees with these findings.

Cox regression analysis showed LVEF, MCV quartiles, ALT, HDL, number of PCI vessels, and stent length were risk factors for restenosis. After adjustment, MCV, ALT and number of PCI vessels were still correlated with restenosis among SCAD patients undergoing PCI. It is surprising that ALT was an independent risk factor for restenosis, though the underlying mechanism remains unknown. We hypothesized that long-term medication use could cause different degrees of liver injury among SCAD patients. Therefore, ALT became an important index of prognosis among SCAD cases undergoing PCI. Stefanini et al. regarded the number of PCI vessels was a vital procedure factor in evaluating PCI [19], and our results are in line with such a conclusion. Our study revealed that MCV quartile were also an independent risk factor. The patients with MCV values within the 1st quartile had high rate of restenosis. However, those in quartile 2, quartile 3, and quartile 4 subgroups did not show significant differences in restenosis incidence. The rate of microcytosis was only 2.2% (5 patients) in our study population, and most of the patients had normal MCV and RDW values. Among these 5 patients, the prevalence of restenosis was 80%. Although the sample size was too small, we still can capture the

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trend that lower MCV value predicted high risk of restenosis. Further study will shift the focus on microcytosis patients, aiming to explore the phenomena, because the underlying mechanism is still unknown. Decreased MCV is a biomarker for several diseases, including iron deficiency anemia, thalassemia, and other chronic diseases (e.g., microcytic anemia). Inflammation is a leading cause of microcytosis [20–23], and inflammatory reaction appears in each and every step of atherosclerosis from its inception to terminal manifestation [24,25]. The above reasons might explain the close association of small red blood cell size with high risk of restenosis.

MCV is a routine part of complete blood count (CBC) results and is measured by automated blood cell counters, making its detection is easy and inexpensive, and thus not imposing an excessive medical burden on patients or society.

Conclusions

Risk stratification based on MCV value may be an effective and easy way to prevent and quickly treat restenosis among SCAD patients experiencing PCI, thus reducing the occurrence of MACCE and improving patient survival.

Study limitations

There are several limitations in this study. First of all, it was a medium-sized, single-center, retrospective study. Therefore, larger-scale and multi-center surveys are required to confirm the results from this study and to elucidate the precise mechanisms underlying the correlations between lower MCV and restenosis among SCAD patients undergoing PCI. In addition, because they were not available for most patients, our analysis did not include data on alcohol consumption, history of heart failure, or cytological/chemical data (e.g., serum iron level, total or unsaturated iron binding capacity [TIBC or UIBC], ferritin, transferrin, reticulocyte count, and erythropoietin) that might affect MCV values.

Conflicts of interest

None.

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