We investigated the association of mean platelet volume (MPV) with culprit lesion severity and major cardiac outcomes (MCOs) in patients with acute coronary syndrome (ACS) with non-ST elevation (NSTE). This study included 344 patients with NSTE-ACS who had significant coronary stenosis at least 50%. They were divided into high MPV group (n=109, upper tertile >9.9 fl) and low MPV group (n=235, lower and mid tertile ≤9.9 fl) according to MPV values on admission. They were followed up for MCOs during 12 months. MCO consisted of the composite end-point of cardiac death, myocardial infarction (MI), recurrent angina or hospitalization. High MPV was independently associated with NSTE-MI [odds ratio (OR) 4.24, 95% confidence interval (CI) 2.52-7.15, P=0.001] and severe culprit stenosis (≥80%) (OR 4.05, 95% CI 2.39-6.83, P=0.001). MPV of 9.9 fl was predictive of severe culprit stenosis with a sensitivity of 73% and specificity of 77% (P < 0.001). At 12 months, MCO rate was higher in high MPV group than low MPV group (39 vs. 26%; P=0.016). This difference resulted from death (6.4 vs. 2.1; P=0.06) and recurrent angina (16.5 vs. 8.9%; P=0.045). The MCO-free survival was worse in patients with high MPV than those with low MPV (61 vs. 74%; P=0.01). In Cox regression analysis, high MPV remained an independent predictor of MCO (hazard ratio 1.52, 95% CI 1.01-2.29, P=0.04) after adjusting for baseline characteristics. Elevated MPV was independently associated with NSTE-MI presentation and severity of culprit stenosis in NSTE-ACS patients. Moreover, MPV greater than 9.9 fl was predictive of a 12-month MCO.