令和 2 年度学位申請論文

# Relationship between obesity and age in the progression of new lesion after percutaneous coronary revascularization －A retrospective cohort study－

（経皮的冠動脈血行再建術後の新規病変の進行における肥満と年齢の関連
－後ろ向きコホート研究－）

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## Abstract

*Background:* Obesity is assumed to be one of the robust risk factors for coronary artery disease (CAD). However, the effects of obesity in different age groups on the progression of atherosclerosis in patients after percutaneous coronary intervention (PCI) remains uncertain. This study aimed to examine the effect of obesity on prognosis in different age groups.

*Methods:* Consecutive patients who underwent urgent or elective PCI were surveyed for this study, and the patients were then divided into an elderly group and a middle-aged with a cut-off age of 70 years. All patients underwent coronary angiography (CAG) or coronary computed tomography angiography (CCTA) 1 year after PCI to examine the progression of atherosclerosis. The primary endpoint was revascularization for a new lesion within 2 years after PCI. The main effects and interactions between obesity and age were examined. Multivariate logistic regression analysis was performed to identify independent predictors of non-target lesion revascularization (non-TLR).

*Results:* Of the 711 patients who met the criteria and were available for follow-up analysis, the incidence of non-TLR within 2 years was 97/711 (13.6%). The higher incidence of non-TLR in obese patients was observed only in the middle-aged group, and, in the multivariate analysis, obesity was independently associated with non-TLR only in the middle-aged group.

*Conclusions:* The findings of the present study would allow us to build the hypothesis that obesity in elderly patients may not be an independent predictor of the incidence of non-TLR, leading that management to prevent non-TLR may vary depending on age.

## 要旨

背景：肥満は冠状動脈疾患（CAD）の強力な危険因子の 1 つであると考えられている。しかしながら経皮的冠動脈血行再建術（PCI）後の患者の動脈硬化の進行に対して年齢が肥満の効果に及ぼす影響については十分明らかではない。本研究は、異なる年齢層の予後に対して肥満が及ぼす影響を調べることを目的とした。

方法：緊急または待機的に PCI を受けた連続症例を調査し、患者を 70 歳をカットオフとして高齢群と中年群に分けた。すべての患者は、動脈硬化の進行を調べるために、PCI の 1 年後に冠動脈造影（CAG）または冠動脈コンピューター断層撮影血管造影（CCTA）を行った。主要評価項目は、PCI 後 2 年以内の新規病変に対する血行再建術（non-TLR）の有無とし、肥満と年齢の主たる影響と交互作用について解析を行った。また多重ロジスティック回帰分析を用いて non-TLR の独立した予測因子を調べた。

結果：選択基準を満たし、2 年間追跡しえた 711 人の患者のうち、2 年以内の non-TLR の発生率は 97/711（13.6%）であった。肥満患者における non-TLR の発生率は、中年群でのみ高かった。肥満は高齢群では関連を認めないが、一方で中年群において non-TLR と独立して関連を認めた。

結論：本研究の結果より高齢患者の肥満は non-TLR 発生の独立した予測因子ではない可能性が示唆された。non-TLR を予防するための体重管理は年齢によって異なる可能性があるという仮説を立てることができた。

## Introduction

Recurrence after percutaneous coronary intervention (PCI) occurs at a constant rate, and, in addition, a new lesion is likely to occur beside the treated lesion. Advances in drug-eluting stents and the technology of PCI have dramatically decreased stent restenosis and target lesion revascularization (TLR). [1] Previous clinical studies showed that the cumulative incidence of TLR within the first year was 7%, and the incidence after 1 year was reported to be around 2%/year,[2] whereas the long-term cumulative incidence of non-TLR continues to increase at a high rate of around 4-6%/year for the first 5 years, indicating that one of four patients will develop new events.[2,3] In order to prevent the progression of a new coronary lesion, it is necessary not only to control coronary risk factors such as diabetes mellitus (DM), hypertension (HT), and dyslipidemia (DL), but also to improve medication adherence[4] and encourage patients to change to a healthier lifestyle,[5,6] such as weight reduction and promoting physical activity and smoking cessation.

Of these, obesity is assumed to be one of the risk factors for coronary artery disease (CAD). During the past three decades, the prevalence of obesity among young Japanese people has increased gradually from 21.4% in 1981-85 to 36.5% in 2016 for men in the 50 to 59 years age bracket,[7,8] indicating that the effect of obesity on cardiovascular events may become one of major risk to be “reduced”. Patients with CAD often have multiple coronary risk factors including obesity, which can result in the development of other coronary risk factors such as HT,[9,10] DM,[10,11] and DL[10] resulting in the progression of atherosclerosis.[12,13] Adipose tissue dysfunction

in obese persons has been reported as a underlying mechanism that promotes atherosclerosis-related diseases such as CAD and cerebral infarction.[14,15] In addition, inflammation due to adipose tissue dysfunction causes atherosclerotic cardiovascular events through metabolic complications and dysregulation of adipocytokines.[16,17] Although obesity offers a survival advantage in patients after PCI,[18–20] previous reports demonstrated a higher incidence of revascularization with the progression of coronary atherosclerosis in obese patients.[21,22] Therefore, the effects of obesity on the progression of atherosclerosis and the prognosis are contradictory.

Our speculation for paradoxical effect of obesity is that obesity may have a different effect on the progression of atherosclerosis according to age. In fact, in Japan, the impact of obesity on the development of acute myocardial infarction (AMI) has been reported only in the middle-aged.[23] In contrast, the cohort study that examined an effect of obesity on the onset of ischemic heart disease in elderly males, the prognostic impact of obesity has been reported.[24] However, no report has published in terms of the effect of obesity on the progression of atherosclerosis after PCI. It is suggested that, in elderly obese patients, the altered cytokine and neuroendocrine profiles may play a role in modulating new lesion progression.[25] Thus, the effect of obesity in different age groups on non-TLR in patients after PCI remains uncertain. This study, therefore, aimed to examine the impact of obesity in the current era of improved post-PCI management, and also to

examine the differences in the effect of obesity on prognosis in different age groups.

## Methods

*Study design and participants*

The present study was conducted as a single-center, retrospective, cohort study. Consecutive patients who underwent urgent or elective PCI at Nagoya Heart Center from May 2013 to March 2016 were surveyed. Patients with any of the following 3 criteria were excluded: 1) chronic hemodialysis before PCI; 2) confirmation angiography not performed within 2 years after PCI; or 3) lack of clinical follow-up. Patients with target lesion revascularization (TLR) were included in the no repeated PCI in this study. All patients underwent coronary angiography (CAG) or coronary computed tomography angiography (CCTA) 1 year after PCI to determine whether coronary artery stenosis had progressed, and the need for revascularization was determined. Progression of a new lesion was defined as the development of a coronary lesion that was not significant at initial PCI but required additional PCI due to ischemic symptoms and/or abnormal results of functional studies, including fractional flow reserve and treadmill exercise testing. The patients' health status and the incidence of cardiovascular events and mortality are maintained in the medical records of the hospital. Only patients who visited our hospital for more than 2 years after PCI and whose medical records were available for follow-up were included in the analysis. No patients who underwent elective PCI received the rehabilitation program post-discharge that intended to reduce vascular events risk and increase in physical activity. The study protocol complied with the principles expressed in the Declaration of Helsinki. This study was approved by the Research

Ethics Committee of the Nagoya University Graduate School of Medicine (Approval No.18-505)

*Definitions*

The deaths of the patients in this study were confirmed using the medical records from our hospital or information obtained from follow-up visits. The present study included information on the baseline characteristics of the patients and their cardiac history and risk factors at the initial PCI. Body mass index (BMI) was calculated at initial PCI by dividing the patient's measured weight (kg) by the square of the height (m), and obesity was defined as a BMI ≥ 25 kg/m2 based on the Japanese criterion for obesity.[26] To compare effects by age, elderly patients were defined as age ≥ 70 years, whereas middle-aged patients were defined as age < 70 years. The clinical definition of DM included a non-fasting glucose ≥ 200 mg/dL, HbA1c ≥ 6.5%, oral hypoglycemic use, or insulin use. HT was defined as taking antihypertensive drugs. DL was defined as a triglyceride (TG) level ≥ 150 mg/dL and/or low-density lipoprotein-cholesterol (LDL-C) level ≥ 140 mg/dL and/or high-density lipoprotein-cholesterol (HDL-C) level < 40 mg/dL and/or treatment on lipid- lowering agents.

The estimated glomerular filtration rate (eGFR) was calculated using the GFR equation for the Japanese population.[27] Chronic kidney disease (CKD) was defined as a baseline eGFR ≤ 60 mL·min–11.73 m–2.[28] TLR was defined as any repeat revascularization procedure (percutaneous

or surgical) of the original target lesion site, including the stented area plus a margin, typically 5 mm proximal and distal to the stent. Multi-vessel disease (MVD) was defined as ≥ 2-vessel disease with angiographic significant stenosis before initial PCI.

*Outcomes*

Revascularization of an initially non-target lesion due to its progression has emerged as a new therapeutic target of CAD in the previous reports.[28,29] Thus, we set revascularization for a non-target lesion as new lesion for primary endpoint within 2 years after PCI in this study.

*Statistical analysis*

The Wilk-Shapiro test was used to assess the normality of data distributions. Continuous variables are presented as means ± standard deviation, or as medians and interquartile range in cases of non-normal distributions. Categorical data are presented as percentages. Baseline characteristics were compared between groups using the unpaired t-test or the Mann-Whitney U test for continuous variables and the chi-squared test for categorical variables.

Multivariate logistic regression analysis was performed to identify the independent prognostic factors for non-TLR. The main effects and interactions of obesity on non-TLR in elderly and middle-aged patients were also analyzed. All tests with two-sided p-values < 0.05 were considered

significant. All statistical analyses were performed using IBM SPSS statistics v23 (SPSS, Inc, Chicago, IL) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[30] which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

## Results

Of the 1,437 patients who underwent PCI during the study period, 711 patients met the criteria and were available for follow-up analysis (Figure 1). Among these patients, the prevalence of obesity was 38%, and 43% of the patients were aged ≥ 70 years. The prevalence of obesity was greater in the middle-aged group (45.9%) than in the elderly group (28.6%). Baseline clinical and angiographic characteristics are shown in Table 1, and patients characteristics according to obesity in each age group (Table 2). Overall, DM and DL were more common in patients with obesity, and age was significantly younger in patients with obesity than in those without. In a group comparison by age, the prevalence of both DM and DL were significantly higher in the middle-aged obese group, but has no statistical difference in the elderly group.

The incidence rate of non-TLR within 2 years was 97/711 (13.6%) patients in this study. Of these 97 patients, 74 (10.4%) had undergone PCI by the 1-year follow-up period. The incidence rate of non-TLR in middle-aged group was greater in obese patients, whereas the reverse relationship was observed in aged group (Figure 2). In addition, the incidence rate distributions according to obesity and comorbidity, sex are presented in each age group in Table 3.

Multivariate logistic regression analysis showed that obesity was associated with non-TLR overall after adjusting for age ≥ 70 years, sex, HT, DM, High LDL-C (≥ 140 mg/dL), CKD, MVD, and prior PCI (Table 4). Furthermore, there was a significant interaction between obesity and age on non-TLR. In the elderly group, there was a significant interaction between obesity and HT on

non-TLR. In contrast, no interaction of obesity and comorbidity, sex was found in the middle-aged group. In the elderly group, HT and DM were significantly associated with non-TLR, whereas obesity and MVD were significantly associated in the middle-aged group (Figure 3).

## Discussion

The findings of this study suggested that obesity may not be an independent predictor of the incidence of non-TLR in elderly patients. The difference in the predictors identified in this study, DM and HT for the elderly group and MVD and obesity for the middle-aged group, suggests that post-PCI management strategies to prevent non-TLR may vary depending on patient characteristics and age. Based on the findings of this study, we propose that obesity in elderly patients may not be uniformly recognized as a risk factor for non-TLR, but should be recognized as a risk in connection with consideration of other comorbidities.

In the present study, the incidence rate of non-TLR was seen in 74 (10.4%) at 1 year and 97 (13.6%) at 2 years in patients who underwent primary PCI and the incidence rate at 2 years was not different between the elderly and the middle-aged groups, 13.9% vs 13.3%, respectively. Glaser et al. reported that approximately 6% of PCI patients had required clinical driven PCI for non-target lesion by 1 year.[31]. The studies in the Japanese population that examined the incidence rate of non-TLR showed rates of approximately 9.5-16% within 1 year[2,3,28] and 21% within 2 years.[2] Another factor considered in generalizing the results is lipid-lowering medications. The importance of LDL-C lowering therapy has been emphasized, and aggressive lipid management has recently been recommended.[32,33] According to the reports of the prescription rate for statins in 2010 in Japan, only 24% of the patients had achieved the level of LDL-C < 100 mg/dL that sufficient for secondary prevention of the time.[34] In our study, in the PCI patients from 2013 to

2016, the achievement rate of LDL-C < 100 mg/dL was as high as 67%, indicating that more aggressive lipid management had been performed. This achievement rate may have led to the low incidence rate of new lesion PCI. The incidence rate of non-TLR and higher achievement rate of LDL-C in our study patients suggests that the findings in this study may provide an acceptable basis for hypothesis building.

In this study, obesity and MVD were independently associated with non-TLR in middle-aged patients that was in consistent with previous reports.[21,28,31] In particular, obesity was independently associated with non-TLR in middle-aged patients, but not in elderly patients. A meta-analysis including aged patients reported that obesity was an independent predictor of repeat revascularization,[21] however, the study did not analyze a group difference depending on age. Regarding the issues of the effects of age on obesity, a recent study showed that obesity was an independent risk factor for AMI in young and middle-aged males, but not in older (60-80 years) or very old males (>80 years).[23] Another study showed that the association between obesity and a cluster of cardiometabolic risk factors was stronger in young than in elderly males.[35] The findings of these studies suggest that the progression of atherosclerosis caused by adipose tissue dysfunction due to obesity may particularly be pronounced in middle-aged patients. However, the underlying mechanisms for the age-related variability of the effects of obesity on new lesion progression has remained unclear.

In consistent with the report of Shiraishi et al.[23] we did not find obesity as a predictor for non-TLR in the elderly group. One possible explanation for this variability is that altered cytokine and neuroendocrine profiles of elderly obese patients may play a key role in modulating new lesion progression.[25] Increased TNF-α and CRP levels at pre-PCI have been reported to predict major adverse cardiac events including revascularization.[36] However, the effect of TNF-α is likely to be modulated by soluble TNF-α receptors from adipose tissue, which results in neutralizing the biologic effects of TNF-α.[37] These studies and the findings in this study imply that the metabolic activity of adipose tissues may act differently depending on age, more aggressively in middle-aged patients and less aggressively in elderly patients, resulting in the cardiovascular protective effect in elderly obese patients.

Another issue related to the cardiovascular protective effect of adipose tissue is its anti-oxidative effect. Oxidative stress increases with age, causing atherosclerosis progression,[38] however, adipose tissue may counteract oxidative stress via endothelial function by producing adiponectin.[39] It has been reported that adiponectin concentrations were positively correlated with age.[40,41] Along with anti-inflammatory effect, anti-oxidative effect of adipose tissues may be modulated in elderly patients, by the effects of adiponectin. Furthermore, da Cruz et al.[42] reported that lower plasma total antioxidant capacity had significant relationships with the presence of HT and DM in community-dwelling elderly persons with chronic diseases. Interestingly, both of HT

and DM were also selected as independent risk factors in the elderly in this study. Another study reported that a higher plasma endothelin-1 level in HT and DM patients was independently associated with a lower plasma antioxidant status.[43] In the present study, approximately 70% of elderly patients had HT and 40% had DM, and those were more prevalent compared with the middle-aged group, suggesting higher oxidative stress in the elderly. Although the findings in this study imply a possibility of anti-oxidative capacity of adipose tissues in the elderly, the underlying mechanisms remains uncertain. Based on the above, we propose that obesity in elderly patients of post-PCI should be manipulated in connection with consideration of other comorbidities.

## Study Limitations

Several limitations need to be discussed. First, this study was retrospective, based on a single center's experience, and the findings of this study should prospectively be confirmed by large samples in multiple facilities before they can be generalized. Second, BMI was measured at baseline, therefore, the effect of changes in BMI on atherosclerotic progression remains unclear. In addition, we could not exclude the possibility of the influence of weight lowering diseases such as malignancy or inflammatory disease. Therefore, changes in BMI after PCI and diseases that cause weight reduction need to be studied in the future. Third, BMI in this study is likely to reflect muscle mass. Other measures of obesity such as waist circumference and the waist-to-hip ratio might better reflect body fat content and distribution than BMI itself. However, BMI is widely

used in daily clinical practice, and the results of this study may be widely applicable. Nevertheless, the findings in this retrospective study hypothesized that unnecessary weight reduction in elderly post-PCI patients should be avoided, further study will need to determine the ideal body weight based on age distribution to prevent the progression of atherosclerosis.

## Conclusion

In conclusion, the findings of the present study would allow us to hypothesize that obesity in elderly patients may not be an independent predictor of the incidence of non-TLR, leading that management strategies to prevent non-TLR may vary depending on age. Obesity in elderly patients may be recognized as a risk factor for non-TLR in connection of consideration with other comorbidities. In addition, since almost patients who underwent elective PCI cannot received the rehabilitation program post-discharge, IoT-based disease management interventions may be useful in the future.

## Acknowledgements

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## Figures

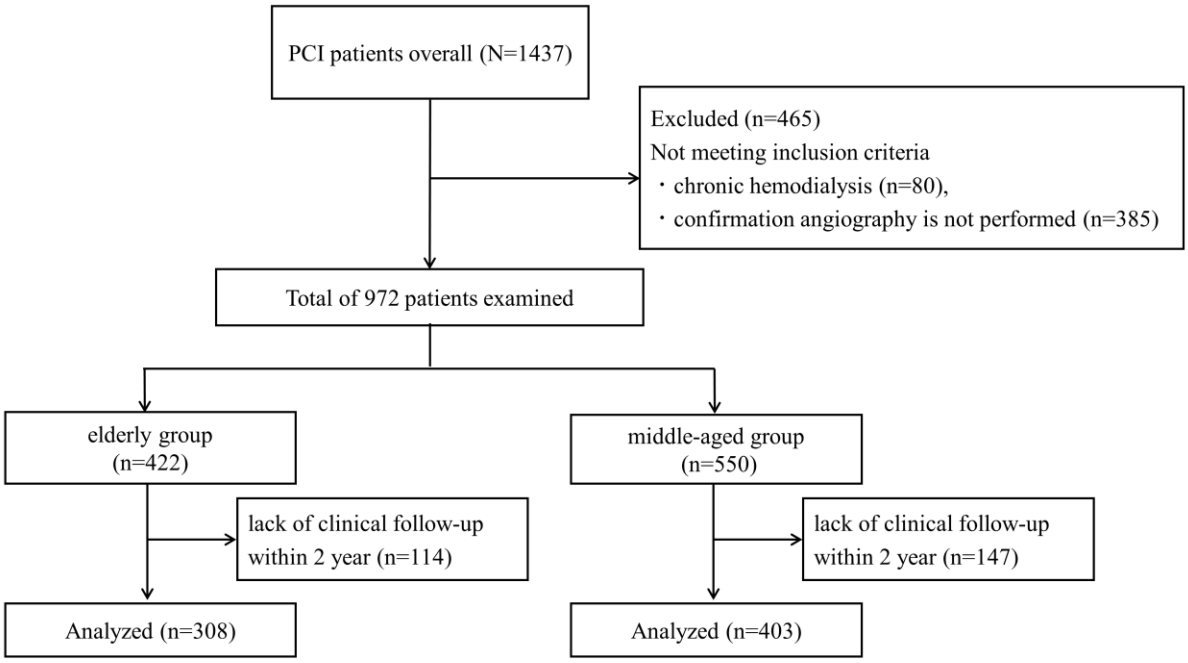
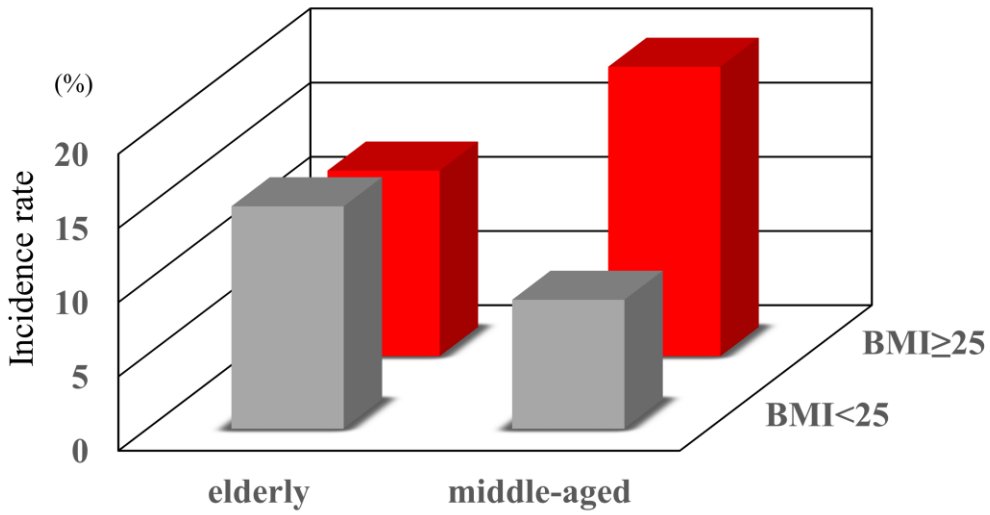



**Figure 1.** Study flow diagram.

The cut-off age for the middle-aged and elderly groups is 70 years.




| | | | |
|---|---|---|---|
| **age** | median[min-max] | 75[70-90] | 62[32-69] |
| **Prevalence of obesity** | | 28.6% | 45.9% |

**Figure 2.** Incidence rate according to obesity in each age group.

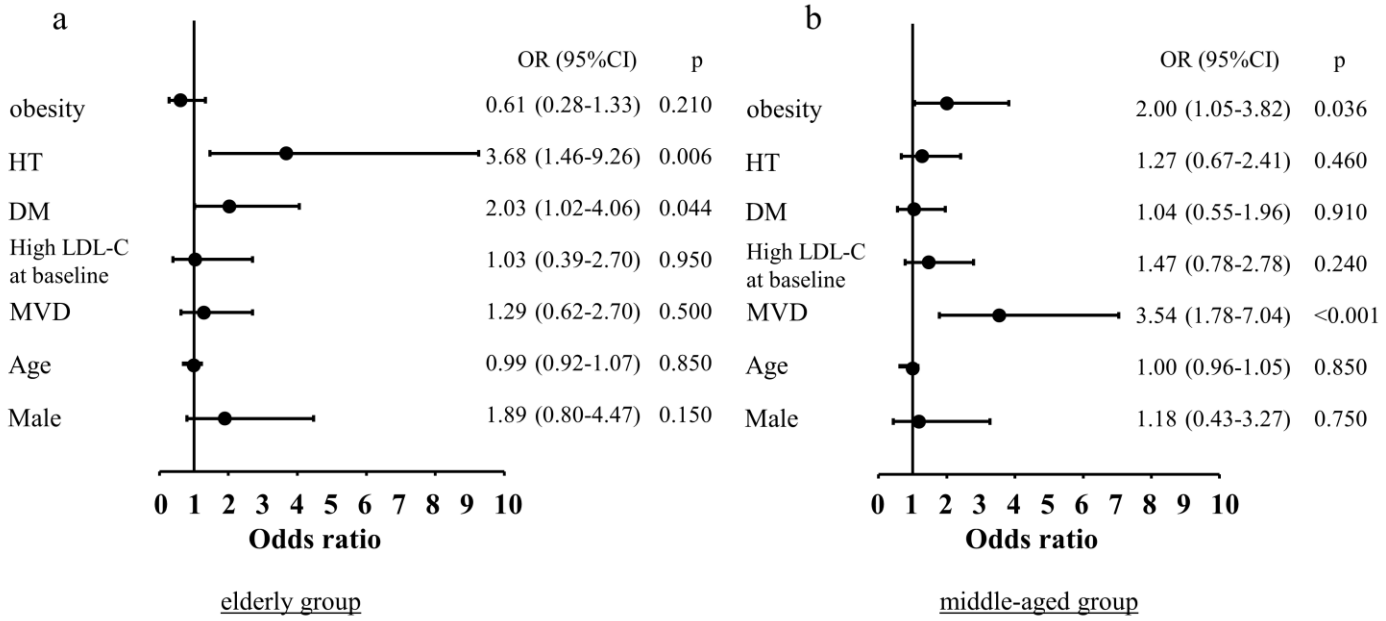



**Figure 3.** Independent predictors of non-TLR in each group.

(a) elderly group (b) middle-aged group. HT = hypertension, DM = diabetes mellitus, MVD = Multi-vessel disease, CI = confidence interval. High LDL-C was defined as a LDL-C level ≥ 140 mg/dL.

## Tables

**Table 1.** Patients characteristics

| | Overall, (N=711) | | |
|---|---|---|---|
| | Non-TLR n=97 | No repeated PCI n=614 | *P* |
| Age, (years) | 68.0 (60.0-74.0) | 67.0 (61.0-74.0) | 0.985 |
| Men, n (%) | 84 (86.6%) | 485 (79.0%) | 0.1 |
| BMI, (kg/m$^2$) | 24.7 (22.6-26.8) | 24.1 (21.9-26.0) | 0.050 |
| BMI < 18.5, n (%) | 1 (1.0%) | 21 (3.4%) | 0.342 |
| BMI ≥ 25, n (%) | 45 (46.4%) | 228 (37.1%) | 0.092 |
| BMI ≥ 30, n (%) | 7 (7.2%) | 32 (5.2%) | 0.468 |
| ACS, n (%) | 16 (16.5%) | 87 (14.2%) | 0.536 |
| Prior PCI, n (%) | 24 (24.7%) | 155 (25.2%) | 1.0 |
| MVD, n (%) | 72 (74.2%) | 312 (50.8%) | < 0.001 |
| Smoking, n (%) | 29 (29.9%) | 150 (25.3%) | 0.381 |
| Comorbidity | | | |
| Diabetes mellitus, n (%) | 42 (43.8%) | 203 (33.3%) | 0.050 |
| Hypertension, n (%) | 72 (74.2%) | 369 (60.1%) | 0.009 |
| Dyslipidemia, n (%) | 71 (73.2%) | 422 (68.7%) | 0.409 |
| Chronic kidney disease, n (%) | 37 (38.1%) | 192 (31.3%) | 0.198 |
| Laboratory data at follow-up | | | |
| LDL-C, (mg/dl) | 92.0 (73.0-112.0) | 89.0 (73.0-108.0) | 0.595 |
| LDL-C < 70, n (%) | 22 (22.7%) | 127 (21.0%) | 0.689 |
| LDL-C < 100, n (%) | 62 (63.9%) | 414 (67.4%) | 0.488 |
| HDL-C, (mg/dl) | 46.0 (40.5-53.6) | 48.2 (40.6-57.7) | 0.102 |
| non HDL-C, (mg/dl) | 118.1 (98.9-140.5) | 114.5 (100.0-137.0) | 0.574 |
| TG, (mg/dl) | 136.0 (107.0-198.0) | 134.0 (93.3-187.0) | 0.117 |
| HbA1c, (%) | 6.0 (5.7-6.7) | 6.0 (5.7-6.4) | 0.638 |
| eGFR, (mL/min/1.73 m$^2$) | 60.5 (51.9-70.5) | 63.1 (54.2-72.1) | 0.118 |
| Medications at follow-up (n=656) | | | |
| Aspirin, n (%) | 96 (100%) | 560 (100%) | 1.0 |
| ACE-Is or ARBs, n (%) | 58 (60.4%) | 309 (55.0%) | 0.374 |
| Calcium channel blockers,n (%) | 37 (38.5%) | 206 (36.7%) | 0.732 |
| Statins, n (%) | 79 (82.3%) | 453 (80.6%) | 0.78 |
| Oral hypoglycemic drugs, n (%) | 36 (37.5%) | 141 (25.1%) | 0.017 |
| Insulin, n (%) | 6 (6.2%) | 12 (2.1%) | 0.035 |

Values are numbers (%) or median with interquartile range. BMI, body mass index; PCI, percutaneous coronary intervention; MVD, multi vessel disease; ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

**Table 2.** Patients characteristics according to obesity in each age group

| | Overall, (N=711) | | | elderly, (N=308) | | | middle-aged, (N=403) | | |
|---|---|---|---|---|---|---|---|---|---|
| | obesity n=273 | Non obesity n=438 | *P* | obesity n=88 | Non obesity n=220 | *P* | obesity n=185 | Non obesity n=218 | *P* |
| Age, (years) | 64.0 (55.0-71.0) | 70.0 (63.0-75.0) | < 0.001 | 74.5 (72.0-78.0) | 75.0 (72.0-79.0) | 0.448 | 59.0 (53.0-64.0) | 63.0 (58.0-66.0) | < 0.001 |
| Men, n (%) | 238 (87.2%) | 331 (75.6%) | < 0.001 | 68 (77.3%) | 153 (69.5%) | 0.208 | 170 (91.9%) | 178 (81.7%) | 0.003 |
| BMI, (kg/m$^2$) | 26.8 (25.7-28.3) | 22.6 (21.0-23.8) | < 0.001 | 26.3 (25.5-27.7) | 22.5 (21.1-23.8) | < 0.001 | 27.1 (25.9-29.0) | 22.8 (20.9-23.7) | < 0.001 |
| ACS, n (%) | 45 (16.5%) | 58 (13.2%) | 0.273 | 8 (9.1%) | 26 (11.8%) | 0.552 | 37 (20.0%) | 32 (14.7%) | 0.185 |
| Prior PCI, n (%) | 68 (24.9%) | 111 (25.3%) | 0.929 | 23 (26.1%) | 60 (27.3%) | 0.888 | 45 (24.3%) | 51 (23.4%) | 0.907 |
| MVD, n (%) | 157 (57.5%) | 227 (51.8%) | 0.142 | 53 (60.2%) | 126 (57.3%) | 0.702 | 104 (56.2%) | 101 (46.3%) | 0.057 |
| Smoking, n (%) | 72 (27.4%) | 107 (25.0%) | 0.531 | 10 (11.9%) | 38 (17.8%) | 0.293 | 62 (34.6%) | 69 (32.2%) | 0.668 |
| Comorbidity | | | | | | | | | |
| Diabetes mellitus, n (%) | 111 (40.8%) | 134 (30.9%) | 0.009 | 37 (42.5%) | 83 (38.1%) | 0.517 | 74 (40.0%) | 51 (23.7%) | 0.001 |
| Hypertension, n (%) | 178 (65.2%) | 262 (59.8%) | 0.154 | 66 (75.0%) | 142 (64.5%) | 0.082 | 112 (60.5%) | 120 (55.0%) | 0.312 |
| Dyslipidemia, n (%) | 207 (75.8%) | 286 (65.3%) | 0.003 | 64 (72.7%) | 148 (67.3%) | 0.414 | 143 (77.3%) | 138 (63.3%) | 0.002 |
| Chronic kidney disease, n (%) | 83 (30.4%) | 147 (33.6%) | 0.41 | 45 (51.1%) | 104 (47.3%) | 0.614 | 38 (20.5%) | 43 (19.7%) | 0.901 |
| BMI, laboratory data and blood pressure at follow-up | | | | | | | | | |
| BMI, (kg/m$^2$) | 26.6 (25.4-28.5) | 22.3 (20.9-23.7) | < 0.001 | 25.9 (25.1-27.8) | 22.1 (20.7-23.7) | < 0.001 | 26.9 (25.8-28.9) | 22.4 (21.1-23.7) | < 0.001 |
| LDL-C, (mg/dl) | 91.0 (74.0-110.0) | 89.0 (72.0-108.0) | 0.343 | 86.0 (74.0-107.0) | 87.0 (71.0-105.0) | 0.443 | 91.0 (74.0-111.3) | 90.0 (73.0-111.0) | 0.718 |
| LDL-C < 70, n (%) | 51 (19.1%) | 98 (22.5%) | 0.297 | 14 (16.1%) | 52 (23.9%) | 0.166 | 37 (20.6%) | 46 (21.1%) | 0.902 |
| LDL-C < 100, n (%) | 177 (64.8%) | 299 (68.3%) | 0.368 | 60 (68.2%) | 154 (70.0%) | 0.785 | 117 (63.2%) | 145 (66.5%) | 0.53 |
| HDL-C, (mg/dl) | 44.1 (37.4-51.2) | 51.0 (42.2-59.8) | < 0.001 | 47.0 (39.1-53.3) | 50.4 (41.6-59.7) | 0.008 | 43.7 (36.5-50.5) | 51.3 (42.7-59.9) | < 0.001 |
| non HDL-C, (mg/dl) | 117.1 (99.7-139.8) | 115.1 (100.1-134.5) | 0.34 | 112.1 (100.0-142.2) | 115.8 (99.6-134.2) | 0.52 | 119.9 (99.2-139.0) | 113.9 (101.1-135.1) | 0.543 |
| TG, (mg/dl) | 146.0 (104.0-203.0) | 127.5 (91.8-185.0) | 0.002 | 140.0 (100.5-180.0) | 122.0 (94.5-169.3) | 0.102 | 152.0 (104.0-213.5) | 134.0 (91.3-193.0) | 0.026 |
| HbA1c, (%) | 6.0 (5.8-6.6) | 5.9 (5.7-6.4) | < 0.001 | 6.1 (5.9-6.6) | 6.0 (5.7-6.5) | 0.056 | 6.0 (5.8-6.6) | 5.9 (5.6-6.2) | < 0.001 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| eGFR, (mL/min/1.73 $m^2$) | 62.9 (55.8-72.4) | 61.2 (52.4-69.7) | 0.072 | 56.4 (44.9-62.7) | 57.7 (48.1-65.7) | 0.365 | 68.0 (59.2-76.3) | 65.8 (57.8-75.1) | 0.303 |
| SBP, (mmHg) | 133.0 (116.0-148.0) | 128.0 (115.0-145.0) | 0.166 | 138.0 (120.0-151.0) | 129.5 (114.0-152.0) | 0.099 | 131.5 (115.8-144.3) | 127.5 (116.0-143.0) | 0.501 |
| DBP, (mmHg) | 71.0 (65.0-80.0) | 67.0 (60.0-75.0) | < 0.001 | 69.0 (60.0-76.0) | 65.0 (55.0-73.0) | 0.057 | 73.0 (67.0-82.0) | 69.5 (63.3-78.0) | 0.001 |
| Medications at follow-up (n=656) | | | | | | | | | |
| Aspirin, n (%) | 253 (100%) | 403 (100%) | 1.0 | 80 (98.8%) | 204 (100%) | 0.284 | 173 (100%) | 199 (99.0%) | 0.501 |
| ACE-Is or ARBs, n (%) | 157 (62.1%) | 210 (51.9%) | 0.012 | 50 (61.7%) | 105 (51.5%) | 0.147 | 107 (62.2%) | 105 (52.2%) | 0.059 |
| Calcium channel blockers,n (%) | 101 (39.9%) | 142 (35.1%) | 0.214 | 31 (38.3%) | 74 (36.3%) | 0.786 | 70 (40.7%) | 68 (33.8%) | 0.197 |
| Statins, n (%) | 211 (83.4%) | 321 (79.3%) | 0.222 | 61 (75.3%) | 153 (75.0%) | 1.0 | 150 (87.2%) | 168 (83.6%) | 0.38 |
| Oral hypoglycemic drugs, n (%) | 90 (35.6%) | 87 (21.5%) | < 0.001 | 30 (37.0%) | 54 (26.5%) | 0.085 | 60 (34.9%) | 33 (16.4%) | < 0.001 |
| Insulin, n (%) | 7 (2.8%) | 11 (2.7%) | 1.0 | 2 (2.5%) | 6 (2.9%) | 1.0 | 5 (2.9%) | 5 (2.5%) | 1.0 |

Values are numbers (%) or median with interquartile range. BMI, body mass index; PCI, percutaneous coronary intervention; MVD, multi vessel disease; ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

**Table 3.** Incidence rate distribution according to obesity and comorbidity, sex in each age group

| | elderly, (N=308) | | | middle-aged, (N=403) | | |
|---|---|---|---|---|---|---|
| | obesity n=88 | Non obesity n=220 | *P* | obesity n=185 | Non obesity n=218 | *P* |
| HT(+) | 12.1% | 20.4% | 0.004 | 19.6% | 10.8% | 0.038 |
| HT(-) | 13.6% | 3.8% | | 16.4% | 7.1% | |
| DM(+) | 18.9% | 18.1% | 0.172 | 18.9% | 11.8% | 0.053 |
| DM(-) | 6.0% | 12.6% | | 18.0% | 8.5% | |
| DL(+) | 14.0% | 16.9% | 0.48 | 17.5% | 8.7% | 0.048 |
| DL(-) | 8.3% | 9.7% | | 21.4% | 10.0% | |
| Male | 11.8% | 17.6% | 0.219 | 18.2% | 10.1% | 0.037 |
| Female | 15.0% | 13.4% | | 20.0% | 5.0% | |

**Table 4.** Logistic regression analysis for the association between obesity and age, comorbidity, sex

| | Obesity | | | P for interaction |
|---|---|---|---|---|
| | OR | 95% CI | p value | |
| Overall * | 1.87 | 1.02-3.43 | 0.043 | |
| Age group ** | | | | 0.04 |
| elderly ( ≥ 70 yo) | 0.61 | 0.28-1.33 | 0.21 | |
| middle-aged ( < 70 yo) | 1.97 | 1.04-3.76 | 0.038 | |
| elderly | | | | |
| comorbidity | | | | |
| HT × obesity | | | | 0.037 |
| HT(+) (n=208) | 0.54 | 0.23-1.25 | 0.15 | |
| HT(-) (n=100) | 3.95 | 0.74-21.10 | 0.11 | |
| DM × obesity | | | | 0.29 |
| DM(+) (n=120) | 1.06 | 0.39-2.86 | 0.91 | |
| DM(-) (n=188) | 0.44 | 0.12-1.58 | 0.21 | |
| DL × obesity | | | | 0.96 |
| DL(+) (n=212) | 0.81 | 0.35-1.84 | 0.61 | |
| DL(-) (n=96) | 0.84 | 0.16-4.37 | 0.84 | |
| sex | | | | |
| sex × obesity | | | | 0.16 |
| Male (n=221) | 0.62 | 0.27-1.45 | 0.27 | |
| Female (n=87) | 2.19 | 0.47-10.10 | 0.32 | |
| middle-aged | | | | |
| comorbidity | | | | |
| HT × obesity | | | | 0.7 |
| HT(+) (n=232) | 2.01 | 0.96-4.22 | 0.064 | |
| HT(-) (n=171) | 2.56 | 0.95-6.86 | 0.062 | |
| DM × obesity | | | | 0.64 |
| DM(+) (n=125) | 1.75 | 0.62-4.91 | 0.29 | |
| DM(-) (n=278) | 2.35 | 1.13-4.89 | 0.022 | |
| DL × obesity | | | | 0.88 |
| DL(+) (n=281) | 2.22 | 1.07-4.63 | 0.032 | |
| DL(-) (n=122) | 2.45 | 0.87-6.93 | 0.09 | |
| sex | | | | |
| sex × obesity | | | | 0.39 |
| Male (n=348) | 1.98 | 1.06-3.70 | 0.032 | |
| Female (n=55) | 4.75 | 0.71-31.90 | 0.11 | |

OR, odds ratio; CI, confidence interval; yo, years old; HT, Hypertension; DM, Diabetes mellitus; DL, Dyslipidemia;CKD, Chronic

kidney disease; MVD, multi vessel disease; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein cholesterol

* Adjusted for age ≥ 70 yo, sex, HT, DM, CKD, High LDL-C (≥ 140 mg/dL) at baseline, MVD and prior PCI in overall.

** Adjusted for age, sex, HT, DM and MVD in each age group.