Peripheral Artery Disease on The Prognosis Value of Patients with Stable Coronary Artery Disease Undergoing Percutaneous Coronary Intervention: A Retrospective, Single-Center Cohort Study

Zeyi Cheng,¹* Miaomiao Qi,²* Zekun Lang,³ Tingting Fang,⁴ Mahboob Alam¹ Jing Yu,⁵ Yingqiang Guo¹

¹Department of Cardiovascular Surgery, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan 610041, China; ²Department of Cardiology, The Second Hospital of Lanzhou University, Lanzhou, Gansu Province, 730000, China; ³The Medical School of Lanzhou University, Lanzhou, Gansu Province, 730000, China; ⁴Department of Cardiology, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan 610041, China ⁵Department of Medicine, Division of Cardiovascular Medicine, Baylor College of Medicine, Houston, Texas, USA.

ABSTRACT

Objective: The purpose of this investigation aimed to clarify the impact of peripheral artery disease (PAD) on the prognosis value of patients with stable coronary artery disease (CAD) who underwent percutaneous coronary intervention (PCI).

Methods: The SPSS 16 software was used for secondary analysis of DRYAD database data. A total of 204 patients were enrolled from Shinonoi General Hospital for newly diagnosed stable CAD and received PCI performance between October 2014 and October 2017. Patients with old myocardial infarction (MI) were excluded. We divided patients into two groups with PAD and without PAD. The primary endpoints were major adverse cardiac events (MACE, defined as all-cause death, non-fatal MI, and non-fatal stroke) and cardiovascular events (defined as cardiovascular death, non-fatal MI, and non-fatal stroke). The secondary outcomes were the individual components of the composite primary outcomes. The median follow-up time was 783 days.

Results: No statistical difference was found between PAD and non-PAD patients of lesional characteristics. Spearman’s rank correlations indicate diabetes mellitus (DM) (P = 0.019) and HBOc (P = 0.009) are positively correlated with PAD. In Kaplan-Meier analysis, patients with PAD predicted poor prognosis in MACE (P < 0.05) and cardiovascular events (P < 0.05). In Multivariable Cox proportional hazards analysis, patients with PAD independently predicted MACE and cardiovascular events.

Conclusions: PAD is a significant mediator for the prognosis of patients with stable CAD who underwent PCI treatment.

INTRODUCTION

PAD is defined as a vascular disease mainly affecting lower extremities characterized by atherosclerotic vascular [Abola 2020]. The prevalence of PAD showed an increasing trend worldwide [Fowkes 2013]. In Europe, the prevalence of PAD reached 5.3% [Olinic 2018]. Its clinical manifestations vary from the reduction of Ankle-Brachial index (ABI) without symptoms, intermittent claudication (IC) to severe ischemic symptoms [Norgren 2007]. Patients with PAD have higher risks of stroke, myocardial infarction (MI) and even cardiovascular mortality [Morris 2014].

CAD is the main cause of death in many countries. In Europe, CAD is responsible for nearly 20% of deaths caused by cardiovascular diseases [Roth 2017]. Because atherosclerosis is a systemic condition, CAD and PAD present the common pathogenesis and risk factors for development, such as smoking, dyslipidemia, hypertension, and diabetes mellitus [Bhatt 2006]. Several studies have suggested that the incidence of major cardiovascular events among patients with symptomatic PAD is higher than those with symptoms of CAD [McKenna 1991]. However, the prevalence of patients with both CAD and PAD ranges from 54% to 69% [Ryu 2012; Nishijima 2017; Global 2017]. These patients developed a particularly poor long-term prognosis. PCI is widely used to improve the survival and prognosis of CAD. The purpose of this investigation aimed to find the impact of PAD on the prognosis value of patients with stable CAD who underwent PCI.

METHODS

Data resource: The data used in this study comes from an open access database DRYAD website (https://DATADRYAD.org). The site allows users to download the original data for Dryad, Dataset (https://doi.org/10.5061/dryad.fn6730j).

Study design: The study design previously has been described [Suzuki 2019]. It was a retrospective, single-center cohort study. The study included patients admitted to Shinonoi General Hospital between October 2014 and October 2017 for newly diagnosed stable CAD who received PCI.
A total of 204 patients were enrolled (median age, 73 years old). The baseline characteristics are shown in Table 1. (Table 1) Of these, 53 patients (26%) had the presence of PAD at baseline. Compared with CAD patients without PAD, CAD patients with PAD had higher HbA1c (6.3% [5.8%-7.0%] vs. 6.0% [5.6%-6.7%], P = 0.009), Triglycerides (134% [87%-199%] vs. 106% [78%-149%], P = 0.024) and presence of diabetes mellitus (26% vs. 47%, P = 0.019). However, no significant correlations were detected between PAD and these clinical indices. (Table 2) The baseline lesional characteristics are shown in Table 3. (Table 3) Among the PAD patients, 28% (15/53) had multi-vessel disease, and 7.5% (4/53) had CTO lesions. No statistical difference was found between PAD and non-PAD patients of lesional characteristics.

Clinical outcomes by PAD status: In this study, during the follow up of 1500 days, 14% (28/204) of patients experienced MACE. The PAD group had 24.5% (13/53) patients who developed MACE, whereas the no PAD group had only 9.9% (15/151). Patients with PAD indicated a higher risk of MACE (24.5% vs. 9.9%, P = 0.008). In multivariate Cox proportional hazards analysis of PAD patients, after adjusting for age, CRP and TG, PAD could predict the risk of MACE. (Table 4) Kaplan-Meier analysis combined with PAD could independently predict MACE (all-cause death, MI, and stroke) (P = 0.015). (Figure 2) In addition, PAD patients also could predict cardiac events (cardiac death, MI, and stroke) (P = 0.034). (Figure 4) However, in terms of all-cause death events or cardiac death events, respectively, PAD patients had no ability of prediction. (Figure 1) (Figure 3) (Figure 5)

RESULTS

Baseline characteristics: A total of 204 patients were
| Variable                              | Overall population (N = 204) | PAD YES (N = 53) | PAD NO (N = 151) | P-value |
|--------------------------------------|------------------------------|------------------|-----------------|---------|
| Age (years)                          | 73 [66-80]                   | 73 [68-80]       | 73 [65-80]      | 0.58    |
| Male sex, n (%)                      | 142 (69)                     | 31 (22)          | 111 (78)        | 0.041   |
| BMI (mmHg)                           | 23.4 [21.0-25.7]             | 22.7 [20.2-25.5] | 23.8 [21.1-25.7]| 0.218   |
| Systolic blood pressure (mmHg)       | 136 [123-147]                | 136 [120-146]    | 138 [125-147]   | 0.179   |
| Diastolic blood pressure (mmHg)      | 76 [70-85]                   | 72 [66-82]       | 79 [71-86]      | 0.007   |
| Hypertension, n (%)                  | 151 (74)                     | 36 (24)          | 115 (76)        | 0.24    |
| Dyslipidemia, n (%)                  | 104 (51)                     | 34 (33)          | 70 (67)         | 0.026   |
| Diabetes mellitus, n (%)             | 73 (36)                      | 26 (36)          | 47 (64)         | 0.019   |
| Atrial fibrillation, n (%)           | 26 (13)                      | 6 (23)           | 20 (77)         | 0.718   |
| OCI, n (%)                           | 35 (17)                      | 17 (49)          | 18 (31)         | 0.001   |
| MACE, n (%)                          | 28 (14)                      | 13 (46)          | 15 (54)         | 0.008   |
| Past smoker, n (%)                   | 101 (49)                     | 27 (27)          | 74 (73)         | 0.808   |
| LVEF (%)                             | 66 [62-68]                   | 67 [63-68]       | 66 [62-68]      | 0.743   |
| Medication                           |                              |                  |                 |         |
| Aspirin, n (%)                       | 202 (99)                     | 52 (26)          | 150 (74)        | 0.436   |
| Thienopiridines, n (%)               | 200 (98)                     | 50 (25)          | 150 (75)        | 0.024   |
| Warfarin, n (%)                      | 5 (2.4)                      | 1 (20)           | 4 (80)          | 0.758   |
| DOAC, n (%)                          | 21 (10)                      | 3 (14)           | 18 (86)         | 0.197   |
| Statin, n (%)                        | 111 (54)                     | 33 (30)          | 78 (70)         | 0.182   |
| Ezetimibe, n (%)                     | 3 (1.5)                      | 1 (33)           | 2 (67)          | 0.77    |
| PPI, n (%)                           | 135 (66)                     | 32 (24)          | 102 (76)        | 0.344   |
| ACE-Is, n (%)                        | 19 (9)                       | 3 (16)           | 16 (84)         | 0.287   |
| ARBs, n (%)                          | 88 (43)                      | 29 (33)          | 59 (67)         | 0.048   |
| Beta-blockers, n (%)                 | 55 (27)                      | 11 (20)          | 44 (80)         | 0.237   |
| MRAs, n (%)                          | 11 (5.4)                     | 1 (9)            | 10 (91)         | 0.189   |
| Laboratory data                      |                              |                  |                 |         |
| Hb (g/dL)                            | 13.9 [12.3-15.0]             | 13.8 [11.8-14.5] | 13.9 [12.5-15.3] | 0.11    |
| Alb (g/dL)                           | 4.0 [3.6-4.3]                | 3.9 [3.5-4.3]    | 4.1 [3.7-4.3]   | 0.123   |
| eGFR (mL/min/1.73m2)                 | 40 [33-75]                   | 59 [39-73]       | 65 [56-76]      | 0.081   |
| AST (U/L)                            | 23 [18-29]                   | 21 [18-27]       | 23 [19-29]      | 0.073   |
| ALT (U/L)                            | 18 [14-26]                   | 17 [12-26]       | 16 [14-27]      | 0.18    |
| T-Chol (mg/dL)                       | 184 [168-208]                | 187 [168-212]    | 183 [163-206]   | 0.476   |
| HDL-Chol (mg/dL)                     | 49 [41-57]                   | 48 [36-58]       | 49 [41-57]      | 0.394   |
| LDL-Chol (mg/dL)                     | 109 [90-129]                 | 105 [89-128]     | 109 [91-130]    | 0.303   |
| Triglycerides (mg/dL)                | 107 [83-160]                 | 134 [87-199]     | 106 [78-149]    | 0.024   |
| CRP (mg/dL)                          | 0.12 [0.04-0.34]             | 0.15 [0.06-0.41] | 0.11 [0.04-0.32] | 0.4    |
| CRP/Alb × 100                        | 2.9 [1.1-8.9]                | 3.6 [0.9-9.9]    | 2.5 [0.9-8.4]   | 0.51    |
| HbA1c (%)                            | 6.0 [5.7-6.7]                | 6.3 [5.8-7.0]    | 6.0 [5.6-6.7]   | 0.009   |
the outcomes [Olin 2010]. Besides, to improve the prognosis, therapies such as antihypertensive therapy and antiplatelet therapy are recommended for PAD patients.

There are several limitations to our study. First, our study is a post-hoc analysis, and all the findings should be considered as hypothesis-generating. Second, the number of enrolled patients is not large enough. Also, the median age of patient was a little high. So, the enrolled patients couldn’t represent the general CAD populations. Meanwhile, we didn’t have objective measures to define the diagnosis of PAD. Third, CAD patients with PAD had a higher risk of major bleeding complications after PCI [Saw 2006]. Unfortunately, the study didn’t report the adverse event as the endpoint.

**CONCLUSION**

Patients with PAD and CAD are under a larger atherosclerotic burden. Meanwhile, these patients often have evidence of polyvascular disease. And they display a high rate of adverse cardiovascular events, including all-cause death, CV death, MI, and stroke. PAD could be a potent mediator for the prognosis of CAD patients. Further research is needed to clarify how to discern the high-risk patients in time and perform intensive therapy to improve the prognosis of these patients.

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Table 2. Univariate Spearman’s rank correlations between PAD and clinical indices

| Variable              | Spearman’s Rank | P-value |
|-----------------------|-----------------|---------|
| Diabetes mellitus     | 0.164           | 0.019   |
| Atrial fibrillation   | -0.025          | 0.719   |
| Past smoker           | 0.017           | 0.809   |
| T-Chol (mg/dL)        | 0.055           | 0.476   |
| HDL-Chol (mg/dL)      | -0.061          | 0.394   |
| LDL-Chol (mg/dL)      | -0.074          | 0.303   |
| CRP (mg/dL)           | 0.06            | 0.4     |
| CRP/Alb × 100         | 0.046           | 0.51    |
| Alb (g/dL)            | -0.108          | 0.123   |
| HbA1c (%)             | 0.189           | 0.009   |

Table 3. Lesional characteristics

| Overall population (N = 204) | PAD YES (N = 53) | PAD NO (N = 151) | P-value |
|-----------------------------|-----------------|-----------------|---------|
| Multivessel disease (%)     | 53 (26)         | 15 (28)         | 38 (72) | 0.654   |
| LMT lesions (%)             | 13 (6)          | 5 (38.5)        | 8 (61.5)| 0.289   |
| Calcified lesions (%)       | 29 (14)         | 8 (28)          | 21 (72) | 0.831   |
| Ostial lesions (%)          | 30 (15)         | 12 (40)         | 18 (60) | 0.058   |
| Bifurcation lesions (%)     | 102 (50)        | 25 (24.5)       | 77 (75.5)| 0.632   |
| CTO lesions (%)             | 12 (6)          | 4 (33)          | 8 (67)  | 0.549   |
| DES use (%)                 | 193 (95)        | 50 (26)         | 143 (74)| 0.92    |
| BMS use (%)                 | 11 (5)          | 3 (27)          | 8 (73)  | 0.92    |
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Figure 1. Kaplan-Meier analysis of PAD in patients with all events. PAD patients (PAD 1) predicted all cause death events (green line). Blue line, non-PAD patients.

Figure 2. Kaplan-Meier analysis of PAD in patients with all events. PAD patients (PAD 1) predicted all-cause death+MI+Stroke events (green line). Blue line, non-PAD patients.

Figure 3. Kaplan-Meier analysis of PAD in patients with all events. PAD patients (PAD 1) predicted cardiac death events (green line). Blue line, non-PAD patients.

Figure 4. Kaplan-Meier analysis of PAD in patients with all events. PAD patients (PAD 1) predicted cardiac death+MI+Stroke events (green line). Blue line, non-PAD patients.
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