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Impact of Peripheral Arterial Disease on Outcomes of Acute Coronary Syndrome

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ABSTRACT

Background: *Peripheral artery disease (PAD) refers to the extracardiac localization of atherosclerotic disease, generally in arteries that vascularize the lower limbs. More than 50% of patients with PAD also have coronary artery disease (CAD). There are concerns about possible differences in mortality rates among hospitalized patients and the need for immediate revascularization during hospital stay across different types of acute coronary syndrome (ACS) when PAD is present.*

Methods: *This was a retrospective study that included 100 patients admitted with ACS between October 2019 and May 2022. Participants were divided into two groups: those with ACS and PAD (n=32) and those without PAD (n=68). We used the SYNTAX score to evaluate the severity of coronary artery disease, the amount of contrast and dose area product (DAP) dosage per patient during the procedure and how these factors vary.*

Results: *There was a 6.8 higher average SYNTAX score among patients with ACS and PAD (p=0.034), which could negatively affect their prognosis. In addition, there was a 12.7-point increase in the SYNTAX score for patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) and PAD (p=0.008). Patients with ACS and concomitant PAD were more likely to require complete revascularization of the left main disease.*

Conclusion: *Patients with PAD and concomitant ACS have more severe CAD, with more frequent involvement of the left main artery than those without PAD.*

Keywords: peripheral artery disease, ankle-brachial index, coronary artery disease, acute coronary syndrome, SYNTAX score.

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INTRODUCTION

Peripheral artery disease (PAD) is characterized by stenosed or obstructed arteries and reduced blood flow. This condition is usually caused by atherosclerosis, whereby atheromatous plaque formation in the arteries impedes normal blood circulation (1). According to data from the literature, the overall prevalence of PAD in adults over 40 years of age is around 10-20%, but it reaches 30-40% in those aged 70 or older (2).

Symptoms of PAD can vary depending on the severity of the condition. Peripheral artery disease is associated with a variety of symptoms, including pain, cramping, or weakness in the legs, particularly when engaging in physical activity. In most cases, the discomfort subsides when the patient stops the action (intermittent claudication). If left untreated, PAD can lead to gangrene and even amputation (3).

Rutherford's scale provides a summary of the range of symptom severity (4).

Lower-extremity PAD refers to narrowing in the arteries of the limbs, namely aortoiliac to pedal segments. Traditionally, atherosclerotic conditions like myocardial infarction receive more attention and research than PAD, although the latter has a similarly relevant impact on the patients' quality of life.

Recent investigations have shown that PAD is directly linked to future myocardial infarction and stroke, which leads to an increase in the mortality risk (5-9). Studies demonstrate a high prevalence of PAD in patients with CAD. (10). Hence, it is relevant to diagnose and establish the severity of both CAD and PAD and establish correlations with the clinical outcomes.

The ankle-to-brachial systolic blood pressure ratio is the most frequently used non-invasive testing tool for PAD diagnosis. There is a requirement for a standard measurement procedure, and an ankle-to-brachial index (ABI) of ≤ 0.9 indicates the presence of the disease (11). Papa *et al* reported that, in elderly patients with documented coronary disease, an ABI < 0.9 corresponded with the severity and progression of CAD. Moreover, based on follow-up visits, an ABI less than 0.9 was associated with a higher cardiovascular event rate (12).

In addition to ABI measurement, there are several methods for identifying PAD, which include duplex ultrasound, magnetic resonance angiography, computed tomography (CT) and invasive angiography (13-15).

Determining whether a patient has an ACS involves assessing his/her clinical presentation, electrocardiogram results and biochemical evidence of myocardial injury. Analyzing if the patient shows ST-segment elevation on a 12-lead electrocardiogram is compulsory to distinguish between ST- and non-ST elevation acute coronary syndromes (16, 17).

Coronary angiography is the gold standard for CAD diagnosis. After angiography, the SYNTAX score is commonly used to evaluate the complexity of CAD. This scoring system takes stock of the severity and location of coronary artery stenoses and the number of vessels affected to determine the overall severity of the disease. The SYNTAX score helps guide treatment decisions for patients with complex CAD, as it can identify those who may benefit from more aggressive treatments such as bypass surgery or angioplasty. The SYNTAX score categorizes patients with CAD into three groups: low (< 22), intermediate (23-32) and high (> 33). In the SYNTAX trial, which included patients with left main disease and multivessel coronary disease, percutaneous coronary intervention (PCI) was compared to coronary artery bypass surgery (CABG). The randomized study showed that patients with SYNTAX scores above 33 had better outcomes with bypass surgery, whereas those with lower SYNTAX scores had equivalent outcomes with PCI (18). Many trials have validated the utility of the SYNTAX score in assessing the complexity and severity of CAD over time (19, 20). Scudeler *et al* stated that the burden of coronary atherosclerosis assessed by the SYNTAX score evaluation alone was not significantly associated with an increased risk of all-cause mortality. However, other studies showed that the SYNTAX score discriminates the risk of cardiovascular death, with one of those being conducted over a period of five years and involving 1 719 patients (21). On the other hand, in a study of 152 patients, Yammine *et al* found that the SYNTAX score correlated with the severity of atherosclerosis in the ascending aorta. Patients with a SYNTAX score of 33 or more had a five-fold higher risk of severe atherosclerosis in the ascending aorta compared to those with a score of 22 or less (22).

Our study aims to examine if the occurrence of PAD raises the probability of having severe CAD among individuals with acute coronary syndrome with no history of PAD before the initial episode of ACS. Our goal is to investigate whether there are any variations among ACS – NSTEACS, ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) – and an ABI < 0.9 regarding the severity and complexity of CAD, the mortality rates during hospital stay and the requirement for urgent re-vascularization during hospitalization.

METHODS

The present retrospective case-control study included 100 patients with ACS who were admitted to the Interventional Cardiology Unit of Elias University Hospital in Bucharest, Romania, between October 2019 and May 2022. Participants were divided into two groups: one group comprised patients with ACS and PAD (n=32) and another one subjects without PAD (n=68). The baseline clinical characteristics at admission of the studied population are stratified in Figure 1.

To estimate how certain indicators affect or are correlated to either an event or another indicator, linear or logistic regressions were performed. All results were obtained using Python programming language, statsmodels package.

The present study included patients admitted with ACS, specifically NSTEACS, NSTEMI and STEMI. All participants were aged 18 years and provided their written informed consent. Our study was conducted in accordance with the Declaration of Helsinki after obtaining the informed consent from all patients and approval from the Ethical Council of Elias University Hospital.

Patients under the age of 18, those with either prior vascular surgeries or angioplasties, or a history of PAD (ABI <0.9), or femoral artery stenosis >50%, or carotid stenosis >60% were all excluded.

The relationship between variables was investigated using two different statistical models. A linear regression model was applied for estimation if the dependent variable took on continuous values. A logistic regression model was implemented when the dependent variable was binary – for example, the occurrence or non-occurrence of an event. A t-test was used to assess the importance of the estimated beta parameter, which implies the effect of the independent variable on the dependent variable.

In this analysis, we set the alpha level at 0.05, a crucial threshold for determining significance. A p-value below this level would indicate that the beta parameter significantly deviates from zero, thereby establishing a robust relationship with the dependent variable.

The present study uses an ABI less than 0.9 as a criterion for matching patients with PAD and ABI > 0.9 for those without PAD.

Following the study protocol, patients were evaluated based on risk factors, age, inflammation and ACS types, including STEACS, STEMI or NSTEMI.

The evaluation comprised various factors such as ABI less than 0.9, other lesions that may require revascularization, the SYNTAX score, the amount of radiation dosage received from diagnostic X-ray examinations (DAP dose), the quantity of contrast used in imaging procedures, the HEART score, the necessity for urgent revascularization during hospitalization, cardiac arrest during hospital stay and LVEF (%) before and after PCI as well as before discharge (Figure 2).

One of our study limitations is the absence of complementary diagnostic methods, such as arterial Doppler or CT angiography, which are essential for accurately assessing the full impact and extent of PAD. While ABI is a valuable tool, it is often insufficient in clinical practice, particularly in managing patients with a high probability of PAD.

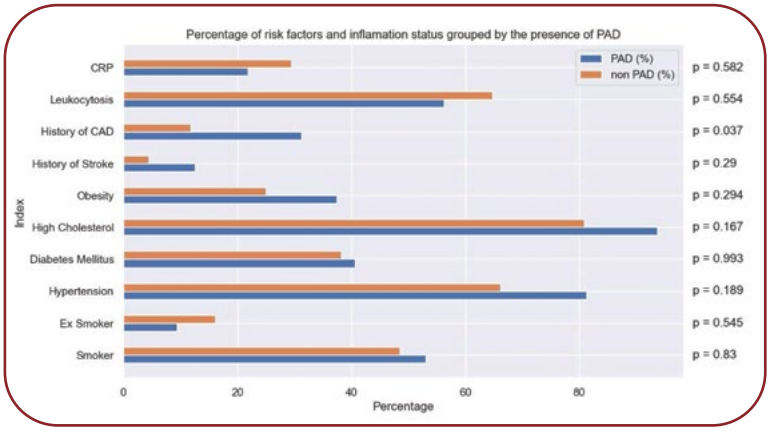

FIGURE 1. Percentage of risk factors and inflammation status grouped by the presence of peripheral artery disease

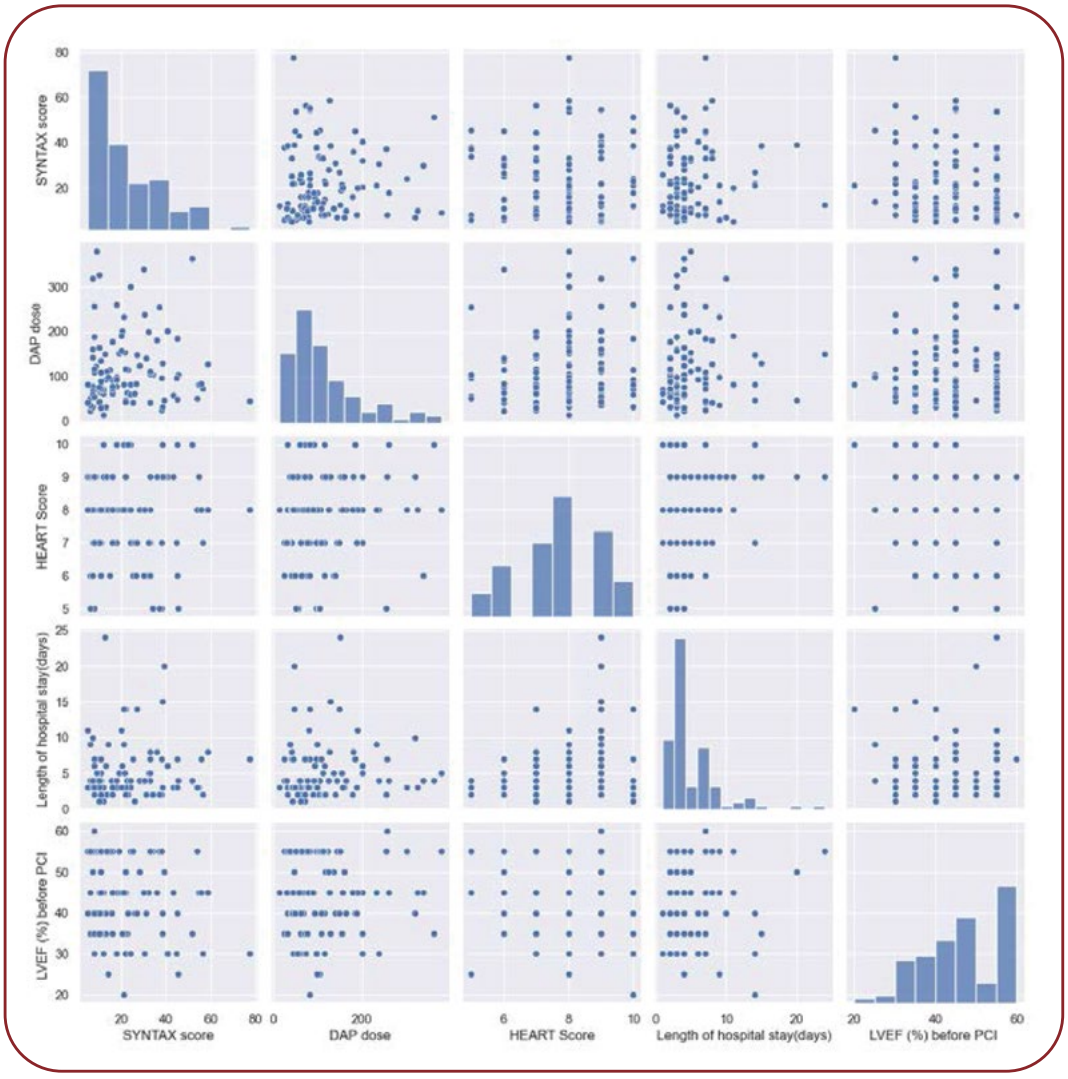

FIGURE 2. Allocations and spread plots for continuous variables

On the first diagonal, the graph illustrates the distribution of descriptive variables. The scatterplots depict patients' characteristics based on these variables, which are shown two by two. It is noticeable that there are no outliers among these variables. In the scatterplot graphs, each point is a patient, and the distribution of points illustrates if there is a correlation between the variables on both axes. In our case, there is no correlation between the variables, as the points are not concentrated along any diagonal line.

We used the Fourth Universal Definition of myocardial infarction to diagnose acute myocardial infarction. A clinical diagnosis of myocardial infarction is made when there is evidence of acute myocardial injury, as indicated by altered levels of cardiac biomarkers, such as high levels of cardiac troponin exceeding the 99th percentile upper reference limit (URL) and/or an increase and/or decline in cardiac troponin levels, in the presence of acute myocardial ischemia.

During the PCI procedure, the radial approach was used following standard techniques. All patients were given a loading dose of either 300-600 mg of clopidogrel or 180 mg ticagrelor, 250 mg of aspirin and an intravenous unfractionated heparin injection at 70-100 IU/kg. After the intervention, patients were prescribed clopidogrel (75 mg daily) or ticagrelor (90 mg twice daily) and aspirin (75-100 mg daily) for a minimum of 12 months. All patients were provided with third-generation drug-eluting stents.

We used quantitative coronary angiography (QCA) to assess coronary artery stenosis to overtake the visual assessment of lumen diameter

and stenosis subjectivism. The SYNTAX score was calculated online (www.SYNTAXscore.com).

Statistical analysis

Data processing was performed using Python 3.10 with packages including pandas, numPy, statsmodels for model estimation and scipy for statistical tests.

RESULTS

The present study included 100 patients with ACS, of whom 74% had STEMI, 10% NSTEMI and 16% NSTEACS. All participants met the inclusion criteria. Subjects had a mean age of 61.03 years ± 12.4 (SD). Of the 100 participants, 80 (80%) were males, and 32 subjects had the ABI < 0.9.

The relationship between the SYNTAX score and PAD in patients with NSTEACS

There is a clear higher tendency for the distribution of patients with ABI < 0.9 and NSTEACS. To measure in more detail how the SYNTAX score varies between these two groups, a logistic regression was performed where the dependent variable is the SYNTAX score, and the independent variable is a dummy variable, which reflects whether the patient belongs to this type.

A patient with ABI <0.9 and NSTEACS tends to have, on average, a 12.7 higher SYNTAX score (95% CI 0.34–21.9, p=0.008). Although the 12.7 estimate has a rather large error, with a wide confidence interval (CI), the trend is positive (p-value 0.008).

Regarding the SYNTAX relationship for NSTEMI and STEMI, the coefficients did not achieve statistical significance, likely owing to limitations within our sample data. This suggests the potential existence of a genuine relationship, albeit unclear in our current dataset. For further elucidation, Table 1 has been appended to provide additional insights.

The relationship between the SYNTAX score less than 22 and PAD in patients with NSTEACS

In the following experiment, linear regression was used to evaluate how a SYNTAX score below 22 decreases patients' chances to have an ABI < 0.9 and NSTEACS. For this purpose, a linear regression was performed, with SYNTAX score being set as the dependent variable and the occurrence of ABI < 0.9 and NSTEACS as independent variable.

This time, the model is statistically significant (p-value 0.012). Hence, there is a higher degree of certainty that having an ABI less than 0.9 and NSTEACS decreases a patient's chances to have a SYNTAX score below 22. In order to ensure a better interpretability of the model, the probabilities for both scenarios of patients, based on the estimated model, will be computed.

Among patients who did not have ABI less than 0.9 and NSTEACS, the probability of having a SYNTAX score below 22 was 63%. On the other hand, among those with ABI < 0.9 and STEACS, the probability of having a SYNTAX score below 22 was only 18%.

These probabilities are only the results of the best estimates, taking into account the data sample. However, there is a high degree of confidence that there is an influence.

How does PAD impact the DAP dose in patients with STEMI?

In order to measure to what extent a patient with ABI < 0.9 and STEMI influences the DAP dose, a linear regression estimate was performed, where the dependent variable was the DAP dose and the independent one a dummy variable which showed if a patient had ABI < 0.9 and

Dependent variable	R squared	Independent variable	Coefficient	P-value	Type
SYNTAX score	0.024	ABI < 09 and NSTEMI	16.7551	0.121	linear
SYNTAX score	0	ABI < 09 and STEMI	-0.5699	0.883	linear
SYNTAX score < 22	0.0003891	ABI < 09 and NSTEMI	-0.3295	0.818	logistic
SYNTAX score 22	7.84E-07	ABI < 09 and STEMI	-0.0053	0.992	logistic
SYNTAX score >33	3.81E-07	ABI < 09 and STEMI	0.0039	0.995	logistic
SYNTAX score > 33	0.008182	ABI < 09 and NSTEMI	1.361	0.343	logistic

TABLE 1. SYNTAX score less than 22 and over 33 based on ankle-to-brachial index (ABI) less 0.9 and non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)

STEMI. Our findings revealed a DAP dose of 35.9 mGy/cm² in patients with STEMI and PAD, which involved a higher risk than those without PAD, although the results were not statistically significant (p=0.078).

How does PAD impact the contrast amount in patients with acute coronary syndrome?

Patients with ABI < 0.9 tend to have, on average, a 22.1 mL-increase in contrast amount (CA). Even though this estimation is not very precise, there is confidence that this value is positive (p-value 0.041).

In patients with PAD and acute coronary syndrome, left main disease is more prevalent for complete revascularization than those without PAD

Patients with ABI less than 0.9 tend to have other lesions requiring revascularization of the left main disease, apart from the culprit. We have high confidence that this is also true in the general population (95% CI 0.129–2.325, p=0.029). In order to have more explainability, the probabilities for both cases of patients with ABI < 0.9 and without are calculated based on the estimated model.

How does PAD impact the SYNTAX score in patients with acute coronary syndrome?

The SYNTAX score distribution depends on the status of a patient, whether he has the ABI < 0.9 or not. Those with ABI < 0.9 tend to have a higher SYNTAX score. Patients with ABI < 0.9 tend to have, on average, a 6.8 higher SYNTAX score (95% CI 0.51 to 13.13, p=0.034). This is only the best estimate, given our sample. Even if it is not precisely known which is its average increase, there is high confidence that the association is present (p= 0.034).

During hospital stay, a few patients experienced cardiac deaths (n=4). Interestingly, one of the deceased patients had the ABI < 0.9. It is important to note that none of patients with ACS and ABI < 0.9 required urgent revascularization.

DISCUSSION

The coexistence of PAD and CAD, along with their impact on the severity and diffuseness of coronary artery disease as well as on patient outcomes, is a current research topic. Recent studies have suggested that an ABI of less than 0.9 can also serve as an essential indicator for predicting the prognosis and mortality of patients who have multiple arterial territory disease, including those with CAD.

Korkmaz *et al* studied the connection between PAD and the complexity of CAD in patients with ACS. They found that subjects with overt and borderline PAD (ABI ≤ 0.99) had higher SYNTAX scores than those with an ABI of 1–1.29 (P < 0.001) (23). A study conducted by Aykan *et al* reports that there is a significant correlation between ABI and SYNTAX score (r=0.650, p < 0.001). Furthermore, the presence of PAD in patients with CAD can estimate that they have a SYNTAX score > 22 with a sensitivity of 45.28% and a specificity of 82.64% (AUC=0.689, 95% CI 0.619–0.763, p < 0.001) (24).

Despite conducting a thorough literature review, we have found no prior studies that have estimated the SYNTAX score association with the presence of PAD in distinct types of ACS. The current study aims to assess the SYNTAX score of patients with ACS and ABI < 0.9. Our research has uncovered novel insights into this pathology. According to our findings, patients with ABI < 0.9 and ACS tend to have a 6.8 higher SYNTAX score on average.

Further analysis revealed that patients with an ABI of 0.9 and NSTEACS tend to have a significantly higher SYNTAX score, with an increase of 12.7. In contrast, there is only 18% probability that patients in this group have a SYNTAX score below 22 . On the other hand, patients without ABI < 0.9 and NSTEACS have a higher probability (63%) of having a SYNTAX score below 22. The extent of coronary atherosclerotic disease is a crucial factor in determining the prognosis of patients with CAD. In our study, we investigated and compared the burden of coronary atherosclerotic disease in STEMI and NSTEMI patients. Our results revealed that subjects with NSTEMI had a significantly greater SYNTAX score than those with STEMI, suggesting a more severe load of coronary atherosclerotic disease.

On average, patients with ABI < 0.9 tend to receive 22.1 mL more contrast agent. Additionally, patients with PAD and STEMI are estimated to have an increased DAP dose of 35.9 mGy/cm². We can conclude that the presence of PAD in ACS patients is an independent

risk factor for increased contrast administration. Patients with STEMI and ABI < 0.9 are exposed to higher amounts of radiation during medical procedures. However, more data from larger groups is needed to make a more precise assessment of this issue.

After culprit artery revascularization, we evaluated revascularization requirements for ACS patients with PAD. The left main disease was the most prevalent for complete revascularization.

CONCLUSION

The present study demonstrates that patients with ACS and PAD have more complex coronary artery disease. The severity of CAD can be estimated based on the type of ACS. Non-ST-segment elevation acute coronary syndrome tends to be associated with more severe disease, as estimated by the SYNTAX score. Additionally, there is a strong correlation between the symptoms related to PAD (claudication, pain at rest, or trophic lesions) and the complexity of coronary artery lesions. The ABI could be used to further classify patients with CAD at greater risk who are likely to require more intensive follow-up or therapeutic intervention.

While the ABI helps identify CAD patients at higher risk due to the occurrence of concomitant PAD, this subgroup requires more than just stratification. Aggressive medical therapy, consistent monitoring, lifestyle modifications and, when necessary, revascularization, must all be part of a comprehensive management plan. Such a targeted approach will help mitigate the increased risk of adverse cardiovascular events in these patients, improving their prognosis and overall quality of life. ❑

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki. Our research in the hospital and data extraction from the hospital archive was approved by the Medical and Health Services Manager of Elias University Emergency Hospital, Bucharest, Romania. Throughout our study, we did not risk creating emotional or physical harm to the patients since our research only entailed data collection and data analysis from the medical sheets and from the hospital's medical informatics system. Our study was conducted under the specific guidelines of the Ethical Committee of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, which states that, since this is a non-interventional study that only entails data collection, ethical approval is not required. Therefore, ethical review and approval were waived for this study as it used existing patient data. The Ethical Committee of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, requires ethical approval only for interventional studies (experimental procedures/ medications that involve humans or animals). Please see the guidelines in the following link: https://umfcd.ro/wp-content/uploads/2021/ NORME_ETICE_PRIVIND_CERCETAREA_ STIINTIFICA/PO%2035%20 Desf%C4%83%C8%99urarea%20 Activit%C4%83%C8%9Bii%20Comisiei%20 de%20Etic%C4%83%20a%20 Cercet%C4%83rii%20%C8%98tiin%C8%9Bifice. doc

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Conflicts of interest: none declared.

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