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Prevalence of alcohol use disorder and its association with disease severity in symptomatic peripheral arterial disease

Federico Biscetti[1,2,3,5]✉, Maria Margherita Rando[1,3,5], Martina Danese[2], Maria Anna Nicolazzi[1,3], Massimo Massetti[2,3], Antonio Gasbarrini[2,4], Giovanni Addolorato[2,4] & Andrea Flex[1,2,3]

Peripheral arterial disease (PAD) is a systemic atherosclerotic condition associated with substantial morbidity and mortality. Although excessive alcohol consumption has been implicated in cardiovascular disease, the prevalence of harmful drinking patterns and their association with PAD severity at clinical presentation remain poorly defined. In this observational cohort study, 103 consecutive patients with symptomatic lower-extremity PAD were enrolled. Alcohol exposure was assessed using the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) questionnaire and Lifetime Drinking History (LDH); AUD was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria. PAD severity was classified by Rutherford categories. Associations between alcohol consumption patterns and PAD severity were evaluated using logistic and ordered logistic regression models. Overall, 24.3% of patients were non-drinkers, 40.8% reported moderate alcohol consumption, 13.5% met criteria for at-risk drinking, and 21.4% were diagnosed with AUD. Patients with AUD were younger, had longer smoking exposure, and higher gamma-glutamyl transferase levels compared with those without AUD. Severe PAD at presentation (Rutherford category 6) was more frequent among patients with AUD than among those without AUD (36.4% vs. 12.3%). In multivariable analyses, AUD remained associated with severe PAD, although with borderline statistical significance. In contrast, at-risk alcohol consumption was not independently associated with PAD severity. Higher daily alcohol intake was associated with increased odds of advanced PAD in univariate analysis. Ordered logistic regression suggested a trend toward a more severe Rutherford category among patients with AUD, although this association did not reach statistical significance. These findings indicate that AUD is common among patients with symptomatic PAD and may be associated with greater disease severity at presentation, supporting the clinical relevance of systematic AUD screening in vascular care settings.

Keywords Peripheral arterial disease, Alcohol Use Disorder, At-risk drinking, Rutherford classification, Cardiovascular risk factors

Abbreviations

PAD	Peripheral arterial disease
AUD	Alcohol use disorder
AUDIT-C	Alcohol Use Disorders Identification Test – Consumption
LDH	Lifetime drinking history
CLTI	Chronic limb threatening-ischemia
WHO	World Health Organization
CAD	Coronary artery disease

[1]Cardiovascular Internal Medicine Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Italy. [2]Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, Rome 00168, Italy. [3]Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Italy. [4]Department of Medical and Surgical sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, Rome 00168, Italy. [5]Federico Biscetti and Maria Margherita Rando contributed equally to this work. ✉email: f.biscetti@gmail.com

IQR	Interquartile range
DSM	Diagnostic and statistical manual of mental disorders
GGT	Gamma-glutamyl transferase
BMI	Body mass index
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
eGFR	Estimated glomerular filtration rate
ABI	Ankle-brachial index
TBI	Toe brachial index
ROC	Receiver operating characteristic
AUC	Area under the curve
TNF-α	Tumor necrosis factor-alpha
IL-1	Interleukin-1
IL-6	Interleukin-6
SD	Standard deviation

Peripheral arterial disease (PAD) represents the clinical manifestation of peripheral atherosclerosis and affects over 230 million individuals worldwide[1]. The spectrum of lower extremity PAD is wide, with manifestations ranging from asymptomatic disease to chronic limb threatening-ischemia (CLTI), characterized by ischemic rest pain, non-healing ulcers, and minor or major tissue loss[2].

Traditional risk factors for PAD include cigarette smoking, diabetes, dyslipidemia, and hypertension[1,3–5]. More recently, inflammation has emerged as a non-traditional but significant determinant of PAD onset and progression[1,6].

Among unconventional cardiovascular risk factors, chronic alcohol consumption has gained attention for its multifaceted impact on vascular health. Long-term and excessive alcohol intake promotes endothelial dysfunction, increases arterial blood pressure, and negatively affects lipid metabolism, glucose regulation, and systemic inflammation through pro-inflammatory mechanisms[7–10]. Furthermore, alcohol intake can alter hemostatic balance by impairing platelet adhesion and interfering with normal fibrinolytic function, thereby contributing to atherogenesis[7,11].

Alcohol Use Disorder (AUD) is a complex condition characterized by pathological alcohol use, loss of control over intake, and physiological dependence, leading to behavioral, cognitive, and physical impairments[12,13]. According to the World Health Organization (WHO), alcohol consumption accounted for 4.7% of all global deaths in 2019[14]. Alcohol-related harm can arise from both chronic exposure and acute intoxication, contributing to the onset of a wide range of alcohol-related diseases[15–18].

While moderate alcohol consumption has been associated with reduced cardiovascular risk in some studies, its protective effect appears to be dose-dependent and diminishes with increasing intake[19]. Indeed, excessive alcohol consumption has been linked to higher risk of coronary artery disease (CAD), heart failure, transient ischemic attack, ischemic and hemorrhagic stroke, and PAD[20–22]. However, the relationship between alcohol consumption and cardiovascular disease remains controversial, with inconsistencies across studies[22,23]. In particular, evidence on the specific association between alcohol intake and PAD is limited.

Epidemiological studies, including the "PREMIDED STUDY", have suggested that moderate alcohol intake, as part of a Mediterranean lifestyle, may reduce PAD incidence[24]. In contrast, other reports have demonstrated an increased risk of PAD with higher alcohol consumption levels (> 45 g/day), or with heavy, irregular drinking patterns[22,25]. Additionally, studies have linked excessive alcohol intake with increased arterial stiffness and higher PAD prevalence among individuals with type 2 diabetes mellitus, as well as with acute alcohol intoxication episodes[26–28].

Despite these observations, the prevalence of pathological alcohol consumption among patients with PAD and its association with disease severity at clinical presentation remain poorly defined.

To address this knowledge gap, the present study was designed to evaluate the prevalence of AUD and at-risk alcohol consumption among patients with lower-extremity PAD, and to investigate their association with PAD severity at clinical presentation.

Results

Study population and alcohol consumption patterns

A total of 103 patients with symptomatic lower-extremity PAD were included in the study. The mean age was 71 years (SD 9.6), and 77.7% of patients were male. Most patients had multiple cardiovascular risk factors, including diabetes mellitus (76.7%), hypertension (78.8%), and dyslipidemia (70.9%). The median (interquartile range - IQR) daily alcohol consumption was around 2 (0–4) alcohol units. Median (IQR) LDL-C levels were 71 mg/dL (51 mg/dL-89.5 mg/dL) and median (IQR) glycated hemoglobin levels were 56 mmol/mol (48 mmol/mol-67 mmol/mol). According to Rutherford classification, 12.6% of patients presented with intermittent claudication (category 3), 33.0% with ischemic rest pain (category 4), 36.9% with minor tissue loss (category 5), and 17.5% with gangrene or major tissue loss (category 6).

With regard to alcohol consumption, 24.3% of patients reported no current alcohol use, 40.8% reported moderate consumption, 13.5% met criteria for at-risk alcohol consumption, and 21.4% were diagnosed with AUD according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria. A history of former alcohol consumption was infrequent and similarly distributed between current non-drinkers and drinkers (7.7% vs. 9.1%, $p = 0.83$).

Median daily alcohol intake was 2 alcohol units (IQR 0–4). Baseline demographic, clinical, and laboratory characteristics of the overall study population are summarized in Tables 1 and 2.

Clinical characteristics associated with AUD

Patients with AUD differed significantly from those without AUD in several demographic and clinical characteristics (Table 3). Compared with patients without AUD, those with AUD were younger (66.4 vs. 72.2 years, $p = 0.011$), had a longer duration of smoking exposure (40 vs. 25 years, $p = 0.014$), and exhibited higher gamma-glutamyl transferase levels (31.5 vs. 21.5 UI/L, $p = 0.018$). Patients with AUD also had a shorter duration

Categorical variables	*n* (%)
Sex	
Men, n (%)	80 (77.7%)
Women, n (%)	23 (22.3%)
Smoking status	
Current smoker, n (%)	35 (34.0%)
Former smoker, n (%)	45 (43.7%)
Comorbidities	
Dyslipidemia, n (%)	73 (70.9%)
High blood pressure, n (%)	81 (78.6%)
DM, n (%)	79 (76.7%)
Type 1 DM, n (%)	3 (2.9%)
Type 2 DM, n (%)	76 (73.8%)
Previous CAD, n (%)	49 (47.6%)
Heart failure, n (%)	24 (23.3%)
Previous CVD, n (%)	11 (10.7%)
Medications	
Metformin, n (%)	39 (37.9%)
Insulin, n (%)	43 (41.7%)
Secretagogue drugs, n (%)	9 (8.7%)
Glinides, n (%)	11 (10.7%)
GLP-1 receptor agonists, n (%)	9 (8.7%)
DPP-4 inhibitors, n (%)	6 (5.8%)
SGLT2 inhibitors, n (%)	12 (11.7%)
ACE inhibitors, n (%)	24 (23.3%)
ARBs, n (%)	37 (35.9%)
Aspirin, n (%)	69 (67.0%)
Clopidogrel, n (%)	26 (25.2%)
Anticoagulants, n (%)	13 (12.6%)
Statins, n (%)	64 (62.1%)
Rutherford classification	
Category 3, n (%)	13 (12.6%)
Category 4, n (%)	34 (33.0%)
Category 5, n (%)	38 (36.9%)
Category 6, n (%)	18 (17.5%)
Alcohol consumption	
AUD, n (%)	22 (21.4%)
At-risk alcohol consumption, n (%)	14 (13.5%)
Moderate alcohol consumption, n (%)	42 (40.8%)
No alcohol consumption, n (%)	25 (24.3%)
Binge drinking, n (%)	9 (8.7%)
Type of alcohol consumed	
Wine, n (%)	72 (69.9%)
Beer, n (%)	14 (13.6%)
Spirits (superalcoholic beverages), n (%)	8 (7.8%)

Table 1. Clinical and demographic characteristics of the study population, categorical variables. Diabetes mellitus (DM); coronary artery disease (CAD); cerebrovascular disease (CVD); Glucagon-like peptid-1 (GLP-1); dipeptidyl peptidase 4 (DPP-4); sodium-glucose transport proteins (SGLT); angiotensin-converting enzyme (ACE); angiotensin II receptor blockers (ARBs); Alcohol Use Disorder (AUD).

Continuous variables	Value
Age, years (SD)	71 (9.6)
BMI, Kg/m2 (IQR)	26 (23.4-28.4)
Diabetes years, n (IQR)	8 (0-20)
Alcohol units per day, n (IQR)	2 (0-4)
Total cholesterol, n (SD)	134.7 (33.6)
LDL-C, mg/dl (IQR)	71 (51-89.5)
HDL-C, mg/dl (SD)	35.82 (11.98)
Triglycerides, mg/dl (IQR)	110 (81-156)
Creatinine, mg/dl (IQR)	1.03 (0.8-1.45)
eGFR, ml/min (IQR)	66 (41-90)
Platelets, n (IQR)	255 (201-308)
GGT, UI/l (IQR)	23 (16-43.5)
ALP, UI/l (IQR)	82.5 (63-106)
ALT, UI/l (IQR)	14 (10-20)
AST, UI/l (IQR)	17 (13-21)
INR (IQR)	1.06 (1.02-1.11)
Total bilirubin, mg/dl (IQR)	0.55 (0.4-0.7)
CRP, mg/l (IQR)	24.35 (7.1-100)
HbA1c, mmol/mol (IQR)	56 (48-67)
AUDIT-C score, n (IQR)	3 (0-4)
Smoking years (IQR)	30 (10-45)
Harmful alcohol years (IQR)	0 (0-30)

Table 2. Clinical and demographic characteristics of the study population, continuous variables. Body mass index (BMI); LDL cholesterol (LDL-C); HDL cholesterol (HDL-C); estimated Glomerular Filtration Rate (eGFR); gamma-glutamyl transferase (GGT); alkaline phosphatase (ALP); alanine aminotransferase (ALT); aspartate aminotransferase (AST); c-reactive protein (CRP); Alcohol Use Disorders Identification Test – Consumption (AUDIT-C).

of diabetes mellitus (1 year vs. 11 years, $p = 0.010$) and better renal function at presentation (96 ml/min vs. 57 ml/min, $p = 0.000$).

Importantly, PAD severity differed substantially between groups. Severe PAD, defined as Rutherford category 6, was significantly more frequent among patients with AUD compared with those without AUD (36.4% vs. 12.3%, $p = 0.008$). In addition, patients with AUD underwent amputations more frequently than those without AUD (45.5% vs. 19.8%, $p = 0.013$). In contrast, patients without AUD more commonly had a history of CAD (53.1% vs. 27.3%, $p = 0.031$) and diabetes mellitus (81.5% vs. 59.1%, $p = 0.027$). The two populations were homogeneous in terms of body mass index (BMI), history of heart failure, cerebrovascular disease, years of arterial hypertension, LDL cholesterol levels, HDL cholesterol, triglycerides, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), INR, total bilirubin, c-reactive protein, and HbA1c levels.

Clinical characteristics associated with at-risk alcohol consumption

A separate comparison was performed between patients with and without at-risk alcohol consumption (Table 4). Patients with at-risk alcohol consumption were older than those without at-risk consumption (78.6 vs. 69.8 years, $p = 0.001$) and had higher AUDIT-C scores, as expected.

No significant differences were observed between the two groups in terms of cardiovascular comorbidities, metabolic profile, inflammatory markers, or PAD severity, including the prevalence of Rutherford category 6 and amputation rates.

Association between alcohol consumption patterns and PAD severity

Logistic regression analyses were conducted to assess the association between alcohol consumption patterns and PAD severity. In all logistic regression analyses, severe PAD was defined as Rutherford category 6, with Rutherford categories 3–5 serving as the reference group. For categorical alcohol exposure variables, patients without AUD (AUD = 0) or without at-risk alcohol consumption were used as the respective reference categories. In analyses including daily alcohol intake, alcohol consumption was modeled as a continuous variable. Effect estimates and corresponding 95% confidence intervals are reported in the respective tables.

In univariate logistic regression analysis, AUD, compared with absence of AUD, was significantly associated with severe PAD (Rutherford category 6 vs. Rutherford categories 3–5) (OR 4.06, 95% CI 1.36–12.09; $p = 0.012$) (Table 5).

In multivariable logistic regression analysis, AUD (reference: no AUD) remained associated with severe PAD (Rutherford category 6 vs. Rutherford categories 3–5), although with borderline statistical significance due to

Variables	AUD ($n = 22$)	No AUD ($n = 81$)	p-value
Men: female, n	22:0	58:23	0.005
Age, years (SD)	66.36 (9.051)	72.21 (10.588)	0.011
Smoking (current), n (%)	17 (77.3%)	18 (22.2%)	0.000
Smoking (former), n (%)	5 (22.7%)	40 (49.4%)	0.025
Dyslipidemia, n (%)	13 (59.1%)	60 (74.1%)	0.096
Hypertension, n (%)	16 (72.7%)	65 (80.2%)	0.445
DM, n (%)	13 (59.1%)	66 (81.5%)	0.027
Type 2 DM, n (%)	12 (54.5%)	62 (76.5%)	0.059
Type 1 DM, n (%)	1 (4.5%)	2 (2.5%)	0.607
Diabetes treatment, n (%)	11 (50%)	65 (80.2%)	0.009
Hypertension treatment, n (%)	16 (72.7%)	64 (79%)	0.733
Metformin, n (%)	7 (31.8%)	32 (39.5%)	0.509
Insulin, n (%)	6 (27.3%)	37 (45.7%)	0.120
Sulfonylureas, n (%)	2 (9.1%)	7 (8.6%)	0.947
Glinids, n (%)	1 (4.5%)	10 (12.3%)	0.293
GLP1 analogs, n (%)	1 (4.5%)	8 (9.9%)	0.432
DPP4 inhibitors, n (%)	1 (4.5%)	5 (6.2%)	0.772
SGLT2 inhibitors, n (%)	2 (9.1%)	10 (12.3%)	0.673
ACE inhibitors, n (%)	6 (27.3%)	18 (22.2%)	0.619
ARBS, n (%)	6 (27.3%)	31 (38.3%)	0.340
CAD, n (%)	6 (27.3%)	43 (53.1%)	0.031
Heart Failure, n (%)	3 (13.6%)	21 (25.9%)	0.226
CVD, n (%)	3 (13.6%)	8 (9.9%)	0.612
Aspirin, n (%)	16 (72.7%)	53 (65.4%)	0.518
Clopidogrel, n (%)	6 (27.3%)	20 (24.7%)	0.804
Anticoagulants, n (%)	2 (9.1%)	11 (13.6%)	0.573
Statins, n (%)	14 (63.6%)	50 (61.7%)	0.870
Rutherford 3, n (%)	1 (4.5%)	12 (14.8%)	0.198
Rutherford 4, n (%)	8 (36.4%)	26 (32.1%)	0.706
Rutherford 5, n (%)	5 (22.7%)	33 (40.7%)	0.120
Rutherford 6, n (%)	8 (36.4%)	10 (12.3%)	0.008
Above the knee PTA, n (%)	13 (59.1%)	47 (58%)	0.928
Below the knee PTA, n (%)	5 (22.7%)	32 (39.5%)	0.135
Amputation, n (%)	10 (45.5%)	16 (19.8%)	0.013
BMI, Kg/m2 (IQR)	26.8 (22.9–28.9)	26.0 (23.4–28.1)	0.799
Number of cigarettes/ day (IQR)	22.5 (20.0–30.0)	20.0 (0.0–30.0)	0.008
Smoking years (IQR)	40.0 (30.0–50.0)	25.0 (0.0–44.5)	0.014
Diabetes years (IQR)	1.0 (0.0–10.0)	11.0 (1.0–24.0)	0.010
Arterial hypertension years (IQR)	0.5 (0.0–10.0)	8.0 (0.0–20.0)	0.075
Creatinine, mg/dl (IQR)	0.7 (0.6–1.0)	1.1 (0.9–1.6)	0.000
eGFR, ml/min (IQR)	96.0 (75.0–100.0)	57.0 (39.0–84.0)	0.000
Total cholesterol, mg/dl (SD)	132.28 (36.12)	135.33 (33.11)	0.714
LDL-C, mg/dl (IQR)	68.5 (50.0–90.0)	73.0 (51.0–89.0)	0.751
HDL-C, mg/dl (SD)	35.00 (15.99)	36.05 (10.77)	0.745
Triglycerides, mg/dl (IQR)	95.0 (77.0–125.0)	111.5 (82.0–162.0)	0.350
Platelets, n (IQR)	281.5 (207.0–318.0)	248.0 (201.0–304.0)	0.301
GGT, UI/l (IQR)	32.5 (20.0–64.5)	21.5 (14.5–34.5)	0.018
ALP, UI/l (IQR)	80.0 (63.0–107.0)	83.0 (63.0–98.0)	0.937
ALT, UI/l (IQR)	14.0 (12.0–22.0)	15.0 (9.0–19.0)	0.334
AST, UI/l (IQR)	17.0 (14.0–20.0)	16.0 (13.0–21.0)	0.665
INR (IQR)	1.1 (1.0–1.2)	1.1 (1.0–1.1)	0.695
Total bilirubin, mg/dl (IQR)	0.6 (0.4–0.6)	0.5 (0.4–0.7)	0.853
CRP, mg/l (IQR)	25.8 (7.7–153.0)	21.1 (5.7–100.0)	0.483
Continued			

Variables	AUD ($n = 22$)	No AUD ($n = 81$)	p-value
HbA1c, mmol/mol (IQR)	50.0 (49.0–67.0)	58.0 (48.0–68.0)	0.561
AUDIT-C score (IQR)	7.5 (0.0–12.0)	2.0 (0.0–4.0)	0.000
Alcohol Unit in a day (IQR)	11.0 (8.0-14.0)	1.0 (0.0-2-0)	0.000
Smoking years (IQR)	40.0 (30.0-50.0)	25.0 (0.0-44.5)	0.014
Harmful alcohol years (IQR)	30.0 (20.0-45.0)	0.0 (0.0-1.0)	0.000

Table 3. Clinical and demographic characteristics of patients with AUD and patients without AUD. Diabetes mellitus (DM); coronary artery disease (CAD); cerebrovascular disease (CVD); Percutaneous Transluminal Angioplasty (PTA); Glucagon-like peptid-1 (GLP-1); dipeptidyl peptidase 4 (DPP-4); sodium-glucose transport proteins (SGLT); angiotensin-converting enzyme (ACE); angiotensin II receptor blockers (ARBs); Alcohol Use Disorder (AUD); body mass index (BMI); LDL cholesterol (LDL-C); HDL cholesterol (HDL-C); estimated Glomerular Filtration Rate (eGFR); gamma-glutamyl transferase (GGT); alkaline phosphatase (ALP); alanine aminotransferase (ALT); aspartate aminotransferase (AST); c-reactive protein (CRP); Alcohol Use Disorders Identification Test – Consumption (AUDIT-C).

wide confidence intervals (OR 64.96, 95% CI 0.97–4352.32, $p = 0.052$). No significant associations were observed for fast blood glucose, creatinine, estimated Glomerular Filtration Rate (eGFR), lipid profile, or HbA1c (Table 6).

Given the close relationship between alcohol use and smoking, an additional multivariable model including AUD, number of cigarettes smoked per day, and smoking duration was made. In this model, AUD (reference: no AUD) remained independently associated with severe PAD (Rutherford category 6 vs. Rutherford categories 3–5) (OR = 6.65, 95% CI: 1.82–24.31, $p = 0.004$), whereas smoking intensity and duration were not significantly associated with PAD severity ($p = 0.544$ and $p = 0.073$, respectively). The model demonstrated good overall fit (LR $\chi^2(3) = 10.17$, $p = 0.0172$; Pseudo $R^2 = 0.1074$) (Supplementary Table 1). In contrast, at-risk alcohol consumption, compared with absence of at-risk drinking, was not associated with severe PAD (Rutherford category 6 vs. Rutherford categories 3–5) in univariate logistic regression analysis

(OR = 1.35, 95% CI: 0.33–5.41, $p = 0.676$). The multivariate model, which included metabolic and renal parameters, was statistically significant overall (LR $\chi^2(8) = 18.12$, $p = 0.0204$; pseudo $R^2 = 0.4477$), but the variable at-risk alcohol consumption was omitted due to perfect prediction or lack of variability within the sample. None of the remaining covariates showed independent associations with Rutherford 6 ($p > 0.05$ for all) (Supplementary Table 2a and 2b).

Daily alcohol intake and PAD severity

To explore a potential dose–response relationship, daily alcohol unit intake was analyzed as a continuous variable. In univariate logistic regression analysis, higher daily alcohol unit intake was significantly associated with severe PAD (Rutherford category 6 vs. Rutherford categories 3–5) (OR 1.10 per additional unit/day, 95% CI 1.01–1.19, $p = 0.021$), corresponding to a 10% increase in the odds of severe PAD for each additional daily alcohol unit consumed (Supplementary Table 3). This finding should be interpreted with caution given the limited sample size.

Receiver operating characteristic (ROC) curve analysis showed a moderate discriminative ability of daily alcohol unit intake for predicting Rutherford category 6 (area under the curve - AUC 0.652) (Fig. 1).

Association between AUD and PAD severity across Rutherford categories

An ordered logistic regression analysis was performed to assess the association between AUD and PAD severity across Rutherford categories 3 to 6. Rutherford categories 3 to 6 were modeled as an ordinal outcome, with patients without AUD serving as the reference category.

The presence of AUD was associated with higher odds of being classified into more severe Rutherford categories (odds ratio 2.19); however, this association did not reach statistical significance (Table 7).

Predicted probability estimates further showed that patients with AUD had a lower probability of presenting with milder PAD stages (categories 3 and 4) and a higher probability of presenting with Rutherford categories 5 and 6 compared with patients without AUD (Table 8).

Discussion

In this observational study of patients with symptomatic lower-extremity PAD, we found a high prevalence of harmful alcohol consumption patterns, with more than one fifth of patients meeting diagnostic criteria for AUD. Importantly, AUD was associated with greater clinical severity of PAD at presentation, particularly with Rutherford category 6 disease. In contrast, at-risk alcohol consumption, as defined by WHO thresholds, was not independently associated with PAD severity in this cohort. We focused our primary analyses on Rutherford category 6 because this stage represents the most advanced and clinically meaningful manifestation of PAD, characterized by gangrene or extensive tissue loss and directly associated with amputation risk. The observed prevalence of AUD in our cohort (21.4%) was almost twofold higher than reported in the general European population (approximately 10.7%)[29]. At-risk alcohol consumption was higher than that observed in previous studies among PAD patients, which ranged from 7% to 16%, depending on the assessment method and population characteristics[30,31]. Differences across studies might reflect heterogeneity in sample size and/or the methods by which alcohol habits were measured. Moreover, the current definition of at-risk drinking varies

Variables	At-risk (n = 14)	No at-risk (n = 89)	*p*-value
Men: female, n	11:3	69:20	0.930
Age, years (SD)	78.57 (8.04)	69.76 (9.36)	0.001
Smoking (current), n (%)	4 (28.6%)	31 (34.8%)	0.645
Smoking (former), n (%)	7 (50%)	38 (42.7%)	0.608
Dyslipidemia, n (%)	10 (71.4%)	63 (70.8%)	0.732
Hypertension, n (%)	12 (85.7%)	69 (77.5%)	0.487
DM, n (%)	13 (92.9%)	66 (74.2%)	0.123
Type 2 DM, n (%)	12 (85.7%)	62 (69.7%)	0.084
Type 1 DM, n (%)	0 (0%)	3 (3.4%)	0.485
Diabetes treatment, n (%)	13 (92.9%)	63 (70.8%)	0.089
Hypertension treatment, n (%)	12 (85.7%)	68 (76.4%)	0.862
Metformin, n (%)	8 (57.1%)	31 (34.8%)	0.109
Insulin, n (%)	5 (35.7%)	38 (42.7%)	0.622
Sulfonylureas, n (%)	3 (21.4%)	6 (6.7%)	0.070
Glinids, n (%)	2 (14.3%)	9 (10.1%)	0.638
GLP1 analogs, n (%)	2 (14.3%)	7 (7.9%)	0.429
DPP4 inhibitors, n (%)	3 (21.4%)	3 (3.4%)	0.007
SGLT2 inhibitors, n (%)	0 (0%)	12 (13.5%)	0.143
ACE inhibitors, n (%)	4 (28.6%)	20 (22.5%)	0.615
ARBS, n (%)	6 (42.9%)	31 (34.8%)	0.560
CAD, n (%)	7 (50%)	42 (47.2%)	0.844
Heart Failure, n (%)	2 (14.3%)	22 (24.7%)	0.390
CVD, n (%)	1 (7.1%)	10 (11.2%)	0.644
Aspirin, n (%)	10 (71.4%)	59 (66.3%)	0.704
Clopidogrel, n (%)	1 (7.1%)	25 (28.1%)	0.093
Anticoagulants, n (%)	3 (21.4%)	10 (11.2%)	0.285
Statins, n (%)	9 (64.3%)	55 (61.8%)	0.858
Rutherford 3, n (%)	1 (7.1%)	12 (13.5%)	0.506
Rutherford 4, n (%)	6 (42.9%)	28 (31.5%)	0.399
Rutherford 5, n (%)	4 (28.6%)	34 (38.2%)	0.487
Rutherford 6, n (%)	3 (21.4%)	15 (16.9%)	0.675
Above the knee PTA, n (%)	10 (71.4%)	50 (56.2%)	0.282
Below the knee PTA, n (%)	4 (28.6%)	33 (37.1%)	0.518
Amputation, n (%)	1 (7.1%)	25 (28%0.1)	0.093
BMI, Kg/m2 (IQR)	24.2 (22.7–29.4)	26.3 (23.4–28.1)	0.855
Number of cigarettes/ day (IQR)	14.0 (4.0–40.0)	20.0 (10–30.0)	0.952
Smoking years (IQR)	32.5 (20.0–45.0)	30.0 (10.0–45.0)	0.792
Diabetes years (IQR)	17.5 (5.0–25.0)	8.0 (0.0–20.0)	0.124
Arterial hypertension years (IQR)	10.0 (5.0–20.0)	6.0 (0.0–15.0)	0.144
Creatinine, mg/dL	1.2 (0.9-1.9)	1.0 (0.8-1.4)	0.438
eGFR, ml/min (IQR)	51.0 (34.0-80.0)	69.0 (43.0-92.0)	0.210
Total cholesterol, mg/dl (SD)	144.58 (40.41)	133.32 (32.60)	0.278
LDL-C, mg/dl (IQR)	71.0 (52.0–94.0)	71.0 (51.0–89.0)	0.983
HDL-C, mg/dl (SD)	35.8 (12.21)	35.82 (12.02)	0.995
Triglycerides, mg/dl (IQR)	107.5 (83.0–142.5)	111.0 (80.0–162.0)	0.940
Platelets, n (IQR)	262.5 (203.0–303.0)	255.0 (201.0–308.0)	1.000
GGT, UI/l (IQR)	19.0 (13.0–22.0)	24.0 (17.0–49.0)	0.094
ALP, UI/l (IQR)	89.5 (66.0–98.0)	80.5 (63.0–107.0)	0.965
ALT, UI/l (IQR)	18.0 (10.0–22.0)	14.0 (10.0–19.0)	0.687
AST, UI/l (IQR)	14.0 (13.0–16.0)	17.0 (14.0–22.0)	0.229
INR (IQR)	1.1 (1.0–1.1)	1.1 (1.0–1.1)	0.776
Total bilirubin, mg/dl (IQR)	0.5 (0.4–0.7)	0.6 (0.4–0.7)	0.745
CRP, mg/l (IQR)	29.5 (6.4–100.0)	23.9 (7.1–123.1)	1.000
Continued			

Variables	At-risk (n = 14)	No at-risk (n = 89)	*p*-value
HbA1c, mmol/mol (IQR)	57.0 (50–66.0)	55.0 (48.0–68.5)	0.970
AUDIT-C score (IQR)	5.0 (4.0–5.0)	2.0 (0.0–4.0)	0.000
Alcohol Unit in a day (IQR)	3.0 (2.0-4.0)	1.0 (0.0-5.0)	0.029
Smoking years (IQR)	32.5 (20.0-45.0)	30.0 (10.0-45.0)	0.792
Harmful alcohol years (IQR)	59 (47.0-60.0)	0.0 (0.0-19.0)	0.000

Table 4. Clinical and demographic characteristics of patients with at-risk alcohol consumption and patients without at-risk alcohol consumption. Diabetes mellitus (DM); coronary artery disease (CAD); cerebrovascular disease (CVD); Percutaneous Transluminal Angioplasty (PTA); Glucagon-like peptid-1 (GLP-1); dipeptidyl peptidase 4 (DPP-4); sodium-glucose transport proteins (SGLT); angiotensin-converting enzyme (ACE); angiotensin II receptor blockers (ARBs); Alcohol Use Disorder (AUD); body mass index (BMI); LDL cholesterol (LDL-C); HDL cholesterol (HDL-C); estimated Glomerular Filtration Rate (eGFR); gamma-glutamyl transferase (GGT); alkaline phosphatase (ALP); alanine aminotransferase (ALT); aspartate aminotransferase (AST); c-reactive protein (CRP); Alcohol Use Disorders Identification Test – Consumption (AUDIT-C).

Rutherford 6	Odds ratio	Std. error	z	*p*-value	[95% confidence interval]
AUD	4.06	2.26	2.51	0.012	1.36 – 12.09
Constant	0.14	0.05	-5.80	<0.001	0.07 – 0.27

Table 5. Univariate logistic regression assessing the association between AUD and Rutherford category 6 (reference: Rutherford categories 3–5; reference for exposure: no AUD). Alcohol Use Disorder (AUD).

Rutherford 6	Odds ratio	Std. Err.	Z	*P* >|z|	[95% Conf. interval]
AUD	64.96143	139.3604	1.95	0.052	0.9696 – 4352.317
FBG	0.9924	0.0115	-0.65	0.514	0.9701 – 1.0153
Creatinine	0.5546	0.5000	-0.65	0.513	0.0947 – 3.2469
eGFR	0.9268	0.0531	-1.33	0.184	0.8283 – 1.0369
Total Cholesterol	0.9667	0.1450	-0.23	0.822	0.7206 – 1.2970
LDL-C	0.9976	0.1400	-0.02	0.987	0.7577 – 1.3136
HDL-C	0.8724	0.1565	-0.76	0.447	0.6137 – 1.2400
Triglycerides	0.9742	0.0319	-0.80	0.426	0.9136 – 1.0389
HbA1c	1.0365	0.0321	1.16	0.247	0.9754 – 1.1014
_cons	330975.6	2,839,905	1.48	0.139	0.0164 – 6.66e+12

Table 6. Multivariate logistic regression assessing the association between AUD and severe PAD, defined as Rutherford category 6 (reference: Rutherford categories 3–5). The reference category for AUD was absence of AUD (AUD = 0). Covariates included metabolic and renal parameters. Alcohol Use Disorder (AUD); fast blood glucose (FBG); estimated Glomerular Filtration Rate (eGFR); LDL cholesterol (LDL-C); HDL cholesterol (HDL-C).

widely between countries around the world and over time within one country, which has been changing over recent years, thereby complicating comparisons.

Comprehensive data regarding the relationship between pathological alcohol drinking patterns diagnosed using standardized clinical criteria and PAD, however, remain scarce.

In our study, the risk of gangrene (defined as Rutherford category 6) was associated with AUD in both univariate and multivariable logistic regression analyses adjusted for established cardiovascular risk factors, although the association in the multivariable model reached only borderline statistical significance, with wide confidence intervals.

This finding is consistent with speculation regarding an association between severe peripheral vascular outcomes and chronic pathological alcohol intake.

Although the ordered logistic regression suggested a trend toward a more severe PAD stage among patients with AUD, this association did not reach statistical significance and should therefore be interpreted as exploratory and hypothesis-generating rather than conclusive. In contrast, higher daily alcohol intake was significantly

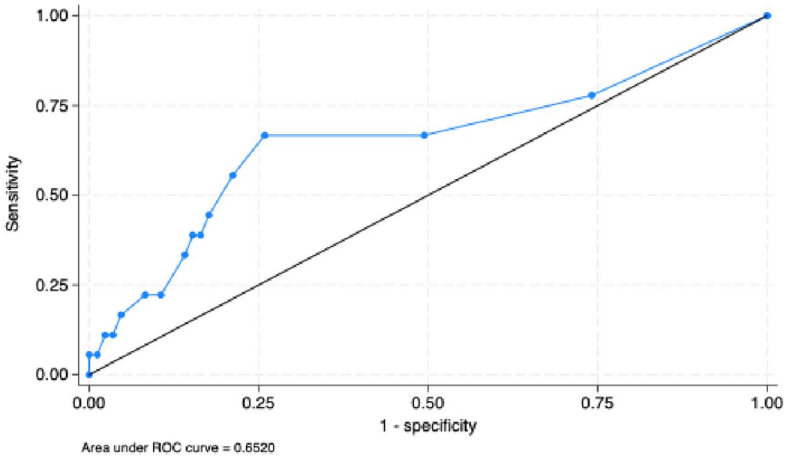

Fig. 1. ROC curve for the prediction of Rutherford 6 category based on daily alcohol unit consumption. The area under the curve (AUC) was 0.652, indicating modest discriminative ability.

Rutherford severity	Coefficient	Std. Err.	z	*P*>|z|	[95% Conf. Interval]
AUD	0.783	0.459	1.70	0.088	[-0.118, 1.683]
/cut1	-1.799	0.306			[-2.399, -1.200]
/cut2	-0.029	0.216			[-0.452, 0.395]
/cut3	1.731	0.285			[1.173, 2.289]

Table 7. Ordered logistic regression results assessing the association between AUD and PAD severity across Rutherford categories 3 to 6, modeled as an ordinal outcome. The reference category for exposure was absence of AUD (AUD = 0). The ordered logistic regression revealed a coefficient for AUD of 0.783, with a standard error of 0.459 and a p-value of 0.088. The odds ratio associated with AUD was calculated as 2.19, indicating that patients with AUD are 2.19 times more likely to be classified in a more severe Rutherford category. Alcohol Use Disorder (AUD).

Rutherford category	AUD = 0 (Probability)	AUD = 1 (Probability)	*p*-value
3	14.2%	7.0%	0.028
4	35.1%	23.7%	0.000
5	35.7%	41.3%	0.000
6	15.0%	27.9%	0.001

Table 8. Predicted probabilities of each Rutherford category (3–6) derived from the ordered logistic regression model, stratified by AUD status. The reference category was absence of AUD (AUD = 0). The predicted probabilities of being classified into the different Rutherford categories for patients with and without AUD are presented above. These results highlight that patients with AUD have a higher probability of being classified into more severe Rutherford categories (4, 5, 6). Alcohol Use Disorder (AUD).

associated with advanced PAD in univariate analysis, although this finding should be interpreted with caution given the limited sample size and the unadjusted nature of the analysis. In this context, the overall direction of these findings is biologically plausible and consistent with existing evidence indicating that ethanol adversely affects the vascular system. O'Neill et al. reported that alcohol consumption over 114 g/week was associated with increased arterial stiffness in men, a known precursor of vascular disease progression, supporting the role of ethanol in promoting the atherosclerotic process[26].

In a case-control study of 100 PAD patients and 100 healthy controls, it was shown that consuming more than 60 drinks a week increased the risk of lower limb atherosclerotic disease[32]. A more recent study conducted on a population of hospitalized diabetic patients showed a higher incidence of PAD (evaluated as the presence of intermittent claudication, ABI < 0.90, ABI > 1.3, and toe brachial index (TBI) < 0.7) in patients consuming more than 8 alcoholic units (1 unit equals 8 g of ethanol) per day[27]. An interesting work by Huang et al. assessed the incidence of PAD in patients presenting to the hospital after acute alcohol intoxication, suggesting that specific alcohol consumption patterns, such as binge drinking, may influence atherosclerotic disease[33]. In a

murine model, it was demonstrated that after four weeks of excessive alcohol use on weekends, the volume of atherosclerotic plaques and serum cholesterol levels increased[34]. Additionally, Averina et al. showed that binge drinking was associated with increased levels of c-reactive protein, creating an inflammatory environment favoring the development of atherosclerosis[35].

It is important to note that previous literature has mainly focused on general associations between alcohol consumption and PAD prevalence or cardiovascular outcomes. Specifically, to our knowledge, no previous studies have investigated the association between the severity of PAD and the presence of AUD, assessed in our work. Therefore, our findings represent a novel contribution to the field, highlighting the potential impact of AUD on the progression and clinical severity of PAD.

Our results could be supported even by existing evidence on the detrimental effects of ethanol on vascular tissues, particularly its role in impairing wound healing[36,37]. However, the observed association between AUD and a more severe PAD at clinical presentation could be partially influenced by behavioral and healthcare access factors. Patients with AUD may be less likely to present for care with mild or nonspecific symptoms in their limbs; this could partially explain their more advanced stage of ischemia when they do finally present. In addition, both AUD and PAD are vastly underdiagnosed and underrecognized conditions[38–40]. The absence of systematic screening for alcohol use in vascular settings, and the usual asymptomatic nature of early-stage PAD, might create a double diagnostic gap, with both disorders discovered only in their later, much more severe stages. This overlap of under recognition may amplify the clinical burden and worsen outcomes in affected patients.

Although our study focuses on the association between severity of PAD and pathological drinking patterns, it was not possible to assess the impact of binge drinking alone on the severity of PAD, as this phenomenon was observed in only three patients. In particular, in our work binge drinking was included in the at-risk alcohol consumption category, which was defined for the rest of the population as a daily intake greater than 2 alcohol units for men and greater than 1 alcohol unit for women and elderly individuals over 65 years old, in accordance with WHO guidelines[41].

Specific to our cohort, we didn't find an association between at-risk alcohol consumption and greater severity of PAD. This may be explained by the small sample size of our group of patients.

Regarding subjects with at-risk alcohol consumption, we can emphasize that the category defined as risky has an older mean age compared to the rest of the population (78.53 years, p-value 0.001) and compared to the population with AUD (66.36 years, p-value 0.011); it is important to note, however, that for patients over 65 consuming just 1 alcohol unit in a day already constitutes at-risk consumption. Our result could suggest that other risk factors play a more significant role in determining PAD in this category of patients, which in turn may explain our research finding of a relationship between severity of PAD and AUD.

Finally, the ROC curve developed showed that an increased daily alcohol consumption was a moderate predictor of the risk of gangrene, suggesting a dose-dependent effect on PAD severity. Although earlier studies (e.g., PREDIMED) reported a protective role of moderate alcohol intake in reducing PAD incidence[42], our findings support the view that this potential benefit is lost beyond a certain threshold, confirming the dose-dependent reversal of alcohol's vascular effects[19].

Several pathophysiological mechanisms may explain the observed association between AUD and PAD severity.

The involvement of inflammation in the development and progression of PAD is well known[43–45]. Chronic alcohol exposure leads to endothelial dysfunction, oxidative stress, and inflammation, promoting atherosclerotic progression and microvascular damage[11,46].

In particular, ethanol enhances the inflammatory response, increasing circulating levels of tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), and stimulating c-reactive protein and NADPH oxidase activity[7,47]. These mediators promote monocyte adhesion, oxidative stress, and lipid peroxidation, accelerating endothelial injury and plaque instability. The oxidative stress generated by alcohol consumption also depletes antioxidant systems, such as glutathione and superoxide dismutase, amplifying vascular damage[7,9]. Moreover, metabolism of ethanol results in the generation of acetaldehyde, a toxic intermediate which reduces nitric oxide bioavailability and activates pro-inflammatory pathways, further contributing to endothelial dysfunction and fostering a pro-inflammatory and pro-thrombotic milieu[48–53].

This environment, along with microvascular alterations associated with chronic alcohol abuse, may contribute to the atherosclerotic burden and the progression from intermittent claudication to CLTI. Although high c-reactive protein levels were observed across groups of our study, the high prevalence of diabetes and other comorbidities may have masked potential differences in inflammatory profiles of the different sub-groups analyzed. However, we should emphasize that the evaluation of the effect of alcohol consumption on levels of c-reactive protein was not the primary aim of this study.

Another mechanism to consider is that heavy alcohol use interferes with glucose and lipid metabolism, exacerbating insulin resistance and dyslipidemia, both key contributors to atherosclerosis[8,54,55]. Nevertheless, in our cohort, LDL cholesterol and glycated hemoglobin levels were within or close to the target ranges recommended by PAD management guidelines in force at the time of enrollment[56]. This suggests that the observed association between AUD and PAD severity is unlikely to be driven by poorer control of conventional metabolic risk factors.

Of interest, as smoking is a major determinant of PAD, we also conducted additional analyses to assess its potential confounding role. In the multivariate logistic regression model including AUD, the number of cigarettes smoked per day, and smoking duration, AUD remained independently associated with severe PAD (Rutherford category 6), whereas neither smoking intensity nor duration showed a statistically significant association.

However, given the strong coexistence of alcohol and tobacco use, a residual confounding effect cannot be entirely excluded.

Notably, patients with AUD were younger and had better renal function but shorter diabetes duration than those without AUD, further supporting the hypothesis that alcohol-related vascular damage may accelerate PAD progression independently of traditional risk profiles.

The association between AUD and amputation risk found in our study, reinforces the hypothesis that chronic alcohol misuse may not only worsen arterial disease but also impair wound healing, increasing tissue susceptibility to ischemic necrosis, and adverse cardiovascular outcomes.

Our findings highlight the clinical importance of systematically assessing pathological alcohol drinking patterns in patients with PAD. The detection and treatment of AUD in this population could represent a modifiable risk factor for disease progression and adverse limb outcomes. Incorporating validated screening tools such as the AUDIT-C and structured interviews into routine vascular assessment may help clinicians identify patients at higher risk and direct them toward appropriate counseling and addiction medicine services. Furthermore, as patients with AUD commonly display concomitant morbidities and lifestyle factors associated with increased risk, a multidisciplinary management strategy that integrate vascular specialists and addiction medicine professionals may be warranted to improve both cardiovascular and limb outcomes.

Although this is the only study to date regarding the association between AUD and a population of PAD patients, we want to point out the limitations in our work. First, the observational, single-center design limits the ability to infer causality. Second, the number of participants was limited, especially in subgroups with at-risk alcohol consumption, and thus statistical power might be insufficient to detect associations.

Third, alcohol intake was self-reported and may have been underestimated, a well-recognized limitation of studies assessing alcohol use. Such underestimation could have led to misclassification of patients with higher levels of consumption into lower-risk categories, which would be expected to bias the results toward the null and attenuate, rather than exaggerate, the observed associations.

Although alcohol consumption assessment relied on self-report, structured interviews and validated questionnaires were administered by a clinician with expertise in addiction medicine, which may have improved the completeness and internal consistency of reported drinking patterns without eliminating the inherent limitations of self-reported data. In addition, patients with chronic conditions known to substantially influence drinking behavior were excluded.

Of note, only a small proportion of current non-drinkers reported former alcohol consumption, and this proportion did not differ significantly from that observed among drinkers, suggesting that misclassification due to a "sick quitter" effect is unlikely in this cohort. Finally, we did not assess long-term outcomes, such as mortality or limb salvage, that would offer additional support to the predictive potential of AUD on PAD. Future multicenter longitudinal studies are needed to validate these findings and to determine whether AUD represents an independent prognostic factor in PAD progression and outcomes.

In conclusion, AUD is highly prevalent among patients with symptomatic PAD and was associated with greater clinical severity at presentation, particularly Rutherford category 6 disease. At-risk alcohol consumption alone was not independently associated with PAD severity. These findings highlight the clinical relevance of identifying AUD in patients with PAD and support the integration of systematic alcohol use assessment into routine vascular care. Given the complex interplay between pathological alcohol use, cardiovascular risk factors, and limb-threatening ischemia, a multispecialty approach involving vascular specialists and addiction medicine professionals may be warranted to optimize patient management. Further prospective studies are needed to confirm these associations and to determine whether targeted interventions addressing pathological alcohol use may improve limb outcomes in this population.

Methods

Study design

This was an observational study conducted in a cohort of patients with lower extremity PAD. The primary objectives of the study were to determine the prevalence of at-risk alcohol consumption and AUD and to assess their association with disease severity at clinical presentation. The study protocol was reviewed and approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, and all procedures were carried out in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Study population and clinical assessment

One hundred and three consecutive patients admitted from February 23, 2019 to July 30, 2020 in the Internal Medicine Cardiovascular Unit of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy with a diagnosis of PAD of the lower limbs at admission were considered for inclusion in this study. The following variables were collected and examined: demographic characteristics, cardiovascular risk factors (smoking status and cumulative exposure, hypertension, diabetes mellitus, dyslipidemia), relevant cardiovascular comorbidities (previous CAD, heart failure, previous cerebrovascular disease), medications, laboratory parameters, alcohol-related variables included drinking status and patterns (non-drinker, moderate drinker, at-risk drinker, binge drinking, AUD), daily alcohol unit intake, duration of at-risk alcohol consumption, type of alcohol consumed, and PAD severity classified according to Rutherford categories.

All patients who met the enrollment criteria described below were included in the study: patients with symptomatic PAD of the lower extremities; age greater than 18 years; ability to sign the informed consent. Participants were excluded if they had anyone of the following criteria: inability or refusal to sign the informed consent for inclusion in the study; confirmed or suspected pregnancy; history of a psychiatric disorder; history of solid or hematological neoplasms or active neoplasia; organ transplant recipient or previous bone marrow transplant; unfavorable prognosis according to the clinician's judgment, or life expectancy of less than twelve months.

The diagnosis of PAD was established based on the diagnostic criteria recommended by international guidelines at the time of enrollment[56]. Inclusion required the presence of at least one instrumental criterion and at least one clinical criterion. Instrumental criteria included: an ABI < 0.90; imaging evidence (e.g., duplex ultrasound or computed tomography angiography) of atherosclerotic lesions causing ≥ 50% arterial stenosis in the affected lower limb. Clinical criteria, defined according to Rutherford classification[57], included one or more of the following signs: severe claudication (Rutherford category 3); ischemic rest pain (Rutherford category 4); a non-healing ulcer in typical ischemic locations, such as the plantar or dorsal surface of the foot, or the toes (Rutherford category 5); gangrene involving any segment of the lower extremity (Rutherford category 6)[56].

Alcohol consumption at the time of admission was assessed with the support of a clinician with expertise in alcohol addiction. The evaluation was conducted using the AUDIT-C, a three-item screening tool administered through a structured interview, designed to identify harmful alcohol consumption[58]. The alcohol history was then taken using the Lifetime Drinking History (LDH), which was also done in interview format. This is a detailed questionnaire which captures life history of alcohol use by an individual including age at first contact with alcohol, periods of consumption and abstinence, per day average number of alcohol units consumed during lifetime, types of beverages usually consumed[18]. Alcohol at-risk use was defined as a daily consumption of more than 2 alcohol units in males and over 1 alcohol unit females and individuals older than 65 years, according to the WHO standards prevailing at the time of inclusion (1 alcohol unit = 10 g of ethanol), for at least one year[41]. Binge drinking, defined as a consumption of more than 4 units in women and more than 5 units in men in a single occasion in the last month[59], was also considered as part of at-risk alcohol consumption. Additionally, the duration of at-risk alcohol consumption, measured in years, was assessed, calculated from the age of initiation of consumption above the defined thresholds[41]. The diagnosis of AUD was made in accordance with the criteria outlined in the DSM-5[60].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with IQR, according to their distribution assessed by Shapiro-Wilk test. Categorical variables were reported as frequencies and percentages. Group comparisons between patients with and without AUD, as well as between those with and without at-risk alcohol consumption, were performed using Student's t-test or Mann–Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables, as appropriate.

To evaluate the association between alcohol consumption patterns and PAD severity, logistic regression analyses were performed. Rutherford category 6 was selected as the primary outcome for logistic regression analyses because it represents the most severe clinical presentation of PAD, characterized by gangrene or extensive tissue loss and frequently associated with the need for amputation.

Odds ratios are reported with 95% confidence intervals for all logistic regression analyses. For the ordered logistic regression model, regression coefficients with corresponding 95% confidence intervals are presented. Univariate models examined the association of AUD, at-risk alcohol consumption, and daily alcohol unit intake with Rutherford category 6 (gangrene and significant tissue loss). Variables with $p < 0.10$ in univariate analysis or with clinical relevance were included in multivariate logistic regression models. Model fit was assessed using likelihood ratio chi-square tests and pseudo R^2 values. In regression tables, "_cons" denotes the constant (intercept) term of the model.

ROC curve analysis was conducted to evaluate the discriminative ability of daily alcohol unit intake in predicting Rutherford category 6. AUC was estimated with 95% confidence intervals.

Finally, an ordered logistic regression model was performed to assess the association between AUD and severity of PAD across Rutherford categories (from 3 to 6). The proportional odds assumption was verified, and predicted probabilities for each stage were calculated to illustrate the impact of AUD on disease progression. A p-value < 0.05 was considered statistically significant.

All statistical analyses were conducted with STATA software, version 18.0 for MacOS (StataCorp LLC, College Station, TX, USA). A two-tailed p-value < 0.05 was considered statistically significant.

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

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Author contributions
Conceptualization, M.M.R., F.B.; methodology, F.B., M.M.R.; data collection, M. D., M.A.N.; data analysis, M.M.R., F.B.; resources, A.F.; data curation, A.F.; writing—original draft preparation, M.M.R.; review and editing, F.B., G.A., A.F.; supervision, M.M., A.G., G.A., A.F. All authors read and approved the final manuscript. All authors have read the document and agree to its publication. Dr Andrea Flex is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for data integrity and data analysis accuracy.

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Competing interests
The authors declare no competing interests.

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The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy. Informed consent was obtained from all subjects involved in the study.

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Correspondence and requests for materials should be addressed to F.B.