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Peripheral artery disease and its clinical relevance in patients with COPD in the COSYCONET study

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Conception and design, SH-W, RAJ, RB, CV, HW. Drafting of the manuscript, SH-W, RAJ, CV, HW. Acquisition and analysis of data, SH-W, RAJ, AKA, CV, AO, HW. Analysis and interpretation of data, SH-W, RAJ, AKA, AO, MW, AO, CV, HW. Drafting the manuscript for important intellectual content, all authors. All coauthors critically revised the article and gave final approval of this version to be published.

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RUNNING TITLE

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Peripheral artery disease (PAD) is associated with morbidity and mortality. However, a high number of individuals with PAD are asymptomatic and unaware of the disorder. The ankle-brachial index (ABI) is not only a common diagnostic measure for PAD but also an indicator of atherosclerosis at other vascular sites. To date, knowledge on the prevalence of PAD as assessed by ABI and the associations of objectively assessed PAD with functional capacity and health status in a large cohort of patients with COPD is scarce.

What This Study Adds to the Field

This study shows that in a large cohort of patients with COPD of all degrees of severity, 8.8% were diagnosed with PAD (ABI $\leq$ 0.9) which is higher than the prevalence in non-COPD controls. Of note, more than two third of these patients did not report PAD in their medical history. Patients with PAD showed a worse functional capacity and worse health status compared to those without PAD. These differences exceeded the thresholds commonly considered as clinically relevant.

ONLINE SUPPLEMENT

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org .

KEY WORDS

Chronic obstructive pulmonary disease, comorbidities, peripheral vascular disease, health status, functional capacity

ABSTRACT

Rationale: Knowledge about the prevalence of objectively assessed peripheral artery disease (PAD) and its clinical relevance in patients with COPD is scarce.

Objectives: We aimed (1) to assess the prevalence of PAD in COPD compared to distinct control groups and (2) to study the association between PAD and functional capacity as well as health status.

Methods: The ankle-brachial index (ABI) was used to diagnose PAD (ABI≤0.9). 6-Minute-Walk-Distance (6MWD), health status (St. George's Respiratory Questionnaire [SGRQ]), COPD Assessment Test [CAT] and EuroQol-5-Dimensions [EQ-5D-3L] were assessed in patients enrolled in the German COPD and Systemic Consequences-Comorbidities Network (COSYCONET) cohort study. Control groups were derived from the Study of Health in Pomerania (SHIP).

Measurements and Main Results: 2,088 patients with COPD (61.1% male, mean [SD] age 65.3 [8.2] years GOLD stage I,II,III,IV: 9.4%,42.5%,37.5%,10.5%, respectively) were included. 184 patients (8.8%; GOLD stage I,II,III,IV: 5.1%,7.4%,11.1%,9.5%, respectively, versus 5.9% in patients with GOLD stage 0 in COSYCONET) had PAD. In SHIP, PAD ranged from 1.8% to 4.2%. COPD patients with PAD had a significantly shorter 6MWD (356 [108] vs 422 [103] m, $p<0.001$) and worse health status (SGRQ: 49.7 [20.1] vs 42.7 [20.0] points, $p<0.001$, CAT: 19.6 [7.4] vs 17.9 [7.4] points, $p=0.004$, EQ-5D VAS: 51.2 (19.0) vs 57.2 (19.6), $p<0.001$). Differences remained significant after correction for several confounders.

Conclusions: In a large cohort of patients with COPD, 8.8% were diagnosed with PAD which is higher than the prevalence in non-COPD controls. PAD was associated with a clinically relevant reduction in functional capacity and health status.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic disease that is primarily characterized by progressive airflow limitation (1). Beyond respiratory impairment, patients with COPD often suffer from coexisting diseases, the majority (up to 98%) showing one or more comorbidities (2, 3). Therefore, the interest in understanding COPD as a complex multisystem disease is increasing (4).

Because of their direct impact on survival (5-7), cardiovascular diseases are probably the most important coexisting diseases in COPD (1). Peripheral artery disease (PAD) is an atherosclerotic process that refers to the occlusion of the arteries in the lower limbs (8). PAD is a risk factor for other cardiovascular diseases and often described as a "silent killer" as a high number of individuals with PAD are asymptomatic and unaware of the disorder (9).

The ankle-brachial index (ABI) is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery (10). The ABI is not only a common diagnostic measure for PAD but also an indicator of atherosclerosis at other vascular sites (10). This renders the ABI a good prognostic marker for cardiovascular events (10), even beyond traditional risk calculations like the Framingham risk score (11).

However, knowledge about the prevalence and clinical relevance of objectively assessed PAD in patients with COPD is scarce. Therefore, we aimed to determine the prevalence of PAD in a large cohort of patients with COPD compared to patients with a similar risk profile but without fixed airflow obstruction (GOLD stage 0), matched non-COPD controls and individuals with an airflow limitation in two epidemiological cohorts. Furthermore, we aimed

to study the associations between PAD and functional capacity as well as disease-specific and generic health status in a large cohort of patients with COPD.

Some of the results have been previously reported in the form of an abstract (12-14).

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METHODS

The patient cohort comprises 2,741 patients who were enrolled in the German COPD and Systemic Consequences-Comorbidities Network (COSYCONET) cohort study which is a multicentre, longitudinal, prospective, observational study focussing on the interaction of lung disorder and comorbidities over time. Patients were recruited from September 2010 to December 2013 in 31 study centres throughout Germany and were eligible if they were ≥40 years of age, had a diagnosis of COPD or symptoms of chronic bronchitis (15). Patients with missing lung function data, unclassified patients, patients with alpha-1 antitrypsin deficiency and patients with missing ABI measurement were excluded from the current analyses resulting in 2,425 patients. 13.9% of these patients (n=337) had a post-bronchodilator ratio of $FEV_1/FVC \geq 70\%$ but (a) had a doctor diagnosis of chronic bronchitis and/or (b) reported ≥3 points on the COPD Assessment Test (CAT) item regarding symptoms of cough and/or (c) reported ≥3 points on the CAT item regarding symptoms of phlegm. These individuals were classified as patients "at risk" for COPD or GOLD stage 0 according to former guidelines (16). In the primary analyses evaluating the associations between PAD and functional capacity as well as health status in patients with COPD, patients with GOLD stage 0 were excluded leading to an analysis of a COPD population of 2,088 patients.

The control groups were based on data from two independent epidemiological cohorts of the Study of Health in Pomerania (SHIP), conducted in Northeast Germany. SHIP is a population based survey investigating 4,308 eligible subjects in the northeast of Germany randomly selected from population registries stratified by age and sex to reach as much as possible representativeness during its baseline examinations (SHIP S0). PAD and lung function investigations are based on the second follow up (SHIP S2) between 2008 and 2012 as well as on a second independent baseline cohort (SHIP-TREND-0) consisting of 4,420 individuals.

Details were presented elsewhere (17). Within a case-control approach, a 1:1 individual randomly matching by sex and age (+/-5 years) was used to match COSYCONET patients with non-COPD controls to compare PAD prevalence. Non-COPD controls were selected from the SHIP population after exclusion of subjects < 40 years, with a pre-bronchodilator ratio of $FEV_1/FVC<0.7$, $FEV_1<85\%$ predicted, or use of inhalation medications (Anatomical Therapeutic Chemical (ATC) code R03). In total, for 1708 COSYCONET patients with COPD (GOLD stage I-IV), non-COPD controls could be matched (see Table E1a in the online data supplement). The selection of non-COPD controls was further extended by also including subjects with a $FEV_1<85\%$ predicted and matching for smoking status (within a case-control approach, a 1:1 individual randomly matching), see Table E1b and E1c in the online data supplement, respectively. In an additional analysis we determined the prevalence of PAD in subjects with airflow obstruction ($FEV_1/FVC<0.7$) in SHIP (see Table E2 in the online data supplement).

In COSYCONET, demographics and clinical characteristics were assessed at the participating study centres. Post-bronchodilator spirometry (45 min after administration of 400µg salbutamol and 80 µg ipratropium bromide) was performed according to ATS/ERS recommendations using established reference values (18). Transfer Factor of the Lung for Carbon Monoxide (TLCO; single breath, mean value of two measurements) was assessed. Predicted values were calculated using previously published reference values (19). Patients were classified according to the spirometric criteria of GOLD (18) and the GOLD group A to D criteria (1). The CAT was used to classify patients into low symptom groups A/C or high symptom groups B/D. Comorbidities (e.g., hypertension, diabetes, peripheral artery disease; assessment by a structured interview), as well as the levels of high-sensitive C-reactive

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protein (hsCRP), cholesterol and triglycerides were assessed and included as possible risk factors for PAD in the current study.

Peripheral artery disease

PAD was objectively diagnosed using the ABI, which represents the ratio of ankle systolic pressure to brachial systolic pressure. In the COSYCONET cohort, systolic pressures were measured by a sphygmomanometer (VASCassist, iSYMED GmbH , Butzbach, Germany) on the left and right side in supine position. The lowest ABI value was selected for analyses as an ABI≤0.90 in either leg is considered evidence of PAD (20). In SHIP, systolic blood pressure was measured with a "Dopplex D900“ (Huntleigh Healthcare Ltd.) doppler ultrasound probe and a blood pressure cuff (Welch Allyn) in both arms and both ankles (anterior and posterior tibial artery) in supine position. A cut-point of ABI≤0.90 was used to define PAD (10). Further details are provided in the online supplement.

Clinical outcome measures

Functional capacity was assessed by the 6-Minute Walk Distance (6MWD) which was conducted according to previous guidelines (21). The minimal clinically important difference (MCID) of the 6MWD is 30 m (22). Predicted values were calculated using previously published reference values (23).

Disease-specific health status was assessed using the COPD-specific St. George’s Respiratory Questionnaire for COPD (SGRQ) (24) and the CAT (25). The SGRQ provides a symptom, activity and impact domain score and a total score, all ranging from 0 to 100 points. The MCID of SGRQ is 4 points for each scale and the total score (26). The CAT consists of eight

items and provides a total score ranging from 0 to 40. The MCID of the CAT is 2 points (27). Higher scores represent worse disease-specific health status in both questionnaires.

Generic health status was assessed using the EuroQol-5-Dimensions (EQ-5D-3L) instrument. It consists of five items (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) with three levels (no problems, some problems and extreme problems) and a visual analogue scale (VAS) for valuing health on a rating scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Utility scores can be obtained from the five items by weighting the answers according to a weighting scheme. The German Time Trade Off (TTO) tariff was used to calculate utility scores ranging from 0 to 1 with higher values indicating better health (28). The MCID of 8 points for the EQ-5D VAS has been proposed for patients with moderate-to-severe COPD (29). A MCID for the EQ-5D utility score is not yet established but may range between 0.08 and 0.10 according to studies in non-COPD patients (30-32). In a previous analysis of the COSYCONET data set comparing disease specific and generic health status instruments the SGRQ showed the best discrimination between COPD grades and was less influenced by self-reported comorbidities, while the EQ-5D-3L utility had a higher weight on self-reported comorbid conditions (33).

Statistics

The current analysis is a cross-sectional analysis of the COSYCONET cohort study (visit 1). Data are presented as mean and standard deviation [SD] or median value and quartiles, depending on the distribution of the data. Characteristics were compared between patients with and without PAD using an Independent Sample T-Test or Mann-Whitney U-Test, as appropriate. Categorical variables were compared using single-proportion χ^2-tests. Logistic regression analyses were performed to detect the association between PAD and age, gender,

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smoking status, TLCO % predicted, GOLD stage, hypertension, diabetes, hsCRP and triglycerides. A further logistic model including patients with GOLD stage 0 has been performed. Possible confounders were identified by univariate analyses; i.e. measures which significantly differ between patients with and without PAD have been included in the multivariate model. Skewed data were log transformed beforehand. General linear models were used to compare functional capacity (i.e., 6MWD) between patients with and without PAD, correcting for possible confounders (age, gender, height, weight, TLCO % predicted, GOLD stage, smoking status, hypertension, myocardial infarction and angina pectoris) and health status between patients with and without PAD, correcting for possible confounders (age, gender, TLCO % predicted, GOLD stage, smoking status, hypertension, myocardial infarction and angina pectoris). Statistics were performed using SPSS 20.0 (SPSS Inc, Chicago, IL) and SAS 9.3 and 9.4 (SAS Institute Inc., Cary, NC). Figures were constructed using GraphPad Prism. Statistical significance was set at $p \leq 0.05$.

RESULTS

On average, COPD patients were 65 years old and had moderate to severe airflow limitation (Table 1). 8.3%, 29.8%, 4.7% and 57.2% of the patients were classified in GOLD group A, B, C, D, respectively.

Prevalence of PAD

PAD (ABI≤0.9) was detected in 8.8% of the patients with COPD (n=184). Of these, 65.8% did not report PAD in their medical history.

PAD was detected in 5.9% of the patients with GOLD stage 0 (n=20). Of these, 55.0% did not report PAD in their medical history.

In age and gender matched non-COPD controls, PAD was detected in 1.8% compared to 8.5% in matched patients with COPD GOLD I-IV (see Table E1a in the online data supplement). Including controls with worse lung function (i.e. FEV_1<85% predicted; see Table E1b in the online data supplement), and those who were matched for smoking status (see Table E1c in the online data supplement), increased the prevalence of PAD in the control group to 2.0% and 2.6%, respectively. Of note, the controls with PAD had a higher BMI, a higher prevalence of obesity and diabetes, and higher levels of triglycerides, but less pack-years of smoking and less frequent hypertension than the age and gender matched COPD patients (see Table E1a-E1c in the online data supplement). A further analysis in subjects with mild airflow limitation (FEV_1/FVC, 0.64; FEV_1, 80.2% predicted) in the SHIP cohorts revealed a PAD prevalence of 4.2% (see Table E2 in the online data supplement). Figure 1 represents the prevalence of the above mentioned groups.

The frequency distribution of ABI values stratified by GOLD 0, GOLD stages and GOLD groups is shown in Figure E1 in the online data supplement. Figure 2 shows the prevalence of PAD stratified by GOLD 0 and GOLD stages I-IV and GOLD groups A-D. The proportion of patients with PAD differs between GOLD stages (GOLD 0/I/II/III/IV: 5.9%/5.1%/7.4%/11.1%/9.6%, p=0.006) and GOLD groups (GOLD 0/A/B/C/D: 5.9%/5.2%/7.1%/7.1%/10.3%, p=0.015).

In patients with COPD, PAD was independently associated with older age, being a current smoker, impaired diffusion capacity, higher levels of triglycerides, hypertension and diabetes (Table 2). Independent predictors remained comparable when patients with GOLD stage 0 were included (see Table E4 in the online data supplement).

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Relation to outcome measures

Patients with COPD and comorbid PAD were older and had worse lung function compared to those COPD patients without PAD. Furthermore, a higher proportion of COPD patients with PAD was male, current smokers and classified as GOLD III patients (Table 1). Descriptive characteristics for patients with GOLD stage 0 stratified by PAD are shown in Table E3 in the online data supplement.

Patients with PAD had a worse functional capacity as assessed with 6MWD (356 [108] vs 422 [103] m, $p<0.001$) compared to those without PAD (Figure 3a, Table 3). Accordingly, 6MWD in terms percent-of-predicted was lower in patients with PAD compared to those without PAD (56.8 (17.0) % predicted vs. 66.3 (16.1) % predicted; $p<0.001$). The differences in 6MWD remained significant after correction for possible confounders (Table 3) and inclusion of patients with GOLD stage 0 (Table E5).

Furthermore, patients with PAD showed a worse disease-specific health status as assessed with SGRQ domain scores and total score, with most pronounced differences in SGRQ activity (67.4 [22.9] vs 56.9 [25.9] points, $p<0.001$) and SGRQ total score (49.7 [20.1] vs 42.7 [20.0] points, $p<0.001$) (Figure 3b, Table 3). Similarly, the CAT score was significantly higher in patients with PAD (19.6 [7.4] vs 17.9 [7.4] points, $p=0.004$). In addition, generic health status was more impaired in patients with PAD (e.g., EQ-5D VAS (51.2 [19.0] vs 57.1 [19.6] points, $p\leq0.001$). Specifically, a higher proportion of patients with PAD reported more 'some problems' or 'severe problems' of mobility (55.4% vs 38.7%, $p<0.001$), self-care (22.3% vs 14.4%, $p=0.004$) and usual activity (58.7% vs 50.3%, $p=0.03$) compared to those without PAD. The differences in disease-specific and generic health status scores remained

significant after correction for possible confounders (except for SGRQ symptom score; Table 3) and inclusion of patients with GOLD stage 0 (Table E5).

DISCUSSION

In a large cohort of patients with COPD of all degrees of severity, 8.8% were objectively diagnosed with PAD. Of note, more than two third of these patients did not report PAD in their medical history. Patients affected by PAD showed a clinically meaningful worse functional capacity and health status compared to those without PAD.

Prevalence

The currently available studies regarding the prevalence of PAD in patients with COPD are rather limited and do not allow to draw firm conclusions. In a Taiwanese cohort of 427 patients with COPD, 8% of the patients have been identified with asymptomatic PAD (34). While the severity stages of COPD in this Taiwanese cohort were comparable to those in our cohort, the generalizability of these data is difficult as almost exclusively male patients (98%) were enrolled in this single-centre study. Other reported frequencies of an ABI < 0.9 in COPD have been derived from smaller single-centre studies and range up to 37% (35-37), with the highest prevalence of 37% in patients hospitalized for an exacerbation of COPD (37). To the best of our knowledge there are no studies available so far that compared the prevalence of objectively diagnosed PAD in COPD with non-COPD controls. The current manuscript shows that the prevalence of PAD in COPD is higher than the prevalence in non-COPD subjects, even after controlling for smoking status, which is known to substantially affect the relationship between COPD and cardiovascular disease (38, 39). Notably, the non-obstructive control subjects had a higher risk profile for PAD than the COPD patients according their BMI and the prevalence of obesity (BMI>30 kg/m2), diabetes, and hypertriglyceridemia,

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which in turn underlines the important role of COPD as a potential and so far underestimated risk factor for PAD. We found the highest prevalence of PAD with 4.2 % in the control subjects with mild airflow obstruction, which is close to the prevalence of PAD of 5.1% in our GOLD stage I patients.

Due to its size, the current study provided enough power to study multiple relationships. PAD was associated with older age, current smoking status, higher levels of triglycerides, hypertension and diabetes, all which are established risk factors of cardiovascular disease. Furthermore, we identified diffusion capacity to be independently associated with PAD in our cohort. The present study is the first showing a relationship between PAD and diffusion capacity for carbon monoxide in patients with COPD. Interestingly, our data are in line with a recent observation showing an association between coronary artery calcification and emphysema severity (40). Thus, both studies together suggest an association between of emphysema and atherosclerotic processes. Previous findings indicated a higher prevalence of PAD in more severe patients with COPD (35, 41) which is supported by our univariate analyses. In a multivariate regression model however, diffusion capacity remained an independent predictor for PAD only, while GOLD stages III and IV were not significant anymore. However, smoking status was the strongest independent predictor of PAD, which is confirmed by a recent meta-analysis demonstrating that smoking status is the highest prevalent risk factor for cardiovascular disease in patients with COPD (38) .

Functional capacity

The 6MWD is assumed to evaluate the integrated responses of all systems involved during exercise, including peripheral circulation (21). Our study clearly demonstrates an association between objectively assessed PAD and functional capacity as quantified by 6MWD in COPD.

Previous smaller studies provided conflicting results, whether or not PAD is associated with 6MWD. While a rather strong association has been shown by Castagna and colleagues in 151 COPD patients with GOLD stages II and III (41), Sun and colleagues did not find a statistical significant difference in 6MWD between patients without PAD and those with PAD (42). Even after adjusting for several confounders, we found a rather large difference in 6MWD that clearly exceeds the MCID of 30 meters compared to those without PAD. Interestingly, asymptomatic PAD patients with an ABI < 0.9 have been found to have a lower 6MWD than matched controls before (43), which further strengthens the findings of our study.

Health status

To the best of our knowledge, the current study is the first evaluating the relationship between objectively assessed PAD and disease-specific as well as generic health status in patients with COPD. Since worse health status has been shown to be associated with diminished physical functioning (44, 45), it is not unexpected that the impairment in health status corresponded to the functional impairment in our cohort. Indeed, impairments in health status were most pronounced in the SGRQ activity domain. However, the difference in all other domains also clearly exceeds the minimum clinically relevant difference of 4 points. It seems to be a general finding that subjects with PAD report an impaired generic health status; this has been demonstrated using the Medical Outcomes Study 36-Item Short-Form Health Survey (46). Although differences in generic health status as measured by EQ-5D were statistically significant in the current study, their clinical relevance might be disputable. Their lower sensitivity in the population studies is in line with reports that disease-specific questionnaires are more sensitive in patients with COPD (47).

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Recently, the COMorbidities in Chronic Obstructive Lung Disease (COMCOLD) index has been developed which includes PAD as one of the five most important comorbidities affecting patients' health status (48). The current study confirms these findings as it demonstrates a clinically relevant association between PAD and disease-specific health status.

Limitations

Although the COSYCONET cohort study is a multicenter, longitudinal, prospective study that included a large number of patients throughout Germany, there are limitations that must be taken into account. First, the methodologies to detect PAD were not the same in SHIP and COSYCONET. However, this should only have a minor impact on the differences in prevalence of PAD since the correlation between both measurement methods is acceptable in healthy subjects and patients with mild PAD with an ABI≤0.9 (10). Only in severe PAD with low ABI ranges there is an overestimation of the actual pressure by the oscillometric method, which does not affect the current prevalence comparison as this is the cut-off level defining mild PAD (10). Second, stops and/or leg pain during the 6MWD have not been investigated which could provide a better understanding of the differences found in 6MWD between COPD patients with PAD and without PAD. However, as the majority of patients had no previous diagnosis of PAD it is likely that they were rather asymptomatic than symptomatic. Indeed, only 10 patients (0.5%) had an ABI≤0.6, which represents the cut-off for severe, symptomatic PAD with intermittent claudication (49). Third, COPD cases and controls were not sampled from the same population (i.e. a nested case control study design) resulting in the potential risk of selection and confounding bias.

CONCLUSIONS

In a large cohort of patients with COPD, 8.8% had an ABI≤0.9 indicating PAD. The prevalence of PAD was higher than the prevalence in matched controls from two epidemiological cohorts. Patients with COPD and PAD showed a clinically relevant impairment of functional capacity and disease-specific health status compared to those without PAD. Our study demonstrates that the presence of PAD is clearly associated with clinically relevant outcome measures that are established for monitoring patients with COPD. Therefore, clinicians should actively look for PAD in patients with COPD to identify patients at risk for vascular events and to fully understand their impairments. Early diagnoses and treatment of PAD in patients with COPD may improve morbidity and mortality which should be investigated in the future.

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FIGURE LEGEND

Figure 1. Prevalences of PAD in patients with COPD and several control groups.

Figure 2. Prevalence of peripheral artery disease (PAD) stratified by GOLD stages and GOLD groups

Figure 3. (a) 6-Minute-Walk-Distance (6MWD) and (b) St. George's Respiratory Questionnaire (SGRQ) stratified by patients with and without peripheral artery disease (PAD)

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Table 1. Baseline Characteristics of COPD patients stratified by peripheral artery disease (PAD)

	Whole group (n = 2088)	Patients with PAD (ABI ≤ 0.9) (n = 184)	Patients without PAD (ABI > 0.9) (n = 1904)
Age, years	65.3 (8.2)	68.5 (7.0)*	65.0 (8.2)
Male, n (%)	1276 (61.1)	131 (71.2)*	1145 (60.1)
Smoking status [a]			
Never smoker, n (%)	114 (5.5)	4 (2.2)*	110 (5.8)
Current smoker, n (%)	550 (26.3)	64 (34.8)*	486 (25.5)
Former smoker, n (%)	1424 (68.2)	116 (63.0)	1308 (68.7)
Packyears [b]	44.0 (25.5-67.5)	45.0 (23.4-72.0)	44.0 (25.5-67.5)
BMI, kg/m^2 [c]			
< 18.5	74 (3.5)	8 (4.3)	66 (3.5)
18.5 – 25.0	758 (36.3)	68 (37.0)	690 (36.3)
25.0 – 30.0	772 (37.0)	69 (37.5)	703 (36.9)
> 30.0	483 (23.1)	39 (21.2)	444 (23.3)
FEV_1, liter ‡	1.4 (1.1-1.9)	1.3 (1.0-1.7)*	1.5 (1.1-2.0)
FEV_1, % predicted	52.9 (18.7)	48.4 (17.5)*	53.4 (18.8)
FEV_1/FVC, % ‡	52.2 (43.4-60.9)	49.6 (41.9-60.4)	52.3 (43.4-60.9)
TLCO [d]	4.5 (1.9)	4.0 (1.9)*	4.6 (1.9)
TLCO, % predicted [d]	52.9 (20.8)	47.5 (20.2)*	53.5 (20.8)
GOLD stage, n (%)			
I	197 (9.4)	10 (5.4)	187 (9.8)

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II	887 (42.5)	66 (35.9)	821 (43.1)
III	784 (37.5)	87 (47.3)*	697 (36.6)
IV	220 (10.5)	21 (11.7)	199 (10.5)
mMRC dyspnea score (%) [e]			
0	168 (8.1)	11 (6.0)	157 (8.3)
1	911 (44.1)	62 (33.9)*	849 (45.0)
2	589 (28.5)	50 (27.3)	539 (28.6)
3	377 (18.1)	53 (29.0)*	324 (17.2)
4	23 (1.1)	7 (3.8)*	16 (0.8)
ABI [‡]	1.2 (1.1-1.2)	0.8 (0.7-0.9)*	1.2 (1.1-1.2)
hsCRP mg/L [‡ f]	4.5 (2.0-7.3)	5.0 (2.2-9.1)*	4.3 (2.0-7.1)
Triglyceride, mg/dL [‡ g]	115.0 (84.0-168.9)	125.0 (93.6-183.8)*	114.0 (83.0-167.6)
Cholesterol, mg/dL [h]	216.2 (44.0)	211.2 (44.7)	216.6 (43.9)
Hypertension, n (%)	1171 (56.1)	131 (71.2)*	1040 (54.6)
Diabetes, n (%)[c]	276 (13.2)	38 (20.7)	238 (12.5)

[‡] = non-parametric tests were used due to skewed data; values expressed as median (IQR).

* $p \leq 0.05$ compared to patients without PAD.

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; TLCO, Transfer Factor of the Lung for Carbon Monoxide; mMRC, modified Medical Research Council scale; ABI, ankle-brachial index; hsCRP, high-sensitive C-reactive protein.

[a]patients with missing data on smoking status (n=4) were classified as 'former smokers'

[b]n=1960 (whole group), n=179 (ABI ≤ 0.9), n=1781 (ABI > 0.9),

[c]n=2087 (whole group), n=184 (ABI ≤ 0.9), n=1903 (ABI > 0.9),

[d]n=1973 (whole group), n=176 (ABI ≤ 0.9), n=1797 (ABI > 0.9);

[e]n=2068 (whole group), n=183 (ABI ≤ 0.9), n=1885 (ABI > 0.9);

[f]n=2065 (whole group), n=182 (ABI ≤ 0.9), n=1883 (ABI > 0.9);

[g]n=2061 (whole group), n=181 (ABI ≤ 0.9), n=1880 (ABI > 0.9);

[h]n=2064 (whole group), n=181 (ABI ≤ 0.9), n=1883 (ABI > 0.9).

Table 2. Independent predictors of peripheral artery disease in patients with COPD GOLD stage I-IV

Covariates	**Exp (B)**	**95% CI for HR**		**p-value**
		Lower	**Upper**	
Age, years	1.072	1.047	1.097	**<0.001**
Gender (male), n	1.311	0.904	1.902	0.153
Smoking status, n				
Smoking status (current smoker)	5.928	1.757	20.003	**0.004**
Smoking status (former smoker)	2.770	0.843	9.099	0.093
GOLD, n				
II	1.143	0.562	2.325	0.713
III	1.714	0.824	3.566	0.150
IV	1.624	0.650	4.061	0.300
TLCO % predicted	0.987	0.977	0.997	**0.009**
hsCRP, mg/L *	1.089	0.954	1.243	0.208
Triglycerides, mg/dL *	1.470	1.077	2.007	**0.015**
Hypertension, n	1.621	1.133	2.319	**0.008**
Diabetes, n	1.518	1.003	2.299	**0.048**

Logistic regression – dependent variable ABI ≤ 0.90 (n=173 with ABI ≤ 0.90 versus n=1763 with ABI > 0.90). Never smokers as well as GOLD I were selected as reference category. Bold printed values represent significant results.

*Abbreviations: see table 1. *logtransformed due to skewed data*

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Table 3. Difference in functional capacity and health status between COPD patients with and without peripheral artery disease (PAD)

Dependent variable	**Total group**	**ABI ≤ 0.9 n = 184**	**ABI > 0.9 N = 1904**	**Unadjusted p-value**	**Adjusted mean difference (95% CI)**	**Adjusted p-value**
6MWD, meters [a]	417 (106)	356 (108)	422 (103)	**<0.001**	-40.9 (-54.5 to -27.4)	<0.001
SGRQ total score, points [b]	43.3 (20.1)	49.7 (20.1)	42.7 (20.0)	**<0.001**	4.30 (1.45 to 7.14)	**0.003**
SGRQ symptom score, points [b]	55.7 (21.3)	59.1 (20.4)	55.4 (21.3)	**0.025**	1.73 (-1.53 to 4.98)	0.298
SGRQ activity score, points [b]	57.9 (25.8)	67.4 (22.8)	57.0 (25.9)	**<0.001**	6.33 (2.86 to 9.79)	**<0.001**
SGRQ impact score, points [b]	30.5 (21.0)	36.1 (22.6)	29.9 (20.8)	**<0.001**	3.96 (0.88 to 7.03)	**0.012**
CAT total score, points [c]	18.1 (7.4)	19.6 (7.4)	17.9 (7.4)	**0.004**	1.13 (0.18 to 2.24)	**0.046**
EQ-5D utility score, points [d]	0.82 (0.2)	0.79 (0.2)	0.82 (0.2)	**0.020**	-0.03 (-0.06 to 0.01)	0.102
EQ-5D VAS, points [e]	56.6 (19.6)	51.2 (19.0)	57.2 (19.6)	**<0.001**	-3.58 (-6.48 to -0.67)	**0.016**

Values expressed as mean (SD). 6MWD, 6-minute-walk-distance; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire; EQ-5D, EuroQol-5 Dimensions

Unadjusted p-value based on independent sample t-test; adjusted p-value based on general linear model after correction for age, gender, height, weight, TLCO % predicted, GOLD stage, smoking status, hypertension, myocardial infarction and angina pectoris for 6MWD and for age, gender, TLCO % predicted, GOLD stage, smoking status, hypertension, myocardial infarction and angina pectoris for health status.

[a] n=2028 (whole group), n=178 (ABI ≤ 0.9), n=1850 (ABI > 0.9),
[b] n=2070 (whole group), n=183 (ABI ≤ 0.9), n=1887 (ABI > 0.9),
[c] n=2075 (whole group), n=182 (ABI ≤ 0.9), n=1893 (ABI > 0.9);
[d] n=2075 (whole group), n=184 (ABI < 0.9), n=1891 (ABI > 0.9)
[e] n=2065 (whole group), n=184 (ABI < 0.9), n=1881 (ABI > 0.9)

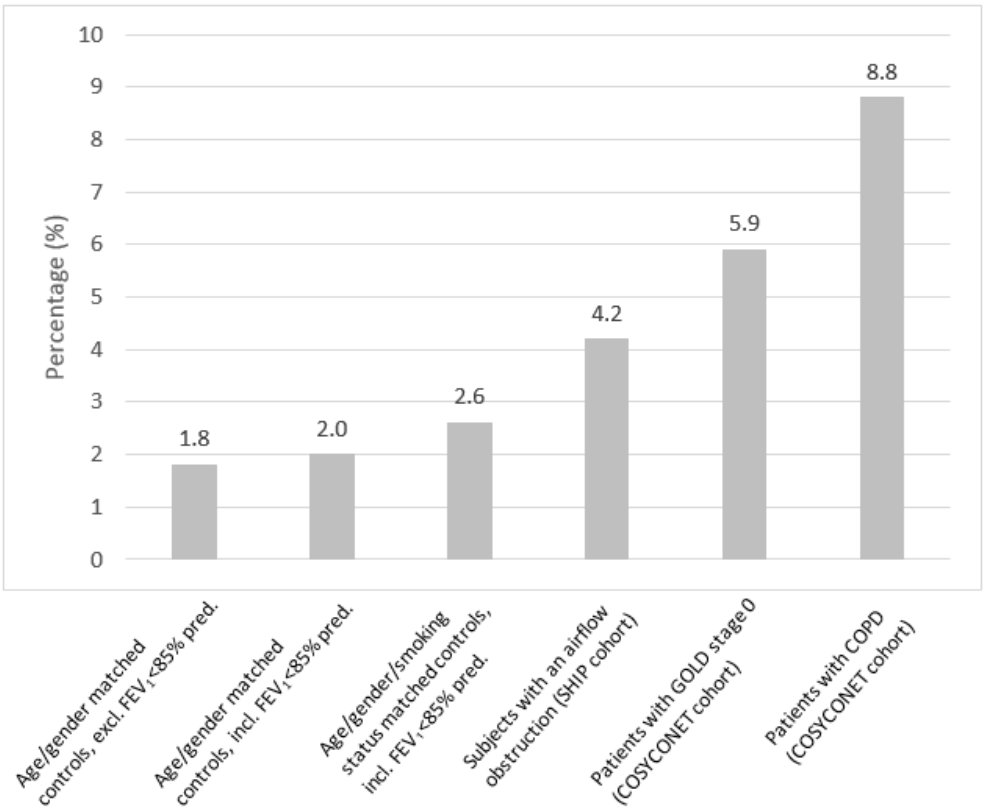

Figure 1.

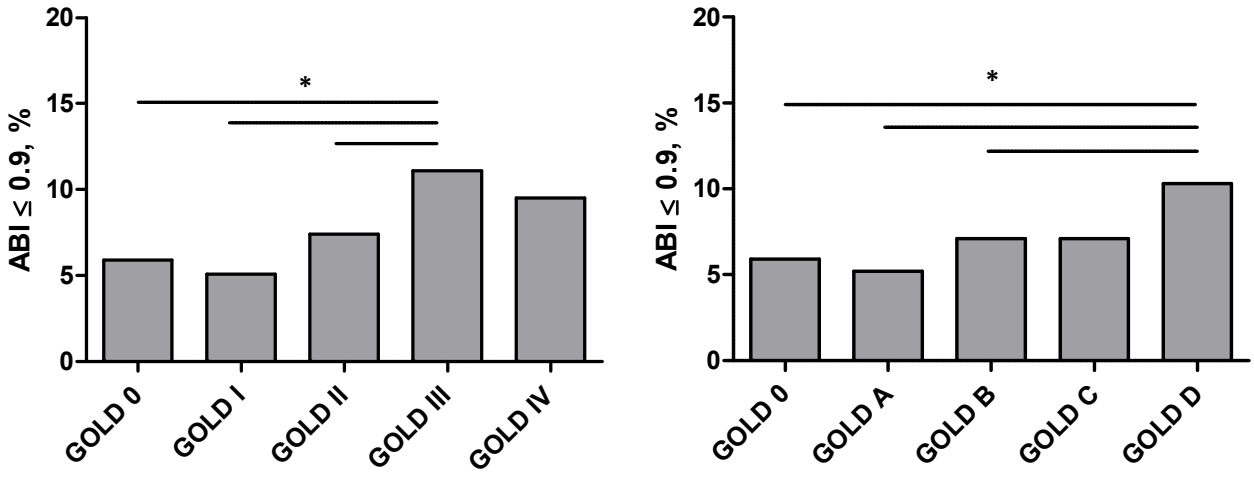

Figure 2.

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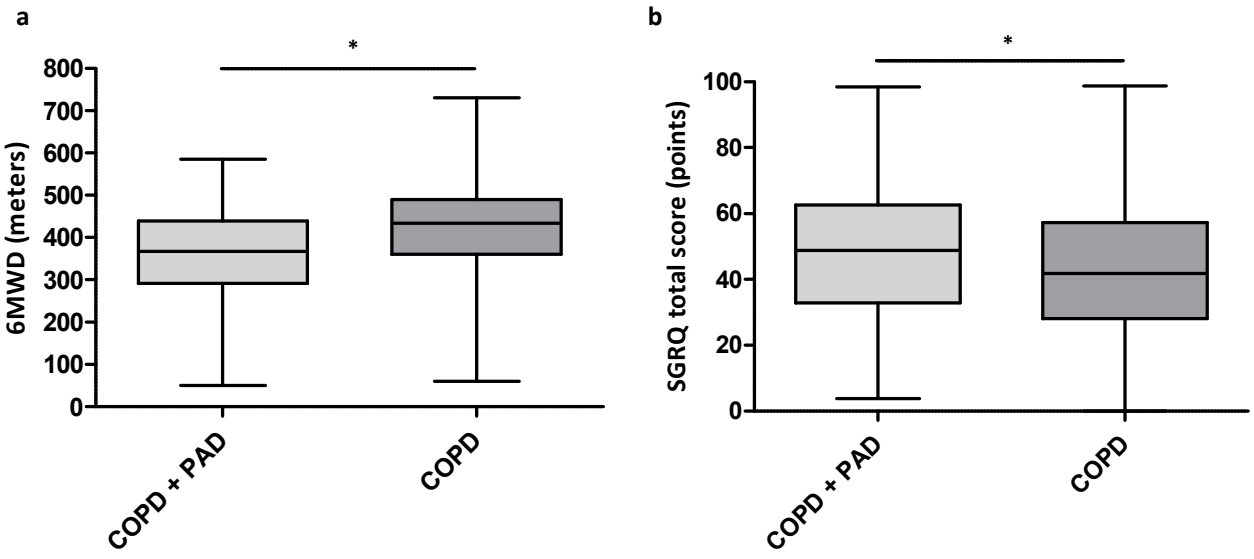

Figure 3.

ONLINE DATA SUPPLEMENT

Peripheral artery disease and its clinical relevance in patients with COPD in the COSYCONET study

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METHODS

During a follow-up visit of the SHIP cohort, all subjects were invited to participate in the ABI examination and lung function examination. We excluded those with missing lung function data, missing ABI data, subjects with less than 40 years of age, and subjects who received at least one of the following medications: selective drugs against obstructive airway diseases (anatomic-therapeutic-chemical [ATC] code R03). Details of lung function examinations that have been used in this study are given elsewhere (1). In brief, lung function examinations were performed using a body plethysmograph equipped with a pneumotachograph (MasterScreenBody/Diff; Jaeger, Hoechberg, Germany), which meets American Thoracic Society criteria and recommendations of the European Respiratory Society (2, 3).

Systolic BP was measured in SHIP with a 'Dopplex D900' (HuntleighHealthcare Ltd.) Doppler ultrasound probe and a BP cuff (Welch Allyn) in both arms (brachial artery) and both ankles (anterior and posterior tibial artery). Measurements were taken in the supine position after at least 10 min of rest. ABI was calculated using the higher of the right and left tibial pressures divided by the higher of the two brachial artery pressuresaccording to the recommendations of the American Heart Association (4). ABI in COSYCONET was calculated analogously using the oscillometric measures.

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RESULTS

When using mMRC (cut-point: ≥ 2) as symptom measure to classify patients into GOLD groups A to D, 28.0%, 10.1%, 24.1% and 37.8% of the patients were classified into GOLD group A, B, C and D, respectively. The proportion of patients with PAD differs between GOLD groups; GOLD A/B/C/D: 7.0%/6.2%/6.5%/12.3%, p<0.001).

Table E1a. Baseline characteristics; COSYCONET GOLD I-IV versus age and gender matched controls from SHIP excluding individuals with FEV_1 < 85% predicted (n=1708)

	COSYCONET			**Matched SHIP-2+SHIP-Trend**		
	Whole group (n = 1708)	Patients with PAD (ABI ≤ 0.9) (n = 145) **(8.5%)**	Patients without PAD (ABI > 0.9) (n = 1563)	Whole group (n = 1708)	Patients with PAD (ABI ≤ 0.9) (n = 31) **(1.8%)**	Patients without PAD (ABI > 0.9) (n = 1677)
Age, years	64.1 (± 8.2)	67.7 (± 7.3)	63.7 (± 8.2)	63.8 (± 8.2)	69.4 (± 10.1)	63.7 (± 8.2)
Male, n (%)	908 (53.2)	93 (64.1)	815 (52.1)	908 (53.2)	23 (74.2)	885 (52.8)
Smoking status						
Never smoker, n (%)	98 (5.7)	2 (1.4)	2 (1.4)	741 (43.4)	6 (20.0)	735 (43.9)
Current smoker, n (%)	478 (28.0)	53 (36.6)	425 ((27.2)	169 (9.9)	6 (20.0)	163 (9.7)

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Former smoker, n (%)	1132 (66.3)	90 (62.1)	1042 (66.7)	796 (46.7)	18 (60.0)	778 (46.4)
Packyears [a]	43.0 (24.9-65.0)	42.9 (21.7-66.4)	43.0 (25.5-65.0)	18.6 (8; 32.0)	27.8 (21.0; 36.0)	18.5 (8.0; 31.4)
BMI, kg/m² [b]	26.8 (± 5.5)	26.5 (± 5.3)	26.8 (± 5.5)	28.7 (± 4.4)	28.8 (± 4.9)	28.7 (± 4.4)
< 18.5	68 (4.0)	7 (4.8)	61 (3.9)	1 (0.1)	-	1 (0.1)
18.5 ≤ BMI < 25.0	613 (35.9)	54 (37.2)	559 (35.8)	327 (19.2)	7 (22.6)	320 (19.1)
25.0 ≤ BMI ≤ 30.0	617 (36.1)	53 (36.6)	564 (36.1)	804 (47.1)	14 (45.2)	790 (47.1)
> 30.0	409 (24.0)	31 (21.4)	378 (24.2)	576 (33.7)	10 (32.3)	566 (33.8)
FEV_1, liter ‡	1.5 (± 0.7)	1.4 (± 0.6)	1.5 (± 0.7)	3.1 (± 0.8)	2.8 (± 0.6)	3.1 (± 0.8)
FEV_1, % predicted	52.8 (± 18.7)	49.8 (± 18.1)	53.1 (± 18.7)	107.6 (± 13.5)	100.2 (± 8.6)	107.7 (± 13.5)
FEV_1/FVC, %	51.8 (± 11.2)	52.4 (± 12.5)	51.7 (± 11.1)	79.8 (± 4.6)	77.8 (± 4.7)	79.9 (± 4.6)
TLCO [c]	4.5 (± 2.0)	3.9 (± 1.9)	4.5 (± 2.0)	7.4 (± 1.8)	6.4 (± 1.6)	7.4 (± 1.8)
TLCO, % predicted [c]	52.7 (± 21.0)	47.3 (± 20.7)	53.2 (± 21.0)	88.4 (± 14.5)	79.9 (± 15.3)	88.6 (± 14.4)
ABI ‡	1.13 (± 0.54)	0.8 (± 0.1)	1.2 (± 0.1)	1.14 (± 0.11)	0.78 (± 0.08)	1.15 (± 0.10)
Triglyceride, mg/dl [d]	141.0 (± 122.0)	154.6 (± 100.7)	139.8 (± 123.8)	158.6 (± 100.3)	236.4 (± 276.6)	157.2 (± 93.6)

Cholesterol, mg/dl [e]	218.5 (± 44.2)	211.3 (± 45.0)	219.1 (± 44.1)	216.4 (± 43.8)	203.0 (± 54.1)	216.7 (± 43.5)
Hypertension, n (%)	942 (55.2)	102 (70.3)	840 (53.7)	731 (42.8)	16 (51.6)	715 (42.6)
Diabetes, n (%) [f]	212 (12.4)	27 (18.6)	185 (11.9)	222 (13.0)	8 (25.8)	214 (12.8)

Values expressed as mean (± SD) or median (IQR). *Abbreviations*: BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; TLCO, Transfer Factor of the Lung for Carbon Monoxide; ABI, ankle-brachial index

COSYCONET: [a]n=1596 (whole group), n=142 (ABI ≤ 0.9), n=1454 (ABI > 0.9); [b]n=1707 (whole group), n=145 (ABI ≤ 0.9), n=1562 (ABI > 0.9); [c]n=1607 (whole group), n=140 (ABI ≤ 0.9), n=1467 (ABI > 0.9); [d]n=1684 (whole group), n=143 (ABI ≤ 0.9), n=1541 (ABI > 0.9); [e]n=1687 (whole group), n=144 (ABI ≤ 0.9), n=1543 (ABI > 0.9); [f]n=1707 (whole group), n=145 (ABI ≤ 0.9), n=1562 (ABI > 0.9).

SHIP: [a]n=623 (whole group), n=17 (ABI ≤ 0.9), n=606 (ABI > 0.9); [Smoking]n=1706 (whole group), n=30 (ABI ≤ 0.9), n=1676 (ABI > 0.9); [c]n=1672 (whole group), n=31 (ABI ≤ 0.9), n=1641 (ABI > 0.9); [d]n=1707 (whole group), n=31 (ABI ≤ 0.9), n=1676 (ABI > 0.9); [e]n=1707 (whole group), n=31 (ABI ≤ 0.9), n=1676 (ABI > 0.9);

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Table E1b. Baseline characteristics; COSYCONET GOLD I-IV versus age and gender matched controls from SHIP including individuals with FEV_1 < 85% predicted (n=1793)

	COSYCONET			**Matched SHIP-2+SHIP-Trend**		
	Whole group (n = 1793)	Patients with PAD (ABI ≤ 0.9) (n = 154) **(8.6%)**	Patients without PAD (ABI > 0.9) (n = 1639)	Whole group (n = 1793)	Patients with PAD (ABI ≤ 0.9) (n = 36) **(2.0%)**	Patients without PAD (ABI > 0.9) (n = 1757)
Age, years	64.4 (± 8.2)	67.9 (± 7.2)	64.0 (± 8.2)	64.2 (± 8.3)	72.0 (± 7.6)	64.1 (± 8.2)
Male, n (%)	983 (54.8)	101 (65.6)	882 (53.8)	983 (54.8)	27 (75.0)	956 (54.4)
Smoking status						
Never smoker, n (%)	106 (5.9)	3 (1.9)	103 (6.3)	769 (42.9)	6 (16.7)	763 (43.4)
Current smoker, n (%)	494 (27.6)	55 (35.7)	439 (26.8)	188 (10.5)	8 (22.2)	180 (10.2)

Former smoker, n (%)	1193 (66.5)	96 (62.3)	1097 (66.9)	836 (46.6)	22 (61.1)	814 (46.3)
Packyears [a]	43.0 (25.1-66.0)	43.0 (21.9-66.4)	43.0 (25.5-66.0)	19.0 (8.3; 32.0)	33.8 (22.0; 39.0)	18.8 (8.0; 31.5)
BMI, kg/m² [b]	26.2 (23.2-29.7)	25.5 (23.2-29.4)	26.2 (23.2-29.8)	28.6 (25.9-31.5)	30.1 (26.3-34.5)	28.5 (25.9-31.4)
< 18.5	69 (3.8)	7 (4.5)	62 (3.8)	1 (0.1)	-	1 (0.1)
18.5 ≤ BMI < 25.0	650 (36.3)	59 (38.3)	591 (36.1)	308 (17.3)	5 (13.9)	303 (17.4)
25.0 ≤ BMI ≤ 30.0	644 (35.9)	55 (35.7)	589 (36.0)	819 (46.0)	13 (36.1)	806 (46.2)
> 30.0	429 (23.9)	33 (21.4)	396 (24.2)	651 (36.6)	18 (50.0)	633 (36.3)
FEV_1, liter [‡]	1.4 (1.1-1.9)	1.3 (1.0-1.8)	1.4 (1.1-2.0)	2.9 (2.4-3.5)	2.5 (2.0-2.8)	2.9 (2.4-3.5)
FEV_1, % predicted	50.9 (38.9-65.7)	46.0 (35.6-58.8)	51.7 (39.3-66.2)	104.8 (94.3-113.7)	93.4 (83.1-104.8)	105.0 (94.5-113.9)
FEV_1/FVC, %	52.3 (43.5-61.0)	51.1 (42.0-61.4)	52.3 (43.6-60.9)	79.5 (76.4-82.4)	76.1 (73.8-80.9)	79.5 (76.4-82.5)
TLCO [c]	4.5 (± 2.0)	4.0 (± 1.9)	4.5 (± 2.0)	7.3 (± 1.9)	6.0 (± 1.7)	7.3 (± 1.9)
TLCO, % predicted [c]	52.8 (± 21.0)	47.0 (± 20.7)	53.3 (± 21.0)	87.3 (± 15.2)	76.9 (± 15.3)	87.5 (± 15.1)

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ABI ‡	1.15 (1.1-1.2)	0.8 (0.7-0.9)	1.2 (1.1-1.2)	1.14 (1.08-1.21)	0.80 (0.72-0.84)	1.14 (1.08-1.21)
Triglyceride, mg/dl [d]	113.0 (82.0-167.0)	119.5 (87.0-184.8)	113.0 (82.0-166.0)	137.7 (98.2-193.0)	172.8 (98.7-292.5)	136.8 (98.2-191.7)
Cholesterol, mg/dl [e]	217.9 (± 44.3)	212.1 (± 44.4)	218.4 (± 44.2)	214.6 (± 43.9)	199.9 (± 48.0)	214.9 (± 43.7)
Hypertension, n (%)	993 (55.4)	110 (71.4)	883 (53.9)	797 (44.5)	24 (66.7)	773 (44.0)
Diabetes, n (%) [f]	229 (12.8)	29 (18.8)	200 (12.2)	271 (15.1)	13 (36.1)	258 (14.7)

Values expressed as mean (± SD) or median (IQR). *Abbreviations*: see Table E1a.

COSYCONET: [a]n=1673 (whole group), n=150 (ABI ≤ 0.9), n=1523 (ABI > 0.9); [b]n=1792 (whole group), n=154 (ABI ≤ 0.9), n=1638 (ABI > 0.9); [c]n=1686 (whole group), n=147 (ABI ≤ 0.9), n=1539 (ABI > 0.9); [d]n=1768 (whole group), n=152 (ABI ≤ 0.9), n=1616 (ABI > 0.9); [e]n=1772 (whole group), n=153 (ABI ≤ 0.9), n=1619 (ABI > 0.9); [f]n=1792 (whole group), n=154 (ABI ≤ 0.9), n=1638 (ABI > 0.9)

SHIP :[a]n=666 (whole group), n=21 (ABI ≤ 0.9), n=645 (ABI > 0.9); [b]n=1779 (whole group), n=36 (ABI ≤ 0.9), n=1743 (ABI > 0.9); [TLCO] n=1753 (whole group), n=36 (ABI ≤ 0.9), n=1717 (ABI > 0.9); [TLCO% predicted]n=1779 (whole group), n=36 (ABI ≤ 0.9), n=1704 (ABI > 0.9); [d]n=1792 (whole group), n=36 (ABI ≤ 0.9), n=1756 (ABI > 0.9); [e]n=1792 (whole group), n=36 (ABI ≤ 0.9), n=1756 (ABI > 0.9);

Table E1c. Baseline characteristics; COSYCONET GOLD I-IV versus age, gender and smoking status matched controls from SHIP including individuals with FEV_1 < 85% predicted (n=1347)

	COSYCONET			**Matched SHIP-2+SHIP-Trend**		
	Whole group (n = 1347)	Patients with PAD (ABI ≤ 0.9) (n = 104) **(7.7%)**	Patients without PAD (ABI > 0.9) (n = 1243)	Whole group (n = 1347)	Patients with PAD (ABI ≤ 0.9) (n = 35) **(2.6%)**	Patients without PAD (ABI > 0.9) (n = 1312)
Age, years	63.2 (± 8.7)	67.2 (± 7.9)	62.9 (± 8.6)	62.7 (± 8.9)	70.1 (± 9.3)	62.5 (± 8.8)
Male, n (%)	819 (60.8)	78 (75.0)	741 (59.6)	819 (60.8)	30 (85.7)	789 (60.1)
Smoking status						
Never smoker, n (%)	114 (8.5)	4 (3.8)	110 (8.8)	114 (8.5)	2 (5.7)	112 (8.5)
Current smoker, n	295 (21.9)	27 (26.0)	268 (21.6)	295 (21.9)	10 (28.6)	285 (21.7)

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(%)						
Former smoker, n (%)	938 (69.6)	73 (70.2)	865 (69.6)	938 (69.6)	23 (65.7)	915 (69.7)
Packyears [a]	44.0 (27.0-69.0)	45.0 (26.0-71.4)	44.0 (27.0-69.0)	18.6 (8.4; 31.5)	27.8 (21.0; 39.0)	18.0 (8.3; 31.0)
BMI, kg/m² [b]	26.5 (23.4-30.0)	26.3 (23.1-29.4)	26.5 (23.5-30.1)	28.8 (26.0-31.6)	29.9 (25.5-33.6)	28.8 (26.0-31.5)
< 18.5	48 (3.6)	3 (2.9)	45 (3.6)	1 (0.1)	-	1 (0.1)
18.5 ≤ BMI < 25.0	462 (34.3)	38 (36.5)	424 (34.1)	229 (21.9)	7 (20.0)	222 (17.0)
25.0 ≤ BMI ≤ 30.0	499 (37.0)	41 (39.4)	458 (36.8)	600 (44.7)	12 (34.3)	588 (45.0)
> 30.0	337 (25.0)	22 (21.2)	315 (25.3)	511 (38.1)	16 (45.7)	495 (37.9)
FEV_1, liter ‡	1.4 (1.1-2.0)	1.3 (1.0-1.8)	1.4 (1.1-2.0)	3.0 (2.5-3.6)	2.6 (2.1-3.1)	3.1 (2.5-3.6)
FEV_1, % predicted	49.5 (37.6-65.0)	44.8 (34.3-58.7)	50.0 (38.1-65.5)	104.1 (93.6-113.1)	93.8 (81.7-104.7)	104.2 (93.8-113.5)
FEV_1/FVC, %	52.1 (43.1-60.8)	49.5 (41.9-61.1)	52.2 (43.2-60.8)	79.2 (76.0-82.1)	76.7 (74.0-80.4)	79.3 (76.2-82.2)
TLCO [c]	4.7 (± 2.0)	4.1 (± 2.0)	4.7 (± 2.0)	7.4 (± 1.8)	6.2 (± 1.7)	7.5 (± 1.8)
TLCO, % predicted [c]	53.8 (± 21.1)	47.8 (± 21.6)	54.4 (± 21.0)	86.7 (± 15.0)	76.3 (± 15.7)	87.0 (± 14.9)

ABI [‡]	1.14 (± 0.15)	0.8 (± 0.1)	1.2 (± 0.1)	1.13 (± 0.12)	0.78 (± 0.09)	1.14 (± 0.10)
Triglyceride, mg/dl [d]	114.0 (84.0-171.0)	115.5 (83.8-187.5)	114.0 (83.8 – 169.0)	143.0 (100.0-204.4)	155.3 (93.9-285.1)	143.0 (100.0-202.6)
Cholesterol, mg/dl [e]	216.9 (± 43.9)	208.2 (± 41.5)	217.7 (± 44.1)	213.5 (± 45.2)	209.8 (± 54.2)	213.6 (± 44.6)
Hypertension, n (%)	750 (55.7)	75 (72.1)	675 (54.3)	584 (43.4)	22 (62.9)	562 (42.8)
Diabetes, n (%)	177 (13.1)	20 (19.2)	157 (12.6)	207 (15.4)	11 (31.4)	196 (14.9)

Values expressed as mean (± SD) or median (IQR). *Abbreviations*: see Table E1a.

COSYCONET: [a]n=1226 (whole group), n=99 (ABI ≤ 0.9), n=1127 (ABI > 0.9), [b]n=1346 (whole group), n=104 (ABI ≤ 0.9), n=1242 (ABI > 0.9), [c]n=1262 (whole group), n=99 (ABI ≤ 0.9), n=1797 (ABI > 0.9); [d]n=1328 (whole group), n=102 (ABI ≤ 0.9), n=1885 (ABI > 0.9); [e]n=1331 (whole group), n=103 (ABI ≤ 0.9), n=1885 (ABI > 0.9);

SHIP: [a]n=813 (whole group), n=23 (ABI ≤ 0.9), n=790 (ABI > 0.9), [b]n=1341 (whole group), n=35 (ABI ≤ 0.9), n=1306 (ABI > 0.9), [c]n=1327 (whole group), n=35 (ABI ≤ 0.9), n=1292 (ABI > 0.9), [TLCO, % predicted] n=1321 (whole group), n=35 (ABI ≤ 0.9), n=1286 (ABI > 0.9), [d]n=1346 (whole group), n=35 (ABI ≤ 0.9), n=1311 (ABI > 0.9); [e]n=1346 (whole group), n=35 (ABI ≤ 0.9), n=1311 (ABI > 0.9);

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Table E2. Baseline characteristics; SHIP individuals with obstructive lung function ($FEV_1/FVC < 0.7$)

	SHIP individuals with obstructive lung function		
	Whole Group (n = 313)	Individuals with PAD (ABI ≤ 0.9) (n = 13) **(4.2%)**	Individuals without PAD (ABI > 0.9) (n = 300)
Age, years	58.9 (± 14.3)	67.5 (± 13.6)	58.5 (± 14.2)
Male, n (%)	190 (60.7)	9 (69.3)	181 (60.3)
Smoking status			
Never smoker, n (%)	98 (31.3)	3 (23.1)	95 (31.7)
Current smoker, n (%)	97 (31.0)	5 (38.5)	92 (30.7)
Former smoker, n (%)	118 (37.7)	5 (38.5)	113 (37.7)
Packyears[a]	22.9 (12.0; 37.0)	24.3 (16.5; 34.6)	22.3 (12.0; 38.3)
BMI, kg/m^2 [b]	27.2 (± 4.4)	27.7 (± 3.6)	27.2 (± 4.5)
< 18.5	-	-	-
18.5 ≤ BMI < 25.0	101 (32.5)	4 (30.8)	97 (32.6)
25.0 ≤ BMI ≤ 30.0	127 (40.8)	4 (30.8)	123 (41.3)
> 30.0	83 (26.7)	5 (38.5)	78 (26.2)
FEV_1, liter ‡	2.5 (± 0.8)	2.1 (± 1.1)	2.6 (± 0.8)
FEV_1, % predicted	80.2 (± 17.6)	70.7 (± 19.0)	80.6 (± 17.5)
FEV_1/FVC, % ‡	64.3 (± 6.1)	61.2 (± 6.1)	64.5 (± 6.1)
TLCO [c]	7.2 (± 2.3)	5.6 (± 1.8)	7.2 (± 2.3)
TLCO % predicted	79.7 (± 17.7)	64.7 (± 14.2)	80.3 (± 17.6)
ABI ‡	1.11 (± 0.13)	0.76 (± 0.08)	1.12 (± 0.10)

Triglyceride, mg/dl [d]	153.5 (± 105.8)	220.9 (± 96.2)	150.6 (± 105.6)
Cholesterol, mg/dl [e]	210.8 (± 43.5)	206.7 (± 46.3)	211.0 (± 43.4)
Hypertension, n (%)	120 (38.3)	9 (69.2)	111 (37.0)
Diabetes, n (%)	29 (9.3)	3 (23.1)	26 (8.7)

Values expressed as mean (± SD) or median (IQR). *Abbreviations*: see Table E1a.

[a]n=166 (whole group), n=8 (ABI ≤ 0.9), n=158 (ABI > 0.9),

[b]n=311 (whole group), n=13 (ABI ≤ 0.9), n=298 (ABI > 0.9),

[c]n=297 (whole group), n=11 (ABI ≤ 0.9), n=286 (ABI > 0.9),

$TLCO\ \%\ predicted$ n=295 (whole group), n=11 (ABI ≤ 0.9), n=284 (ABI > 0.9),

[d]n=312 (whole group), n=13 (ABI ≤ 0.9), n=299 (ABI > 0.9);

[e]n=311 (whole group), n=13 (ABI ≤ 0.9), n=298 (ABI > 0.9);

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Table E3. Independent predictors of peripheral artery disease (PAD) in patients with COPD and in patients with GOLD stage 0 (combined group)

Covariates	**Exp (B)**	**95% CI for HR**		
		Lower	**Upper**	**p-value**
Age, years	1.072	1.049	1.096	**<0.001**
Gender (male), n	1.227	0.866	1.738	0.249
Smoking status, n				
Smoking status (current smoker)	6.170	2.129	17.883	**0.001**
Smoking status (former smoker)	2.705	0.959	7.631	0.060
GOLD, n				
I	0.925	0.408	2.097	0.852
II	1.056	0.598	1.864	0.851
III	1.595	0.886	2.870	0.120
IV	1.522	0.687	3.372	0.300
TLCO % predicted	0.987	0.978	0.996	**0.006**
hsCRP, mg/L *	1.127	0.996	1.276	0.057
Triglycerides, mg/dL *	1.457	1.083	1.959	**0.013**
Hypertension, n	1.696	1.202	2.394	**0.003**
Diabetes, n	1.554	1.055	2.286	**0.026**

Logistic regression – dependent variable ABI ≤ 0.90 (ABI ≤ 0.90 = 1; n=204). Never smokers as well as GOLD 0 were selected as reference category. Bold printed values represent significant results.
Abbreviations: TLCO, Transfer Factor of the Lung for Carbon Monoxide; hsCRP, high-sensitive C-reactive protein. **logtransformed due to skewed data*

Table E4. Baseline Characteristics of patients wild GOLD stage 0 stratified by peripheral artery disease (PAD)

	Whole group (n = 337)	Patients with PAD (ABI ≤ 0.9) (n = 20)	Patients without PAD (ABI > 0.9) (n = 317)
Age, years	64.8 (9.6)	67.2 (6.9)	64.6 (9.8)
Male, n (%)	172 (51.0)	10 (50.0)	162 (51.1)
Smoking status			
Never smoker, n (%)	47 (13.9)	1 (5.0)	46 (24.0)
Current smoker, n (%)	85 (25.2)	9 (45.0)	76 (24.0)
Former smoker, n (%)	205 (60.8)	10 (50.0)	195 (61.5)
Packyears	33.0 (15.3-59.4)	36.8 (13.5-57.0)	32.3 (15.5-60.0)
BMI, kg/m^2			
< 18.5	7 (2.1)	1 (5.0)	6 (1.9)
18.5 – 24.9	79 (23.4)	2 (10.0)	77 (24.3)
25.0 – 30.0	115 (34.1)	7 (35.0)	108 (34.1)
> 30.0	136 (40.4)	10 (50.0)	126 (39.7)
FEV_1, liter	2.3 (0.8)	1.9 (0.6)	2.3 (0.8)
FEV_1, % predicted	80.1 (18.6)	73.2 (13.5)	80.5 (18.8)
FEV_1/FVC, %	76.4 (72.3-80.4)	75.7 (72.8-82.1)	76.4 (72.3-80.4)
TLCO [a]	6.1 (2.0)	5.2 (1.8)	6.1 (2.0)
TLCO predicted [a]	72.4 (20.0)	66.5 (20.1)	72.8 (20.0)
mMRC dyspnea score (%) [b]			
0	47 (13.9)	-	47 (14.8)

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1	172 (51.0)	9 (45.0)	163 (51.4)
2	80 (23.7)	5 (25.0)	75 (23.7)
3	34 (10.1)	5 (25.0)	29 (9.1)
4	2 (0.6)	1 (5.0)	1 (0.3)
ABI	1.2 (1.1-1.3)	0.8 (0.7-0.8)	1.2 (1.1-1.3)
hsCRP mg/L[c]	5.0 (2.0-9.0)	10.5 (3.8-14.0)	5.0 (2.0-8.2)
Triglyceride, mg/dL[d]	134.0 (101.9-191.3)	153.0 (98.0-256.0)	134 (102.0-188.0)
Cholesterol, mg/dL [e]	214.7 (43.0)	204.4 (48.7)	215.3 (42.6)
Self-reported hypertension, n (%)	209 (62.0)	17 (85.8)	192 (60.6)
Self-reported diabetes, n (%)	70 (20.8)	8 (40.0)	62 (19.6)

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity, mMRC, modified Medical Research Council scale; ABI, ankle-brachial index; hsCRP, high-sensitive C-reactive protein.

[a] n = 317 (whole group), n=19 (ABI ≤ 0.9), n=298 (ABI > 0.9)

[b] n=355 (whole group), n=20 (ABI ≤ 0.9), n=315 (ABI > 0.9)

[c] n= 327 (whole group), n=19 (ABI ≤ 0.9), n=310 (ABI > 0.9)

[d] n = 330 (whole group), n=19 (ABI ≤ 0.9), n = 311 (ABI > 0.9)

[e] n = 329 (whole group), n=19 (ABI ≤ 0.9), n = 310 (ABI > 0.9)

Table E5. Difference in functional capacity and health status between COPD patients and patients with GOLD stage 0 with and without peripheral artery disease (PAD)

Dependent variable	**Total group**	**ABI ≤ 0.9 n = 204**	**ABI > 0.9 N = 2221**	**Unadjusted p-value**	**Adjusted mean difference (95% CI)**	**Adjusted p-value**
6MWD, meters	420 (107)	355 (109)	426 (105)	**<0.001**	-45.0 (-57.8 to -32.1)	**<0.001**
SGRQ total score, points	42.8 (20.1)	49.8 (20.2)	42.2 (20.0)	**<0.001**	4.63 (1.93 to 7.34)	**0.001**
SGRQ symptom score, points	55.8 (21.2)	58.9 (20.4)	55.4 (21.3)	**0.030**	1.27 (-1.81 to 4.34)	0.419
SGRQ activity score, points	56.6 (26.2)	67.0 (22.9)	55.6 (26.2)	**<0.001**	6.66 (3.31 to 10.0)	**<0.001**
SGRQ impact score, points	30.2 (20.9)	36.5 (22.9)	29.6 (20.6)	**<0.001**	4.57 (1.67 to 7.47)	**0.001**
CAT total score, points	18.1 (7.4)	19.7 (7.4)	17.9 (7.3)	**0.001**	1.15 (0.11 to 2.19)	**0.031**
EQ-5D utility score, points	0.82 (0.2)	0.77 (0.2)	0.82 (0.2)	**0.003**	-0.03 (-0.06 to -0.00)	**0.038**
EQ-5D VAS, points	56.9 (19.5)	50.7 (18.9)	57.4 (19.4)	**<0.001**	-4.20 (-6.95 to -1.45)	**0.003**

Values expressed as mean (SD). 6MWD, 6-minute-walk-distance; CAT, COPD Assessment Test; SGRQ, St. George's Respiratory Questionnaire; EQ-5D, EuroQol-5 Dimensions
Unadjusted p-value based on independent sample t-test; adjusted p-value based on general linear model after correction for age, gender, height, weight, TLCO % predicted, GOLD stage, smoking status, hypertension, myocardial infarction and angina pectoris for 6MWD and for age, gender, TLCO % predicted, GOLD stage, smoking status, hypertension, myocardial infarction and angina pectoris for health status.

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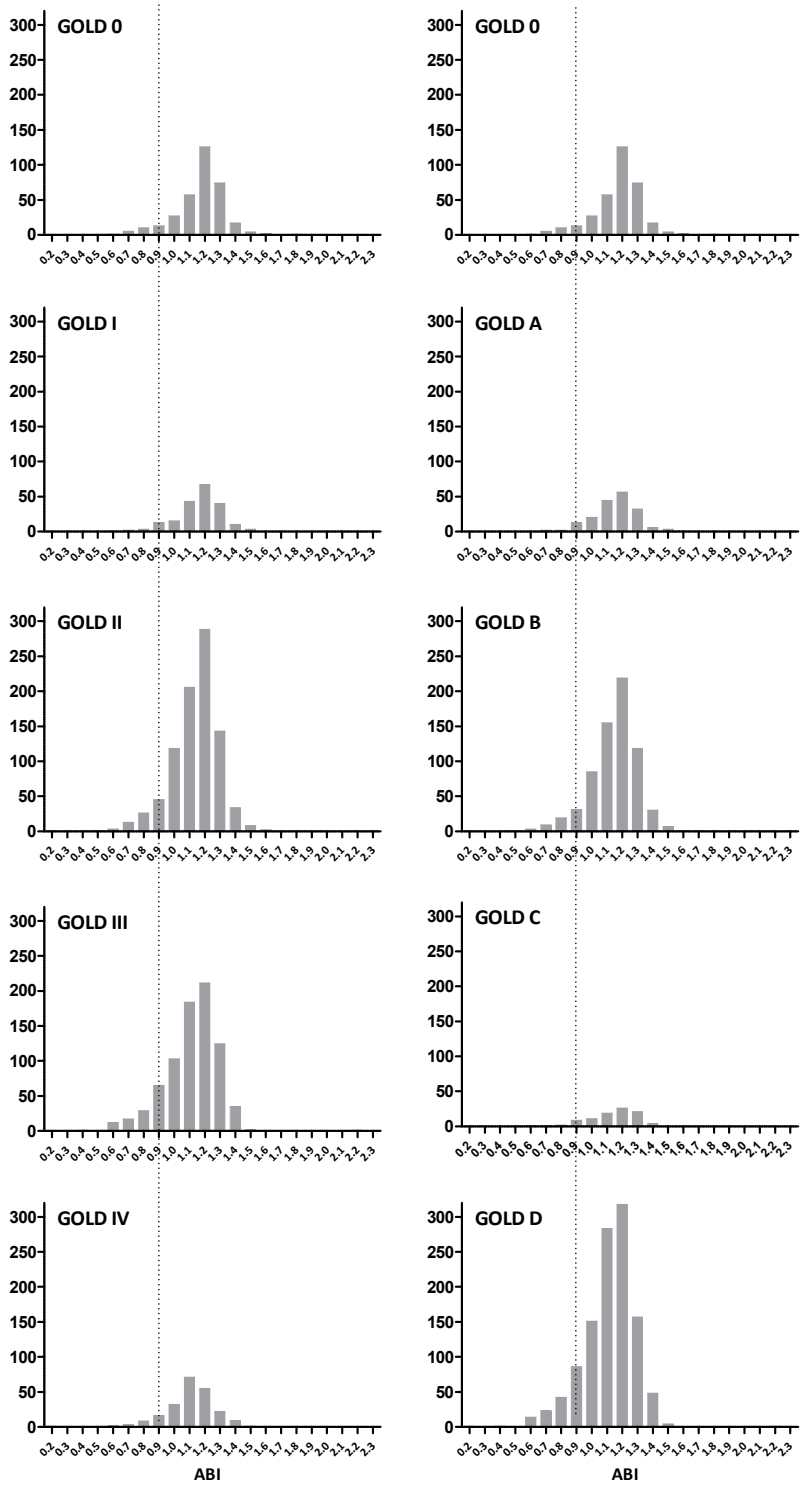

Figure E1. Frequency distribution of ankle-brachial index (ABI) values stratified by GOLD stages and GOLD groups. Y-axis represents number of patients.

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