Serum Gamma-Glutamyl Transferase Activity as a Potential Novel Cardiovascular Biomarker in COPD

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BACKGROUND: Gamma-glutamyl transferase (gamma-GT) is an enzyme present in the cell membranes, which is used as a new biomarker in prediction of inflammation, myocardial infarction, stroke, and cardiac death. The objective of this study was to investigate the relationship between serum levels of gamma-GT and cardiovascular disease in subjects with COPD and the correlation between serum gamma-GT level and degree of the limitation of air flow in COPD. METHODS: A total of 70 subjects (46.1%) with Global Initiative for Chronic Obstructive Lung Disease (GOLD) A-B and normal function of the liver and biliary tract (mean age [IQR] 59 [51.75–70] y; 77.1% men) and 82 subjects (53.9%) with GOLD C-D (mean age [IQR] 59 [56–66] y; 79.3% men) participated. Serum levels of gamma-GT and C-reactive protein were measured and compared between the 2 groups. RESULTS: The serum level of gamma-GT was found to be significantly ($P < .001$) higher in the GOLD stage C and D group than in the GOLD stage A and B group. Mean values of C-reactive protein, aspartate aminotransferase, and alanine aminotransferase did not differ significantly between the 2 groups. The prevalence of cardiovascular disease was statistically significantly higher in subjects in the GOLD stage C and D group than in the GOLD stage A and B group ($P < .001$). The serum level of gamma-GT was higher in subjects with COPD with coexisting cardiovascular disease than in those without cardiovascular disease (64 units/L [interquartile range 57–72.5] vs 17.5 units/L [interquartile range 10–25]). CONCLUSIONS: Our results demonstrate that serum levels of gamma-GT may be helpful in grading the severity of COPD as the marker of oxidative stress, and there is a strong correlation between high serum levels of gamma-GT and cardiovascular events in subjects with COPD. *Key words: gamma-glutamyl transferase; chronic obstructive pulmonary disease; cardiovascular disease.* [Respir Care 2016;61(11):1465–1471. © 2016 Daedalus Enterprises]

Introduction

Today, COPD is recognized as the third leading cause of death worldwide.[1] Patients with COPD are more likely to have preexisting cardiovascular disease and a higher risk of acute events, hospitalizations, and death from cardiovascular disease.[2,3] Because of this strong relationship, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) initiative recognizes cardiovascular disease as the most important coexisting disease with COPD and suggests that it should be routinely sought in patients with COPD but makes no recommendation regarding how this should be done.[4]

The discovery of new biomarkers that could be helpful in determination of cardiovascular risk in patients with COPD could help to develop personalized therapy for that specific phenotype. To be clinically practicable, these biomarkers should be easily measurable, noninvasive, and inexpensive. In this context, gamma-glutamyl transferase (gamma-GT) could be a promising biomarker to determine patients with COPD who have an increased risk for poor cardiovascular prognosis.[5]

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Gamma-GT is an enzyme found in the cell membranes of numerous tissues, especially the liver, bile duct, and kidneys. Gamma-GT is well known to be increased in hepatobiliary dysfunction and in alcohol abuse.[6] Previous studies have demonstrated that an increased level of gamma-GT is strongly associated with prognosis in cardiopulmonary disorders such as heart failure, acute myocardial infarction, and coronary artery disease.[7,8]

In light of all of this information, the objective of this study was to investigate the associations of serum gamma-GT level with degree of the limitation of air flow and cardiovascular events in subjects with COPD. We also examined the relationships between serum levels of gamma-GT and the pulmonary function test; Modified British Medical Research Council dyspnea scale (MMRC); history of exacerbation and hospitalization; and serum levels of C-reactive protein, alanine aminotransferase, and aspartate aminotransferase.

Methods

Study Population and Study Design

The study population consisted of subjects admitted to the Chest Diseases Clinic of Necip Fazıl State Hospital who were determined to have a confirmed diagnosis COPD based on the criteria established by the GOLD. According to the new recommendations by GOLD, FEV_1 is not an adequate criterion alone in evaluation of disease severity. Accordingly, a combined evaluation system is recommended based on spirometric classification of subjects and/or risk of exacerbation in addition to the evaluation of symptoms. A COPD assessment test or the MMRC is recommended in the GOLD guidelines to evaluate symptoms. The GOLD criteria for COPD stages are defined as follows: (1) GOLD A: GOLD 1 or 2 (mild to moderate mild limitation of air flow) and/or 0–1 exacerbation/y and no hospitalization due to exacerbation, MMRC 0–1 or COPD assessment test (CAT) score <10; (2) GOLD B: GOLD 1 or 2 (mild to moderate mild limitation of air flow) and/or 0–1 exacerbation/y or no hospitalization due to exacerbation, MMRC ≥2 or COPD assessment test score ≥10; (3) GOLD C: GOLD 3 or 4 (severe or very severe limitation of air flow) and/or ≥2 exacerbations/y or ≥1 hospitalization due to exacerbation, MMRC 0–1 or COPD assessment test score <10; (4) GOLD D: GOLD 3 or 4 (severe or very severe limitation of air flow) and/or ≥2 exacerbations/y or ≥1 hospitalization due to exacerbation, MMRC ≥2 or COPD assessment test score ≥10.[9] We divided the subjects with COPD into 2 groups: Group 1 consisted of the subjects with COPD with mild to moderate limitation of air flow (GOLD A-B), and Group 2 included the subjects with COPD with severe or very severe limitation of air flow (GOLD C-D).

QUICK LOOK

Current knowledge

COPD is a common and disabling disease and the third leading cause of global mortality after ischemic heart disease. Exacerbations of COPD accelerate pulmonary function decline, affecting the quality of life in patients with COPD, and, moreover, remain the major contributors to morbidity and mortality. Cardiovascular comorbidities are prevalent in patients with COPD and of great importance, since they have a negative impact on patients' health status.

What this paper contributes to our knowledge

There has been increasing interest in potential molecules that can be measured accurately and reproducibly to be used in COPD as biomarkers to predict clinically important outcomes. Such molecules have been successfully used in cardiovascular diseases; therefore, cardiac biomarkers have attracted attention for their potential use in COPD. The results of our study showed a strong association between high serum gamma-flutamyl transferase levels and cardiovascular events in subjects with COPD.

Patients with a history of hepatobiliary disorders, alcohol abuse, or any other acute diseases were excluded from the study. Demographics and medical history of subjects were collected utilizing a standardized questionnaire including metabolic and cardiovascular diseases, history of exacerbation and hospitalization in the last 1 y, and habits. Cardiovascular disease was identified in cases where the subjects had coronary artery disease, heart failure, or arrhythmia. Coronary artery disease was defined as having a clinical history of coronary artery disease, an abnormal outcome of stress test, including ischemia, or coronary stenosis >50% identified on a coronary angiogram. Heart failure was defined as having a functionally or structurally disturbed ventricular filling or blood ejection. Arrhythmia was defined as having an irregular heart beat, including too fast or too slow heart rates.

Smoking history was assessed using pack-years and calculated by multiplying the number of daily consumed cigarettes by years of smoking. The study was approved by the ethics committee of Sutcu Imam University, and written informed consent was received from all subjects.

Laboratory Analyses

Blood samples were collected from the antecubital vein in each subject after overnight fasting. The gamma-GT

Table 1.   Demographic and Clinical Characteristics of the Study Group

Characteristics	Group 1 GOLD A-B COPD	Group 2 GOLD C-D COPD	P
Age, median (IQR) y	59 (51.8–70)	59 (56–66)	.73
Male sex, n (%)	54 (77.1)	65 (79.3)	.86
CVD, n (%)	32 (45.7)	64 (78)	<.001
Smoking history, median (IQR) pack-years	40 (30–48)	38 (34.75–45)	.39
MMRC, median (IQR)	1 (1–2)	2 (1–3)	<.001
Exacerbation/hospitalization, median (IQR)	0 (0–1)	1 (0.75–2)	<.001
Traditional risk factors for CVD			
Diabetes mellitus, n (%)	10 (14.3)	11 (13.4)	.01
Hypertension, n (%)	25 (35.7)	55 (67.1)	<.001
BMI, median (IQR) kg/m^2	24.75 (22.5–27.45)	24.65 (22.5–28,18)	.98
Pulmonary function test results			
FVC, median (IQR) L	3.21 (2.67–3.84)	1.45 (0.65–1.87)	<.001
FVC, median (IQR) % predicted	82.15 (75–88.18)	55 (45–65)	<.001
FEV$_1$, median (IQR) L	2.35 (2.06–2.62)	0.88 (0.4–1.32)	<.001
FEV$_1$, median (IQR) % predicted	66.5 (58–81)	40 (32–47.25)	<.001
FEV$_1$/FVC, median (IQR)	64 (58.8–66.8)	57 (52–65.5)	<.001
Laboratory variables			
C-reactive protein level, median (IQR) mg/dL	9 (5.38–15)	10.5 (6.75–15)	.39
Gamma-GT level, median (IQR) units/L	28.5 (15.5–58)	63.5 (48–74.25)	<.001
AST level, median (IQR)units/L	21 (14.75–31)	18.5 (13–27)	.24
ALT level, median (IQR) units/L	23 (14–31)	20 (12–28)	.30

GOLD = Global Initiative for Chronic Obstructive Lung Disease
IQR = interquartile range
CVD = cardiovascular disease
MMRC = modified Medical Research Council dyspnea scale
BMI = body mass index
Gamma-GT = gamma-glutamyl transferase
AST = aspartate aminotransferase
ALT = alanine aminotransferase

activity was measured with the Roche-Hitachi autoanalyzer using the original kits. In addition, the relationships of the pulmonary functions of these parameters were further studied.

Statistical Analysis

Statistical analysis was performed utilizing SPSS 18.0 (SPSS, Chicago, Illinois). The continuous variables were tested for normality of their distribution and expressed as median and interquartile ranges (IQRs), whereas the categorical variables are given as frequencies and percentages. The differences between 2 groups were compared using the Mann-Whitney test, whereas multiple groups were compared using one-way analysis of variance, followed by the Tukey post hoc test for multiple comparisons for subjects with COPD. The chi-square test was used to analyze categorical variables. Multivariate logistic regression analysis was performed to evaluate the risk factors for cardiovascular disease in COPD, incorporating all factors that showed values of $P < .05$ in the univariate analyses. The correlations between continuous variables were measured through Spearman correlation coefficients (r). All

P values are 2-sided, and P values of $<.05$ were considered significant.

Results

A total of 152 subjects who met the selection criteria were enrolled in this study: 70 (46.1%) with GOLD stages A and B and 82 (53.9%) with GOLD stages C and D. The groups are described in Table 1. The groups showed no significant difference in terms of age, sex, body mass index, and total duration of smoking ($P = .73$, $P = .86$, $P = .98$, and $P = .39$, respectively). The mean FEV$_1$ level of group 2 was 0.88 (0.4–1.32) L, and the mean FVC level was found to be 1.45 (0.65–1.87) L. The levels of FEV$_1$ and FVC were found to be significantly lower in GOLD stage C and D group compared with the GOLD stage A and B group ($P < .001$) (Table 1).

The mean value of gamma-GT in COPD with coexisting group is 64 and the mean value of gamma-GT in Group 2 GOLD C and D COPD is 63.5. The level of gamma-GT was found to be significantly ($P < .001$) higher in the GOLD stage C and D group than in the GOLD stage A and B group. No statistically significant difference was
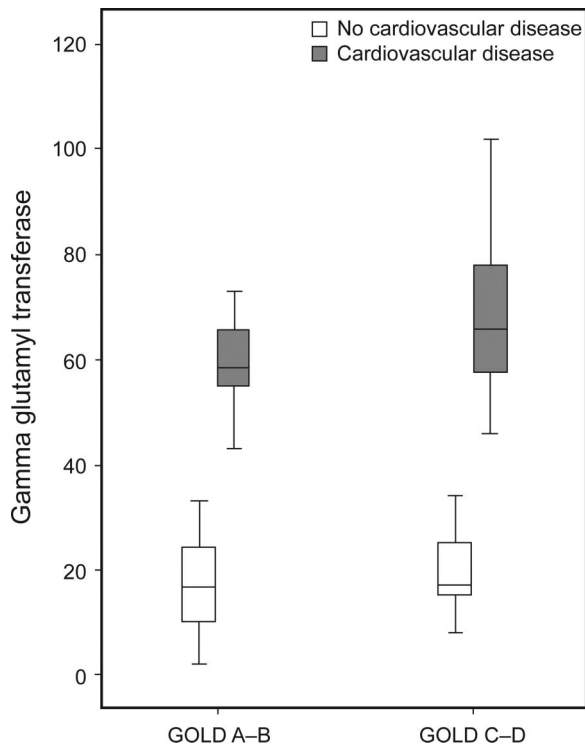
Fig. 1. Distribution of gamma-glutamyl transferase level in subjects with COPD with and without cardiovascular disease. Subjects were grouped as GOLD A-B and GOLD C-D. Center lines represent the median value, whereas the upper and lower border of each boxes represent the 3rd and 1st quartiles, respectively. Whiskers represent 5th and 95th percentile.

Fig. 2. Correlation of gamma-glutamyl transferase level and FEV_1 in subjects with COPD with mild to moderate air flow limitation (GOLD A-B). $P < .001$.

Fig. 3. Correlation of gamma-glutamyl transferase level and FEV_1 in subjects with COPD with severe to very severe air flow limitation (GOLD C-D). $P < .001$.

found in the mean values of C-reactive protein, aspartate aminotransferase, and alanine aminotransferase between the 2 groups (Table 1). The prevalence of cardiovascular disease was statistically significantly higher in subjects in the GOLD stage C and D group compared with those in the GOLD stage A and B group ($P < .001$) (Table 1). Also, the prevalence of hypertension was found to be significantly higher in the GOLD stage C and D group ($P < .001$) than in the GOLD stage A and B group. No statistically significant difference was found in the prevalence of diabetes mellitus between the 2 groups (Table 1). The serum level of gamma-GT was higher in subjects with COPD with coexisting cardiovascular disease than in those without cardiovascular disease (median 64 [IQR 57–72.5] units/L vs 17.5 [IQR 10–25] units/L) (Fig. 1). The optimal cutoff value of gamma-GT to have cardiovascular disease was measured as >42 IU/L, with 97% sensitivity and 98% specificity.

The level of gamma-GT was negatively correlated with FEV_1 in subjects in the GOLD stage A and B group ($P = .004$, r = −0.343) (Fig. 2). There was a positive correlation between the level of gamma-GT and FEV_1/FVC in subjects in GOLD stages C and D ($P = .046$, r = −0.221) (Fig. 3).
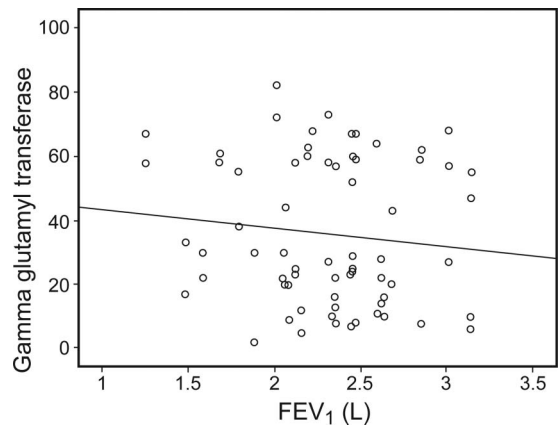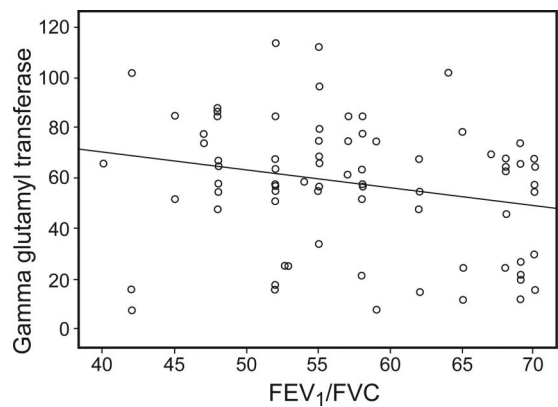
The numbers for the MMRC and exacerbation/hospitalization were found to be significantly greater in the GOLD stage C and D group ($P < .001$) compared with the GOLD stage A and B group. Gamma-GT was significantly different between MMRC groups in GOLD A-B ($P < .001$). Pairwise comparison revealed that gamma-GT for MMRC 2 was significantly higher than in the MMRC 0 ($P = .001$) and MMRC 1 groups ($P = .001$). Also, gamma-GT was significantly different between MMRC groups in GOLD C-D ($P < .001$). Pairwise comparison revealed that gamma-GT of MMRC 2 ($P = .002$), MMRC 3 ($P < .001$), and MMRC 4 were significantly higher than MMRC 1 ($P = .02$).

The potential factors for identifying cardiovascular disease were further studied using an univariate procedure. Then all parameters found to be associated with cardiovascular disease with a significance level below 0.1 were evaluated in a multiple regression analysis. The final regression model included age, sex, hypertension, and diabetes mellitus, and in conclusion, independent predictors

Table 2. Risk Factors for Cardiovascular Diseases in Subjects With COPD: Multivariate Analysis

Risk Factor	Odds Ratio	95% CI	P
Age (y)	1.00	0.96–1.05	.89
Male sex	0.32	0.1–0.99	.048
C-reactive protein (mg/dL)	1.00	0.94–1.08	.91
Body mass index (kg/m^2)	0.86	0.75–0.99	.036
Hypertension	5.63	2.31–13.74	<.001
Diabetes mellitus	0.98	0.27–3.56	.98
Exacerbation/hospitalization	3.39	1.89–6.06	<.001

of cardiovascular disease were found to be the number of exacerbations/hospitalizations and hypertension in subjects with COPD (Table 2).

Discussion

The present study yielded 2 major findings. First, the serum level of gamma-GT was found to be significantly higher in the GOLD stage C and D group compared with the GOLD stage A and B group. Second, subjects in the GOLD stage C and D group were found to show a higher prevalence of cardiovascular disease. To the best of our knowledge, this is the first study to compare the gamma-GT level by especially considering cardiovascular events and oxidative stress in subjects with COPD.

COPD is a chronic inflammatory lung disease that is known to have several systemic features, including an increased risk of cardiovascular disease. There is now considerable evidence regarding the relationship between COPD and cardiovascular disease. In a large cohort of subjects with COPD, the prevalence of coronary artery disease was significantly higher at 33.6% compared with a matched cohort without COPD, which had a 27.1% prevalence of coronary artery disease.[10] Numerous population studies have demonstrated that the limitation of air flow as specified by FEV_1 or FEV_1/FVC is a predictor of cardiovascular risk.[11] FEV_1 is also an independent predictor of cardiovascular mortality in COPD. The Lung Health Study[2] reported that fatal coronary events were increased by 28% and nonfatal coronary events by 20% for every 10% decrease in FEV_1 among subjects who had mild to moderate COPD. Similarly, in our study, the rate of cardiovascular disease was 78% in subjects with COPD with severe or very severe limitation of air flow, whereas this rate was found to be 45.7% in subjects with COPD who had mild to moderate limitation of air flow.

The exact mechanism of gamma-GT activity in cardiovascular system diseases is yet to be established. Among the most important mechanisms proposed for the relationship between gamma-GT and cardiovascular disease is the effects of gamma-GT on oxidative stress and glutathione

mechanism. In one study,[12] gamma-GT activity has been detected in the atheroma plaque of carotid and coronary arteries, and gamma-GT found in the atherosclerotic plaques has been suggested to play a role in the formation and rupture of the plaques via catalysis of the oxidation of LDL. In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, Stojakovic et al[13] examined the association of gamma-GT with all-cause and cardiovascular mortality in 2,556 subjects with and 699 subjects without angiographic evidence of coronary artery disease. The authors demonstrated that serum levels of gamma-GT predict total and cardiovascular mortality in persons with coronary artery disease independently of other cardiovascular risk factors.

The exact mechanism responsible for the increased risk of cardiovascular disease in patients with COPD is not clear; however, numerous mechanisms have been proposed, including systemic inflammation. It is well known that COPD is associated not only with pulmonary but also with systemic inflammation. It has been proposed that systemic inflammation may also play a role in the extrapulmonary features associated with COPD, such as increased risk of cardiovascular disease.[14] When increased systemic inflammation is present, patients with COPD are particularly susceptible to vascular events following an exacerbation.[15] Thus, cardiovascular risk associated with COPD may be reduced along with a decrease in the frequency of exacerbation. The serum level of C-reactive protein is positively correlated with the level of gamma-GT, suggesting that there may be an underlying association between oxidative stress and general inflammation-exacerbated COPD.[16] A strong correlation between C-reactive protein and gamma-GT was described for the first time by Lee et al.[17] In their study on a large healthy population, the authors found a correlation between C-reactive protein and increased gamma-GT, which is one of the markers of oxidative stress. Numerous subsequent studies investigated the association between C-reactive protein and gamma-GT and reported a positive correlation.[16,17] Additionally, in a study by Ulus et al[18] conducted on subjects with acute coronary syndrome, high serum level of gamma-GT level was found to be an independent predictor for major cardiovascular events over 1- and 6-month follow-up periods and a better marker than C-reactive protein, whereas a positive correlation was reported between serum levels of C-reactive protein and gamma-GT. In our study, the level of gamma-GT was found to be much higher in the GOLD stage C and D group than in the GOLD stage A and B group. In addition, serum level of gamma-GT was higher in subjects with COPD with cardiovascular disease compared with those without cardiovascular disease (64 units/L [IQR 57–72.5] units/L vs 17.5 units/L [IQR 10–25] units/L). However, we did not find any significant correlation between C-reactive protein and cardiovascular dis-

ease in subjects with COPD, which might be due to sample size, subject selection, and inclusion-exclusion criteria of the study.

Oxidative stress is another mechanism responsible for an increased risk of cardiovascular disease in subjects with COPD. COPD has been associated with both local pulmonary and systemic oxidative stress.[19] Ischemic heart disease has also been associated with systemic oxidative stress. Several traditional risk factors, such as hypertension, diabetes, hypercholesterolemia, and smoking, are associated with increased production of oxygen free radicals from the smooth muscle cells and vascular endothelium. Reactive oxygen species have been shown to cause atherosclerosis through numerous mechanisms.[14]

In systemic inflammation, the circulating oxidants increase, whereas the antioxidant capacity decreases. Antioxidants are found in the systemic circulation (ascorbate and glutathione) and the epithelial lining fluid (glutathione, ceruloplasmin, ascorbic acid, and mucin). Xenobiotic-metabolizing enzymes support the body to protect against oxidative stress. Glutathione S-transferase is among these enzymes. Gamma-GT, which has an important role in antioxidant defense, is an enzyme responsible for the extracellular catabolism of glutathione, and the level of gamma-GT is a commonly used diagnostic test for liver diseases in clinical practice.[20] In general, an abnormally elevated gamma-GT level is considered as a marker of alcohol abuse and liver damage. However, these factors cannot explain the relationships of gamma-GT with pulmonary function and COPD, because FEV_1 and FVC are clearly decreased, and the prevalence of COPD increased the subjects who had normal alanine aminotransferase levels and irregular alcohol consumption habits.[21] The mechanism or mechanisms that link serum gamma-GT, which is a type of liver enzyme from a conventional viewpoint, to pulmonary function and COPD are yet to be clarified. One possible explanation is that the serum level of gamma-GT is associated with the pulmonary function as an early and sensitive biomarker of oxidative stress in humans.[22] Also, chronic systemic oxidative stress is the primary pathophysiological mechanism for COPD. Because of its role in the degradation of antioxidant glutathione, gamma-GT is recognized as a biomarker of oxidative stress.[23] In the present study, the serum level of gamma-GT was significantly higher in subjects with COPD with severe and very severe limitation of air flow than in those with mild to moderate limitation of air flow. In addition, there was a negative correlation between FEV_1 and gamma-GT level of subjects with COPD with mild to moderate limitation of air flow and between FEV_1/FVC of subjects with COPD with severe to very severe limitation of air flow.

Among the traditional risk factors of the development of cardiovascular disease, smoking is the causative factor in the majority of individuals with COPD and is an effector

in the development of coronary artery disease. Because COPD and smoking are inextricably linked, it is difficult to show that the increased risk of cardiovascular disease is due to COPD alone in subjects with COPD. It is also very difficult to correct for cigarette smoke exposure statistically in studies. So, smoking seems likely to play an important role in the development of cardiovascular disease in COPD.[14] In our study, there was no significant difference between the groups in terms of total duration of smoking.

Other traditional cardiovascular risk factors are also common in COPD. In the Atherosclerosis Risk in Communities Study, investigators have reported an increased prevalence of hypertension and diabetes in subjects with COPD compared with healthy individuals, which was even more evident in GOLD stages C and D.[24] Consistently, in our study, also the prevalence of hypertension was higher in GOLD stages C and D, but no significant difference was found between the groups in terms of diabetes mellitus.

There are some limitations of our study. This is a cross-sectional study, and the potential causal relationship between COPD and high serum gamma-GT levels cannot be concluded. However, the findings of this study have some important implications for the identification of cardiovascular outcomes in COPD stages and for the management and prognosis of these patients.

The results of our study indicate that gamma-GT may be helpful in grading the severity of COPD. The related increase in this marker may represent a possible pathophysiological mechanism underlying the increased cardiovascular morbidity of patients with COPD and detecting earlier the cases at a higher risk for developing the associated cardiovascular complications. Further prospective studies with a greater number of subjects are warranted to better clarify this issue.

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