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The Role of Gamma-Glutamyl Transferase in Acute Exacerbation of Chronic Obstructive Pulmonary Disease Severity: A Cross-Sectional Study

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ABSTRACT

Introduction: Gamma-glutamyl transferase (GGT) is a liver enzyme that is involved in inflammation and oxidative stress. It has been hypothesized that elevated GGT may occur secondary to oxidative stress in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and can be used as an indicator of inflammation in these patients. The present study aimed to determine the relationship between serum GGT and arterial blood gas (ABGs) on the one hand and COPD severity in AECOPD patients on the other hand.

Methods: Patients with AECOPD were evaluated for disease severity based on the global initiative for chronic obstructive lung disease (GOLD), Modified British Medical Research Council (mMRC), COPD Assessment Test (CAT), and spirometry assessment upon admission at the hospital. Moreover, the GGT level in patients was analyzed based on the severity of the disease. The data were analyzed using SPSS software (version 25.0) by proper statistical tests. The significance level was $P<0.05$.

Results: The mean±SD of the CAT score in the patients was obtained at 19.6± 4.6. According to the mMRC scale, most patients were grade 2 (n=29, 52.7%) and grade 1 (n=17, 30.9%), respectively. In addition, according to GOLD criteria, most patients (n=34, 61.8%) had moderate and severe (n=16, 29.1%) disease, respectively. The median (IQR) GGT levels in patients with mMRC 0-1 were 28.7 (12.98) IU/L, and those with mMRC 2-4 were 21 (33) IU/L (P=0.770). Additionally, the median (IQR) of GGT levels in patients in GOLD A-B were obtained at 26(18) IU/L, and in patients in GOLD C-D were reported as 18 (23.80) IU/L (P=0.222). The results showed a significant positive relationship between GGT level and AECOPD severity (r=+0.277, P=0.04). Moreover, a significant negative relationship was observed between GGT level and forced vital capacity (FVC) (r=-0.268, P=0.04). According to the Pearson correlation test, There was no significant correlation between GGT level with arterial HCO3 (P=0.123), PCO2 (P=0.511), PO2 (P=0.888), FEV1 (P=0.356), and FEV1/FVC (P=0.975).

Conclusion: In conclusion, while a significant positive relationship was found between GGT levels and AECOPD severity, the study suggests that serum GGT levels may not have clinical efficacy in differentiating between patients with varying intensities of AECOPD periods. Further research with larger sample sizes and consideration of additional factors is warranted to confirm these findings.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic inflammatory condition featured by chronic and progressive airflow restriction and multiple significant clinical manifestations that may lead to reduced functional capacity and health status (1). Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is usually described as an acute deterioration of respiratory symptoms in patients with underlying COPD, which may lead to additional treatment (2). Periods of acute exacerbation during the typical course of COPD are associated with a significant mortality rate and impose a heavy economic and social burden on health systems (1, 3). It is estimated that 20-40% of COPD patients experience moderate exacerbations at least once a year, while up to 15% of patients suffer from more than one exacerbation (4). Patients with AECOPD showed the fastest decline in lung functional capacity (5), poorer quality of life (6), an increased risk for subsequent exacerbations, heart attacks, cerebrovascular accidents, and higher mortality (7-10). Today, the assessment of the AECOPD severity methods are not clearly reliable; until recently, the severity of AECOPD has been detected using spirometry as a system of limitation rating the degree of airflow (11). However, it has been recognized that forced expiratory volume in 1s (FEV1) alone is an unreliable marker for the severity of the disease (12).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has presented a multidimensional assessment system for detecting symptoms of this disease, which includes the modified Medical Research Council (mMRC) score or the chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) (13). Inflammation is the most important factor in the pathogenesis of COPD. In COPD, inflammation occurs in the airways, blood vessels, and lung parenchyma. Moreover, it has systemic effects in addition to local effects (14, 15). Serum gamma-glutamyl transferase (GGT) is one of the biomarkers investigated in recent decades for its role in oxidative stress and inflammation (16). Several studies have been performed on the relationship between GGT and COPD. However, their results are not consistent (17-20). A few studies showed that serum GGT may be useful in grading the severity of AECOPD (18). However, in some other studies, there was no association between the disease severity and serum GGT level (20).

Against this backdrop, this study seeks to elucidate the connection between serum GGT levels and COPD severity. By addressing the inconsistencies in existing literature, we aim to contribute valuable insights into the potential role of GGT as a biomarker in assessing the severity of COPD.

Materials and Methods

Study Design

The present cross-sectional study comprised 55 patients with AECOPD who were referred to the emergency departments of Imam Reza and Ghaem Hospitals of Mashhad, Iran from March 2020 to September 2021. The inclusion criteria included the existence of GOLD criteria for AECOPD (sudden increase in breathlessness, exacerbation of cough and sputum, and sputum change), the possibility of hospitalization, willingness to participate in the study, and all included patients were in moderate AECOPD based on GOLD criteria for COPD (as the patients referred to the hospital emergency department). However, those with a history of liver disease (e.g. liver cirrhosis, pancreatic and gallbladder disease), alcohol consumption, phenobarbital and phenytoin intake, and liver enzyme disorders were excluded from the study. The study was approved by the Institutional Ethics Committee of Mashhad University School of Medicine (approval number: IR.MUMS.MEDICAL.REC.1398.246, approval date: 18-06-2019) and all participants gave written informed consent.

According to the correlational studies sample size formula, the sample size was estimated due to Bozkus et al (18) study using the correlation coefficient between GGT and FEV1, considering r= 0.36, α=0.05, and β= 0.2 as 58 patients; however, only 55 patients were included from March 2020 to September 2021 to our study.

Data Information

The collected data were included: A) demographic characteristics (i.e sex, age, and smoking status); B) laboratory data which were investigated based on the 5 cc of blood samples (i.e levels of gamma Glutamyl transferase (GGT), CRP, aspartate aminotransferase (AST), alanine transaminase (ALT) levels, and arterial blood gases (ABG)); C) clinical manifestations (i.e COPD severity, dyspnea, comorbidities, forced expiratory volume in 1s [FEV1] and FVC and FEV1/FVC ratio, physical examination, , body mass index (BMI)); these data were collected from the participants after obtaining informed written consent from them. Dyspnea during COPD was assessed using the mMRC (21). In addition to these assessments, serum GGT levels were assessed based on GOLD (22), mMRC scale (21), CAT (23), and spirometry test. The severity of the disease was assessed retrospectively based on CAT, mMRC, and spirometry parameters according to the patients' previous examination which was held at most three months before the exacerbation.

1ry outcome is considered to assess the relationship between serum GGT level and the severity of COPD, and the 2ry outcomes are considered to assess the relationship between serum GGT level and spirometry findings in patients with COPD during the moderate acute exacerbation and to assess the relationship between serum GGT level during the AECOPD and ABGs findings in patients with COPD during the moderate acute exacerbation.

Based on GOLD criteria (22), patients' AECOPD ranged from A to D which corresponded to mild, moderate, severe, and very severe. According to mMRC classification (21), patients were required to determine the extent of their breathlessness by choosing one of the options where 0= breathless only after a heavy exercise and 4=too breathless to leave the house. The CAT questionnaire (23) consisted of eight items including such symptoms as chest tightness, breathlessness, cough, sputum, activity limitation, confidence, sleep, and energy, on a scale of 0-5. The total score for this questionnaire ranged between 0 (no impact) and 40 (the worst impact).

Statistical Analysis

Variables were described according to their type (quantitative or qualitative) using descriptive indexes (mean, standard deviation, frequency, and frequency percentage). The variables' normality in the groups was determined through the Shapiro-Wilk test to analyze the quantitative variables. Afterward, a two-group independent t-test was used to compare the means between groups in the case of normal variables (or Mann-Whitney U test as the non-parametric equivalent). Moreover, the Chi-square test or Fisher's exact test (if required) was adopted to compare the distribution of qualitative variables in the groups. The Pearson correlation was used to present the relationship between variables. The data were analyzed using SPSS software (version 25.0). The significance level was $P<0.05$.

Results

The sample size comprised 55 patients with acute exacerbation of COPD. The mean±SD CAT score in the patients was estimated at 19.6±4.6. According to mMRC scale, most patients were grade 2 (n=29, 52.7%). Also, according to GOLD criteria, the majority of patients had moderate (n=34, 61.8%) and severe (n=16, 29.1%) disease, respectively. The severity of the disease is shown in Table 1 based on the various criteria (table 1).

Demographics

Demographic characteristics of patients according to disease severity in relation to the mMRC are presented in Table 2. The mean age of patients with grades 2-4 mMRC was significantly higher than patients with grades 0-1 mMRC (64.4±8.3 and 59.4±5.9 years, respectively, P=0.036). Moreover, the frequency of ischemic heart disease and hypertension in patients with 2-4 mMRC was significantly higher than that in patients with 0-1 mMRC (P=0.001, 0.027, respectively). In the assessment of disease severity in relation to mMRC, no significant difference was observed between body mass index, sex, and smoking status (table 2).

Table 1. COPD severity based on various criteria used in the present study.

		Frequency (N) (n=55)	Percent (%)
CAT [Mean ± Standard deviation(min-max)]		19.6± 4.6 (4-32)	
mMRC grades	**0**	5	9.1
	1	17	30.9
	2	29	52.7
	3	4	7.3
	4	0	0
GOLD	**Mild (A)**	2	3.6
	Moderate (B)	34	61.8
	Server (C)	16	29.1
	Very severe (D)	3	5.5

Table 2. COPD severity and the studied parameters according to mMRC.

Variable	mMRC 0-1 (n=22)	mMRC 2-4 (n=33)	P-value for normality*	P-value
	Mean ± Standard deviation (95%CI)	Mean ± Standard deviation (95%CI)		
Age, y	59.4 ± 5.9 (57.14 to 61.66)	64.4 ± 8.3 (61.8 to 67)	0.787	0.036
BMI, kg/m2	25.6± 1.8 (26.17 to 25.03)	25.6± 1.5 (25.99 to 25.21)	0.039	0.932
CRP (mg/dL)	12.7±1.6 (12.93 to 12.47)	14.1±1.7 (14.3 to 13.9)	0.001	0.753
PH	7.3± 0.02 (7.296 to 7.304)	7.3± 0.07 (7.288 to 7.312)	0.002	0.158
HCO3 (mEq/L)	27.3± 1.5 (27.26 to 27.34)	28.1± 4.3 (28.02 to 28.18)	<0.001	0.455
PaCo2, mmHg	45.5	46.4	0.119	0.134
O2 saturation, %	90.2±2.3 (90.48 to 89.92)	90.5±2.2 (90.72 to 90.28)	0.255	0.716
AST, U/l	17.1±1.4 (16.86 to 17.34)	19.3±6.3 (18.42 to 20.18)	0.201	0.212
ALT, U/l	15.7±6.6 (14.24 to 17.16)	19± 7.8 (17.59 to 20.41)	0.028	0.150
FEV1 (%) [Median, (IQR)]	66 (11)	52 (18)	0.944	0.015
FVC (%)	70.7±7.6 (64.67 to 76.73)	60.5±10.5 (53.7 to 67.3)	0.326	0.0001
FEV1/FVC [Median, (IQR)]	68 (6)	63 (13)	0.055	0.001
	Frequency (%)	**Frequency (%)**		
Sex Male	16 (72.7)	19 (57.6)	<0.001	
female	6 (27.3)	14 (42.4)		0.252
Smoking status	15 (71.4)	19 (59.4)	<0.001	0.371
Ischemic heart disease	0	13 (39.4)	<0.001	0.001
Hypertension	6 (27.3)	19 (57.6)	<0.001	0.027
Dyspnea	19 (86.4)	30 (90.9)	<0.001	0.456

Abbreviation : AST : Aspartate transaminase, **ALT**: Alanine transaminase, **FEV1**: Forced expiratory volume at 1 second, **FVC :** Forced vital capacity

* Shapiro-Wilk Test

No significant relationship was found between dyspnea and ABG parameters (HCO3, PaCo2, PH) in terms of disease severity according to mMRC. Also, no significant association was found between O2 saturation, AST, and ALT in terms of severity according to mMRC classification.

Disease severity based on mMRC

The comparison of spirometry parameters in terms of disease severity (according to mMRC classification) revealed that the median level of FEV1 in patients with grades 2-4 was significantly lower, compared to patients with grades 1-0 (52% and 66%, respectively, P=0.015). Moreover, the mean±SD FVC level in patients with grades 2-4 was significantly lower compared to patients with grades 0-1 mMRC (60.5±10.5% and 70.7±7.6%, respectively, P=0.0001). Mean FEV1/FVC was significantly lower in patients with grades 2-4 than in patients with grades 0-1 (63% and 68%, respectively, P=0.001) (Table 2).

The independent-sample t-test result indicated that GGT levels in patients with grades 0-1 were not significantly different compared to those with grades 2-4. Moreover, median (IQR) GGT levels in these patients were 28.7 (12.98) IU/L and 21 (33) IU/L, respectively. The result of the Mann-Whitney test with p=0.770 was not statistically significant (Figure 1).

Disease severity based on GOLD

No significant difference was observed between the two groups as regards demographic features in terms of disease severity, according to GOLD criteria (P-values for age:0.369, BMI:0.217, sex:0.520, smoking status:0.741, ischemic heart disease:0.314, and hypertention:0.836) (Table 3).

In terms of the severity of the disease, a comparison of CRP levels in relation to GOLD did not present a significant difference (P=0.343) (Table 3).

Based on the results, the level of arterial PaCO2 in patients with GOLD A-B severity (45 mmHg) was significantly lower, compared to patients with GOLD C-D severity (48 mmHg) (P=0.005); however, PH (mean [IQR]: 7.4 [0.04] v.s. 7.3 [0.05]) and HCO3 (mean [IQR]: 27 [2] v.s. 28 [2]) were not significantly different in the two groups (P=0.070 and 0.093, respectively).

In addition, the comparison of O2 saturation and characteristics of patients didn't show a significant relationship in terms of disease severity (according to GOLD) (P=0.060).

A comparison of spirometry parameters in patients in terms of disease severity (according to GOLD criteria) showed that the mean±SD FEV1 level of patients with C-D severity was significantly lower, compared to patients with A-B severity (40.8±9.5% and 64.4±7.4%, respectively, P=0.0001). Furthermore, the mean±SD FVC level in patients with GOLD C-D severity was significantly lower than that in patients with GOLD A-B severity (54.4±8.5 and 69.9±7.2 percent, respectively, P=0.0001). Furthermore, in patients with GOLD C-D severity, the mean±SD FEV1/FVC was significantly lower compared to patients with GOLD A-B severity (54.4±12.9% and 68±5.7%, respectively, P=0.001) (Table 3).

A comparison of GGT levels in patients with GOLD A-B and those with GOLD C-D revealed no statistically significant difference. The median (IQR) of GGT levels in these patients were obtained at 26(18) IU/L and 18 (23.80) IU/L, respectively, which were not significant with the Mann-Whitney test and P=0.222 (Figure 2).

Correlation with GGT

The correlation between GGT level, ABG, and disease severity was also investigated according to CAT. The results showed that there was a positive correlation among GGT levels and CAT score (r=0.277, P=0.04). Moreover, a negative correlation was observed between GGT level and FVC (r=0.268, P=0.048). Eventually, there was no significant association between GGT level with HCO3 (P=0.123), PCO2 (P=0.511), PO2 (P=0.888), FEV1 (P=0.356), and FEV1/FVC (P=0.975) (Table 4).

Table 3. COPD severity and the studied parameters according to GOLD.

Variable	GOLD A-B (n=36)	GOLD C-D (n=19)	P-value for normality*	P-value
	Mean ± Standard deviation	Mean ± Standard deviation		
Age, y [95%CI]	63.9±7.7 (63.47 to 64.33)	63.7±9.2 (62.99 to 64.41)	0.787	0.369
BMI, kg/m2 [95%CI]	25.6± 1.7 (25.15 to 26.04)	26.1± 1.2 (25.88 to 26.32)	0.039	0.217
CRP (mg/dL) [Median, (IQR)]	10(16)	9 (12)	0.001	0.343
PH [Median, (IQR)]	7.4 (0.04)	7.3 (0.05)	0.002	0.079
HCO3(mEq/L)) [Median, (IQR)]	27 (2)	28 (2)	<0.001	0.093
PaCo2, mmHg	45 (5)	48 (3)	0.119	0.005
O2 saturation, % [95%CI]	90.9±2.2 (90.33 to 91.47)	89.7±2.2 (88.92 to 90.48)	0.255	0.060
AST, U/l [95%CI]	18.8± 5.9 (20.24 to 17.36)	18.7± 8.5 (21.55 to 15.85)	0.201	0.928
ALT, U/l [95%CI]	16 (10)	18 (10)	0.028	0.901
FEV1 (%) [95%CI]	64.4 ± 7.4 (59.81 to 68.99)	40.8± 9.5 (32.69 to 48.91)	0.944	0.0001
FVC (%) [95%CI]	69.9±7.2 (65.44 to 74.36)	54.4±8.5 (47.15 to 61.65)	0.326	0.0001
FEV1/FVC [95%CI]	68±5.7 (64.47 to 71.53)	54.4± 12.9 (43.39 to 65.41)	0.055	0.0001
	Frequency (%)	Frequency (%)		
Sex			<0.001	
Male	24 (66.7)	11 (57.9)		0.520
female	12 (33.3)	8 (42.1)		
Smoking status	23 (65.7)	11 (61.1)	<0.001	0.741
Ischemic heart disease	7 (19.4)	6 (31.6)	<0.001	0.314
Hypertension	16 (44.4)	9 (47.4)	<0.001	0.836
Dyspnea	31 (86.1)	18 (94.7)	<0.001	0.314

Abbreviation : **AST:** Aspartate transaminase, **ALT:** Alanine transaminase, **FEV1:** Forced expiratory volume at 1 second), **FVC :** forced vital capacity).

* Shapiro-Wilk Test

Table 4. Correlation of GGT level with different variables in the present study.

Variable	P-value for normality*	r	P-value**
CAT	0.035	+0.277	0.04
PaO2, mmHg	0.255	+0.019	0.888
PaCo2, mmHg	0.119	-0.090	0.511
HCO3, mEq/L	<0.001	0.223	0.123
FEV1	0.944	-0.127	0.356
FVC	0.326	-0.268	0.048
FEV1/FVC	0.055	+0.004	0.975

** Pearson test

* Shapiro-Wilk Test

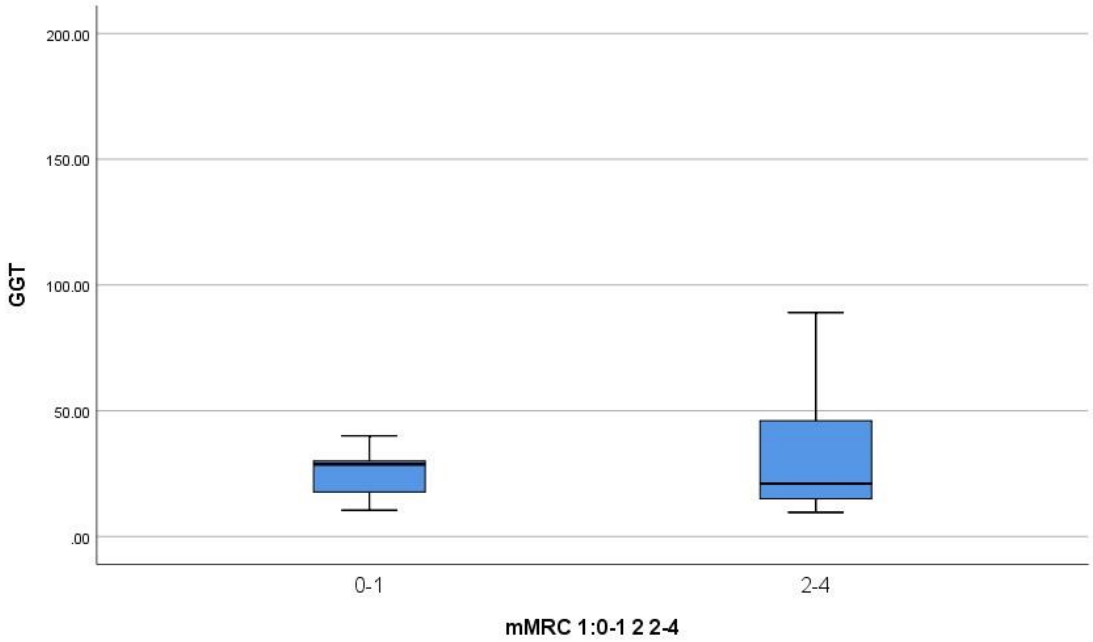

Figure 1: Median (IQR) GGT levels (IU/L) in terms of AECOPD severity according to mMRC scale.

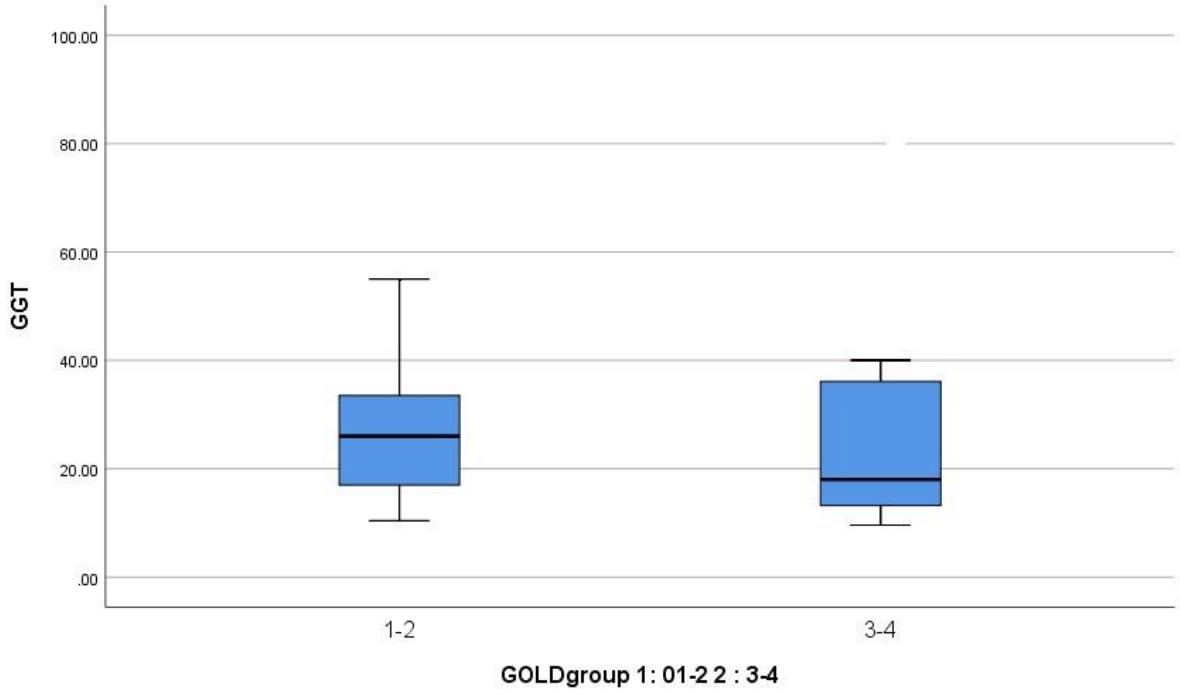

Figure 2. Median (IQR) GGT levels (IU/L) in terms of AECOPD severity according to GOLD.

Discussion

Based on the obtained results, serum GGT levels in patients with acute/moderate exacerbation of mild/moderate COPD were not significantly different from those in patients with severe/very severe COPD. Moreover, no correlation was observed among GGT level, disease severity, and arterial blood gases according to CAT criteria and spirometry parameters.

Serum GGT is one of the biomarkers that has been considered in studies on oxidative stress, especially in patients with COPD in recent decades (16). Several studies have been performed on the relationship between GGT and COPD with conflicting results (17-20). In this study, no association was found between GGT level and the severity of AECOPD according to the mMRC scale and GOLD criteria. However, a significant negative relationship was reported between GGT serum levels and FVC, indicating an increase in serum levels in patients with more severe exacerbation. However, it should be noted that previous studies aimed to compare the level of GGT in people with COPD to that in healthy individuals and evaluate the diagnostic value of GGT in distinguishing the steady state of COPD from acute exacerbation of COPD and not differentiating intensities of the exacerbation of this disease.

The studies by Biljak et al. (2013) (17) and Cepelak et al. (2006) (19) investigated the role of serum GGT evaluation in determining the oxidative capacity as well as the level of inflammation in patients with stable COPD. The findings of both studies suggested that the serum GGT levels were significantly higher in patients than in healthy individuals. Biljak et al. presented that the concentration of CRP and activity of GGT were increased in COPD patients, as compared to healthy controls ($p < 0.05$). Additionally, found a significant weak positive correlation between CRP and GGT in COPD patients ($r = 0.202$, $p = 0.0371$). There were no differences in GGT activity ($p = 0.606$) or CRP concentration ($p = 0.573$) between groups of patients when subdivided according to the severity of the COPD (17). Cepelak et al showed a higher GGT activity in 10% of ex-smokers and 5% of COPD patients as compared with nonsmokers and smokers; however, there were no significant differences in GGT catalytic activity between non-smokers, smokers, ex-smokers, and COPD patients ($P>0.05$) (19). In one of the few studies to evaluate the serum level of GGT in terms of COPD severity (based on GOLD criteria), Bozkus et al. (2016) showed that serum GGT levels in patients with severe/very severe COPD were significantly higher than those in patients with mild/moderate COPD. Moreover, they observed a significant negative relationship between serum GGT level and spirometry criteria (18). In their reports, GGT was significantly different between MMRC groups in GOLD C-D ($P < 0.001$). Additionally, revealed that GGT of MMRC 2 ($P = 0.002$), MMRC 3 ($P < 0.001$), and MMRC 4 were significantly higher than MMRC 1 ($P = 0.02$). Moreover, the level of GGT was weak negatively correlated with FEV1 in subjects in the GOLD stage A and B group ($P = 0.004$, $r = -0.343$); however, there was a moderate positive correlation between the level of GGT and FEV1/FVC in subjects in GOLD stages C and D ($P = 0.046$, $r = -0.221$) (18). Biljak et al. reported no significant association between COPD severity and serum GGT level (17) which confirmed the findings of the present study regarding the lack of differences in GGT levels in terms of the severity of acute exacerbation of COPD (based on GOLD and mMRC scale). Despite differences between the results of various studies on the relationship between GGT and disease activity, it seems that the increased level of this serum marker can be a manifestation of increased oxidative status and disruption of antioxidant processes in patients with COPD (24). The differences between studies could be due to several factors including differences in the studied population's age, race, COPD severity, COPD treatment, and other underlying disease

The results also revealed that patients with higher disease intensities were older and had underlying diseases (ischemic heart disease and hypertension). These findings confirmed those reported by Jones et al. (2014) indicating that patients with higher severity (based on mMRC classification) were older and had more underlying diseases (25). However, other studies including those carried out by Arkhipov et al. (2017) and

Augusti et al. (2013) did not find a relationship between underlying diseases and age with disease severity after examining the characteristics of patients, based on GOLD criteria (12, 26). These differences between studies could be due to the studied population's underlying diseases, COPD treatment, and socio-demographic condition.

Moreover, regarding the relationship between spirometry parameters in patients and disease severity (following mMRC criteria), the results indicated that FEV1, FVC, and FEV1 / FVC levels were significantly lower in patients with higher disease severity. In fact, the spirometry parameters are including vital capacity (VC), FVC, and FEV at timed intervals of 0.5, 1.0 (FEV1), 2.0, and 3.0 seconds, forced expiratory flow 25–75% (FEF 25–75) and maximal voluntary ventilation (MVV); on the other hand, mMRC subjectively classifies the severity of dyspnea in patients with COPD; therefore, it can be stated that the mentioned objective parameters (FEV1, FVC, and FEV1 / FVC) were significantly lower in patients higher disease severity while assessed subjectively. Consistently, Jones et al. (2013) reported that all spirometry parameters of patients with COPD were negatively correlated with the intensity of the disease (25). The same result was also reported by Haughney, suggesting that FEV1 levels were significantly lower in patients with higher intensity of COPD (27).

The present study could be known as one of the few studies conducted in order to identify a valid marker for differentiating various severities of acute exacerbation of COPD, which can be called the most important strong point of our study. On the other hand, the lack of basic evaluation of GGT (during the initial diagnosis of COPD), a small sample size, and a cross-sectional design of the study- which lead to a lack of follow-up of patients to investigate the predictive role of GGT in determining the outcomes of the acute exacerbation, length of stay in the hospital, exacerbation frequencies in different months of the year- are among the limitations of the present study.

Conclusion

Based on the obtained results, in patients with acute exacerbation of mild to moderate COPD, serum GGT levels were not significantly different from those in severe /very severe patients. Furthermore, there was a significant relationship between GGT level, arterial blood gas level, and AECOPD severity based on the CAT. Eventually, results indicated that (based on GOLD and mMRC criteria) GGT cannot be used to differentiate patients with different intensities of COPD.

Abbreviations

GGT: Gamma-glutamyl transferase , **AECOPD:** Acute exacerbation of chronic obstructive pulmonary disease, **GOLD:** global initiative for chronic obstructive lung disease, **mMRC:** Modified British Medical Research Council, **CAT:** COPD Assessment Test , **FVC:** Forced vital capacity, **COPD:** Chronic obstructive pulmonary disease , **FEV1:** Forced expiratory volume in the first second, **ABG:** Arterial blood gases, **BMI:** Body mass index (BMI), **AST:** Aspartate transaminase, **ALT:** Alanine transaminase, **IQR:** Interquartile range, **CRP:** C-reactive protein.

Ethics approval and consent to participate

The protocol for conducting the present study was approved by the ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1398.24; 18-06-2019). All experiments were performed in accordance with relevant guidelines and regulations, and written informed consent was obtained from all of the participants.

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