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Serum immunoglobulin levels in group E of chronic obstructive pulmonary disease: insights for clinical management and immunoglobulin therapy strategies

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Abstract

Objective The study aimed to characterize serum immunoglobulin (Ig) concentrations and their relationship with clinical and paraclinical features in patients with COPD group E in the stable stage. Additionally, the study focused on evaluating the relationship between serum Ig levels and the risk of exacerbations over the next 12 months, thereby clarifying the role of serum Ig deficiency in affecting the future risk for these patients.

Methods A prospective observational study assessed IgG, IgA, IgM, and IgE levels in 67 COPD patients and 30 healthy controls at Military Hospital 103 from October 2017 to August 2020. Primary outcomes included Ig isotype levels in COPD patients, with secondary outcomes exploring differences compared to controls and associations with clinical variables.

Results COPD patients showed significantly lower IgG concentrations and higher IgA levels than controls. IgM and IgE levels did not differ significantly. Subgroup analysis revealed notable decreases in IgG1 and IgG3 concentrations, with 10.4% of patients exhibiting reduced IgG levels and 0.3% diagnosed with common variable immunodeficiency. No significant associations were found between Ig levels and exacerbation risk or clinical variables.

Conclusions Serum IgG and IgM concentrations were significantly reduced in COPD patients compared to normal individuals, with IgG1 and IgG3 concentrations notably low. Serum IgA levels were significantly higher in COPD patients compared with normal controls. However, no significant association was found between Ig concentrations, particularly serum IgG deficiency and its subclasses, with the frequency and risk of exacerbations during 12 months of longitudinal follow-up. Caution is warranted in the use of immunoglobulin therapy in the treatment of COPD patients.

Trial registration An independent ethics committee approved the study (Ethics Committee of Military Hospital 103 (No. 57/2014/VMMU-IRB), which was performed in accordance with the Declaration of Helsinki, Guidelines for Good Clinical Practice.

Keywords COPD, Immunoglobulin defficiency, CVID, Immunoglobulin therapy, IVIG

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Background

COPD is a global health burden characterized by significant morbidity, mortality, and socioeconomic implications [1]. Recurrent respiratory infections are the primary cause of acute exacerbations of COPD (AECOPD) and have a detrimental impact on disease prognosis. Reduced serum Ig levels may contribute to a higher risk of respiratory infections and future exacerbations [2]. Studies have demonstrated an association between reduced serum IgA and IgG levels and increased exacerbation risk in COPD patients [3, 4]. Additionally, frequent COPD exacerbations may indicate an underlying antibody deficiency syndrome, with Ig replacement therapy shown to be effective in reducing exacerbation incidence [5]. Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by recurrent respiratory tract infections, including otitis media, sinusitis, bronchitis, and pneumonia [6]. Defective adaptive immunity and low serum immunoglobulin levels play a crucial role in the susceptibility of CVID patients to respiratory infections [7]. Identifying CVID among COPD patients is crucial, as treatment can alleviate symptoms and prevent recurrent infections, thereby improving outcomes [8]. The diagnosis of CVID should be considered in patients with recurrent upper and/or lower respiratory tract infections, particularly those caused by encapsulated or atypical bacteria [6].

In patients with humoral immunodeficiency, immunoglobulin therapy such as intravenous immunoglobulin (IVIG) has been shown to effectively prevent recurrent infections [9]. Similarly, in patients with COPD, hypogammaglobulinemia is associated with increased risks of AECOPD and hospitalizations [10]. Although there is no established IgG threshold level that predicts recurrent AECOPD, evidence suggests that the relationship between serum IgG level and AECOPD risk is linear and extends into the "normal" range. IVIG has been associated with a reduction in AECOPD rates [11]. Notably, the overall rate of AECOPD decreases consistently across the severity of COPD or baseline serum IgG level. These observations, along with others, suggest that Ig treatment may effectively reduce the frequency of recurrent AECOPD. There may be an immediate effect of Ig, such as decreased inflammatory state or reduced autoantibodies in the acute phase of AECOPD [12].

However, there are still many differing opinions about the relationship between serum Ig levels and the risk of COPD exacerbations. Additionally, the use of IVIG for COPD patients is also controversial and has not achieved general consensus. Our study has the potential to provide valuable insights into the association between Ig levels and both clinical and subclinical characteristics of COPD patients, as well as their risk of experiencing AECOPD, including frequency and severity. The results from this research may significantly enhance our understanding of humoral immunity relevant to COPD pathophysiology and clinical outcomes. Additionally, identifying Ig levels as a potential 'treatable trait' in this population could pave the way for novel therapeutic interventions aimed at modulating humoral immunity to improve COPD management and patient outcomes.

Methods

The study adopted a prospective, descriptive design. We used the convenience sampling method, involving a group of 67 COPD patients undergoing treatment at the Respiratory Center of Military Hospital 103 in Vietnam, all of whom were in the stable COPD phase. Patients were selected based on specific criteria, including a post-bronchodilator FEV1/FVC ratio of $<70\%$, consistent with the Global Initiative for COPD guidelines [13]. Patients were categorized into group E according to GOLD 2023 [1]. Exclusion criteria comprised individuals with concurrent conditions such as asthma, autoimmune diseases, malignancy, congestive heart failure, pulmonary tuberculosis, and those who had received systemic corticosteroid treatment within the previous 30 days. Clinical data, as well as exacerbation information over the ensuing 12 months, were meticulously recorded. The control group was composed of 30 healthy individuals aged ≥ 45 years without any specific chronic diseases, autoimmune, metabolic, cancerous or infections. They were selected for measuring serum Ig levels as reference values for the test result in patients.

Data Acquisition: Epidemiological, demographic, clinical, and therapeutic data were obtained upon admission using a standardized medical record format. For primary outcome analysis, descriptive statistics were utilized to present serum levels of IgG, IgG subclasses (IgG1, IgG2, IgG3, IgG4), IgA, IgM, and IgE in COPD patients. Comparative analysis was conducted between Ig levels in healthy controls and COPD patients. Secondary outcome analysis focused on exploring associations between serum Ig levels and COPD severity according to the GOLD criteria, FEV1 scores, serum albumin, C-reactive protein (CRP), procalcitonin (PCT) levels, white blood cell (WBC) count, and the incidence rate of AECOPD over the subsequent 12 months.

Immunoglobulin Evaluation: Blood samples were collected and allowed to clot at room temperature for 30 min, followed by centrifugation at 1200 rpm for 10 min. Serum was then separated, aliquoted, and stored at -80°C until further use. Immunoglobulin levels (IgG, IgA, and IgM) and IgG subclasses (IgG1, IgG2, IgG3, IgG4) were measured using the immunofluorescence technique with the Invitrogen kit from Thermo Fisher Scientific (Vienna, Austria) at the Immunology laboratory of Vietnam Military Medical University in Hanoi,

Vietnam. Normal ranges of immunoglobulins were referenced from Furst et al. [14].

Immunoglobulin Species	Mean Concentration [range], mg/dL
IgG	989 [600–1600]
IgG1	[670–1050]
IgG2	[250–420]
IgG3	[54–100]
IgG4	[38–67]
IgA	200 [60–330]
IgM	120 [45–150]
IgE	0-0.2

Statistical analysis: The data were subjected to medical statistical methods and analyzed using SPSS 20.0 software. For immunoglobulin levels and other continuous clinical outcome, median and interquartile range (IQR) values are reported. Discrete variables are reported as percentages. Correlation between immunoglobulin levels with clinical outcomes and demographics were analyzed by Spearman's correlation coe cient test in the whole population and separately in the subgroups with low and normal immunoglobulin values. Bivariate comparisons of clinical outcomes and demographics between subjects with low vs. normal IgG or IgM were performed using Mann-Whitney U test for continuous variables and using the Chi-squared test for categorical variables. A p-value ≤ 0.05 was considered statistically signicant.

Table 1 The demographics, biomedical characteristics of the study population

Indices	Patients ($n=67$)
Age, years	71.9 ± 7.9
Sex (male)	65 (97)
Smoking History	64 (95,5)
Duration of disease, years	6.3 ± 5
BMI (kg/m^2)	18.7 ± 3.3
mMRC score	2.9 ± 0.6
Post-bronchodilator FEV1, % predicted	46.8 ± 22.8
FEV_1/FVC, %	46.9 ± 11.2
GOLD stage	
GOLD 1	06 (9)
GOLD 2	21 (31,3)
GOLD 3	22 (32,8)
GOLD 4	18 (26,9)
Chest X-ray	
Emphysema	03 (4,5)
Chronic bronchitis	40 (59,7)
Combine	24 (35,8)
White blood cells (G/L)	11.8 ± 6.7
Albumin (g/l)	37.9 ± 4.5
CRP (mg/dL)	42.1 ± 53.3
PCT (ng/mL)	0.3 ± 1
Arterial blood gas	
PaO2, mmHg	80.8 ± 24.7
PaCO2, mmHg	44.6 ± 11.5
pH	7.4 ± 0.05
AECOPD in next 12 months	3 ± 1.1
AECOPD relate hospitalization in next 12 months	15 (22.4)

Data are presented as $\overline{X}$ ± SD and n (%)

Results

Baseline characteristics and serum immunoglobulin levels in patients with COPD

Patients were predominantly male (97%), average age 71.9±7.9 years. Smoking: 95.5% cases, average disease duration 6.3±5 years. Average BMI: 18.7±3.3, mMRC score: 2.9±0.6. FEV1%: 46.8±22.8%, FEV1/FVC index: 46.9±11.2%. GOLD stage distribution: GOLD 3 (32.8%), GOLD 2 (31.3%), GOLD 4 (26.9%). White blood cell count: slightly elevated (11.8±6.7 G/L), CRP significantly increased (42.1±53.3 mg/l). Arterial blood gas indices normal, PaCO2 tended to rise (44.6±11.5 mmHg). Over next 12 months: average of 3±1.1 exacerbations, 22.4% required hospitalization (Table 1).

In comparison to the healthy middle-aged control group, the COPD patient group showed significantly lower serum IgG concentrations (1150.6 vs. 2032.2 mg/dl), primarily driven by a decline in IgG1 levels. The average IgA concentration of the COPD group was significantly higher than that of the control group (133.8 vs. 45 mg/dl). Decreased IgA level was present in 17.9% of COPD patients compared to 96.7% in the control group ($p<0.001$). There were no significant differences in IgM and IgE levels between the two groups. In the COPD group, 10.4% of patients had decreased serum IgG concentrations compared to none in the control group. Decreased IgG1, IgG3, and IgG4 levels were observed more frequently in the COPD group. CVID was identified in 0.3% of the COPD group (Table 2).

Associations of serum immunoglobulin concentrations with clinical and subclinical characteristics in group E COPD patients

Our analysis of serum Ig concentrations and various characteristics revealed several insights. Individuals with reduced IgG levels tended to be older (75.5±7.9 vs. 71.1±7.8 years). Smoking history, disease duration, BMI, and mMRC dyspnea scale score didn't significantly affect IgG concentrations. Airflow obstruction measures (GOLD classification, FEV1%, FEV1/FVC%) showed no notable differences between low and normal IgG groups ($p>0.05$). However, the chronic bronchitis phenotype was more common in the low IgG group. Parameters like white blood cell count, albumin concentration, CRP, and PCT levels didn't differ significantly between the two groups. Similarly, no statistically significant differences were found in the relationship between IgA levels and individual, clinical, and paraclinical characteristics (Table 3).

Table 2 Serum ig concentrations comparison between COPD and Control Groups

Indices	Stable COPD (*n* = 67)	Control (*n* = 30)	*p*
IgG,mg/dL	1150.6 (269.6–4519.8)	2032.2 (1062.5–5325.8)	< 0.001
IgG1	507.3 (126.2–3444)	1293.65 (646.6–4387.3)	< 0.001
IgG2	469.5 (78.2–1356.7)	474.95 (114.8–1002)	> 0.05
IgG3	55.9 (7.5–368.2)	131.6 (53.7–202.3)	< 0.05
IgG4	46.3 (3.2–595)	92 (11.8–203.9)	< 0.01
IgM, mg/dL	370.6 (101.9–2150.6)	306.7 (161.9–669)	> 0.05
IgA, mg/dL	133.8 (37–407.3)	45 (24.3–62.7)	< 0.001
IgE, mg/dL	0.056 (0.005–1.18)	0.055 (0.017–0.48)	> 0.05
Low IgG	07 (10.4)	0	0.06
Low IgG1	49 (73.1%)	01 (3.3%)	0
Low IgG2	14 (20.9)	04 (13.3%)	0.37
Low IgG3	33 (49.3)	01 (3.3)	0
Low IgG4	29 (43.3)	03 (10)	0.001
Low IgM	0	0	
Low IgA	07 (17.9)	29 (96.7)	< 0.001
High IgE	08 (10.4)	02 (6.7)	0.4
CVID	02 (03)	0	0.3

Data are presented as median (IQR) and n (%)

In our study, specific associations within IgG concentration subgroups were identified. In the low IgG1 concentration group, a higher proportion of patients were in GOLD stage 4 compared to the normal IgG1 group (32.7% vs. 11.1%). Additionally, serum PCT concentration was significantly higher in the low IgG1 group than the normal IgG1 group (0.1±0.2 vs. 0.8±1.9 ng/ml). Individuals with low IgG2 levels were older on average compared to the normal group (76.8±6.7 vs. 70.6±7.8 years) (Table 4). Furthermore, the disease duration in the low IgG3 group was significantly longer compared to the normal group (7.6±6.3 vs. 5.1±2.9 years) (Table 5). However, no statistically significant relationships were found between the remaining factors and IgG subgroup concentrations.

During the 12-month longitudinal follow-up, individuals with low serum IgG levels experienced a higher frequency of exacerbations per year compared to the normal group (3.4±1.5 vs. 2.9±1). Similarly, the group with high serum IgE levels also had more frequent exacerbations than the normal group (3.2±1.1 vs. 2.9±1). However, no significant differences were found between the two groups regarding the phenotype of frequent exacerbations and the frequency of exacerbations requiring hospitalization. (Table 6).

Analyzing the correlation between serum IgG concentration and the number of exacerbations during the next 12 months of follow-up, classified by exacerbation severity and frequency of exacerbations, no significant correlation was found (Figs. 1 and 2).

Table 3 Correlation of low IgG and IgA levels with demographic and Biomedical characteristics in COPD patients

Indices	IgG level		IgA level	
	Low (n = 11)	***Normal (n = 56)***	***Low (n = 12)***	***Normal (n = 55)***
Age, years	75.5 ± 7.9	71.1 ± 7.8	71.8 ± 8.2	71.9 ± 8
p	0.09		0.98	
Smoking, yes	11 (100)	53 (94.6)	12 (100%)	52 (94.5)
p	0.4		0.4	
Duration of disease, years	6.7 ± 5.2	6.2 ± 5	7.1 ± 6.5	6.1 ± 4.6
p	0.76		0.6	
BMI, kg/m^2	19.9 ± 3.6	18.5 ± 3.2	19.4 ± 3.5	18.6 ± 3.2
p	0.25		0.4	
GOLD stage				
GOLD 1	03 (27.3)	03 (5.4)	03 (25)	03 (5.5)
GOLD 2	04 (36.4)	17 (30.4)	01 (8.3)	20 (36.4)
GOLD 3	03 (27.3)	19 (33.9)	06 (50)	16 (29.1)
GOLD 4	01 (9.1)	17 (30.4)	02 (16.7)	16 (29.1)
p	0.08		0.03	
mMRC score	3 ± 0.4	2.9 ± 0.6	2.8 ± 0.8	3 ± 0.6
p	0.6		0.5	
Chest X-ray				
Hyperinflated	0	03 (5.4)	01 (8.3)	02 (3.6)
Chronic bronchitis	08 (72.7)	32 (57.1)	07 (58.3)	33 (60)
Combine	03 (27.3)	21 (37.5)	04 (33.3)	20 (36.4)
p	0.5		0.8	
FEV_1, % predicted	60.3 ± 28.2	45.3 ± 21.9	50.3 ± 31.5	46.4 ± 21.9
p	0.1		0.7	
FEV_1/FVC, %	47.6 ± 10.4	46.8 ± 11.4	44 ± 10.7	47.2 ± 11.3
p	0.8		0.4	
WBC, G/L	11.2 ± 4.1	11.9 ± 7.1	11 ± 4.8	12 ± 7.1
p	0.64		0.6	
Albumin (g/l)	37.5 ± 5.7	38 ± 4.2	37.6 ± 4.2	38 ± 4.6
p	0.8		0.8	
CRP (mg/dL)	36 ± 15.6	43.3 ± 7.2	27 ± 54.7	45.4 ± 53
p	0.7		0.3	
PCT (ng/mL)	0.1 ± 0.03	0.3 ± 0.1	0.2 ± 0.3	0.3 ± 1.1
p	0.1		0.8	

Data are presented as $\overline{X}$ ± SD and n (%)

Discussion

Baseline characteristics and serum immunoglobulin levels in patients with COPD

Compared with the control group, we observed significantly lower serum IgG concentrations and subgroups in the COPD patient group, with IgG1 experiencing the greatest decline. In the COPD group, 10.4% of patients exhibited decreased serum IgG concentrations compared to the normal reference threshold. Notably, the rates of decreased serum IgG subgroup levels were 73.1% for IgG1, 49.3% for IgG3, and 43.3% for IgG4. Conversely, IgA levels in the COPD group were significantly higher than in the control group. There were no significant differences in IgM and IgE

Table 4 Correlation of IgG1 and IgG2 levels with Clinical and Biomedical characteristics in COPD patients

Indices	IgG1 level		IgG2 level	
	Low (*n* = 49)	Normal (*n* = 18)	Low (*n* = 14)	Normal (*n* = 53)
Age, years	71.9 ± 7.7	71.7 ± 8.8	76.8 ± 6.7	70.6 ± 7.8
p	0.9		0.007	
Smoking, yes	48 (98)	16 (88.9)	14 (100)	50 (94.4)
p	0.1		0.3	
Duration of disease, years	6.6 ± 5.6	5.5 ± 2.8	7.9 ± 5.8	5.9 ± 4.7
p	0.4		0.3	
BMI, kg/m^2	18.6 ± 3.1	19.2 ± 3.9	18.7 ± 3.6	18.6 ± 3.3
p	0.6		0.9	
GOLD stages				
GOLD 1	06 (12.2)	0	02 (14.3)	04 (7.5)
GOLD 2	12 (24.5)	09 (50)	03 (21.4)	18 (34)
GOLD 3	15 (30.6)	07 (38.9)	06 (42.9)	16 (30.2)
GOLD 4	16 (32.7)	02 (11.1)	03 (21.4)	15 (28.3)
p	0.06		0.6	
mMRC score	3 ± 0.6	2.9 ± 0.6	3.1 ± 0.4	2.9 ± 0.7
p	0.9		0.08	
Chest X-ray				
Hyperinflated lungs	03 (6.1)	0	0	03 (5.7)
Chronic bronchitis	28 (57.1)	12 (66.7)	11 (78.6)	29 (54.7)
Combine	18 (36.7)	06 (33.3)	03 (21.4)	21 (39.6)
p	0.5		0.2	
$FEV_{1,}$ % predicted	45.9 ± 24.4	49.4 ± 18.3	47.8 ± 23.8	46.6 ± 22.8
p	0.5		0.8	
FEV_1/FVC, %	45.8 ± 11.5	49.9 ± 9.9	48.3 ± 9	46.5 ± 11.8
p	0.1		0.5	
WBC, G/L	11.5 ± 6.8	12.6 ± 6.6	11.7 ± 5.9	11.8 ± 6.9
p	0.5		0.9	
Albumin (g/l)	38.2 ± 4.3	37.2 ± 5.1	37.7 ± 4.9	38 ± 4.4
p	0.5		0.8	
CRP (mg/dL)	37.9 ± 51.1	53.6 ± 59.2	34.1 ± 49.6	44.2 ± 54.6
p	0.3		0.5	
PCT (ng/mL)	0.1 ± 0.2	0.8 ± 1.9	0.09 ± 0.08	0.36 ± 1.15
p	0.01		0.1	

Data are presented as $\overline{X}$ ± SD and n (%)

Table 5 Correlation of IgG3 and IgG4 levels with clinical and biomedical characteristics in COPD patients

Indices	IgG3 level		IgG4 level	
	Low (*n* = 33)	Normal (*n* = 34)	Low (*n* = 29)	Normal (*n* = 38)
Age, years	72.9 ± 7.7	70.9 ± 8.2	73.8 ± 8.1	70.4 ± 7.6
p	0.3		0.08	
Smoking, yes	32 (97)	32 (94.1)	27 (93.1)	37 (97.4)
p	0.6		0.4	
Duration of disease, years	7.6 ± 6.3	5.1 ± 2.9	7.1 ± 6	5.7 ± 4
p	0.04		0.2	
BMI, kg/m^2	19.1 ± 3.3	18.4 ± 3.4	18.9 ± 3.3	18.6 ± 3.3
p	0.4		0.7	
GOLD stages				
GOLD 1	04 (12.1)	02 (5.9)	03 (10.3)	03 (7.9)
GOLD 2	09 (27.3)	12 (35.3)	10 (34.5)	11 (28.9)
GOLD 3	10 (30.3)	12 (35.3)	11 (37.9)	11 (28.9)
GOLD 4	10 (30.3)	08 (23.5)	05 (17.2)	13 (34.2)
p	0.7		0.5	
mMRC score	3 ± 0.6	2.9 ± 0.6	2.9 ± 0.6	3 ± 0.6
p	0.8		0.5	
Chest X-ray				
Hyperinflated lungs	02 (6.1)	01 (2.9)	02 (6.9)	01 (2.6)
Chronic bronchitis	23 (69.7)	17 (50)	18 (62.1)	22 (57.9)
Combine	08 (24.2)	16 (47.1)	09 (31)	15 (39.5)
p	0.1		0.6	
$FEV_{1,}$ % predicted	46.4 ± 24	47.2 ± 22.1	48.4 ± 21.3	45.6 ± 24.2
p	0.9		0.6	
FEV_1/FVC, %	45.5 ± 10.2	48.3 ± 12.1	48.7 ± 9.8	45.6 ± 12.1
p	0.3		0.2	
WBC, G/L	11.4 ± 4.9	12.2 ± 8.1	10.3 ± 3.6	12.9 ± 8.2
p	0.6		0.09	
Albumin (g/l)	37.7 ± 5	38.1 ± 4	38.6 ± 4.2	37.4 ± 4.7
p	0.7		0.3	
CRP (mg/dL)	49.4 ± 60.9	35 ± 44.7	38.6 ± 49.6	44.8 ± 56.5
p	0.2		0.6	
PCT (ng/mL)	0.4 ± 1.4	0.2 ± 0.4	0.4 ± 1.5	0.2 ± 0.4
p	0.4		0.6	

Data are presented as $\overline{X}$ ± SD and n (%)

Table 6 Association between decreased serum ig concentration and risk of AECOPD in the next 12 months

Indices	IgG		IgA		IgE	
	Low (*n* = 07)	Normal (*n* = 60)	Low (*n* = 07)	Normal (*n* = 60)	High (*n* = 08)	Normal (*n* = 59)
AECOPD/12 months	3.4 ± 1.5	2.9 ± 1	3.1 ± 1.3	3 ± 1.1	3.2 ± 1.1	2.9 ± 1
p	0.3		0.7		0.5	
≥ 2 AECOPD/12 months	06 (85.7)	55 (91.7)	06 (85.7)	55 (91.7)	07 (87.5)	54 (91.5)
p	0.6		0.6		0.7	
AECOPD relate hospitalization, yes	01 (14.3)	14 (23.3)	01 (14.3)	14 (23.3)	01 (12.5)	14(23.7)
p	0.5		0.6		0.5	

Data are presented as $\overline{X}$ ± SD and n (%)

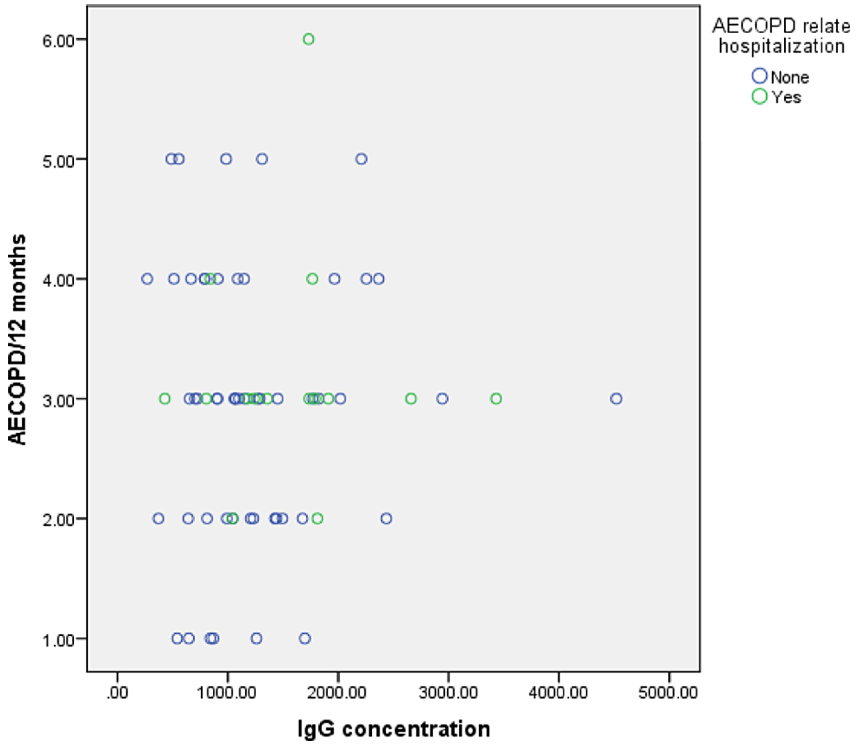

Fig. 1 Scatter Plot Showing the Correlation Between Serum IgG Concentration and the Number of Exacerbations Over the Next 12 Months, Classified by Exacerbation Severity

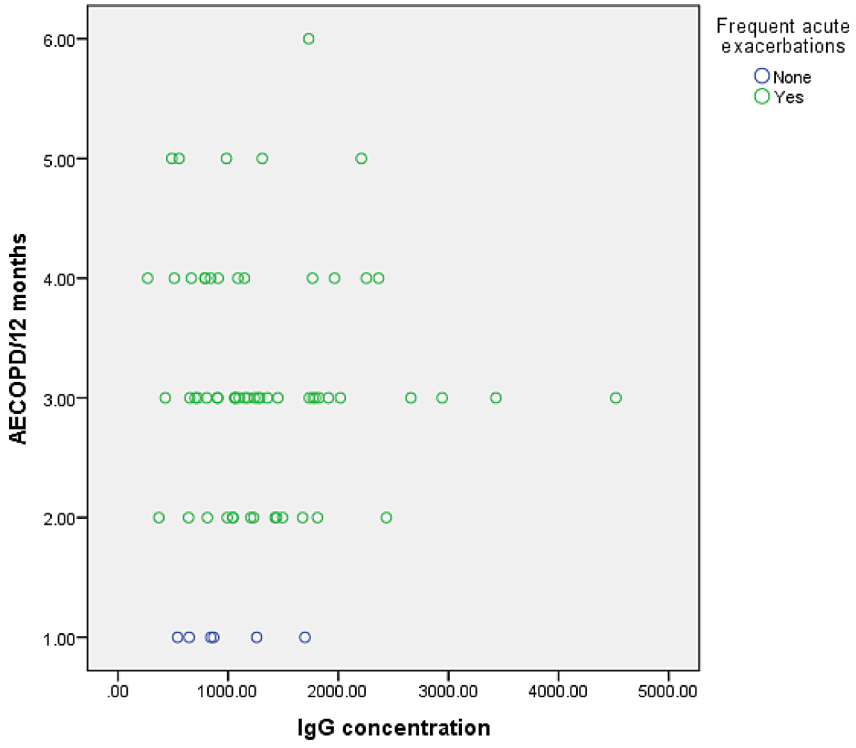

Fig. 2 Scatter Plot Showing the Correlation Between Serum IgG Concentration and the Number of Exacerbations Over the Next 12 Months, Classified by Frequency of Exacerbations

concentrations. Additionally, we identified 2 cases (0.3%) of CVID within the COPD group.

Humoral immune defects are a spectrum of diseases that represent the most common primary immunodeficiency disorders. The adult antibody deficiency syndromes include CVID, selective IgA deficiency (SIgAD), and specific antibody deficiency (SAD). The prevalence of antibody deficiencies ranges from 1:500 in SIgAD to about 1:25,000 in CVID. About 32% of patients with CVID develop pneumonia, and about 23% develop bronchiectasis [15]. The likelihood of hypogammaglobulinemia increases with increased severity of COPD and is associated with increased mortality. IgG subclass deciency, especially IgG2 deciency, is also common in patients with COPD and IgG subclass levels correlate with poor outcomes. The cause for low immunoglobulin levels in patients with COPD is multifactorial including, possibly, the fact that oral corticosteroids may decrease IgG levels [16].

Studies on serum Ig concentrations have revealed significant fluctuations in Ig concentration thresholds, influenced by a myriad of factors, including immune response dynamics. In the context of chronic inflammation, interleukin-6 (IL-6) is recognized as a promoter of Ig synthesis. A study by A. Gonzalez Quintela (2008) among adults found average IgG concentrations at 1118 mg/dl, IgM at 147 mg/dl, and IgA at 262 mg/dl. Notably, IgA tends to be higher in men compared to women, while IgG and IgM levels are higher in women. Regarding age distribution, IgG and IgA concentrations were observed to gradually increase with age, with no significant difference in IgM concentrations across age groups. Furthermore, IgA concentrations exhibit a tendency to be higher in groups with obesity and metabolic disorders characterized by elevated glucose and blood fat levels, while no disparities were noted in IgG and IgM concentrations. These findings underscore the complex interplay of Ig concentrations with demographic and metabolic factors [17].

According to Williamson et al. (2014), normal serum Ig concentrations were as follows: IgG: 768–1632 mg/dl, IgM: 60–263 mg/dl, IgA: 82–453 mg/dl, IgE: 0.01–0.04 mg/dl [18]. Kim et al. (2016), concentrations of IgG subclasses are as follows: IgG1: 382.4–928.6 mg/dL, IgG2: 241.8–700.3 mg/dL, IgG3: 21.8–176.1 mg/dL, IgG4: 3.9–86.4 mg/dL [19].

According to Samea et al. (2011), there was a significantly higher increase in IgE levels in the serum of patients with stable and acute COPD compared to the control group. IgE concentrations were also higher and showed differences when comparing during and outside exacerbations of COPD. However, it was observed that bronchial asthma patients had increased serum IgE levels compared to the COPD group [20].

McCullagh et al. (2017), the study focused on changes in serum antibody levels and immune response with antibody replacement therapy in COPD patients experiencing≥2 exacerbations/year. The results revealed that 69% of patients exhibited the common multiple immune deficiency syndrome. Among these patients, 27.6% had general antibody deficiency, 69% had specific antibody deficiency, and 3.4% had selective IgA deficiency [5].

In a study conducted by Pia Holma et al. in Finland, the mean serum IgG concentration among 5430 participants at age 46 years was 11.20 g/L. Two standard deviations below and above the mean were 6.84 g/L and 15.56 g/L, respectively. Among the participants, 57 had serum IgG levels of 6.8 g/L or lower, while 162 had levels above 15.6 g/L. IgG subclasses were measured for individuals with serum IgG levels lower than 5.0 g/L or higher than 20.0 g/L. In all cases, the subclass findings were consistent with an even distribution [7].

Several factors contribute to secondary immunodeficiency in COPD patients, with prominent ones supported by substantial evidence including prolonged exposure to cigarette smoke, extended use of corticosteroids, and nutritional deficiencies. Prolonged exposure to cigarette smoke, a significant risk factor for COPD development, can detrimentally affect immune function. Similarly, the extended use of corticosteroids, often prescribed to manage COPD exacerbations and inflammation, may suppress the immune system, increasing susceptibility to infections. Additionally, malnutrition and deficiencies in essential nutrients, common in COPD due to factors like reduced appetite and increased energy expenditure during breathing, can weaken the immune system, further exacerbating immunodeficiency in these patients. In this study, we observed a notable decrease in serum Ig concentrations among COPD patients compared to controls of similar race and age. This finding indicates that serum antibody deficiency is a prevalent condition in individuals with COPD. It is plausible that this deficiency contributes to the frequent exacerbations of the disease associated with respiratory infections.

Associations of serum immunoglobulin concentrations with clinical and subclinical characteristics in Group E COPD patients

Our analysis of the relationship between serum Ig concentrations and various individual, clinical, and paraclinical characteristics revealed several key findings. Firstly, we observed that the average age of individuals with reduced IgG levels was higher compared to those with normal IgG concentrations (75.5±7.9 vs. 71.1±7.8 years old). Factors such as smoking history, disease duration, body mass index (BMI), and the modified Medical Research Council (mMRC) dyspnea scale score did not demonstrate a significant impact on the difference in IgG

concentrations between the two groups. Additionally, no notable disparities were recorded in measures of airflow obstruction, including GOLD classification, forced expiratory volume in one second (FEV1%) and the ratio of FEV1 to forced vital capacity (FEV1/FVC%), between individuals with low and normal IgG levels ($p>0.05$). However, there was a tendency for the chronic bronchitis phenotype to be more prevalent in the group with reduced serum IgG levels. Furthermore, parameters such as blood white blood cell count, albumin concentration, serum C-reactive protein (CRP), and procalcitonin (PCT) levels showed no significant differences between the two groups. Similarly, when examining the relationship between IgA levels and individual, clinical, and paraclinical characteristics, no statistically significant differences were noted.

In the study by Holm et al. (2020), no significant difference was observed in inflammatory parameters between two groups of COPD patients with antibody deficiency and those without serum antibody deficiency [21]. Pia Holma et al., serum IgG concentrations were measured at age 46 years in a cohort of 5430 individuals. The results revealed an association between current smoking and low serum IgG levels in both males and females. Specifically, serum IgG concentrations were 10.3 g/L among current smokers and 11.5 g/L among non-smokers, indicating a significant difference ($p<0.001$). However, the mean serum IgG concentration in former smokers did not differ from that of non-smokers [7].

In the study, we identified specific associations within subgroups of IgG concentrations. Firstly, in the group with low IgG1 concentrations, a higher proportion of patients were observed in GOLD stage 4 compared to the normal IgG1 concentration group (32.7% vs. 11.1%). Additionally, the serum PCT concentration in the low IgG1 concentration group was significantly higher than in the normal IgG1 group (0.1±0.2 vs. 0.8±1.9 ng/ml). Furthermore, individuals with low IgG2 levels exhibited a significantly higher average age compared to the normal group (76.8±6.7 vs. 70.6±7.8 years). Additionally, the duration of disease in the low IgG3 group was significantly longer compared to the normal group (7.6±6.3 vs. 5.1±2.9 years). However, no statistically significant relationships were found between the remaining factors and the concentration of IgG subgroups.

Antibodies are crucial components of the body's adaptive immune system, providing defense against pathogens. Complete or partial deficiency in these antibody classes can increase the risk of various infectious diseases. Among these, IgG holds particular importance, constituting 70–80% of total serum antibodies and serving as a primary defense mechanism against extracellular threats. IgG is further divided into four subclasses, each with distinct roles in immune defense. IgG1 is primarily involved in combating protein-derived antigens, while IgG2 contributes to resistance against microbes with polysaccharide coatings. IgG3 plays a critical role in the immune response against respiratory viruses, and IgG4 is particularly important in fighting respiratory infections [14]. Indeed, it's crucial to emphasize that serum antibody deficiency doesn't always equate to immunodeficiency. Even if an individual has slightly reduced total antibody levels, their body may still be capable of mounting a specific immune response tailored to combat particular pathogens. This highlights the complexity of the immune system, where various factors beyond serum antibody levels contribute to overall immunity and defense against infections [10].

During the longitudinal follow-up spanning 12 months, we observed that the group with low serum IgG levels experienced a higher frequency of exacerbations per year compared to the normal group (3.4±1.5 vs. 2.9±1). Similarly, the group with high serum IgE levels also had exacerbations occurring more frequently than the normal group (3.2±1.1 vs. 2.9±1). However, we found no significant differences between the two groups in terms of the phenotype of multiple exacerbations and the frequency of exacerbations requiring hospitalization.

Indeed, immune deficiencies, particularly IgG deficiencies, are linked to recurrent infections in patients with chronic airway diseases like bronchial asthma, COPD, or bronchiectasis. IgG3, comprising about 2–4% of total serum IgG, is the most frequently observed subclass deficiency in chronic airway diseases and is closely associated with the risk of recurrent infections and exacerbations. It's important to note that an individual may experience a deficiency in one IgG subclass without a general IgG deficiency, or they may have a combined deficiency of multiple subclasses. This highlights the complexity and variability of immune responses in these conditions [19, 22].

In a study conducted by Kim et al. (2016) in Korea involving 59 adult patients with bronchial asthma and COPD, the findings revealed that IgG3 deficiency was the most prevalent (88.1%), followed by IgG4 deficiency (15.3%). Common infectious complications observed included pneumonia (60.2%), recurrent bronchitis (15.9%), and sinusitis (12.5%), with a lower incidence of extrapulmonary infections. Pus bacillus was identified as the primary cause of pneumonia, followed by Klebsiella pneumoniae, pneumococcus, and Moraxella catarrhalis. These findings underscore the significance of IgG subclass deficiencies in predisposing individuals with chronic airway diseases to recurrent infections, highlighting the importance of targeted interventions and management strategies [19].

In the study conducted by Leitao Filho et al. (2018), it was found that 18.8% of patients exhibited a deficiency

in at least one IgG subclass. The incidence of decreased IgG1-4 subclasses was 4.5%, 5.7%, 7.6%, and 7%, respectively. Notably, simultaneous reduction of two or more subclasses ranged from 0.2 to 2.9%. Differences were observed in the decline of IgG1 and IgG2 levels between the group with two or more exacerbations compared to the group with one or fewer exacerbations. Additionally, 25% of moderate and severe COPD patients experienced a decline in IgG levels. Specifically, it was observed that up to 50–100% of these individuals exhibited a phenotype characterized by frequent exacerbations and a high likelihood of hospitalization due to exacerbations. These findings underscore the importance of evaluating IgG subclass levels in COPD patients, especially those with a history of exacerbations, to better understand and manage their disease progression [23].

The role of defective adaptive immunity and low serum IgG concentration is well established in CVID patients suffering from recurrent pneumonia and respiratory tract complications. It has also been shown that patients with milder forms of hypogammaglobulinemia may suffer from respiratory infections. Although these patients benefit from IgG replacement therapy, they may remain fully asymptomatic for years. Early diagnosis and consideration of IgG replacement therapy is believed to be beneficial. Not only low but even high serum IgG concentrations were associated with respiratory infection burden. Elevated serum IgG in older individuals may also indicate risk of pneumonia-related mortality and recurrent pneumonia although mechanisms are incompletely described [7].

In a retrospective analysis by Cowan et al. (2015), involving 14 cases of COPD patients with serum antibody deficiency who underwent antibody replacement therapy, the authors reported a reduction in the frequency of moderate and severe exacerbations. This suggests that antibody replacement therapy may be beneficial in managing COPD patients with serum antibody deficiency, potentially mitigating the recurrence of exacerbations and improving disease outcomes [11].

In a study by Bermejo Martin et al. (2014), the association between serum Ig deficiency and death due to infection was investigated in 172 patients. The findings revealed that concomitant deficiencies in IgG1, IgM, and IgA were associated with an increased risk of death in patients with severe sepsis or septic shock. These results suggest that supplementing exogenous Ig may aid in improving treatment outcomes in patients with severe sepsis, particularly in cases where multiple Ig deficiencies are present. This highlights the potential importance of tailored immunomodulatory therapies, such as Ig adjuvant therapy, in managing severe infections and improving patient survival [24].

Indeed, the existing literature on the prognostic role and exacerbation frequency associated with decreased IgG levels in COPD remains limited and somewhat inconclusive. Different studies present varying perspectives on this issue [7, 16, 25, 26]. There is currently insufficient strong evidence to confirm a clear relationship between decreased IgG concentrations and exacerbation frequency or to establish the prognostic value of IgG concentrations regarding exacerbation risk. This uncertainty stems from the influence of numerous factors on serum IgG concentration, such as malnutrition and prolonged corticosteroid use in treatment. Further research is needed to elucidate the complex relationship between IgG levels and exacerbation risk in COPD, considering the multifactorial nature of this condition and its management [27].

In our study, we did not investigate the relationship between serum Ig levels and the frequency or risk of exacerbations. Additionally, we did not find a significant correlation between serum IgG concentration and the risks of exacerbation frequency and severity after 12 months of follow-up. This suggests that although there is a decrease in serum Ig concentrations, especially IgG, this immunodeficiency does not clearly affect the prognosis of the risk of acute exacerbations in COPD patients. This finding may be due to the small sample size of our study. Additionally, the recurrence rate of acute exacerbations is influenced by various factors such as patient treatment compliance, quality of care, and disease management conditions. Furthermore, all patients in our study belonged to group E, with Ig concentrations lower than the average threshold of the control group. Therefore, no significant differences were observed when comparing factors within the COPD group. Moreover, the severity of exacerbations is affected by multiple factors, including disease stage, degree of airflow obstruction, and co-morbidities, rather than solely by infections related to Ig deficiency. These factors collectively contribute to the complexity of exacerbation outcomes in COPD patients.

It's important to acknowledge the limitations of our study. Firstly, being a single-center study, the generalizability of our findings may be limited. Secondly, the sample size utilized in the study was relatively small, and it included only COPD patients in group E. Therefore, our findings offer initial insights into the characteristics of serum Ig concentrations in group E COPD patients and their association with clinical and paraclinical characteristics and future exacerbation risk. Further research with larger sample sizes, multicenter studies, inclusion of patients across various disease stages, and longer follow-up periods are needed to comprehensively evaluate changes in serum Ig concentrations and exacerbation risk in COPD patients. Subsequent studies can inform specific recommendations for the use of immunoglobulin therapy such as IVIG in COPD treatment.

Conclusions

The study found that serum IgG and IgM concentrations are notably reduced in COPD patients compared to healthy individuals, with particularly low levels of IgG1 and IgG3 subclasses in COPD patients. Conversely, serum IgA levels were significantly higher in COPD patients compared to normal controls. However, there was no significant association between Ig concentrations, especially serum IgG deficiency and its subclasses, with the frequency and risk of exacerbations during a 12-month longitudinal follow-up. The study suggests exercising extreme caution when considering immunoglobulin therapy in COPD treatment. Immunoglobulin therapy may be considered in severe COPD exacerbations with clear evidence of respiratory infection.

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Author contributions
The literature search was performed by CNH, TTB. Data collection was performed by CNH, CHX, TVM. All authors contributed equally to the analysis and interpretation of data of the article: CNH, TTB, TBD, and CNH drafted the manuscript. All authors have read and approved the final manuscript.

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Data availability
The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data were not publicly available because of privacy and ethical restrictions.

Declarations

Ethics approval and consent to participate
The study protocol underwent review and received approval from the Ethics Committee of Military Hospital 103 (No. 57/2014/VMMU-IRB), and all participants provided written informed consent. The methodology outlined in this manuscript strictly adheres to these approvals.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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