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Assessment of hyaluronic acid in COPD patients as a prognostic biomarker

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Abstract

Background One essential element of the extracellular matrix is hyaluronic acid (HA). It has been claimed that HA and its metabolism are different in the lungs of patients with chronic obstructive pulmonary disease (COPD). The present study investigated the predictive significance of serum level of HA in patients with COPD and monitored changes in its level in these patients because of therapy.

Methods HA was assessed in 60 patients with stable COPD (divided into subgroups I and II) and 20 healthy controls and then repeated after 3 and 6 months in COPD patients.

Results Most of the patients were males (63.3%), and their ages ranged from 30 to 90. The serum level of HA was significantly increased in subgroups I and II (269.33 ± 4, 290 ± 4, respectively), compared to the control group (147.5 ± 1) with a significant difference in its level between both ($p < 0.0001$). The serum level of HA was significantly decreased in both subgroups 3 and 6 months later following adjustment of treatment and associated with improvement in pulmonary function test. There were significant positive correlations between HA and age as well as smoking index. Its level correlated negatively with forced expiratory volume in the first second (FEV1%), forced vital capacity (FVC%), and FEV1/FVC.

Conclusions HA is a useful marker for identifying clinical stability in COPD patients and for follow-up in the efficacy of treatment.

Keywords COPD, HA, Extracellular matrix

Background

Chronic obstructive pulmonary disease (COPD) is a progressive condition marked by persistent restriction in airflow and a heightened chronic inflammatory response to noxious particles or gases in the airways and the lung [1].

The extracellular matrix (ECM) is made up of a dynamic assemblage of structural components like glycosaminoglycans and collagens. Hyaluronic acid (HA), a widely distributed, naturally occurring glycosaminoglycan, can be found in connective tissue of mammalian, including the lung [2]. There is growing evidence that the pathophysiology of the lung is significantly influenced by HA and its breakdown products [3]. High-molecular-weight HA (> 1000 kDa) contains anti-inflammatory, antiangiogenic, and immunosuppressive properties that support cell survival. Low-molecular-weight HA (150–350 kDa), on the other hand, is formed during inflammation and has pro-inflammatory and pro-angiogenic properties. Also, it promotes cell migration [4]. HA supports connective tissue stability, extracellular matrix organization,

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mucociliary clearance, tissue moisture control, and healing processes. As a result, HA is a promising treatment option for treating lung and other respiratory illnesses [5]. Indeed, HA abnormalities may contribute to the pathophysiology of COPD [6].

Methods

The purpose of this research was to investigate the predictive significance of HA in patients with COPD and monitor changes in its level in these patients because of therapy.

This experimental study was carried out in the chest department at outpatient clinics at Benha University hospitals. The study included 90 patients from the start. During the period of follow-up, 30 patients were excluded as they experienced disease exacerbation. So, 60 patients with stable COPD were involved and divided into two groups, subgroups I and II according to GOLD (2021). Subgroup I consisted of 30 patients with stages I and II of the disease who did not need to use inhaled corticosteroid (ICS) continuously, and subgroup II consisted of 30 patients with stages III and IV of the disease who needed to use ICS continuously. Twenty subjects who appeared to be in good health were also included in the study as a control group.

According to Gold (2021), COPD patients were identified when they had post-bronchodilator forced expiratory volume in the 1st second/forced vital capacity (FEV1/FVC) less than 70% and had symptoms like chronic cough, sputum production, dyspnea, and/or history of exposure to the risk factor. Patients with acute exacerbation of COPD, illnesses that cause increase or decrease HA such as asthma, pulmonary fibrosis, hypertension, allergic rhinitis, and rheumatoid arthritis, as well as patients under the age of 18 years, were disqualified from the study.

All subjects underwent a thorough history taking and clinical examination, a posteroanterior and left-lateral chest X-ray, and a pulmonary function test (spirometry, using pulmonary function equipment (JAEGER CareFusion 234, GmbH, Leibnizstr, Hoechberg, Germany) (it was repeated at 3 and 6 months with measurement of the level of HA). Each patient completed three consecutive pre-bronchodilator trials. The trial with the best performance was chosen. Additionally, each patient underwent the test three successive times 15 min after the bronchodilator to ascertain whether the airway obstruction was reversible. An inhaled bronchodilator is given by a metered-dose inhaler (MDI). B2-adrenergic aerosol (salbutamol 200–300 μm) was used because it has a rapid onset of action usually within minutes [7]. A percentage of the predicted value for each recorded outcome was used to express it. Predicted values were calculated according to a system developed by Quanjer et al. [8]. Also, laboratory investigations were done and included complete blood count (CBC), erythrocyte sedimentation rate (ESR), liver function tests [aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP)], kidney function tests (urea, creatinine), and measurement of the serum level of HA using enzyme-linked immunosorbent assay (ELISA) which was repeated after 3 and 6 months in COPD patients [9]. Normal hyaluronic acid levels are between 0 and 75 ng/ml.

Blood samples were collected from all subjects. A volume of 5 ml of venous blood was collected. For a CBC, 1 ml of blood was placed into EDTA containing vacutainer and thoroughly mixed, and this was conducted using an automated hematology system (Sysmex XE 5000; Sysmex America, Inc., Mundelein, USA). The remaining blood was transferred in sterile disposable vacuum blood-collecting tubes (red tubes). The serum was separated by centrifugation, and serum was separated for measurement of liver and kidney function tests, alkaline phosphatase (ALP) using a Biosystem A15 autoanalyzer (BioSystems S.A, Barcelona, Spain); the remaining serum was stored at < -20 °C. Serum level of HA using enzyme-linked immunosorbent assay (ELISA) was measured and repeated after 3 and 6 months in COPD patients. Detection ranges 4.94–400 ng/ml. Sensitivity: the minimum detectable dose of HA is typically less than 1.64 ng/ml. All data were collected and statistically analyzed.

Statistical analysis

Statistical Program for Social Science (SPSS) version 25 (Armonk, NY: IBM Corp.), which was used to code, enter, and analyze the data, was used to collect data throughout time, perform basic clinical examinations and lab investigations, and assess outcomes. Using the Shapiro–Wilk and Kolmogorov–Smirnov tests, the data were examined for normality.

Following the type of data, mean was used to represent quantitative data, and number and percentage were used to represent qualitative data. Standard deviation (SD): statistical analysis Student *t*-test was used to compare two groups with normal distributions for quantitative variables (for parametric data). Mann–Whitney *U*-test (for nonparametric data), this test of significance was used to compare two groups with quantitative variables that do not have a normal distribution. The chi-square test (χ^2) was used to study comparison and association between two qualitative variables. The least significant difference (LSD) approach was utilized to compare groups pairwise using the ANOVA (f) test, a test of significance for comparisons between three or more groups with quantitative variables. The Kruskal–Wallis test (nonparametric test) is a statistical test of significance used to compare three or

more groups with quantitative variables that are not normally distributed. To compare between more than two periods or stages, the Friedman test (a nonparametric test) is employed, along with the post hoc test (Dunn's) for pairwise comparisons. Pearson's correlation test was used to perform correlation. A *p*-value of less than 0.05 was considered statistically significant and less than 0.001 for strong significant results.

Results

Eighty subjects were enrolled in this study, 60 patients with COPD, and 20 apparently healthy subjects as a control group. All groups were matched regarding gender, age, body mass index (BMI), and smoking index (calculated by multiplying the total number of years smoked by the daily cigarette intake).

Most of the patients were males and their ages ranged from 30 to 90 (Table 1). Gold classification was distributed in subgroup1: 14 (46.7%) Gold1 and 16(53.3%) Gold 2 and in subgroup 2: 12 (40%) Gold3 and 18 (60%) Gold 4. There was significant improvement in spirometric pulmonary function after 3 and 6 months associated with decreased levels of HA (Table 2). The serum level of HA was significantly increased in subgroups I and II compared to the control group with a significant difference in its level between both subgroups as it was lower in subgroup I (Table 3). The serum level of HA was significantly decreased in both subgroups 3 and 6 months later following adjustment of treatment and associated with improvement in pulmonary function test (spirometry) (Table 4). Also, there were significant positive correlations between HA and age as well as smoking index. Its level correlated negatively with FEV1%, FVC%, and FEV1/FVC (Table 5). Hyaluronic was found to be a very good predictor for FEV1 with highly significant sensitivity and specificity during each visit (Table 6, Figs. 1, 2 and 3).

Discussion

The advancement of respiratory disorders like COPD is linked to modifications in the ECM elements in the lungs [10]. HA synthesis is downregulated, and hyaluronidase 1 (HYAL-1) is upregulated, which results in poor HA metabolism in the airway smooth muscle cells of COPD patients and reduced HA production. Additionally, acute COPD exacerbations are linked to an increase in HYAL activity in bronchoalveolar lavage and a subsequent breakdown of HA, which may aggravate airway inflammation and lead to a loss of lung function [11]. In the current work, there was a statistically significant difference between the control group and patients' subgroups I and II as regards FEV1%Pred, FVC %Pred, and FEV1/FVC in the first visit, as they were lower in subgroup II than subgroup I and control group. Another study found that COPD patients' lung functions — including FEV1%pred, FVC% pred, FEV1/FVC, transfer factor for carbon monoxide (TLCO) predicted, and residual volume (RV) predicted — were considerably lower than those of smokers and nonsmokers as controls corroborated these findings [12]. In subgroups I and II, there was a substantial improvement in pulmonary function between visits 2 and 3 compared to visits 1 and 2, respectively. Additionally, we discovered that subgroup I performed better than subgroup II throughout three visits, showing proper management and control, in terms of FEV1%Pred, FVC% Pred, and FEV1/FVC.

In this study, there was a statistically significant difference in the levels of serum HA between the two subgroups and the controls, with subgroup II having the greatest levels in the first visit compared to subgroup I

Table 1 Statistical analysis of demographic data between control group and patients' subgroups I and II

	Subgroup I ($n=30$)	Subgroup II ($n=30$)	Control group ($n=20$)	Test of sig	*p*-value
Gender					
Male (no. /%)	(19/63.3%)	(18 / 60.0%)	(13/65.0%)	$\chi^2=0.142$	0.931
Female (no. /%)	(11/36.7%)	(12/40.0%)	(7/35.0%)		
Age (years)					
(Min.–max.)	(38–87)	(30–90)	(30–86)	$F=0.798$	0.454
Mean ± SD	61.8 ± 11.43	64.30 ± 15.63	59.20 ± 15.17		
BMI					
(Min.–max.)	(18–29)	(18–27)	(18–29)	$F=0.364$	0.969
Mean ± SD	23.03 ± 3.06	22.37 ± 2.93	22.80 ± 3.25		
Smoking index					
(Min.–max.)	(0–580)	(0–540)	(0–580)	$F=0.734$	0.483
Mean ± SD	269.33 ± 216.60	242.00 ± 207.75	232.50 ± 45.0		

(χ^2) chi-square test, *F* ANOVA test, *p p*-value for comparing between the studied groups, *BMI* body mass index, *SD* standard deviation, *Min* minimum, *Max* maximum

Table 2 Comparison between patient's subgroups I and II as regards spirometric pulmonary function in the three visits

		Groups		Test of sig	
		Subgroup I (*n* = 30)	**Subgroup II (*n* = 30)**	***U***	***p*-value**
FEV1 %Pred	**Visit 1**	60.80 ± 5.37	34.83 ± 5.69	0.00	0.000**
	Visit 2	67.57 ± 6.52	43.67 ± 5.55	0.00	0.000**
	Visit 3	70.20 ± 5.54	49.30 ± 5.16	0.00	0.000**
Fr		54.89	56.00		
***p*-value**		0.000**	0.000**		
Post hoc test		P1 = 0.00** P2 = 0.00** P3 = 0.00**	P1 = 0.00** P2 = 0.00** P3 = 0.00**		
FVC %Pred	**Visit 1**	88.56 ± 5.14	73.63 ± 3.99	7.50	0.000**
	Visit 2	96.96 ± 5.12	81.53 ± 4.06	4.50	0.000**
	Visit 3	99.03 ± 5.05	83.76 ± 3.63	3.50	0.000**
Fr		60.00	60.00		
***p*-value**		0.000**	0.000**		
Post hoc test		P1 = 0.00**, P2 = 0.00**, P3 = 0.00**	P1 = 0.00**, P2 = 0.00**, P3 = 0.00**		
FEV1/FVC	**Visit 1**	68.43 ± 3.70	46.23 ± 5.12	0.00	0.000**
	Visit 2	69.80 ± 4.47	53.13 ± 4.70	2.50	0.000**
	Visit 3	70.03 ± 3.64	59.50 ± 4.11	10.00	0.000**
Fr		32.27	36.00		
***p*-value**		0.000**	0.000**		
Post hoc test		P1 = 0.00** P2 = 0.00** P3 = 0.00**			

FEV1 forced expiratory volume in the first second, *FVC* forced vital capacity, *U* Mann–Whitney U, *Fr* Friedman test, *p-value < 0.05 is significant, **p-value ≤ 0.001 highly significant, *P1* visit 1 vs visit 2, *P2* visit 1 vs visit 3, *P3* visit 2 vs visit 3

Table 3 Comparison between the patients and control group regarding hyaluronic acid (HA) ng/ml on visit 1

Hyaluronic acid (HA) ng/ml	**Groups**			**Test of sig**		**Post hoc test**
	Subgroup 1 (no. = 30)	**Subgroup 2 (no. = 30)**	**Control group (no. = 20)**	***H***	***p*-value**	
Visit 1	269.33 ± 40	290 ± 40	14.75 ± 10	46.25	0.000**	P1 = 0.007* P2 = 0.00** P3 = 0.00**

P1 subgroup 1 vs subgroup 2, P2 control group vs subgroup 1, P3 control group vs subgroup 2. *P-value < 0.05 is significant, **p-value ≤ 0.001 strong significant, *H* Kruskal–Wallis test H, *no.* number

Table 4 Comparison between patients' subgroups 1 and 2 as regards hyaluronic acid (HA) ng/ml in the three visits

Hyaluronic acid (HA) ng/ml	**Groups**		**Test of sig**	
	Subgroup 1 (no. = 30)	**Subgroup 2 (no. = 30)**	***U***	***p*-value**
Visit 1	269.33 ± 42.58	290 ± 43.07	336.5	0.007*
Visit 2	221 ± 40.97	248 ± 42.21	296	0.020*
Visit 3	163.33 ± 29.63	190.67 ± 31.28	215	0.000**
P1	0.000**	0.000**		
P2	0.000**	0.000**		
P3	0.000**	0.000**		

U Mann–Whitney U, *P1* visit 1 vs visit 2, *P2* visit 1 vs visit 3, *P3* visit 2 vs visit 3. *p-value < 0.05 is significant. **p-value ≤ 0.001 strong significant

Table 5 Correlation between levels of hyaluronic acid with different parameters in COPD patients during first visit

Studied parameters	Level of hyaluronic acid	
	Correlation	*p*-value
Age	0.512	0.000**
BMI	0.041	0.715
Smoking index	0.273	0.014*
FEV1%Pred	−0.824	0.000**
FVC %Pred	−0.596	0.000**
FEV1/FVC	−0.849	0.000**

COPD chronic obstructive pulmonary disease, *BMI* body mass index, *FEV1* forced expiratory volume in the first second, *FVC* forced vital capacity

* Significant

** Strong significant

and the control groups, respectively. Pertseva and his colleagues' study, which included 74 COPD patients, provided additional evidence for our findings. The COPD patients were divided into two subgroups: subgroup 1 included patients with mild COPD (I and II stage of disease), and subgroup 2 included patients with severe COPD (III and IV stage of disease). They discovered a statistically significant rise in HA levels in 2 subgroups compared to controls, which included 24 patients [9]. Another study found that after adjusting for baseline variations in age and sex, plasma HA was lower in COPD patients compared to non-smoker controls ($p=0.0185$). These variations were brought on by differential numbers and BMI in the groups under study [12]. In addition, we discovered that the levels of HA in the two subgroups decreased significantly following

Table 6 ROC curve for the performance of HA in predicting FEV1 during the three visits

	AUC	Cutoff value	Sensitivity	Specificity	*p*-value	95% confidence interval	
						Lower bound	Upper bound
1st visit	0.823	≥ 275	73.7%	81%	0.000**	0.719	0.926
2nd visit	0.663	≥ 215	72.4%	53.3%	0.03*	0.524	0.802
3rd visit	0.753	≥ 165	82.8%	56.7%	0.001*	0.628	0.877

ROC receiver operating characteristic, *FEV1* forced expiratory volume in the first second, *AUC* area under the curve

* Significant

** Strong significant

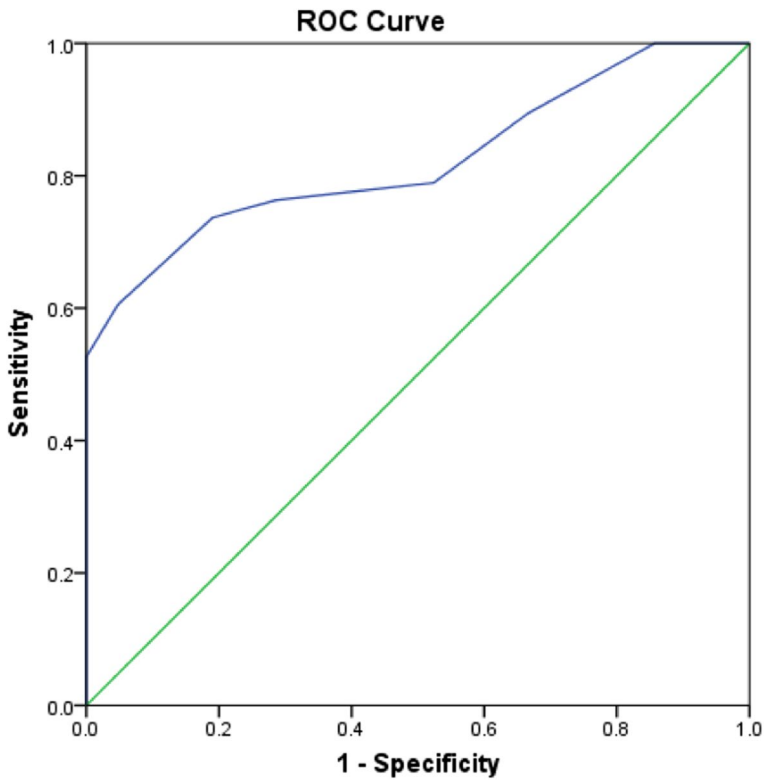

Fig. 1 ROC curve for the performance of HA in predicting FEV1 during the first visit

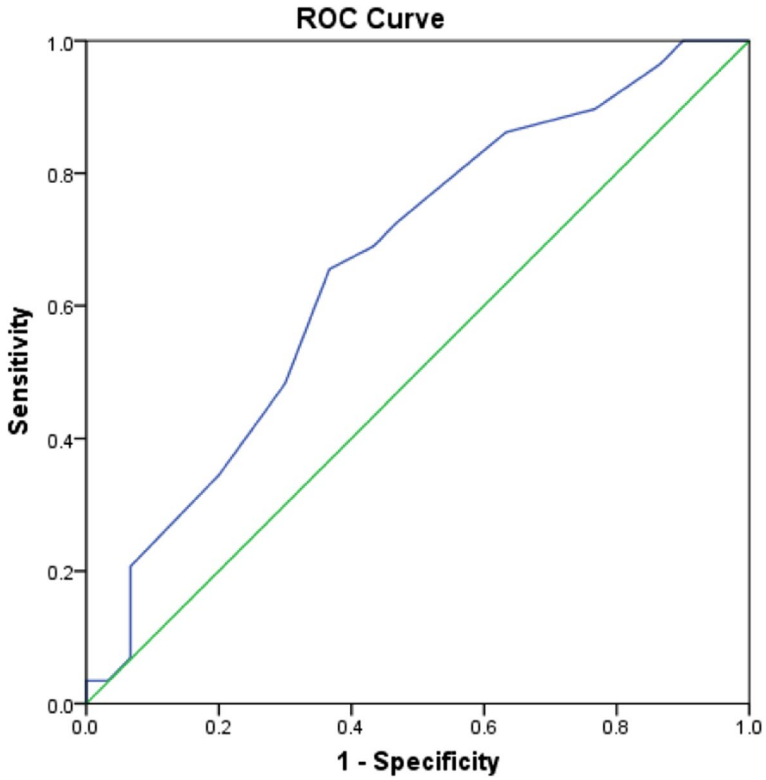

Fig. 2 ROC curve for the performance of HA in predicting FEV1 during the second visit

correct treatment, and that subgroup I's levels were consistently statistically lower than those of group II. In line with this finding, a study was conducted to evaluate the utility of HA in COPD patients and its function as a measure of the efficacy of anti-inflammatory therapy (AIT). It was found that COPD patients had considerably greater levels of HA before AIT than the control group. However, 3 months after adequate care, the level of HA dramatically dropped in all patients compared to the prior visit, matching the level of the control group. This indicates that the substantial reduction in HA levels in COPD patients may be a sign of the efficiency of AIT [9]. Since it has been demonstrated that glucocorticoids and long-acting beta-2 agonists (LABAs) affect HA turnover, a different study found that treatment could alter HA serum levels. Most of the COPD patients who took part in that study were receiving either ICSs (81% of the patients) or an ICS + LABA combination (61.3%). Following the adjustment of the medication, the level of HA dramatically decreased in all patients when compared to the prior visit [13]. On the other hand, there were no noticeable differences in HA levels between the groups of COPD patients taking ICSs, systemic corticosteroids, or ICS + LABA and those who were not getting any medication. The asymmetry in the number of COPD patients receiving or not receiving treatment may be the cause of this disparity [4]. This may suggest that circulating HA can be used as an independent predictor of survival in COPD patients, allowing for the prediction of disease activity and subsequent outcomes. Determine COPD patients who would benefit from the application of more intensive therapeutic procedures, such as lung transplantation, in the future [14]. Pro-collagen types III and VI, the main collagens present in the lung interstitium and major bronchi, were substantially correlated with serum levels of HA. These suggest that HA, like collagens, is a component of the elevated ECM turnover in COPD, a process that dictates the severity of the disease and clinically important outcomes [4]. The level of HA in this study was positively connected with age and smoking index but negatively correlated with FEV1% Pred, FVC% Pred, and FEV1/FVC, according to Spearman's rank correlation coefficient analysis. Like this, Fedotov and his coworkers showed that COPD patients had HA concentrations in their serum that were three to five times greater than those of healthy individuals ($p = 0.0001$). The relationship between HA concentration and FEV1 was shown to be inverse ($p = 0.006$), demonstrating the development of small bronchial obstruction and remodeling [15]. Contrary to our findings, another

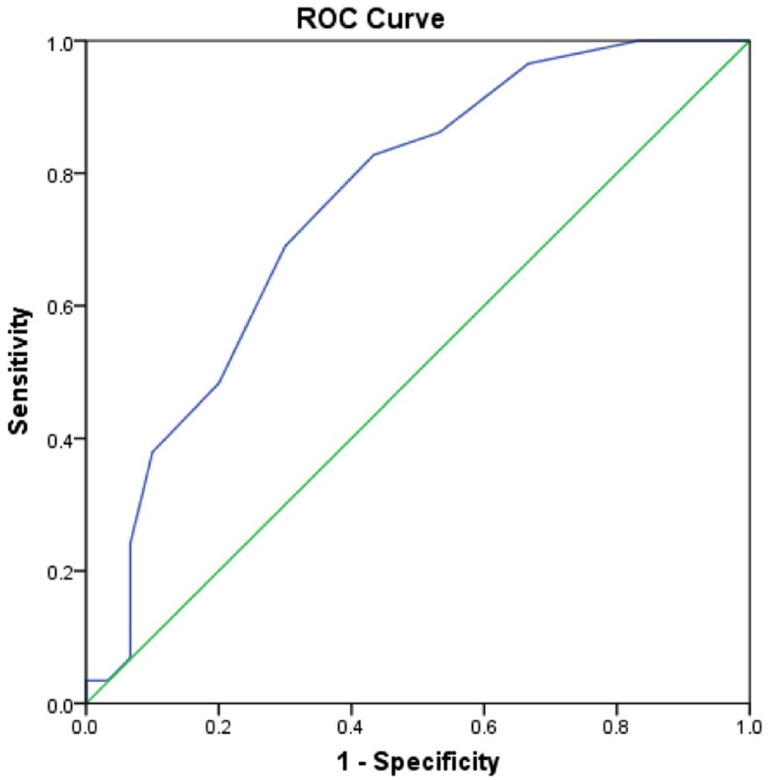

Fig. 3 ROC curve for the performance of HA in predicting FEV1 during the third visit

study found no relationship between HA and the age of the patients or their history of smoking. However, they found a strong negative association between HA and hyaluronidase ($p=0.031$) and the anticipated FEV1% in the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) group, indicating that the degree of obstruction may be connected to the rate of HA degradation. Additionally, they discovered that in neither of the patient groups did HA significantly correlate with either residual volume% predicted or diffusing capacity of the lung for carbon monoxide% predicted, indicating that increased degradation of HA may be related to airway obstruction rather than emphysema [11]. Carro and Martinez-Garcia proposed that HA, as collagens, is a component of COPD's enhanced extracellular matrix turnover, a process that influences the severity of the condition [16]. Additionally, a study conducted by Vernooy and his colleagues found a favorable correlation between HA levels in the serum of stable COPD patients and their age ($p=0.001$), post-bronchodilatation FEV1% predicted ($p=0.002$), and FEV1/FVC ($p=0.025$) [5]. In contrast, Pertseva and his colleagues' research of 74 patients with stable COPD found no link between HA and disease severity ($r=-0.109$; $p=0.355$) [9]. In the current study, HA showed high accuracy, sensitivity, and specificity in predicting FEV1. So, it can be used as a good indicator of the severity and prognosis of COPD. According to Papakonstantinou and his associates, HA was connected to the degree and course of COPD. The breakdown products of HA that are produced by HYAL-1 may contribute to COPD. By detecting circulating HA, one can predict the course of the disease and its eventual consequences. Furthermore, they concluded that HA, like collagens, plays a role in the accelerated turnover of extracellular matrix (ECM) in COPD. This process is responsible for determining the severity of the disease and clinically significant outcomes, which show an association between HA and COPD severity, outcome, and overall survival [4].

Several limitations were experienced. First, the sample size of the studied groups was relatively small. Also, the effect of smoking status on the level of HA could not be assessed separately. Furthermore, the impact of COPD exacerbation and its etiology on HA level could not be evaluated. Finally, the differences in local and systemic HA need more studies and better understanding.

Conclusion

It is clear from this study that HA is a useful marker for identifying clinical stability in COPD patients. A marker for follow-up and efficacy of treatment from visit to visit could be the HA level. It is advised to monitor HA in stable COPD patients regularly to determine how effectively the medication controls the condition. To emphasize our conclusion, additional research with a larger sample size and a greater geographic scope is advised. To precisely determine the diagnostic value of HA in patients with chronic obstructive pulmonary disease, more patients, a longer period of follow-up, and multicenter experience are all required.

Abbreviations

COPD	Chronic obstructive pulmonary disease
HA	Hyaluronic acid
FEV1	Forced expiratory volume in first second
FVC	Forced vital capacity
ECM	Extracellular matrix
KDa	Kilodalton
GOLD	Global initiative for chronic obstructive lung disease
ICS	Inhaled corticosteroids
MDI	Metered-dose inhaler
CBC	Complete blood count
ESR	Erythrocyte sedimentation rate
AST	Aspartate aminotransferase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ELISA	Enzyme-linked immunosorbent assay
SPSS	Statistical Program for Social Science
SD	Standard deviation
LSD	Least significant difference
ANOVA	Analysis of variance
BMI	Body mass index
HYAL-1	Hyaluronidase
TLCO	Transfer factor for carbon monoxide
RV	Residual volume
AIT	Anti-inflammatory therapy
LABAs	Long-acting beta-2 agonist

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Authors' contributions

AAI, made substantial subscription to the conception and plan of the work; MHK, contributed in acquiring, evaluating, and explaining evidence; AMN, contributed to the design of new software utilized in this work; DAA, outlined the work and rescripted it; MMO, participated in the data collection and the drafting of the manuscript; and MEE, helped in data interpretation and draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from Benha University Research Ethics Review Committee (Rc 35–11-2023), and official permission was obtained from the head of chest department of the faculty of medicine. All participants gave their consent following the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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