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ORIGINAL RESEARCH

A Multicenter Study of COPD and Cognitive Impairment: Unraveling the Interplay of Quantitative CT, Lung Function, HIF-1α, and Clinical Variables

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Purpose: The exact link between cognitive impairment (CI) and chronic obstructive pulmonary disease (COPD) is still limited. Thus, we aim to find the relationship and interaction of quantitative CT (QCT), lung function, HIF-1α, and clinical factors with the development of CI among COPD patients.

Patients and Methods: A cross-sectional multicentre study was conducted from January 2022 to December 2023. We collected clinical data, spirometry, CT images, and venous blood samples from 114 COPD participants. Cognitive impairment assessment using the Montreal Cognitive Assessment Indonesian version (MoCA-Ina) with a cutoff value 26. The QCT analysis consists of lung density, airway wall thickness, pulmonary artery-to-aorta ratio (PA:A), and pectoralis muscles using 3D Slicer software. Serum HIF-1α analysis was performed using ELISA.

Results: We found significant differences between $\%LAA_{-950}$, age, COPD duration, BMI, FEV_1 pp, and FEV_1/FVC among GOLD grades I–IV. Only education duration was found to correlate with CI ($r = 0.40$; $p < 0.001$). We found no significant difference in HIF-1α among GOLD grades ($p = 0.149$) and no correlation between HIF-1α and CI ($p = 0.105$). From multiple linear regression, we observed that the MoCA-Ina score was influenced mainly by $\%LAA_{-950}$ ($p = 0.02$) and education duration ($p = 0.01$). The path analysis model showed both %LAA and education duration directly and indirectly through FEV_1 pp contributing to CI.

Conclusion: We conclude that the utilization of QCT parameters is beneficial as it can identify abnormalities and contribute to the development of CI, indicating its potential utility in clinical decision-making. The MoCA-Ina score in COPD is mainly affected by $\%LAA_{-950}$ and education duration. Contrary to expectations, this study concludes that HIF-1α does not affect CI among COPD patients.

Keywords: chronic obstructive pulmonary disease, cognitive impairment, emphysema lung, hypoxia inducible factor

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is marked by persistent and progressive respiratory symptoms and airflow obstruction, which are associated with intrapulmonary and extrapulmonary complications such as cognitive impairment (CI).[1] There is a wide range of CI prevalence among COPD, ranging from 4% to 61%, and a recent study indicates that 18.4% of individuals with mild CI (MCI) may develop dementia within a year.[2,3] The presence of CI in COPD has substantial consequences, such as poor medication adherence, smoking cessation, and functional dependency, that can affect the self-management of COPD patients. Thus, early detection of those with MCI is needed to prevent early deterioration and intervention.[2]

With a deeper insight into the pathomechanism and conducting thorough evaluations beyond spirometry, early prevention, and intervention can be done to avoid CI and its progression to dementia that occurs in many COPD patients. Up until now, the exact links between COPD and CI are unknown, but hypoxia, inflammation, and vascular abnormalities in COPD are thought to be the cause of neuronal damage that leads to CI. These conditions can be assessed by clinical factors or examination, such as pulmonary function test (PFT), radiological imaging, or serological analyses. Particularly in hypoxia, increased expression of HIF-1α has been observed in correlation with worsening COPD due to its function as an oxygen homeostasis regulator.[4] Making the association between HIF-1α and COPD severity a favoured study topic.[5–7]

The standard for diagnosing and classifying COPD severity is a pulmonary function test (PFT) using spirometry. However, high-resolution CT scan (HRCT) is becoming a phenomenon among COPD cases due to its ability to identify abnormalities not detected by pulmonary function tests, phenotyping COPD cases into emphysema-dominant or airway-dominant, and further quantify the number of abnormalities such as parenchymal destruction and bronchial thickening.[8,9] Common intrapulmonary quantitative CT (QCT) parameters that can precisely and objectively evaluate COPD phenotypes are the percentage of low attenuation area ($\%LAA_{-950}$) during inspiration with a threshold <−950 Hounsfield Units (HU) for emphysema and percentage wall area (%WA) for chronic bronchitis. However, previous studies have also found intrathoracic extrapulmonary QCT parameters to be well correlated with COPD diagnosis and severity, such as pulmonary artery-to-aorta ratio (PA:A), pectoralis muscle area (PMA), and pectoralis muscle density (PMD).[10–14] HRCT, together with the benefit of QCT, may lead to earlier identification and treatment. The importance of early detection of COPD, especially in early and moderate stages, may have a favourable impact on disease progression and clinical outcome, including mitigating future complications such as CI.

The primary aim of this study is to find the relationship and interaction of various quantitative CT (QCT) parameters, lung function, HIF-1α, and clinical factors with the development of CI among COPD patients. This study is the first to assess the role of QCT parameters in the pathomechanism of CI in patients with COPD. With a deeper insight into the pathomechanism and conducting thorough evaluations beyond spirometry, early prevention, and intervention can be done to avoid CI and its progression to dementia that occurs in many COPD patients.

Material and Methods

Subject Recruitment

This cross-sectional study is a multi-center study focusing on the role of clinical and QCT characteristics of CI in COPD. This study received two ethical approvals, that is, Ethical Committee of Persahabatan Hospital (no: 02/KEPK-RSUPP/01/2022), which allow us to recruit participants from Persahabatan Hospital from January 2022. Another ethical approval released by the Faculty of Medicine, University of Indonesia (no: KET-133/UN2.F1/ETIK/PPM.00.02/2022), which allowed us to recruit participants from three other hospitals (Cipto Mangunkusumo Hospital, Gatot Soebroto Army Hospital, and Jakarta Islamic Hospital Cempaka Putih) from February 2022. The overall study recruitment starts from January 2022 until December 2023. All procedures used in this study adhered to the institutional and national research committee's ethical requirements and the Declaration of Helsinki. All patients who participated in this study were adults and had given written informed consent. In this study, we calculated the minimum number of subjects using the multiple linear regression equation, resulting in a requirement of 90 patients. For path analysis, following the rule of thumb suggests a minimum of 5 observations per estimate parameter, and considering a total of 15 estimated parameters, a minimum sample of 75 patients was necessary. Eventually, we used the larger minimum sample size, which is 90 patients.

Out of all patients referred or diagnosed with COPD (n = 620) in four different hospitals from January 2022 to December 2023, we included only 114 patients aged 40–80 years, with a FEV_1/FVC value of <70%, no exacerbations in the previous month, and had basic literacy skills (elementary school level). Exclusion criteria included subjects with a history of severe anxiety disorders and depression (evaluated using General Anxiety Disorder-7 [GAD-7] and Patient Health Questionnaire-9 [PHQ-9]), communication difficulties, history of head injury, stroke, brain tumor, epilepsy, brain injury, active pulmonary tuberculosis, post-TB obstruction syndrome, cystic fibrosis, interstitial lung disease, lung cancer, and history of COVID-19 in the last one month, history of lung or brain surgery, lung or brain radiotherapy, and individuals with alcoholism or a history of drug abuse.

Spirometry

A spirometry test (EasyOnePro®, ndd Medical Technologies) was done to obtain lung function data of vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume at 1s (FEV_1) pre- and post-bronchodilator. Variables used in this study are FEV_1/FVC (%) for diagnosing COPD and FEV_1 pp (%) for classifying COPD severity based on GOLD criteria. All spirometry assessment performed is in accordance with the American Thoracic Society (ATS).[15]

Quantitative CT

All thoracic CT acquisitions use 128-slice HRCT (Siemens Perspective) with full inspiration without contrast with the following parameters: 120−140 kVP, 30−60 mAs, and matrix size 512 × 512 pixels. The CT image was then reconstructed using a standard algorithm with a cut thickness of 0.625 mm and a cut interval of 5 mm, a window width of 1500 HU, and a window level of −600 HU. All the images were reconstructed and transferred to workstations for QCT assessment (%LAA_{-950}, %WA, PA:A, PMA, and PMD) using 3D Slicer software version 5.30. The %LAA_{-950} parameter was performed throughout the lungs with a density limit setting of <- 950 HU. We restricted the measurement of %WA in the 3rd generation bronchi in the right upper lobe of the lung due to its location being perpendicular to the imaging plane, making it appear circular in the standard axial imaging plane and less susceptible to motion artifact.[16–19] Moreover, Nakano et al[20] showed that the assessment of large airway dimensions can reflect pathological abnormalities in the smaller airways and evaluation of the airway walls in smaller airways increased the risk of overestimation in CT scans. The ratio of PA:A was taken from the largest diameter value of the pulmonary artery and aorta in one level in the axial cut. The ratio of PA:A >1 is used due to numerous studies that have demonstrated its correlation with more severe COPD manifestations and its significant link to the presence of pulmonary hypertension.[21–23] PMA and PMD measurements were performed at the axial cut just above the aortic arch, and segmentation was carried out to describe the region of interest (ROI) (Figure 1). An agreement regarding the location determination of %WA, pulmonary artery and aorta diameter assessment, as well as pectoralis delineation was reached by three radiologists.

HIF-1α Analysis

From peripheral venous, 3 mL of blood was collected. The blood sample was centrifuged at 3000 rpm for 10 minutes at 25°C to separate serum sample from blood products. Blood serum was then stored at −80°C before the examination was carried out simultaneously. HIF-1α examination was performed using Human HIF-1α ELISA Kit ab171577 (SimpleStep ELISA® microplate) reagent. The detection technique used in this assessment is colorimetric, set at a wavelength of 450 nm, using a microplate spectrophotometer [Multiskan GO, Thermo scientific] through SkanIt 3.2 software.

Cognitive Assessment Tool

All included subjects' cognitive functions were assessed by two neurologists using the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina). This test primarily examined visuospatial/executive skills (trail-making test, copying a 3D cube, and drawing a clock following verbal commands), naming ability (identifying three animal figures), memory performances (memorizing and recalling a five-word list after a delay), attention capabilities (direct and inverse span, interference inhibition test, and a serial subtraction of 100–7), language proficiency (repetition of two complex sentences and phonological fluency), abstraction skills (quick analogy test). This test only took about 10 minutes with a total score of 30 and the common score used for diagnosing MCI is 26.[24]

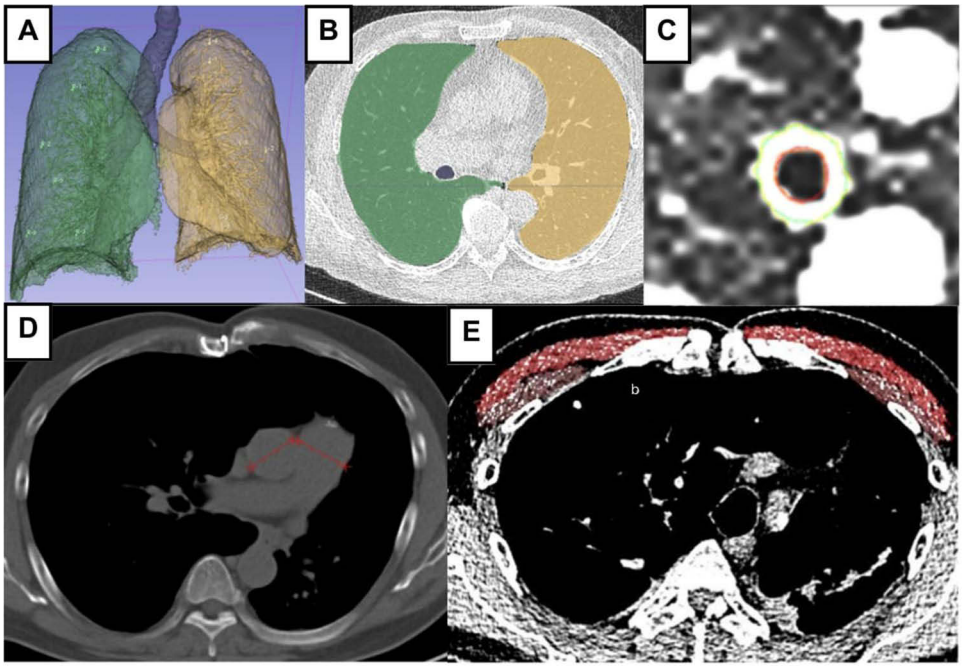

Figure 1 QCT evaluation using 3D slicer software. (**A** and **B**) Density evaluation based on $\%LAA_{-950}$ after lung segmentation to define emphysema. (**C**) Airway evaluation in the third generation of the right lung resulting in %WA. (**D**) An HRCT axial view, mediastinum window to measure PA:A ratio and (**E**) Measurement PMA and PMD on the level right above the aortic arch showing pectoralis muscle segmentation (bright red = major pectoralis muscle; brownish red = minor pectoralis muscle).
Abbreviations: *QCT, quantitative CT scan; HRCT, high-resolution CT scan; $\%LAA_{-950}$, percentage of lung attenuation area <−950 HU; %WA, wall area percentage; PA:A ratio, pulmonary artery-to-aorta ratio; PMA, pectoralis muscle area; PMD, pectoralis muscle density.*

Statistical Analysis

Statistical analysis of this study used Statistical Program for Social Science (SPSS) version 26. The comparison of subjects' characteristics was analyzed with univariate analysis of variance (ANOVA), while variables were categorical using the chi-square test. All data are presented as absolute numbers, mean ± standard deviation (SD), and percentages. Correlation analyses using the Pearson test assessed the clinical and radiological parameters' correlation with cognitive scores. Variables with a correlation score <0.25 were then included in multiple linear regression analysis to evaluate the association between variables. Path analysis using Jeffrey's Amazing Statistics Program (JASP) was conducted to find the magnitude of influence and interaction between clinical and radiological parameter variables with cognitive scores.

Results

There were 114 subjects in GOLD I–IV included in this study, and subjects' characteristics were stratified by GOLD (Table 1). Significant differences between GOLD I–IV were seen among clinical parameters, except education duration, Brinkman index, MoCA-Ina score, and HIF-1α. However, among QCT parameters, only $\%LAA_{-950}$ ($p < 0.001$), indicating emphysema, showed significant differences between GOLD, and others do not show substantial differences.

Table 2 showed that only education duration positively correlates with MoCA-Ina score ($r = 0.40$; $p < 0.001$). In the categorical comparison (Table 3), besides education duration ($p = 0.008$), BMI was significantly associated with MoCA-Ina score ($p = 0.003$). No other QCT or clinical parameters were correlated with the MoCA-Ina score.

Variables analyzed in the multiple linear regression are BMI, education duration, HIF-1α, %LAA, %WA, and FEV_1 pp. The data distribution was normal, and there was no heteroscedasticity. All variables had tolerance values greater than 0.1, and the VIF values were less than 10, indicating no multicollinearity. The Durbin-Watson value of 2.223 was greater than the dU of the Durbin-Watson table value of 2.2131, showing no autocorrelation. According to the linear regression results, education duration ($p = 0.01$) and $\%LAA_{-950}$ ($p = 0.02$) can be independent predictors of CI (Table 4).

Table 1 Participants' Characteristics

Parameters	GOLD				p-value
	GOLD I (n = 16)	GOLD II (n = 39)	GOLD III (n = 43)	GOLD IV (n = 16)	
Quantitative CT					
%LAA$_{-950}$, %	29.1 ± 8.2	29.5 ± 8.7	35.4 ± 8.5	40.98 ±8.2	<0.001*
%WA, %	70.0 ± 5.9	68.9 ± 9.96	69.5 ± 7.69	68.57 ±7.97	0.952
PA:A ratio	0.8 ± 0.2	0.8 ± 0.2	0.86 ± 0.2	0.88 ± 0.2	0.195
PMA, mm^2	731.9 ± 211.4	732.8 ± 358.9	720.8 ± 393.5	647.1 ± 156.3	0.846
PMD, HU	38.7 ± 9.8	35.4 ± 11.4	35.8 ± 7.8	36.2 ± 10.4	0.707
Clinical					
Age (</≥ 60 years)[a]	3/13	13/26	10/33	11/5	0.005*
Education duration, years	12.6 ± 4.2	11.3 ± 3.3	10.9 ± 4.2	11.3 ± 3.7	0.489
COPD duration (</≥ 5 years)[a]	6/10	27/12	20/23	13/3	0.014*
BMI, kg/m^2	25.5 ± 4.9	23.0 ± 4.8	21.1 ± 4.1	20.6 ± 3.8	0.003*
Brinkman index (cigarettes-year)	583.8 ± 634.1	603.5 ± 604.3	801.5 ± 820.4	680 ± 570.3	0.556
MoCA-Ina score	23.56 ± 4.0	23.26 ± 4.1	22.40 ± 3.8	22.06 ± 4.6	0.564
FEV$_1$pp, %	91.6 ± 10.8	62.6 ± 10.6	39.3 ± 6.2	23.8 ± 5.5	<0.001*
FEV$_1$/FVC, %	64.7 ± 4.7	56.7 ± 7.9	46.7 ± 10.3	36.5 ± 7.4	<0.001*
HIF-1α (pg/mL)	126.3 ± 3.0	51.2 ± 12.2	56.4 ± 46.1	48.8 ± 2.0	0.149

Notes: All variables are stated as Mean ± SD (ANOVA) unless stated otherwise. [a]Categorical variables using the Chi-square test are stated as absolute numbers. *p<0.05.

Abbreviations: %LAA$_{-950}$, percentage of lung attenuation area <−950 HU; %WA, percentage of wall area; BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; FEV$_1$/FVC, forced expiratory volume in one second to forced vital capacity ratio; FEV$_1$pp, forced expiratory volume in one-second percentage predicted; GOLD, Global Initiative of Chronic Obstructive Lung Disease; MoCA-Ina, Montreal cognitive assessment – Indonesian version; PA:A ratio, pulmonary artery to aorta ratio; PMA, pectoralis muscle area; PMD, pectoralis muscle density; HIF-1α, Hypoxia-inducible factor one alpha; QCT, quantitative CT.

Table 2 Correlation of QCT Parameters, Lung Function, HIF-1α, and Clinical Factors with MoCA-Ina Score

Parameter	MoCA-Ina Score	
	r	p
Quantitative CT		
%LAA$_{-950}$, %	0.15	0.103
%WA, %	0.14	0.139
PA:A ratio	−0.10	0.276
PMA, mm^2	0.08	0.386
PMD, HU	0.09	0.325

(*Continued*)

Table 2 (Continued).

Parameter	MoCA-Ina Score	
	r	p
Clinical		
Age, years	−0.09	0.32
Education duration, years	0.40	< 0.001*
COPD duration, years	0.04	0.70
BMI, kg/m^2	0.15	0.124
Brinkman index, cigarette-years	0.11	0.259
FEV_1/FVC, %	0.02	0.822
FEV_1 pp, %	0.14	0.150
HIF-1α, pg/mL	−0.15	0.105

Notes: All results were obtained from the Pearson test. *p<0.05.
Abbreviations: $\%LAA_{-950}$, percentage of lung attenuation area <−950 HU; %WA, percentage of wall area; BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume in one second to forced vital capacity ratio; FEV_1pp, forced expiratory volume in one-second percentage predicted; HIF-1α, Hypoxia-inducible factor 1α; MoCA-Ina, Montreal cognitive assessment – Indonesian version; PA:A ratio, pulmonary artery to aorta ratio; PMA, pectoralis muscle area; PMD, pectoralis muscle density; QCT, quantitative CT.

Table 3 Comparison of QCT Parameters, Lung Function, HIF-1α, and Clinical Factors with MoCA-Ina Score

Parameter	MoCA-Ina Total Score		p
	< 26 (n = 84)	≥ 26 (n = 30)	
PA:A ratio[a]			
< 1	71 (62.3%)	25 (21.9%)	1.00
≥ 1	13 (11.4%)	5 (4.4%)	
GOLD[b]			
GOLD I	10 (8.8%)	6 (5.3%)	0.47
GOLD II	27 (23.7%)	12 (10.5%)	
GOLD III	34 (29.8%)	9 (7.9%)	
GOLD IV	13 (11.4%)	3 (2.6%)	
COPD Group[b]			
Group A	25 (21.9%)	6 (5.3%)	0.14
Group B	18 (15.8%)	12 (10.5%)	
Group E	41 (36%)	12 (10.5%)	

(*Continued*)

Table 3 (Continued).

Parameter	MoCA-Ina Total Score		p
	< 26 (n = 84)	**≥ 26 (n = 30)**	
HIF-1α			
> 49.8 pg/mL	38 (33.3%)	19 (16.7%)	0.09
≤ 49.8 pg/mL	46 (40.4%)	11 (19.6%)	
Age			
≥ 60 years	59 (51.8%)	18 (15.8%)	0.30
< 60 years	25 (21.9%)	12 (10.5%)	
BMI			
≥ 18.5	55 (48.2%)	28 (24.6%)	0.003*
< 18.5	29 (25.4%)	2 (1.8%)	
Gender[a]			
Men	76 (66.7%)	25 (21.9%)	0.32
Women	8 (7%)	5 (4.4%)	
Education duration			
≥ 12 years	47 (41.2%)	25 (21.9%)	0.008*
< 12 years	37 (32.5%)	5 (4.4%)	
Smoking status[a]			
Yes	73 (64%)	23 (20.2%)	0.24
No	11 (9.6%)	7 (6.1%)	
Brinkman index[b]			
Mild	22 (19.3%)	11 (9.6%)	0.18
Moderate	28 (24.6%)	5 (4.4%)	
Severe	34 (29.8%)	14 (12.3%)	
Hypertension			
Yes	41 (36%)	12 (10.5%)	0.41
No	43 (37.7%)	18 (15.8%)	

Notes: All results were obtained from the chi-square test unless stated otherwise. [a]Fisher-Exact. [b]Likelihood Ratio. *p < 0.05.

Abbreviations: BMI, Body Mass Index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative of Chronic Obstructive Lung Disease; MoCA-Ina, Montreal cognitive assessment – Indonesian version; PA:A ratio, pulmonary artery to aorta ratio; HIF-1α, Hypoxia-inducible factor one alpha.

To understand the role of the MoCA-Ina score, we used path analysis. As shown in Figure 2, Tables 5 and 6, the final model highlights our result that education duration and $\%LAA_{-950}$ significantly impact cognitive impairment (CI), both directly and indirectly, through FEV1 pp. The model fits the data well, indicated by a CFI of 0.99, RMSEA of 0.04, and a chi-square value of 4.73 at 12 degrees of freedom (p = 0.32).

Table 4 Predictor Value Toward CI

Parameter	Unstandardized β	Standardized Coefficient β	t	p	Collinearity	
					Tolerance	VIF
%LAA$_{-950}$	0.11	0.25	2.36	0.02*	0.65	1.53
%WA	0.04	0.09	1.01	0.31	0.86	1.15
HIF-1α	−0.004	−0.12	−1.36	0.18	0.94	1.07
FEV_1 pp	0.03	0.17	1.70	0.09	0.76	1.32
Education duration	0.32	0.30	3.23	0.01*	0.82	0.12
BMI	0.08	0.01	0.91	0.36	0.64	0.16

Notes: R^2 = 0.23; *adjusted* R^2 = 0.19, p < 0.001 *p < 0.05
Abbreviations:%LAA$_{-950}$, percentage of lung attenuation area <−950 HU; %WA: percentage of wall area; BMI, body mass index; CI, cognitive impairment; FEV_1pp, forced expiratory volume in one-second percentage predicted; HIF-1α, Hypoxia inducible factor one alpha.

Discussion

All subjects in this study have a mean MoCA-Ina score ranging from 22 to 23, indicating the presence of CI across various stages of COPD. Despite the absence of statistical differences, the MoCA-Ina score decreased with increasing GOLD severity. However, there is still a significant positive correlation with education duration, as anticipated. According to the theory of cognitive reserve, which states that education can preserve cognitive abilities, even in the face of physiological and anatomical changes associated with aging and illness.[25] This preservation potentially inhibits the manifestation of clinical symptoms and signs of disease and thus, explains our findings. The consistent educational duration data observed across all GOLD groups likely contribute to the limited variations in MoCA-Ina scores among different COPD severity groups.[26,27]

BMI has significant differences among GOLD severity, indicating that lower weight is associated with worsening lung function. This inverse relationship where increased COPD severity leads to weight loss and cachexia may be driven by higher energy consumption, reduced peripheral oxygen availability, muscle disuse, and systemic inflammation.[28] Despite its significant differences, there was no correlation between BMI and CI. Diverse theories exist about the BMI-CI connection. Mun, et al[29] stated that higher BMI has been linked to better neurocognitive scores, suggesting minimal CI risk. While Qu, et al[30] reported midlife obesity is associated with higher dementia risk. The obesity paradox theory suggests that in older adults, obesity may protect cognitive function due to increased availability of vitamins and microelements, infrequent occurrence of adipose tissue dysfunction, elevated estrogen levels, and metabolic medications, including metformin, statin, and acetylsalicylic acid, which may improve clinical condition and also delaying the aging process.[31]

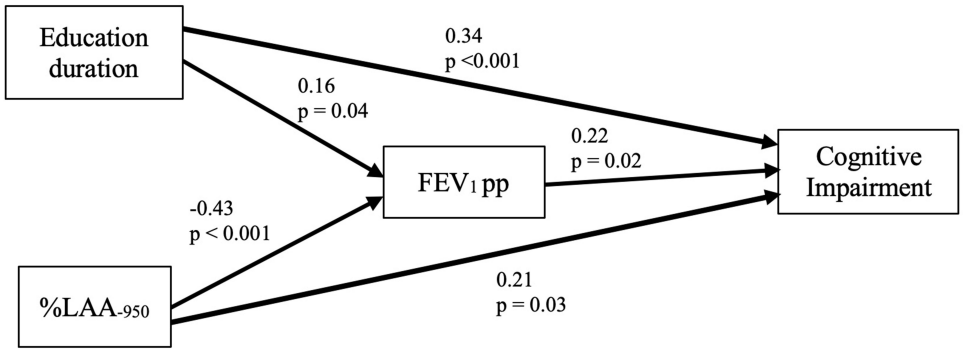

Figure 2 Path analysis model with cognitive impairment. Both %LAA$_{-950}$ and education duration directly and indirectly through FEV_1 pp contribute to CI development.
Abbreviations: %LAA$_{-950}$, percentage of lung attenuation area <−950 HU; CI, cognitive impairment; FEV_1 pp, forced expiratory volume in one-second percentage predicted.

Table 5 Qualification Measurement of Path Analysis with Cognitive Impairment

Assessment	Value
n =114; X^2(df) = 4.73(4); p = 0.32	
Comparative Fit Index (CFI)	0.99
Bollen's Incremental Fit Index (IFI)	0.99
Tucker -Lewis Index (TLI)	0.94
Bentler-Bonett Non-normed Fit Index (NNFI)	0.94
Bentler-Bonett Normed Fit Index (NFI)	0.94
Goodness of Fit Index (GFI)	1.00
Root mean square error of approximation (RMSEA)	0.04
Standardized root mean square residual (SRMR)	0.03

Table 6 The Regression Coefficient of Path Analysis with Cognitive Impairment

Predictor	Output	Estimation	Std. Error	p	95% CI (lower;upper)	Standardized
%LAA$_{-950}$	MoCA-Ina	0.09	0.04	0.03*	0.01;0.17	0.21
%WA	MoCA-Ina	0.06	0.04	0.11	−0.01;0.14	0.13
Age	MoCA-Ina	−0.06	004	0.12	−0.14;0,02	−0.13
Education duration	MoCA-Ina	0.35	0.09	<0.001*	0.18;0.52	0.34
HIF-1α	MoCA-Ina	−0.004	0.003	0.21	−0.009;0.002	−0.10
FEV_1 pp	MoCA-Ina	0.04	0.02	0.02*	0.006; 0.07	0.22
%LAA$_{-950}$	HIF-1α	0.09	1.34	0.94	−2.53;2.71	0.007
%WA	HIF-1α	0.05	1.34	0.97	−2.58;2.68	0.004
Age	HIF-1α	0.73	1.35	0.59	−1.93;3.38	0.05
Education duration	HIF-1α	−4.98	2.88	0.08	−10.62;0.65	−0.16
FEV_1 pp	HIF-1α	0.63	0.55	0.26	−0.46;1.71	0.12
%LAA$_{-950}$	FEV_1 pp	−1.03	0.20	<0.001*	−1.43;-0.64	−0.43
Education duration	FEV_1 pp	0.96	0.48	0.04*	0.03;1.89	0.16
%WA	FEV_1 pp	−0.12	0.27	0.60	−0.56;0.33	−0.04
Age	FEV_1 pp	0.40	0.23	0.07	−0.04;0.84	0.15

Notes: R^2 FEV_1 pp= 0.25. R^2 HIF-1α = 0.04. R^2 CI= 0.22. *p < 0.05. %LAA-950: percentage of lung attenuation area <−950 HU; %WA: percentage of wall area; FEV1pp: forced expiratory volume in one-second percentage predicted; HIF-1α: Hypoxia-inducible factor 1α; MoCA-Ina: Montreal cognitive assessment – Indonesian version;

Emphysema, as indicated by %LAA$_{-950}$, significantly differs across the GOLD group. The increase in %LAA$_{-950}$ confirms emphysema progression in advanced COPD stages.[32] This aligns with recent findings that local changes in alveolar micromechanics within damaged lung may drive lung injury progression that showed an increase in %LAA$_{-950}$ along GOLD stages.[33–36] This study noted a decrease in %WA with increasing GOLD severity, consistent with previous

research.[32] This occurrence may be attributed to the impact of the airway size and wall thickness on the %WA result. When both factors increase in size or other factors, such as lung distortion, alter the airway's standard size and shape, the %WA value may not accurately reflect obstruction. In emphysematous conditions, lung parenchyma destruction destabilizes the airway, leading to collapse.[37] Another explanation could be that higher GOLD grades are more associated with irreversible airway damage and degradation, while lower GOLD grades are associated with a higher of %WA due to the presence of smooth muscle hypertrophy and hyper-responsiveness of the airway.[32]

Although the education duration is the only variable that correlates with the MoCA-Ina score, our multivariate regression analysis has revealed that both %LAA and education duration can independently predict CI. This indicates that emphysema quantification and CI are better understood when considering multiple predictors simultaneously. Path analysis reveals that CI, measured by MoCA-Ina score, is directly influenced by $\%LAA_{-950}$ and education duration and indirectly through FEV_1 pp. Emphysema's direct correlation with CI may involve reduced acetylcholine (ACh) production, a crucial neurotransmitter that influences neuronal excitability and is linked to an oxygen-dependent enzyme. It is proposed that even brief episodes of hypoxia, lasting as little as 15 minutes, could lead to a decline in ACh synthesis.[7] In non-hypoxic, CI may occur due to the presence of arterial stiffness. Emphysema is thought to correlate with arterial stiffness due to shared susceptibility to elastin degradation both in the lungs and major vessels.[38] Maclay et al[38] observed systemic inflammation and reactive oxygen species, which are abundant among COPD patients, also contribute to arterial stiffness through extrapulmonary elastin degradation. However, the specific biomolecular mechanism linking COPD and CI remains unclear, as the HIF-1α result did not correlate with GOLD severity or MoCA-Ina score.

Our study found that HIF-1α has neither direct nor indirect effect on CI. HIF, a transcription factor activated by hypoxia, includes HIF-1 and HIF-2 responding to acute hypoxia due to a reduction of *prolyl hydroxylase* (PHD) activity.[39] HIF-1 expression peaks after 4 hours of hypoxia, decreasing significantly by 8 hours, while HIF-2 expression peaks at 8 hours and remains elevated for 24 hours.[40] During prolonged hypoxia, there is a sequential overlap of HIF-1 and HIF-2 responses, referred to as the HIF switch. Cellular oxygen redistribution leads to PHD reactivation, restarting HIF-1α degradation. Reduced histone deacetylase 2 and 7 (HDAC-2 and HDAC-7) in severe COPD may inhibit HIF-1α activation, leading to inadequate hypoxic response.[41,42] The absence of HIF-1α expression in our study may be due to the predominance of severe COPD subjects and stable condition participants, none experiencing acute hypoxia during recruitment. We suggested that low-grade inflammation, a hallmark of COPD, is linked to various extrapulmonary manifestations and could contribute to cognitive decline. COPD patients have elevated levels of inflammatory markers like TNF-α, IL-6, IL-8, CRP, and nitrites/nitrates (NOx).[43] These markers can cross the blood–brain barrier, potentially triggering neuroinflammation and affecting cognitive function, similar to the mechanism involved in AD.[44,45]

Considering the result of our study and other literature, we proposed mechanisms of CI development in individuals with COPD (Figure 3). Firstly, shorter education duration affects CI both directly and indirectly through a decreased cognitive reserve and FEV_1 pp reduction. Destruction of the lung parenchyma, represented by %LAA, will also, directly and indirectly, result in CI due to a larger emphysematous area, which will have a lower FEV_1 pp value, indicating hypoxia. Other QCT parameters such as %WA, PA:A, and PMA are supposedly affected by the COPD duration to influence CI significantly. HIF-1α serves as a mediator that triggers neuronal cell apoptosis. However, low-grade systemic inflammation may also play a role in CI development in chronic conditions.

The study's strengths include its multicentre design at a referral hospital, the high response rate, and the use of identical CT scan models. This study offers new insights into COPD, highlighting how QCT parameters, particularly % LAA, can represent lung function and predict CI. Limitations of this study are not considering comorbidities like diabetes or SLE that cause low-grade inflammation, not incorporating other lung parameters and lung vessel disease that could contribute to a broader comprehension of the correlation between those variables and not confirming brain pathology through brain imaging. Thus, we suggest future research to consider low-grade inflammation causes, quantitative assessment of small pulmonary vessels, and brain imaging to strengthen findings and explore other mechanisms of CI in COPD.

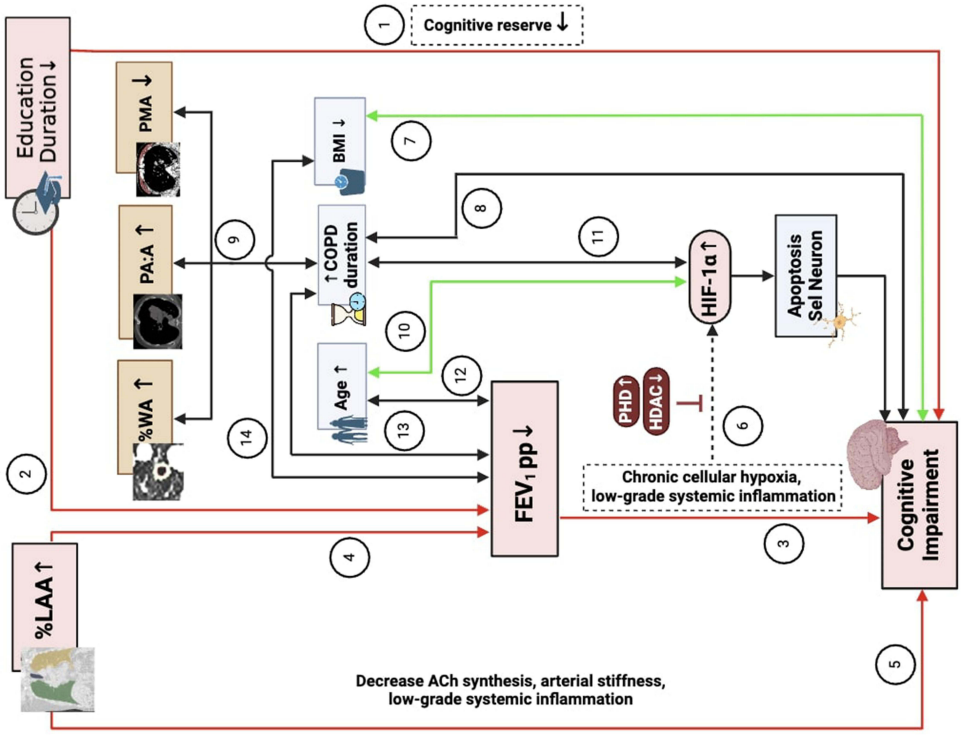

Figure 3 Proposed Mechanism of CI Development in COPD. ① Duration of education affects directly in CI, ② Duration of education affects indirectly in CI through FEV_1 pp, ③ FEV_1 pp affects directly in CI, ④ %LAA indirectly affects in CI through FEV_1 pp, ⑤ %LAA directly affects in CI, ⑥ Chronic cellular hypoxia and low-grade inflammation induce HIF-1α expression that cause neuron cell apoptosis and CI, ⑦ BMI correlates with CI, ⑧ Duration of COPD correlates with CI, ⑨ Duration of COPD that correlates with % WA, PA:A, and PM, ⑩ Age correlates with HIF-1α, ⑪ Duration of COPD correlates with CI, ⑫ Age correlates with FEV_1, ⑬ Duration of COPD correlates with FEV_1, ⑭ BMI correlates with FEV_1.

Conclusion

In conclusion, cognitive impairment in COPD patients is directly and indirectly influenced by %LAA and education duration through FEV1 pp. No link was found between HIF-1α and CI in COPD patients, suggesting low-grade systemic inflammation might pose a better mechanism. Our study highlights the importance of using QCT parameters, lung function, and clinical variables in evaluating and managing COPD.

Ethical Approval and Consent to Participate

This study received two ethical approvals, that is, Ethical Committee of Persahabatan Hospital (no: 02/KEPK-RSUPP /01/2022), which allow us to recruit participants from Persahabatan Hospital from January 2022. Another ethical approval released by Faculty of Medicine, University of Indonesia (no: KET-133/UN2.F1/ETIK/PPM.00.02/2022), which allow us to recruit participants from three other hospitals (Cipto Mangunkusumo Hospital, Gatot Soebroto Army Hospital, and Jakarta Islamic Hospital Cempaka Putih) from February 2022. All procedures used in this study adhered to the institutional and national research committee's ethical requirements and the Declaration of Helsinki. All participants in this study are adults and have given a written informed consent before enrolled in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or

critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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