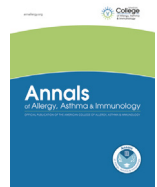




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Association between cognitive function and asthma in adults

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ABSTRACT

Background: Cognitive deficits are associated with asthma globally; however, the association between cognitive function and asthma has not been fully elucidated.

Objective: To assess the relationship between asthma and cognitive function.

Methods: A total of 202 patients with asthma aged older than 18 years were analyzed retrospectively from August 2019 to February 2020. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) test. We compared the associations of clinical parameters with cognitive function (MoCA, ≥ 23 vs < 23) and lung function (forced expiratory volume in 1 second [FEV1], $\geq 70\%$ vs $< 70\%$).

Results: Of the total participants, 89 (44.1%) indicated cognitive impairment, of whom 23.1% were aged less than 65 years and 72.9% were aged 65 years or older. MoCA scores were significantly different according to age (24.91 ± 3.89 for ages < 65 years vs 19.11 ± 5.11 for ages ≥ 65 years, $P < .001$) and lung function (23.29 ± 5.17 for FEV1 $\geq 70\%$ vs 21.23 ± 5.21 for FEV1 $< 70\%$, $P = .006$), but not according to asthma control (22.35 ± 5.38 for nonsevere asthma vs 22.88 ± 4.91 for severe asthma, $P = .55$). Age (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.014–1.13; $P = .01$), educational status (OR, 6.068; CI, 2.175–16.927; $P = .001$), and asthma duration (OR, 1.007; CI, 1.001–1.013; $P = .02$) were significantly associated with cognitive impairment.

Conclusion: Cognitive impairment was largely observed in adults (44.1%) with asthma and was more prevalent in older adults than in younger adults. Longer asthma duration and lower lung function were more associated with cognitive dysfunction.

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Introduction

Mild cognitive impairment (MCI) is a transitional state between the cognition of normal aging and mild dementia. People with MCI have an increased risk of developing Alzheimer's disease at a rate of 10% to 15% per year or a prodrome of dementia.¹ Cognitive impairment is a complex chronic condition, and its prevalence increases with age.² The presence of coexisting chronic conditions such as chronic obstructive pulmonary disease and vision or hearing impairment increases health care utilization and contributes to a higher risk of serious health outcomes.³

Asthma in adults and adolescents is a lifelong condition; asthma in early childhood is often outgrown, with different degrees of severity, causing considerable health and economic burden.⁴ Individuals with asthma may experience intermittent and prolonged periods of hypoxemia, especially during the period of poorly

controlled asthma or exacerbations.⁵ Neuronal damage resulting from hypoxia and oxidative stress caused by pulmonary dysfunction negatively influences the brain.^{6,7} Cognition is important in patients with asthma because it is a predictor of medication nonadherence.^{8,9} A recent meta-analysis found an association between cognitive function and individuals with asthma.¹⁰ Cognitive deficits were associated with asthma globally, involving academic achievement and executive functioning across the life span of individuals with asthma compared with the healthy population. The association between cognitive function and asthma has not been fully elucidated. This study aimed to assess the relationship between asthma and cognitive function. We hypothesized that patients with older age or poor asthma control have a greater risk of cognitive impairment.

Methods

Participants and Study Design

This study was conducted at Dong-A University Hospital from August 2019 to February 2020. A total of 202 adult patients with asthma aged older than 18 years were included, and the diagnosis

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of asthma was based on clinical symptoms, spirometry with bronchodilator test, and airway hyperresponsiveness to methacholine or mannitol. Patients with a history of traumatic brain injury or cerebral diseases, including dementia, were excluded.

We compared the associations of clinical parameters with cognitive function (Montreal Cognitive Assessment [MoCA], ≥ 23 vs < 23) and lung function (prebronchodilator forced expiratory volume in 1 second [FEV₁], $\geq 70\%$ vs $< 70\%$).

Assessment

The MoCA was used to screen for cognitive impairments to differentiate normal aging from MCI. The MoCA evaluates 8 cognitive abilities, including visuospatial executive function, naming, episodic memory, attention, language, abstraction, and orientation. The scores range from 0 to 30 and it takes 10 minutes to administer; a score of 25 or below indicates MCI.¹¹ In this study, the Korean version of MoCA was used, with a sensitivity of 89% and specificity of 84% for screening MCI, using a cutoff score of 23.¹² Thus, in this study, a Korean version of MoCA score less than 23 was defined as MCI. The MoCA test was performed in patients who experienced acute asthma exacerbation requiring systemic steroid treatment for more than 3 days or received systemic steroid for other medical conditions were assessed after 12 weeks.

The clinical characteristics of the study participants, including age, sex, extrapulmonary comorbidities (including cardiac disease, diabetes mellitus, hypertension, and upper airway disease), smoking status, socioeconomic status, and duration of asthma, were analyzed by reviewing the electronic medical records. Household income was classified into 2 categories: low (patients with medical assistance) or middle-high (patients with health insurance). A self-administered, 4-item questionnaire was administered to determine the patients' health status (5-point scale: fair, poor, good, very good, and excellent) and educational status. Atopy was determined by conducting an allergen skin prick test or ImmunoCAP (Phadia, Uppsala, Sweden). Patients who had a mean wheal diameter of greater than or equal to 3 mm to any allergen in the skin prick test or had serum specific immunoglobulin E (IgE) levels greater than or equal to 0.35 kU/L to common inhalant allergens were categorized as atopic. Severe asthma was defined as 3 or more exacerbations requiring systemic steroid treatment for more than 3 days despite the Global Initiative for Asthma step 4 or 5 therapy in the previous 12 months, or any severe life-threatening asthma attack. This study was approved by the institutional review board of Dong-A University Hospital, Busan, Republic of Korea (DAUHIRB-19-175), and informed consent was not required in this retrospective study.

Statistical Analysis

Categorical variables were presented as frequencies and proportions and continuous variables as mean plus or minus SD and absolute numbers. To assess for statistical significance, the Student's *t* test or Mann-Whitney *U* test was used for continuous variables, and Pearson's χ^2 test was used for categorical variables. A logistic regression analysis was performed to estimate the association between the clinical parameters and MCI. The correlation between MoCA score and asthma duration or lung function was calculated using Pearson's coefficient and was adjusted for age and educational status. Statistical analysis was performed using Statistical Product and Service Solutions, version 18.0 (SPSS Inc, International Business Machines, Chicago, Illinois). A *P* value of less than .05 was considered significant.

Results

Demographic and Clinical Characteristics of the Participants

A total of 202 patients were included in this study. The mean age of the study participants was 59.47 plus or minus 14.92 years. Of them, 85 (42.1%) were older adults (≥ 65 years), and 55.2% were women. The mean MoCA score was 22.47 plus or minus 5.27, and 89 participants (44.1%) exhibited cognitive impairment (MoCA score of < 23) (Table 1). The distribution of participants with MCI according to age is listed in Figure 1. The proportion of MCI was higher in older patients than in younger patients; however, cognitive dysfunction was also observed in middle-aged patients. The mean duration of asthma was 105.34 plus or minus 82.65 months, and the mean FEV₁ was 74.88 plus or minus 20.15%. A total of 81 participants (40.1%) had an FEV₁ of less than 70% predicted and 43 (21.3%) had severe asthma. In addition, 90 patients (44.6%) had airway hyperresponsiveness. Approximately half of the participants were atopic (54%), and most patients (83.6%) were treated with inhaled corticosteroids (Table 1).

There were significant differences in age, educational status, the prevalence of hypertension, and upper airway diseases, including allergic rhinitis and chronic sinusitis with or without nasal polyps, MoCA score, and FEV₁ between patients who were divided into 2 groups according to cognitive or lung function. However, no significant differences were observed in sex, smoking status, income, and general health status between the patient groups. A comparison between patients with and without severe asthma revealed no significant differences in clinical parameters (data not reported). MoCA scores were significantly different according to age (24.91 ± 3.89 for < 65 years vs 19.11 ± 5.1 for ≥ 65 years, $P < .001$) and lung function (23.29 ± 5.17 for FEV₁ $\geq 70\%$ vs 21.23 ± 5.21 for FEV₁ $< 70\%$, $P = .006$), but not according to asthma severity (22.35 ± 5.38 for nonsevere asthma vs 22.88 ± 4.91 for severe asthma, $P = .55$) (Fig 2).

MoCA scores were found to be negatively correlated with asthma duration ($r = -0.175$, $P = .01$) and positively correlated with prebronchodilator FEV₁ (L) ($r = 0.428$, $P < .001$) and post-bronchodilator FEV₁ (L) ($r = 0.442$, $P < .001$) (Table 2). However, no correlations were observed between the MoCA scores and asthma duration or lung function after adjusting for age and educational status.

Risk Factors for Cognitive Impairment by Logistic Regression Analysis

In the univariate analysis, various variables including age, body mass index (BMI), educational status, hypertension, upper airway disease, asthma duration, and FEV₁ were associated with cognitive impairment ($P < .05$). Other factors such as smoking and income status, inhaled corticosteroid use, and severe asthma were not associated with cognitive impairment. In the logistic regression analysis, age (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.014–1.13; $P = .01$), educational status (OR, 6.068; CI, 2.175–16.927; $P = .001$), and asthma duration (OR, 1.007; CI, 1.001–1.013; $P = .02$) were significantly associated with cognitive impairment (Table 3).

Discussion

Asthma is a common chronic inflammatory disease and affects persons of all ages; it has different degrees of severity throughout the life of patients with asthma. A high prevalence of cognitive dysfunctions has been reported in patients with asthma.^{13–15} A total of 95 adult inpatients with asthma had a brief psychological test, and 65% displayed cerebral dysfunction with signs of memory impairment.¹⁵ They were individuals with severe and perennial asthma; however, the patients' average age was only 37 years.

Table 1
Clinical Characteristics of the Total Study Participants

Characteristic	Total N = 202 (%)	Cognitive function			Lung function		
		MoCA <23, n = 89 (%)	MoCA ≥23, n = 113 (%)	P value	FEV1 ≥70%, n = 121 (%)	FEV1 <70%, n = 81 (%)	P value
Age, ^a y	59.47 ± 14.92	68.03 ± 5.7	52.72 ± 15.3	<.001	56.05 ± 16	64.57 ± 11.49	<.001
Female	112 (55.2)	52 (58.4)	60 (53.1)	.44	69 (57)	43 (53.1)	.58
BMI, ^a kg/m ²	23.9 ± 3.64	24.53 ± 3.22	23.44 ± 3.9	.03	24.24 ± 3.93	23.5 ± 3.16	.15
Smoking status							
Never-smoker	129 (63.9)	59 (66.3)	70 (61.9)	.59	82 (67.8)	47 (58)	.12
E-smoker	30 (14.9)	14 (15.7)	16 (14.2)		13 (10.7)	17 (21)	
Current smoker	43 (21.3)	16 (18)	27 (23.9)		26 (21.5)	17 (21)	
Income							
Low	28 (13.9)	16 (18)	12 (10.6)	.13	17 (14)	11 (13.6)	.92
Middle-high	184 (86.1)	73 (72)	101 (89.4)		104 (86)	70 (86.4)	
Education							
Less than high school	87 (43.1)	63 (70.8)	24 (21.2)	<.001	42 (34.7)	45 (55.6)	.003
More than or equal to high school graduate	125 (56.9)	26 (29.2)	89 (78.8)		79 (65.3)	36 (44.4)	
General health							
Fair, poor, good	147 (72.4)	67 (75.3)	80 (70.8)	.47	87 (71.9)	60 (74.1)	.73
Excellent, very good	55 (27.1)	22 (24.7)	33 (29.2)		34 (28.1)	21 (25.9)	
Hypertension	48 (23.8)	34 (38.2)	14 (12.4)	<.001	17 (14)	31 (38.3)	<.001
Upper airway disease	144 (71.3)	51 (57.3)	93 (82.3)	<.001	94 (77.7)	50 (61.7)	.01
MoCA ^a	22.47 ± 5.27	17.6 ± 3.92	26.3 ± 2.03	<.001	23.29 ± 5.17	21.23 ± 5.21	.006
Asthma duration, ^a mo	105.34 ± 82.65	123.92 ± 84.81	90.58 ± 78.16	.004	104.19 ± 82.39	107.05 ± 83.52	.81
Severe asthma	43 (21.3)	16 (18)	27 (23.9)	.30	26 (21.5)	17 (21)	.93
ICS treatment	168 (83.6)	75 (84.3)	93 (83)	.81	88 (73.3)	80 (98.8)	<.001
FEV1, ^a %	74.88 ± 20.15	70.99 ± 20.98	77.95 ± 19.01	.01	88.46 ± 11.46	54.59 ± 11.3	<.001
Atopy	109 (54)	55 (61.8)	54 (47.8)	.047	59 (48.8)	50 (61.7)	.07

Abbreviations: BMI, body mass index; E-smoker, electronic smoker; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MoCA, Montreal Cognitive Assessment.

^aData presented as mean plus or minus SD.

Moreover, neuropsychological behavior deficits in remembering spatial configurations, and incidental memory were observed in 35% of children aged 9 to 14 years with severe asthma.¹³ The risk of MCI assessed using the MoCA in patients aged 55 years and older with mild asthma increased to 78%.¹⁴ Asthma severity and frequent exacerbations are associated with cognitive impairment. Patients with moderate or severe persistent asthma had poorer health perception than those with mild asthma.¹⁶ Elderly patients with

asthma had lower oxygen saturation and indicated impaired cognitive performance such as digit symbol substitution and serial subtraction tasks compared with healthy age-matched individuals.⁵ The blood oxygen saturation of participants was significantly correlated with their performance on tasks. In this study, 44.1% of the participants exhibited cognitive impairment; of them, 30.3% were aged less than 65 years, whereas 69.7% were aged 65 years and older. Patients with cognitive impairment had lower

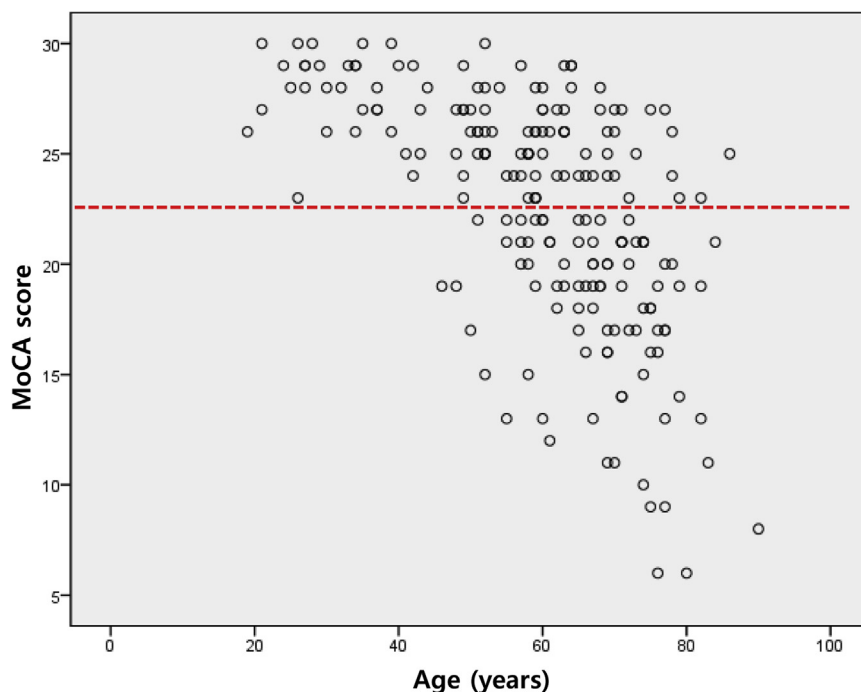


Figure 1. Distribution of study participants with mild cognitive impairment according to age. The horizontal bar indicates mild cognitive impairment defined as a MoCA score of less than 23. MoCA, Montreal Cognitive Assessment.

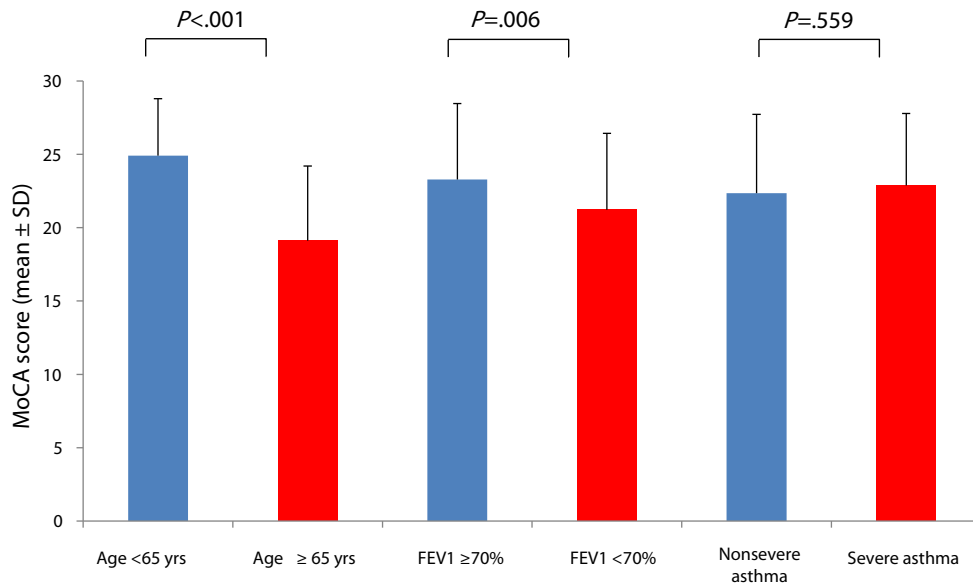


Figure 2. Comparison of MoCA scores according to age, lung function, and asthma severity. FEV1, forced expiratory volume in 1 second; MoCA, Montreal Cognitive Assessment.

lung function and longer asthma duration than those without cognitive impairment, but there was no difference in the severity of asthma between them.

Asthma can affect brain function because the brain tissues are sensitive to decreases in oxygen levels. Asthma attacks can cause cerebral hypoxia¹⁷ and lead to neural abnormalities.⁷ Intermittent hypoxia during chronic asthma impaired the learning and memory ability of mice, which cannot be attenuated by steroid treatment in the mice model.¹⁸ Neural changes from hypoxia-ischemia in vulnerable brain regions with high metabolic demands, such as the hippocampus, could translate into cognitive dysfunction. The hippocampus is the primary neural region involved in memory.¹⁹ Reduced hippocampal volume²⁰ and substantial changes in the hippocampal metabolites²¹ were observed in individuals with asthma compared with healthy controls, which may influence cognitive deficits.

Asthma and cognitive function can reciprocally influence each other. Proper control of asthma improved cognitive functions. Patients with dementia or MCI reported increased cognitive function after 1 year of optimal asthma treatment.²² Notably, 24 of 40 patients (60%) with asthma who were treated with inhaled corticosteroids reported decreased MoCA scores.²³ In addition, deficits in cognition had a detrimental effect on the ability to properly perform spirometry for the diagnosis of asthma,²⁴ medication adherence^{25,26} and inhaler technique.²⁷

Several factors, including asthma control status and severity, socioeconomic status, racial or ethnic minorities, BMI, and use of corticosteroids, were associated with cognitive impairment in individuals with asthma.^{5,10,14,22,23,28} A recent meta-analysis¹⁰

reported asthma severity to be a key moderator, with the greatest cognitive deficits associated with severe asthma. The greatest cognitive burden was found in patients with asthma who were younger men from vulnerable socioeconomic and racial or ethnic minority backgrounds. In this study, patients with asthma with cognitive impairment were older and had a higher BMI, higher prevalence of hypertension, lower educational status and lung function, and longer asthma duration. Severe asthma was not associated with cognitive impairment. The demographic characteristics of patients in this study are somewhat different from those included in the meta-analysis.¹⁰ In the meta-analysis, 55% were child-focused studies (study participants' mean age of 25 years), comprising various races and ethnicities, with most patients having a low household income. In this study, the participants were all Korean adults, with most of them having mid to high household income. In addition, the definition of severe asthma in this study is different from the other studies.^{13,15,16} These factors might affect the different results.

The prevalence of cognitive impairment, including MCI and dementia, increases with age^{2,29} and levels of education and are greatly related to cognitive function.^{30,31} The prevalence of hypertension was significantly higher in patients with cognitive impairment than in those without cognitive impairment, and hypertension was also associated with cognitive impairment (but no significant difference were noted). Hypertension accelerates the arteriosclerotic changes in the brain, which increases the resistance to blood flow and reduces perfusion, causing vascular cognitive impairment.^{32,33}

MoCA score was negatively correlated with asthma duration after controlling for age and education, and asthma duration was associated with cognitive impairment in the logistic regression analysis. Furthermore, the duration of asthma was also found to be associated with the degree of airflow limitation, which suggested that prolonged inflammation may lead to airway remodeling.^{34,35} Patients with cognitive impairment indicated lower lung function than those without cognitive impairment, and lung function was also associated with cognitive function.

This study had several limitations. First, it was a retrospective cross-sectional study. Cognitive function was assessed using only the MoCA. However, the MoCA is widely used for MCI detection. We could not evaluate the effect of changes in cognitive function on

Table 2
Correlation Between MoCA Score vs Asthma Duration and Lung Function

Characteristics	r	P value	r ^a	P value
Asthma duration, mo	−0.175	.01	−0.012	.86
Prebronchodilator FEV1, L	0.428	<.001	0.084	.23
Prebronchodilator FEV1, %	0.156	.02	−0.008	.91
Postbronchodilator FEV1, L	0.442	<.001	0.102	.15
Postbronchodilator FEV1, %	0.2	.004	0.043	.54

Abbreviations: FEV1, forced expiratory volume in 1 second; MoCA, Montreal Cognitive Assessment.

^ar adjusted for age and educational status.

Table 3

Risk factors for Cognitive Impairment by Logistic Regression Analysis

Characteristics	Univariate	P value	Multivariate	P value
	Odds ratio (95% confidence interval)		Odds ratio (95% confidence interval)	
Age, y	1.112 (1.075–1.15)	<.001	1.07 (1.014–1.13)	.01
BMI, kg/m ²	1.088 (1.004–1.179)	.03	1.065 (0.923–1.227)	.38
Current smoking	0.698 (0.349–1.395)	.30	0.592 (0.187–1.869)	.37
Low income	1.845 (0.823–4.123)	.13	1.471 (0.406–5.324)	.55
Low education	8.986 (4.729–17.072)	<.001	6.068 (2.175–16.927)	.001
Hypertension	4.371 (2.161–8.841)	<.001	3.439 (0.997–11.863)	.05
Upper airway diseases	0.289 (0.152–0.547)	<.001	0.722 (0.233–2.235)	.57
Asthma duration, y	1.005 (1.001–1.009)	.006	1.007 (1.001–1.013)	.02
Prebronchodilator FEV1, %	0.983 (0.969–0.997)	.01	1.0 (1.001–1.013)	.99
ICS treatment	1.097 (0.515–2.327)	.81	0.497 (0.123–2.015)	.32
Severe asthma	0.698 (0.349–1.395)	.30	0.918 (0.277–3.043)	.88

Abbreviations: BMI, body mass index; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid.

asthma control or vice versa. Second, the study population was largely heterogenous. Comorbid conditions, including allergic or psychological diseases, asthma medication, and asthma severity, can affect cognition.^{10,36} The study population only included a small number of patients who experienced depression or anxiety (3.0%), and most study participants had upper airway disease, including allergic rhinitis. In particular, age affected the cognitive function. Cognitive deficits were observed in younger and in older patients with asthma, and we found that cognitive deficits were more common in older patients with asthma.

Cognitive impairment was observed in adults with asthma. Individuals with asthma who were older adults and had hypertension, longer asthma duration, and lower lung function were more likely to develop cognitive dysfunction. Thus, it is necessary to assess cognitive functions for individuals with asthma. Early identification and improvement of cognitive dysfunction in individuals with asthma would be helpful to achieve better asthma control and outcome. A longitudinal follow-up study is needed to evaluate the risk factors for cognitive impairment in patients with asthma and the association between asthma control and cognitive function using a large population.

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