Special Issue Article "Vitamin B12" **Research Article**

Characterisation of Vitamin B12 Level and its Relationship with Cognitive Performance in the Community-Dwelling Elderly

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ARTICLE INFO

Received Date: May 28, 2022
Accepted Date: April 20, 2022
Published Date: April 22, 2022

KEYWORDS

Clock-drawing test
Mini-mental state examination
Body mass index

Citation for this article: João Senger, Joana Emilia Senger, Neide Maria Bruscato, Berenice Maria Werle and Emilio Hideyuki Moriguchi. Characterisation of Vitamin B12 Level and its Relationship with Cognitive Performance in the Community-Dwelling Elderly. Nutrition And Food Science Journal. 2022; 5(1):132

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ABSTRACT

Introduction: In the current scenario of population aging, the over-80s is the age group that is growing the most, proportionally. This subset is at greater risk of cognitive deficits and nutritional deficiencies, with negative impacts on quality of life.

Objectives: To identify associations between vitamin B12 deficiency and cognitive deficit among very old seniors. The study design is cross-sectional and population based. A total of 153 seniors over the age of 80 years (86±4 years), residents of the municipal district of Veranópolis, RS, Brazil, were recruited. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Clock-Drawing Test (CDT), and vitamin B12 levels were assayed. Sociodemographic data were obtained using a standardised questionnaire. Associations were assessed using multivariate analyses.

Results: The prevalence of cognitive deficit was 47.7% (95% CI 39.7-55.7) according to the MMSE and 58.2% (95%CI 50.3-66.1) according to the CDT. In adjusted analyses, cognitive deficit according to the MMSE was linearly and positively associated with age only. Cognitive deficit assessed by the CDT was 5 times more frequent among those with low serum concentrations of vitamin B12. Other variables with positive associations were older age, widowhood, lower level of education, and taking prescription drugs with central nervous system activity. Being single, living with offspring, or living alone were protective factors against cognitive deficit.

Conclusions: Cognitive deficit in this population of very old seniors proved positively associated with advanced age, widow hood, and low level of education. However, regarding nutritional status, only low serum vitamin B12 concentration was associated with cognitive deficit.

INTRODUCTION

According to data from the World Health Organisation (WHO), there are currently around 841 million people aged 60 years or over. This number will double by 2025 and in 2050 will reach two billion, 80% of whom will be living in low-income and middle-income countries [1]. This demographic transition will be accompanied by an epidemiological transition which will involve changes in the health and nutritional status of older people, increasing the risks of infectious, chronic, neurodegenerative, and cardiovascular diseases. Dementia is the most common group of neurodegenerative conditions, causing cognitive deficit, which is a devastating complication for the older people affected and their families [2,3]. Although it is estimated that 66% of cases of dementia worldwide are located in developing countries, less than 10% of population-based research into neurodegenerative diseases, cognitive deficit, and dementia is conducted in these countries [4,5]. Globally, the incidence and prevalence of dementia increase exponentially with age, doubling every 5 years, approximately, from 60 years of age onwards. After 64 years of age, the prevalence is around 5 to 10%, and annual incidence is around 1 to 2%, reaching 15 to 20% and 2 to 4%, respectively, after 75 years of age [6].

Nutritional deficiencies, particularly vitamin B12 deficiency and protein-energy malnutrition, are associated with worse cognitive performance, even among patients without dementia [7,8,9]. Abnormal nutritional status is a predictor of severity and progression of cognitive deficits [10]. Studies show that low concentrations of vitamin B12 and elevated homocysteine are related to acceleration of cognitive decline [11]. A lack of nutrients in the diet can lead to cerebral deficits and cognitive impairment. In other words, malnutrition, which causes physical frailty among older people, also causes cognitive changes, resulting in an entity currently referred to as cognitive frailty [12]. High homocysteine levels have been associated with endothelial dysfunction, reduced nitric oxide activity, atherosclerosis, and subsequent increased risk of several cardiovascular and cerebrovascular problems that can lead to cerebral atrophy, increasing cerebral aging and cognitive decline [13].

The combination of factors such as malnutrition, frailty, and cognitive deficits is frequent among very old people, which is exactly the subset of the population that, proportionally, is growing the most worldwide, which is why studying these no so logical entities is so important. Therefore, the present study aimed to identify associations between vitamin B12 deficiency and cognitive deficit among very old seniors.

METHODS

This cross-sectional study was conducted in 2015 and has a population-based sample of very old seniors; residents of the urban and rural areas of the municipal district of Veranópolis in Rio Grande do Sul, the southernmost state of Brazil. This municipal district is located in the north east of the state of Rio Grande do Sul, 170 km from the state capital, Porto Alegre, at an altitude of 705 m, and has a subtropical climate. Life expectancy in Veranópolis is around 77.9 years for women and 73.2 years for men. This municipal district is one of the 20 towns with more than 17000inhabitantswiththe highest life expectancy in Brazil. It is estimated that there are 1010 residents over the age of 80 years (357 mena nd 653 women) [14].

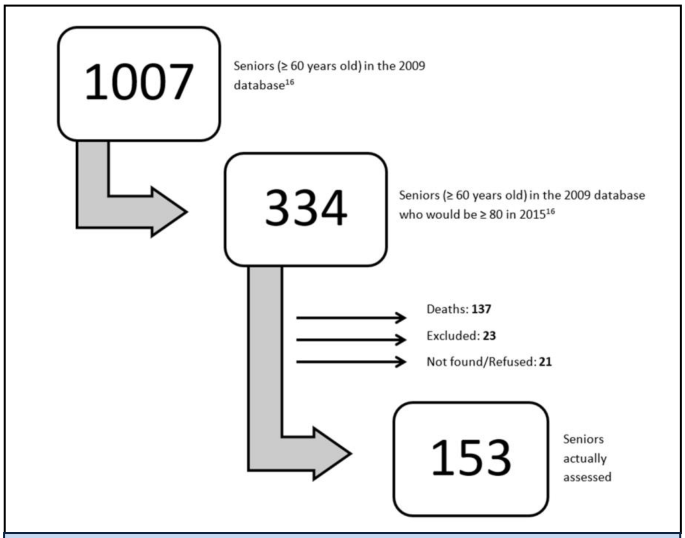

Figure 1: Flow diagram illustrating participants in 2009 and 2015.

The sample size was calculated to estimate the prevalence of cognitive deficit based on data from the study by Herrera et al. [15] conducted in the town of Catanduva in Sao Paulo, Brazil, which found a 23.5% prevalence of cognitive deficit among people over the age of 80 years. Considering a margin of error of 6 percentage points and a 95% confidence level, 161 individuals would be needed. Adding 10% to account for losses from the sample takes the number to 177 individuals. The sample size calculation for analysis of associations with malnutrition was based on the following assumptions: a 95% confidence level, 80% power, 3:1 ratio of not exposed to exposed, a 23.5% prevalence of the outcome among the not exposed (based on the study by Herrera et al [15]) and a prevalence ratio of 2, which resultedin184 individuals. Adding 10% to this number to account for possible losses resulted in 212 individuals. The sample was selected from a population of seniors who had participated in a 2009 study with the initial objective of profiling the characteristics of the elderly population for the Influenza Vaccination Campaign and who were 80 years or older in 2015. In 2009, a casual systematic sampling process was used, which was described by Quatrin et al [16]. A total of 334 of the participants would be 80 years or older in 2015. It proved possible to study 153 of these, who participated up to the end of the study (Figure 1).

Data were collected using a structured questionnaire, which had been standardised and pre-tested, covering demographic and socioeconomic variables, nutritional assessment, cognitive and neurological assessments, and biochemical tests (serum vitamin B12 and albumin assays). Collections were conducted at the town hospital and in the seniors' homes. The study outcome was cognitive deficit as assessed using the Mini-Mental State Examination (MMSE) and the Clock-drawing Test (CDT) neuropsychological examinations. The MMSE is a cognitive assessment scale that is used for investigation and monitoring of cognitive decline among people at risk of dementia, as is the case of very old seniors. It has been widely used all over the world since it was first proposed by Folstein et al [17]. In Brazil, the MMSE was first proposed by Bertolucci et al., [18] who observed that the total MMSE score is dependent on the level of education. It was later modified by Brucki et al. [19] for use in Brazil with the following cut off points for normality, which vary according to the level of education: Illiterate – over 20 points; 4 years of schooling – over 25 points; 5to 8 years of schooling – over 26 points; 9to 11 years of schooling – over 28 points; and more than 11 years of schooling – over 29 points. The scale achieved 84% sensitivity and 60% specificity when a 23/24 cut off point was used with a sample of seniors seen at a mental health clinic.

The CDT is a simple neuropsychiatric instrument that can be easily administered to assess a range of cognitive functions [20]. There has been considerable interest in the CDT over the last 20 years because of its role as an early screening tool for cognitive decline, especially in older seniors, since it is capable of identifying changes before they are detected with the MMSE, primarily because it has greater sensitivity for early executive function compromise. The three different CDT in use yield similar results, with the Shulman scale performing best (sensitivity 74.2 to 84.8%; specificity 66.7 to 89.9%). The demographic variables analysed included age group (80-84 years/85-89 years/≥90 years), sex (male/female), marital status (married/single or widowed), who the participant lives with (partner/offspring/alone), and area of residence (urban/rural). The socioeconomic variable used was total schooling, which was categorised, on the basis of its distribution, as <4 years/4 years/≥ 5 years.

The Mini Nutritional Assessment (MNA), 10developed to detect malnutrition in seniors, was used to assess nutritional status. The MNA is based on a series of simple anthropometric measurements, such as Body Mass Index (BMI), waist circumference (although in very old seniors fat is redistributed to the central region, compromising the value of this measurement when compared with younger people), arm circumference, leg circumference, and percentage weight loss during the last year. It also includes a general assessment of the patient (six questions related to lifestyle, use of medications, and functional capacity), a subjective assessment (self-view of health and nutrition), and a dietary questionnaire (eight questions related to number of meals, food and liquid intakes, and feeding autonomy) [10].

Weight and height measurements were used to calculate BMI, which was classified according to the cut off points suggested by the WHO: normal weight, from 18.5 to 24.9 kg/m^2; overweight, from 25 to 29.9 kg/m^2; and obese, ≥30 kg/m^2. Waist circumference was used to detect abdominal obesity with cut-offs of ≥88 cm for women and ≥94 cm formen [21].

The MNA scores anthropometric measurements (wrist circumference and BMI), food intake, motility, psychological problems or acute diseases and global assessment (arm circumference, leg circumference, medication, skin lesions, eating habits, and self-reported health status) as separate stages. If the sum of Screening points is >12 the senior is classified as well-nourished and the test is stopped, whereas a score<11 requires completion of the remainder of the questionnaire, the general Assessment, and a total final score of >24 classifies nutritional status as normal, 17 to 23.9 as at risk of malnutrition, and <17 as malnourished [22]. Serum vitamin B12 was assayed using the immunoassay technique (Perkin-Elmer kits, Wallac Oy, Turku, Finland). A serum vitamin B12 concentration greater than 200pg/mL (148pmol/L) was defined as normal [7,23]. Use of drugs was assessed by counting the number of drugs taken daily by the participants. The number of prescription drugs (0-3/4-6/≥7) and the number of drugs with Central Nervous System (CNS) activity (none/≥1) were analysed. Drugs with CNS activity included tranquillisers, anti-depressants, and anti-parkinsonian drugs, among others. Data were double input using EPIDATA in order to avoid data entry errors and inconsistent data. Data analysis began with a description of absolute and relative frequencies of independent variables and their relationships to the outcome studied according to the assessment instruments, using Fisher's exact test and the chi-square test for linear trend. Since the outcomes dichotomous and because the sample is relatively small, logistic regression was used to estimate crude and adjusted odds ratios. The adjusted analysis only included variables with statistical significance lower than 20% ($p<0.2$). A significance level of less than 5% ($p<0.05$) was used to detect associations. All analyses were performed using STATA, version 12.1. The study conforms with the ethical principles regulating studies of this nature, as laid out in National Health Council resolution 466/12. The research protocol was approved by the Ethics Committee at the Universidade do Vale dos Sinos, and all participants signed free and informed consent forms before the research project was started.

RESULTS

Of 334 seniors who participated in the 2009 study and would have been 80 or over in 2015, 137 had died, 23 were excluded, and 21 could not be located or refused to participate. Therefore, analyses were conducted with a total of 153 seniors aged 80 years or over in 2015 (Figure 1).

The mean age of interviewees was 86 years (standard deviation = 4). Most of the participants were female (69%), widowed or single (62%), living in urban areas (78%), and had 4 years or fewer of schooling (80%). Of the whole sample, 67% were overweight or obese (BMI ≥25) and 61% had abdominal obesity. Regarding malnutrition diagnoses, just 6.5% were classified as having mild malnutrition according to the MNA criteria and none of them met the criteria for BMI, or waist, arm, or calf circumferences. The results for number of medications showed that 64% of the elderly participants took at least 4 drugs and 52.3% took at least one drug with CNS activity. Approximately 30% consumed proton-pump inhibitors, which are known to influence the absorption of vitamin B12 in older people. The biochemical test results showed that 13% had a serum vitamin B12 concentration ≤ 200 pg/mL (Table 1).

Table 1: Distribution of sample and percentages of abnormal results on Clock-drawing Test (CDT) and Mini MentalState Examination (MMSE) by independent variables, in seniors from Veranópolis, RS, Brazil (n=153).

Variables	n	%	% abnormal CDT	p*	% abnormal MMSE	p*
Age group						
80-84 years	79	51.6	49.4	0.004	35.4	<0.001
85-89 years	48	31.4	62.5		47.9	
≥ 90 years	26	17.0	80.4		84.6	
Sex						
Female	105	68.6	61.0	0.429	50.5	0.311
Male	48	31.4	54.2		41.7	
Marital status						
Married	59	38.6	59.3	0.047	32.2	0.001
Widowed/Single	94	61.4	58.5		57.5	
Living with						
Partner	67	43.8	59.7	0.133	32.8	0.001
Offspring	58	37.9	65.5		67.2	
Alone	28	18.3	42.9		42.9	
Area						
Urban	119	77.8	58.0	0.930	48.7	0.634
Rural	34	22.2	58.8		44.1	
Total schooling						
≥ 5 years	31	20.3	45.2	0.017	38.7	0.125
4 years	62	40.5	54.8		45.0	
< 4 years	60	39.2	70.0		55.0	
BMI classification						
Normal weight	51	33.3	60.8	0.599	47.1	0.723
Overweight	67	43.8	61.2		46.3	
Obese	35	22.9	51.4		51.4	
Waist circumference						
Normal	59	38.6	61.0	0.662	45.8	0.702
Abdominal obesity (F ≥88 cm/ M ≥94 cm)	94	61.4	57.4		48.9	
Mini Nutritional Assessment score						
Normal (>13.5)	143	93.5	58.7	0.938	46.9	0.421
Mild malnutrition (17-23.5)	10	6.5	60.0		60.0	
Prescription drug use						
0-3 drugs	55	35.9	61.8	0.887	56.4	0.349
4-6 drugs	52	34.0	53.8		38.5	
≥ 7 drugs	46	30.1	60.9		47.8	
Drugswith CNS activity						
None	73	47.7	52.1	0.104	45.2	0.553
≥ 1 drug	80	52.3	65.0		50.0	
Vitamin B12 level						
> 200 pg/mL	133	86.9	56.4	0.115	46.6	0.484
≤ 200 pg/mL	20	13.1	75.0		55.5	

BMI, body mass index; CNS, central nervous system.

*Fisher's exact test and chi-square test for linear trend.

The prevalence of cognitive deficit was 58.2% (95%CI 50.3-661) according to the CDT and 47.7% (95%CI 39.7-55.7) according to the MMSE (data not shown in tables).Higher prevalence rates of cognitive deficit were found with both assessment instruments among the older participants and widows (Table 1). The analyses of cognitive deficit measured by the CDT were adjusted for age group, marital status, who the participant lives with, and total schooling, and the results are shown in (Table 2). It was found that the likelihood of having cognitive deficit increased linearly with age (seniors over the age of 90 had a 6 times greater likelihood of an abnormal CDT result, when compared to those in the age range 80 to 84 years);was around 9 times greater among those who were widowed/single, when compared with married participants; increased linearly in an inverse relationship with level of education (5 times greater among those with 4 years or less of schooling, when compared to those with 5 years or more of schooling); and was 2.5 times greater among individuals who took drugs with CNS activity, when compared with those who did not. In contrast, being single and living with offspring or living alone were protective factors against cognitive deficit. The likelihood of cognitive deficit was also 5 times greater among those who had low serum vitamin B12 concentrations than those with normal concentration (Table 2). The analyses of cognitive deficit measured by the MMSE were also adjusted for age group, marital status, who the participant lives with, and total schooling and revealed that seniors over the age of 90 had a 7 times greater likelihood of an abnormal MMSE score, when compared with those aged 80 to 84 years (Table 3).

Table 2: Crude and adjusted Odds Ratios (OR) for abnormal Clock-drawing Test (CDT) by independent variables, among seniors from Veranópolis, RS, Brazil (n=153).

Variables	Crude OR	p*	Adjusted OR†	p*
Age group				
80-84 years	1	0.005	1	0.001
85-89 years	1.71 (0.82-3.55)		2.95 (1.21-7.18)	
≥ 90 years	4.31 (1.48-12.6)		6.35 (1.85-21.78)	
Marital status				
Married	1	0.117	1	0.035
Widowed	1.12 (0.57-2.21)		8.73 (1.22-62.50)	
Single	0.11 (0.01-1.01)		0.33 (0.03-3.92)	
Living with				
Partner	1	0.140	1	0.036
Offspring	1.28 (0.62-2.66)		0.10 (0.01-0.79)	
Alone	0.51 (0.21-1.24)		0.07 (0.01-0.53)	
Total schooling				
≥ 5 years	1	0.018	1	0.005
4 years	1.47 (0.62-3.51)		1.92 (0.68-5.44)	
< 4 years	2.83 (1.16-6.95)		4.96 (1.54-15.96)	
Drugs with CNS activity				
None	1	0.105	1	0.025
≥ 1 drug	1.71 (0.89-3.28)		2.48 (1.11-5.56)	
Vitamin B12 level				
> 200 pg/mL	1	0.123	1	0.012
≤ 200 pg/mL	2.32 (0.80-6.75)		5.37 (1.44-19.97)	

CNS, central nervous system.

*Wald tests for heterogeneous proportionsand linear trend.

†Adjusted for age group, marital status, who the participant lives with, and total schooling.

Table 3: Crude and adjusted Odds Ratios (OR) for abnormal Mini-Mental State Examination (MMSE) by independent variables, among seniors from Veranópolis, RS, Brazil (n=153).

Variables	Crude OR	p*	Adjusted OR†	p*
Age group				
80-84 years	1	<0.001	1	0.001
85-89 years	1.66 (0.81-3.48)		1.75 (0.77-4.01)	
≥ 90 years	10.02 (3.13-31.98)		7.11 (2.10-24.08)	
Marital status				
Married	1	0.001	1	0.257
Widowed	3.28 (1.64-6.58)		2.77 (0.58-13.23)	
Single	0.35 (0.04-3.12)		0.58 (0.06-5.98)	
Living with				
Partner	1	<0.001	1	0.433
Offspring	4.20 (1.99-8.88)		0.18 (0.22-6.09)	
Alone	1.53 (0.62-3.79)		0.61 (0.12-3.01)	
Total schooling				
≥ 5 years	1	0.123	1	0.334
4 years	1.30 (0.54-3.14)		1.14 (0.41-3.20)	
< 4 years	1.94 (0.80-4.68)		1.40 (0.45-4.32)	
Serum albumin level				
> 3.5 g/dL	1	0.073	1	0.104
≤ 3.5 g/dL	7.07 (0.83-6.24)		6.16 (0.61-62.50)	

CNS, central nervous system.

*Wald tests for heterogeneous proportions and linear trend.

†Adjusted for age group, marital status, who the participant lives with, and total schooling.

DISCUSSION

The primary objective of this study was to assess the relationship between vitamin B12 levels and cognitive function in very old seniors (over 80s) living in the community. In Brazil, the prevalence of cognitive deficit among seniors aged 80 years or older is reported as 23.5% in a study conducted by Herrera et al.15in the town of Catanduva. The prevalence observed in the present study was 58.2% according to the CDT and 47.7% according to the MMSE, which is well above the rate in the reference article. This could be due to the high frequency of CNS drug use in the population investigated (51% of the seniors studied took drugs with CNS activity).

The prevalence of cognitive deficit, both according to the MMSE and according to the CDT, was higher at more advanced ages, among widows, and among those with less education. Seniors who reported using CNS drugs also had a higher frequency of cognitive deficit when assessed by the CDT. Inouye et al. [24] observed that North-American seniors in the top tercile for performance in cognitive screening tests had a higher level of education, higher income, better health status, absence of depressive symptoms (took fewer drugs with CNS activity),and were more engaged in social and physical activities compared with seniors with intermediate and low performance. Along the same lines, in a study by Ylikosk et al., [25] groups with better performance in cognitive screening tests had greater participation in social activities and a higher level of education. Our data are in line with these published data, since those with a higher level of education and lower consumption of CNS activity drugs exhibited less cognitive deficit.

In the adjusted analysis of CDT results, living alone reduced the likelihood of cognitive deficit, which appears contradictory. Our interpretation of this finding is that those who reported living alone might be more independent because they are healthier, while those living with offspring would be more dependent.

With regard to the relationship between nutritional status and cognitive deficit according to the CDT, those who had low vitamin B12 levels had a 5 times greater likelihood of scoring low on the CDT than those with normal levels of the vitamin, which is considered essential for neuronal function. Vitamin B12 deficiency is common in seniors, reaching rates of 2 to 4%, 9 because of atrophic gastritis, which increases with aging, causing absorption difficulties [26]. Vitamin B12 deficiency may be associated with neurological deterioration, and cognitive deficit [27], which supports the results observed in the present study. It is accepted in clinical practice that dementia caused by vitamin B12 deficiency is considered a potentially reversible form, that is, if the deficiency is corrected, the cognitive deficit is often reversed [28].

While cross-sectional studies have demonstrated an association between low plasma vitamin B12 levels and low MMSE scores, the results of prospective studies have proved controversial [29]. It should be considered that our sample had a very low percentage of altered serum vitamin B12 and albumin levels. However, this is a relatively well-nourished population and only 20 of these seniors had abnormal vitamin B12 levels and just nine had abnormal albumin. Therefore, the possibility of type II statistical errors cannot be ruled out.

In relation to other indicators of nutritional status (BMI; waist, calf, and arm circumference; and the MNA), only the MNA identified mild malnutrition (6.5%) among the study participants. No significant association was observed between these variables and cognitive deficit. Published data show a positive association between higher BMI and lower morbidity and mortality after 70 years of age [30,31].

Although our study was unable to demonstrate a relationship between malnutrition and cognitive deficit (there was a higher prevalence of abnormal CDT and MMSE results among those with mild malnutrition according to the MNA, but this was not significant), there are reports in the literature showing that cognitive deficit can be a factor that leads to malnutrition, provoking weight gain or loss, or nutritional deficits. Apathy, lack of initiative, and loss of sense of smell contribute to reduced nutritional intake, mediated by reduced motivation to prepare meals, greater likelihood of missing meals, and reduced interest in food. Other possible explanations for weight loss, in the presence of cognitive deficit, include reduced appetite because of limbic system dysfunction and hypothalamus abnormalities [32]. These mechanisms could explain the conflicting results of previous studies [33]. Our findings are compatible with the idea that cognitive performance in very old seniors is a process and the result of many different factors associated with lifestyle, socioeconomic conditions, and health (absence of chronic degenerative and psychiatric diseases), as previous studies have shown [25,27,34].

One important limitation of the present study is the losses from the original sample that served as a basis for recruitment. However, losses are expected in a study of seniors over the age of 80 years. At the time the present study was conducted, the eligible population was below the target sample size, and we were able to analyse only 153 individuals. Also, selection bias cannot be ruled out.

CONCLUSION

The prevalence of cognitive deficit according to the MMSE and according to the CDT was higher among those of more advanced age, among those who were widowed, and among those with fewer years of schooling, as the demonstrated in the world literature. With regard to the relationship between vitamin B12 levels and cognitive deficit, a significant association was observed between low serum vitamin B12 concentration and the outcome when assessed using the CDT. Since this was a population with low prevalence rates of vitamin deficiency and malnutrition according to the MNA and other anthropometric measurements, the sample size may not have had enough statistical power to detect associations between cognitive deficit and the nutritional variables chosen.

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