



**HAL**  
open science

## High Serum Vitamin B12 Levels Associated with C-Reactive Protein in Older Patients with Cancer

Anne-Laure Couderc, Eddy Puchades, Patrick Villani, Robin Arcani, Laure Farnault, Aurélie Daumas, Anais Courcier, Laurent Greillier, Fabrice Barlesi, Florence Duffaud, et al.

► **To cite this version:**

Anne-Laure Couderc, Eddy Puchades, Patrick Villani, Robin Arcani, Laure Farnault, et al.. High Serum Vitamin B12 Levels Associated with C-Reactive Protein in Older Patients with Cancer. *Oncologist*, 2020, 25 (12), pp.e1980-e1989. 10.1634/theoncologist.2019-0894 . hal-03585217

**HAL Id: hal-03585217**

**<https://hal.science/hal-03585217>**

Submitted on 5 Jul 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## High Serum Vitamin B12 Levels Associated with C-Reactive Protein in Older Patients with Cancer

ANNE-LAURE COUDERC<sup>a,ε,h</sup>, EDDY PUCHADES,<sup>b</sup> PATRICK VILLANI,<sup>a,ε,h</sup> ROBIN ARCANI,<sup>a,b,ε</sup> LAURE FARNAULT,<sup>b</sup> AURÉLIE DAUMAS,<sup>a,ε,j</sup> ANAIS COURCIER,<sup>a,ε</sup> LAURENT GREILLIER,<sup>c,j</sup> FABRICE BARLES,<sup>c,j</sup> FLORENCE DUFFAUD,<sup>d,j</sup> SÉBASTIEN SALAS,<sup>d,j</sup> RÉGIS COSTELLO,<sup>b,j</sup> GAËTAN GENTILE,<sup>j</sup> VINCENT PRADEL,<sup>e</sup> PIERRE SUCHON,<sup>f,i</sup> GEOFFROY VENTON<sup>b,j</sup>

<sup>a</sup>Geriatric and Therapeutic Unit, Internal Medicine, <sup>b</sup>Hematology and Cellular Therapy Department, <sup>c</sup>Multidisciplinary Oncology and Therapeutic Innovations Unit, <sup>d</sup>Oncology Unit, <sup>e</sup>Public Health Department, and <sup>f</sup>Hematology Laboratory Unit, Assistance Publique–Hôpitaux de Marseille (AP-HM), Marseille, France; <sup>ε</sup>PACA West Coordination Unit for Geriatric Oncology (UCOG), Marseille, France; <sup>h</sup>Etablissement Français du Sang, Anthropologie, Droit, Ethique en Santé, Centre National de la Recherche Scientifique (CNRS), Marseille, France; <sup>i</sup>Centre de Recherche en Cardiovasculaire et Nutrition (C2VN), Institut National de Recherche pour l'Agriculture, l'Alimentation et l'Environnement (INRAE), INSERM, Marseille, France; <sup>j</sup>Aix-Marseille Université, Marseille, France

Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** High serum vitamin B12 levels • C-reactive protein • Early death • Unplanned hospitalization • Older patients with cancer

### ABSTRACT

**Background.** A Comprehensive Geriatric Assessment (CGA) has been proposed to assess prognosis and to adapt oncological care in older patients with cancer. However, few biological markers are incorporated in the CGA.

**Methods.** This comparative study on older patients with cancer was realized before final therapeutic decision and during a CGA that included biological markers. Our objective study was to know if the serum vitamin B12–C-reactive protein index (BCI) can help to estimate early death and unplanned hospitalization. Associations between BCI and unplanned hospitalization or mortality were analyzed using ordered multivariate logistic regression.

**Findings.** We included 621 older cancer adults in outpatient care with a median age of 81 years (range, 70–98 years) from September 2015 to May 2018. In this study, 5.6% of patients died within 3 months, 8.8% had

unplanned hospitalization within 1 month, and 11.4% had unplanned hospitalization within 3 months. Hypercobalaminemia was present in 83 patients (13.4%), and 34 patients (5.5%) had BCI >40,000. According to the multivariate analysis, BCI was a prognostic factor of mortality within 3 months and unplanned hospitalizations at 1 and 3 months. Impaired activities of daily living (ADL) and palliative care were also risk factors for mortality within 3 months. Impaired instrumental ADL, low albumin level, and palliative care were risk factors for unplanned hospitalization at 1 month.

**Interpretation.** BCI could be routinely added to the CGA process, as part of a pretreatment workup, in order to assess more precisely the frailties and to adapt oncological care in older patients treated for cancer. *The Oncologist* 2020;25:e1980–e1989

**Implications for Practice:** Aging comes with an increase of frailties and comorbidities. To identify frailties in older patients with cancer, this study used a Comprehensive Geriatric Assessment, which allowed for the adaptation of each treatment plan in accordance with the individual needs of the patients. However, biological characteristics were not included in this assessment. This study showed that hypercobalaminemia and vitamin B12 -C-reactive protein index may be potential markers for cancer with poor prognosis, particularly in the older population. These biological markers can be used in geriatric oncology and general medicine.

Correspondence: Anne-Laure Couderc, M.D., Geriatric and Therapeutic Unit, Internal Medicine, Assistance Publique–Hôpitaux de Marseille (AP-HM), Marseille, France. Telephone: +330491744530; e-mail: anne-laure.couderc@ap-hm.fr Received November 21, 2019; accepted for publication July 17, 2020; published Online First on August 19, 2020. <http://dx.doi.org/10.1634/theoncologist.2019-0894>

No part of this article may be reproduced, stored, or transmitted in any form or for any means without the prior permission in writing from the copyright holder. For information on purchasing reprints contact [Commercialreprints@wiley.com](mailto:Commercialreprints@wiley.com). For permission information contact [permissions@wiley.com](mailto:permissions@wiley.com).

## INTRODUCTION

Older persons make up a large percentage of the cancer population. Currently, cancer affects nearly 60% of people aged  $\geq 65$  years in Europe and nearly 50% of people aged  $> 65$  years in the U.S. [1, 2]. For many years, older patients with cancer have been treated according to their physiological age regardless of their state of health. The development of geriatric oncology has greatly improved the management of these older patients, with a Comprehensive Geriatric Assessment (CGA) being conducted before and during cancer treatment on older patients with cancer who are identified as frail according to the G8 screening tool [3–5]. CGA assesses geriatric frailties and syndromes to improve oncological treatment outcomes in older patients and to propose a personalized care plan. But biological characteristics are not included in this CGA.

Yet, Carmel et al. in 1977 reported a significant association between high serum vitamin B12 levels, or hypercobalaminemia (HCbl), and solid tumors. HCbl in solid tumors is related to an excess synthesis of transcobalamins by the tumor or an increase in haptocorrin secondary to hyperleukocytosis [6–8]. In the same way, HCbl may also be a potential marker for cancer with poor prognosis, in particular in the geriatric population [9, 10]. Likewise, the vitamin B12–C-reactive protein index (BCI) has been proposed as a prognostic indicator in patients with metastatic cancer [9]. In the study by Kelly et al., an elevated BCI ( $> 40,000$ ) predicts poor survival in patients with advanced cancer with a median survival of 29 days [11].

To determine whether BCI would be an interesting biological marker in terms of survival and unplanned hospitalization in patients aged  $\geq 70$  years with cancer, we conducted a comparative study in older patients referred for CGA prior to oncological treatment.

## MATERIALS AND METHODS

### Population Description

This comparative study was conducted at Marseille University Hospital in France from September 2015 to May 2018 on 621 patients aged  $\geq 70$  years. Patients were referred from the oncology and surgery units to perform a CGA before initiation of any oncological treatment. This CGA was realized in the Geriatric Day Hospital, and the included patients were assessed in outpatient care.

### Ethics

This study was approved by the ethics committee. All the patients were registered at baseline in compliance with the French database and privacy law (Commission Nationale de l'Informatique et Liberté registration number: 2017-33).

### Clinical and Laboratory Data

Oncological, geriatric, and biological data were collected prospectively, but thereafter, the final oncological treatment administered by the clinicians, overall survival (OS), and

unplanned hospitalizations were recorded retrospectively. Patients who had received vitamin B12 supplementation in the weeks preceding CGA and patients who were hospitalized during the CGA time were excluded from the study.

For each patient, the following data were collected during the CGA:

- a. Demographics (age, sex), lifestyle (home vs. follow-up and rehabilitation care vs. nursing home), tumor site (solid vs. hematological malignancy), extension of the tumor (localized or advanced disease), treatment strategy (active vs. palliative) decided by oncologists after CGA, and concordance between anticipated treatment strategy before CGA and treatment decision after CGA.
- b. Functional status determined using activities of daily living (ADL) according to Katz et al. and instrumental ADL (IADL) according to Lawton et al.; mobility determined using the Timed Up and Go test (TUG), the unipodal test, gait speed, and whether patients had had a fall in the 3 months preceding the CGA; and nutritional status using weight, body mass index (BMI), and Mini Nutritional Assessment (MNA). In addition, we collected performance status (PS) and ONCODAGE (G8) [5, 12–18].
- c. Laboratory data: hemoglobin (Hb), albumin level, vitamin B12, C-reactive protein (CRP), and BCI, which is the product of multiplying the CRP level with the vitamin B12 level ( $B12 \times CRP$ ).
- d. Evolution: OS, unplanned hospitalization.

The validated cutoffs for scales as recommended and for laboratory data are specified in Table 1.

### Statistical Analysis

OS is the time between the diagnosis of the disease and death whatever the cause. Patients who were alive and relapsed at the end of the follow-up were censored. All quantitative variables are presented using descriptive statistics: number of subjects and average. Qualitative variables are described by absolute frequencies and percentages (proportion). Variables with  $p < .05$  were considered significant. The log-rank test and univariate Cox models were used for comparisons of survival. Variables significant in univariate analysis with a significance  $p < .2$  were considered as eligible to be included in the multivariate Cox model. However, for the survival model, as the number of events was low (32 deaths), we did not enter simultaneously in the multivariate Cox model all the variables significant in univariate analysis. We decided to keep in the final model only three of the significant variables, choosing those that had the least missing data. The same procedure was chosen for the multivariate logistic regressions on unplanned hospitalizations (within 1 or 3 months), with a total number of four significant variables in the final models (number of events = 52 and 66, respectively). For the three multivariate models, adjustment on age was tested (although age was not significant in univariate analysis) but was not kept as it did not improve the models. Statistical analyses were performed with SPSS Software for Windows version 17.0.

**Table 1.** Patient demographics and clinical and geriatric characteristics (*n* = 621)

Characteristics	Patients <i>n</i> (%)
Sex ratio	
Women	241 (38.8)
Men	380 (61.2)
Age (median: 81 years)	
70–75 years	92 (14.8)
75–85 years	379 (61)
>85 years	150 (24.2)
Lifestyle	
Home	553 (89.0)
Nursing home	31 (5.0)
Follow-up and rehabilitation unit	37 (6.0)
ADL	
6	390 (62.8)
<6	231 (37.2)
IADL	
<4	322 (51.8)
4	298 (48.0)
Missing	1 (0.2)
BMI	
<18	27 (4.4)
18–21	85 (13.7)
21	506 (81.5)
Missing	3 (0.4)
Tumor type	
Solid	585 (94.0)
Hematological malignancy	36 (5.8)
Missing	1 (0.2)
Metastatic stage <sup>a</sup>	
No	349 (59.7)
Yes	205 (35.0)
Missing	31 (5.3)
Anticipated treatment strategy	
Active	568 (91.5)
Palliative	34 (5.5)
Missing	19 (3.0)
Treatment	
In concordance with CGA	504 (81.2)
Not in concordance	98 (15.8)
Missing	19 (3.0)
MNA	
<17	74 (12.0)
17–23.5	255 (41.0)
>23.5	260 (41.9)
Missing	32 (5.1)
TUG	
<20 s	205 (33.0)
≥20 s	394 (63.5)
Missing	22 (3.5)

(continued)

**Table 1.** (continued)

Characteristics	Patients <i>n</i> (%)
Unipodal test	
<5 s	400 (64.4)
≥5 s	105 (16.9)
Missing	116 (18.7)
Gait speed	
≥0.8 m/s	381 (61.4)
<0.8 m/s	168 (27.1)
Missing	72 (11.5)
Hb	
Hb ≥10 g/dL	546 (87.9)
Hb <10 g/dL	74 (11.9)
Missing	1 (0.2)
HCbl	
≤569 pmol/L	537 (86.4)
>569 pmol/L	83 (13.4)
Missing	1 (0.2)
BCI	
>40,000	34 (5.5)
≤40,000	582 (93.7)
Missing	5 (0.8)
PS	
<2	426 (68.5)
≥2	138 (22.2)
Missing	58 (9.3)
G8	
≤14/17	425 (68.5)
>14/17	94 (15.1)
Missing	102 (16.4)
Albumin	
<30	17 (2.7)
30–35	65 (10.5)
>35	528 (85.2)
Missing	10 (1.6)
Fall within 3 months	
No	508 (81.8)
Yes	112 (18.0)
Missing	1 (0)

<sup>a</sup>*n* = 585 solid tumors.

Abbreviations: ADL, activities of daily living; BCI, B12 × C-reactive protein index; BMI, body mass index; CGA, Comprehensive Graphic Assessment; Hb, hemoglobin; HCbl, hypercobalaminemia; IADL, instrumental activities of daily living; MNA, Mini Nutritional Assessment; PS, performance status; TUG, Timed Up and Go test.

## RESULTS

### Patient Characteristics and CGA

In our study, 621 patients were recruited. The median age was 81 years (range, 70–98 years), and 61% were men. HCbl was present in 83 patients (13.4%), and 34 patients

**Table 2.** Type of tumors

Tumor	Type	Patients (n = 621), n (%)
Lung (excluding mesothelium)	Solid tumor	142 (23)
Prostate cancer	Solid tumor	134 (22)
Gastrointestinal tract	Solid tumor	79 (13.2)
Breast cancer	Solid tumor	59 (10)
Basal cell and squamous cell carcinoma	Solid tumor	28 (5)
Kidney cancer	Solid tumor	25 (4)
Head and neck cancer	Solid tumor	24 (3.9)
Myeloma	Hematological malignancy	15 (2.4)
Urothelial tumor	Solid tumor	14 (2.3)
Ovary cancer	Solid tumor	13 (2)
Diffuse large B-cell lymphoma	Hematological malignancy	12 (2)
Cervical cancer	Solid tumor	11 (1.8)
Endometrial cancer	Solid tumor	10 (1.6)
Hepatocellular carcinoma	Solid tumor	10 (1.6)
Pancreas	Solid tumor	9 (1.4)
Thyroid cancer	Solid tumor	8 (1.3)
Melanoma	Solid tumor	7 (1.1)
Bile duct carcinoma	Solid tumor	6 (1)
Mesothelium	Solid tumor	5 (0.8)
T-cell lymphoma	Hematological malignancy	5 (0.8)
Chronic lymphoid leukemia	Hematological malignancy	2 (0.3)
Acute myeloid leukemia	Hematological malignancy	1 (0.1)
Chronic myeloid leukemia	Hematological malignancy	1 (0.1)
Other tumor	Solid tumor	1 (0.1)

(5.5%) had BCI >40,000. The majority of tumors were solid (94.2% of patients), in particular, lung cancer in 23% of patients, prostate cancer in 22%, gastrointestinal tract cancer in 13.2%, and breast cancer in 10%; 205 (35%) patients had metastatic cancer. All types of tumor are detailed in Table 2. The majority of patients (81.2%) received the treatment chosen by clinicians after CGA.

Patient demographics, as well as the clinical and geriatric characteristics, are presented in Table 1.

In our study, 32 patients (5.6%) died within 3 months; no survival data were available for 51 patients (data for these patients were censored at the last known date they were alive). Of early deaths, 19 (59.4%) were attributable to cancer progression, 5 (15.6%) to treatment-related complications (cardiac decompensation on grade 3 anemia, septic shock on postchemotherapy grade 4 neutropenia, nosocomial infection on pleural drainage, and two preoperative surgical complications), 5 (15.6%) to other reasons (two gastrointestinal bleedings, cerebral hemorrhage,

cerebral thrombophlebitis, fall with cranial trauma), and the last 3 (9.4%) to unknown reasons. Fifty-two patients (8.8%) had unplanned hospitalization within 1 month; no data were available for 29 patients. Sixty-six patients (11.4%) had unplanned hospitalization within 3 months; no data were available for 40 patients. The median follow-up time was 10 months (range, 1–35 months).

### Early Death Within 3 Months

Univariate and multivariate Cox models for 3-month survival are presented in Table 3.

In univariate analysis, the risk of 3-month mortality was significantly higher in patients with palliative treatment, impaired geriatric factors (ADL, TUG, MNA, unipodal test, gait speed, and BMI), anemia, Hcbl, and BCI >40,000. In the multivariate Cox model, palliative treatment (hazard ratio [HR], 4.6; 95% confidence interval [CI], 1.9–11.0), impaired ADL (HR, 2.5; 95% CI, 1.14–5.53), and BCI (HR, 6.39; 95% CI, 2.68–15.4) remained significantly associated with the outcome.

Another multivariate model (not shown) using Hcbl instead of BCI had comparable results, with palliative treatment and impaired ADL remaining significantly associated with the 3-month mortality risk.

### Unplanned Hospitalization Within 1 Month

After logistic regression, the following factors remained independently associated with a 1-month unplanned hospitalization risk: palliative care (vs. active treatment) (odds ratio [OR], 2.77; 95% CI, 1.03–6.88), BCI >40,000 (OR, 3.31; 95% CI, 1.26–8.32), albumin level <35 g/L (OR, 1.87; 95% CI, 1.04–3.24), and IADL (OR, 2.06; 95% CI, 1.05–4.23) (Table 4).

### Unplanned Hospitalization Within 3 Months

After logistic regression, the following factors remained independently associated with a 3-month unplanned hospitalization risk: BCI >40,000 (OR, 5.12; 95% CI, 2.20–12.27) and albumin level <35 g/L (OR, 1.71; 95% CI, 0.98–2.89) (Table 5).

## DISCUSSION

In outpatient care for older patients with cancer, identifying factors associated with a higher risk of early death or unplanned hospitalizations are essential in determining the risk profile of each patient. Establishing prognostic factors in this older population with cancer is all the more useful because advanced age has been identified as predictive of mortality and the rate of unplanned hospitalizations is higher in older adults than young adults [19, 20]. To our knowledge, this is the first study to show that BCI is a marker for higher rates of unplanned hospitalization in older patients with cancer. In accordance with the literature, our study confirms the link between BCI and mortality in this same population.

The association between Hcbl and solid neoplasms has been described in a few studies [6, 21, 22]. Furthermore, Hcbl is an anomaly frequently observed in hematological malignancies [8, 21]. Hcbl predicts early death in the cancer

**Table 3.** Factors associated with a 3-month mortality risk in older patients with cancer (Cox model)

Variables	Univariate			Multivariate (n = 535)		
	Alive (n = 538), n (%) <sup>a</sup>	Died (n = 32), n (%) <sup>a</sup>	p value	Coefficient	HR (95% CI)	p value
<b>Age</b>						
70–75 years	82 (15.2)	4 (12.5)				
75–85 years	324 (60.3)	19 (59.4)				
>85 years	132 (24.5)	9 (28.1)	.63			
<b>Metastatic stage<sup>b</sup></b>						
Yes	178 (35.5)	15 (51.7)				
No	324 (64.5)	14 (48.3)	.07			
<b>BMI</b>						
<18	20 (3.7)	2 (6.3)				
18–21	66 (12.3)	12 (37.5)	<.0001			
>21	450 (83.6)	18 (56.3)				
<b>Palliative treatment</b>						
Yes	22 (4.1)	7 (21.9)		1.5	4.6 (1.9–11.0)	.006
No	499 (92.8)	24 (75)	<.0001		1	
<b>ADL</b>						
<6	187 (34.8)	19 (59.4)	.004	0.9	2.5 (1.14–5.53)	.02
6	349 (64.9)	12 (37.5)			1	
<b>MNA<sup>b</sup></b>						
<17	60 (11.2)	8 (25)				
17–23.5	218 (40.5)	12 (37.5)	.003			
<23.5	241 (44.8)	6 (18.8)				
<b>TUG<sup>b</sup></b>						
<20 s	360 (66.9)	12 (37.5)	.004			
≥20 s	165 (30.6)	17 (53.1)				
<b>Unipodal test<sup>b</sup></b>						
<5 s	374 (69.5)	26(81.3)	.005			
≥5 s	104 (19.3)	1 (3.1)				
<b>Gait speed<sup>b</sup></b>						
≥0.8 m/s	342 (63.6)	11 (34.3)				
<0.8 m/s	135 (25.1)	16 (50)	.001			
<b>Hb</b>						
≥10 d/dL	483 (89.8)	22 (68.8)				
<10 d/dL	54 (10.1)	10 (31.3)	.0006			
<b>HCbl</b>						
≤569 pmol/L	478 (88.8)	19 (59.4)				
>569 pmol/L	60 (11.2)	13 (40.6)	<.0001			
<b>BCI</b>						
>40,000	21 (3.9)	8 (25)	<.0001	1.85	6.39 (2.68–15.4)	<.0001
≤40,000	513 (95.4)	24 (75)			1	

<sup>a</sup>Total percentages do not always reach 100% because of missing data.

<sup>b</sup>Metastatic stage: n = 554 patients; Unipodal test: n = 505 patients; Gait speed: n = 504 patients; TUG: n = 599 patients; MNA: n = 589 patients. For all other variables, missing values <5%.

Abbreviations: ADL, activities of daily living; BCI, B12 × C-reactive protein index; BMI, body mass index; CI, confidence interval; Hb, hemoglobin; HCbl, hypercobalaminemia; HR, hazard ratio; MNA, Mini Nutritional Assessment; TUG, Timed Up and Go test.

population and in hospitalized older patients [10, 23–25]. Of the 621 patients included in our study, 13.4% had HCbl, whereas in the study by Zulfiqar et al. on 190 patients hospitalized in an acute geriatric unit, 25.3%

had HCbl [25]. Patients ≥75 years of age were more likely to have HCbl ( $p = .0416$ ). In another similar study by Salles et al. on 488 older outpatients, 33.8% had HCbl, whereas in the study by Tal et al. on 1,570 patients with a mean age of

**Table 4.** Factors associated with a 1-month unplanned hospitalization risk in older patients with cancer (logistic regression)

Variables	Univariate			Multivariate (n = 559)	
	Unplanned hospitalization (n = 52), n (%) <sup>a</sup>	No unplanned hospitalization (n = 540), n (%) <sup>a</sup>	p value	OR (95% CI)	p value
<b>Age</b>					
70–75 years	7 (13.5)	80 (14.8)			
75–85 years	32 (61.5)	329 (60.9)			
>85 years	13 (25.0)	131 (24.6)	0.96		
<b>Metastatic stage<sup>b</sup></b>					
Yes	25 (48.1)	180 (33.3)			
No	22 (42.3)	327 (60.5)	.002		
<b>Palliative treatment</b>					
Yes	9 (17.3)	22 (4.1)		2.77 (1.03–6.88)	.03
No	41 (78.8)	502 (93)	.0002	1	
<b>ADL</b>					
<6	27 (51.9)	189 (35)	.02		
6	25 (48.1)	349 (64.6)			
<b>IADL</b>					
<4	38 (73.1)	268 (49.6)	.002	2.06 (1.05–4.23)	.04
4	14 (26.9)	272 (50.4)		1	
<b>MNA<sup>b</sup></b>					
<17	12 (23.1)	57 (10.6)			
17–23.5	27 (51.9)	218 (40.4)	.0006		
>23.5	11 (21.2)	239 (44.3)			
<b>Malnutrition</b>					
Yes	32 (61.5)	189 (35)	.0001		
No	18 (34.6)	347 (64.3)			
<b>TUG<sup>b</sup></b>					
<20 s	23 (44.2)	357 (66.1)	.02		
≥20 s	23 (44.2)	171 (31.7)			
<b>Fall within 3 months</b>					
No	34 (65.4)	453 (83.9)			
Yes	18 (34.6)	86 (15.9)	.001		
<b>Hb</b>					
≥10 g/dL	38 (73.1)	483 (89.4)			
<10 g/dL	14 (26.9)	56 (10.4)	.0008		
<b>HCbl</b>					
≤569 pmol/L	36 (69.2)	476 (88.1)			
>569 pmol/L	16 (30.8)	64 (11.9)	.0003		
<b>BCI</b>					
>40,000	12 (23.1)	21 (3.9)	<.0001	3.31 (1.26–8.32)	.01
≤40,000	40 (76.9)	514 (95.2)		1	
<b>Albumin</b>					
30–35 g/L	21 (39.4)	56 (10.6)	<.0001	1.87 (1.04–3.24)	.03
>35 g/L	31 (59.6)	472 (87.4)		1	
<b>G8<sup>b</sup></b>					
≤14	39 (75)	372 (68.9)	.04		
>14	2 (3.8)	89 (16.5)			

(continued)



Table 4. (continued)

Variables	Univariate			Multivariate (n = 559)	
	Unplanned hospitalization (n = 52), n (%) <sup>a</sup>	No unplanned hospitalization (n = 540), n (%) <sup>a</sup>	p value	OR (95% CI)	p value
PS <sup>b</sup>					
<2	25 (48.1)	387 (71.7)			
≥2	20 (38.5)	111 (20.6)	<b>.001</b>		

<sup>a</sup>Total percentages do not always reach 100% because of missing data.

<sup>b</sup>Metastatic stage: n = 554; patients; G8: n = 502 patients; PS: n = 543 patients; TUG: n = 599; MNA: n = 589. For all other variables, missing values <5%.

Abbreviations: ADL, activities of daily living; BCI, B12 × C-reactive protein index; CI, confidence interval; Hb, hemoglobin; HCbl, hypercobalaminemia; IADL, instrumental activities of daily living; MNA, Mini Nutritional Assessment; OR, odds ratio; PS, performance status; TUG, Timed Up and Go test.

81 years, 50% had HCbl [10, 24]. The frequency of HCbl in our study was similar to that observed by Chiche et al.; 18.5% of patients in the internal medicine unit with a mean age of 77 years had HCbl, and 23% of patients in the study had cancer [21]. Likewise, in the study by Jammal et al. on 3,702 hospitalized patients, 12% had HCbl [26]. These differences in the prevalence of HCbl can be explained by the fact that the inclusion criteria were different (geriatric population or cancer population) and that laboratory standards for serum vitamin B12 levels vary from one hospital to another.

Geissbülher et al. recently tested the BCI. In this study on 161 older patients with a median age of 76 years, an elevated BCI (>40,000) was associated with a 3-month mortality of 90% in patients with advanced cancer [9]. Kelly and coworkers predicted an elevated BCI (>40,000) as a factor of poor prognosis in 329 older patients with advanced and metastatic cancer ( $p < .01$ ) [11]. In our study, only 5.5% of patients had a BCI >40,000 versus 38.9% in the study by Kelly et al. because our metastatic cancer rate was lower than in the studies by Geissbülher et al. and Kelly et al. [9, 11]. Using multivariate analysis in our study, BCI ( $p < .0001$ ) was prognostic factor of 3-month mortality. These results were similar to those of the studies described previously [9, 11].

Concerning prognostic factors for unplanned hospitalizations within 1 and 3 months, our work is innovative. In the oncological literature, there are little data on factors influencing early hospitalizations in older patients with cancer [27, 28]. Multivariate analysis showed that BCI >40,000 persisted as a prognostic factor for unplanned hospitalizations within 1 and 3 months ( $p = .01$  and  $p = .0002$ , respectively). In fact, BCI factor predicts poor survival and the risk of unplanned hospitalization in older ambulatory patients with cancer.

In our study, geriatric disabilities and several screening tools for vulnerability were selected as survival prognostic and unplanned hospitalization factors. Functional status impairment according to ADL was statistically significant for 3-month OS ( $p = .02$ ), and IADL was statistically significant for unplanned hospitalizations within 1 month ( $p = .04$ ). Loss of functional capacity could increase the risk of treatment-related complications and the risk of poor outcomes in older patients with cancer [29]. Functional capacities concern mobility disorders, cognitive impairment,

depression, and sensorial disorders. ADL score was associated with OS in other studies about older patients with cancer [30, 31], and IADL score was independently associated with unplanned hospitalizations of patients with ovarian cancer [31]. Consequently, functional capacities are an essential part of the CGA in order to organize home care to ensure the good progress of the oncological treatment and to avoid hospitalizations [4]. Some studies have shown the impact of IADL on survival of older patients with cancer [31, 32], and IADL is included in the Chemotherapy Risk Assessment Scale for High Age (CRASH) chemotoxicity score [33]. Nutritional status is also very important for survival of older patients with cancer and the risk of treatment complications. In our work, albumin level < 35 g/L was an unplanned hospitalization risk factor within 1 and 3 months ( $p = .03$  and  $p = .05$ , respectively). In the literature, low albumin level was associated with overall survival in solid tumors and hematological malignancies [31, 34] but not with hospitalizations of older patients with cancer.

Age and, in particular, age groups (70–75 years, 75–85 years, and >85 years) have no influence on OS and unplanned hospitalization risk in our work. In the literature, the influence of age on outcomes of older patients with cancer is controversial, in particular in the “oldest-old” subgroup (>85 years). In the chemotoxicity scores Cancer and Aging Research Group (CARG) and CRASH, age was included only in the CARG score [33, 35]. In a recent predicting death score in older adults with colon cancer, age >82 years was selected as prognostic factor [36]. But older age alone should not be decisive for oncological treatment decision making; patient decisions and high-risk factors such as functional status (IADL or ADL), malnutrition, and cognitive or mobility impairment are more important [37].

We recommend that BCI be determined routinely before initiation of oncological treatment in older patients with cancer because it is a prognostic factor of early death, and CRASH score or the score for assessing the risk of chemotoxicity in older patients could be proposed in this population [33, 35]. BCI would be a risk factor in this early hospitalization scoring system.

This study also has some limitations, as it was monocentric. Survival and unplanned hospitalization rates were calculated after CGA and not after initiation of oncological treatment, but some patients had been hospitalized or died



**Table 5.** Factors associated with a 3-month unplanned hospitalization risk in older patients with cancer (logistic regression)

Variables	Univariate			Multivariate (n = 548)	
	Unplanned hospitalization (n = 66), n (%) <sup>a</sup>	No unplanned hospitalization (n = 515), n (%) <sup>a</sup>	p value	OR (95% CI)	p value
<b>Age</b>					
70–75 years	9 (13.6)	79 (15.3)			
75–85 years	42 (63.7)	310 (60.2)			
>85 years	15 (22.7)	126 (24.5)	.86		
<b>Metastatic stage<sup>b</sup></b>					
Yes	29 (43.9)	173 (33.6)	.15		
No	35 (53.0)	306 (59.4)			
<b>Palliative treatment</b>					
Yes	6 (9.0)	22 (4.2)	.15	1.36 (0.43–3.73)	.54
No	57 (86.3)	478 (92.8)		1	
<b>Lifestyle</b>					
Home	51 (77.3)	468 (90.9)			
Follow-up and rehabilitation unit	6 (9.1)	19 (3.7)			
Nursing home	9 (13.6)	28 (5.4)	<b>.002</b>		
<b>ADL</b>					
<6	35 (53)	175(34.0)	<b>.002</b>		
6	30 (45.5)	339 (65.8)			
<b>IADL</b>					
<4	45 (68.2)	254 (49.3)	<b>.005</b>	1.60 (0.89–2.96)	.12
4	21 (31.8)	261 (50.7)		1	
<b>MNA<sup>b</sup></b>					
<17	15 (22.7)	54 (10.5)			
17–23.5	30 (45.5)	210 (40.8)	<b>.0004</b>		
>23.5	16 (24.2)	231 (44.9)			
<b>Malnutrition</b>					
Yes	38 (57.6)	181 (35.1)	<b>.0003</b>		
No	26 (39.4)	331 (64.3)			
<b>Hb</b>					
≥10 g/dL	49 (74.2)	463 (89.9)			
<10 g/dL	17 (25.8)	51 (9.9)	<b>.0003</b>		
<b>BCI</b>					
>40,000	15 (22.7)	17 (3.3)	<b>&lt;.0001</b>	5.12 (2.20–12.27)	<b>.0002</b>
≤40,000	50 (75.8)	494 (95.9)		1	
<b>Albumin</b>					
30–35 g/L	21 (31.8)	54 (10.4)	<b>&lt;.0001</b>	1.71 (1.00–2.89)	<b>.05</b>
>35 g/L	43 (65.2)	451 (87.6)		1	

<sup>a</sup>Total percentages do not always reach 100% because of missing data.

<sup>b</sup>Metastatic stage: n = 554 patients; MNA: n = 589 patients. For all other variables, missing values <5%.

Abbreviations: ADL, activities of daily living; BCI, B12 × C-reactive protein index; CI, confidence interval; Hb, hemoglobin, IADL, instrumental activities of daily living; MNA, Mini Nutritional Assessment; OR, odds ratio.

before initiation of oncological treatment. Furthermore, reasons for unplanned hospitalization were not prospectively recorded. The geriatric population is very heterogeneous with a high median age (81 years); therefore, our

study included various tumor sites and various tumor stages. Finally, comorbidities were not studied in our work, and liver diseases or renal failure could increase serum vitamin B12 levels.

The strengths of the study include data on unplanned hospitalizations at 1 and 3 months in older patients with cancer, which have been reported in very few studies in the oncology literature. This work included a large number of older ambulatory patients (621 persons). Serum vitamin B12 levels and BCI are not used in practice and could be easy and convenient in ambulatory and general medicine.

## CONCLUSION

BCI (B12  $\times$  CRP) is prognostic factor of early death in older patients with cancer before initiation of oncological treatment. However, BCI is also a prognostic factor of unplanned and early hospitalizations in this same ambulatory population. In our work, other factors influenced unplanned hospitalizations at 1 month: IADL and albumin level. A future study to develop an early hospitalization score in older

cancer adults in outpatient care would integrate IADL, albumin level, and BCI.

## AUTHOR CONTRIBUTIONS

**Conception/design:** Anne-Laure Couderc, Eddy Puchades, Geoffroy Venton  
**Provision of study material or patients:** Anne-Laure Couderc, Eddy Puchades

**Collection and/or assembly of data:** Anne-Laure Couderc, Eddy Puchades, Pierre Suchon, Geoffroy Venton

**Data analysis and interpretation:** Anne-Laure Couderc, Pierre Suchon, Geoffroy Venton

**Manuscript writing:** Anne-Laure Couderc, Eddy Puchades, Geoffroy Venton  
**Final approval of manuscript:** Anne-Laure Couderc, Eddy Puchades, Patrick Villani, Robin Arcani, Laure Farnault, Aurélie Dumas, Anais Courcier, Laurent Greillier, Fabrice Barlesi, Florence Duffaud, Sébastien Salas, Régis Costello, Gaëtan Gentile, Vincent Pradel, Pierre Suchon, Geoffroy Venton

## DISCLOSURES

The authors indicated no financial relationships.

## REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356–387.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
3. Wildiers H, Heeren P, Puts M et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014;32:2595–2603.
4. Mohile SG, Dale W, Somerfield MR et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO Guideline for Geriatric Oncology summary. *J Oncol Pract* 2018;14:442–446.
5. Soubeyran P, Bellera C, Goyard J et al. Screening for vulnerability in older cancer patients: The ONCODAGE Prospective Multicenter Cohort Study. *PLoS One* 2014;9:e115060.
6. Carmel R, Eisenberg L. Serum vitamin B12 and transcobalamin abnormalities in patients with cancer. *Cancer* 1977;40:1348–1353.
7. Ermens AAM, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. *Clin Biochem* 2003;36:585–590.
8. Andrès E, Serraj K, Zhu J et al. The pathophysiology of elevated vitamin B12 in clinical practice. *QJM* 2013;106:505–515.
9. Geissbühler P, Mermillod B, Rapin CH. Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: A prospective study over five years. *J Pain Symptom Manage* 2000;20:93–103.
10. Salles N, Herrmann F, Sakbani K et al. High vitamin B12 level: A strong predictor of mortality in elderly inpatients. *J Am Geriatr Soc* 2005;53:917–918.
11. Kelly L, White S, Stone PC. The B12/CRP index as a simple prognostic indicator in patients with advanced cancer: A confirmatory study. *Ann Oncol* 2007;18:1395–1399.
12. Katz S, Ford AB, Moskowitz RW et al. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA* 1963;185:914–919.
13. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179–186.
14. Podsiadlo D, Richardson S. The timed “Up & Go”: A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–148.
15. Vellas BJ, Wayne SJ, Romero L et al. One-leg balance is an important predictor of injurious falls in older persons. *J Am Geriatr Soc* 1997;45:735–738.
16. Friedman PJ, Richmond DE, Baskett JJ. A prospective trial of serial gait speed as a measure of rehabilitation in the elderly. *Age Ageing* 1988;17:227–235.
17. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. *Clin Geriatr Med* 2002;18:737–757.
18. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–655.
19. Lee SJ, Lindquist K, Segal MR et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006;295:801–808.
20. Walter LC, Brand RJ, Counsell SR et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;285:2987–2994.
21. Chiche L, Jean R, Romain F et al. Clinical implications of high cobalamin blood levels for internal medicine [in French]. *Rev Med Interne* 2008;29:187–194.
22. Arendt JFH, Farkas DK, Pedersen L et al. Elevated plasma vitamin B12 levels and cancer prognosis: A population-based cohort study. *Cancer Epidemiol* 2016;40:158–165.
23. Kane SP, Murray-Lyon IM, Paradinas FJ et al. Vitamin B12 binding protein as a tumour marker for hepatocellular carcinoma. *Gut* 1978;19:1105–1109.
24. Tal S, Shavit Y, Stern F et al. Association between vitamin B12 levels and mortality in hospitalized older adults. *J Am Geriatr Soc* 2010;58:523–526.
25. Zulfiqar AA, Sebaux A, Dramé M et al. Hypervitaminemia B12 in elderly patients: Frequency and nature of the associated or linked conditions. Preliminary results of a study in 190 patients. *Eur J Intern Med* 2015;26:e63–e64.
26. Jammal M, Deneuille T, Mario N et al. High plasmatic concentration of vitamin B12: An indicator of hepatic diseases or tumors [in French]. *Rev Med Interne* 2013;34:337–341.
27. Aparicio T, Jouve JL, Teillet L et al. Geriatric factors predict chemotherapy feasibility: Ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. *J Clin Oncol* 2013;31:1464–1470.
28. Hamaker ME, Buurman BM, van Munster BC et al. The value of a comprehensive geriatric assessment for patient care in acutely hospitalized older patients with cancer. *The Oncologist* 2011;16:1403–1412.
29. Couderc AL, Boulahssass R, Nouguerède E et al. Functional status in a geriatric oncology setting: A review. *J Geriatr Oncol* 2019;10:884–894.
30. Ferrat E, Paillaud E, Laurent M et al. Predictors of 1-year mortality in a prospective cohort of elderly patients with cancer. *J Gerontol A Biol Sci Med Sci* 2015;70:1148–1155.
31. Falandry C, Weber B, Savoye AM et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: A GINECO prospective trial. *Ann Oncol* 2013;24:2808–2813.
32. Maione P, Perrone F, Gallo C et al. Pre-treatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: A prognostic analysis of the multicenter Italian lung cancer in the elderly study. *J Clin Oncol* 2005;23:6865–6872.
33. Extermann M, Boler I, Reich RR et al. Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 2012;118:3377–3386.

**34.** Peyrade F, Jardin F, Thieblemont C et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2011;12:460–468.

**35.** Hurria A, Mohile S, Gajra A et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J Clin Oncol* 2016;34:2366–2371.

**36.** Retornaz F, Guillem O, Rousseau F et al. Predicting chemotherapy toxicity and death in

older adults with colon cancer: Results of MOST study. *The Oncologist* 2020;25:e85–e93.

**37.** Kenis C, Bron D, Libert Y et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: Results of a prospective multicentric study. *Ann Oncol* 2013;24:1306–1312.