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Clément Gouraud,[a] Elena Paillaud,[a,b] Claudia Martinez-Tapia,[a] Lauriane Segaux,[a,c] Nicoleta Reinald,[a,b,d] Marie Laurent,[a,b] Lola Corsin,[b] Nicolas Hoertel,[e,f,g] Mathilde Gisselbrecht,[e,h] Elise Mercadier,[e,h] Pascaline Boudou-Rouquette,[i] Anne Chahwakilian,[j] Sylvie Bastuji-Garin,[a,c,d] Frédéric Limosin,[e,f,g] Cédric Lemogne,[e,f,g,†] Florence Canouï-Poitrine,[a,d,†] on behalf of the ELCAPA Study Group

[a]Clinical Epidemiology and Ageing Unit, Université Paris-Est, Créteil, France; [b]Geriatric Department, [c]Clinical Research Unit (URC-Mondor), and [d]Public Health Department, Henri-Mondor Hospital, AP-HP, Créteil, France; [e]Faculty of Medicine, Paris Descartes University, Sorbonne Paris Cité, Paris, France; [f]Service de Psychiatrie de l'adulte et du sujet âgé, Hôpitaux Universitaires Paris Ouest, AP-HP, Paris, France; [g]Centre Psychiatrie et Neurosciences, Inserm, U894, Paris, France; [h]Division of Geriatrics, European Georges Pompidou Hospital, AP-HP, Paris, France; [i]Medical Oncology Department, Cochin Hospital, AP-HP, Paris, France; [j]Department of Gerontology, Geriatric Oncology Unit, Broca Hospital, AP-HP, Paris, France

[†]Contributed equally.

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

Key Words. Depression • Epidemiology • Cancer • Psycho-oncology • Old age • Cluster

Abstract

Background. The expression of depressive symptoms in older people with cancer is heterogeneous because of specific features of age or cancer comorbidity. We aimed to identify depressive symptom profiles in this population and describe the associated features including survival.

Materials and Methods. Patients ≥70 years who were referred to geriatric oncology clinics were prospectively included in the ELCAPA study. In this subanalysis, depressive symptoms were used as indicators in a latent class analysis. Multinomial multivariable logistic regression and Cox models examined the association of each class with baseline characteristics and mortality.

Results. For the 847 complete-case patients included (median age, 79 years; interquartile range, 76–84; women, 47.9%), we identified five depressive symptom classes: "no depression/somatic only" (38.8%), "no depression/pauci-symptomatic" (26.4%), "severe depression" (20%), "mild depression" (11.8%), and "demoralization" (3%). Compared with the no depression/pauci-symptomatic class, the no depression/somatic only and severe depression classes were characterized by more frequent comorbidities with poorer functional status and higher levels of inflammation. "Severe" and "mild" depression classes also featured poorer nutritional status, more medications, and more frequent falls. Severe depression was associated with poor social support, inpatient status, and increased risk of mortality at 1 year (adjusted hazard ratio, 1.62, 95% confidence interval, 1.06–2.48) and 3 years (adjusted hazard ratio, 1.49; 95% confidence interval, 1.06–2.10).

Conclusion. A data-driven approach based on depressive symptoms identified five different depressive symptom profiles, including demoralization, in older patients with cancer. Severe depression was independently and substantially associated with poor survival. ***The Oncologist*** 2019;24:e458–e466

Implications for Practice: Older patients with cancer present with distinct profiles of depressive symptomatology, including different severity levels of depression and the demoralization syndrome. Clinicians should use a systematic assessment of depressive symptoms to adequately highlight these distinct profiles. Geriatric and oncological features are differently associated with these profiles. For instance, severe depression was associated with more frequent comorbidities with poorer functional, poor nutritional status, polypharmacy, frequent falls, inpatient status and poor social support. Also, severe depression was independently and substantially associated with poor survival so that the identification and management of depression should be considered a high priority in this population.

Correspondence: Clément Gouraud, M.D., M.P.H., Service de santé publique, Hôpital Henri-Mondor, 51 avenue du Maréchal de Lattre de Tassigny 94010 Créteil cedex, France. Telephone: 33-149-812-508; e-mail: clement.gouraud0@gmail.com Received May 29, 2018; accepted for publication October 18, 2018; published Online First on December 31, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0322

Introduction

Both cancer and depression are common in older people, which constitute the majority and a growing proportion of patients with cancer, with 60% of new cancer diagnoses concerning patients 65 years or older in France or the U.S. [1, 2]. The prevalence of major depression is estimated at 9% [3] among older people and is two to four-fold greater in patients with cancer than in the general population [4]. Both major depression and subthreshold depressive symptoms, hereafter referred to as depression, are associated with adverse outcomes in the context of cancer, such as delayed diagnosis [5, 6], impaired quality of life [7], less specialized interventions [5], and shorter survival [7, 8], especially in older patients [7].

The expression of depressive symptoms in older patients with cancer is complex, with greater heterogeneity than in younger counterparts [9]. Therefore, studies analyzing outcomes associated with depression must account for this heterogeneity to avoid yielding inconsistent results because of difficulties attributing depressive symptoms to depression, cancer, or both, as well as peculiarities of geriatric depression.

Depressive symptoms among patients with cancer may result from the psychological impact of the disease, symptoms, or treatment side effects as well as from cancer-induced biological modifications. Inflammation may induce a "sickness behavior" that shares many symptoms with depression, such as fatigue, sleep disturbances, or reduced appetite [10]. Furthermore, features of geriatric depression add complexity to the interpretation of depressive symptoms [11, 12], thus making the diagnosis of depression among older patients with cancer especially challenging. For instance, older people may be less likely to exhibit the core symptoms low mood and anhedonia [13] or other symptoms thought to be more specific in the context of cancer, namely feelings of guilt. Moreover, older people with depression are more likely to exhibit somatic symptoms and complaints [11].

Because of this complexity, several attempts have aimed to identify more homogeneous depressive profiles in these populations. A number of these works rely on latent class analysis (LCA) of reported symptoms [14]. In this case, depression is considered an underlying (e.g., "latent") attribute, each class representing a distinct subtype of depression. For patients with cancer, Zhu et al. described a three-class solution distinguished by severity [15]. For older people, Hybels et al. identified four classes of patients with depression that differed by intensity and by exhibiting somatic symptoms and suicidal ideation [12]. Nevertheless, no study specifically involved older patients with cancer.

We hypothesized that the observed heterogeneity in depressive symptoms presented by older patients with cancer could be explained by the existence of different homogeneous classes. This study aimed to identify these classes, to characterize them according to geriatric and oncologic factors, and to assess their prognostic value regarding survival.

Materials and Methods

Population

The Elderly Cancer Patients (ELCAPA) cohort study prospectively includes in- and outpatients aged 70 years or more with solid or haematological malignancies, referred for a geriatric assessment (GA) before deciding on the anticancer strategy or on a new therapeutic modality [16]. The present study included patients referred to the geriatric oncology clinics of two university hospitals in the Paris urban area, France, between January 2007 and December 2012. Informed consent was obtained from all patients before inclusion. The protocol was approved by the appropriate ethics committee (CPP Ile-de-France I, Paris, France). The ELCAPA cohort study was registered at ClinicalTrials.gov (NCT02884375).

Data Collection

At baseline, all patients underwent a GA, made by a physician specialized in geriatric oncology, which is a semi-structured interview that includes an assessment of psychological and somatic symptoms of depression and completion of the French version of the mini-Geriatric Depression Scale, 4 items [16]. Symptoms of depression were not assessed with standardized questions as in a structured interview but were among the clinical features that physicians had to systematically search for and report (supplemental online Table 1). The GA also included assessment of functional status, mobility, nutrition, cognitive status, social support, comorbidities, antidepressant treatment at the time of GA, and polypharmacy using standardized tools and scales previously described [17]. Final cancer treatment decision and blood levels of C-reactive protein [CRP] were recorded.

Vital status was determined from continuous follow-up via medical records and by annual campaigns through the public records office for patients lost to follow-up.

Statistical Analysis

Identification of Classes

LCA was performed with Latent Gold 5.0 (Statistical Innovations; Belmont, MA) to identify classes of patients with distinct profiles of depressive symptoms. Classes and profiles are two facets of the same phenomenon; we refer to classes for statistical methods and results and to profiles for clinical description and interpretation.

LCA is based on the assumption that a latent variable explains associations among a set of indicators [14, 18]. We defined indicators as symptoms that would reflect depression and selected them taking into account their clinical relevance and rate of missing value. Selected indicators included the psychological symptoms sadness (self-reported or assessed by clinician), loss of pleasure or interest (defined as one's feeling that his or her life is empty or not feeling happy most of the time), negative thoughts (feelings of worthlessness or hopelessness), and anxiety and the somatic symptoms insomnia, fatigue, decreased appetite, pain complaints, and gastrointestinal symptoms. We also included gender and history of depression as active covariates.

The number of classes is not a priori known, so models containing 1 to k classes are estimated. A good model would display (a) a nonsignificant bootstrap *p* value for the model fit by use of the likelihood ratio chi-square statistic (L2); (b) the lowest value of Bayesian information criteria

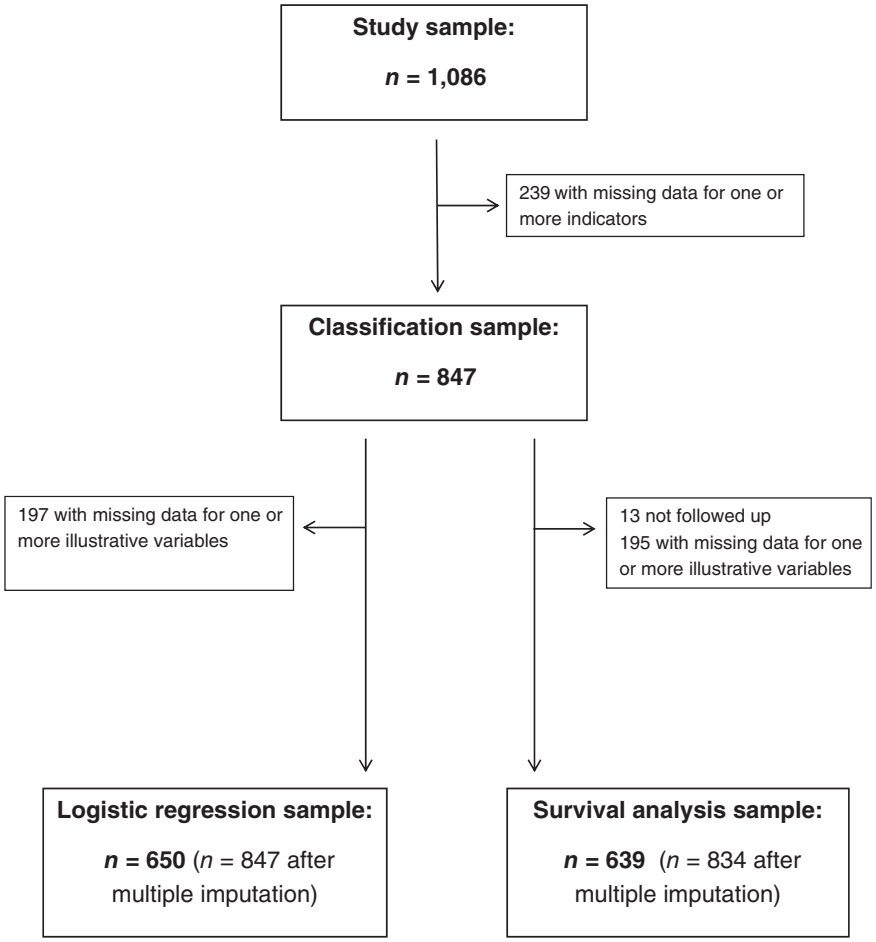


Figure 1. Flow of participants in the study. Describes the flow of participants and the sample size for each step included in the study, classification sample, and analysis sample.

(BIC), sample size-adjusted BIC (SABIC), and Akaike information criterion with 3 as the penalized factor (AIC3); and (c) nonsignificant improvement in fit between the model with k classes as compared with k + 1 classes [19]. Model discrimination is reflected by entropy (≥0.6 indicating good class separation) [20, 21]. The "local independence" hypothesis is verified by analyzing the bivariate residuals (BVRs). Values "substantially larger than one" identify local dependencies. An alternative is then to include "direct effects" [18]. Once the final model is selected, individuals are assigned to the class for which they have the highest posterior class membership probability.

Associated Factors and Survival

Categorical and continuous variables were compared across classes by Pearson's chi-square test or Fisher's exact test and ANOVA or Kruskal-Wallis test, respectively. Variables associated with class membership with $p < .2$ were included in multivariable multinomial logistic regression models. We explored correlations between variables illustrating similar domains by using Cramer's V; values ≥0.3 indicated strong correlation. Adjusted odds ratios and their 95% confidence intervals (CIs) were estimated in a model containing all confounders. Because of numerous missing values for CRP level, we included it in a distinct model. We identified the best fractional polynomial to handle CRP by using the "mfp" command in Stata.

We examined survival at 1- and 3-year follow-up. We reported Kaplan-Meier survival curves and median survival. Cox proportional-hazards regression was used to estimate hazard ratios in a multivariable model adjusting for other prognostic factors [22, 23].

We imputed missing values by using 10-fold multiple imputation by chained equations.

Logistic regression and survival analysis involved use of Stata 13.0 (StataCorp, College Station, TX). The significance threshold was $p < .05$ and all tests were two-tailed.

Results

Our study included 1,086 patients (median age, 79 years; interquartile range, 76–84; 48.7% female). Most frequent tumor sites were colorectal (21.1%) and breast (17.0%), and 42.5% of the patients had metastasis. Eighty-three percent of patients were previously untreated. Figure 1 presents the flow of patients.

Regarding LCA, a five-class solution fit the best, showing a nonsignificant bootstrap L2 p value and low AIC3 and SABIC values. (supplemental online Table 2) Furthermore, the bootstrapped likelihood ratio test showed no fit improvement with the six-class model. BVR analysis revealed moderately

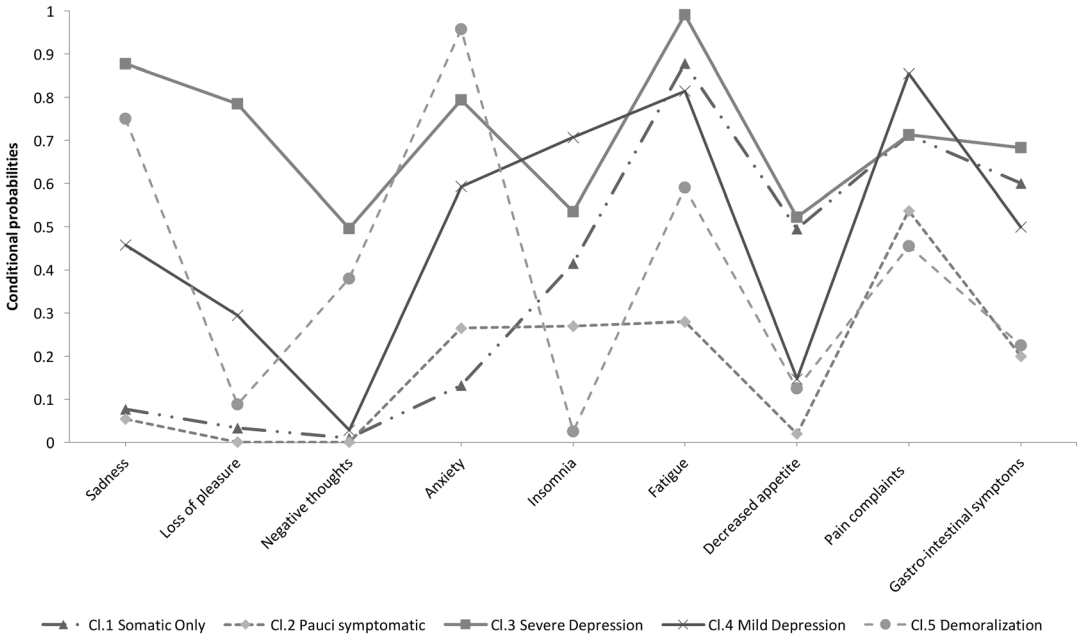


Figure 2. Symptom profiles for the 5 classes: conditional probabilities of presenting each indicator for a specific class (n = 847). Presents the conditional probabilities of presenting each indicator for the 5 identified classes: Class 1 no depression/somatic only, class 2 no depression/pauci-symptomatic, class 3 severe depression, class 4 mild depression, and class 5 demoralization.
Abbreviation: Cl, class.

elevated values for two pairs of indicators (insomnia-pain complaints and gastrointestinal symptoms-pain complaints), so we included direct effects for these pairs in the final model. Entropy for this final five-class model was 0.63.

Figure 2 reports the conditional probabilities of the indicators for each of the five latent classes. Class 1 was characterized by low probability of psychological symptoms and high probability of somatic symptoms, so we labeled it "no depression/somatic only"; class 2 was characterized by low probability of all symptoms, so we labeled it "no depression/pauci-symptomatic"; and class 3 was characterized by high probability of all symptoms, so we labeled it "severe depression." Compared with class 3, class 4 was characterized by lower probabilities of sadness, loss of pleasure, or interest and anxiety—an almost null probability for presenting negative thoughts—and similar probability of somatic symptoms, except for decreased appetite, which was lower. Therefore, we labeled class 4 "mild depression." Finally, class 5 was characterized by high probability of sadness and anxiety, with values close to those observed for class 3 "severe depression," and low probability of somatic symptoms. Furthermore, class 5 featured a high probability of negative thoughts, which contrasted with a very low probability of loss of pleasure or interest. Based on these specific features, we labeled this class "demoralization" in reference to the demoralization syndrome [23].

Each patient was assigned to a class: 38.8% to class 1, no depression/somatic only; 26.4% to class 2, no depression/pauci-symptomatic; 20% to class 3, severe depression; 11.8% to class 4, mild depression; and 3% to class 5 demoralization.

Regarding the active covariates, patients in class 4 mild depression had a more frequent history of depression, as did patients in class 3 severe depression, but to a lesser extent. Patients in class 4 mild depression were more frequently women (data not shown).

Regarding the probability of belonging to a specific class, only a few symptoms were specific enough to a given class to predict class membership when taken alone. Presenting loss of pleasure or interest or negative thoughts was associated with belonging to class 3 severe depression (0.74 and 0.81, respectively). The probability of belonging to class 2 no depression/pauci-symptomatic was 0.69 with absence of fatigue. Of note, with this approach examining symptoms one by one, classes 4 mild depression and 5 demoralization were difficult to disentangle.

Table 1 reports the characteristics of each class by univariable analysis. Most variables—demographic, cancer-related, functional, nutritional, cognitive, biological, or antidepressant treatment at time of the GA—seemed to differ between classes.

Several geriatric parameters were correlated, which led to collinearity in the multivariable model, particularly among functional indices. We chose Cumulative Illness Rating Scale for Geriatrics number of grade 3 and 4 conditions (CIRS-G index) for the multivariable model because it reflects comorbidities and their impact on functional status more specifically than does Eastern Cooperative Oncology Group Performance Status (ECOG-PS) or activities of daily living (ADL), which capture a global health status.

Results obtained by multivariable analysis for class 5 demoralization are not shown because of imprecise ORs due to the small sample size of this class (n = 25). On multivariable analysis, with class 2 no depression/pauci-symptomatic as the reference, class 1 no depression/somatic only patients were more likely to have metastasis (p = .017), altered nutritional status (p < .001), and comorbidities with severe impact on functional status (p = .022;

Table 1. Characteristics associated with the five classes on univariable analysis

Characteristics	Class 1,[a] 329 (38.8)	Class 2,[a] 224 (26.4)	Class 3,[a] 169 (20.0)	Class 4,[a] 100 (11.8)	Class 5,[a] 25 (3.0)	*p* value
Demographics						
Age, mean (SD), yr	79.5 (5.5)	79.5 (6.1)	81.0 (5.4)	79.74 (5.57)	79.8 (4.45)	.08
Female gender, *n* (%)	147 (44.68)	95 (42.22)	74 (43.79)	82 (82.00)	8 (32.00)	<.001
Inpatients, *n* (%)	133 (40.43)	44 (19.64)	102 (60.36)	18 (18)	9 (36.00)	<.001
Inadequate social support,[b] *n* (%)	64 (19.45)	36 (16.00)	70 (41.42)	19 (19.00)	1 (4.00)	<.001
Cancer						
CRC, *n* (%)	83 (25.23)	43 (19.20)	22 (13.02)	17 (17.00)	2 (8.00)	<.001
Prostate, *n* (%)	31 (9.42)	46 (20.54)	19 (11.24)	4 (4.00)	4 (16.00)	
Breast, *n* (%)	36 (10.94)	44 (19.64)	21 (12.43)	38 (38.00)	6 (24.00)	
Urinary system, *n* (%)	50 (15.20)	35 (15.63)	24 (14.20)	14 (14.00)	5 (20.00)	
Upper GI tract/liver/pancreas, *n* (%)	60 (18.24)	19 (8.48)	33 (19.53)	7 (7.00)	3 (12.00)	
Hematologic malignancies, *n* (%)	26 (7.90)	18 (8.04)	18 (10.65)	10 (10.00)	3 (12.00)	
Other,[c] *n* (%)	43 (13.07)	19 (8.48)	32 (18.93)	10 (10.00)	2 (8.00)	
Metastatic status M1/Mx, *n* (%)	155 (57.20)	64 (34.41)	82 (61.65)	32 (41.03)	9 (42.86)	<.001
Previously untreated, *n* (%)	269 (81.76)	191 (85.27)	141 (83.43)	84 (84.00)	19 (76.00)	.710
ECOG_PS >2, *n* (%)	174 (52.89)	49 (21.88)	120 (71.01)	44 (44.44)	10 (40.00)	<.001
ADL						
Median (IQR)	6 (1.5)	6 (0)	5.25 (2.5)	6 (1)	5.5 (1)	<.001
<6, *n* (%)	149 (46.42)	52 (23.64)	107 (65.24)	43 (43.00)	13 (52.00)	<.001
Falls						
History (6 months), *n* (%)	99 (30.75)	45 (20.18)	75 (45.45)	35 (35.00)	4 (16.00)	<.001
TGUG, *n* (fails) (%)	111 (37.76)	44 (20.75)	78 (56.12)	30 (32.26)	8 (34.78)	<.001
Nutrition						
MNA, n (%)						
<17	68 (21.32)	6 (2.76)	58 (34.94)	10 (10.20)	1 (4.17)	<.001
17–23	125 (39.18)	42 (19.35)	77 (46.39)	34 (34.69)	9 (37.50)	
>23	126 (39.50)	169 (77.88)	31 (18.67)	54 (55.10)	14 (58.33)	
Loss of weight,[d] *n* (%)	131 (42.39)	29 (13.68)	80 (52.29)	22 (23.40)	5 (20.83)	<.001
Cognitive functioning						
Cognitive dysfunction,[e] *n* (%)	86 (27.74)	58 (27.10)	62 (38.27)	21 (22.58)	8 (33.33)	.052
Comorbidities						
CIRS-G index,[f] *n* (%)	139 (64.35)	66 (44.59)	88 (75.86)	29 (46.77)	7 (36.84)	<.001
Polypharmacy (*n* ≥ 5), *n* (%)	225 (68.39)	134 (59.56)	142 (84.02)	74 (74.00)	14 (56.00)	<.001
Inflammation						
CRP level, median (IQR)	16.35 (53.55)	4.6 (12.9)	28 (78.5)	6 (21.5)	11.9 (40.25)	<.001
Previous antidepressant treatment	31 (9.54)	18 (8.18)	37 (22.02)	22 (22.22)	3 (12.00)	<.001

[a]Class size, *n* (%). Class 1 no depression/somatic only; class 2 no depression/pauci-symptomatic; class 3 severe depression; class 4 mild depression; class 5 demoralization.
[b]Inadequate social support defined as no primary caregiver or inadequate support at home or no strong circle of family and friends able to meet the needs of the patient.
[c]Other tumors included lung, ovary, uterus, head and neck, skin, thyroid, and unknown primary tumor site.
[d]Loss of weight was defined as loss of ≥3 kg in 1 month or ≥6 kg in 6 months.
[e]Cognitive dysfunction defined as MMSE ≤24 or diagnosis by a clinician.
[f]Number of patients with condition of grade 3 or 4.
Abbreviations: ADL, activities of daily living; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CRC, colorectal cancer; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; ELCAPA, Elderly Cancer Patient; GI, gastrointestinal; IADL, instrumental activities of daily living; IQR, interquartile range; MNA, Mini Nutritional Assessment; TGUG, time get-up and go test.

Table 2). These two last characteristics also persisted for patients in class 3 severe depression ($p \leq .001$ and .003), who were also more likely to be inpatients ($p < .001$) and have inadequate social support ($p < .001$), history of falls ($p = .010$), and polypharmacy ($p = .008$). Class 4 mild depression was associated with worst nutritional status

Table 2. Multinomial multivariate logistic regression analysis of factors associated with the different classes (n = 642)

Characteristics	Class 1 ND/somatic only	Class 2 ND/pauci-symptomatic	Class 3 severe depression	Class 4 mild depression
Demographics				
Female gender	1.49 (0.88–2.51)	Ref	1.22 (0.63–2.38)	8.79 (3.48–22.22)
Inpatient status	1.65 (0.94–2.90)	Ref	3.47 (1.78–6.75)	0.44 (0.17–1.17)
Inadequate social support[a]	1.11 (0.62–1.99)	Ref	3.21 (1.69–6.12)	0.98 (0.41–2.30)
Cancer				
CRC	Ref	Ref	Ref	Ref
Prostate	0.63 (0.29–1.36)	Ref	1.41 (0.51–3. 90)	1.78 (0.40–7.97)
Breast	0.63 (0.30–1.32)	Ref	1.63 (0.59–4.47)	1.63 (0.63–4.23)
Urinary system	1.03 (0.50–2.09)	Ref	2.05 (0.80–5.29)	1.72 (0.57–5.19)
Upper GI tract/liver/pancreas	1.05 (0.50–2.17)	Ref	1.61 (0.64–4.07)	0.43 (0.10–1.90)
Hematologic malignancies	0.64 (0.26–1.61)	Ref	0.70 (0.22–2.25)	2.59 (0.66–10.2)
Other[b]	0.76 (0.33–1.75)	Ref	1.40 (0.51–3.81)	1.66 (0.50–5.53)
Metastatic status M1/Mx	1.75 (1.11–2.77)	Ref	1.67 (0.92–3.03)	1.71 (0.87–3.34)
Geriatric				
CIRS-G index[c]	1.70 (1.08–2.67)	Ref	2.52 (1.38–4.61)	1.63 (0.85–3.14)
History of falls (6 months)	1.46 (0.88–2.42)	Ref	2.20 (1.21–3.98)	1.93 (0.97–3.80)
Nutrition; loss of weight[d]	3.32 (1.93–5.73)	Ref	4.33 (2.28–8.21)	3.23 (1.43–7.29)
Cognitive dysfunction[e]	0.80 (0.48–1.36)	Ref	0.73 (0.39–1.37)	0.44 (0.21–0.96)
Polypharmacy; $n \geq 5$	1.38 (0.88–2.17)	Ref	2.41 (1.26–4.60)	2.10 (1.07–4.12)
Previous antidepressant treatment	0.86 (0.38–1.95)	Ref	2.31 (0.99–5.43)	2.93 (1.20–7.17)

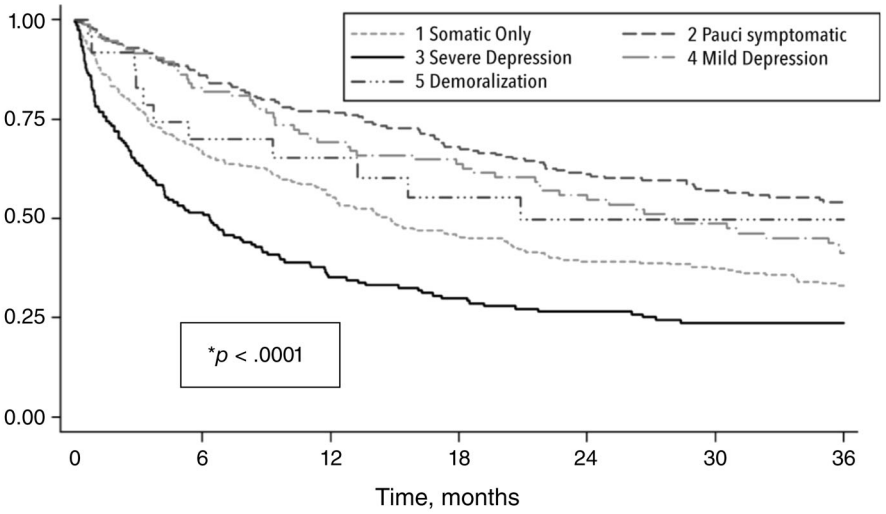
Data are adjusted odds ratios (95% confidence interval).
[a]Inadequate social support defined as no primary caregiver or inadequate support at home or no strong circle of family and friends able to meet the needs of the patient.
[b]Other tumors included lung, ovary, uterus, lung, head and neck, skin, thyroid, and unknown primary tumor site.
[c]number of patients with condition of grade 3 or 4.
[d]Loss of weight defined as loss of ≥3 kg in 1 months or ≥6 kg in 6 months.
[e]Cognitive dysfunction defined as MMSE ≤24 or diagnosis by a clinician.
Abbreviations: ADL, activities of daily living; BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CRC, colorectal cancer; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; GI, gastrointestinal; IADL, instrumental activities of daily living; IQR, interquartile range; MNA, Mini Nutritional Assessment; ND, no depression; TGUG, time get-up and go test.

(p = .005), antidepressant treatment at GA (p = .019), and polypharmacy (p = .032). As expected, female gender was still highly associated with class 4 mild depression (p < .001). Age was no longer associated with class membership on multivariable analysis. Unexpectedly, cognitive impairment was negatively associated with class 4 mild depression (p = .039) after adjustment for CIRS-G and gender.

CRP data were available for 478 patients. Multivariable analysis revealed increased CRP level in class 1 no depression/somatic only and class 3 severe depression (adjusted OR, 4.22; 95% CI, 1.69–10.55; p = .002 and adjusted OR, 5.28; 95% CI, 1.87–14.86; p = .002). These ORs did not differ between classes 1 and 3.

Multiple imputation for missing data yielded similar results (n = 847; data not shown).

Figure 3 presents survival curves according to the five identified profiles. Survival was better in class 2 no depression/pauci-symptomatic (median, 45.5 months), then gradually decreased from class 4 mild depression (median, 28.1 months) to class 1 no depression/somatic only (median, 14.8 months), then class 3 severe depression (median, 6.3 months). Known prognostic factors and factors associated with survival on univariable analysis included tumor site in association with metastatic status, age, functional status/comorbidities, nutritional status, mobility [21, 22], cognitive impairment, inpatient status, polypharmacy, planned treatment strategy, and antidepressant treatment at the time of GA. Nevertheless, anti depressant treatment at GA was not an independent factor for survival in multivariable analysis ($p \geq .112$) and is unlikely to be a confounder because it is not known to be associated with survival in this population and obviously does not increase the risk of depression. Therefore, this variable was not included in the final multivariable model. In this multivariable analysis, only class 3 severe depression remained significantly associated with increased mortality as compared with class 2 no depression/pauci-symptomatic at both 1-year (adjusted hazard ratio, 1.62; 95% CI, 1.06–2.48) and 3-year (adjusted hazard ratio, 1.49; 95% CI, 1.06–2.10) follow-up. When replacing CIRS-G with another variable that reflects functional impairment, such as ADL or ECOG-PS, estimations were similar. In sensitivity analysis, including antidepressant treatment at GA in the multivariable model yielded similar results (adjusted hazard ratio at 1 year, 1.55; 95% CI,



No. at risk							
Classe 1 Somatic Only	323	210	170	135	114	99	67
Classe 2 Pauci-symptomatic	221	184	162	141	123	105	83
Classe 3 Severe depression	168	83	54	45	39	31	26
Classe 4 Mild depression	97	77	64	58	48	40	33
Classe 5 Demoralization	25	16	13	11	9	9	8

Figure 3. Kaplan-Meier plots of overall 3-year survival for each of the 5 classes. Presents the Kaplan-Meier survival curves of overall 3-year survival for each of the 5 classes and the numbers at risk for each class. The severe depression class shows lower survival. *p value for unadjusted log-rank test.

1.01–2.40; at 3 year: adjusted hazard ratio, 1.47; 95% CI, 1.04–2.08).

Multiple imputation for missing data regarding baseline geriatric and oncological factors yielded similar results regarding survival (n = 834; data not shown).

Discussion

We identified five distinct profiles of depressive symptoms by using a data-driven approach: isolated somatic symptoms, most likely due to the physical impact of cancer (class 1 no depression/somatic only), few overall symptoms (class 2 no depression/pauci-symptomatic), and three profiles featuring psychological symptoms of depression. Among the latter, two mainly differed in the intensity of depressive symptoms (class 3 severe depression and class 4 mild depression), whereas one was consistent with qualitative features pertaining to the demoralization syndrome (class 5 demoralization), previously described among patients with cancer [24]. These profiles were also distinctly associated to several oncologic and geriatric features. Class 3 severe depression was independently associated with poor survival.

Our results are consistent with previous studies reporting the identification, by LCA, of depressive profiles differing in the intensity of presented symptoms [25]. Moreover, our study highlighted another profile that differs qualitatively from severe and mild depression, with high probability of sadness and negative thoughts contrasting with a remarkable absence of loss of pleasure or interest, consistent with the definition of demoralization [24]. Demoralization has been defined as a psychological state of loss of meaning and subjective incompetence, with thoughts of hopelessness and helplessness. Critical differences with depression have been described and notably include a "preserved magnitude of motivation" [24] that results clinically in a unique combination of negative thoughts, typically hopelessness, with a lack of anhedonia and a potential ability to benefit from psychological support, especially meaning-focused interventions [26]. The data-driven identification of this profile by LCA, rather than through a theory-driven diagnosis instrument, may substantiate demoralization as a clinical entity separate from depression, as suggested by early conceptualization [24]. Comorbidity between demoralization and major depression could be frequent [27] and could explain the small number of patients in class 5 demoralization, if we consider that some patients in class 3 may present both depression and demoralization. On one hand, because we did not use specific criteria for the diagnosis of demoralization, the prevalence of this syndrome could not be ascertained. On the other hand, the data-driven identification of a profile matching this clinical description without theory-driven interview is all the more convincing. The present results should also be interpreted in light of the clinical implications of demoralization in patients with cancer, especially its influence on suicide risk [28] or end-of-life decisions [29], and its relevance as a target for psychosocial interventions.

Our results agree with previous cross-sectional studies identifying depression-associated factors. In older patients with cancer, inpatient status, polypharmacy, inadequate social support, functional or nutritional impairment were independently associated with depression [16, 30, 31]. In older people without cancer, inadequate social support was also associated with depression [3], as were functional impairment [32] and comorbidities [3, 32]. In patients with cancer of all ages, lack of social support [33] was consider a risk factor for depression.

Although both class 1 no depression/somatic only and class 3 severe depression were associated with elevated levels of CRP, there was no statistical difference in the strength of this association between the two classes. This result is nonetheless consistent with the association of major depression with elevated inflammation in the absence of physical comorbidities [34].

Several meta-analyses identified depression as independently associated with poor survival in patients with cancer [7, 8]. Indeed, other studies of older patients with cancer failed to find depression independently associated with poor survival [22]. This situation might result from the use of other diagnosis criteria and confirms the importance of a global assessment of depression, accounting for the full range of relevant symptoms. Of note, the increased mortality associated with depression has been observed in other clinical populations as well as in community settings [35] so that the underlying mechanisms may not be specific to cancer. These mechanisms may include higher stage of the disease at the time of diagnosis, associated health behaviors (poor medical adherence or failure to quit smoking) [36], associated biological features such as inflammation, and lower quality of delivered care.

Our study presents several strengths. First, LCA allows integrating the results of objective statistical criteria with a comprehensive clinical perspective; our five-class solution was clinically meaningful while meeting statistical indices of parsimony and goodness of fit. Also, the use of a routine GA allowed us to explore a wide range of associated factors. Finally, the longitudinal nature of the study enabled the assessment of the prognostic value of our classification.

Some limitations should be acknowledged. Although the semistructured interview of the GA asked physicians to systematically search for and report symptoms of depression, these symptoms were not assessed through standardized questions as in a structured interview. Also, we did not include guilt or suicidal ideation as indicators. However, these two symptoms are specifically less frequent in older patients with depression [11]. Furthermore, classical depression scales may lack accuracy for assessing depression in older patients with cancer [37]. Indeed, in this population, classical criteria could be insufficient to accurately identify depression, and the use of alternative criteria [38] could be pertinent [9]. We also acknowledge that missing data led to exclude participants from the logistic regression and survival analysis, decreasing the sample size, possibly leading to selection bias. To address this limitation, we ran a secondary analysis using multiple imputation, which showed similar results. Also, a large percentage of patients had metastasis at the inclusion (42.5%), which may be because of the setting of specialized geriatric oncology clinics.

Our study has several implications. Our results could be used to stratify participants in further studies, identify biomarkers or evaluate therapeutic interventions, because the different profiles may actually represent different psycho and/or physiopathologic underlying mechanisms. Trajectories of depressive symptoms should be explored in this population as Avis et al. did in patients after breast cancer [39]. The use of tools designed to identify demoralization and/or other psychosomatic syndromes, such as the Diagnostic Criteria for Psychosomatic Research, may also help to describe links between clinical syndromes more accurately [40]. From a clinical perspective, our study underlines the importance of a systematic assessment of depressive symptoms using a global approach. The poor prognostic value of severe depression also points out the need for developing adequate strategies that may help decrease mortality and improve quality of life in these patients. Further studies are warranted to discriminate the role of biological or behavioral pathways because such understanding may inform therapeutic interventions to decrease excess mortality associated with depression.

Conclusion

We identified five distinct profiles of depressive symptoms in older patients with cancer, using a data-driven approach: (a) few overall symptoms; (b) somatic symptoms only, likely due to the impact of cancer symptoms per se (rather than previous cancer treatment); (c) severe depression; (d) mild depression; and (e) a qualitatively distinct profile consistent with demoralization syndrome. Geriatric and oncologic factors were independently associated with the different profiles and the severe depressive profile independently predicted poor survival.

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Author Contributions

Conception/design: Clément Gouraud, Cédric Lemogne, Florence Canouï-Poitrine

Collection and/or assembly of data: Elena Paillaud, Nicoleta Reinald, Marie Laurent, Mathilde Gisselbrecht, Elise Mercadier, Pascaline Boudou-Rouquette, Anne Chahwakilian

Data analysis and interpretation: Clément Gouraud, Elena Paillaud, Claudia Martinez-Tapia, Lauriane Segaux, Nicolas Hoertel, Sylvie Bastuji-Garin, Frédéric Limosin, Cédric Lemogne, Florence Canouï-Poitrine

Manuscript writing: Clément Gouraud, Elena Paillaud, Claudia Martinez-Tapia, Lauriane Segaux, Nicoleta Reinald, Marie Laurent, Lola Corsin, Nicolas Hoertel, Mathilde Gisselbrecht, Elise Mercadier, Pascaline Boudou-Rouquette, Anne Chahwakilian, Sylvie Bastuji-Garin, Frédéric Limosin, Cédric Lemogne, Florence Canouï-Poitrine

Final approval of manuscript: Clément Gouraud, Elena Paillaud, Claudia Martinez-Tapia, Lauriane Segaux, Marie Laurent, Lola Corsin, Nicolas Hoertel, Mathilde Gisselbrecht, Elise Mercadier, Pascaline Boudou-Rouquette, Anne Chahwakilian, Sylvie Bastuji-Garin, Frédéric Limosin, Cédric Lemogne, Florence Canouï-Poitrine
Technical support: Elena Paillaud, Claudia Martinez-Tapia, Lauriane Segaux
Development of methodology: Clément Gouraud, Cédric Lemogne, Florence Canouï-Poitrine

Disclosures

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