



Anxiety and depression in patients with advanced cancer during the COVID-19 pandemic

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Abstract

Objective Cancer patients are at increased risk for psychological difficulties and COVID-19. We sought to analyze anxiety and depression levels during the COVID-19 pandemic and the association between sociodemographic, clinical, and psychological factors in patients with advanced cancer.

Methods A prospective, multicenter cohort of 401 consecutive patients with newly diagnosed, advanced cancer completed the Brief Symptom Inventory, Michel Uncertainty in Illness Scale, Herth Hope Index, and Cancer Worry Scale between February 2020 and May 2021. Linear regression analyses explored the effects of uncertainty, hopelessness, and cancer worry on anxiety and depression, adjusting for sociodemographic and clinical variables.

Results The incidence of anxiety and depression was 36% and 35%, respectively. Emotional distress was greater among women, patients < 65 years of age, and those with an estimated survival of > 18 months. Linear regression analysis revealed that being female, preoccupation about cancer, and hopelessness were associated with increased levels of anxiety ($p < 0.001$) and depression ($p < 0.001$) and younger age was associated with a higher risk of anxiety. No differences in anxiety or depression levels were found in relation to marital status, children, educational level, cancer type, histology, stage, or type of treatment.

Conclusions Patients with advanced cancer who initiated treatment during the pandemic experienced high levels of depression and anxiety. Early diagnosis and the development of intervention strategies are necessary, especially for specific patient subgroups, such as young women with long survival times.

Keywords Advanced cancer · COVID-19 · Anxiety · Depression · Hopelessness

Introduction

In December 2019, a novel viral pneumonia of unknown cause emerged in China. After extensive sequencing analysis of lower respiratory tract samples, this new virus was found to belong to the coronavirus family and the disease it caused was named “severe acute respiratory syndrome coronavirus-2” (SARS-CoV-2) [1]. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 spread like wildfire around the world and was subsequently declared a pandemic by the World Health Organization (WHO) [2]. Since the first

case, more than 135 million cases have been reported worldwide, including more than 2.5 million deaths [3].

The first confirmed case in Spain was reported on January 31 [4]. Following the announcement of the first case, the government designated many public and some private hospitals “pandemic hospitals” and new inpatient wards exclusively for COVID-19 patients were set up. Faced with this situation, several new orders were implemented in hospitals. For example, in-person physician visits were replaced by videoconferencing or calling patients, the number of polyclinics was reduced, and non-emergency surgeries were postponed. As a result, access to healthcare was hindered for people with chronic diseases, such as cancer patients who need regular evaluations in the hospital.

Receiving a diagnosis of cancer and the subsequent treatment procedures are perceived by many patients as stressful.

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Oncology patients may be more susceptible to depression or anxiety for different reasons, such as reaction to the cancer diagnosis, the presence of symptoms secondary to the tumor itself or the treatments received, and the uncertainty surrounding the risk of recurrence or disease progression [5]. In this context, cancer patients are at higher risk of suffering psychological problems compared to healthy individuals [6]. Studies suggest that untreated psychological issues in cancer patients (especially depression) are associated with a range of destructive outcomes, such as worse treatment adherence, lower survival rates, increased healthcare costs, and poorer quality of life [7, 8].

Several predictors of anxiety and depression in cancer patients have been described. Some studies have shown that age, gender, education level, and other factors are associated with mood in cancer patients [9–11]. Studies have also been conducted to evaluate the effects of positive psychological resources, such as hope, self-efficacy, optimism, and social support, on anxiety and depression in cancer patients.

Cancer patients are more vulnerable to COVID-19 infection and secondary complications due to immunosuppression from antineoplastic treatments, concomitant comorbidities, and multiple visits to hospitals for treatment or diagnostic tests [12]. During the COVID-19 pandemic, several scientific societies and expert groups published guidelines on how to modify clinical practice to protect cancer patients. The recommendations of the Spanish Society of Medical Oncology (SEOM) for the management of these patients were basically avoid initiating or delay the initiation of potentially myelosuppressive treatment if the clinical situation permitted, modify the frequency of treatment, or reduce doses, reduce visits and length of hospital stay, and promote telemedicine. On the other hand, many oncologic surgeries were delayed or diverted to referral centers at the onset of the pandemic.

Considering that the COVID-19 pandemic has caused high rates of psychological issues even in the general population [13]; thus, cancer patients who are already susceptible in this regard are more likely to experience psychological distress. Indeed, recent studies evaluating psychological symptoms in individuals with different types of cancer during the COVID-19 pandemic have revealed rates of 30% for depression and 30–69% for anxiety [14, 15].

Through this study, we aimed to determine the incidence of anxiety and depression in patients who initiated systemic treatment for advanced cancer during the COVID-19 pandemic, and analyze the association between clinical and sociodemographic factors and with psycho-psychological symptoms.

Materials and methods

Participants and procedures

This was a multicenter, prospective, cross-sectional study. A consecutive sample of advanced cancer patients was recruited at 15 medical oncology departments at different hospitals in Spain, between February 2020 and March 2021. The beginning of recruitment coincided with the development of the first wave of COVID-19 in Spain, when the incidence and mortality rates were higher, while more than half of the sample was recruited in the second and third waves, when the incidence of infected patients was reduced. Patients were selected at their first visit to the medical oncologist in which diagnosis, stage, incurable disease status, and systemic antineoplastic treatment options were explained. Eligible patients were ≥ 18 years with histologically confirmed advanced cancer who were not candidates for surgery or other therapy with curative intent. Patients with physical conditions, comorbidity, and/or age that represented a contraindication in the opinion of the attending oncologist to receive antineoplastic treatment; those who had received cancer treatment in the previous 2 years for another advanced cancer; or with any underlying personal, family, sociological, geographical, and/or medical condition that could hinder the patient's ability to participate in the study were excluded. This research was conducted in accordance with current ethical principles and received previous approval from the Ethics Review Committees at each institution and from the Spanish Agency of Medicines and Health Products (AEMPS; identification code: ES14042015). The study comprised the completion of several questionnaires and collection of clinical data from the interview and medical records. Data collection procedures were similar at all hospitals and data relating to the participants were obtained from the institutions where they received treatment. Participation was voluntary, anonymous, and did not affect patient care. All participants signed informed consent prior to inclusion. Data were collected and updated by the medical oncologist, through a web-based platform (www.neoetic.es).

Measures

Demographic information including age, sex, marital status, children, educational level, and employment status and the questionnaires were reported in writing by the patients. The four questionnaires (BSI, MUIS, HHI, CWS) were completed by the patient at home in the interval between the first visit to the oncologist and the start of systemic treatment. Clinical variables related to cancer,

antineoplastic treatment, and outcomes were collected by the medical oncologist from the medical records.

Brief Symptom Inventory (BSI) is one of the most widely instruments to assess anxiety and depression in clinical cases [16]. The scale consists of 18 items, but we only analyzed the 12 items related to the anxiety and depression scales, and not the somatization scale because the latter could be confused with physical symptoms. These 12 items are divided into 2, 6-item subscales. The anxiety subscale evaluates symptoms of nervousness, tension, motor restlessness, apprehension, and panic states, while the depression subscale measures symptoms of disaffection and dysphoric mood, e.g., those reflecting self-deprecation, anhedonia, hopelessness, and suicidal ideation. Each item is scored on a 5-point Likert scale and the score for each subscale ranges from 0 to 24 with higher scores indicating greater anxiety or depression. Raw scores are converted to *T*-scores based on gender-specific normative data. To identify individuals with significant levels of anxiety and depression, the BSI applies the clinical case-rule [17] originally developed for SCL-90. According to the cut-off values recommended by Derogatis [16], patients whose *T*-score ≥ 67 were considered to have “possible anxiety or depression”, and a *T*-score ≥ 63 were categorized as having “probable anxiety or depression.” The Spanish version of the BSI has proven good reliability and validity in Spanish patients [17]. The Cronbach’s alpha for the anxiety and depression scales was 0.80 and 0.75 respectively [18].

Uncertainty was appraised using the 5-item **Michel Uncertainty in Illness Scale (MUIS)** [19]. This questionnaire examines reactions to uncertainty, ambiguous situations, and the future. Items are scored on a Likert scale ranging from 1 (no at all characteristics of me) to 5 (entirely characteristics of me), yielding possible scores of 5–25; higher scores signify more uncertainty. Cronbach’s alpha was 0.83 [19].

Hope was evaluated by the 12-item **Herth Hope Index (HHI)**. Hope is characterized by the strength and confidence that the patient shows in himself and/or in the medical team to cope with his uncertainty. Items are scored on a 4-point Likert scale, with total scores ranging from 12 to 48, lower scores evidence greater hopelessness. In this study, Cronbach’s alpha for the scale was 0.97 [20].

Cancer Worry Scale (CWS) assesses preoccupations about cancer recurrence and the impact of these worries on daily functioning, which is a major concern in patients with metastatic cancer [21]. Seven items are rated on a 4-point Likert scale. Possible scores ranged from 6 to 24, with higher scores pointing to more worry. In this study, Cronbach’s alpha for the scale was 0.90 [21].

Statistical analyses

Subjects’ sociodemographic and clinical characteristics are expressed as means and standard deviations for continuous variables and as numbers and proportions for categorical variables. Independent sample *t* test and one-way analysis of variance ANOVAs were performed to assess variations in anxiety and depression with respect to sociodemographic and clinical variables. If the unidirectional ANOVA was significant, a least significant different test was performed for paired comparisons. Pearson’s correlation determined the level of association and linear regression analyses explored the effects of uncertainty, hopelessness, and cancer worry on anxiety and depression, with adjustment for sociodemographic and clinical variables. Those sociodemographic and clinical variables that significantly correlated with anxiety or depression in the univariate analysis were introduced into the linear regression analysis as adjusted variables. The assumptions underlying regression analysis were controlled (e.g., linear relationship, multivariate normality, no or little multicollinearity, and homoscedasticity). For all analyses, significance was set at $\alpha < 0.05$. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software, 25.0 version (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

Results

Sociodemographic-clinical features

At the time of data cutoff (May 2021), 426 cancer patients had been contacted and the data pertaining to 401 were finally analyzed. A total of 25 were excluded (4 failed to meet the inclusion criteria, 5 met an exclusion criterion, and 16 had incomplete data). Women accounted for 52.1%, with a mean age of 64.1 years (standard deviation (SD)=10.6, range 34–88). Most were married or partnered (71.6%), had children (79.6%), and had a primary level of education (46.6%). All patients’ employment status was retired or unemployed. As for clinical characteristics, the most common tumors were bronchopulmonary (30.9%), colorectal (13.7%), and pancreatic (10.5%). Adenocarcinoma histology was the most frequent (62.6%) and most cancers were stage IV (79.3%). The most common treatment was chemotherapy (56.6%), chemotherapy with immunotherapy (18%), and others (25.4%). Estimated survival was less than 18 months in 48.6% of the sample (see Table 1).

Incidence of anxiety and depression

According to the cutoff values recommended by Derogatis [16], clinically significant symptom of anxiety and

Table 1 Sociodemographic and clinical characteristics

Characteristics	N=401 N (%)
Sex	
Male	192 (47.9)
Female	209 (52.1)
Age	
≤ 65 years	201 (50.1)
> 65 years	200 (49.9)
Marital status	
Married/partnered	287 (71.6)
Not partnered	114 (28.4)
<i>p</i> value	
Child	
No children	82 (20.4)
With children	319 (79.6)
Educational level	
Primary	187 (46.6)
High school or higher	214 (53.4)
Cancer type	
Bronchopulmonary	124 (30.9)
Colorectal	55 (13.7)
Pancreas	42 (10.5)
Others	180 (44.9)
Histology	
Adenocarcinoma	251 (62.9)
Others	150 (37.4)
Cancer stage	
Locally advanced	83 (50.7)
Metastatic disease (IV)	318 (79.3)
Estimated survival	
< 18 months	193 (48.6)
≥ 18 months	206 (51.4)
Type of treatment	
Chemotherapy	227 (56.6)
Immunotherapy	31 (7.7)
Chemotherapy and immunotherapy	72 (18.0)
Others	71 (17.7)

depression was present in 36% and 35% (T score ≥ 67) and 29% and 17% had some symptoms of anxiety and depression (T score ≥ 63 to < 67), respectively. Binomial test analyses indicated that there were sociodemographic and clinic differences between patients in levels of anxiety or depression (see Table 2). Women had more anxiety ($M=66.3$, $SD=7.8$ versus $M=63.0$, $SD=7.9$) ($F_{(1,399)}=17.501$, $p=0.001$, effect size $\eta^2=0.042$) and more depressive symptoms ($M=63.9$, $SD=6.9$ versus $M=61.6$, $SD=6.6$) ($F_{(1,399)}=11.358$, $p=0.001$, effect size $\eta^2=0.028$) than men. Patients diagnosed with advanced cancer under 65 years of age exhibited more anxiety ($M=65.8$, $SD=7.9$ versus $M=63.9$, $SD=7.9$)

Table 2 Univariate analysis including sociodemographic and clinical characteristics

Characteristics	Anxiety Mean (SD)	Depression Mean (SD)
Sex		
Male	63.0 (7.9)	61.6 (6.6)
Female	66.3 (7.8)	63.9 (6.9)
<i>p</i> value	0.001	0.001
Age		
≤ 65 years	65.8 (7.9)	63.4 (6.7)
> 65 years	63.6 (7.9)	62.1 (7.1)
<i>p</i> value	0.005	0.071
Marital status		
Married/partnered	64.7 (8.3)	62.6 (6.9)
Not partnered	65.6 (7.2)	63.3 (6.8)
<i>p</i> value	0.855	0.377
Children		
No children	64.8 (7.3)	63.9 (6.3)
Have children	64.6 (8.2)	62.6 (7.0)
<i>p</i> value	0.823	0.478
Educational level		
Primary	64.9 (7.8)	63.2 (6.9)
High school or higher	64.5 (8.1)	62.4 (6.8)
<i>p</i> value	0.553	0.291
Cancer type		
Bronchopulmonary	64.4 (7.8)	62.5 (7.1)
Colorectal	65.6 (8.6)	64.8 (7.6)
Pancreas	63.6 (8.0)	61.7 (6.3)
Others	64.8 (7.8)	62.6 (6.5)
<i>p</i> value	0.645	0.101
Histology		
Adenocarcinoma	65.0 (7.7)	62.9 (6.9)
Others	64.1 (8.3)	62.5 (6.8)
<i>p</i> value	0.298	0.646
Cancer stage		
Locally advanced	64.6 (7.9)	62.4 (6.8)
Metastatic disease (IV)	64.7 (8.1)	62.9 (6.9)
<i>p</i> value	0.888	0.601
Estimated survival		
< 18 months	63.8 (7.9)	65.5 (8.0)
> 18 months	65.5 (8.0)	63.1 (7.2)
<i>p</i> value	0.043	0.334
Type of treatment		
Chemotherapy	64.9 (8.0)	63.0 (6.9)
Immunotherapy	63.1 (8.1)	61.5 (7.0)
Chemotherapy and immunotherapy	65.1 (8.3)	63.0 (6.7)
Others	64.7 (8.0)	62.6 (7.0)
<i>p</i> value	0.629	0.736

Abbreviations: *SD*, standard deviation. Bold values indicate significance at the 5% level

($F_{(1,399)} = 7.889$, $p = 0.005$, effect size $\eta^2 = 0.019$) than those aged 65 years or older. Participants with an estimated survival of more than 18 months had more anxiety symptoms ($M = 65.5$, $SD = 8.0$ versus $M = 63.8$, $SD = 7.9$ versus) ($F_{(1,399)} = 4.108$, $p = 0.043$, effect size $\eta^2 = 0.010$) than patients with an estimated survival of less than 18 months. No differences in anxiety or depression levels were found in relation to marital status, children, educational level, cancer type, histology, stage, or kind of treatment.

Correlations and predictors of psychological symptoms

Pearson's correlation analyses revealed that anxiety and depression were positively related with preoccupation about cancer, uncertainty, and hopelessness (all $p = 0.001$). Age was negatively correlated with anxiety symptoms ($r = -0.140$, $p = 0.005$), but not with depression symptoms (see Table 3).

Linear regression analyses revealed that variations in age, being female, preoccupation about cancer, and hopelessness accounted for 34% of the variance in anxiety symptoms ($F = 35.202$, $p < 0.001$). On the other hand, preoccupation, hopelessness, and being woman explained 37% of the variance in depression symptoms ($F = 40.315$, $p < 0.001$) (see Table 4).

Table 3 Pearson's correlations between psychological variables

Variables	1	2	3	4	5	6
1. BSI. Anxiety	1					
2. BSI. Depression	0.762**	1				
3. MUIS. Uncertainty	0.463**	0.402**	1			
4. CWS. Preoccupation	0.060**	0.075**	0.206**	1		
5. HHI. Hope	-0.366**	-0.490**	-0.097	0.040	1	
6. Age	-0.140**	-0.086	0.058	0.042	-0.004	1

** $p < 0.001$ (two-tailed)

Abbreviations: *BSI*, Brief Symptom Inventory; *MUIS*, Michel Uncertainty in Illness Scale; *CWS*, Cancer Worry Scale; *HHI*, Herth Hope Index

Table 4 Linear regression analysis to determine protective factors for lower levels of anxiety and depression; unstandardized coefficients, significance, adjusted r^2 , and variance analysis

BSI	Anxiety				Depression			
	Variable	β	p	R^2 Adj F	β	p	R^2 Adj F	
MUIS. Uncertainty	0.004	0.813	0.313	22.203	0.034	0.338	24.82	
HHI. Hope	-0.329	<0.001			-0.455	<0.001		
CWS. Preoccupation	0.410	<0.001			0.335	<0.001		
Age (years)	-0.095	0.022			-0.056	0.167		
Survival (months)	0.063	0.130			0.024	0.546		
Gender: female	0.112	0.008			0.088	0.032		

Gender categorized "female" versus "male." Bold values indicate the significant at 5% level

Abbreviations: *MUIS*, Michel Uncertainty in Illness Scale; *HHS*, Herth Hope Index; *CWS*, Cancer Worry Scale

Discussion

This is the first study to assess the incidence of anxiety and depression in patients with advanced cancer in Spain during the COVID-19 pandemic based on a prospective series of individuals who were going to initiate anti-tumor treatment. The aim of our study was to determine the incidence of anxiety and depression and their relationship with clinical and psychosocial factors. In our series, we found an incidence of anxiety of around 36% and of depressive symptoms of 35%. These results coincide with those of other studies carried out during the pandemic in the oncologic population in which anxiety levels were found to be between 9.3 and 31% and depression between 8.9 and 36% [14, 15, 22, 23]. One of the first studies was published by Li JuanJuan and included 658 patients with breast cancer in February 2020 and found that 8.9% of the sample suffered from severe anxiety and 9.3% had severe depression. In another series of individuals with non-Hodgkin's lymphoma published by Romito F. that included 77 patients with hematological disease, 36% and 31% suffering anxiety and depression, respectively. This high incidence could be due to cancer patients' fear of COVID-19 infection, complications secondary to this infection due to immunosuppression, delays in diagnostic tests and treatment,

and how becoming ill with COVID can interfere with the evolution of their neoplasm.

The lifetime prevalence of depression and anxiety disorders is approximately twofold in women compared to males. The US National Institute of Mental Health reports that the prevalence of an anxiety disorder is as much as 60% greater in women than in men and that the onset, severity, and clinical course differ significantly in women [24, 25]. In our sample, females with advanced cancer displayed higher levels of anxiety and depression and anxiety levels were greater in patients aged less than 65 years. Young women diagnosed with any type of advanced cancer are particularly vulnerable to distress disorders as they see their expected life roles and responsibilities changed, generally with respect to their family and work environment, contemplating the loss of their future due to early mortality [26, 27]. Studies in women with breast cancer suggest that younger patients are more vulnerable to psychological distress than older patients [28].

Our study is one of the first to relate mood disorders to estimated survival at the time of diagnosis in advanced disease, demonstrating that anxiety levels are higher in patients with an estimated survival of more than 18 months compared to patients with an estimated survival of less than 18 months. Earlier evidence shows that anxiety levels increase at the time of diagnosis of advanced cancer, generally in relation to perceiving imminent death, and then gradually decrease in the year following diagnosis [29]. However, this evolution does not play out in the same way in all cancer patients; in fact, some patients continue to suffer anxious symptoms years after diagnosis. There are very few studies that relate estimated survival following a diagnosis of advanced cancer to anxiety and depression. In the meta-analysis published by Mitchell AJ., which included 94 studies in the onco-hematological population, no association was found between mood disorders and type of cancer or tumor stage or between palliative and non-palliative settings [30]. Possible explanations for the findings of our study include the fear of the evolution of the disease, prolonged suffering, both their own and their loved ones' in the face of an incurable disease, and losing control over oneself with increased dependence on others, all of which may generate greater psychological distress [31].

We found that being a young woman and having high levels of hopelessness and worry correlated with 34% of the variance in anxiety levels. However, when it comes to depression, age is removed from the equation, but being female, preoccupation about cancer, and hopelessness remain and would account for 37% of the variance. This indicates that positive expectations (hope) about the evolution of the disease may help to decrease anxiety and depression. Previously published studies have indicated that younger individuals suffer greater emotional distress in relation to the diagnosis of cancer, as they are still seeking professional stability and creating a family [32, 33].

Age tends to be a factor related to variations in depression levels, with lower levels and less existential distress at older ages. Although results in the literature are contradictory, we have not found this relationship in our study or have other previously published studies, as in the case of the Latin American population with breast cancer [34].

The findings of this study should be considered in conjunction with its limitations. First, the present study was cross-sectional in nature; therefore, it was not possible to determine the directionality of the observed relationships or how much or how long the pandemic may have affected outcomes. Second, although the BSI questionnaire has proven its reliability as a screening tool, it should be used in tandem with a multidisciplinary, clinical approach to detecting and managing depression and anxiety. Third, in this analysis, cut-off scores were used, transforming continuous into dichotomous variables for comparability with other series, which can lead to a loss of power and precision. Finally, we used self-report instruments, which can lead to response bias, such as social desirability and memory errors.

This work enables us to draw various conclusions with relevant implications for our clinical practice. Anxiety and depression incident rates are very high in patients with metastatic cancer who are going to start antineoplastic treatment, especially in times of pandemic. Therefore, especially in this context, it is necessary to carry out an early psychological assessment, in as much as these disorders can interfere and have a negative impact on patients' evolution and prognosis. This study highlights the need for psychological care by teams specialized in psycho-oncology with a comprehensive and multidisciplinary approach from the time of diagnosis of advanced cancer.

After an initial assessment and considering the results of our study, special consideration should be given to patients with longer estimated survival times, who are female, and younger individuals, as they represent a subgroup that is particularly susceptible to exhibiting high levels of emotional distress.

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Author contribution B.O.P., C.C., and P.J.F developed the project, analyzed the data, and drafted the manuscript. The other authors recruited patients and provided clinical information, comments, and improvements to the manuscript. All authors participated in the interpretation and discussion of data, and the critical review of the manuscript.

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Data availability Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) software, 25.0 version (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). The code is available upon request to the authors.

Code availability Patients are identified by an encrypted code known only to the local researcher. The code of the analyses is available upon request to the authors.

Declarations

Ethics approval The study was approved by the Research Ethics Committee of the Principality of Asturias (May 17, 2019) and by the Spanish Agency of Medicines and Medical Devices (AEMPS) (identification code: L34LM-MM2GH-Y925U-RJDHQ). The study has been performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. This study is an observational, non-interventionist trial.

Consent to participate Signed informed consent was obtained from all patients.

Consent for publication Informed consent and approval by the national competent authorities includes permission for publication and diffusion of the data.

Conflict of interest The authors declare no competing interests.

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