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





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## Resilience, Social Support, and Anxious Preoccupation in Patients with Advanced Cancer during COVID-19 Pandemic

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### ABSTRACT

This study examines the mediating role of social support between anxious preoccupation and resilience in patients with cancer during COVID-19. NEOtic\_SEOM is a prospective, multicenter study involving individuals with advanced, unresectable cancer who completed the following scales: Resilience (BCRS), Social Support (Duke-UNC-11), and anxious preoccupation subscale of the Mini-Mental Adjustment to Cancer (M-MAC) before starting antineoplastic treatment. Between March 2020 and July 2021, 507 patients (55% male; mean age, 65) were recruited. No differences in resilience were observed based on sociodemographic or clinical characteristics. Social support in people with advanced, unresectable cancer promotes both decreased anxious preoccupation and greater resilience.

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Anxiety; cancer; COVID-19; resilience; social support

### Introduction

Cancer negatively impacts subjects' mental state; 38% of patients suffer from anxiety that may have been exacerbated by COVID-19 confinement and restrictions (1). During the coronavirus pandemic, most were obligated to be alone during hospital stays and many consultations were conducted by phone or internet, which may have negatively impacted the confidential and affective support perceived by patients. In addition, the virus' high infectivity and the severity of the disease in the early months of the pandemic contributed to increasing people's fear of death and feelings of loneliness, sadness, and irritability (2,3).

Resilience is a complex concept, best defined as an individual's ability to recover or bounce back from adverse or stressful events that can lessen their vulnerability by helping them achieve

an optimal state when faced with environmental risks (4,5). It is a dynamic construct, in that it is modulated by changes in physical status or environment, altering an individual's ability to adapt to adverse situations (4,5). Resilience can wane the fear of side effects of antineoplastic treatment and cancer recurrence (6).

Social support is the perception of feeling valued and integrated into social groups (7,8). Several studies have confirmed that feeling protected by others can lessen anxious preoccupation and bolster resilience in people with cancer (9–12).

A diagnosis of cancer and need for complex treatments are associated with high stress and a substantially increased risk of anxiety. In a series of patients with resected cancer, anxiety was estimated to be present in 23–50% (13). This incidence is expected to be greater in patients with incurable advanced cancer for whom life

expectancy is shortened, prognosis is uncertain, and dependent on the benefit achieved with the antineoplastic treatment administered (14).

Few studies have examined the impact of social support and anxious preoccupation on psychological resilience in patients with incurable advanced cancer who are not eligible to receive treatment with curative intent. These individuals typically develop anxious preoccupation ascribable to the uncertainty they face regarding the prognosis of their disease and the antineoplastic treatment-related toxicity, all of which can negatively impact their mental health. Our study is pivotal insofar as it provides a window through which we can understand how social support mediates between anxious preoccupation and resilience in these subjects during the COVID-19 pandemic. Furthermore, these variables have been affected by the psychological impact this pandemic has had on these individuals, causing them to suffer greater anxious preoccupation about becoming infected, experiencing more complications of their underlying disease, and about the reorganization of healthcare services that has led to greater disruption of the care received (15,16). Nevertheless, it appears that having cancer may have prepared these patients for the existential anguish caused by the pandemic, developing greater capacity to recover and considerable resilience from mental health impairment (17,18).

There is increasing awareness of incorporating the effect of sex on cancer outcomes. Along the same line, the SAGER (Sex and Gender Equity in Research) guidelines have been designed to guide authors in integrating sex assessment in manuscripts as part of the editorial process (19). In addition, previous research in regard to resilience, social support and anxious preoccupation has shown differences between men and women. In Spanish NEOcoping study, women with breast cancer sought more social support from friends, whereas participants with colon cancer turned more to relatives for support, and women with cancer had more psychological distress than men (20,21).

We hypothesize that anxious preoccupation may be associated with psychological resilience, mediated by the presence of social support, and

that sociodemographic variables, such as gender may influence psychological resilience.

## Material and methods

### *Patients and study design*

NEOetic\_SEOM is a consecutive, prospective, multi-institutional study (15 medical oncology departments) of the Bioethics Group of the Spanish Society of Medical Oncology (SEOM). The study was approved by the ethics committee of each center and by the Spanish Agency for Medicines and Medical Products (AEMPS; code: ES14042015). It was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

The study was designed before the start of the SARS-COV-2 outbreak, but the entire recruitment process took place during the pandemic, recognized as a public-health emergency of international concern. Participants were  $\geq 18$  years of age; had a histologically confirmed advanced, unresectable cancer, and were candidates for systemic treatment. Exclusion criteria comprised conditions that the oncologist deemed contradicted for anticancer therapy or participation in the study, as well as individuals who had received oncological treatment in the previous two years. Recruitment was consecutive and was carried out by the medical oncologist at the visit during which they informed the patient of the diagnosis and treatment alternatives for the cancer.

### *Variables and questionnaires*

Clinical data were collected by the oncologist from the patient interview and medical history. Those patients who agreed to participate signed the consent form, were given instructions on how to fill in the hardcopy questionnaires, completed them at home, and handed them to the support staff at the next visit. All data and scales were collected through an online web platform ([www.neoetic.es](http://www.neoetic.es)) by the oncologist (medical data) and by the study support staff (the completed hardcopy questionnaires handed in by the participants). The scales used were: Brief Resilient Coping Scale (BCRS) (22), Duke-UNC-11 Functional Social Support Questionnaire (23),

and the anxious preoccupation subscale of the Mini-Mental Adjustment to Cancer (Mini-MAC) (23,24).

Resilience was assessed using the four-item Brief Resilient Coping Scale (BCRS) (22). This questionnaire is designed to capture the extent to which an individual copes resiliently with stress. Items are graded on a 5-point Likert scale from 1 (does not describe me at all) to 5 (describes me very well). Scores range from 4 to 20 with higher scores indicating greater resilience. Cronbach's alpha was 0.76 (22).

Social support was measured using the Duke-UNC-11 Functional Social Support Questionnaire (Duke-UNC-11) (23,24). This instrument assesses two dimensions of social support: confidant support (received from people to whom the patient can communicate intimate feelings) and affective support (received from those who express positive empathy towards them). Items are graded on a 5-point Likert scale from 1 (much less than I would like) to 5 (as much as I would like). Scores range from 11 to 55; the higher the score, the more perceived social support. Cronbach's alpha was 0.93 (23).

The anxious preoccupation subscale of the Mini-Mental Adjustment to Cancer (M-MAC) scale was developed to quantify maladaptive coping in response to cancer (24). The questionnaire consists of eight items, each of which measures the tendency to worry about cancer as an event that provokes feelings of devastation, anxiety, fear, and apprehension. Each statement is rated on a 4-point Likert scale ranging from 1 (definitely does not apply to me) to 4 (definitely applies to me). The scale revealed a reliability of 0.94 in the Spanish sample (25).

The participants' comorbidities based on the International Classification of Diseases (ICD) diagnosis codes were categorized using the Elixhauser Comorbidity Index, which includes 29 disease conditions; Elixhauser scores were calculated using the method proposed by van Walraven and colleagues (26,27).

Estimated median overall survival was divided into  $>$  or  $\leq$  18 months. The median survival for advanced lung cancer without driver mutations, the most frequent cancer in the series, is

approximately 18 months; thus, this was the cut-off point chosen (28).

### Statistical analyses

Count data were expressed as frequency and percentage (%); measurement data were reported as mean and standard deviations (SD). Additional descriptive analyses were performed grouping patients by type of cancer and type of treatment. Independent sample *t*-test and ANOVA were used to compare the psychological resilience score by the participants' different demographic characteristics. Pearson's correlation analysis measured the correlation between variables. Multivariate linear stepwise regression was used to examine the influencing factor of psychological resilience. A 95% bias-corrected bootstrap confidence interval (CI) was calculated for the effect of anxious preoccupation on resilience through social support (29). A power analysis determined that a minimum of 85 participants was needed to obtain high power ( $\alpha=0.80$ ) and effect sizes of 0.15 with  $\alpha=0.05$ . All statistical tests were two-sided and significance was set at  $p<0.05$ . Data were statistically analyzed using the Statistical Package for Social Sciences (SPSS) for Windows 23.0 (SPSS Inc., Chicago, IL).

## Results

### Sociodemographic characteristics and their influence on resilience

A total of 544 patients were recruited, 37 of whom were excluded from the study (11 because they failed to meet inclusion criteria; 5 met an exclusion criterion, and 21 had incomplete data). The final study sample consisted of 507 individuals; 55% ( $n=277$ ) were male, and the mean age was 65 years ( $SD=10.2$ ). Most were married or partnered (83%), with a primary education (47%). All were retired or unemployed. The most common cancers were bronchopulmonary (31%), colorectal (15%), and pancreatic (10%) and the most frequent histology was adenocarcinoma (59%). All had an unresectable cancer; 21% were locally advanced and 79% were stage IV. All were to receive systemic antineoplastic treatment, the most frequent one being chemotherapy (52%),

**Table 1.** Characteristics and psychological resilience ( $n = 507$ ).

Variables	$n$ (%)	Resilience M (SD)	Statistics	
			t/f	$p$ Value
Sex				
Male	277 (55)	14.3 (4.0)	-5.01	0.617
Female	230 (45)	14.5 (3.8)		
Age (years)				
≤ 65	237 (46)	14.5 (3.7)	0.654	0.513
>65	270 (54)	14.3 (4.0)		
Marital				
Married or partnered	372 (83)	14.4 (3.9)	0.427	0.670
Unpartnered	135 (17)	14.2 (3.8)		
Educational level				
Primary school and below	241 (47)	14.2 (3.7)	-0.944	0.345
High school and above	266 (53)	14.5 (4.0)		
Tumor site				
Broncho-pulmonary	155 (31)	14.8 (3.6)	1.020	0.405
Colon	78 (15)	14.6 (3.8)		
Pancreas	49 (10)	13.8 (4.8)		
Breast	29 (6)	13.5 (4.3)		
Stomach	24 (5)	14.7 (4.5)		
Others	172 (34)	14.2 (3.8)		
Histology				
Adenocarcinoma	230 (59)	14.3 (3.8)	-0.356	0.722
Others	207 (41)	14.4 (4.0)		
Metastasis				
Advanced locally	115 (21)	13.7 (3.8)	-1.894	0.059
IV	391 (79)	14.5 (3.9)		
Survival				
More than 18 months	249 (49)	14.3 (4.1)	-0.250	0.803
Less than 18.1 months	257 (51)	14.4 (3.7)		
Treatment				
Chemotherapy (CT)	262 (52)	14.5 (3.8)	1.296	0.257
CT + targeted drug	52 (10)	13.8 (4.6)		
CT + immunotherapy	50 (10)	14.1 (3.6)		
Immunotherapy	36 (7)	14.5 (4.1)		
Targeted therapy	25 (5)	14.2 (3.6)		
Others	82 (16)	14.1 (4.0)		
Elixhauser comorbidities				
≤4	167 (32)	14.3 (3.9)	-0.852	0.394
>4	339 (68)	14.4 (3.9)		

M: mean; SD: standard deviation.

associated with targeted drugs (10%) or immunotherapy (10%). Estimated median overall survival was <18 months in 49% of the sample.

The total resilience score was 14.4 (SD = 3.9). No significant differences were found based on sociodemographic (sex, age, marital status, educational level) and clinical (primary tumor site, presence of metastases (stage), tumor histology, antineoplastic treatment, Elixhauser comorbidities, estimated median overall survival) characteristics (see Table 1).

### **Correlations between variables and multiple linear regression analysis for psychological resilience**

The results of the correlation analyses revealed associations between anxious preoccupation, social support, and resilience. Anxious preoccupation and social support accounted for 24.1% of

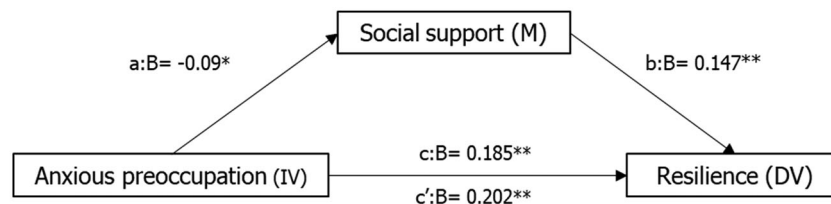
the variance in resilience ( $F = 120.18$ ,  $p = 0.001$ ) and anxious preoccupation was a significant predictor of resilience ( $B = 0.185$ ,  $p = 0.001$ ). The direct effect of anxious preoccupation on resilience (effect = 0.18, SE = 0.08, 95% CI [0.01, 0.32],  $p = 0.001$ ), the effect of anxious preoccupation on social support (effect = -0.09, SE = 0.02, 95% CI [0.01, 0.10],  $p = 0.012$ ), and the effect of social support on resilience (effect = 0.147, SE = 0.60, 95% CI [0.64, 2.14],  $p = 0.001$ ) were significant. The indirect effect indicated that social support mediated the relationship between anxious preoccupation and resilience (effect = 0.20, SE = 0.10, 95% CI [0.05, 0.41], Sobel  $z = 1.78$ ,  $p = 0.004$ ), see Figure 1. The model indicated that patients with advanced cancer who reported greater social support improved their resilience despite the presence of anxious preoccupation.

### **Discussion**

This study is one of the few conducted in individuals with incurable, advanced cancer who have undergone antineoplastic therapy during the COVID-19 pandemic that explores the mediating role of perceived social support between anxious preoccupation and resilience and confirms that, the greater the perceived social support, the less anxious preoccupation and greater resilience.

Patients with unresectable locally advanced cancer fare worse than those with metastatic cancer. This may be due to prognostic uncertainty given that, despite the absence of metastasis, the cancer is unresectable, and they will receive similar systemic antineoplastic treatment as patients with metastatic cancer. Moreover, many patients with unresectable, locally advanced cancer are likely to have received confirmation of incurability and the palliative nature of systemic treatment at the visit with the medical oncologist when they were given the study questionnaires. In contrast, individuals with metastatic cancer are more likely to have already known that their disease is incurable before then and, hence, will have had more time to come to terms with the prognosis (14). We have been unable to determine any differences in resilience across treatment types, even though, overall, targeted treatments in cancers with driver mutations and immunotherapy tend





**Figure 1.** The mediator model of social support. a = direct effect of independent variable (IV) on mediator (M). b = direct effect of mediator on dependent variable (DV). c = direct effect of IV on DV. c' = indirect effect of IV on DV. \* $p < 0.05$ . \*\* $p < 0.01$ . The first step represents social support regressed on anxious preoccupation. The second step represents resilience regressed on anxious preoccupation. The third step represents resilience regressed on anxious preoccupation and social support.

to yield better survival results than standard chemotherapy. This may be due to the fact that patients lack the medical knowledge necessary to understand the efficacy of different treatment regimens and varieties of treatment, as well as the prognosis of their cancer (30). The oncologist may also find it difficult and/or avoid conveying this information at the first visit. These findings and hypotheses should be explored in future studies designed for this purpose.

One Chinese study determined that perceived social support, resilience, and hope affected the quality of life in people with bladder cancer (10), whereas another one confirmed the role of social support to mediate between resilience and quality of life in breast cancer sufferers (40%, stage II) (9). Although most studies find a positive association between social support and resilience in people with non-metastatic colon or breast cancer (31,32), a Turkish study noted that social support can change quality of life for the worse given patients' fear of abandonment if they were perceived as psychologically resilient (33). In lung cancer, two Chinese studies have discovered that providing social support and reducing symptom preoccupation enhance resilience in patients (34,35). Similarly, we have seen a positive correlation between social support and psychological resilience in our series. In this regard, the influence of the COVID-19 pandemic has been analyzed in earlier studies, such as the one conducted in Danish subject that revealed that, thanks to family support at critical times, the participants developed low levels of anguish and high degrees of resilience, regardless of the COVID-19 restrictions. Another study conducted in individuals with breast cancer also detected that resilience and family support can lessen the

negative psychological effect provoked by the pandemic (36,37).

In contrast, the study by Castellon et al. evinced no association between resilience and perceived stress, yet did confirm greater resilience among men, possibly given that the female participants were more likely to have breast cancer, and most had undergone mastectomy, a procedure that entails psychological stress that can affect resilience (38). As for the effect of the COVID-19 pandemic, it has been seen to aggravate psychological distress, which correlates negatively with resilience (39). Nonetheless, subjects with advanced cancer have perceived COVID-19 as a shorter term threat and had less anxiety and greater resilience compared with the rest of the population (40). The findings of our study have corroborated that anxious preoccupation has a negative association with resilience.

As for limitations, the cross-sectional nature does not enable us to determine the directionality of the observed relationships or how long the COVID-19 pandemic may have affected our results. In contrast, the limited representation of certain cancer subtypes, such as breast cancer, which is highly prevalent, but yields a lower percentage of advanced-stage cases, does not allow us to generalize the data to specific cancer sites. Despite controlling for sociodemographic, clinical, psychological, and family variables, this study cannot rule out the possibility that some other, un contemplated factor may have modulated resilience, nor can it quantify the specific effect of COVID-19. The study was conducted during the pandemic but designed before it; hence, no COVID-19-specific variables were included. Furthermore, the questionnaires were completed by the participants themselves with

the possibility of response bias due to interpretation errors. Thus, the results should be used in conjunction with a clinical assessment.

In conclusion, our study attests to the importance of good social support in individuals with unresectable advanced cancer, to assuage anxious preoccupation about prognosis, antineoplastic treatment, or complications associated with COVID-19 and develop greater resilience. This must be confirmed in longitudinal studies and clinical trials. Should these data be confirmed, future lines of research might advocate psychosocial interventions especially for individuals lacking social support or in whom high levels of anxiety are detected.

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## Ethical 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.

## Author contributions

A.R., 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.

## Transparency declaration

The lead author states that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author states that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

## Declaration of interest

The authors declare that they have no conflict of interest related to the scope of this work.

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## Data availability statement

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.

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.

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