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RESEARCH PAPER

ASSOCIATIONS BETWEEN PERSONALITY TRAITS, PERCEIVED STRESS AND DEPRESSIVE SYMPTOMS IN GYNECOLOGICAL CANCER PATIENTS CHARACTERIZED BY THE SHORT AND LONG ALLELE VARIANT OF THE 5-HTTLPR GENOTYPE: PRELIMINARY RESULTS

Salvatore Iuso, Lucia Monacis, Luigi Nappi, Stefania Malerba, Giovanna D'Andrea, Mario Altamura, Maurizio Margaglione, Antonello Bellomo, Annamaria Petito

Abstract

Objective: The study explored associations between personality traits, perceived stress and symptoms of depression in oncological patients characterized by the two variants of the serotonin transporter (5-HTTLPR) polymorphisms.

Method: The sample was composed of 41 gynecological cancer patients who completed self-reported questionnaires including the NEO Five-Factor Inventory, the dimension of depression-dejection (D/D) of the Profile of Moods State and the Perceived Stress Scale (PSS). The polymerase chain reaction was also employed to identify genotypes in the serotonin (5HTT) polymorphism.

Results: The one-way ANOVA test, across the 5-HTTLPR genotype groups, showed significant effects of the short variants on neuroticism (p=0.009) and of the long variant on agreeableness (p=0.022), as well as a tendency to a statistical significance of the l/l variant on consciousness (p=0.074). Bivariate correlations showed positive correlations of neuroticism with both psychopathological symptoms (D/D r=0.522; PSS r=0.586) in the combined group S, negative association of agreeableness with depression (D/D r=-0.613) and of consciousness with depression (D/D r=-0.750) and perceived stress (PSS r=-0.702) in the group of the long variant of 5-HTTLPR genotype.

Conclusions: Personalized medicine should consider the interaction between genotype and phenotype in reducing levels of clinical psychological distress, highlighting how psychotherapeutic processes should improve patients' quality of life.

Key words: 5-HTTLPR genotype, depression, perceived stress, personality traits, gynecological cancer patients

Salvatore Iuso[1], Lucia Monacis[2], Luigi Nappi[3], Stefania Malerba[1], Giovanna D'Andrea[1], Mario Altamura[1], Maurizio Margaglione[1], Antonello Bellomo[1], Annamaria Petito[1]
[1] Department of Clinical and Experimental Medicine, University of Foggia, Italy, email: iuso.salvatore@libero.it; smalerba@ospedaliriunitifoggia.it; giovanna.dandrea@unifg.it; mario.altamura@unifg.it; maurizio.maraglione@unifg.it; antonello.bellomo@unifg.it; annamaria.petito@unifg.it
[2] Department of Humanities, University of Foggia, Italy; email: lucia.monacis@unifg.it
[3] Department of Medical and Surgical Sciences, University of Foggia, Italy; email: luigi.nappi@unifg.it

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Corresponding author
Lucia Monacis
E-mail: lucia.monacis@unifg.it

Introduction

A strong body of evidence shows the coexistence of maladaptive psychosocial phenomena with both affective dysregulations (increased anxiety states and deflected mood) and alterations in physiological behaviors (insomnia and increased perception of fatigue) during the experience of cancer (Etchegary et al., 2017). Diagnosis and cancer treatment induce a strong level of acute and chronic stress, thus reducing the level of quality of life (Zerbinati et al., 2021). Cancer patients, who generally experience a significant level of stress, can be considered as real candidates to test diathesis stress models. Being both diagnosis and treatment mainly recommended for patients with life stress, this stress could be causing or exacerbating relative psychological disorders, such as symptoms of depression and anxiety (Petito et al., 2020). In addition, clinical psychological distress may lead patients to be reluctant to seek medical attention and be twice as likely to face the risk of suicide than the general population (Walker et al., 2014). Additionally, suicide risk factors could include a feeling of being a burden to others, loss of autonomy, a desire to control their own death, physical symptoms, despair, existential worries, lack of social support and fear of the future (Altamura et al., 2017). On the other hand, there is evidence of the effectiveness of psychotherapy in treating depressive symptoms and improving both stress levels and quality of life (Maniaci et al., 2020). Studies on the effectiveness of mind-body therapies for depression, highlight the effectiveness of the Functional Therapy Program for depression and its psychological correlates, thus confirming the role of psychotherapy in improving

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mood (Cuijpers et al., 2020; Maniaci et al., 2021). The effect of stress on the immune system is well known, and both psychotherapeutic and pharmacological treatments should aim to improve patients' mood in order to improve their response to chemotherapy and other cancer treatments.

Past research reported that diagnoses of post-traumatic stress disorder (PTSD) appear to be limited to a small minority of women who survive early-stage breast cancer (Cordaba et al., 2017) even if subthreshold symptoms are more common. Cancer recurrence is strongly associated with intrusion symptoms of PTSD in the presence of persistent depression or anxiety, poor psychological adaptation and poor quality life (Kim et al., 2018). Diagnosis and treatment in advanced stages disease are the most stressful life events among patients mainly affected by ovarian, uterine or endometrial cancer. A recent investigation reported an increased level of depression from 12.77% to 25.53% in women with advanced gynecological cancer (Rahnea-Nita et al., 2019). For these women, changes in body image, sexual dysfunction and infertility dramatically affected their quality of life, since they had to re-handle their relationship with family members, friends and partners, and they are compelled to face the unknown with regard to their job, family income and lives in general.

A recent critical review (Caruso et al., 2017) has reported different risk factors in depressive spectrum disorders ranging from biological to non-biological (individual and interpersonal-social) variables. Indeed, in oncological research it is well established that biological aspects, through the interactions among pathophysiological pathways, are particularly important in determining a sort of brain-arousal profile which is an indicative risk for depression.

With regard to genetic makeup in response to treatment and cancer patients' survival, its role on emotional and behavioral states in conditions of psychophysical stress during oncological treatment pathways is much discussed. Indeed, when looking at the general association between the expression of polymorphism and serotonin transporter gene (5-HTTLPR) with depression symptoms, inconsistent findings have emerged. Caspi and colleagues (2003) reported a significant moderating role of 5-HTTLPR on influence of stressful life events in depression. In other words, in relation to stressful life events, individuals with one or two copies of the short allele exhibited more depressive symptoms and suicidality than subjects homozygous with long allele. Similarly, Kang and colleagues (2017) demonstrated that short allele may cause a genetic predisposition towards suicidal ideation in patients after 2 weeks of acute coronary syndrome. Recently, Kim and colleague (2018) has found significant association between the short variant of the 5-HTTLPR genotype and depressive symptoms in breast cancer patients. Conversely, other researchers did not confirm this association in oncological samples (Suppli et al., 2015). Therefore, no consensus has yet been reached on the question of whether and under which conditions 5-HTTLPR genotype affects vulnerability to depression when people deal with severely stressful life events. In this direction, it seems reasonable to hypothesize the conjunction of the S-allele of 5-HTTLPR with other individual risk factors, such as personality constructs, that could lead individuals to a higher risk of depressive symptoms.

Among the non-biological variables, previous research examined associations between personality traits and increasing vulnerability to depressive symptoms in oncology patients. Findings generally confirmed that individuals with high levels of neuroticism are more likely at risk of depression and anxiety in various cancer types (Morgan et al., 2017). Moreover, Langford and colleagues (2020) have examined the relationship between personality traits and coping strategies in oncology patients undergoing chemotherapy. Overall, these findings suggest that personality constructs may have a stronger influence on coping when individuals are faced with more serious stressors, such as cancer. In addition, the predisposition to different vulnerability to affective spectrum disorders comes from the disease experience. Langford and colleagues (2020) suggested that assessment of perceived stress and consequently stressful situation effects can be mediated by individual personality characteristics. The lack of emotional and psychological balance prior to cancer diagnosis can therefore be considered as a risk factor on increasing vulnerability to stress factors during treatment. Indeed, personality may influence how stressors are experienced, including frequency, intensity and nature of stressors (Bolger & Zuckerman, 1995). For example, a person affected by cancer and with high neuroticism and emotional instability could experience diagnosis of cancer as more threatening or severe, feel more fear and emotional distress, and show impaired ability to cope with stress.

With regard to the association between 5-HTTLPR genotype and personality traits, a prior meta-analysis indicated conflicting findings, probably due to small sample size and different inventories used to measure personality traits (Munafò et al., 2006). The picture becomes more complex if we look at the most investigated personality trait, neuroticism, which was found to be unrelated to and related to the 5-HTT polymorphisms (Petito et al., 2016; Esmaeilzadeh et al., 2020).

Navrady and colleagues (2018) suggest that polygenic risk for depressive disorder is associated with an increased likelihood of both clinical and self-reported depression, replicating previous findings. Li and colleagues (2019) found significant main effects of self-reported neuroticism on late life depression.

However, to the best of the authors' knowledge, no empirical evidence of this association on emotional distress symptoms has been provided in oncological patients. These analyses could be useful in identifying those highly vulnerable psychological and personological dimensions that could support oncological well-structured personalized psychotherapy interventions for the management of anxiety-depressive symptoms and for the improvement of quality of life. Following this purpose, the current preliminary study intended to explore not only the interplays between phenotypes related to five personality traits and the short and long variants of the 5-HTTLPR genotype, but also the patterns of associations of personality traits with distress symptoms in each specific genotype group.

Materials and Methods

Participants and procedure

The sample was composed of 41 gynecological oncological patients recruited from University Gynecology Department of Foggia between July 2018 and December 2019. Research protocol and participation approval for this study was voluntary. This study uses data from a random sample of Caucasian women born between 1950 and 1981 with gynecologic cancer. 43.9% of our sample had earned

a middle school diploma, another 43.9% had earned a high school diploma, 7.3% had earned an elementary school diploma, and 4.9% had earned a college degree. 87.8% of our sample were married women, 4.9% were single women, and 7.3% were separated women. Eligible patients received an explanation about the study procedures and they were asked to sign informed consent. We enrolled participants at least 4 weeks after cancer diagnosis to ensure that anxiety symptoms persisted beyond the initial adjustment to diagnosis. In addition, the recruited patients were not terminally ill.

Patients who were prescribed psychotropic drugs other than benzodiazepines were not eligible for the study. These are standard components of many chemotherapy regimens to decrease symptoms such as nausea. Patients who presented suicidal ideation, thought disorder or psychosis were excluded from recruitment. The study protocol was approved by the Institutional Review Board Ethics Committee of Hospital – University Foggia (Code number 93/CE/16).

Measures

In order to exclude the presence in our sample of subjects suffering from a psychiatric disorders, the structured clinical interview was conducted for the DSM-5 (SCID-5-CV) (First et al., 2015).

Personality traits were measured with the NEO Five-Factor Inventory (NEO-FFI) (Costa & McCrae, 1989). The personality description is considered in five dimensions: neuroticism, extraversion, agreeableness, openness and conscientiousness. The inventory included a total of 60 items, twelve items for each dimension, rated in five-point Likert scale from 0 (completely disagree) to 4 (completely agree). Cronbach's alpha values ranged from 0.78 to 0.85 and values of test-retest reliability ranged from 0.78 to 0.83.

The Profile of Moods State (McNair et al., 1971) was used to evaluate the patient's mood in the last week. The instrument is composed by 65 items, which identify the following six different factors: tension-anxiety (T/A), depression-dejection (D/D), anger-hostility (A/H), vigor-activity (V/A), confusion-bewilderment (C/B) and fatigue-inertia (F/I). In this study, the depression-dejection dimension composed by 15 items was used to measure the impact of depressive states on patients' quality of life. Each item rated on 4-point Likert scale anchors by ranging from 'Not at all' to 'Extremely'. The scale showed good internal consistency ($\alpha = 0.89$) and test-retest reliability (ICC = 0.86).

The perceived stress levels were measured by the Perceived Stress Scale (PSS) (Cohen, 1988). The tool includes 10 queries measuring which life degree has been experiencing as unpredictable, uncontrollable, and overloaded. For each item, individuals were asked to indicate how often they felt in a certain way. PSS scores range from 0 to 40. Higher scores indicate higher perceived stress. Cronbach's alpha was 0.87 and the Intra-class Correlation Coefficient (ICC) for test-retest reliability was 0.84.

DNA collection and analysis

The DNA analysis was carried out by the Medical Genetics Unit of the University of XXX. A blood sample was collected into ethylenediaminetetraacetic acid or sodium citrate by each participant and DNA was extracted from peripheral blood leukocytes according to standard protocols (Miller et al., 1988).

DNA amplification was amplified using the '2 flanking primers' suggested in 1996 by Heils and colleagues (1996): nt-1416,-13975-HTTL:5'GAGGGACTGAGCTGGACAACCAC, nt-910,-889. These primer sets amplify a 484/528 fragment corresponding to the SLC6A4_C short and long allele, respectively. The PCR conditions were slightly modified from Heils and colleagues (1996). The PCR reaction was carried out in a total volume of 20 µL consisting of 100 ng of genomic DNA, 0.1 µmol of primers per liter, 40-µmol/L deoxynucleotide triphosphates, 20-µmol/L7-deaza-2'deoxyguanosine, and 1 AmpliTaq unit with the appropriate buffer inside Mastercycler polymerase chain reaction thermal cycler (Eppendorf, Hamburg, Germany). Cycling conditions were as follows: 1 denaturing cycle at 95°C for 5 minutes, 2 cycles with a touchdown annealing temperature of 63°C and 62°C, respectively for 30 seconds, and 38 cycles with annealing temperature at 61°C. Final DNA elongation was at 72°C for 10 minutes. DNA bands were visualized in prestained (0.4-µg/mL ethidium bromide) 3% agarose gels that were run for 1 hour at 120 V.

Statistical analyses

Descriptive statistics related to age and mean scores of all psychological constructs for each genotype group were calculated. The one way ANOVA test was performed to analyze main differences across genotype groups in age and personality traits. Bivariate correlations were analyzed among the constructs of interest in each genotype group and in the combined genotype group. All statistical analyses were performed using a standard software package (STATA version V.15.1; StataCorp).

Results

The sample was composed of 41 gynecological oncological patients who had no history of neurologic, psychiatric disorders or alcohol and other drug dependence disorders. The participants average age was 58.15 (SD = 14.01), ranged within 18–65 years. The entire recruited sample was affected by gynecological endometrial cancer and all patients had undergone radio-chemotherapy. The genotype subgroups did not differ significantly on age [s/s = 65 (SD = 12.36); s/l = 58.86 (SD = 11.14); l/l = 64.09 (SD = 13.59)], all $p > 0.05$. The distribution of 5-HTTLPR genotype alleles in the sample was in the Hardy-Weinberg equilibrium ($p > 0.05$).

The mean scores on the NEO-FFI Five Personality sub-scales for each genotype group are presented in **table 1**. The one way ANOVA test across the 5-HTTLPR genotype groups [i.e., group S (s/s + s/l); l/l; l/s; s/s] indicated a significant main effect of the s/s genotype on neuroticism [χ^2 (3) = 16.03, $p = 0.009$]. Post-hoc analyses revealed a recessive effect of the short allele of the 5-HTTLPR gene with an increased neuroticism score in the s/s genotype group and in the combined group S compared to the s/l and l/l group ($p < 0.05$). A main effect of the l/l genotype on agreeableness [χ^2 (3) = 9.623, $p = 0.022$] was also found. Post-hoc analyses revealed a significant difference between the l/l genotype and group S (s/s + s/l). The l/l group presented higher agreeableness scores. Regarding conscientiousness, results proved a tendency to a statistical significance of the l/l genotype [χ^2 (3) = 6.932, $p = 0.074$]. No significant main effects emerged across genotype groups on extraversion [χ^2 (3) = 6.457,

Table 1. *Association between 5-HTTLPR genotype and NEO-FFI, Mean ± SD*

Genotype	N	N	E	O	A	C
l/l	11	18.43 ± 6.006	27.25 ± 5.965	20.35 ± 3.175	35.04 ± 2.842	38.84 ± 4.181
l/s	23	21.65 ± 7.042	25.23 ± 4.544	22.03 ± 5.495	30.53 ± 5.805	35.84 ± 4.338
s/s	7	24.75 ± 5.42	24.95 ± 7.33	21.5 ± 1.5	33 ± 3.367	38.7 ± 4.177
s/s + s/l	30	22.38 ± 6.743	25.17 ± 5.183	21.91 ± 4.84	31.11 ± 5.388	36.51 ± 4.442
p		0.009***	0.091	0.399	0.022*	0.074

N, Neuroticism; E, Extraversion; O, Openness; A, Agreeableness; C, Conscientiousness;
* p <0 .05, ** p <0 .01, *** p < 0.001.

$p = 0.091$)] and openness [χ^2 (3) = 2.947, $p = .399$)].

Correlation analyses were run between the three personality traits and the main constructs of interest in the combined group S (s/s + s/l). The data indicated that neuroticism was positively related to depressive mood states and perceived stress, agreeableness was marginally associated with depressive mood states and unrelated to perceived stress and, finally, conscientiousness was unrelated to depressive mood states and perceived stress (**table 2**).

Table 2. *Correlation between personality traits, POMS D/D and perceived stress level in Group S (ss + sl) (n = 30)*

NEO Neuroticism	
POMS D/D	0.522***
PSS	0.586***
NEO Agreeableness	
POMS D/D	-0.327
PSS	-0.137
NEO Coscientiouness	
POMS D/D	-0.231
PSS	-0.251

POMS D/D, Depression/Dejection; PSS, Perceived Stress Scale. ***p<0.001

In addition, given the effects of the long variant on agreeableness and conscientiousness observed in ANOVA analysis, further bivariate associations were examined between the three personality traits and the outcomes in each separate genotype group. As for neuroticism, findings indicated that it was unrelated to depressive mood states and positively associated to perceived stress in the s/s group; it was postively related with depression and perceived stress in the l/s group, and unrelated with the variables of interest in the l/l group. As for agreeablness, it was negatively related to depressive symptoms. Finally, findings indicated that agreeablness was negatively related to depression, conscientiousness was negatively related to depression and perceived stress in the l/l group, and no significant associations emerged between these two personality traits and the outcomes in the remaing genotype groups (**table 3**).

Discussion

Cancer diagnosis is a stressful life event with an objective negative impact on individuals' quality of life. It also implies an increasing risk of death and often involves intense and severe treatment with acute and long-lasting side effects (Seiler & Jenewein, 2019). To improve patients' psychological well-being and mental health, the identification and assessment of those highly vulnerable to psychological and personological dimensions could facilitate the application of tailored-psychosocial interventions. In attempt to suggest some

Table 3. *Bivariate correlations among the variables of interest in each genotype group*

	POMS D/D	PSS	Neuroticism	Agreeableness	Coscientiouness
Genotype l/l (n =11)					
POMS D/D	-	0.554	0.237	-0.613*	-0.750**
PSS	0.554	-	0.188	-0.101	-0.702**
Genotype l/s (n =23)					
POMS D/D	-	0.504*	0.597**	-0.329	-0.219
PSS	0.504*	-	0.620**	-0.307	-0.134
Genotype s/s (n =7)					
POMS D/D	-	0.111	-0.012	-0.431	-0.494
PSS	0.111	-	0.952***	0.687	0.260
Genotype s/s + s/l (n =30)					
POMS D/D	-	0.430*	0.522**	-0.327	-0.231
PSS	0.430*	-	0.586***	-0.137	-0.251

POMS D/D, Depression/Dejection; PSS, Perceived Stress Scale; *p<0.05; **p<0.01; ***p<0.001

practical implications in psychological interventions, the general aim followed in this current study was to provide empirical evidence of the effect of 5-HTTLPR genotype on personality traits and the associations among personality traits, perceived stress and vulnerability to depression across the different genotype groups. In addition, the hypothesis of a mediating role of neuroticism between perceived stress and depressive symptoms among gynecological cancer patients with expression of the S genetic polymorphism was also evaluated.

Results obtained through ANOVA analyses suggest a significant genotype group effect on personality traits. In particular, neuroticism, which is a personality trait referred to pessimistic attitudes and distressing reactive tendencies, seemed to be highly associated with the 5-HTTLPR short component expression (s/s) and with the combined group (s/s + s/l). This finding replicates previous studies reporting that short allele, which has also been found to lead to lower 5-HTT mRNA levels, was associated with an increase in levels of neuroticism (Altamura et al., 2019; Esmaeilzadeh et al., 2020).

On the other hand, agreeableness, which is a tendency to be compassionate and cooperative towards others rather than suspicious and antagonistic, seemed to be related to the 5-HTTLPR long variant. Finally, conscientiousness, which refers to the tendency to act dutifully and to show self-discipline and planned behaviors, seemed to be marginally linked to the 5-HTTLPR long variant. The two observed effects of the long variant allele indicated a significant increase of agreeableness levels and a trend towards a significant increase in conscientiousness level compared to the counterpart SS allele carriers. Although this preliminary evidence should be viewed with caution due to the small and clinical sample, the present findings could be aligned to some degree to results reported by Harro and colleagues (2009) among children and adolescents, and by Nestor and colleagues (2021) among university students, which show significant effects of the two variants of the 5-HTTLPR on the two personality traits.. The remaining FFI traits, e.g., openness and extraversion, did not differ significantly among genotypes. However, future investigations are needed to replicate these results.

The interpretations related to protective and risk factors of three aforementioned traits were supported if looked at the results emerged from the association between personality traits, perceived stress and depressive symptoms in the combined S group (s/s + s/l) and in the LL group. Indeed, the negative associations of conscientiousness with depression and perceived stress may also suggest that this trait, which is an adaptive disposition, could be considered as protective factor in reducing depressive symptoms and perceived stress in cancer patients characterized by the long variant of the 5-HTTLPR genotype. Likewise, the negative association of agreeableness with depression might further support the hypothesized protective factor of the trait against depressive symptoms. In other words, this trait is likely to reduce the risk of experiencing higher levels of depression among cancer patients. Patients with higher levels of agreeableness could be defined more resilient, as long as they could report better psychological functioning in terms of both negative affect and depression (Langford et al., 2020), being the finest users of adaptive or engagement coping strategies (Bolger & Zuckerman, 1995).

In contrast, the positive associations of neuroticism with perceived stress and depressive symptoms found in the combined S group corroborate prior studies that show (i) an interplay between phenotypes related to neuroticisms and the 5-HTTLPR genotype short variants (Esmaeilzadeh et al., 2020); (ii) significant associations of the S-allele linked to neuroticism with affective disorders (Karg et al., 2011); (iii) an increased level of depression risks in individuals characterized by the S-allele variant of the 5-HTTLPR genotype and previously exposed to stressful life events (Caspi et al., 2003).

Such findings also contribute to gathering consensus on the current debate by casting a positive light on the 5-HTTLPR genotype specific conditions affecting vulnerability to depression in presence of severely stressful life events, such as cancer diagnosis and treatment. In this vein, the expected result is consistent with recent investigation examining the relation of 5-HTTLPR with depressive symptoms (Zerbinati et al., 2021) and with the general connections between neuroticism, perceived stress and depressive mood state in various cancer types, albeit the genetic makeup was not taken into account (Morgan et al., 2017).

Polygenic risk scores could allow patients with depressive disorder to be stratified for antidepressant response. Ward and colleagues (2018) used Polygenic Risk Scores for neuroticism as putative predictors of antidepressant response. Polygenic Risk Scores for depressive disorder and neuroticism did not significantly predict antidepressant response but there was a consistent direction of effect, whereby greater genetic loading for depressive and neuroticism were associated with less favorable response.

To sum up, this preliminary study may extend the existing literature showing that, in the presence of stressful events, such as cancer diagnosis and treatment, the psychological tendency to exhibit negative emotions together with genetic configuration of the 5-HTTLPR short form may be significantly associated with the occurrence of depressive symptoms in women affected by gynecological cancer, and that agreeableness and conscientiousness with genetic configuration of the 5-HTTLPR long form could be considered as protective factor against adverse emotional distress.

Conclusions

The main strength of the current study lies in showing that specific molecular genetic information, such as the 5-HTTLPR polymorphism, connected to certain personality traits can be considered as a starting point to identify patients at higher risk of anxiety disorders, mood disorders and PTSD and to support them with pharmacological and psychotherapeutic treatment. Therefore, personalized medicine should take into account the interaction between genotype and phenotype in reducing levels of clinical psychological distress, by highlighting how psychotherapeutic processes should identify comorbidities in the oncology field. This would have an impact on the somatic component of anxiety and depression, on immunological processes and on patients' quality of life (Petito et al., 2020). However, some limitations should be noted. The small sample size limits the power relationship between the depressive symptomatology and the 5-HTTLPR genetic polymorphism. Future studies with a broader sample should replicate these findings. In addition, multiple confounding factors may have influenced the prevalence of depressive moods, such as the average duration of cancer disease and the severity of neoplasm. Finally, the cross-sectional nature of the study can only explore relationships amongst

the variables without proving causal relationships. Consequently, longitudinal research should be carried out to examine the causation effects.

Author Contributions

Conceptualization, S.I., L.M., and A.P.; methodology, S.I., and L.M.; acquisition of data: L.N., M.A., and A.B.; investigation, data curation, I.S. and A.P.; data analysis and interpretation: S.M., G. D'A., M.M., L.M., and S.I.; writing—original draft preparation, L.M, and A.P.; writing—review and editing, L.M and A.P.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board Ethics Committee of Hospital – University Foggia (Code number 93/CE/16).

Data Availability Statemen

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Therefore, they are available from the corresponding author upon reasonable request.

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