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Depression and psycho-existential correlates in cancer outpatients: A longitudinal real-life study

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ABSTRACT

Background: Depression is prevalent and clinically significant among cancer patients, being associated with poorer quality of life, treatment non-adherence, and increased mortality. However, few studies have investigated major depression and its relationship with psycho-existential dimensions using structured diagnostic tools and longitudinal designs in real-world psycho-oncology settings.

Aim and method: This study aimed to assess the prevalence of major depression in cancer outpatients receiving integrated psycho-oncology care and to examine longitudinal changes in psychological and existential variables over six months, with a focus on baseline depression status. A total of 221 outpatients were assessed at baseline using the Patient Health Questionnaire-9. Measures included distress, anxiety, somatization, embitterment, loss of dignity, demoralization, post-traumatic growth, and traumatic stress. At six months, 156 patients completed follow-up assessments. All participants received supportive-expressive psychotherapy with elements of meaning-centered therapy and pharmacological treatment when indicated. Data were analyzed using paired *t*-tests and mixed models for repeated measures..

Results: At baseline, 35.3% of patients met criteria for major depression. Depressed patients showed higher levels across all psychological and existential measures and lower post-traumatic growth. Longitudinal analyses revealed significant improvements across multiple domains, particularly among depressed patients, including embitterment and loss of dignity. Mixed-model analyses indicated significant group-by-time interactions in most variables.

Conclusions: These findings confirm the high prevalence of major depression in cancer outpatients and its association with emotional and existential distress. Integrated psycho-oncological care was associated with meaningful psychological improvements over time, especially in patients with baseline depression, supporting the need for structured screening and tailored interventions.

1. Introduction

Receiving a cancer diagnosis is widely recognized as one of the most emotionally distressing events in an individual's life, often triggering significant psychological reactions such as anxiety, depression, and existential fear [1]. High-impact reviews and large-scale studies confirm the pervasive emotional cost of cancer across different patient populations and disease phases [2–5].

Estimates indicate that the prevalence of full-blown depression or subclinical depressive symptoms among persons diagnosed with cancers ranges from approximately 5% to 49%, depending on tumor type, disease stage, treatment phase, care setting, and the assessment method

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used [2,6–8].

Depression and depressive symptoms in oncology has been consistently associated with worse clinical outcomes, including reduced adherence to medical treatment, longer hospital stays, increased suicide risk, diminished quality of life, and elevated cancer-specific mortality [4,9–12]. Meta-analytic data suggest that even subclinical depressive symptoms, as well as demoralization, may cause several negative consequences [13,14], including an increase in mortality by up to 25%, with a risk rising to 39% for patients with major or minor depression [4], as also confirmed in our experience [15].

The relationship between cancer and depression is now understood to be bidirectional. On the one hand, the stress of diagnosis, treatment burden, and fear of recurrence may lead to the onset of depressive symptoms. On the other, depression can worsen cancer outcomes through behavioral factors (e.g., non-adherence, poor self-care) and biological pathways (e.g., HPA axis dysregulation, immunosuppression) [10,16,17].

Despite the clinical relevance of this issue, the global literature remains highly heterogeneous, with wide variability in study designs, diagnostic criteria, and population characteristics. A recent umbrella review analyzing 128 meta-analyses highlighted this inconsistency and stressed the need for high-quality, context-specific data, particularly from non-English-speaking countries [18].

In the Italian context, some multicenter studies have explored psychological distress and psychiatric morbidity in individuals diagnosed with cancers, mainly through self-report tools such as the distress thermometer (DT), the Hospital Anxiety and Depression Scale (HADS) and the Brief Symptom Inventory (BSI-53) [19]. Although these studies provided essential epidemiological insights, sometimes using diagnostic interviews for major depression [20,21], the evolution of symptoms over time was never assessed, except a few exception [22]. Caruso et al. (2017) offered a conceptual review of depressive spectrum disorders in cancer care, helping to clarify diagnostic challenges and clinical needs, including the association of depressive symptoms with other psychological dimension [9].

A key diagnostic and clinical challenge in psycho-oncology is the differentiation of depression from related but not fully overlapping constructs such as demoralization, a condition characterized by helplessness, hopelessness, and loss of meaning [23]. This distinction is clinically relevant because it may affect both diagnostic accuracy and treatment planning, including the indication for interventions specifically targeting existential suffering, meaning-making, and dignity-related concerns [24]. In parallel, prior evidence suggests that depression in persons diagnosed with cancer rarely occurs in isolation, but is frequently accompanied by anxiety, somatic distress, hopelessness, diminished sense of meaning, and compromised dignity preservation [9,25,26,27]. These interrelated dimensions may in turn contribute to broader forms of suffering, including trauma-related symptomatology, loss of purpose, existential distress, and embitterment [7,28,29,30], [31,32]. At the same time, clinical and psychodynamic perspectives suggest that engagement with illness-related existential concerns may also activate processes of meaning reconstruction and narrative integration, through which patients re-elaborate their experience and reposition it within their broader life story [33]. Taken together, these observations support the view that depression in oncology should be examined within a broader psychological and existential framework, and provide the rationale for assessing a range of correlated dimensions – including anxiety and somatic symptoms, sense of dignity, demoralization, trauma-related symptoms, and positive psychological changes related to meaning-making processes - rather than depressive symptoms alone [34]. This perspective is consistent with psychodynamic and existential approaches in psycho-oncology, which emphasize how cancer-related distress is deeply intertwined with concerns about meaning, identity, finitude, and relational existence [33]. Given the multidimensional nature of depression in oncology, characterized by the interplay between affective, cognitive, and existential processes, the selection of psychological and existential variables in the present study was guided by their documented clinical relevance and frequent co-occurrence with depressive symptoms in cancer settings.

Identifying these patterns is crucial for developing tailored, multidimensional interventions, whose effects have been scarcely investigated in Italian diagnosed with cancers in real-world psycho-oncology settings. In order to address this gap, the present study aims (i) to assess depressive symptoms with standardized diagnostic tools aligned with DSM criteria, in order to estimate its prevalence at baseline (T0) among patients attending a psycho-oncology service, irrespective of a formal psychiatric diagnosis; (ii) to examine the associations between depression at baseline and a range of psychological and existential outcomes, including anxiety, somatization, embitterment, hostility, demoralization, post-traumatic growth, and dignity; and (iii) to evaluate the longitudinal changes in these outcomes over six months of integrated treatment, exploring whether the presence or absence of depression at baseline is associated with different clinical trajectories.

2. Materials and methods

2.1. Study design and participants

This was a longitudinal observational study conducted between November 2023 and July 2025 at the Psycho-oncology Program, Integrated Department of Mental Health and Pathological Addiction, Local Health Trust (LHT) and S. Anna University Hospital in Ferrara, Emilia-Romagna Region (ERR), Northern Italy (Italy). The study was part of the National Recovery and Resilience Plan (NRRP) project PNRR-MAD-2022 − 12,375,899. A consecutive sampling strategy was adopted. All eligible adult outpatients referred to the psycho-oncology service during the study period were invited to participate, without additional selection procedures. All participants were adult cancer outpatients who accessed the psycho-oncology service either through referral by their oncologist, general practitioner, or via self-initiated request. Referrals could occur at different stages of the illness trajectory, including diagnosis, active treatment, remission, or disease progression Inclusion criteria were: (i) age $\geq$ 18 years; (ii) confirmed diagnosis of cancer (iii) no cognitive impairment not allowing to complete self-report questionnaires; (iv) no diagnosis of a severe psychiatric disorder pre-dating the cancer diagnosis (e.g., schizophrenia, bipolar disorder); (v) ability to complete assessments, considering language, literacy, or sensory functioning.

Exclusion criteria were: (i) age $<$ 18 years; (ii) absence of a confirmed cancer diagnosis; (iii) cognitive impairment preventing completion of self-report measures; (iv) presence of a severe psychiatric disorder pre-dating the cancer diagnosis (e.g., schizophrenia, bipolar disorder); and (v) inability to complete assessments due to language, literacy, or sensory limitations.

The study was approved by the Ethics Committee of the Area Vasta Emilia Centro, which served as the competent ethics committee of reference (protocol code: 199/2023/Disp/AUSLFe) and was conducted in accordance with the Declaration of Helsinki.

2.2. Power analysis

A prevalence of 35% was selected for sample size estimation based on a conservative interpretation of the international literature, which reports a wide range of depression rates among persons diagnosed with cancers (5%–49%) depending on cancer type, disease stage, assessment method, and clinical setting [2,7]. This value reflects the upper half of reported estimates and was deemed clinically realistic for a psycho-oncology outpatient population assessed using structured tools such as the PHQ-9. Adopting a 95% confidence level and a precision of $\pm$6%, the required sample size was calculated at approximately 243 participants.

2.3. Procedure

All eligible patients were administered the Mini International Neuropsychiatric Interview (M.I.N·I) [35] as part of the clinical assessment within the Psycho-Oncology Program, allowing the formulation of a psychiatric diagnosis according to the International Classification of Diseases (ICD-9-CM), with established reliability in Italian oncology settings [21].

Standardized instruments was administered at baseline (t0) during the first clinical contact. Patients who continued treatment were reassessed at six-month follow-up (t1).

All patients received a supportive-expressive (SE) psychotherapy integrated with a meaning-centered focus. The intervention consisted of an approximately 12-session psychodynamic treatment delivered every 20 days, with flexibility based on patients' clinical conditions. The therapeutic approach followed a supportive–expressive continuum, combining emotional support, validation, and coping enhancement with the exploration of core relational and emotional themes [36,37].

The intervention addressed key psychological and existential domains, including depressive symptoms, uncertainty about the future, loss of control, changes in relationships, isolation, death anxiety, and meaning-making processes. The aim was to enhance emotional regulation, relational flexibility, and adaptive coping in the context of illness, while supporting patients in making sense of their experience and integrating it into a broader personal narrative [36,37].

Psychotherapy was delivered by psychiatrists and clinical psychologists, all formally trained as psychotherapists and experienced in psycho-oncology, with specific training in existential approaches, including meaning-centered psychotherapy and CALM (Managing Cancer and Living Meaningfully) [38,39]. Regular structured weekly supervision was conducted by a senior psycho-oncologist (RC), ensuring consistency in therapeutic orientation and shared clinical objectives. Outcome assessors were distinct from treating clinicians.

When clinically indicated, psychotherapy was combined with psychopharmacological treatment (e.g., antidepressants, benzodiazepines), prescribed and monitored according to routine clinical practice. No experimental intervention was applied.

2.4. Measures

2.4.1. Primary outcome measure

The primary outcome measure was the 9-item Patient Health Questionnaire (PHQ-9) [40], a DSM-concordant, self-report instrument widely used to assess depression severity items are rated on a four-point Likert scale (0–3), with a total score ≥ 10 indicating clinically relevant depressive symptomatology [41]. The PHQ-9 has been validated in the Italian population and demonstrates good convergent validity and clinical utility as a screening and severity measure [42,43]. Two additional items assessing suicidal ideation and functional impairment were included for clinical risk evaluation but were not incorporated into the total score.

2.4.2. Secondary measures

A series of tools were used to measure other psychological and existential aspects, as secondary outcomes. More specifically, the Demoralization Scale (DS), a 24-item self-report instrument assessing core dimensions of demoralization, including loss of meaning, dysphoria, disheartenment, and helplessness [44]. Items are rated on a five-point Likert scale (0–4), with established thresholds indicating low ($\leq$10), moderate (11–36), and high (>37) demoralization. The Italian version has shown good validity and clinical applicability [45,46].

The Posttraumatic Growth Inventory (PTGI) is a 21-item self-report measure assessing positive psychological changes following traumatic experiences [27]. It evaluates domains including new possibilities, appreciation of life, relationships, personal strength, and spirituality. The PTGI is widely used in oncology settings where it has shown clinically meaningful associations with psychological distress, well-being, and somatic symptoms, supporting its relevance in the assessment of adaptation to cancer [47]. The Italian version has undergone cross-cultural validation, with confirmatory factor analyses supporting the original five-factor correlated structure and demonstrating measurement invariance across gender, thus providing evidence of robust construct validity [48].

The Patient Dignity Inventory (PDI) is a 25-item self-report measure assessing dignity-related distress in patients with serious illness [49]. Items refer to the previous week and are rated on a 1–5 scale, with higher scores indicating greater distress. The Italian version has been validated in a sample of oncology outpatients undergoing active treatment for solid and hematological cancers, supporting its applicability beyond end-of-life contexts [26,50]. Factor analytic findings (exploratory and confirmatory) supported a unidimensional structure, with a single factor accounting for 48% of the variance. Concurrent validity was demonstrated by significant associations with both physical and psychological symptoms and an inverse relationship with spiritual well-being, while the absence of correlation with religiosity supports the discriminant validity of the construct. Test–retest analyses over a two-week interval further indicated adequate temporal stability (concordance coefficient = 0.73; 95% CI 0.64–0.83) [50].

The Post-Traumatic Embitterment Disorder (PTED) self-rating scale is a 19-item instrument designed to assess embitterment reactions to negative life events, with items rated on a five-point scale (0–4), where higher scores indicate greater embitterment. The construct of embitterment refers to a maladaptive response to events perceived as unjust, characterized by persistent feelings of bitterness, anger, intrusive thoughts, and avoidance, and associated with significant functional impairment. The scale has demonstrated good test–retest reliability and validity in capturing these clinically relevant features [51,52].

The Brief Symptom Inventory (BSI-18) assesses general psychological distress across somatization, anxiety, and depression dimensions [53]. A Global Severity Index (GSI) provides an overall measure of distress. The instrument has demonstrated good diagnostic validity, with adequate discrimination between clinical and non-clinical populations (AUC $\geq$ 0.80) [53] and has been validated in Italian oncology populations [20]. Clinically interpretable cut-offs have been proposed, with a T-score $\geq$ 63 indicating probable caseness, although evidence suggests greater utility as a screening tool rather than for precise case identification. In this study, the hostility subscale was additionally included due to its clinical relevance in medical populations [20,54,55].

The Impact of Event Scale-Revised (IES-R) is a 22-item self-report measure assessing post-traumatic stress symptoms across intrusion, avoidance, and hyperarousal domains [56]. Scores $\geq$33 are indicative of probable PTSD. The instrument has been validated in Italian samples with exploratory and confirmatory factor analyses supporting a clear three-factor structure and demonstrating good construct validity. Evidence of convergent validity has also been reported through associations with measures of dissociative experiences, supporting its clinical relevance in assessing trauma-related distress. [57].

All measures were administered at baseline (t0) and at follow-up (t1) to evaluate changes over time.

2.5. Statistical analysis

PHQ-9 cut-off score $\geq$ 10 was used to identify patients with or without a depressive condition. Descriptive statistics were used to summarize sociodemographic and clinical variables for the entire sample and stratified by depression status. Between-group comparisons of categorical variables employed chi-squared tests, while continuous variables were analyzed using *t*-tests for normally distributed data, and Mann Whitney *U* tests for non-normal distributions. Normality assumptions were evaluated with the Kolmogorov–Smirnov test. Paired t-tests assessed within-group changes in scale scores between t0 and t1. For each outcome measure, mixed-effects models for repeated measures

(MMRM) were applied to evaluate the effect of time, depression status, and their interaction on symptom severity. These models adjusted for covariates including education level, marital status, employment status, and tumor stage. An interaction term between time and depression status was included to examine differential changes over time between groups. To control for the risk of type I error due to multiple comparisons, the Bonferroni correction was used. All analyses were performed using R software (version 4.4.2). A p-value <0.05 was considered statistically significant.

3. Results

Two-hundred and thirty patients were recruited over the study period. Nine declined participation due to disinterest in undergoing the full testing battery, leaving 221 patients consenting to participate. Although the final sample was slightly below the threshold, the resulting 95% confidence interval (29.3%–41.8%) remains sufficiently narrow to support the descriptive validity of our prevalence estimate in this context.

Of the initial 221 participants, 156 completed the six-month follow-up (t1), while 65 were lost to follow-up. The main reasons for attrition

Table 1
Sociodemographic and clinical characteristics of the whole sample and by depression status.

Sociodemographic characteristics	N = 221	PHQ9 depressi no 143 (64.7)	PHQ9 depressi yes 78 (35.3)	p-value
Age, mean (SD)	57.2 (11.1)	57.3 (11.2)	56.9 (11.1)	0.77[a]
Sex, Male, N (%)	31 (14.0)	23 (16.1)	8 (10.2)	0.23[b]
Education, N (%)				0.48[b]
None/ Elementary School/Middle School	79 (35.7)	54 (37.8)	25 (32.1)	
High School/Degree	142 (64.3)	89 (62.2)	53 (67.9)	
Education, Number of years, mean (SD)	11.9 (3.9)	11.9 (3.8)	11.7 (4.2)	0.68[a]
Marital status, N (%)				0.80[b]
Without partner	84 (38)	90 (62.9)	47 (60.2)	
Married/Living together	137 (62.0)	53 (37.1)	31 (39.7)	
Employment, N (%)				0.06[b]
Employed	123 (55.7)	78 (54.5)	45 (57.7)	
Other	96 (43.4)	64 (44.8)	32 (41.0)	
Unknow	2 (0.9)	1 (9.7)	1 (1.3)	
Clinical characteristics				
Cancer Site, N (%)				0.10[b]
Other	25 (11.3)	18 (12.6)	7 (9.0)	
Blood	6 (2.7)	2 (1.4)	4 (5.1)	
Brain	4 (1.8)	4 (2.8)	0 (0.0)	
Gastroenteric	23 (10.4)	11 (7.7)	12 (15.4)	
Breast	130 (58.8)	85 (59.4)	45 (57.7)	
Ovary	9 (4.1)	5 (3.5)	4 (5.1)	
lung	12 (5.4)	7 (4.9)	5 (6.4)	
Prostate	7 (3.2)	7 (4.9)	0 (0.0)	
Womb	5 (2.3)	4 (2.8)	1 (1.3)	
Cancer Stage, N (%)				
I	86 (50.6)	67 (56.3)	19 (37.2)	0.03[b]
II or III	84 (49.4)	52 (43.7)	32 (62.7)	
Surgery, yes, N (%)	145 (65.6)	90 (63.4)	54 (69.2)	0.47[b]
Therapy, N (%)				0.76[b]
Other	20 (9.1)	12 (8.4)	8 (10.2)	
Chemo	67 (30.5)	44 (31.0)	23 (29.5)	
Chemo+hormon	8 (3.6)	5 (3.5)	3 (3.8)	
Radiotherapy	17 (7.7)	11 (7.7)	6 (7.7)	
Radiotherapy+chemotherapy	19 (8.6)	11 (7.7)	8 (10.3)	
Radio+chemo+hormons	10 (4.5)	4 (2.8)	6 (7.7)	
Radio+hormons	12 (5.5)	7 (4.9)	5 (6.4)	
hormons	23 (10.5)	16 (11.3)	7 (9.0)	
None	44 (20.0)	32 (22.5)	12 (15.4)	
Chemo drugs, yes, N (%)	105 (47.5)	66 (46.1)	39 (50.0)	0.05[b]
Antidepressants, yes, N (%)	62 ()	10 (7)	52 (66.7)	0.18[b]
Scale at baseline				
PHQ9	7 (5.5)	/	/	
BSI	21.1	13.6 (9.2)	34.9 (16.2)	<0.001[c]
Anxiety	(15.8)	4.8 (4.3)	10.0 (5.7)	
Hostility	6.4 (5.3)	1.5 (1.9)	4.3 (4.5)	<0.001[c]
Somatization	2.4 (3.2)	3.5 (2.8)	7.1 (4.2)	<0.001[c]
	4.6 (3.7)			<0.001[c]
PTED	33.3 (16.6)	26.7 (14.8)	45.1 (12.7)	<0.001[c]
PTGI	55.4 (27.1)	60.6 (27.8)	46 (23.2)	<0.001[c]
PDI	27.4 (20.9)	19.8 (17.4)	41.2 (19.7)	<0.001[c]
IES	29.2 (18.0)	23.7 (16.4)	39.9 (16.0)	<0.001[c]
Demoralization	29.2 (16.9)	21.4 (11.5)	43.4 (16.2)	<0.001[c]
Demoralizzati, yes, N (%)	91 (41.2)	30 (21.8)	61 (78.2)	<0.001[b]

[a] t-test.
[b] Chi-squared test.
[c] Mann-Whitney test.

included medical deterioration or disease progression ($n = 29$), treatment interruption or dropout from psycho-oncological care ($n = 26$), death ($n = 6$), and loss of contact or incomplete data ($n = 4$). There were no significant differences in baseline psychological or demographic variables between those who completed follow-up and those lost to follow-up.

3.1. Sample characteristics

The total sample consisted of 221 adult outpatients diagnosed with cancer (mean age = 57.2 ± 11.1 years; 14% male), with an average age at baseline of 57.2 years (SD = 11.1). Most of the patients were female (86%), married (62%), employed (55.7%). and owned a high school diploma or a degree (64.3%). Almost 60 % (58.8%) presented breast cancer, 65.6% underwent surgery, and 30.5% received chemotherapy. and 28% were taking antidepressants.

According to the clinical interview the diagnoses were quite heterogenous with most patients ($n = 118$, 53%) not meeting the criteria for a ICD-10 psychiatric diagnosis while about 12% had a diagnosis of major depression (n = 26), 15% of anxiety disorders ($n = 33$) and 20% adjustment disorders ($n = 44$). Based on the PHQ-9 scores, at baseline, 78 participants (35.3%) met criteria for clinically significant depressive symptoms (PHQ-9 ≥ 10), while 143 (64.7%) fell below this threshold.

A total of 41% ($n = 91$) of the patients met the criteria for demoralization (DS). The analyses further showed that 21.8% ($n = 30$) of these individuals were not concurrently experiencing clinically significant symptoms of depression.

No significant differences emerged between depressed and non-depressed patients with respect to age, sex, education, marital status, or employment at baseline (all $p < 0.05$). However, a significantly higher proportion of depressed patients were in cancer stage II or III compared to their non-depressed counterparts (62.7% vs. 43.7%; $p = 0.03$) (Table 1).

Regarding cancer treatment, no statistically significant group differences were observed in the use of surgery, chemotherapy, radiotherapy, or hormone therapy. A non-significant trend toward higher use of chemotherapy was noted in the depressed group. The use of antidepressants at baseline was higher in depressed patients ($p < 0.001$).

3.2. Baseline psychological and existential profile by depression status

At baseline (t0), patients with depression exhibited significantly higher scores ($p < 0.001$) than those without depression across all psychological and existential measures, including the BSI-18– total and subscales (Somatization, Anxiety, Hostility); the PTED Scale; the PDI the IES-R the DS-IT.

Conversely, depressed patients reported significantly lower scores compared to non-depressed patients on the PTGI ($p < 0.001$) (Table 1).

3.3. Pre–post changes in psychological and existential outcomes (paired comparisons)

In the whole subgroup with available follow-up data at t1 ($n = 156$), statistically significant improvements were observed between t0 and t1 on several dimensions: PTED ($\delta = -11.3$; $p < 0.001$); PDI ($\delta = -12.0$; $p < 0.001$); IES ($\delta = -4.9$; $p = 0.019$); DS-IT ($\delta = -3.0$; $p = 0.048$); PTGI ($\delta = +14.2$; $p < 0.001$).

Important improvements were observed over time in the subgroup of patients with baseline depression (PHQ-9 ≥ 10; $n = 46$) across most outcomes: BSI total ($\delta = -6.9$; $p = 0.020$); BSI anxiety and hostility subscales ($p < 0.005$); PTED ($\delta = -16.9$; $p < 0.001$); PDI ($\delta = -22.9$; $p < 0.001$); IES ($\delta = -13.0$; $p = 0.003$); DS-IT ($\delta = -9.4$; $p = 0.002$); PTGI ($\delta = +17.5$; $p = 0.004$) (Table 2).

3.4. Longitudinal effects by depression status (MMRM analyses)

Mixed models for repeated measures (MMRM) estimated that patients with baseline depression presented significantly higher initial levels of distress and existential suffering across all psychological indicators than patients who were not depressed (all $p < 0.001$).

Group-by-time interaction effects showed that patients with depression experienced significantly greater reductions in PTED ($p = 0.035$ unadjusted model; $p = 0.003$ adjusted model); PDI ($p = 0.001$ adjusted model); IES-R ($p = 0.009$ unadjusted model; $p < 0.001$ adjusted model); and DS-IT ($p < 0.001$ adjusted model) compared to patients without depression at T0 PTGI scores increased significantly in both groups. While the group*time term was not statistically significant in the unadjusted model ($p = 0.45$), it reached statistical significance after accounting for covariates ($p = 0.040$).

No statistically significant interaction effects were found for the BSI

Table 2
Paired *T*-Test between time points within the whole sample and within the group with a PHQ9 > 9/10 at time 0.

Whole Sample N 156				
Scale	T0, mean (SD)	T1, mean (SD)	Mean Difference	Paired t-test
PHQ9	6.4 (5.1)	5.7 (3.9)	0.75	$T = 1.4$; $p = 0.17$
BSI	18.8 (14.0)	17.1 (13.1)	1.7	$T = 1.2$; $p = 0.24$
Anxiety	6.2 (5.1)	4.6 (3.9)	1.6	**$T = 2.5$; p = 0.01**
Hostility	2.2 (2.7)	3.2 (2.9)	-1	**T = -2.3; p = 0.02**
Somatization	4.4 (3.5)	4.5 (2.9)	−0.2	T = -0.5; $p = 0.63$
PTED	28.8 (16.8)	17.6 (14.7)	11.3	**$T = 7.2$; p < 0.001**
PTGI	55.3 (24.2)	69.5 (24.3)	−14.2	**T = -4.8; p < 0.001**
PDI	23.8 (20.4)	11.8 (15.0)	12.0	**$T = 5.8$; p < 0.001**
IES	27.8 (19.1)	22.9 (12.9)	4.9	**$T = 2.4$; p = 0.019**
Demo	26.9 (15.8)	23.9 (13.7)	3.0	**$T = 2.0$; p = 0.048**
Only patients with PHQ9 > 9/10 at time 0 (N 46)				
Scale	**T0,** mean (SD)	**T1,** mean (SD)	**Mean Difference**	**Paired t-test**
BSI	31.3 (14.0)	24.3 (14.4)	6.9	**T = 2.4; p = 0.02**
Anxiety	10.3 (4.9)	6.0 (3.1)	4.3	**$T = 3.4$; p = 0.002**
Hostility	3.5 (3.7)	3.9 (2.1)	−0.4	T = -0.5; p = 0.63
Somatization	7.0 (3.3)	6.0 (2.3)	1	$T = 1.6$; $p = 0.12$
PTED	43.5 (13.3)	26.6 (18.8)	16.9	**$T = 5.0$; p < 0.001**
PTGI	46.4 (23.5)	63.9 (25.8)	−17.5	**T = -3.1; p = 0.004**
PDI	41.2 (21.3)	18.3 (20.8)	22.9	**$T = 4.9$; p < 0.001**
IES	40.5 (16.6)	27.5 (13.8)	13	**$T = 3.8$; p < 0.001**
Demo	40.0 (17.8)	30.6 (16.6)	9.4	**$T = 2.9$; $p = 0.0056$**

total or its subscales, suggesting that general psychological distress improved comparably across groups (Table 3; Fig. 1).

4. Discussion

This study provides clinically relevant insights into the psychological and existential burden of depression among outpatients diagnosed with cancer, as well as their longitudinal response to integrated psycho-oncology care in a real-world setting. Within an Italian psycho-oncology program, we observed that over one-third of patients exhibited clinically significant depressive symptoms at baseline. In addition, a substantial proportion of patients met criteria for demoralization, and notably, a relevant subgroup (21.8%) did not present concurrent clinically significant depressive symptoms. This finding confirms that demoralization and depression, while overlapping, may represent partially distinct constructs, with demoralization reflecting a specific form of existential distress not necessarily captured by depressive symptomatology. In psycho-oncology, such distress often emerges in relation to fundamental existential concerns—including finitude, isolation, loss of meaning, and threats to personal identity—which may not be fully encompassed by conventional diagnostic frameworks for depression. As highlighted in psychodynamic and existential perspectives, cancer can act as a trigger that exposes underlying psychological conflicts and challenges patients' sense of coherence, agency, and life meaning, contributing to experiences of helplessness, shame, and existential suffering [33]. These individuals also showed markedly higher levels of general distress, somatization, anxiety, hostility, embitterment, and trauma-related symptoms, along with reduced post-traumatic growth, compared to non-depressed peers.

These findings are consistent with the growing international literature highlighting the multifaceted impact of depressive syndromes in cancer care [9,58]. The inclusion of a wide range of psychological dimensions—beyond the most commonly studied anxiety and depression—enabled a more nuanced understanding of patients' internal experience. Constructs such as embitterment, perceived loss of dignity, demoralization, and post-traumatic growth are increasingly recognized in oncology as critical to understanding patients' coping trajectories and overall well-being [25,26,38,39]. Their systematic assessment in clinical practice and real-world settings contributes to the growing body of evidence in these evolving domains.

Another notable strength lies in the ecological validity of the sample and setting. Patients were enrolled in a public outpatient psycho-oncology service, allowing for a representative view of psychological suffering in routine care. The psychotherapeutic intervention itself, based on supportive-expressive principles and enriched with meaning-centered strategies, was deliberately flexible and adapted to the patient's existential awareness and evolving needs—a model aligned with current recommendations for personalized, dignity-conserving care in advanced cancer [25,39,59,60].

Importantly, our findings indicate a differential treatment effect in favour of patients who presented with elevated depressive symptoms (PHQ-9 $\geq$ 10) at baseline. Specifically, these individuals not only showed greater reductions in depressive and general psychological distress outcomes, but also experienced more pronounced improvements in existential domains such as demoralization, dignity, trauma-related burden, and embitterment. This pattern suggests that the reduction of depressive symptoms may facilitate broader psychological change: once core depressive symptoms improve, patients might be more able to engage with and benefit from psychotherapeutic and pharmacological components of care that address wider dimensions of

Table 3
MMRM derived T0 and T1 least squares means and 95% confidence intervals and group by time interactions for the outcome measures for dep si vs dep no.

	T0		p*	T1		p*	p**
	Mean (CI)			Mean (CI)			
Outcome	Dep si	Dep no		Dep si	Dep no		
BSI	34.9 (32.2, 37.6)	13.7 (11.7, 15.6)	**<0.001**	25.5 (21.4, 29.5)	13.7 (10.8, 16.6)	**<0.001**	**<0.001**
BSI adjusted^	34.3 (31.0, 37.7)	13.3 (11.1, 15.5)	**<0.001**	22.5 (17.6, 27.4)	14.4 (11.3, 17.5)	**0.006**	**<0.001**
BSI-Anxiety	10.1 (8.8, 11.4)	4.8 (3.9, 5.6)	**<0.001**	7.0 (5.5, 8.6)	3.8 (2.7, 5.0)	**0.001**	0.06
BSI-Anxiety adjusted^	10.0 (8.5, 11.4)	4.7 (3.7, 5.7)	**<0.001**	6.6 (2.5, 10.7)	3.1 (1.4, 4.8)	0.12	0.40
BSI-Hostility	4.3 (3.5, 5.1)	1.5 (1.0, 2.1)	**<0.001**	3.5 (2.5, 4.5)	2.7 (2.0, 3.4)	0.19	**0.01**
BSI- Hostility adjusted^	4.3 (3.4, 5.2)	1.4 (0.8, 2.0)	**<0.001**	2.2 (−0.8, 5.3)	1.2 (0.0, 2.5)	0.53	0.24
BSI- Somatization	7.2 (6.2, 8.1)	3.4 (2.8, 4.0)	**<0.001**	6.7 (5.6, 7.8)	3.6 (2.8, 4.4)	**<0.001**	0.39
BSI- Somatization adjusted^	6.9 (6.0, 7.9)	3.5 (2.9, 4.1)	**<0.001**	5.7 (3.0, 8.4)	2.3 (1.2, 3.5)	**0.02**	0.95
PTED	45.2 (42.1, 48.3)	26.8 (24.5, 29.1)	**<0.001**	27.2 (22.6, 31.8)	15.2 (12.0, 18.4)	**<0.001**	**0.035**
PTED adjusted^	45.6 (41.7, 49.4)	25.7 (23.2, 28.2)	**<0.001**	22.2 (16.6, 27.7)	13.2 (9.8, 16.6)	**0.007**	**0.003**
PTGI	45.7 (39.9, 51.6)	60.6 (56.3, 64.9)	**<0.001**	62.2 (53.3, 71.1)	72.7 (66.0, 79.3)	0.06	0.45
PTGI adjusted^	45.6 (38.2, 53.0)	63.6 (58.7, 68.4)	**<0.001**	69.7 (58.6, 80.7)	73.4 (66.1, 80.7)	0.6	**0.04**
PDI	41.2 (37.4, 45.1)	19.8 (16.9, 22.6)	**<0.001**	18.3 (12.6, 24.0)	9.8 (5.7, 13.9)	**0.02**	**0.001**
PDI adjusted^	39.9 (35.1, 44.8)	18.5 (15.3, 21.7)	**<0.001**	14.0 (7.2, 20.8)	9.3 (5.0, 13.6)	0.25	**<0.001**
IES	39.9 (36.4, 43.3)	23.7 (21.2, 26.2)	**<0.001**	27.4 (22.2, 32.6)	21.0 (17.4, 24.6)	**0.05**	**0.009**
IES adjusted^	38.7 (34.5, 42.9)	22.5 (19.8, 25.3)	**<0.001**	21.8 (15.5, 28.1)	20.8 (17.0, 24.7)	0.80	**<0.001**
Demo	43.4 (40.4, 46.3)	21.5 (19.3, 23.6)	**<0.001**	31.8 (27.4, 36.2)	20.9 (17.9, 24.0)	**<0.001**	**<0.001**
Demo adjusted^	44.3 (40.7, 47.9)	20.5 (18.2, 22.8)	**<0.001**	28.3 (23.1, 33.6)	21.2 (18.0, 24.4)	**0.02**	**<0.001**

^Adjusted for the following covariates: Education, Marital status, Employment status, Cancer stage.
* = Bonferroni least significant difference test comparing dep si dep no at T0 and T1.
** = *P*-values for the group (dep si dep no) by time interaction effect over the xxx months of treatment.

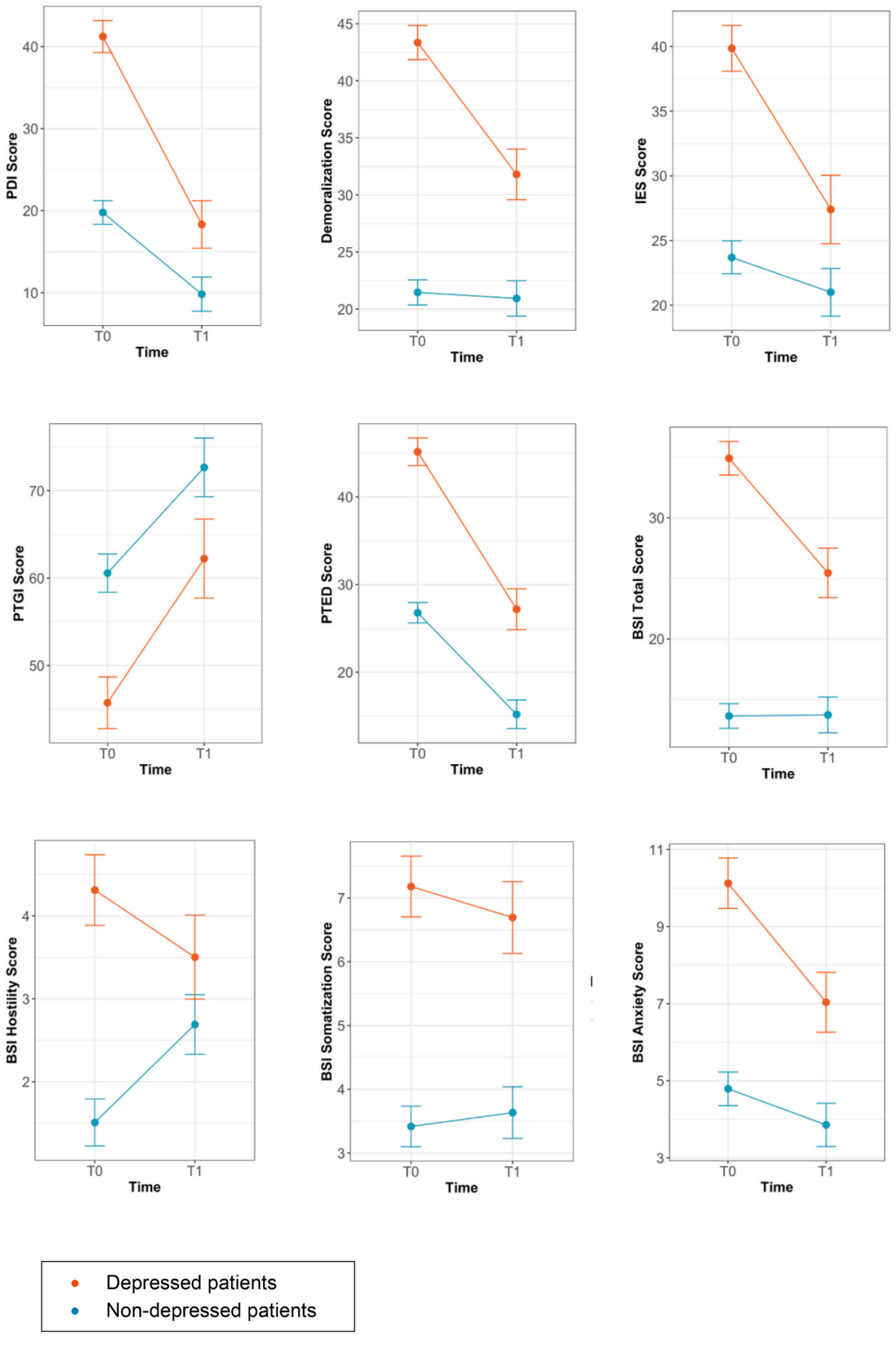


Fig. 1. Least square means of scores over time.

suffering. However, given the observational, non-randomized design and the concurrent timing of improvements across domains, no causal inferences can be drawn regarding the directionality of these effects. These results nonetheless align with previous findings in psycho-oncology showing that treatment effects tend to be larger among patients with higher baseline distress—possibly because there is more "room for improvement" (i.e., fewer floor effects) [61,62].

The group-by-time interactions observed in MMRM analyses therefore point to the responsiveness of depressed patients to integrated psycho-oncology care, emphasizing the clinical relevance of early psychological assessment and tailored interventions. From both a clinical and theoretical perspective, these findings support the view that addressing depression in psycho-oncology may not only alleviate mood symptoms, but also facilitate broader changes in meaning-making processes, helping patients reframe their illness experience and integrate it into a more coherent narrative of personal identity and values.

Nonetheless, several limitations must be acknowledged. The study employed a naturalistic, non-randomized design without a control group, which restricts the ability to draw causal inferences about treatment efficacy. The single-center nature of the study may limit the generalizability of findings. In addition, the predominance of female participants and breast cancer cases further limits generalizability to other cancer populations. Although the PHQ-9 is a well-validated screening tool for depression, the reliance on self-report instruments may be vulnerable to reporting biases. Attrition represents another potential source of bias, since nearly one third of participants did not complete follow-up, mainly due to clinical deterioration, death, or treatment discontinuation, potentially leading to an overestimation of improvement among those who remained in care. Psychopharmacological treatment was not standardized and may have acted as a confounding factor. Moreover, the inclusion of multiple psychological and existential constructs may have introduced partial construct overlap. The six-month follow-up limits conclusions on long-term outcomes. Furthermore, the sample was not stratified by cancer type or treatment modality, and oncologic variables were not included in the longitudinal models. Importantly, the set of sociodemographic covariates included in the models was limited to education, marital status, and employment status; other potentially relevant variables, such as income and social support, were not assessed and may represent sources of residual confounding to be addressed in future research. Another potential limitation of the present study concerns the flexible and non-manualized nature of the intervention, along with the absence of formal fidelity procedures, which may limit replicability and make it difficult to determine the extent to which outcomes are attributable to specific intervention components. Finally, the total sample size ($n = 221$) did not reach the initially estimated target of 243 patients for optimal precision in prevalence estimation. No structured system was used to assess patients without a formal psychiatric diagnosis, whose conditions might have been more accurately characterized using instruments such as the Diagnostic Criteria for Psychosomatic Research [63,64].

Despite these limitations, the present findings provide clinically meaningful insights into the psychological and existential dimensions of depression in persons diagnosed with cancer within real-world psycho-oncology settings. Early identification of depressive symptoms may help optimize and personalize treatment strategies. While all patients can benefit from integrated psychotherapeutic and psychopharmacological interventions, those presenting with higher levels of baseline distress may experience broader and more multidimensional improvements, extending beyond mood to existential and trauma-related domains. The observed changes—particularly in domains such as demoralization, dignity, trauma-related burden, and embitterment—underscore the need to move beyond symptom reduction as the sole therapeutic goal in psycho-oncology. Future research should build on these findings by adopting controlled designs, integrating diagnostic interviews, and exploring mechanisms of change that sustain psychological and existential recovery in persons diagnosed with cancer.

5. Conclusions

This study offers compelling evidence that depression in persons diagnosed with cancers is common and deeply interwoven with psychological distress and existential suffering. Within a real-world outpatient psycho-oncology setting, we found that individuals with baseline depressive symptoms reported more severe impairments across emotional and existential domains, yet also showed greater improvements following a flexible, integrated psychopharmacologic and psychotherapeutic approach.

These findings support the clinical value of early identification and personalized intervention for depression in oncology, particularly when the therapeutic model addresses both affective distress and existential meaning. While further controlled studies are needed to confirm causality and explore mechanisms of change, this work contributes robust data to a growing field and emphasizes the importance of multidimensional care strategies in alleviating suffering and fostering psychological growth in subjects with cancers.

CRediT authorship contribution statement

Rosangela Caruso: Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Marco Cruciata:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Maria Giulia Nanni:** Writing – review & editing, Validation. **Martino Belvederi Murri:** Writing – review & editing. **Luigi Zerbinati:** Writing – review & editing. **Stefano Tugnoli:** Writing – review & editing. **Ester Allegro:** Writing – review & editing. **Marina Pantuso:** Writing – review & editing. **Klaudio Shakaj:** Writing – review & editing. **Tommaso Toffanin:** Writing – review & editing. **Maria Ferrara:** Writing – review & editing. **Barbara Zaccagnino:** Writing – review & editing. **Anna Francesca Olivetti:** Writing – review & editing, Writing – original draft. **Ilaria Dominicano:** Methodology, Formal analysis, Data curation. **Luigi Grassi:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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