Title: **The association of demoralization with mental disorders and suicidal ideation in patients with cancer**

Running head: Demoralization and mental disorders

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Précis: Clinically relevant demoralization frequently occurs independently of a mental disorder in patients with cancer and has a unique contribution to suicidal ideation. Demoralization is a useful concept to identify profiles of psychological distress symptoms amenable to interventions improving psychological well-being in patients with cancer.

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Abstract

Background: Demoralization refers to a state in which there is a perceived inability to cope, associated with a sense of disheartenment, loss of hope and meaning. We aimed to investigate the co-occurrence vs. independence of demoralization with mental disorders and suicidal ideation to evaluate its features as a concept of distress in the context of severe illness.

Method: In a cross-sectional sample of 430 mixed cancer patients, we assessed demoralization with the Demoralization Scale (DS), the 4-week-prevalence of mood, anxiety, and adjustment disorders and suicidal ideation with the standardized Composite International Diagnostic Interview-Oncology (CIDI-O), and depressive symptoms with the Patient-Health-Questionnaire-9 (PHQ-9). We compared the relative risk for mental disorders associated with demoralization to that associated with depression.

Results: Clinically relevant levels of demoralization were present in 21% of the patients. Demoralization co-occurred with a mood/anxiety disorder in 7%; 14% were demoralized in absence of any mood/anxiety disorder. Demoralization and adjustment disorder co-occurred in 2%. The relative risk for any mood/anxiety disorder was 4.0 in patients with demoralization (95%CI 2.5 to 6.2) and 3.0 in those with depression (95%CI 1.9 to 4.6). Demoralization, but not depression, was associated with a significantly increased risk for suicidal ideation after controlling for mental disorders (RR=2.0, 95%CI 1.1 to 3.5).

Conclusion: Clinically relevant demoralization frequently occurs independently of a mental disorder in patients with cancer and has a unique contribution to suicidal ideation. Demoralization is a useful concept to identify profiles of psychological distress symptoms amenable to interventions improving psychological well-being in this population.

Key words: Demoralization, depression, mental disorder, mood disorder, anxiety disorder, adjustment disorder, suicidal ideation, cancer

Introduction

During cancer diagnosis, treatment, and rehabilitation, psychological distress may occur on a continuum from normal fear, worry, or sadness to severe anxiety, depression, and existential despair [1]. Along this continuum, different approaches have been used to understand patterns of cancer-related distress. Two such approaches are mental disorders and demoralization.

At the more severe end, the diagnosis of a mental disorder identifies a clearly defined pattern of morbidity. Towards the middle of the spectrum, adjustment disorders represent a category of poor coping that is rather nonspecific, yet dominant in psycho-oncological practice [2]. At the lower end of the spectrum of distress, sub-threshold symptoms may not qualify as disorders yet remain clinically important to treat. Recent epidemiological studies and meta-analyses indicate that prevalence rates for mental disorders, especially mood and anxiety disorders, are comparable in mixed cancer patients and the general population [3–5]. Given that psychological distress in cancer patients is not necessarily captured by such diagnoses, there is a need to identify clinically significant psychological problems that lie beyond the current psychiatric classification in this population [6].

Demoralization is one approach to conceptualize psychological distress in the context of a life-threatening illness [7]. Its historical understanding [8,9] has been applied to the cancer setting, in which a perceived lack of control, uncertainty, and the loss of social roles and life goals are common existential challenges [10,11]. Approximately one fifth of cancer patients show clinically relevant levels of demoralization according to recent reviews [12,13]. Its severity may range from the middle of the distress spectrum, where adjustment disorders are located, to the extreme end.

The demoralization syndrome is defined by lowered morale and a perceived incapacity to cope that can become associated with a sense of helplessness and failure, and the loss of self-worth, hope and meaning in life [10]. Demoralization is distinct from depression in that, in the former, the capacity to experience pleasure in the present may be preserved and lowering of mood and loss of interest may not be present [14]. Demoralization is associated instead with a feeling of being unable to accomplish

things that personally matter *in the future*, which may generate a sense of meaninglessness and futility [15].

Demoralization may be an important risk factor for suicidal ideation in patients with cancer. Robinson et al. [16] and Fang et al. [17] have found significant associations between demoralization and the wish to hasten death. Further evidence on this relationship is yet needed, especially on the extent to which demoralization may predict suicidal ideation independently of mental disorders. Determining the contribution of demoralization to suicidal ideation may have value in developing relevant therapeutic interventions in this population.

Notwithstanding the clear conceptual and clinical differentiation between demoralization and mental disorders, they can occur comorbidly. There is still limited evidence about the extent to which demoralization occurs independently or in association with diagnosed mental disorders in individuals with cancer. Such knowledge is required to distinguish potential subgroups of cancer patients with different psychosocial support needs due to different profiles of distress. Previous work has shown moderate to high correlations between demoralization and self-reported depression (r=.33 to r=.80) and self-reported anxiety (r=.67 to r=.72) [18–25]. This is similar to mixed anxiety-depressive states. The results of these studies do not, however, differentiate well between patients with and without a mental disorder and vary considerably due to the different self-report measures used.

The present study thus aimed to determine (a) the co-occurrence versus independence of demoralization and mood, anxiety, and adjustment disorders, as assessed by a standardized diagnostic interview in a sample of mixed cancer patients; (b) the relative risk for mental disorders associated with demoralization; and (c) the relative contribution of demoralization to suicidal ideation beyond the impact of mental disorders. We compared the results for demoralization to those for self-reported depression as a widely used approach to assess psychological distress in patients with cancer. We expected to identify a relevant subgroup of patients who were demoralized without a mental disorder.

Methods

Participants and procedures

We studied a subsample of cancer patients recruited to an epidemiological cross-sectional study [26]. Patients in the larger study were recruited while receiving treatment from oncological inpatient clinics at acute care hospitals, specialized outpatient cancer care facilities, and cancer rehabilitation centers across northern Germany. Exclusion criteria were age younger than 18 or older than 75 years, severe cognitive or physical impairment, and language barrier. After providing written informed consent, participants were screened with the Patient-Health-Questionnaire-9 (PHQ-9). Patients with sum scores ≥9 were further assessed by a standardized diagnostic interview for mental disorders. Patients with sum scores <9 were randomly assigned to the interview. All patients completed a set of self-report questionnaires (see study protocol for further detail [27]). This study was approved by the research ethics committee of the Hamburg Medical Association (ref. number 2768).

Of 5889 eligible patients, 4020 (68%) agreed to participate in the study. Reasons for non-participation were lack of interest (55%), symptom burden (33%), organizational barriers (6%), and other/unspecified (6%). As reported elsewhere [26], non-participants were younger, but did not differ in gender. A subsample of 936 patients completed the Demoralization Scale. In this subsample, 236 screened ≥9 on the PHQ-9 and were assigned to the standardized interview (CIDI-O), of which 149 completed the interview. 700 patients screened <9 on the PHQ-9, of which 411 were randomly assigned to the CIDI-O. Among these, 281 completed the interview. In total, 430 patients completed the CIDI-O and were analyzed in this study.

Measures

Demographic data were collected by a standardized questionnaire. Disease-related characteristics were obtained from medical charts.

We used the standardized computer-assisted *Composite International Diagnostic Interview for Oncology (CIDI-O)* to assess the 4-week prevalence of mood, anxiety, and adjustment disorders as well as suicidal ideation [28]. The CIDI-Oncology enables diagnosis of adjustment disorders in response to specific cancer-related stressors [29]. In accordance with DSM-IV criteria, adjustment disorder was diagnosed where distress was problematic, out of proportion to the clinical setting and causing impairment, and no other axis I disorder was present and symptoms did not persist for longer than 6 months. Suicidal ideation was present if one or more of the following three symptoms were reported during the diagnostic interview: frequent thoughts about death, wish to die, or contemplation of suicide.

The *Demoralization Scale (DS)* is a 24-item self-report measure. It follows the conceptual framework developed by Clarke and Kissane [10,30]. The scale assesses feelings of disheartenment and being trapped, a sense of failure and reduced self-worth, regret, dysphoria, and the loss of meaning and purpose over the past two weeks. Total scores may range from 0 to 96. Clinically relevant levels of demoralization were defined by a cut-off ≥30 [31].

The *Patient Health Questionnaire-9 (PHQ-9)* is a self-report measure of depression according to DSM-IV/V criteria [32]. Total scores may range from 0 to 27. Scores ≥10 indicate at least moderate depression.

Data analysis

Descriptive analyses of sample characteristics, prevalence of mental disorders, and self-report measures were conducted. Analyses were weighted to control for the oversampling of patients with PHQ-9 depression scores ≥9. We determined the frequency of highly demoralized patients with/without a mental disorder by cross-tabulations within R package sjPlot [33].

We then determined the extent to which mental disorders were more frequent among patients with demoralization compared to those without demoralization. We calculated relative risks (RR) for mental disorders in patients with demoralization relative to those without demoralization using Poisson regression with robust standard errors as implemented in R package sandwich [34] (model 1). Second, we repeated these analyses for self-reported depression (model 2). In model 3, we compared the relative risk for mental disorders associated with demoralization to that associated with depression by testing a model with demoralization and depression as simultaneous predictors. We then calculated the contribution of demoralization to suicidal ideation beyond mental disorders by testing the impact of demoralization after adjustment for mental disorders (model 4a). We also determined the contribution of demoralization to suicidal ideation beyond adjustment disorder in the subgroup of patients without a mood/anxiety disorder (model 4b). We repeated these analyses for self-reported depression (models 5a and 5b) and demoralization and depression combined (models 6a and 6b). To explore how a higher threshold for demoralization caseness would affect the association of demoralization with mental disorders, we repeated all analyses using a higher cut-off score on the demoralization scale. This enabled comparison of results for a cut-off ≥35 to those for a cut-off ≥30.

There was no multicollinearity in multivariate models, as variance inflation factors were <1.4. All models that included suicidal ideation were calculated after removing the suicidal ideation item of the PHQ-9 (no. 9) and the Demoralization Scale (no. 20) to avoid construct overlap. Missing values occurred in 1.9% of responses for self-report measures of demoralization, depression, and physical symptoms and were mean-imputed. We used R version 3.3.0 [35].

Results

Sample characteristics and prevalence of mental disorders and suicidal ideation

Demographic and disease-related sample characteristics are shown in Table 1. The 4-week prevalence for mental disorders and suicidal ideation is shown in Table 2. The mean demoralization score was 20.6 (SD=13.6). Clinically relevant levels of demoralization were present in 21% of the patients. The mean PHQ-9-depression score was 6.06 (SD=4.5). 22% showed clinically relevant levels of depression. The correlation between self-reported demoralization and self-reported depression was r=.69*** (95%CI .63 to .73).

Please insert **Table 1** about here

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Association of demoralization with mental disorders and suicidal ideation

Figure 1 shows the co-occurrence vs. independence of cases of demoralization and mental disorders according to CIDI-O. As shown in graph A, demoralization co-occurred with a mood/anxiety disorder in 7.1% and with adjustment disorder in 2%. 13.5% of the patients were demoralized in absence of any mood or anxiety disorder, and 11.1% were demoralized in absence of any mood, anxiety or adjustment disorder. Graph B shows that 17.2% of the patients were demoralized but did not fulfill criteria for a mood disorder. Comparing graphs B and C, 3.4% of the sample had comorbid demoralization and mood disorder, while 5.5% had comorbid demoralization and anxiety disorder. Two thirds of those with a mood disorder were demoralized (graph B), while half of those with an

anxiety disorder were demoralized (graph C); 64.8% of the total sample were neither demoralized nor diagnosed with any mental disorder (graph A). With suicidal ideation, demoralization co-occurred in 4.7%.

Please insert **Figure 1** about here

Table 3 shows the association of demoralization with mental disorders and suicidal ideation compared to self-reported depression. Demoralization was associated with a significantly increased risk for a mood disorder (RR=7.8, 95%CI 3.4 to 17.9), anxiety disorder (RR=3.7, 95%CI 2.2 to 6.1), and suicidal ideation (RR=3.5, 95%CI 1.9 to 6.2). Among those without a mood or anxiety disorder, demoralization was also associated with a significantly increased risk for suicidal ideation (RR=2.8, 95%CI 1.2 to 6.7), but not with an increased risk for adjustment disorders (RR=1.2, 95%CI 0.6 to 2.3). Compared to self-reported depression, demoralization was associated with a similar relative risk for a mood disorder, and with a somewhat greater relative risk for an anxiety disorder and suicidal ideation. Combining demoralization and depression as simultaneous predictors (table 3, model 3) showed that demoralization had a significant contribution to mood/anxiety disorders and suicidal ideation beyond the impact of self-reported depression. In these combined models, the contribution of demoralization was significantly greater than that of self-reported depression, except in the case of mood disorders.

Please insert **Table 3** about here

Table 4 presents the relative risk for suicidal ideation associated with demoralization and self-reported depression after adjustment for the impact of any mental disorders. Demoralization had a significant contribution to suicidal ideation beyond the impact of mental disorders (model 4a) (RR=2.0, 95%CI 3.5 to 15.1). In the total sample, demoralization thus explained a significant amount of variance in suicidal ideation that was not already explained by mental disorders. Among those without a mood/anxiety disorder, demoralization was associated with a significantly increased risk for suicidal ideation beyond the impact of adjustment disorders (model 4b) (RR=2.3, 95%CI 2.6 to 14.4). If only those without a mood/anxiety disorder were considered, demoralization thus explained a significant amount of variance in suicidal ideation that was not already explained by adjustment disorders. We repeated the same analyses for self-reported depression in order to evaluate the contribution of depressive symptoms beyond a diagnosed mental disorder (models 5a and 5b). We found no significant associations for self-reported depression in these analyses.

Please insert **Table 4** about here

For comparison, we recalculated all analyses using a higher, more conservative cut-off ≥35 on the demoralization scale [13]. Applying this higher threshold did not affect the association of demoralization with anxiety disorder, adjustment disorder and suicidal ideation (see Supplementary Material for detailed results). That is, for those variables, the risk associated with demoralization remained largely unchanged as compared to the present cut-off. However, using a higher cut-off led to a considerably greater association between demoralization and mood disorders. The higher cut-off hence led to a greater overlap of demoralization and mood disorders, which reduced the contribution that demoralization could have on suicidal ideation beyond mental disorders

Discussion

Of 430 cancer patients with mixed tumor sites, 14% showed clinically relevant demoralization without fulfilling criteria for a mood/anxiety disorder. 11% had severe demoralization in absence of any disorder, including diagnoses of adjustment disorder. Demoralization and mood/anxiety disorders were comorbid in 7% of the sample; demoralization and adjustment disorders were comorbid in 2%. 65% were neither demoralized nor diagnosed with any mental disorder under study. Demoralization was associated with a significantly increased risk for suicidal ideation beyond the impact of mental disorders.

Demoralization co-occurred with mood disorders in 3% of the sample, while 17% were demoralized in absence of a mood disorder. These results are comparable to those of Grassi et al. [36], who found combined diagnoses of depression and demoralization in 6% of patients with breast and gastrointestinal cancer, with 23% being demoralized but not depressed. Using cut-offs on self-report measures to define clinically relevant depression, others found that a mean percentage of 20% of patients were demoralized but not depressed, based on the current cut-off ≥30 on the Demoralization Scale [22,23,31]. A similar rate of 19% was found using a revised version of the Demoralization Scale [18]. These findings validate the concept of demoralization as a distinct dimension of distress in the context of cancer [37].

Demoralization was significantly associated with suicidal ideation in this study. Consistent with the results of Fang et al. [17], demoralization had a greater contribution to suicidal ideation than depression. Our results are also consistent with the negative association of demoralization with the will to live [18] and with the reported association between hopelessness and suicidal ideation in cancer populations [38,39]. Of note, the present study showed that demoralization has an additional significant impact on suicidal ideation beyond the impact that mental disorders have on suicidal ideation. Fang et al. [17] have found that demoralization mediates the relationship between distress and suicidal ideation in the cancer context. Such distress may be related to the loss of social or professional roles, the sense of

dignity and meaning, and to the perceived inability to change this state [11]. Our results indicate that those problems are relevant for suicidal ideation, independent of whether a mental disorder is present or not. Attention toward symptoms of demoralization may help to prevent suicidal ideation and alleviate severe existential despair among patients who do and who do not have a mental disorder.

We found only a weak association between demoralization and adjustment disorders. This may be explained by the current narrow DSM criteria for adjustment disorder in terms of anxious or depressed mood specifiers. Demoralization may appear to have relatively little in common with adjustment disorder when this definition is applied. In contrast, we argue that demoralization ought not be viewed simply as a weaker form of a mood or anxiety disorder. Our results rather support the utility of a diagnosis of "adjustment disorder with demoralization", where the specifier of demoralization more aptly captures a broader subgroup who are struggling to adapt [40]. Such individuals who do not fulfill criteria for a full-blown psychiatric disorder may nevertheless benefit from a therapeutic intervention [6].

Taking demoralization into account may add valuably to the picture of clinically relevant psychological distress in the context of life-threatening disease. The diminished opportunities and perception of an uncontrollable future in the context of cancer may contribute to symptoms of demoralization, such as feeling trapped, discouraged, and unable to go on. This demoralization syndrome has distinct treatment implications. It has been observed to respond little to antidepressant psychopharmacological treatment [7]. It is further more frequent among patients reporting difficulty in end-of-life communication and decision-making [15,19]. Existential and meaning-focused therapeutic interventions can specifically address the loss of purpose and morale to go on [41,42]. They can support patients to deal with disease-related losses and fears and focus on what matters most in the future [43].

Our results showed that demoralization was more common when a mood disorder, anxiety disorder, or suicidal ideation were present. Those with comorbid mental disorders, suicidal ideation, and more severe demoralization may be a particularly high-risk group. Further knowledge is still needed

concerning the interrelationship of demoralization and symptoms of mental disorders, which may be mutually reinforcing. One the one hand, comorbidity between demoralization and mental disorders may occur if the inability to cope with an external stressor becomes increasingly connected with a pervasive loss of pleasure, anxiety, and rumination [10]. On the other hand, individuals with a pre-cancer history of a psychiatric disorder may more likely experience anhedonic depression. Among those, it is possible that prolonged loss of pleasure connects with loss of hope and feeling that life is no longer worth living [44]. Future research should consider the interrelationship of specific symptoms across these broader categories. Identifying subtypes of symptom profiles could be of value in the development of psychological interventions; such profiles could also improve the evaluation of interventions when used as outcomes of their effectiveness.

There are limitations to the present study. As part of a representative epidemiological study, the majority of participants were diagnosed with early stage disease. While this reflects the population distribution of illness severity among German cancer patients, the results may not be generalizable to individuals with more advanced disease. However, in earlier studies of mixed samples, tumor stage has played only a small role in demoralization levels and was of relevance only in combination with other risk factors [21,45]. Further, we used a distribution-based cut-off score to identify clinically relevant demoralization, although, a "gold standard" based on a structured clinical interview for demoralization against which a cut-off score could be evaluated has yet to be defined. However, the applied cut-off was located at approximately the same percentile (21%) of the distribution compared to the PHQ-9 cut-off defining clinically relevant self-reported depression (22%), indicating that the threshold is neither overinclusive nor overly conservative. Additional analyses showed that using a higher cut-off moved demoralization closer toward mood disorders at the extreme end of the distress continuum and limited its independent association with suicidal ideation. While diagnostic criteria for the demoralization syndrome have been proposed, the appropriate threshold of severity requires further investigation [6,12]. Finally, the Demoralization Scale also includes more non-specific dysphoric symptoms, reflecting the clinical complexity of the syndrome. Recent approaches measure existential

distress more specifically [46] or focus on impaired coping and loss of meaning as in a revised version of the present scale [47].

The results of this study indicate that demoralization is a relevant and distinct dimension of distress in patients with cancer. Clinically significant levels of demoralization frequently occur independently of a diagnosis of mood, anxiety, and adjustment disorder, as currently defined, although these states are comorbid in a subgroup of patients. The association between demoralization and mental disorders indicates interrelations between particular symptoms of demoralization, depression, and anxiety that require further study. The frequency of demoralization and its independent association with suicidal ideation highlights the need to consider interventions to alleviate this state of existential distress in patients who do and who do not fulfill criteria for a psychiatric disorder. Our results suggest that demoralization is a useful concept to identify profiles of psychological distress symptoms among patients with severe physical disease.

References

1. Holland JC, ed. *Psycho-oncology.* Third edition: Oxford University Press; 2015.
2. Li M, Hales S, Rodin G. Adjustment disorders. In: Holland JC, ed. *Psycho-oncology*. Third edition: Oxford University Press; 2015:274-280.
3. Mehnert A, Koch U. Prevalence of acute and post-traumatic stress disorder and comorbid mental disorders in breast cancer patients during primary cancer care: a prospective study. *Psychooncology*. 2007;16(3):181-188. doi:10.1002/pon.1057.
4. Vehling S, Koch U, Ladehoff N, et al. Prevalence of affective and anxiety disorders in cancer: systematic literature review and meta-analysis. *Psychother Psychosom Med Psychol*. 2012;62(7):249-258. doi:10.1055/s-0032-1309032.
5. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011;12(2):160-174. doi:10.1016/S1470-2045(11)70002-X.
6. Kissane DW. Demoralization: A life-preserving diagnosis to make for the severely medically ill. *J Palliat Care*. 2014;30(4):255-258.
7. Robinson S, Kissane DW, Brooker J, Burney S. A review of the construct of demoralization: history, definitions, and future directions for palliative care. *Am J Hosp Palliat Care*. 2016;33(1):93-101. doi:10.1177/1049909114553461.
8. Frank JD. Psychotherapy: the restoration of morale. *Am J Psychiatry*. 1974;131(3):271-274.
9. Engel GL. A psychological setting of somatic disease: the `giving up - given up' complex. *Proc R Soc Med*. 1967;60(6):553-555.
10. Clarke DM, Kissane DW. Demoralization: its phenomenology and importance. *Aust N Z J Psychiatry*. 2002;36(6):733-742.
11. Vehling S, Mehnert A. Symptom burden, loss of dignity, and demoralization in patients with cancer: A mediation model. *Psychooncology*. 2014;23(3):283-290. doi:10.1002/pon.3417.

12. Tecuta L, Tomba E, Grandi S, Fava GA. Demoralization: A systematic review on its clinical characterization. *Psychol Med*. 2014:1-19. doi:10.1017/S0033291714001597.
13. Robinson S, Kissane DW, Brooker J, Burney S. A systematic review of the demoralization syndrome in individuals with progressive disease and cancer: a decade of research. *J Pain Symptom Manage*. 2015;49(3):595-610. doi:10.1016/j.jpainsymman.2014.07.008.
14. Figueiredo JM de. Depression and demoralization: Phenomenological differences and research perspectives. *Compr Psychiatry*. 1993;34(5):308-311.
15. Kissane DW. The contribution of demoralization to end of life decisionmaking. *Hastings Cent Rep*. 2004;34(4):21-31.
16. Robinson S, Kissane DW, Brooker J, Hempton C, Burney S. The relationship between poor quality of life and desire to hasten death: A multiple mediation model examining the contributions of depression, demoralization, loss of control, and low self-worth. *J Pain Symptom Manage*. doi:10.1016/j.jpainsymman.2016.08.013.
17. Fang C-K, Chang M-C, Chen P-J, et al. A correlational study of suicidal ideation with psychological distress, depression, and demoralization in patients with cancer. *Support Care Cancer*. 2014;22(12):3165-3174. doi:10.1007/s00520-014-2290-4.
18. Robinson S, Kissane DW, Brooker J, et al. Refinement and revalidation of the demoralization scale: The DS-II-external validity. *Cancer*. 2016;(14):2260-2267. doi:10.1002/cncr.30012.
19. Vehling S, Kamphausen A, Oechsle K, Hroch S, Bokemeyer C, Mehnert A. The Preference to Discuss Expected Survival Is Associated with Loss of Meaning and Purpose in Terminally Ill Cancer Patients. *J Palliat Med*. 2015;18(11):970-976. doi:10.1089/jpm.2015.0112.
20. Costantini A, Picardi A, Brunetti S, et al. La versione italiana della Demoralization Scale: uno studio di validazione. *Riv Psichiatr*. 2013;48(3):234-239. doi:10.1708/1292.14291.
21. Vehling S, Oechsle K, Koch U, Mehnert A. Receiving palliative treatment moderates the effect of age and gender on demoralization in patients with cancer. *PLoS ONE*. 2013;8(3):e59417. doi:10.1371/journal.pone.0059417.

22. Lee CY, Fang CK, Yang YC, et al. Demoralization syndrome among cancer outpatients in Taiwan. *Support Care Cancer*. 2012;20(10). doi:10.1007/s00520-011-1332-4.

23. Mehnert A, Vehling S, Hoecker A, Lehmann C, Koch U. Demoralization and depression in patients with advanced cancer: validation of the German version of the demoralization scale. *J Pain Symptom Manage*. 2011;42(5):768-776. doi:10.1016/j.jpainsymman.2011.02.013.

24. Vehling S, Lehmann C, Oechsle K, et al. Global meaning and meaning-related life attitudes: Exploring their role in predicting depression, anxiety, and demoralization in cancer patients. *Support Care Cancer*. 2011;19(4):513-520. doi:10.1007/s00520-010-0845-6.

25. Mullane M, Dooley B, Tiernan E, Bates U. Validation of the Demoralization Scale in an Irish advanced cancer sample. *Palliat Support Care*. 2009;7(3):323-330. doi:10.1017/S1478951509990253.

26. Mehnert A, Brähler E, Faller H, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. *J Clin Oncol*. 2014;32(31):3540-3546. doi:10.1200/JCO.2014.56.0086.

27. Mehnert A, Koch U, Schulz H, et al. Prevalence of mental disorders, psychosocial distress and need for psychosocial support in cancer patients – study protocol of an epidemiological multi-center study. *BMC Psychiatry*. 2012;12(1):70. doi:10.1186/1471-244X-12-70.

28. Hund B, Reuter K, Jacobi F, et al. Adaptation des Composite International Diagnostic Interview (CIDI) zur Erfassung komorbider psychischer Störungen in der Onkologie: Das CIDI-O. *Psychother Psych Med*. 2014;64(03/04):101-107. doi:10.1055/s-0033-1357174.

29. Hund B, Reuter K, Harter M, et al. Stressors, symptom profile, and predictors of adjustment disorder in cancer patients. Results from an epidemiological study with the composite international diagnostic interview, adaptation for oncology (CIDI-O). *Depress Anxiety*. 2016;33(2):153-161. doi:10.1002/da.22441.

30. Kissane DW, Clarke DM, Street AF. Demoralization syndrome - a relevant psychiatric diagnosis for palliative care. *J Palliat Care*. 2001;17(1):12-21.

31. Kissane DW, Wein S, Love A, Lee XQ, Kee PL, Clarke DM. The Demoralization Scale: a report of its development and preliminary validation. *J Palliat Care*. 2004;20(4):269-276.

32. Löwe B, Kroenke K, Herzog W, Grafe K. Measuring depression outcome with a brief self-report instrument: sensitivity to change of the Patient Health Questionnaire (PHQ-9). *J Affect Disord*. 2004;81(1):61-66. doi:10.1016/S0165-0327(03)00198-8.

33. Luedecke D. sjPlot: data visualization for statistics in social science. 2016;http://CRAN.R-project.org/package=sjPlot.

34. Zeileis A. Object-oriented Computation of Sandwich Estimators. *Journal of Statistical Software*. 2006;16(1):1-16. doi:10.18637/jss.v016.i09.

35. R Development Core Team. *R: A language and environment for statistical computing*. Vienna, Austria; 2008.

36. Grassi L, Sabato S, Rossi E, Biancosino B, Marmai L. Use of the diagnostic criteria for psychosomatic research in oncology. *Psychother Psychosom*. 2005;74(2):100-107. doi:10.1159/000083168.

37. Grassi L, Nanni MG. Demoralization syndrome: New insights in psychosocial cancer care. *Cancer*. 2016;122(14):2130-2133. doi:10.1002/cncr.30022.

38. Wilson KG, Dalgleish TL, Chochinov HM, et al. Mental disorders and the desire for death in patients receiving palliative care for cancer. *BMJ Supp Pall Care*. 2016;6(2):170-177. doi:10.1136/bmjspcare-2013-000604.

39. Rodin G, Lo C, Mikulincer M, Donner A, Gagliese L, Zimmermann C. Pathways to distress: the multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. *Soc Sci Med*. 2009;68(3):562-569. doi:10.1016/j.socscimed.2008.10.037.

40. Kissane DW, Bobevski I, Gaitanis P, et al. Exploratory examination of the utility of demoralization as a diagnostic specifier for adjustment disorder and major depression. *General Hospital Psychiatry*. 2017. doi:10.1016/j.genhosppsych.2017.01.007.

41. Breitbart W, Rosenfeld B, Pessin H, Applebaum A, Kulikowski J, Lichtenthal WG. Meaning-Centered Group Psychotherapy: An effective intervention for improving psychological well-being

in patients with advanced cancer. *J Clin Oncol*. 2015;33(7):749-754. doi:10.1200/JCO.2014.57.2198.

42. Guerrero-Torrelles M, Monforte-Royo C, Rodríguez-Prat A, Porta-Sales J, Balaguer A. Understanding meaning in life interventions in patients with advanced disease: A systematic review and realist synthesis. *Palliative Medicine*. 2017;11(4). doi:10.1177/0269216316685235.
43. Nissim R, Freeman E, Lo C, et al. Managing Cancer and Living Meaningfully (CALM): A qualitative study of a brief individual psychotherapy for individuals with advanced cancer. *Palliat Med*. 2012;26(5):713-721. doi:10.1177/0269216311425096.
44. Rafanelli C, Guidi J, Gostoli S, Tomba E, Porcelli P, Grandi S. Subtyping demoralization in the medically ill by cluster analysis. *Eur J Psychiat*. 2013;27(1):7-17. doi:10.4321/S0213-61632013000100002.
45. Vehling S, Lehmann C, Oechsle K, et al. Is advanced cancer associated with demoralization and lower global meaning? The role of tumor stage and physical problems in explaining existential distress in cancer patients. *Psychooncology*. 2012;21(1):54-63. doi:10.1002/pon.1866.
46. Lo C, Panday T, Zeppieri J, et al. Preliminary psychometrics of the Existential Distress Scale in patients with advanced cancer. *Eur J Cancer Care*. 2016;doi:10.1111/ecc.12597. doi:10.1111/ecc.12597.
47. Robinson S, Kissane DW, Brooker J, et al. Refinement and revalidation of the demoralization scale: The DS-II-internal validity. *Cancer*. 2016:doi:10.1002/cncr.30015. doi:10.1002/cncr.30015.

Table 1: Demographic and disease related sample characteristics (N=430)

Variable	N	%
Age, mean (SD)	56.7 (11.6)	
Gender		
Female	217	50.5
Male	213	49.3
Cohabitation	318	78.5
Education		
Elementary school (8-9 years)	100	23.4
Junior high school (10 years)	141	32.9
High school (12-13 years)	112	26.2
University	75	17.5
Tumor diagnosis		
Breast	101	23.5
Prostate	105	24.4
Hematological	53	12.3
Gastrointestinal	43	10.0
Gynecologic	33	7.7
Lung	27	6.3
Other	68	15.8
Treatment setting		
Inpatient	105	24.4
Outpatient	200	46.5
Rehabilitation, inpatient	125	29.1
Advanced cancer	108	25.1
No. of physical symptoms, mean (SD)[a]	5.9 (3.9)	

[a]Assessed by the problem list of the Distress Thermometer (DT), possible range: 0-21.

Table 2: 4-week prevalence of CIDI-O diagnosed mental disorders and suicidal ideation (N=430)

	Prevalence%	95% CI
Any mood disorder[#]	5.0%	2.9 to 7.0
Any anxiety disorder[$]	11.3%	8.3 to 14.3
Adjustment disorder	10.2%	7.3 to 13.1
Suicidal ideation[†]	9.3%	6.9 to 11.7
Suicidal ideation in absence of a mood/anxiety disorder	5.8%	3.4 to 8.2

[#]Assessment of major depressive disorder, dysthymic disorder, bipolar I disorder, bipolar II disorder, single manic episode, hypomania.

[$]Assessment of agoraphobia, panic disorder, social phobia, specific phobias (animal, natural environment, blood-injection-injury, and situational type), generalized anxiety disorder, post-traumatic stress disorder, single panic attack, or anxiety disorder NOS.

[†]Presence of one of three symptoms: frequent thoughts about death, wish to die, contemplation of suicide.

Table 3: Association of demoralization and self-reported depression with relative risk for mental disorders and suicidal ideation (N=430)

	Any mood disorder		Any anxiety disorder		Adjustment disorder[#]		Suicidal ideation[$]		Suicidal ideation in absence of a mood/anxiety disorder[#$]	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Model										
1) Demoralization	7.8***	3.4 to 17.9	3.7***	2.2 to 6.1	1.2	0.6 to 2.3	3.5***	1.9 to 6.2	2.8*	1.2 to 6.7
2) Depression	7.7***	3.2 to 18.8	2.3***	1.4 to 3.8	1.5	0.8 to 2.6	2.4**	1.4 to 4.2	1.4	0.6 to 3.3
3) Demoralization	4.0*	1.3 to 12.1	3.3***	1.8 to 5.8	0.9	0.4 to 2.1	3.4***	1.6 to 5.2	3.1*	1.3 to 7.7
Depression	3.7*	1.1 to 12.1	1.3	0.7 to 2.3	1.5	0.7 to 3.1	1.5	0.8 to 2.7	0.8	0.3 to 2.0

Note:

The RR (relative risk) for any mood/anxiety disorder was 4.0*** in patients with demoralization (95%CI 2.5 to 6.2), and 3.0*** (95%CI 1.9 to 4.6) in patients with self-reported depression.

The RR for any mental disorder including adjustment disorder was 2.5*** (95%CI 1.8 to 3.4) in patients with demoralization, and 2.2*** (95%CI 1.6 to 3.0) in patients with self-reported depression.

[#]Association calculated in subgroup without a mood or anxiety disorder (n=370).

[$]Association calculated after removing suicidal ideation items from PHQ (no. 9) and Demoralization scale (no. 20).

*p<.05, **p<.01, ***p<.001.

Table 4: Association of demoralization and self-reported depression with relative risk for suicidal ideation beyond mental disorders (N=430)

	Suicidal ideation[$]			Suicidal ideation in absence of a mood/anxiety disorder[#$]	
	RR	**95% CI**		**RR**	**95% CI**
Model 4a)			*Model 4b)*		
Any mental disorder	7.3***	3.5 to 15.1	Adjustment disorder	6.2***	2.6 to 14.4
Demoralization	2.0*	1.1 to 3.5	Demoralization	2.3*	1.1 to 5.3
5a)			*5b)*		
Any mental disorder	8.5***	4.3 to 17.0	Adjustment disorder	7.0***	3.0 to 16.1
Depression	1.5	0.9 to 2.4	Depression	1.1	0.5 to 2.6
6a)			*6b)*		
Any mental disorder	7.2***	3.5 to 14.8	Adjustment disorder	6.3***	2.7 to 14.8
Demoralization	1.8*	1.1 to 3.3	Demoralization	2.5*	1.1 to 6.0
Depression	1.2	0.7 to 2.0	Depression	0.8	0.4 to 1.8

[#]Association calculated in subgroup without a mood or anxiety disorder (n=370).

[$]Association calculated after removing suicidal ideation items from PHQ (no. 9) and Demoralization scale (no. 20).

[*]p<.05, [**]p<.01, [***]p<.001.

Figure Legend:

Figure 1: Frequencies of mental disorder cases and non-cases according to CIDI-O vs. demoralization cases and non-cases in the total sample (N=430). Note that diagnosis of adjustment disorder was made in absence of a mood/anxiety disorder only.

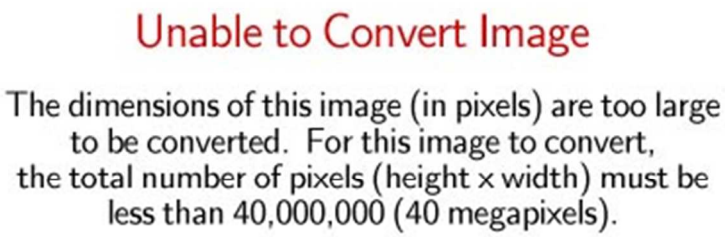

Figure 1: Frequencies of mental disorder cases and non-cases according to CIDI-O vs. demoralization cases and non-cases in the total sample (N=430). Note that diagnosis of adjustment disorder was made in absence of a mood/anxiety disorder only.
Figure 1

Supplementary Material: Results using a cut-off ≥35 on the Demoralization Scale

The overall prevalence of demoralization was 14.8% using a score ≥35 as threshold for clinically relevant demoralization. The co-occurrence between demoralization and suicidal ideation was 3.3%.

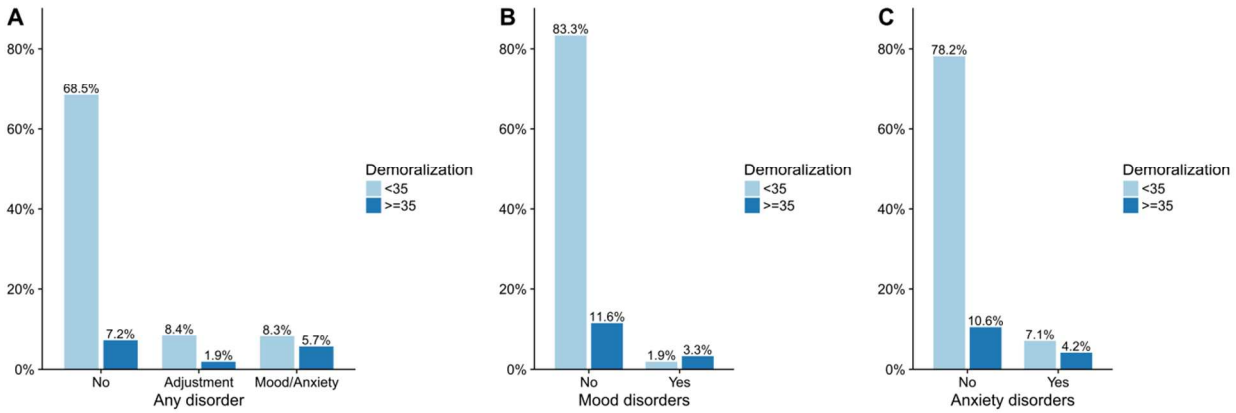

Figure 2: Frequencies of mental disorder cases and non-cases according to CIDI-O vs. demoralization cases and non-cases (cut-off ≥35) in the total sample (N=430). Note that diagnosis of adjustment disorder was made in absence of a mood/anxiety disorder only.

Table 5: Association of demoralization (cut-off ≥35) and self-reported depression with relative risk for mental disorders and suicidal ideation (N=430)

	Any mood disorder		Any anxiety disorder		Adjustment disorder[#]		Suicidal ideation[$]		Suicidal ideation in absence of a mood/anxiety disorder[#$]	
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Model										
1)										
Demoralization	10.1***	4.6 to 22.2	3.4***	2.1 to 5.6	1.3	0.6 to 2.5	3.4***	1.9 to 5.9	2.3	0.9 to 5.9
2)										
Depression	7.7***	3.2 to 18.8	2.3***	1.4 to 3.8	1.5	0.8 to 2.6	2.4**	1.4 to 4.2	1.4	0.6 to 3.3
3)										
Demoralization	5.3**	1.7 to 16.9	2.8***	1.6 to 4.8	0.9	0.4 to 2.3	2.6***	2.6 to 4.5	2.5	1.0 to 6.1
Depression	3.3	0.9 to 11.3	1.5	0.8 to 2.5	1.5	0.7 to 3.1	1.6	0.9 to 2.8	0.9	0.4 to 2.3

Note: The RR (relative risk) for any mood/anxiety disorder was 4.0*** in patients with demoralization (95%CI 2.6 to 6.2), and 3.0*** (95%CI 1.9 to 4.6) in patients with depression. The RR for any mental disorder including adjustment disorder was 2.6*** (95%CI 1.9 to 3.6) in patients with demoralization, and 2.2*** (95%CI 1.6 to 3.0) in patients with depression.

[#]Association calculated in subgroup without a mood or anxiety disorder (n=370).

[$]Association calculated after removing suicidal ideation item from PHQ (no. 9) and Demoralization scales (no. 20).

*p<.05, **p<.01, ***p<.001.

Table 6: Association of demoralization (cut-off ≥35) and self-reported depression with relative risk for suicidal ideation beyond mental disorders (N=430)

	Suicidal ideation[$]			Suicidal ideation in absence of a mood/anxiety disorder[#$]	
	RR	**95% CI**		**RR**	**95% CI**
Model 4a)			*Model 4b)*		
Any mental disorder	8.5***	4.3 to 17.0	Adjustment disorder	7.0***	3.0 to 16.1
Demoralization	1.7	1.0 to 3.1	Demoralization	1.7	0.7 to 4.4
5a)			*5b)*		
Any mental disorder	7.6***	3.7 to 15.7	Adjustment disorder	6.4***	2.7 to 15.2
Depression	1.5	0.9 to 2.4	Depression	1.1	0.5 to 2.6
6a)			*6b)*		
Any mental disorder	7.5***	3.7 to 15.3	Adjustment disorder	6.5***	2.8 to 15.4
Demoralization	1.6	0.9 to 2.8	Demoralization	1.9	0.7 to 4.8
Depression	1.2	0.7 to 2.1	Depression	0.9	2.0 to 0.7

[#]Association calculated in subgroup without a mood or anxiety disorder (n=370).

[$]Association calculated after removing suicidal ideation items from PHQ (no. 9) and Demoralization scale (no. 20).

[*]p<.05, [**]p<.01, [***]p<.001.

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