Journal of Public Health Research

eISSN 2279-9036 https://www.jphres.org/

J Public Health Res 2021 [Epub ahead of print]

Citation
Sancassiani F, Massa E, Pibia C, et al. **The association between Major Depressive Disorder and premature death risk in hematologic and solid cancer: a longitudinal cohort study.**

J Public Health Res 2021;xx:2247

doi: 10.4081/jphr.2021.2247

The association between Major Depressive Disorder and premature death risk in hematologic and solid cancer: a longitudinal cohort study

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Acknowledgments: the present study is supported by P.O.R. SARDEGNA F.S.E. 2014-2020, Asse III-Istruzione e Formazione, Obiettivo Tematico: 10-Obiettivo Specifico, 10.5-Azione dell'accordo di Partenariato; 10.5.12-Avviso di chiamata per il finanziamento di Progetti di ricerca–Anno 2017.

Key words: depression, oncology, hematology, psychosocial health, death risk

Authors' contributions: FS and MGC have the idea and organized the study; they also wrote the first draft of the article. FS, EM and MGC coordinated the reworking of the draft after the suggestions of all the co-authors. CP, GP, LB, GC, OM, EM, EL collected the data during the evaluations and contribute to the discussion of the findings. JL, AEN, MS, GC, GLN contributed to the interpretation and discussion of the findings and revised the initial draft into a more general framework. All authors contributed to the writing of the final manuscript, which they all approved for submission. Each author has studied the manuscript in the submitted form, has agreed being cited as co-author, and has accepted the order of authorship.

Conflict of interests and funding: none

Ethical Issues: The study was approved by the independent Ethical Committee of the Azienda Ospedaliero Universitaria di Cagliari, Italy (N°: PG/2018/13269). A written informed consent was obtained from each subject after they were provided with full descriptions of the aims and procedures

of the study, made aware of data protection and ensured they could terminate at any time. All procedures were carried out in accordance with the Helsinki Declaration.

Significance for public health

This cohort study lasting 9 months pointed out a high prevalence of Major Depressive Disorder (MDD) among people with cancer. During the time of observation, 36 deceases occurred. A strong association was observed regarding the survival rates between the MDD exposed subjects who died along the time and the MDD not exposed who survived. This association could be due to the consequences of MDD, if considering that it was not found any significant association between MDD among patients who died and a worse HRQoL when the MDD episode had been occurred, nor with age, gender, cancer stage and site. These findings point out the importance of the early detention of MDD among people with cancer, to promptly provide effective interventions for a good management of symptoms related to cancer and depression. Further studies are needed to explore the causal association between MDD and premature death in people suffering from cancer.

Abstract

Background: the aim was to verify the association between Major Depressive Disorders (MDD) and the risk of premature death in people with oncological diseases, and to collect evidence about the causality of a possible association from a longitudinal perspective.

Design and Methods: it is a cohort study lasting 9 months, involving people with solid or hematologic cancers. The assessment was conducted by an *ad hoc* form to collect socio-demographic and clinical-oncological data, the PHQ-9 to screen MDD (cut-off ≥10) and the SF-12 to evaluate HRQoL. Relative Risk (RR) of early death between MDD exposed and not-exposed and Kaplan-Meier survival were carried out.

Results: people exposed to MDD during the follow-up were 107/263 (40.7%). Among them, 36 deceased during the observation period. Overtime, having MDD and death' occurrence showed a strong association (RR=2.15; 95% CI (1.10-4.20); χ^2=5.224, p=0.0022), confirmed by Kaplan-Meier survival analysis (χ^2=4.357, p=0.037). Among people who died, there was not any association between MDD, age, gender, HRQoL, cancer stage and site.

Conclusions: the study confirms the association between MDD and early death in people with cancer. The absence of any association between the onset of MDD and advanced stage of cancer may suggest that it could be due to the consequences of MDD in worsening the clinical conditions related to cancer. The findings point out the relevance of MDD' early detention among people with cancer.

Introduction

Major Depressive Disorder (MDD) is a recurring condition and a leading source of disability worldwide [1, 2]. MDD is associated with impairment of Health-related Quality of Life (HRQoL) [3] and with premature death for all-cause of mortality [4, 5], included suicide [6].

People suffering from depression have high rates of comorbidity with other psychiatric and non-psychiatric disorders [7]; some studies showed that comorbid condition with MDD had worsened prognosis and showed higher mortality of the same conditions without depression [5, 8, 9, 10]. However, this data is still poorly confirmed, and the causal links of this association are not well clarified yet.

The World Health Organization pointed out that, in 2018, 9.6 million people worldwide are died from cancer [11]. The prevalence of MDD among individuals with cancer is approximately 12.5%, which is up to four-times the rate reported in population-based samples, that is around 3.3% [10, 12].

Among patients with cancer, MDD was shown to be associated with a variety of negative clinical outcomes, such as poor compliance with anti-cancer treatment [13] and low level of HRQoL [14, 15, 16, 17]. Several studies found that people suffering from cancer with comorbid MDD had higher early death risk [5, 8, 10, 18]. However, as described above for the general comorbidity of MDD with other diagnosis, so far little evidence has been accumulated to try to understand the causal link between early death and MDD in people suffering from cancer.

The primary end point of the present study was to verify the association between MDD episode over time (9 months) and higher death risk in people with solid and hematological cancers in a prospective analysis. Another aim was to establish if there were differences between other outcome indicators in the group of people with early death and, particularly, if the onset of MDD is associated with worse severity in the evolution of the tumor pathology. This is, in fact, a fundamental element to begin to understand whether it is depression that causes worsening in clinical conditions and death or vice-versa.

Design and Methods

Study design

It is a cohort study, lasted 9 months. Among a study population of people with solid or hematological cancers, two cohorts were assessed: one included people exposed to at least one MDD episode (MDD-E) during the observation period; the other one was composed by MDD not-exposed (MDD-NE). The main outcome was the number of deaths in the two cohorts. People in the

cohort with depression were those that, at the baseline, showed a depressive episode or those that had the onset of depressive episode during the observational period (changing of cohort). Furthermore, we also built a case control study on the cohort (cases: people with depressive episode; controls: people without depressive episode), to verify the factors associated with death at the beginning of the study.

Recruitment procedures, study sample and Ethical issues

Since 2018, the study has been conducting in Cagliari, Italy, at the Oncology Unit, University-Hospital and at the Hematology Unit and Stem Cell Transplantation Center, "Businco" Hospital. The study population includes people aged≥18 years, of both genders, with histologic confirmation of a solid or hematologic malignant cancer and receiving active anti-cancer treatment. After the baseline evaluation (T0), the study protocol includes a series of repeated measures for each subject: after 3 (T1), 6 (T2) and 9 months (T3) from T0.

The study was approved by the independent Ethical Committee of the Azienda Ospedaliero Universitaria di Cagliari, Italy (N°: PG/2018/13269). A written informed consent was obtained from each subject after they were provided with full descriptions of the aims and procedures of the study, made aware of data protection and ensured they could terminate at any time. All procedures were carried out in accordance with the Helsinki Declaration.

Assessment tools

Ad-hoc form was used to collect socio-demographic and clinical-oncological anamnestic data: gender; age; marital status; employment status; educational level; kind of the oncology service; time from taking in charge at the oncology unit; cancer site and stage; intent of treatment; toxicity of treatments according to Common Toxicities Criteria for Adverse Events (CTCAE) [19], response and adherence to treatment.

The Italian Version [20] of the "Patient Health Questionnaire" (PHQ-9) [21] was used to assess depressive symptoms in the last two weeks. The PHQ-9 is a self-questionnaire usually used in population studies that could be administered also by phone for screening MDD or for the evaluation of the severity of depressive symptoms. It is relatively feasible, pointing out scores to each of the nine DSM-IV-TR criteria for MDD, proposed in the form of 9 item. As a continue variable to establish the severity of depressive symptoms, the scores of each item can range from 0 (complete absence) to 3 (almost every day). To screen MDD, the total score assigns ranks within the following: 0-4 (minimal), 5-8 (mild), 9-14 (moderate), 15-19 (moderately severe), 20-27 (severe).

The Italian version [22] of the self-report questionnaire "Short Form Health Survey – 12 item" (SF-12) [23] was administered to evaluate the perceived HRQoL in the last month. The instrument includes 12 items and investigates two sub-dimensions (physical and psychosocial health). The total score ranges from 12 to 47, with higher scores reflecting a better perceived HRQoL.

Statistical Analyses

Data collection and data-entry in a dedicate database were anonymously for each subject. Data were analyzed with the Statistical Package for Social Science (SPSS) version 24 (Chicago, Illinois 60606, US).

Descriptive statistics were used for continuous (mean±sd; N and %) and nominal (N and %) variables, to point out the socio-demographic and clinical-oncological characteristics of the samples at the baseline (T0), after 3 months (T1), 6 months (T2) and 9 months (T3), data regard N (%) of evaluated patients.

PHQ-9 score ≥10 was used to define MDD-E subjects during the period of observation. To calculate the Relative Risk (RR), the two cohorts (MDD-E and MDD-NE) were evaluated overtime about the death' and other inauspicious outcomes' incidences by χ^2 test and the Kaplan-Meier survival function.

One-way ANOVA, Kruskal-Wallis and χ^2 test were used to evaluate the association between MDD and HRQoL, age, gender, cancer stage and site at T0, as well as between MDD-E subjects who died overtime and HRQoL when the MDD episode had been occurred, age, gender, cancer stage and site at T0.

Results

The study cohort includes N 263 people with solid (201, 76.4%) and hematologic cancers (62, 23.6%) (Table 1). Women were 132 (50.2%); the mean±sd age was 61.2±13.6 years. More than half had a high-school diploma or a university degree (139; 52.6%). Most of the subjects were married (175; 66.5%), 57 (21.7%) singles, 10 (3.8%) divorced and 21 widows (8%); (see Table 1 for details and the other characteristics of the study cohort).

People with a Depressive Episode during the cohort were 107/263 (40.7%), people without 156/263 (59.3%). Along time of the observation, in the "MDD-Exposed" cohort, months/person were 586.5. In the "MDD-Not Exposed" cohort, months/person were 900 (see Table 2).

Table 2 also shows that, at T1, after 3 months from the baseline, N 23 (8.7%) people were deceased, at T2, after 6 months from the baseline, other N 11 (4.2%) people were deceased and at T3, after 9 months from the baseline, other N 2 (0.8%) people were deceased. Furthermore, considering the 36

deaths occurred in the overall sample, 21 occurred in the cohort of people exposed to MDD (MDD-E) and 15 in the cohort of people not exposed to MDD (MDD-NE), the Relative Risk (RR) was=2.15; 95% CI (1.10-4.20); χ^2=5.224, p=0.0022), the Kaplan-Meier survival curve confirmed the result (Log-Rank Mantel-Cox χ^2=4.357, p=0.037; see Table 3, Figure 1).
Table 4 shows that female gender (χ^2 with Fisher exact test=4.338, df 1, p=0.045) and a worse HRQoL (F=51.008, df 1,261,262; p=0.000) were significantly associated with MDD.
Finally, as shown in Table 5, among the 21 MDD-E and the 15 MDD-NE subjects who died along the time, the SF-12 mean±sd scores when the MDD episode had been occurred were 26.7±7.3 and 27.6±5.7 respectively, without any significant difference. Considering age, gender, the cancer stage and site at T0, there were not any significant difference between the two groups.

Discussion

The present study pointed out that, according to PHQ-9≥10 score, 40.7% patients with a solid or hematological cancer presented at least one MDD episode along the time of observation. This data is higher if compared with a previous meta-analyses [24] that pointed out a pooled mean prevalence of depression in patients with cancer ranged from 8% to 24%, depending by the type of instrument used to assess MDD (other self-report questionnaire different from PHQ-9 or semi-structured diagnostic interviews based on DSM-III-R/IV or ICD-10 criteria), the type of cancer and treatment phase. However, the use of PHQ-9 as MDD screening instrument in the oncological field is high recommended [25, 26, 27] and, ideally, it might be followed by an evaluation by a semi-structured interview based on DSM or ICD criteria (i.e.: SCID) when the costs and benefits of routinely screening all patients with cancer admit to use of both kind of tools [27]. This is not the case of the present study, in which the assessment was carried out only by self-reported instruments. Hence, the higher MDD prevalence obtained should be confirmed by diagnoses obtained with semi-structured interviews, also because of the PHQ-9 ≥10 score used as the cut-off to detect MDD exposed patients. In fact, this is a threshold usually recommended for screening general medical and primary care patients, but it allows to reduce the number of MDD false-positive subjects at the cost of missing more false-negatives [26], and this could be a limitation. The study confirms also that MDD is more prevalent among women [2, 28] and that MDD is associated with a worse HRQoL in people suffering from cancer [3, 14, 15, 17].
Furthermore, the present study pointed out that, from the baseline, 36 deceases occurred. A significant difference in the Relative Risk (RR) was observed regarding only the survival rates between the 21 MDD exposed subjects who died along the time and the 15 MDD not-exposed subjects who survived. There could be two main hypotheses to explain this association.

One of these regards the impact of the MDD in worsening the clinical conditions of people suffering from cancer, precipitating the occurrence of death. Patients with cancer and MDD could suffer from a significant distress and impaired functioning, such as a lack of interest in daily activities, including the poor inclination to taking care of themselves, as well as from several disturbances in sleeping and eating. Otherwise, patients with cancer could just start to "let themselves go" because of the worsening in their clinical conditions due to cancer, resulting in a bad mood that could degenerate in MDD episode. Both hypotheses could be right.

However, findings pointed out any significant association between MDD episodes among patients who died and a worse HRQoL when the MDD episode had been occurred, nor with other factors such as age, gender and the cancer stage and site at T0 (baseline). This is an important indication that may confirm the role of MDD in worsening the clinical conditions of people suffering from solid or hematological cancers, also by increasing the death risk.

Other studies pointed out that MDD or severe depressive symptoms are independent risk factors for cancer mortality, mainly when cancer is in advanced stadium [29, 30], with a 26% greater mortality rate among patients with depressive symptoms and a 39% higher mortality rate among those with a diagnosis of MDD [9].

Otherwise, differently also from the findings of the present study, some research showed that the impact of MDD on mortality rate may change by cancer site: being higher in people with lung, gastrointestinal and brain cancer, and lower in those with urogenital and skin cancer [31].

In any case, an amount of studies, conducted also by animal models, agreed on some hypothesis to explain the relation between depression and cancer, mainly from behavioral and neuro-biological perspectives [9, 10, 32, 33, 34, 35]. One hypothesis regards the chronic activation of the hypothalamus-pituitary-adrenal (HPA) axis, that could be a mediator of the effect of depression on cancer progression [35]: an excessive activation of the HPA axis may modify the functioning of the cellular immune system, increasing the potential for malignant cancer fast progression.

Furthermore, pro-inflammatory cytokines (i.e.: interleukin-1α and β, tumor necrosis factor-α, interleukin-6) are modified by emotions, and have been shown to increase in depression by a dysregulated production and functioning linked also to a disrupted HPA axis activation that may influence cancer outcomes and prognosis [34, 35, 36].

Other hypotheses regard the role of psychosocial stressors as modulators of immune response in depression and cancer [10]. Particularly, poor social support, lack of familiar bonding, a history of childhood trauma and adverse life experiences increase the vulnerability to chronic diseases, including MDD and cancer [37], as well as to cancer mortality across several kinds of cancer [30]. Particularly, these psychosocial factors are associated with cognitive difficulties, mainly on

memory, which could have a role in diminishing treatment compliance [10], as well as with unhealthy lifestyle, such as delay in treatment-seeking, eating and sleeping habits, smoking and alcohol abuse, lack of physical activity [30].

Notably, findings of the present study showed another interesting data regarding patients who died along the time of observation. Even if mostly of these patients, both those exposed or not exposed to MDD, exhibited a severe cancer stadium (the 4^{th}) at the baseline, there was not any significant association between this variable and the occurrence of MDD episodes along the time, nor with the cancer site as already said above. These evidences confirm that MDD may precipitate the clinical outcomes of patients with cancer and increases their death risk.

Furthermore, this data points out the importance of the early detention of depressive symptoms and other early signs of psychosocial distress in this kind of population by prompt and reliable screening interventions. In this way, it is possible to support people suffering from cancer in managing the impact of MDD since its early signs.

In addition to antidepressant [13], several psychosocial interventions may be effective in improving depressive symptoms and psychosocial distress, by enhancing resilience, social support and adaptive coping strategies to stress management, such as cognitive behavioral therapy, mindfulness-based therapy, multimodal approaches including psychoeducational interventions, counseling, hypnosis and relaxation techniques, therapeutic dialogue provided by a “trained helper”, motivational interviewing [10, 38, 39, 40].

The present study has some limitations. Firstly, the small sample size did not allow to perform robust analyses for confounding factors, regarding all the variables that may be associated with death’ risk in people with cancer (i.e.: the kind of hematologic cancer). The analyses performed in this study allowed to point out just several associations with MDD exposition, without establish a cause-effect direction. Furthermore, MDD exposition was evaluated just by a self-report screening instrument (PHQ-9), without a standardized diagnostic interview based on DSM or ICD criteria. Finally, it was estimated the sum months/person to fix the occurrence of the decease and the MDD episode just on the basis of the timing of observation (3 months from one to another evaluation, until 9 months) by the mean about months elapsed between successive evaluations.

References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015 22;386:743-800.
2. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health 2013;34:119-38.
3. Carta MG, Aguglia E, Bocchetta A, et al. The use of antidepressant drugs and the lifetime prevalence of major depressive disorders in Italy. Clin Pract Epidemiol Ment Health 2010;6:94-100.
4. Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. Erratum in: JAMA Psychiatry 2015;72:736. Erratum in: JAMA Psychiatry 2015;72:1259JAMA Psychiatry 2015;72:334-41.
5. Machado MO, Veronese N, Sanches M, et al. The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. BMC Med 2018;16:112.
6. Scocco P, Idotta C, Mareschi T, et al. Do interpersonal events buffer or worsen depressive and grief related symptoms in people bereaved through suicide? Death Stud 2020:1-10. Online ahead of print. doi: 10.1080/07481187.2020.1855608
7. Rackley S, Bostwick JM. Depression in medically ill patients. Psychiatr Clin North Am 2012;35:231-47.
8. Cuijpers P, Vogelzangs N, Twisk J, et al. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. Am J Psychiatry 2014;171:453-62.
9. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. Cancer 2009;115:5349-61.
10. Bortolato B, Hyphantis TN, Valpione S, et al. Depression in cancer: The many biobehavioral pathways driving tumor progression. Cancer Treat Rev 2017;52:58-70.
11. World Health Organization. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: World Health Organization; 2020. Available from: https://apps.who.int/iris/handle/10665/330745
12. Lutgendorf SK, Andersen BL. Biobehavioral approaches to cancer progression and survival: Mechanisms and interventions. Am Psychol 2015;70:186-97.
13. Ostuzzi G, Matcham F, Dauchy S, et al. Antidepressants for the treatment of depression in people with cancer. Cochrane Database Syst Rev 2018;4:CD011006.
14. van Dams R, Grogan T, Lee P, et al. Impact of health-related quality of life and prediagnosis risk of major depressive disorder on treatment choice for stage I lung cancer. JCO Clin Cancer Inform 2019;3:1-8.
15. Arrieta O, Angulo LP, Núñez-Valencia C, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann Surg Oncol 2013;20:1941-8.
16. Mantovani G, Astara G, Lampis B, et al. Evaluation by multidimensional instruments of health-related quality of life of elderly cancer patients undergoing three different "psychosocial" treatment approaches. A randomized clinical trial. Support Care Cancer

1996;4:129-40.
17. La Nasa G, Caocci G, Morelli E, et al. Health related quality of life in patients with onco-hematological diseases. Clin Pract Epidemiol Ment Health 2020;16:174-9.
18. Zonderman AB, Costa PT Jr, McCrae RR. Depression as a risk for cancer morbidity and mortality in a nationally representative sample. JAMA 1989;262:1191-5.
19. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106:dju244.
20. Rizzo R, Piccinelli M, Mazzi MA, et al. The Personal Health Questionnaire: a new screening instrument for detection of ICD-10 depressive disorders in primary care. Psychol Med 2000;30:831-40.
21. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 1999;282:1737-44.
22. Apolone G, Mosconi P, Quattrociocchi L, et al. [Questionario sullo stato di salute SF-12 Versione Italiana].[in Italian]. Milano: Istituto di Ricerche Farmacologiche Mario Negri; 2001.
23. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
24. Krebber AM, Buffart LM, Kleijn G, et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 2014;23:121-30.
25. Andersen BL, Rowland JH, Somerfield MR. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology Guideline adaptation. J Oncol Pract 2015;11:133-4.
26. Thekkumpurath P, Walker J, Butcher I, et al. Screening for major depression in cancer outpatients: the diagnostic accuracy of the 9-item patient health questionnaire. Cancer 2011;117:218-27.
27. Hartung TJ, Friedrich M, Johansen C, et al. The Hospital Anxiety and Depression Scale (HADS) and the 9-item Patient Health Questionnaire (PHQ-9) as screening instruments for depression in patients with cancer. Cancer 2017;123:4236-43.
28. Kuehner C. Why is depression more common among women than among men? Lancet Psychiatry 2017;4:146-58.
29. Lloyd-Williams M, Shiels C, Taylor F, Dennis M. Depression--an independent predictor of early death in patients with advanced cancer. J Affect Disord 2009;113:127-32.
30. Pinquart M, Duberstein PR. Associations of social networks with cancer mortality: a meta-analysis. Crit Rev Oncol Hematol 2010;75:122-37.
31. Hartung TJ, Brähler E, Faller H, et al. The risk of being depressed is significantly higher in cancer patients than in the general population: Prevalence and severity of depressive symptoms across major cancer types. Eur J Cancer 2017;72:46-53.
32. Najjar S, Pearlman DM, Alper K, et al. Neuroinflammation and psychiatric illness. J Neuroinflammation 2013;10:43.
33. Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol

Psychiatry 2013;18:595-606.
34. Dantzer R, O'Connor JC, Freund GG, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46-56.
35. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol 2004;5:617-25.
36. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer 2008;8:887-99.
37. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull 2011;137:959-97.
38. Zhang MF, Wen YS, Liu WY, et al. Effectiveness of mindfulness-based therapy for reducing anxiety and depression in patients with cancer: A meta-analysis. Medicine (Baltimore. 2015;94:e0897-0.
39. Galway K, Black A, Cantwell M, et al. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients. Cochrane Database Syst Rev 2012;11:CD007064.
40. Spencer JC, Wheeler SB. A systematic review of Motivational Interviewing interventions in cancer patients and survivors. Patient Educ Couns 2016;99:1099-105.

Table 1. Socio-demographic and clinical characteristics of the study sample.

VARIABLE		**N**	**%**
Gender	Male	131	49.8
	Female	132	50.2
Marital status	Single	57	21.7
	Married	175	66.5
	Divorced	10	3.8
	Widow	21	8
Employment status	Housewife	32	21.2
	Unemployed	13	8.6
	Employed	49	31.5
	Retired	57	37.7
Education level	< Primary school	1	0.4
	Primary school	32	12.2
	Secondary school	93	35.4
	High school	100	38
	University degree	32	12.2
	Military Academy	1	0.4
	Higher	4	1.5
Kind of service	Day Hospital	217	82.5
	Hospital Ward	46	17.5
Timing of taking care at the Oncology service	First visit	9	3.4
	<6 months	102	38.8
	6-12 months	48	18.3
	>12 months	103	39.2
	Not evaluated	1	0.4
Cancer site	Gastroenteric	94	35.7
	Gynecological	32	12.2
	Breast	32	12.2
	Lung	16	6.1
	Head and neck	1	0.4

	Rare	9	3.4
	Uro-genital	17	6.5
Cancer stage	1	10	3.8
	2	29	11
	3	45	17.1
	4	178	67.7
	Not evaluated	1	0.4
Toxicity of treatments°	0	72	47,7
	1	25	16,6
	2	38	25,2
	3	14	9,3
	4	2	1,3
Intent of treatment	Adjuvant	41	15.6
	New adjuvant	4	1.5
	Curative	31	11.8
	Palliative	156	59.3
	Maintenance	25	9.5
	Support	5	1.9
	Not evaluated	1	0.4
Response to treatment	Absence of cancer	38	14.4
	Ongoing	82	31.2
	In progress	47	17.9
	Partial	25	9.5
	Stable	65	24.7
	Not evaluated	6	2.3
Adherence after 3 months of treatment	No	27	10.3
	Yes	229	87.1
	Not evaluated	7	2.7

°The toxicity of treatment was scored from 0 (mild) to 4 (death), according to common toxicities criteria. (CTC), version 4.0 [19]; available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

Table 2. The association between MDD "Positive-exposed" subjects according to PHQ-9 ≥10 score and deceases occurred from T0 to T3 (9 months).

	PHQ-9 ≥10 "positive" (exposed to MDD)	**PHQ-9<10 "negative" (not exposed to MDD)**	
			total
From T0 to T3 (9 months) N (%)	107 (40.7%)	156 (59.3%)	263 (100%)
months/person (sum)	586.5	900	9 months (from T0 to T3)
Deceases (After 3 months from the baseline - T1) N (%)			23 (8.7%)
Deceases (After 6 months from the baseline – T2) N (%)			11 (4.2%)
Deceases (After 9 months from the baseline – T3) N (%)			2 (0.8%)
Deceases (total) N (%)	21 (58.3%)	15 (41.7%)	36 (100%)
Relative Risk (RR)			2.15; 95% CI (1.10-4.20) χ^2=5.224, p=0.0022

Table 3. Kaplan-Meier survival analysis about MDD exposed and not exposed subjects who died over time (9 months).

Status	**Total**	**N deceased**	**Censored (survivors)**			**Associations**	**X² test**	**Df**	**P**
			N	**%**		Log-rank (mantel-cox)	4.357	1	0.037
Mdd exposed	107	21	86	80.4%		Breslow (generalized wilcoxon)	3.884	1	0.049
Mdd not exposed	156	15	141	90,4%		Tarone-ware	4.133	1	0.042

Table 4. Factors associated with MDD (PHQ-9 ≥10) in the overall sample.

	SF-12 mean±sd (T0)	**Age mean±sd**	**Gender F/M N (%)**	**Cancer stage at T0 (1,2,3,4)**	**Cancer site at T0**
PHQ-9 ≥10 "positive" (exposed to MDD) **N=107**	29.05±6.3	61.2±14.3	F=62/107 (57.9%) M=45/107 (42.1%)	Stage 1= 6/107 (5.6%) Stage 2= 9/107 (8.4%) Stage 3= 18/107 (16.8%) Stage 4= 74/107 (69.2%)	Blood= 22/107 (21%) Breast= 15/107 (14%) Gastroenteric= 41/107 (38%) Gynecological= 12/107 (11%) Head and Neck= 0/107 (0%) Lung= 4/107 (4%) Rare= 3/107 (3%) Uro-Genital= 10/107 (9%)
PHQ-9<10 "negative" (not exposed to MDD) **N=156**	34.3±5.5	61.2±13.2	F=70/156 44.9(%) M=86/156 (55.1%)	Stage 1= 4/156 (2.6%) Stage 2= 20/156 (12.8%) Stage 3= 27/156 (17.3%) Stage 4= 104/156 (66.7%) Not reported= 1/156 (0.6%)	Blood= 40/156 (25%) Breast= 17/156 (11%) Gastroenteric= 53/156 (34%) Gynecological= 20/156 (13%) Head and Neck= 1/156 (1%) Lung= 12/156 (8%) Rare= 6/156 (4%) Uro-Genital= 7/156 (4%)
One-way ANOVA	F=51.008, df 1,261,262	F=0.001, df 1,261,262			
χ^2			4.338, df 1		6.332, df 7
Kruskal-Wallis				0.082, df 1	
p	0.000	0.978	0.045*	0.774	0.499*

*Fisher exact test

Table 5. Factors associated with death in the overall sample [MDD (PHQ-9 ≥10)].

	SF-12 mean±sd (corresponding to MDD episode)	**Age mean±sd**	**Gender F/M N (%)**	**Cancer stage at T0 (1,3,4)**	**Cancer site at T0**
PHQ-9 ≥10 "positive" (exposed to MDD) who died **N=21**	26.7±7.3	63.3±13.1	F=11/21 (52.4%) M=10/21 (47.6%)	Stage 1=1/21 (5%) Stage 3=3/21 (14%) Stage 4=17/21 (81%)	Blood=0/21 (0%) Breast=1/21 (5%) Gastroenteric=14/21 (66%) Gynecological=1/21 (5%) Head and Neck=0/21 (0%) Lung=2/21 (9.5%) Rare=1/21 (5%) Uro-Genital=2/21 (9.5%)
PHQ-9<10 "negative" (not exposed to MDD) who died **N=15**	27.6±5.7	65.7±12.3	F=4/15 (26.7%) M=11/15 (73.3%)	Stage 1=0/15 (0%) Stage 3=2/15 (13%) Stage 4=13/15 (87%)	Blood=1/15 (6.7%) Breast=1/15 (6.7%) Gastroenteric=8/15 (53.1%) Gynecological=1/15 (6.7%) Head and Neck=1/15 (6.7%) Lung=1/15 (6.7%) Rare=1/15 (6.7%) Uro-Genital=1/15 (6.7%)
One-way ANOVA	F=0.168, df 1,34	F=0.310, df 1,34			
χ^2			2.380, df 1		4.228, df 7
Kruskal-Wallis				0.246, df 1	
p	0.684	0.582	0.176*	0.620	0.902*

*Fisher' exact test

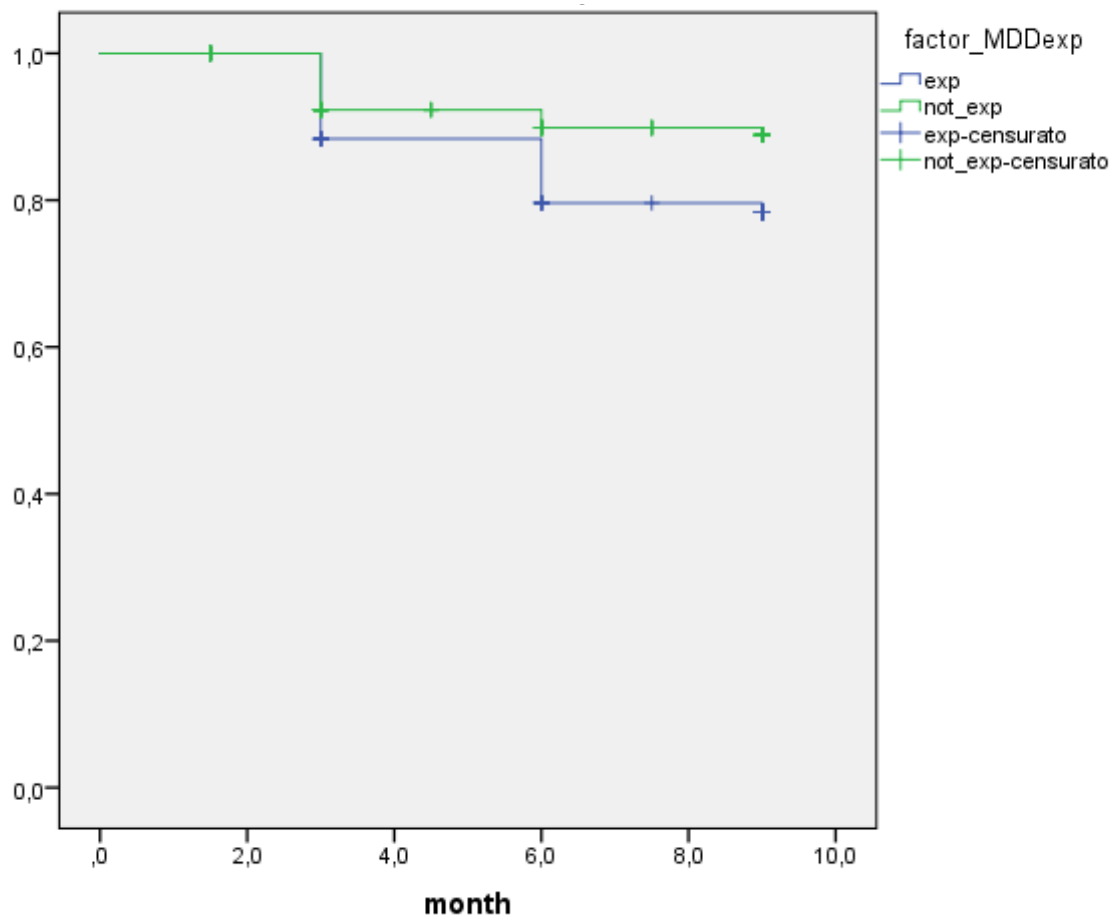

Figure 1. Kaplan-Meier survival function: differences about MDD exposed and not exposed subjects who survived over time (9 months).