**ASSOCIATION BETWEEN DEPRESSIVE DISORDER AND CLINICAL FACTORS AND ITS IMPACT ON SURVIVAL IN MEXICAN PATIENTS WITH ADVANCED CANCER IN PALLIATIVE CARE SERVICE.**

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**ABSTRACT**

**Introduction**. Depressive disorder (DD) is one of the most common mental disorders in palliative cancer patients. It has been one of the most underdiagnosed and untreated disorders in patients at the end of life. Additionally, DD is an important factor for the presence of desire to hasten death, a lower functional status, survival and quality of life, a poor therapeutic adherence and greater intensity of physical symptoms. **Objective.** To identify the frequency of depressive disorder, its impact on overall survival and its relation with clinical and sociodemographic characteristics in patients with advanced cancer seen at a palliative care service in Mexico. **Methods.** A prospective, observational, cross-sectional study of patients within a palliative care service of the National Institute of Cancerology in Mexico City were recruited. Clinical factors were assessed by the Edmonton Symptom Assessment System (ESAS), functionality by the Karnofsky performance score and survival clinical prediction by the Palliative Prognostic Index. A semi-structured clinical interview according to the DSM-5 criteria to identify major depressive disorder was carried out by a psychiatrist from February 2018 to January 2019. **Results.** One hundred patients were recruited, 69 were female, median age was 57 years. Twenty-four patients met the criteria for depressive disorder. In the univariate analysis, patients with DD showed more intense physical symptoms, lower functionality, and poorer survival, compared to patients without DD. In the multivariable regression analysis, lower functionality was associated with DD OR 5.4 (95%CI 1.2-25.1) *p* = .026. Median overall survival in patients with DD was 5 months vs 27 months in those with no DD, *p* = .0289. **Conclusion.** The presence of depressive disorder is associated with a lower functionality and a worse prognosis in patients with advanced cancer. Improving strategies to improve early diagnosis and treatment of depressive disorder in patients with advanced cancer should be encouraged.

**Keywords: Depression, Palliative Care, Advanced Cancer, Survival, Physical symptoms**

**INTRODUCTION**

The aim of palliative care is the multidisciplinary support and care of the patient in order to improve her/his quality of life and of those closest to them (i.e. family care givers and close friends). This is achieved by early problem identification, integral evaluation and control of the physical problems such as pain, psychological suffering and spiritual issues; as well as their social needs, helping them to live the best possible way until their death (1).

In order to achieve these objectives, there are multiple challenges, including the presence of mental health that imply additional suffering (2,3). Delirium, anxiety and major depressive disorders are the most common. Unfortunately, these are not always diagnosed and therefore many times go by undertreated (4,5).

In our palliative care unit, the frequency of depressive disorder (DD) is still not known (6), medical literature state that the prevalence of DD in patients with advanced cancer seen at palliative care centers is 14% (12-20.4%)(7–9), which is higher than in the general population (10). Although DD is frequently found in palliative cancer patients, it is usually under recognized and undertreated (11).

Depressive disorder is associated with a decreased in the perception of quality of life (12), longer hospitalization time, greater weight loss, lower functionality, worse treatment adherence, more frequent and intense physical symptoms such as fatigue and pain(13–15). DD is also associated with a higher suicidal risk and the desire to hasten death(16–22). Furthermore, the presence of a DD has been associated with a shorter overall survival (15,23,24); therefore, DD increases the disability in those patients with oncologic conditions (18).

The aim of the present study was to identify the frequency of depressive disorder, its impact on overall survival, and its relationship with clinical and sociodemographic characteristics in patients with advanced cancer seen at our palliative care service in Mexico.

**MATERIAL AND METHODS**

A prospective observational study was conducted. Consecutive cases of patients with advanced cancer sent to the palliative care service at the National Institute of Cancer (Mexico City) were included from February 2018 to January 2019. Inclusion criteria included were confirmed diagnosis of cancer, age >18 years, with a Karnofsky performance score (KPS) >50 (25). Exclusion criteria: Delirium, psychotic disorder, currently using antidepressant, central nervous system metastases (CNSm), not being able to answer the interview and/or questionnaires.

Proceedings: All patients were interviewed by a psychiatrist (ORM), who during the interview collected sociodemographic data, performance status, completed the Edmonton Symptom Assessment System (ESAS) (26) tool for symptom assessment and the palliative prognostic index (PPI). After that, a medical interview according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM*-*5*) (27) for the diagnosis of depressive disorder was performed. Patients diagnosed with depressive disorder were prescribed with pharmacological treatment and/or psychotherapy according to the severity of the disorder. A survival cutoff was determined at end of August 2019.

**Statistical analysis**

Demographic and clinical characteristics are presented as frequencies, median and interquartile range (IQR). To study the relevance of the presence or absence of the depressive disorder, chi-square/Fisher exact or Wilcoxon test was used. To establish associations a univariable analysis was carried out. A multivariable model was constructed from those variables with statistically significant values defined as *p* < .05. For the analysis, we excluding depression and anxiety, due to content overlap with depressive disorder. Survival was estimated with Kaplan-Meier curves and comparisons between groups were done with the Log-Rank test. All calculations were done with Stata version 12 (StataCorp. 2011. Stata Statistical Software, TX).

**Ethical considerations**

All interventions were approved and supervised by the scientific and ethical research institutional committees. All patients approved and signed informed consent. The registry number of our Institutional Review Board (017/004/CPI) (CEI/1114/17).

**RESULTS**

One-hundred patients were included, after the interview, 24 were fulfilled the criteria for depressive disorder. Median age at the time of the interview was 56.5 years, Table 1 describes the characteristics of the population comparing whether depressive disorder was present or absent. No significant differences were seen in age, gender, marital status, scholarship, religion, previous occupation, or primary site of cancer.

Patients with DD had significantly worse performance status (KPS <70 47.6% vs 52.4%) *p* = .000, different Palliative Prognostic Index (PPI) *p* = .004, and higher intensity of symptoms mainly pain (*p* = .0004), fatigue (*p* = 0.0002), nausea (*p* = .026), drowsiness (*p*= .026), dyspnea (*p* = .002) and insomnia (*p* = .009) as seen in Table 1 and Figure 1.

Once the multivariable model was constructed, the factor associated with the presence of depressive disorder was poor performance status (KPS <70) OR 5.4 (95%CI 1.2-25.1) *p* = .026, as seen in Table 2.

Median overall survival was better in the absence of depressive disorder group 26.7 months vs. 5.2 months log-rank *p* = .0289. The probability of 1-year survival was 39% for those with depressive disorder compared to 63% in those without DD, this tendency was also seen at a 2-year period (28% vs 54%) as seen in Figure 2.

**DISCUSSION**

In a prospectively study of one-hundred palliative cancer patients seen at a palliative care unit, the presence of depressive disorder diagnosed with the gold-standard was found in 24 patients. The presence of DD was associated with a higher number and intensity of physical symptoms, a worse functional status, and as shorter survival.

To the best of our knowledge, our study is the first to report the association of depressive disorder diagnosed by a psychiatric interview (28) with sociodemographic variables, physical symptoms, functionality and its impact on survival in advanced cancer patients in a Latin-American population.

It is known that depressive disorder is frequent in palliative cancer patients seen at palliative care units, we found a 24% prevalence, higher than other reports (7-9), this was expected, for the method we used to diagnose DD, the sample size, and the population is different from previous reports.

We found no relationship between the presence of DD and age, gender, years in education, married status, religion, previous occupation and oncologic diagnosis, similar to the findings reported by Lloyd-Williams et al (2004), but different to the findings from the study done by Grotmol KS et al (2019), who found a relationship between DD and gender, age, years in education, and cancer diagnosis (13,14).

In our study we had an association between the presence of DD and a higher frequency and intensity of physical symptoms, this is ought to the intimate association of the perception of physical symptoms in depressed patients (13, 14). This perception might lead to a tougher control of physical symptoms such as pain and fatigue. In the same way, we found an association between DD and functionality, for a poor independent state (KPS <70) was the most important factor associated with the presence of DD, increasing 5.4 times its risk (OR 5.4).

Previous reports have also established that DD is associated with a shorter survival in patients with advanced cancer, with a 62% of one-year mortality (23).

An increase in the inflammatory state, in patients with advanced cancer, might be linked with the presence of depressive disorder (29); some studies have reported a close relation between inflammation and DD in advanced cancer patients, probably due to an increase in the symptom burden and a decrement in their functionality (30). This pro-inflammatory state has also been associated with a diminished response to oncologic and antidepressant treatments (31,32), and therefore with a poorer survival (30,33).

Several limitations in the present study should be described, a relatively small sample size when compared to other studies (34) should be noted, although to avoid this bias, the gold-standard test was used to diagnose DD. A referral bias should be also considered, for all patients were seen at a single cancer referral center.

The present study evidences the need to develop better strategies to identify DD in patients with advanced cancer seen at palliative care units, such as shorter interviews or self applied scales. This study will help the clinician to know the high frequency of DD and its implication in these patients, therefore making it an interesting line of research for its early diagnosis and their treatment interventions, either pharmacological or psychotherapeutic, to improve the quality of life.

**CONCLUSION**

Depressive disorder in palliative cancer patients referred for palliative care is very common, the presence of this disorder is associated with a higher burden of physical symptoms, a lower functionality and a worse prognosis. Strategies to improve the detection of depressive disorder are needed to determine if its early treatment increases the quality of life in these patients. More research is warranted in order to understand the factors associated with depressive disorder, inflammation and the survival in palliative cancer patients.

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**TABLES AND FIGURES**

Table 1. Comparison of sociodemographic and clinical characteristics of the patients with or without depression (N=100)

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Depression (n=24) | Without depression (n=76) | *p* Value |
| n | % | n | % |
| Age Median (RI) | 57.5 (50-65) |  | 55 (45.5-67) |  | 0.680 |
| Sex |  |  |  |  | 0.824 |
| Female | 17 | 24.6 | 52 | 75.4 |
| Male | 7 | 22.6 | 24 | 77.4 |
| Schooling (years) Median (RI) | 8.5 (6-10.5) |  | 9 (6-12) |  | 0.806 |
| Marital status |  |  |  |  |  |
| Married / Co-habiting | 12 | 22.6 | 41 | 77.4 | 0.736 |
| Single | 12 | 25.5 | 35 | 74.5 |
| Religious  |  |  |  |  | 0.422  |
| Without religion | 0 | 0.0 | 2 | 100.0 |
| With religion | 24 | 24.5 | 74 | 75.5 |
| Previous occupation |  |  |  |  |  |
| Self-employed | 7 | 25.0 | 21 | 75.0 | 0.846 |
| Agriculture | 1 | 25.0 | 3 | 75.0 |
| Employed | 8 | 28.6 | 20 | 71.4 |
| Student | 0 | 0.0 | 3 | 100.0 |
| Homemaker | 8 | 21.6 | 29 | 78.4 |
| Oncologic diagnosis  |  |  |  |  |  |
| Head and neck | 2 | 28.6 | 5 | 71.4 | 0.695 |
| Unknown | 0 | 0.0 | 1 | 100.0 |
| Gastrointestinal | 2 | 20.0 | 8 | 80.0 |
| Gynecological | 6 | 30.0 | 14 | 70.0 |
| Hematologic | 1 | 25.0 | 3 | 75.0 |
| Liver and bile ducts | 1 | 50.0 | 1 | 50.0 |
| Breast | 6 | 31.6 | 13 | 68.4 |
| Skin and soft tissue | 3 | 30.0 | 7 | 70.0 |
| Lung  | 1 | 12.5 | 7 | 87.5 |
| Urological | 2 | 10.5 | 17 | 89.5 |
| Karnofsky |  |  |  |  | **0.000** |
|  ≤ 70 | 10 | 47.6 | 11 | 52.4 |
|  ≥ 80 | 14 | 17.7 | 65 | 82.3 |
| PPI |  |  |  |  |  |
|  A | 13 | 17.3 | 62 | 82.7 | **0.004** |
|  B | 10 | 43.5 | 13 | 56.5 |
|  C | 1 | 50.0 | 1 | 50.0 |
| ESAS |  |  |  |  |  |
| Pain Median (RI) | 5 (0.5-8) |  | 0 (0-3) |  | **0.0004** |
| Fatigue Median (RI) | 7.5 (4.5-9) |  | 3 (0-5) |  | **0.0002** |
| Nausea Median (RI) | 0 (0-5) |  | 0 (0-0.5) |  | **0.026** |
| Drowsiness Median (RI) | 5 (0.5-8) |  | 0 (0-3.5) |  | **0.026** |
| Apetite Median (RI) | 5 (0-9.5) |  | 1.5 (0-4) |  | **0.000** |
| Well-being Median (RI) | 6 (2-8) |  | 2 (0-5) |  | **0.000** |
| Dyspnea Median (RI) | 0 (0-4.5) |  | 0 (0-0.5) |  | **0.002** |
| Insomnia Median (RI) | 0 (0-7) |  | 0 (0-3.5) |  | **0.009** |

PPI. Palliative Prognostic Index

Figure 1. Symptoms and their intensity in a group of patients with advanced cancers with and without depression



Table 2. Logistic regression that explores the risk factors associated with the presence of depression disorder (N = 100).

|  |  |  |  |
| --- | --- | --- | --- |
| Variables | OR | *p* Value | 95% confidence interval  |
| Karnofsky |  |  |  |
|  ≥ 80  | Ref. |  |  |
|  ≤ 70  | 5.430254 | **0.026** | 1.219-24.070 |
| PPI |  |  |  |
|  A | Ref. |  |  |
|  B | 0.7533244 | 0.729 | 0.152-03.729 |
|  C | 0.5378833 | 0.727 | 0.016-17.459 |
| Pain | 1.156 | 0.197 | 0.927-01.440 |
| Fatigue | 1.132697 | 0.29 | 0.899-01.426 |
| Nausea | 0.9532436 | 0.703 | 0.745-01.218 |
| Drowsiness | 1.15706 | 0.153 | 0.947-01.413 |
| Apetite | 1.039745 | 0.696 | 0.855-01.264 |
| Well-being | 1.041736 | 0.697 | 0.847-01.280 |
| Dyspnea | 1.00256 | 0.983 | 0.794-01.265 |
| Insomnia | 1.120416 | 0.273 | 0.914-1.373 |

PPI. Palliative Prognostic Index

Figure 2. Kaplan Meier curve of overall survival in patients with depressive disorder versus those who did not had depressive disorder.



**REFERENCES**

1. The International Association for Hospice and Palliative Care IAHPC. Global Consensus based palliative care definition [Internet]. 2018. Available from: https://hospicecare.com/what-we-do/projects/consensus-based-definition-of-palliative-care/definition/

2. Chochinov HM. Depression in cancer patients. Lancet Oncol. 2001 Aug;2(8):499–505.

3. Trachsel M, Irwin SA, Biller-Andorno N, Hoff P, Riese F. Palliative psychiatry for severe persistent mental illness as a new approach to psychiatry? Definition, scope, benefits, and risks. BMC Psychiatry [Internet]. 2016 Dec [cited 2018 Feb 7];16(1). Available from: http://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-016-0970-y

4. Rodríguez-Mayoral O, Reyes-Madrigal F, Allende-Pérez S, Verástegui E. Delirium in terminal cancer inpatients: short-term survival and missed diagnosis. Salud Ment. 2018 Feb;41(1):25–9.

5. Sharpe M, Strong V, Allen K, Rush R, Postma K, Tulloh A, et al. Major depression in outpatients attending a regional cancer centre: screening and unmet treatment needs. Br J Cancer. 2004 Jan 26;90(2):314–20.

6. Rodríguez-Mayoral O, Rodríguez-Ortíz B, Ascencio-Huertas L, Peña-Nieves A, Verástegui E, Allende-Pérez S, et al. Validation of the Brief Edinburgh Depression Scale (BEDS) in a Mexican population with advanced cancer in a palliative care service. Palliat Support Care. 2018 Sep 26;1–5.

7. Mitchell AJ, Meader N, Davies E, Clover K, Carter GL, Loscalzo MJ, et al. Meta-analysis of screening and case finding tools for depression in cancer: Evidence based recommendations for clinical practice on behalf of the Depression in Cancer Care consensus group. J Affect Disord. 2012 Oct;140(2):149–60.

8. Alemayehu M, Deyessa N, Medihin G, Fekadu A. A descriptive analysis of depression and pain complaints among patients with cancer in a low income country. Hashimoto K, editor. PLOS ONE. 2018 Mar 7;13(3):e0193713.

9. Chochinov HM, Wilson KG, Enns M, Lander S. Prevalence of depression in the terminally ill: effects of diagnostic criteria and symptom threshold judgments. Am J Psychiatry. 1994 Apr;151(4):537–40.

10. Wagner FA, González-Forteza C, Sánchez-García S, García-Peña C, Gallo JJ. (2012). Enfocando la depresión como problema de salud pública en México. Salud Mental, 35(1), 3–11. Salud Ment. 2012;35(1):3–11.

11. Rhondali W, Perceau E, Berthiller J, Saltel P, Trillet-Lenoir V, Tredan O, et al. Frequency of depression among oncology outpatients and association with other symptoms. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2012 Nov;20(11):2795–802.

12. Grotmol KS, Lie HC, Hjermstad MJ, Aass N, Currow D, Kaasa S, et al. Depression—A Major Contributor to Poor Quality of Life in Patients With Advanced Cancer. J Pain Symptom Manage. 2017 Dec;54(6):889–97.

13. Lloyd-Williams M, Dennis M, Taylor F. A prospective study to determine the association between physical symptoms and depression in patients with advanced cancer. Palliat Med. 2004 Sep;18(6):558–63.

14. Grotmol KS, Lie HC, Loge JH, Aass N, Haugen DF, Stone PC, et al. Patients with advanced cancer and depression report a significantly higher symptom burden than non-depressed patients. Palliat Support Care. 2019 Apr;17(2):143–9.

15. Arrieta Ó, Angulo LP, Núñez-Valencia C, Dorantes-Gallareta Y, Macedo EO, Martínez-López D, 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 Jun;20(6):1941–8.

16. Breitbart W, Rosenfeld B, Pessin H, Kaim M, Funesti-Esch J, Galietta M, et al. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA. 2000 Dec 13;284(22):2907–11.

17. Rodríguez-Mayoral O, Ascencio-Huertas L, Verástegui E, Delgado-Guay MO, Allende-Pérez S, Servicio de Cuidados Paliativos, Instituto Nacional de Cancerología, Ciudad de México, México., et al. The desire to hasten death in advanced cancer patients at a Mexican palliative care service. Salud Ment. 2019 Jul 13;42(3):103–9.

18. Wilson KG, Chochinov HM, Skirko MG, Allard P, Chary S, Gagnon PR, et al. Depression and anxiety disorders in palliative cancer care. J Pain Symptom Manage. 2007 Feb;33(2):118–29.

19. Ballard ED, Pao M, Henderson D, Lee LM, Bostwick JM, Rosenstein DL. Suicide in the medical setting. Jt Comm J Qual Patient Saf. 2008 Aug;34(8):474–81.

20. Zhong B-L, Li S-H, Lv S-Y, Tian S-L, Liu Z-D, Li X-B, et al. Suicidal ideation among Chinese cancer inpatients of general hospitals: prevalence and correlates. Oncotarget. 2017 Apr 11;8(15):25141–50.

21. Rodríguez-Mayoral O, Pérez-Esparza R, Domínguez-Ocadio G, Allende-Pérez S. Ketamine as augmentation for the treatment of major depression and suicidal risk in advanced cancer: Case report. Palliat Support Care. 2019 Aug 9;1–3.

22. Wilson KG, Dalgleish TL, Chochinov HM, Chary S, Gagnon PR, Macmillan K, et al. Mental disorders and the desire for death in patients receiving palliative care for cancer. BMJ Support Palliat Care. 2016 Jun;6(2):170–7.

23. 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 Feb;113(1–2):127–32.

24. Lin P-H, Liu J-M, Hsu R-J, Chuang H-C, Chang S-W, Pang S-T, et al. Depression Negatively Impacts Survival of Patients with Metastatic Prostate Cancer. Int J Environ Res Public Health. 2018 Sep 29;15(10):2148.

25. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer. 1980 Apr 15;45(8):2220–4.

26. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991;7(2):6–9.

27. American Psychiatric Association. Manual diagnóstico y estadístico de los trastornos mentales - DSM 5. Buenos Aires: Médica Panamericana; 2014.

28. Irving G, Lloyd-Williams M. Depression in advanced cancer. Eur J Oncol Nurs. 2010 Dec;14(5):395–9.

29. Howren MB, Lamkin DM, Suls J. Associations of Depression With C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis: Psychosom Med. 2009 Feb;71(2):171–86.

30. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. Biol Psychiatry. 2003 Aug;54(3):283–94.

31. McFarland DC, Shaffer K, Breitbart W, Rosenfeld B, Miller AH. C‐reactive protein and its association with depression in patients receiving treatment for metastatic lung cancer. Cancer. 2019 Mar;125(5):779–87.

32. Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An Inflammatory Biomarker as a Differential Predictor of Outcome of Depression Treatment With Escitalopram and Nortriptyline. Am J Psychiatry. 2014 Dec;171(12):1278–86.

33. Jacobs JM, Traeger L, Eusebio J, Simon NM, Sequist LV, Greer JA, et al. Depression, inflammation, and epidermal growth factor receptor (EGFR) status in metastatic non-small cell lung cancer: A pilot study. J Psychosom Res. 2017 Aug;99:28–33.

34. Davis MP, Hui D. Quality of life in palliative care. Expert Rev Qual Life Cancer Care. 2017 Nov 2;2(6):293–302.