Global Journal of Medical Research: K
Interdisciplinary
Volume 23 Issue 2 Version 1.0 Year 2023
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Prospective Cohort Study of Death Related to Opioid use in Older Patients with a Diagnosis of Cancer

By Hugo Moura de Albuquerque Melo, Jurema Telles de Oliveira Lima, Flávia Augusta de Orange, Maria Julia Gonçalves de Mello, Mirella Rebello Bezerra, Fabrício Oliveira Souto & José Luiz de Lima FIlho

Federal University of Pernambuco

Abstract- *Context:* Opioids use in older adults with cancer is growing, as do world population over 60 years of age.

Objectives: This study aimed to evaluate the association between the use of opioids and death in older patients with a cancer diagnosis.

Methods: We performed the analysis in a prospective cohort study with an internal comparison group. Statistical modeling considered clinical and laboratory variables. The cohort included 747 patients. Of these, 59 patients were using opioids, and they were selected to form the exposed group. Of the remaining 688, 59 were randomized to compose the group not exposed to opioids.

Keywords: *analgesics, opioid; fatal outcome; neoplasms, geriatric assessment.*

GJMR-K Classification: *DDC Code: 616.994061 LCC Code: RC262*

Strictly as per the compliance and regulations of:

A Prospective Cohort Study of Death Related to Opioid use in Older Patients with a Diagnosis of Cancer

Death Related to Opioid use in Older Patients with Cancer

Hugo Moura de Albuquerque Melo [α], Jurema Telles de Oliveira Lima [σ], Flávia Augusta de Orange [ρ], Maria Julia Gonçalves de Mello [ω], Mirella Rebello Bezerra [¥], Fabrício Oliveira Souto [§] & José Luiz de Lima FIlho [χ]

Abstract- ***Context:*** Opioids use in older adults with cancer is growing, as do world population over 60 years of age.

Objectives: This study aimed to evaluate the association between the use of opioids and death in older patients with a cancer diagnosis.

Methods: We performed the analysis in a prospective cohort study with an internal comparison group. Statistical modeling considered clinical and laboratory variables. The cohort included 747 patients. Of these, 59 patients were using opioids, and they were selected to form the exposed group. Of the remaining 688, 59 were randomized to compose the group not exposed to opioids.

Results: Opioid users were three times more likely to die and had a 3.69-fold greater chance of infection than those who did not use opioids. A normal score on the Mini Nutritional Assessment Short-Form reduced the chance of death by 73%, while a normal score on the overall standard Mini Nutrition Assessment score reduced the odds of death by 81%. The proposed statistical model reflects the high specificity of the correlation between death and opioid use.

Conclusion: In the group of older adults with cancer investigated, it can be inferred that there is evidence of association between clinical data, such as comorbidities and malnutrition, and mortality. This outcome was also reported when opioid use was associated with this population.

Keywords: analgesics, opioid; fatal outcome; neoplasms, geriatric assessment.

Corresponding Author α: Laboratório de Imunopatologia Keizo Asami, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil, NAI-Núcleo de Atenção ao Idoso, Federal University of Pernambuco Jornalista Aníbal Fernandes Ave., CDU, Recife-PE, Brazil.
e-mail: hugo.amelo@ufpe.br
Author § χ: Laboratório de Imunopatologia Keizo Asami, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.
Author σ ρ ω ¥: Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Pernambuco, Brazil.
Author α: Hospital das Clínicas da Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil.

I. Introduction

The world population over 60 years of age grows at a rate of 3% a year, being projected 1.4 billion by 2030 and 2.1 billion by 2050 and could reach 3.1 billion by 2100 [1]. These predictions in developing countries, such as Brazil, are occurring more intensely than in developed societies [2]. Aging must be seen, therefore, as one of the significant challenges of contemporary public health [3], and the management of the related complexity represents an increasingly common problem [4,5].

Age advancement is associated with a progressive decline in the functional reserve of multiple systems and a higher incidence of chronic-degenerative diseases, such as cancer, with age being the most critical risk factor for its advance. Cancer occurs more in people over 65 years of age than in younger patients. It is believed that an increase of approximately 70% in the number of new cases of cancer will occur in the next two decades [6-12].

For clinical evaluation of an elderly population with cancer, a comprehensive geriatric assessment (CGA) is recommended, using different instruments, basing the choice of the type of treatment and its contraindications on the profile of the patient. Among the symptomatic therapeutic options in older people with cancer are opioids for the treatment of pain or control of dyspnea [13-16].

Despite the beneficial results of opioids, these drugs can promote adverse effects [17], such as gastrointestinal symptoms (mainly constipation and nausea), dependence, analgesic tolerance, immunosuppression, and dysfunction in the intestinal barrier, leading to greater susceptibility to infections and impact on survival. Therefore, the use of these drugs has been related to death [17-22].

The objective of this study was to evaluate the association between the use of opioids and death in this geriatric population using statistical modeling, considering clinical and laboratory variables.

II. Materials and Methods

a) Design of the study

This was a prospective cohort study in older adults with a diagnosis of cancer, and we applied a group of internal comparisons. A total of 118 patients referred from 8 regional hospitals were included, attended from January 2015 to November 2017 at the Institute of Integral Medicine Professor Fernando Figueira (IMIP), a regional center of oncologic care.

Patients with skin cancer of the nonmetastatic basal cell or squamous cell carcinoma type and those who had undergone previous surgical treatment were excluded from follow-up. Patients were divided into two groups: exposed or not exposed to the use of opioids. Fifty-nine patients were exposed to opioid use, and the second group, nonexposed to opioid use, was composed of 59 patients.

This study was approved for execution by the Committee of Health Ethics of the Federal University of Pernambuco (CAEE: 00317118.4.0000.5208). The research was performed in accordance with relevant guidelines/regulations, and the informed consent was obtained from all participants.

b) Data collection

Data were collected according to the routine established at the Outpatient Clinic of Oncogeriatrics. After we evaluated their eligibility criteria and they signed the consent form, the patients were assessed by a multidisciplinary team consisting of a geriatrician, oncologist, nurse, physiotherapist, speech therapist, occupational therapist and physical educator. Sociodemographic, laboratory and clinical data were collected. According to the follow-up protocol, each participant was contacted by the team at least once a month during the follow-up period until the occurrence of death.

c) Variables analyzed

Exposure to opioids was defined as the recorded use of these drugs continuously since the first consultation in the outpatient clinic.

Death was defined as mortality occurred within any period after the date of entry into the study.

The demographic data selected were age gender, skin color, family status, schooling; smoking and use of alcohol.

Healthcare-associated infection was defined as any notification of an event with infectious characteristics, whether in an outpatient clinic or in a hospital environment, confirmed by laboratory tests and clinical history of the disease in the medical record.

Laboratory markers assessed were hemoglobin (12 to 17.4 g/dL), leukocytes (3.400 to 9.600 cells/mcL), and platelets (140,000 to 400,000/μL), which were considered abnormal when they were higher or lower than the normal ranges (in parentheses).

Tumor data included the primary topography (prostate, digestive system, breast, female gynecological system, urinary system, lung, and others) and metastatic disease (present or absent metastasis).

In the CGA performed for this study, the Charlson Comorbidity Index (CCI), the Karnofsky Performance Scale (KPS), the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS-15), the Mini-Nutrition Assessment Short Form (MNA-SF) and the Mini-Nutritional Assessment (MNA) were used[23-30].

The changes in these instruments were analyzed as risk factors for the primary outcome, death. Data were considered in terms of normal or abnormal scores. Abnormal scores of the instruments were defined as CCI$\geq$ 2, KPS $\leq$ 50, GDS $\geq$ 5, MMSE $<$18 with no schooling and $<$24 with schooling, MNA-SF $<$12, and MNA$<$24. Patients with abnormal MNA-SF ($<$ 12) were submitted in a complementary way to the global MNA. The MNA score was stratified into patients at risk of malnutrition and malnourished (score $\leq$ 23.5) and those without nutritional risk ($\geq$ 24); patients with normal MNA-SF ($\geq$ 12) were considered as without nutritional risk.

d) Statistical analysis

To perform the bivariate analysis, the Pearson nonparametric chi-square test was used. The observed frequencies were obtained directly from the sample data, while the expected frequencies were calculated from these frequencies. The data were analyzed in the software R, version 3.5.0.

Considering death as the primary outcome and to find a function that could explain this variable response based on the other explanatory variables together, a model that is a particular case of generalized linear models has been proposed [31].

Duplication of information was withdrawn at data entry, and then we observed which variables directly affected the death/nondeath of the patient. Initially, all variables were included, and those that were not significant were removed one by one (according to which contributed least). After adjusting the model, it was necessary to observe if there were any flaws in its fit. For this, the diagnosis and residues of the proposed model were analyzed, and the quality (goodness) of the adjustment was analyzed to infer the predictive power of the model.

Once the proposed model was validated, its interpretation was based on the odds ratio function. This model was able to define the probability of death of the patients. Statistical modeling is used in predictive and explanatory studies in health research. When the dependent variable is binary (identifying whether an event occurs), the explanatory model includes a set of variables associated with a probability of event

occurrence (either as factors or as markers of protection or risk) [32].

Linear statistical modeling has become an essential tool in predictive and explanatory studies because of its ease of interpretation. In the formal structure of a linear model, each variable is multiplied by a coefficient, which, when standardized, directly measures the relative importance of the variable it accompanies [33].

For this study, it was considered that the dependent variable assumed only two values, 0 for nondeath and 1 for death, making this a Bernoulli variable [31]. It is also known that a repetition of 'successes' and 'failures' provides that Y (observation of the response-death variable) assumes a binomial distribution.

The model initially proposed is given by:

$$\log\left(\frac{\pi(\mathrm{X})}{1-\pi(\mathrm{X})}\right) = \eta,$$

in which:

X is the matrix of the values assumed by the explanatory variables; and

$\pi(\mathrm{x})$ is the probability that the patient will die due to the explanatory variables.

We can also write the model as follows:

$$\eta = \beta_0 + \beta_1 \mathrm{Opioid} + \beta_2 \mathrm{Infection} + \beta_3 \mathrm{Hemoglobin} + \beta_4 \mathrm{Leukocytes} + \beta_5 \mathrm{MNA\ Triage\ SF} + \beta_6 \mathrm{MNA\ Global\ Score}$$

III. Results

Table 1 presents the classification, operational definition, and categorization of sociodemographic and clinical-laboratory variables of the patients who used opioids and those who did not. Age, skin color and leukocyte count were significantly different between groups.

Looking at variables related to the tumor, Table 2 shows that approximately 40% of those who did not use opioids and 35% of those who used opioids had a tumor of the female genital tract. Moreover, approximately 91% of those who did not use opioids and 32% of those who used opioids had tumors in the process of metastasis. It was also observed that both the topography distribution of the tumors and the absence or presence of metastasis were significantly different between the groups that did not use opioids and those that used opioids.

Table 3 presents the classification, operational definition, and categorization of the variables related to the CGA. Similar behavior was observed between the two groups in the predominance of the CCI for the absence of comorbidities. The Charlson Index also showed that approximately 37% of patients using opioids had a high rate of comorbidities, compared to approximately 12% of those who did not use them, with a significant difference. In the evaluation of pain, approximately 47% of those who did not use opioids reported that they did not feel pain, and a similar percentage of patients who used opioids felt much pain, so the distribution of reported pain was significantly different between groups. According to the score of the MNA-SF, approximately 56% of users of opioids were malnourished, which was significantly higher than the nonuse group by the chi-square test. In the global score of the MNA, approximately 50% of those who did not use opioids and of those who did were classified as malnourished.

After that, we tabulated (Table 4) the classification, operational definition, and categorization of death by group. According to Table 4, approximately 75% of the opioid group died (p=0,0214), and 70% of deaths occurred within 180 days after the date of entry into the study. Among opioid users who died, the following tumor distributions were observed: gastrointestinal tract (36%), lung (25%), followed by others (16%), prostate (9%), female genital tract (7%), urinary system (4%) and breast (3%).

Table 5 presents the odds ratios of the variables in the model, along with their respective p-values and their standard errors. According to Table 5, the variables were statistically significant for the proposed model. It can be noted, as well, that users of opioids were three times more likely to die than those who did not use opioids; those who had an infection had 3.69 times the chance of dying of those who did not; those with abnormal leukocytes were 14 times as likely to die compared to those with normal leukocytes; and normal hemoglobin reduced by 67% the chance of death.

A normal score on the short form of the MNA reduced the chance of death by 73%, while a normal score on the global MNA reduced the odds of death by 81%. Based on these data, all variables were tested, and we selected those that allowed us to calculate the probability that a patient who used opioids died. This probability is given by:

$$\pi = \frac{e^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4}}{1+\ e^{\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4}}$$

$$\pi = \frac{e^{-2,8860\ +1,1268\ +1,3068+2,6531}}{1+\ e^{-2,8860\ +1,1268\ +1,3068\ +2,6531}} = \ 0{,}9003$$

Figure 1A shows the envelope graph, showing that the assumption that the response variable (death) assumed a binomial distribution was valid; that is, the frequency distribution of the data was adequate for the probability distribution.

The residues of Pearson were compared against the observations, that is, how well the observation was predicted by the model. There was a

random behavior of the residues, which confirmed the power of the model (Figure 1B).

Figure 1C shows the residues of the components of the deviation against the observations. It was observed that these residues also presented random behavior around zero and were concentrated within the limit of the specification, corroborating the validation of the proposed model. After performing the statistical analysis of the diagnosis, the predictive power of the model was assayed in the form of the area below the ROC curve.

According to Figure 1D, the area below the curve represented 85% coverage, reflecting the high specificity between death and use of opioids in the studied group under this model.

IV. Discussion

In this study, from a population of 748 patients from an outpatient clinic of oncogeriatrics, 118 were studied (59 exposed to the use of opioids and 59 nonexposed randomized patients) by comparing sociodemographic, laboratory, and clinical data to analyze the chance of death, with the use of opioids as an independent predictive factor influencing this outcome.

Among the sociodemographic variables, age and skin color reached statistical significance, as did leukometry in the laboratory analysis. The topography of the tumor and the existence of metastasis also yielded significant results in the analysis between the groups. It was interesting to note that among the nonopioid-exposed group, there was a higher frequency of older people, healthcare-associated infection, potentially more aggressive tumors, such as gastric and pulmonary tumors, and more patients with metastasis. These characteristics would be expected to be found more frequently in the group of opioid users, which in this study was the group that had the highest death rate, and that would supposed to be more fragile.

On the other hand, the CCI, the KPS, the pain variable of the QLQ-30, and the results of the MNA-SF were shown to be independent factors in the analysis between the groups of users and nonusers of opioids, suggesting a higher frequency with a statistical difference to the opioid group.

In studies conducted in older populations with cancer, in which a CGA was used, there was a positive correlation with mortality, in association with the presence of comorbidity and nutritional risk, as identified in our study. These data were reported in a systematic review by Yourman et al., which confirmed the association of comorbidities, with mortality in 6 to 12 months [34-37].

The CCI, used in our study, considers diagnoses and the severity of the clinical condition to reach a prognostic score for the patient. Due to the relevance of its results in association with unfavorable outcomes, such as mortality, its use in the older population with cancer is considered necessary because of the predictive power for the risk of death and, along with that, an indirect impact on the therapeutic decision [23; 38-41].

When discussing the evaluation of nutritional status, however, there are several descriptions of the association between the worst prognosis and mortality in research in older adults with cancer. When investigating a population older than 70 years with tumors in several sites, Soubeyran et al. found a three-fold greater chance of dying, as well as a low score in MNA, in its studied population, data compatible with those found in our sample. Martucci et al. corroborated the MNA-SF as a predictor of mortality in older adults with cancer, as suggested in our population [36, 37; 42-48].

In a retrospective cohort of 468 patients conducted by Edwards et al., there was a correlation of the KPS as a predictor of overall survival in older patients with cancer, as was also evidenced by Yourman et al., in line with the data we found. There is evidence, as well, that pain in older adults with cancer, when it interferes with routine and quality of life, is seen as arisk factor for mortality. It thus seems that there is a basis for the association between the prediction of mortality and the geriatric evaluations analyzed [36, 49]. However, in the search for the association between the outcome of death and the use of opioids, there is still discordant information [50, 51]. In the present study, we found three times the chance of death in opioid users compared to those who did not use opioids. It was noticed, with the construction of a statistical model, that there was a high association between death as the primary outcome and the use of opioids, reaching 85% specificity in the prediction of death, according to the analysis of the ROC curve.

In a retrospective cohort of 50.658 patients on Tennessee Medicaid, the use of opioids in patients with nononcologic pain was associated with high rates of outpatient mortality (115/10.000 patient-years among users of morphine) for causes other than overdose. This finding was corroborated by the study of Ray et al., which showed a 1.64-fold increased risk for all-cause mortality for patients on chronic therapy with an opioid compared to those who underwent analgesia with anticonvulsants or a low dose of antidepressant [52, 53].

In contrast, a retrospective study that investigated the association between survival and prescription of opioids in a total of 17.202 individuals, found that the prescription rate of opioids was 1.22 times higher among oncologic survivors than in controls without a diagnosis of cancer [50].

We discussed that there is an association reported in the scientific literature between mortality and

prognostic indicators used in CGA, such as comorbidities (CCI), performance status (KPS), and malnutrition (MNA), and between opioid use and mortality. In this context, our study is the first one of which we are aware to accurately infer in the older population with cancer that the use of an opioid is a predictor of mortality, establishing a correlation between these data unifying the associations to death in the same studied population.

Among the patients investigated, we also identified that those who had an infection had 3.69 times the chance of dying of uninfected patients among users of opioids. Cumulative studies have shown that treatment with opioids may be associated with many negative pathophysiological consequences, including respiratory depression, immunosuppression, constipation, and a loss of homeostasis and intestinal barrier, increasing the risk of sepsis [18-22, 55, 56].

Consistent with prior laboratory studies, there is a recent analysis suggesting that septic patients treated with opioids have increased mortality rates compared to those not treated with opioids (mortality within 28 days of 10.35% for patients treated with opioids versus 2.4% for those not treated, with $p < 0.001$ after adjustment for various confounding factors) [55-58].

It is known that among these patients, higher pain is correlated with lower quality of life and that pain, per se, is already associated with increased mortality. Thus, there is no benefit in avoiding opioids in the context of moderate to severe pain. In contrast, there is a high prevalence of pain in oncology patients and the older population, and abandoning the effectiveness of pain control provided by the use of opioids, without an equivalent replacement, is both inhumane and deleterious, given the very significant adverse effect of pain and stress on the progression of cancer [22; 50; 59; 60].

It is also important to note that our group of patients, with a high degree of comorbidity (high ICC), low functionality (KPS <50) and malnourished (by MNA-SF), represents a group of older adults in frail condition. In these cases, deprescription is a fundamental practice aiming to reduce polypharmacy and the side effects of drugs by expunging nonfundamental drugs. This reasoning does not necessarily exclude opioids but those drugs that, when combined, have a high risk of death [61-63].

This study has the strengths of a longitudinal cohort, in which the patients who composed the samples were referred from 8 regional centers, from Pernambuco state in Northeast Brazil, to a specialized outpatient clinic in a teaching hospital of significant size. The nonexposed group was randomized and matched to the group exposed in the analysis. An individual follow-up was performed, and changes or variations in the characteristics of the participants were controlled so that the analytical method was rigorously applied in the longitudinal interpretation of the data. The scales used in CGA are all validated and used internationally.

However, it was an exploratory study with a heterogeneous population of older patients with cancer, with several histological diagnoses. The associations found should be confirmed for specific tumor groups and in other populations. There was no control or standardization of the type of opioid or the dose, only the determination in the first consultation that the patient had taken some opioid drug continuously. In addition, the studied group had characteristics that exposed it to the depletion of immunity, such as the presence of cancer per se and older age, which already introduces a higher chance of death [18, 22, 49, 62].

V. Conclusion

In the group of older adults with cancer investigated, it can be inferred that there is evidence of association between clinical data, such as comorbidities and malnutrition, and mortality. This outcome was also reported when opioid use was associated with this population. Therefore, it is suggested the practice of responsible deprescription, in the case of older adult patients, when association between factors related to frailty (such as malnutrition and comorbidities) and polypharmacy and, always, stimulate safe prescribing, because opioids are fundamental medications for the quality-of-life of those in pain and their safe use should continue to be encouraged, when it is the best therapeutic alternative.

Funding

No funding has been received for the conduct of this study and/or preparation of this manuscript.

Conflicts of Interest

No conflicts of interest to declare.

Author Contributions

Study concepts: Hugo Moura de Albuquerque Melo, Jurema Telles de Oliveira Lima, José Luiz deLima Filho;

Study design: Hugo Moura de Albuquerque Melo, Jurema Telles de Oliveira Lima, Julia Gonçalves de Mello, Mirella Rebello Bezerra, Fabrício Oliveira Souto, José Luiz de Lima Filho;

Data acquisition: Hugo Moura de Albuquerque Melo, Jurema Telles de Oliveira Lima, Mirella Rebello Bezerra;

Data analysis and interpretation: Hugo Moura de Albuquerque Melo, Jurema Telles de Oliveira Lima, Flávia Augusta de Orange, Maria Julia Gonçalves de Mello, Mirella Rebello Bezerra, Fabrício Oliveira Souto, José Luiz de Lima Filho;

Statistical analysis: Hugo Moura de Albuquerque Melo, Fabrício Oliveira Souto, José Luiz de Lima Filho;

Manuscript editing: Hugo Moura de Albuquerque Melo, Fabrício Oliveira Souto, José Luiz de Lima Filho;

Manuscript review: Hugo Moura de Albuquerque Melo,Maria Julia Gonçalves de Mello, Mirella Rebello Bezerra, Fabrício Oliveira Souto, José Luiz de Lima Filho.

References Références Referencias

1. United Nations. Department of Economic and Social Affairs. Population Division. World population prospects: the 2017 revision, volume II: demographic profiles. New York: United Nations, 2017.
2. World Health Organization. Integrated care for older people: guidelines on community-level interventions to manage declines in intrinsic capacity. Switzerland: World Health Organization, 2017.
3. Miranda GMD, Mendes ACG, Silva ALA. O envelhecimento populacional brasileiro: desafios e consequências sociais atuais e futuras. Rev BrasilGeriatrGeront 2016; 19(3): 507-519. https://doi.org/10.1590/1809-98232016019.150140.
4. Cohen, AA. Complex systems dynamics in aging: new evidence, continuing questions. Biogerontology 2016; 17(1): 205-220. https://doi.org/10.1007/s10522-015-9584-x.
5. Vallet-Regí M, Manzano M, Rodriguez-Mañas L, Checa LM, Aapro M, Balducci L. Management of Cancer in the Older Age Person: An Approach to Complex Medical Decisions. Oncologist 2017; 22(3). https://doi.org/10.1634/theoncologist.2016-0276.
6. Falandry C, Bonnefoy M, Freyer G, Gilson E. Biology of cancer and aging: a complex association with cellular senescence. J Clinic Oncol 2014; 32(24): 2604-2610. https://doi.org/10.1200/JCO.2014.55.1432.
7. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley J. Age and cancer risk: a potentially modifiable relationship. American J Preventive Med 2014; 46(3): 7-15. https://doi.org/10.1016/j.amepre.2013.10.029.
8. Hazeldine J, Lord JM. Innate immunosenescence: underlying mechanisms and clinical relevance. Biogerontology 2015; 16(2): 187-201. https://doi.org/10.1007/s10522-014-9514-3.
9. Tremblay D, Charlebois K, Terret C, Joannette S, Latreille J. Integrated oncogeriatric approach: a systematic review of the literature using concept analysis. BMJ Open 2012; 2(6): e001483. https://doi.org/10.1136/bmjopen-2012-001483.
10. Pedersen JK, Engholm G, Skytthe A, Christensen K, Academy of Geriatric Cancer Research. Cancer and aging: epidemiology and methodological challenges. Acta Oncol 2016; 55: 7-12. https://doi.org/10.3109/0284186X.2015.1114670.
11. Kowdley GC, Merchant N, Richardson JP, Somerville J, Gorospe M, Cunningham SC. Cancer surgery in the elderly. The Sci World J 2012; 2012. https://doi.org/10.1100/2012/303852.
12. Global Burden Of Disease Cancer Collaboration, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncology 2017; 3(4): 524-548. https://doi.org/10.1001/jamaoncol.2016.5688.
13. Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older 102 cancer patients: an update on SIOG recommendations. Ann of Oncol 2015; 26(2): 288-300. https://doi.org/10.1093/annonc/mdu210.
14. Kenis C, Wildiers H. (Org.). Practice guideline: Comprehensive Geriatric Assessment (CGA) in oncological patients. SIOG [Internet]. 2011 [acessed 20 oct 2018]. Available in: http://siog.org/files/public/cga_practice_guideline_wildiers_jul2011.pdf.
15. National Cancer Comprehensive Network (NCCN). Older adult oncology: version 2.2017. [S.l.]: NCCN, 2017.
16. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician 2008; 11: 133-53.
17. Roy S, Ninlovic J, Banerjee S, Chaborneau RG, Das S, Dutta R, et al. Opioid drug abuse and modulation of immune function: consequences in the susceptibility to opportunistic infections. J. Neuroimmune 2011; 6(4): 442-65. https://doi.org/10.1007/s11481-011-9292-5.
18. Brack A, Rittner HL, Stein C. Immunosuppressive effects os opioids-clinical relevance. J. Neuroimmune Pharmacol 2011; 6(4): 490-502. https://doi.org/10.1007/s11481-011-9290-7.
19. Ma J, Wang J, Wan J. Morphine disrupts interleukin-23 (IL-23) /IL-17 – mediated pulmonary mucosal host defense against Streptococcus pneumoniae infection. Infect Immun 2010; 78(2): 830-7. https://doi.org/10.1128/IAI.00914-09.
20. Gregorian RSJ, Gasik A, Kwong WJ, Voeller S, Kavanagh S. Importance of side effects in opioid treatment: a trade-off analysis with patients and physicians. J Pain 2010; 11(11): 1095–108. https://doi.org/10.1016/j.jpain.2010.02.007.
21. Wang F, Meng J, Zhang L, Johnson T, Chen C, Roy S. Morphine induces changes in the gut microbiome and metabolome in a morphine dependence model. Sci Rep 2018; 8(1): 3596p. https://doi.org/10.1038/s41598-018-21915-8.
22. Zhang R, Meng J, Lian Q, Chen X, Bauman B, Chu H, et al. Prescription opioids are associated with higher mortality in patients diagnosed with sepsis: A

retrospective cohort study using electronic health records. PLoS ONE 2018; 13(1): e0190362. https://doi.org/10.1371/journal.pone.0190362.
23. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40(5): 373-83.
24. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, editor. Evaluation of chemotherapeutic agents. New York: Columbia University Press 1948: 191-205.
25. Folstein MF, Folstein SE, McHugh PR. A Practical Method for Grading the Cognitive State of Patients for the Clinician. J Psychiatr Res 1975;12(3):189-98.
26. Lourenço RA, Veras RP. Mini-Exame do Estado Mental: características psicométricas em idosos ambulatoriais. Rev Sau Pub 2006; 40(4): 712-719. https://doi.org/10.1590/S0034-89102006000500023.
27. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982; 17(1): 37-49.
28. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the Mini Nutritional Assessment Short-Form (MNA®-SF): A practical tool for identification of nutritional status. J Nutr Health Aging 2009; 13(9): 782-788.
29. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999; 15(2): 116-22.
30. Vellas B, Villars H, Abellan G, Soto ME, Rolland Y, Guigoz Y, et al. Overview of the MNA® - Its History and Challenges. J Nutr Health Aging 2006; 10(6): 456-465.
31. Agresti A. An Introduction to Categorical Data Analysis. Wiley: Florida, 2007.
32. González-Ferrer V, González-Ferrer Y, Ramírez-Marino M. Statistical Modeling in Health Research: Purpose Drives Approach. MEDICC Review 2017; 19(2-3): 1-4.
33. Hernán MA, Robins JM. Instruments for causal inference: an epidemiologist´s dream? Epidemiol. 2006; 17(4): 360–72.
34. Wildiers H, Kenis C. "Comprehensive geriatric assessment (CGA) in older oncological patients: why and how?." J Geriatr Oncol 2012; 3(2): 174-176. https://doi.org/10.1016/j.jgo.2011.11.005.
35. Mariano C, Williams G, Deal A, Alston S, Bryant AL, Jolly T, et al. "Geriatric assessment of older adults with cancer during unplanned hospitalizations: An opportunity in disguise." The oncologist 2015; 20(7): 767-772. https://doi.org/10.1634/theoncologist.2015-0023.
36. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK, et al. "Prognostic indices for older adults: a systematic review." JAMA 2012; 307(2): 182-192. https://doi.org/10.1001/jama.2011.1966.
37. Graham E, Whitehead MA, Robinson D, O'Neill D, Langhorne P. "Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis randomizedised controlled trials." BMJ 2011; 343: d6553. https://doi.org/10.1136/bmj.d6553.
38. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. Ageing Res Rev 2011; 10(4): 430-439. https://doi.org/10.1016/j.arr.2011.03.003.
39. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47(11): 1245-51.
40. Marchena GJ, Acosta MMA, Hemmersbach MM, Conde MA, Roque CC, Hernandez RJ. The age-adjusted Charlson Comorbidity Index as an outcome predictor of patients with acute mesenteric ischemia. Ann Vasc Surg 2009; 23(4): 458-464. https://doi.org/10.1016/j.avsg.2008.10.008.
41. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014; 32(24): 2595-603. https://doi.org/ 10.1200/JCO.2013.54.8347.
42. Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, Mertens C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. J Clin Oncol 2012;30(15): 1829-1834. https://doi.org/10.1200/JCO.2011.35.7442.
43. Martucci RB, Barbosa MV, D'Almeida CA, Rodrigues VD, Bergman A, De Pinho NB, et al. Undernutrition as independent predictor of early mortality in elderly cancer patients. Nutrition 2017; 34: 65-70. https://doi.org/10.1016/j.nut.2016.09.011.
44. Blanc-Bisson C, Fonck M, Rainfray M, Soubeyran P, Bourdel-Marchasson I. Undernutrition in elderly patients with cancer: Target for diagnosis and intervention. Crit Rev Oncol Hematol2008; 67: 243-254. https://doi.org/10.1016/j.critrevonc.2008.04.005.
45. Gu W, Zhang G, Sun L, Ma Q, Cheng Y, Zhang H. Nutritional screening is strongly associated with overall survival in patients treated with targeted agents for metastatic renal cell carcinoma. J Cachexia Sarcopenia Muscle 2015; 6(3): 222-230. https://doi.org/ 10.1002/jcsm.12025.
46. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2012; 104(5): 371-385. https://doi.org/10.1093/jnci/djr556.

47. Aapro M, Arends J, Bozzetti F, Fearon K, Grunberg SM, Herrstedt J. Early recognition of malnutrition and cachexia in the cancer patient: a position paper of a European School of Oncology Task Force. Ann Oncol 2014; 25(8): 1492-1499. https://doi.org/10.1093/annonc/mdu085.
48. Ferrat E, Paillaud E, Laurent M, Le Thuaut A, Caillet P, Tournigand C, et al. Predictors of 1-year mortality in a prospective cohort of elderly patients with cancer. J GerontolA Biol Sci Med Sci 2015; 70(9): 1148-1155. https://doi.org/ 10.1093/gerona/glv025.
49. Edwards BJ, Zhang X, Sun M, Song J, Khalil P, Karuturi MS, et al. Overall survival in older patients with cancer. BMJ Supportive & Palliative Care 2018: p 1–11. https://doi.org/10.1136/bmjspcare-2018-001516.
50. Smith D, Wilkie R, McBeth J. Pain and Mortality in Older Adults: The Influence of Pain Phenotype. Arthritis Care & Research 2018; 70(2): 236–243. https://doi.org/10.1002/acr.23268.
51. Sutradhar R, Lokku A, Barbera L. Cancer survivorship and opioid prescribing rates: population-based matched cohort study among individuals with and without a history of cancer. Cancer 2017; 123(21): 4286-93. https://doi.org/10.1002/cncr.30839.
52. Chung CP, Dupont WD, Murray KT, Hall K, Stein CM, Ray WA. Comparative out-of-hospital mortality of long-acting opioids prescribed for non-cancer pain: a retrospective cohort study. Pharmacoepidemiol Drug Saf 2018. https://doi.org/10.1002/pds.4619.
53. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic non-cancer pain. JAMA 2016; 315(22): 2115-2423. https://doi.org/10.1001/jama.2016.7789.
54. Oderda GM, Evans RS, Lloyd J, Lipman A, Chen C, Ashburn M, et al. Cost of Opioid-Related Adverse Drug Events in Surgical Patients. J Pain and Symptom Management. 2003; 25(3): 276–83.
55. Hilburger ME, Adler MW, Truant AL, Meissler JJ Jr, Satishchandran V, Rogers TJ, et al. Morphine induces sepsis in mice. J Infect Dis 1997; 176(1): 183–8.
56. Meng J, Yu H, Ma J, Wang J, Banerjee S, Charboneau R, et al. Morphine Induces Bacterial Translocation in Mice by Compromising Intestinal Barrier Function in a TLR- Dependent Manner. PLoS One 2013; 8: e54040. https://doi.org/10.1371/journal.pone.0054040.
57. Meng J, Banerjee S, Li D, Sindberg GM, Wang F, Ma J, et al. Opioid Exacerbation of Gram-Positive Sepsis, Induced by Gut Microbial Modulation, Is Rescued by IL-17A Neutralization." Sci Report 2015; 5:e10918. https://doi.org/ 10.1038/srep10918.
58. Banerjee S, Meng J, Das S, Krishnan A, Haworth J, Charboneau R, et al. Morphine induced exacerbation of sepsis is mediated by tempering endotoxin tolerance through modulation of miR-146a. Sci. Rep 2013; 3: 1977. https://doi.org/10.1038/srep01977.
59. Chau I, Fuchs CS, Ohtsu A, Barzi A, Liepa AM, Cui ZL, et al. Association of quality of life with disease characteristics and treatment outcomes in patients with advanced gastric cancer: Exploratory analysis od RAINBOW and REGARD phase III trials. Eur J Cancer 2018; 107: 115-123. https://doi.org/10.1016/j.ejca.2018.11.013.
60. Wigmore T, Farquhar-Smith P. Opioids and cancer: friend or foe? CurrOpin Support Palliat Care 2016; 10(9): 109-118. https://doi.org/10.1097/SPC.0000000000000208.
61. Steinman MA, Landefeld CS. Overcoming Inertia to Improve Medication Use and Deprescribing. JAMA, 2018; 320(18): 1867. http://doi.org/10.1001/jama.2018.16473.
62. _.Frailty, polypharmacy, and deprescribing. Drug and Therapeutics Bulletin, 2016; 54(6): 69–72. http://doi.org/10.1136/dtb.2016.6.0408.
63. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med. 2017; 14(10): e1002396. http://doi.org/10.1371/journal.pmed.1002396.

Table 1: Classification, operational definition, and categorization of sociodemographic and clinical-laboratory variables

		Nonuse of opioids		Use of opioids		P-value
		n	%	n	%	
Age	60 - 70	12	20,34	33	55,93	0,0002
	71 - more	47	79,66	26	44,07	
Gender	Male	27	45,76	31	52,54	0,5807
	Female	32	54,24	28	47,46	
Skin Color	White	12	20,34	31	52,54	< 0,0001
	Nonwhite	47	79,66	28	47,46	

Living with a partner	With partner	22	37,29	31	52,54	0,0957
	Without partner	37	62,71	28	47,46	
Schooling	Up to 4 years	47	79,66	41	69,49	0,2046
	More than 4 years	12	20,34	18	30,51	
Smoking	Yes	2	3,39	3	5,08	1,0000
	No	57	96,61	56	94,92	
Alcohol misuse	Yes	25	42,37	34	57,63	0,1408
	No	34	57,63	25	42,37	
Healthcare-associated infection	Yes	43	72,88	32	54,24	0,0558
	No	16	27,12	27	45,76	
Hemoglobin	Normal	26	44,07	36	61,02	0,0971
	Anemia	33	55,93	23	38,98	
Leukocytes	Normal	56	94,92	42	71,19	0,0014
	Abnormal	3	5,08	17	28,81	
Platelets	Normal	51	86,44	44	74,58	0,1632
	Abnormal	8	13,56	15	25,42	

Table 2: Variables related to the tumor

		Nonuse of opioids		Use of opioids		P-value
		n	%	n	%	
Topography of the tumor (ICD 10)	Prostate	6	10,17	2	3,39	0,0053
	Gastrointestinal tract	12	20,34	6	10,17	
	Breast	2	3,39	17	28,81	
	Female genital tract	24	40,68	21	35,59	
	Urinary System	3	5,08	2	3,39	
	Lung	8	13,56	4	6,78	
	Others	4	6,78	7	11,86	
Metastasis	Absence	5	8,47	19	32,20	0,0029
	Presence	54	91,53	40	67,80	

ICD 10 – International Classification of Diseases, Version 10.

Table 3: Classification, operational definition and categorization of variables related to CGA

		Nonuse of opioids		Use of opioid		P-value
		n	%	n	%	
Charlson Comorbidity Index (CCI)	Absence	45	76,27	35	59,32	0,0028
	Low	7	11,86	2	3,39	
	High	7	11,86	22	37,29	
Karnofsky Performance Scale (KPS)	≤ 50	7	11,86	23	38,98	0,0015
	>50	52	88,14	36	61,02	
Scale of the abbreviated Geriatric Depression (GDS-15)	Normal	2	3,39	8	13,56	0,1011
	Low	41	69,49	33	55,93	
	Medium/High	16	27,12	18	30,51	
Score of the Mini Mental State Examination (MMSE)	Normal	27	45,76	27	45,76	0,8706
	Medium	20	33,90	22	37,29	
	Severe	12	20,34	10	16,95	

Assessment of pain, from the scale of quality of life (QLQ-30 of the EORTC)	No pain	26	44,07	5	8,47	< 0,0001
	Few pain	8	13,56	9	15,25	
	Moderate pain	16	27,12	19	32,20	
	Much pain	9	15,25	26	44,07	
Score of the Short Form of the Mini Nutritional Assessment (MNA-SF)	Normal	24	40,68	12	20,34	0,0027
	Risk of malnutrition	20	33,90	14	23,73	
	Malnourished	15	25,42	33	55,93	
Global score of the Mini Nutritional Assessment (MNA)	Normal	30	50,85	29	49,15	0,1069
	Risk of malnutrition	25	42,37	30	50,85	
	Malnourished	4	6,78	0	0,00	

CGA – Comprehensive Geriatric Assessment

QLQ 30 – Quality of Life Questionnaire

EORTC – European Organization for Research and Treatment of Cancer

Table 4: Classification, operational definition, and categorization of the most severe adverse event (outcome) – death.

		Nonuse of opioids		Use of opioids		p-value
		n	%	n	%	
Death	Yes	20	33,90	44	74,58	0,0214
	No	39	66,10	15	25,42	
Death within 180 days	Yes	11	55,00	31	70,45	0,3562
	No	9	15,25	13	29,55	
Death between 180 and 360 days	Yes	4	6,78	7	15,91	0,7806
	No	16	27,12	37	84,09	
Death more than 360 days	Yes	5	8,47	6	13,64	0,4476
	No	15	25,42	38	86,36	

Table 5: Estimates of the parameters and significance of the variables selected in the model to explain the probability of a patient who uses opioid to die.

Coefficients	Odds	Standard error	Pr(>|z|)
Intercepted	0,0558	1,4215	0,0423
Opioid	3,0858	0,4804	0,0190
Infection	3,6943	0,5140	0,0110
Hemoglobin	0,3243	0,5093	0,0270
Leukocytes	14,1980	1,1140	0,0172
MNA Triage SF	0,2657	0,5339	0,0131
MNA Global Score	0,1845	0,9030	0,0612

MNA – Mini Nutritional Assessment

SF – Short Form