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COVID-19 MORTALITY IN ELDERLY WITH CANCER

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ABSTRACT

The COVID-19 pandemic has been affecting the world, presenting high rates of contamination, transmission and mortality. Elderly patients, especially oncologic may report more severe cases and worst prognostics within the infection context. The aim of the present study was to conduct a systematic review regarding the COVID-19 mortality rates in elderly with cancer diagnose. Methods: a systematic review was conducted in the following databases: PubMed, Web of Science, LILACS and SciELO; the primary descriptor "*mortality*" was crossed with the secondary descriptors "*neoplasms*", "*coronavirus infection*" and "*elderly*". The search did not restricted the studies by language, publishing period or access type. Results: initially 191 articles were found with 43 presenting potential relevance for full analysis. However, only 4 studies filled the eligibility criteria. Conclusion: the COVID-19 mortality rate in elderly with cancer was mildly higher and seems to be related to the tumor disease characteristics.

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INTRODUCTION

The severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) was described for the first time at the city of Wuhan – China in December 2019. This condition became known as COVID-19 and presented fast dissemination and was considered a pandemic in April 2020 (KHAN *et al.*, 2020). This pathogen presents characteristics of fast interpersonal propagation, morbidity and fatal potential to men; and also elicit concerns towards health issues for several populations. Moreover, there seems to be a special interest in identifying the most susceptible individuals and, therefore, at more risk of aggravations, either by virulence or immune response in the context of SARS-COV-2 (NGUYEN *et al.*, 2020). The population group that caught the attention of sanitary authorities were the elderly, especially those with comorbidities, such as cancer. Besides the spectrum of neoplastic clinical manifestations, there are also those related to the several types of treatments applied (GRASSELLI *et al.*, 2020). In general, therapeutic decisions should benefit a more efficient and less invasive approach in order to reduce the risk of adverse outcomes. In a few selected cases this process may demand benefits are marginal and there are safer alternative therapeutic options available (DESIDERI *et al.*, 2020). Although immune vulnerability points seem to be particularly praised, the psychologic and social health of elderly patients should be considered, such as: abandonment and strangeness feelings, decline in communication and comprehension not only due to isolation but also because of the use of masks and facial protection, loss of autonomy and resulting dependency (FRATINO *et al.*, 2020; ZHANG *et al.*, 2020). Besides, social restrictions and shielding may lead to a significant decrease in physical activities that can also contribute or speed up the loos of muscle mass and bone density, as well as mobility and functional impairment in elderly (DESIDERI *et al.*, 2020; GRIMMER *et al.*, 2019). Thus, the pandemic scenario not only promoted behavioral changes while facing the risk of COVID-19 contamination, but also caused implications that were not initially predicted enabling a worst prognostic for the elderly population with cancer due to the immunosuppressive systemic treatment needed and by antineoplastic treatments (chemotherapy and/or surgery). Therefore, the aim of the present study was to conduct a systematic review regarding the COVID-19 mortality rates among the elderly with cancer diagnosis.

MATERIALS AND METHODS

This systematic review was carried out according to the recommendations proposed by the*checklist* from*Preferred Reporting Items for Systematic reviews and Meta-Analyse* (PRISMA), specific for observational studies (GALVÃO; PANSANI; HARRAD, 2015). The study was registered in the "International Prospective Register of Systematic Reviews" (PROSPERO) in 2020 (CRD42020213070). Studies as of 2019 were included; in any language, the reported the mortality and other aspects related to elderly with malignant neoplasia undergoing treatment by surgery, radiotherapy or systemic treatments (chemotherapy, hormonal therapies, targeting therapy or immunotherapy) that contracted the COVID-19 infection. Articles with intervention protocols; with only pharmacologic interventions; with only therapeutic interventions; and studies where the population was not being treated for cancer were excluded. Two independent reviewers conducted the search strategy in September 2020, using terms from the English language that were in accordance with the *MeSH* (*Medical Subject Headings*). The primary descriptor "*mortality*" was crossed with the secondary descriptors "*neoplasms*", "*coronavirus infection*" and "*elderly*". The search did not restricted the articles by language, publishing period or access type (free or restrict). Database consulted were: Medline (Via PubMed), *Scientific Electronic Library Online* (SciELO), Latin American & Caribbean Health Sciences Literature (LILACS – via Bireme) and*Web of Science*. Initially, duplicated studies were excluded. Titles, abstracts and descriptors/key-words of every article identified by the search strategy were evaluated independently by two reviewers. In case of conflict, a third reviewer was requested for a consensus and tiebreaker. Thus, two reviewers evaluated the full content of pre-selected articles according to the eligibility criteria adopting the same tiebreaker strategy from the previous phase. Lastly, data was extracted regarding the studies, samples, results and outcomes characteristics.

RESULTS

Database searches found 191 articles with 43 presenting potential relevance for full analysis. However, only 4 studies filled the eligibility criteria, presented in Figure 1.

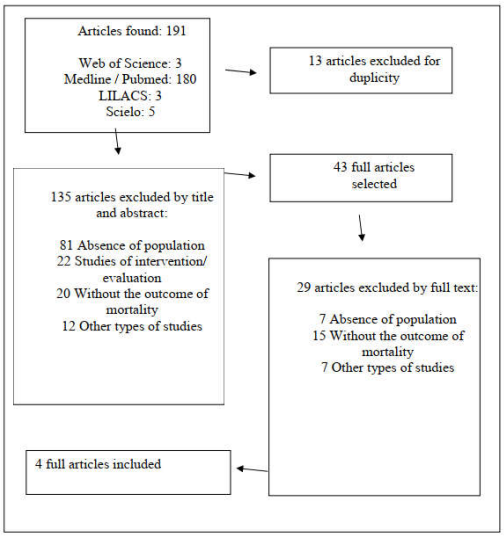

Figure 1.Fluxogramofsearchstrategy. Passo Fundo, RS, 2020

All included studies were published in 2020, in indexed periods at the Medline database and with Impact Factors ranging from 2.840 to 8.665. As for the origin, three studies were from Italy (FERRARA *et al.*, 2020; GONFIOTTI *et al.*, 2020; OMARINI *et al.*, 2020) and one from China (ASSAAD *et al.*, 2020). Overall, data from 60 elderlies were analyzed, mostly males with mean age of 68,78 years (Table1).

The outcomes addressed by the selected studies were: associated comorbidities, evaluation instruments and intervention protocols for CIVD-19, antitumor treatment and mortality (Table 2) (ASSAAD *et al.*, 2020; FERRARA *et al.*, 2020; GONFIOTTI *et al.*, 2020; OMARINI *et al.*, 2020). The description and prevalence of comorbidities, such as: diabetes, cardiovascular diseases, rheumatic diseases, among others varied between studies highlighting systemic arterial hypertension, described within three studies with a 30,23% mean (ASSAAD *et al.*, 2020; GONFIOTTI *et al.*, 2020; OMARINI *et al.*, 2020). Chronic obstructive pulmonary disease was cited in two studies (ASSAAD *et al.*, 2020; GONFIOTTI *et al.*, 2020) with values varying between them, reporting a 34,3% mean. Lastly, obesity was evaluated in two studies with 25,4% mean (ASSAAD *et al.*, 2020; OMARINI *et al.*, 2020). Pharmacological interventions applied in this oncologic patients with COVID-19 differed significantly among the studies. GONFIOTTI *et al*., 2020 reported the use of Lopinavir, Ritonavir, HCQ, MWH, and another study used chloroquine analog and tocilizumab (ASSAAD *et al*.,2020) differing from one that used only chloroquine (FERRARA *et al*., 2020). Subjects included in the Omarini *et al*. (2020) study did not referred its interventions for COVID-19. Antitumor interventions followed specific protocols related to the tumor's characteristics, two studies used pharmacological interventions (ASSAAD *et al.*, 2020; OMARINI *et al.*, 2020), one did not mention the strategy used (FERRARA *et al.*, 2020) and in the other 100% of the population was submitted to surgical interventions (GONFIOTTI *et al.*, 2020). The mortality outcome also varied significantly between studies from 14,5% to 66%, with a 35,62% mean. The study with the lowest mortality described not finding any relationship between the lethality and antitumor treatment type, however, deaths were slightly higher in the COVID-19 group (ASSAAD *et al.*, 2020). On the other hand, the study with highest mortality related its data with the tumor disease type and not with the COVID-19 infection (FERRARA *et al.*, 2020).

DISCUSSION

The initial literature search identified 191 articles and after the duplicity exclusion phase and eligibility criteria, four studies were fully investigated having a high Impact Factor and were from China and Italy. In total, 60 elderly individuals were included with mean age of 68,78 years, prevalence of males and mean mortality rate of 35,62%.

The COVID-19 spread has its origin in Asia with the first described case in China (SHEREEN *et al.*, 2020). The virus presented fast dissemination around the world and a high number of infected individuals in Italy and United States (RAFIQ; BATOOL; BAZAZ, 2020). The countries with highest contamination are compatible with que origin of the studies included in this review, three Italian (FERRARA *et al.*, 2020; GONFIOTTI *et al.*, 2020; OMARINI *et al.*, 2020) and one Chinese (ASSAAD *et al.*, 2020). All of them were selected from de Medline database via PubMed.

Regarding the number of individuals within the studies, Assaad*et al.*(2020), reported the higher number of participants when compared to others Ferrara*et al.*(2020),Gonfiotti*et al.* (2020), Omarini*et al.* (2020). Mean age was 68,78 years and the literature descriptionsfor COVID-19 patients report mean age of 65 years (XIE *et al.*, 2020); and for elderly with cancer and also infected with COVID-19 raged between 63 to 65 years (YANG *et al.*, 2020; ZHANG *et al.*, 2020).

Our findings reveal a prevalence of males, the same as described by literature with men reporting up to double rates of contamination by COVID-19 when compared to females (GRASSELLI *et al.*, 2020; WU *et al.*, 2020; XIE *et al.*, 2020). The subjects included in this review presented associated comorbidities, such as: smoking, obesity, high blood pressure and diabetes. There is evidence that the main risk factors for severe COVID-19 are: age, male gender, smoking and chronic diseases (GARIBALDI *et al.*, 2021; WU *et al.*, 2020; ZHOU *et al.*, 2020).

Regarding pharmacological therapeutic interventions for COVID-19 infection, the same were widely contrasting within the included studies. Such aspects limit the determination over the relationship of medication for handling the COVID-19 infection and the outcomes highlighted here.

prior to the SARS-COV-2 RT-PCR data collection in the elderly with COVID-19 group. On the other hand, Omarini *et al*. (2020) did not considered differences between antitumor drugs for patients in its study. Ferrara *et al*. (2020), however, included patients in any acute myeloid leukemia (AML) treatment stage, pre or post bone marrow transplant, chemotherapy or even preservation.

Table 1. Characterization of samples from selected articles (n=04). Passo Fundo/RS, 2020

Reference	Number of Subjects	Age (mean and standard deviation)	Sex
11.Assaad S, et al.	N= 40	63,8 (> 60 years)	35%♀ 65% ♂
35. Omarini, C. et al., 2020	N= 09	74 (range 65-86 years),	44,5%♀; 55,5% ♂
40. Ferrara, F. et al., 2020	N= 06	63,33 (range 60-69 years)	66,66%♀; 33,33% ♂
41. Gonfiotti, A. et al., 2020	N= 05	74.0 years(range 67–80 years)	0%♀; 100% ♂

Subtitle: mean± standard deviation; ♀ (female sex); ♂ (male sex) Source: Elaborated by the own authors.

Table 2. Characterization of selected articles and mortality protocols (n=04). Passo Fundo/RS, 2020

Reference	Covid-19 Diagnose Test	COVID-19 Intervention Protocol	Antitumor Treatment	Mortality Rate
11. Assaad S, et al.	swab nasal and pharyngeal.	None of the 302 patients received "treatment" for COVID-19 (azithromycin, chloroquine, lopinavir/ritonavir, rendesivir), but all foo the patients received COVID-19 intervention/treatment since they were a part of another trial: 1 chloroquine analog and 1 tocilizumab.	Conventional non-target directed: immunotherapy; a; Anti-proteasomes; mTOR inhibitors; Antiangiogenics and some patients did not received any pharmacological treatment	Mortality of 14,5% (8/55 patients with positive SARS-COV-2 RT-PCR results). Mortality was higher in the subgroup of patients with metastatic diseases: 24/30 (80%).
35. Omarini, C. et al., 2020	Not described.	No intervention was mentioned (COVID-19 treatment): observational study.	Anti-Immunotherapy: Monoclonal antibodies Conventional chemotherapy Radiotherapy Combined (conventional chemo + Monoclonal AB)	Mortality of 22%
40. Ferrara, F. et al., 2020	swab nasal andpharyngeal	lopinavir-ritonavir (3/10); chloroquine (5/10); tocilizumab (2/10); azithromycin (3/10).	Not described.	Mortality of 66%
41. Gonfiotti, A. et al., 2020	swab nasal andpharyngeal	● 4 patients received: ● Lopinavir (14) ● Ritonavir (14) ● HCQ (14) ● LMWH (31) ● 1 patient received: ● Lopinavir (6) ● Ritonavir (6) ● HCQ (13) ● Darunavir (7) ● Cobicistat (7) ● LMWH (59)	100% Surgery	Mortality of 40%

Source: Elaborated by the own authors.

This aspect also supports the current fragility of pharmacological treatments with consolidated evidence for handling COVID-19 (FALAVIGNA *et al.*, 2020). On the topic of antitumor therapies, the selection criteria seem to be well scientifically stablished, in opposition to the anti-COVID-19 therapies. However, those interventions consider the cancer variety, for example: if the tumors are solid or hematological besides the age, performance-status and comorbidities of people submitted to those treatments. Those aspects also became very relevant due to its influence to immune response that will impact the evolution of the COVID-19 infection (NGUYEN *et al.*, 2020). A relevant outcome from our study is that there was no difference in mortality among antitumor medicines up to 30 days

Yet, it should be considered in this study that AML is a disease with high mortality, with increased severity when combined with COVID-19 infection. Gonfioti *et al.* (2020) included only patients submitted to surgery after lung cancer without any other oncological intervention, reporting high rates of mortality (40%) for those infected with COVID-19.

Supporting this data, in a study carried out in China (TIAN *et al.*, 2020) two patients with operable lung cancer were analyzed: the first, female, 84 years old, diabetic and hypertensive and the second, male, 73 years old, hypertensive. Both underwent surgery and had no symptoms of COVID-19 at the moment of the procedure but with

symptoms of infection and positive test results at operatory evolution. As an outcome, the first patient passed away 29 days after surgery while the other patients received hospital discharge after 20 days of surgery, supporting the importance of the relationship between age, cancer and SARS-COV-2 infection. The mechanisms by which the cancer associated condition influences the COVID-19 death risk remain unknown. It is not clear if it is related to cancer patients age group, coexisting causes (health conditions and/or comorbidity), cancer staging or recently applied cancer treatment.

Among the 302 individuals included in the study the mortality rate was 8,9% (22/247) for patients with a negative result for SARS-COV-2 RT-PCR and 14,5% (8/55) for patients with a positive result for SARS-COV-2 RT-PCR. Thus, mortality was higher (80% (24/30)) in the subgroup of patients with metastatic diseases. The significant risk factor for death in univariate and multivariate analysis were male sex, Karnofsky (KPS) <60 performance status, relapse treatment and respiratory symptoms (defined as at least two out of three: fever, dry cough, dyspnea) (ASSAAD *et al.*, 2020).

In Italy, a research conducted with 1257 patients undergoing active anticancer treatment from February to March, only 9 (0,71%) were diagnosed with COVID-19. The mortality rate was 22% (2/9), both with gastrointestinal tumor. The high mortality rate suggested that all of the patients undergoing active anticancer treatment with flu symptoms should be carefully selected for COVID-19 infection (OMARINI *et al.*, 2020).

From 1 to 31 of March 2020, 10 cases of AML were diagnosed with positive-SARS-CoV-2. Five patients (50%) passed away after an average of 8 days (interval from 5 to 26). The COVID-19 infection caused na impact in the AML patients survival rate as well as in the possibility of receiving the ideal type of treatment (FERRARA *et al.*, 2020).

Five patients with lung cancer diagnose reported positive results for COVID-19 and the mortality within 30 days was of 40% (2/5). Regarding main comorbidities associated with cancer in this study, smoking was reported in 100% (5/5) of cases, followed by chronic obstructive pulmonary disease (CPOD) (3/5), peripheral obstructive arterial disease (2/5), rheumatoid arthritis (1/5), hypothyroidism (1/5), high blood pressure (1/5), alcoholism (1/5), bullous emphysema (1/5) and psoriasis (1/5). However, the authors presented that the SARS-CoV-2 infection that resulted in severe cases of COVID-19 and consequently death were not related to other contagious sources or complications (GONFIOTTI *et al.*, 2020). A study conducted in China in 2020 concluded that patients with lung cancer did not had a higher probability of developing severe events when compared to patients with others types of cancer (1/5 [20%] patients with lung cancer vs 8/13 [62%] patients with other types of cancer), still patients with cancer in general worsened more quickly than those without this condition (average time for severe event of 13 days vs 43 days, respectively) progressing to death (LIANG *et al.*, 2020).

The COVID-19 pandemic has a strong impact in healthcare systems around the world. Comprehending its aspects and outcomes in mortality in elderly patients with cancer seems to be a relevant strategy to manage this groups health properly. This groups mortality was higher when compared to general population and did not presented any relationship with the type of intervention used for tumor control or SARS-COV-2 infection, however a relationship with tumor characteristics was found. The present study had limitations due to the heterogeneity of studied populations regarding tumor characteristics and interventions as well as COVID-19 interventions. New research that includes more homogeneous populations and meta-analysis are necessary.

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