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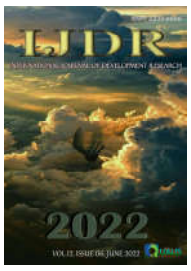

RESEARCH ARTICLE OPEN ACCESS

MORTALITY IN ONCOLOGIC PATIENTS WITH SARS-COV-2 INFECTION: A SYSTEMATICREVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: The infection with the new coronavirus, SARS-CoV-2, is responsible for the disease COVID-19, which is associated with more serious outcomes in oncologic patients, as they are more vulnerable to get the viral infection and also to develop severe cases of the disease, as they have an immune system compromised not only by the treatment but also by the tumor itself. **Objectives:** Analyze the risk factors linked to increased mortality in cancer patients with COVID-19, in addition to evaluating the mortality rate in these patients. **Methods:** This is a systematic review with meta- analysis made through the SciELO, VHL and Pubmed databases with the descriptors "COVID 19", "Coronavirus" and "Oncology", in addition to the Boolean operator "AND". Initially, 13,288 articles were found, after applying inclusion and exclusion criteria, 1,452 studies remained. Of these, the titles and abstracts of 146 were read, after which 41 works were selected for full reading, of which 20 met the criteria to be included in the review. **Results:** In total, 43,366 cases of cancer patients were analyzed, of which 4,567 died. The overall study mortality rate was 32% (I^2 = 0%); and the risk factors associated with increased mortality identified in the meta-analysis were Age > 60 years (95% CI: [1,164; 5,112]; P=0.018; I^2=0%; p=0.517); male sex (CI95%: [1,092-1,273]; P<0.001; I^2=0.0%; p=0.496), presence of Diabetes Mellitus (CI95%: [1,058-1,544]; P=0.011; I^2=0%; p=0.397) and active cancer (CI95%: [1,363-2,643]; P<0.001; I^2=0%; p=0.93). **Conclusion:** There are several risk factors associated with increased mortality in cancer patients, including advancing age, presence of comorbidities such as diabetes mellitus, active cancer and a higher stage of cancer.

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INTRODUCTION

Coronaviruses (CoVs) are part of a large family of single-stranded RNA viruses that cause numerous diseases, whose manifestations range from the common cold to more severe conditions such as severe acute respiratory syndrome (SARS). In December 2019, Chinese scientists isolated a new strain of coronavirus, which had not been previously identified in humans, in patients who had respiratory distress in the city of Wuhan, which was called SARS-CoV-2, responsible for the disease COVID-19.[1,2] Due to the high rate of infection by the virus, the World Health Organization (WHO) issued a pandemic alert in order to minimize the possible dissemination of the new coronavirus.[3] In this respect, the identification of risk factors/ comorbidities it's relevant for the outcome of COVID-19 and the importance of this in public policies or risk stratification in medical services. Since the beginning of the pandemic, neoplasms are seen as a risk factor associated with more severe outcomes in patients affected by COVID-19, since cancer patients are more vulnerable to get the SARS-CoV-2 infection and also to develop a more severe disease, because of their compromised immune system by both the treatment and the tumor itself. [4,5,6,7] It is known that when comparing cancer and non- cancer patients with

SARS-CoV-2 infection, epidemiological, clinical and prognostic differences can be observed. An example of this is the study by Ferrari BL et al 8 that observed the risk of mortality is higher in cancer patients than in the general population.[9,10,11] Is observed that there are some factors associated with worse outcomes in cancer patients with COVID-19, such as advanced age, smoking and the presence of active disease. [8] The diagnosis of SARS-CoV-2 infection can be difficult in these patients, since the signs and symptoms of COVID-19, such as fever, dyspnea, nausea, and others,are similar to those presents in cancer or antineoplastic treatment reactions.[8,12] Therefore, oncologic patients need specialized management and attention due to high mortality, and the decision on whether or not to postpone cancer treatment must be agreed with the patient, who must know the consequences of this decision on their condition.[13] The mortality rate of cancer patients with COVID-19 and the risk factors associated with it have been approached by several articles so far. In brief, this study aims to review the data found on these topics, having as the main objective evaluate the risk factors linked to increased mortality in cancer patients with SARS-CoV-2 infection and also the mortality rate in these patients.

METHODS

Research outline: This is a systematic review with meta-analysis that mainly aims to assess therisk factors associated with increased mortality in cancer patients with SARS-CoV-2 infection. In that case, the Scientific Electronic Library Online (SciELO), Virtual Health Library (BVS) and Medical Literature Analysis and Retrieval System Online (Medline/ PubMed) databases were used to search for articles related to this topic. Furthermore, “COVID 19” (D1), “Coronavirus” (D2) and “Oncology” (D3) were defined as descriptors, in addition to the Boolean operator “AND” as well. Thus, to expand the number of articles as much as possible, the associations “D1” AND “D3” and “D2” and “D3” were also used.

Inclusion and Exclusion Criteria: The inclusion criteria were defined as: randomized trial and observational studies (cohort, cross-sectional and case-control) published between 2020 and 2021, with no language restrictions. Furthermore, the exclusion criteria used were: articles that did not discuss the topic or that did not present enough data to achieve the objective proposed in this study. In addition, guidelines, clinical case report and review articles were excluded.

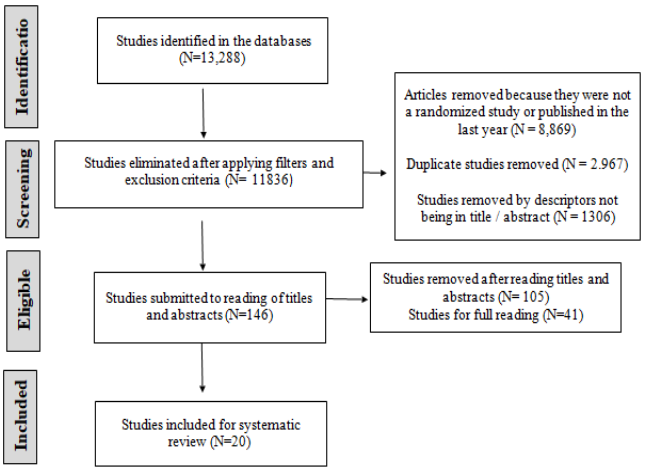
Data extraction: The selection of articles was carried out independently by two reviewers (ML and ES) to become possible to apply the Kappa index and, as a result, analyze the agreement index, and if necessary, a third elected reviewer (MP) would choose an article at the point of intersection of the previous reviewers (ML and ES), in order to remove the initial discrepancy (Table 1). When applying the Kappa index, a value of 0.6794 was obtained, which, according to Landis and Koch, is interpreted as a strong agreement as a substantial value, making it possible to proceed with the systematic review and meta-analysis.

Table 1. Kappa index

Index	Category 1*	Category 2**
Category Kappa	0.6794	0. 6794
Category Kappa Standard Error	0.0801	0.0759
95% confidence interval of category Kappa	Sup: 0. 8364 Inf: 0. 5307	Sup: 0. 8281 Inf: 0.5224

*Articles included in the study **Articles excluded in the study

Selection of studies: Initially, 13,288 articles were found in the databases. After applying the inclusion and exclusion criteria, 11,836 articles were removed, remaining 1,452. Thereafter, the descriptors were restricted to become included only in the title and/or abstract, leaving 146 studies for the reading of titles and abstracts to be carried out, in order to exclude articles that did not talk about the proposed theme. After that, 41 works were chosen for full reading. After reading, 21 articles that did not contain enough data to be able to meet the objectives of this study were excluded. As a result, 20 articles were defined to compose the database for this systematic review and meta-analysis (Figure 1).



Source: research data, 2021.

Figure 1. PRISMA diagram flow of the study

Included articles: In Table 2, it is possible to analyze the studies included for analysis in this systematic review and meta-analysis. It is noteworthy that only two journals (10%), of which the studies were published, have an impact factor of less than 1.0.

Statistical Analysis: We used R Core Team 2021 (4.1.0) for all analysis and we adopted 5%confidence interval. We used mortality rate as analyzed measure and Adjusted Odds Ratio and Hazard Ratio for each exposure factor were the risk measures analyzed, beyond your confidence intervals. The natural logarithms of risk measures and their confidence interval, the method of DerSimonian and Laird as random effects model andthe Mantel-Haenszel model for estimating heterogeneity. Heterogeneity was considered important when the I^2 was greater than 50%, indicating the use of random effects models instead of fixed effects. If necessary, the sensitivity analysis was done byremoving the studies one by one to investigate the source of the divergence. The publication bias evaluation was made with a funnel scatter plots and linear regression test.

RESULTS

In total, 43,366 cases of oncologic patients were analyzed, of which 21,492 weremale and 21,376 were female. Regarding the number of deaths, there were 4,567 cases. Initially, the global mortality rate in this study was 29%, however it was observed an important heterogeneity, with I^2 = 99%. In that case the sensitivity analysis was performed removing studies to investigate the origin of the divergence, consequently it was necessary to remove 8 studies [16,18,20,25,28,30,32,34]. After that, a global mortality rate of 32% was reached [CI= 31%; 34%], showing a low percentage of heterogeneity with I^2 =0% (Table 3). Through Table 4, it is possible to analyze that only the study by Álvarez MAL et al[15] presented a high mortality rate when compared to the global rate, which was 42% [CI= 26%; 59%]. While Smith M et al[33] found a lower mortality rate when compared to the global one, of 28% [CI= 19%; 39%]. When evaluating the risk factors associated with increased mortality in cancer patients with COVID-19, shows that Age > 60 years increased the risk of mortality by 2.4 times (CI95%: [1,164; 5,112]; P=0.018; I^2=0%; p=0.517); male sex (CI95%: [1.092-1,273]; P<0.001; I^2=0.0%; p=0.496) and presence of Diabetes Mellitus (CI95%: [1.058-1.544]; P=0.011; I^2=0%; p=0.397) by about 1.2 times.

Table 2. Characteristics of the studies selected for review.

Article	Journal	Tipe of study	Local of study
Álvarez MAL *et al*	Medicina Clínica (English Edition) FI: 1.635	Observational	Madrid
Assaad S *et al*	European Journal of Cancer FI: 7.275	Retrospective	France
Elkrief A *et al*	European Journal of Cancer FI: 7.275	Multicentric cohort	Canada
Ferrari BL *et al*	JCO Global Oncology FI: 32.956	Multicentric cohort	Brazil
Fu C *et al*	Journal of the American Chemical Society FI: 15.419	Control-case	New York
Galindo RJSC *et al*	Revista Brasileira de Saúde Materno	Transversal cohort	Pernambuco
Garassino MC *et al*	The Lancet Oncology FI: 41.316	Internacional cohort	Italy, France, Switzerland, China, Netherlands, UK, Spain, USA
García-Suárez JG *et al*	Journal of Hematology & Oncology FI: 2.832	Multicentric	Madrid
Guarneri V *et al*	European Journal of Cancer FI: 7.275	Observational	Italy
Joode K *et al*	European Journal of Cancer FI: 7.275	Nacional cohort	Netherlands
Li H *et al*	BMJ Health & Care Informatics FI: 1,4 Retrospective	UK	
Martin S *et al*	The oncologist FI: 5.025	Retrospective	France
Nakamura S *et al*	International Journal of Clinical Oncology FI: 2.743	Retrospective unicêntrico	Tokyo
Oliveira LC *et al*	Support Care Cancer FI: 2.635	Retrospective cohort	Rio de Janeiro
Provencio M *et al*	Lung Cancer FI: 4.702	Prospective	Spain
Ramaswamy A *et al*	Cancer Medicine FI: 3.362	Cohort	Mumbai
Segura PP *et al*	Medicina Clínica FI: 0.787	Observacional	Spain
Sharafeldin N *et al*	Journal of Clinical Oncology FI:32.956 Coorte multicêntrico	USA	USA
Smith M *et al*	Gynecologic oncology FI: 4.540	Retrospectivo	New York
Zhang H *et al*	Cancer FI: 5.742	Coorte multicêntrico	China

IF: impact fact. USA: United States of America. UK: United Kingdom. **Source:** research data, 2021.

Table 3. Evaluation of the mortality rate in the studies

Study	Events	Total	Proportion 95%-CI
Álvarez MAL *et al*	15	36	0.42 [0.26; 0.59]
Assaad S *et al*	30	302	0.10 [0.07; 0.14]
Elkrief A *et al*	71	252	0.28 [0.23; 0.34]
Ferrari BL *et al*	33	198	0.17 [0.12; 0.23]
Fu C *et al*	70	233	0.30 [0.24; 0.36]
Galindo RJSC *et al*	49	68	0.72 [0.60; 0.82]
Garassino MC *et al*	66	200	0.33 [0.27; 0.40]
García-Suárez JG *et al*	227	697	0.33 [0.29; 0.36]
Guarneri V *et al*	57	170	0.34 [0.26; 0.41]
Joode K *et al*	114	351	0.32 [0.28; 0.38]
Li H *et al*	64	275	0.23 [0.18; 0.29]
Martin S *et al*	63	212	0.30 [0.24; 0.36]
Nakamura S *et al*	11	32	0.34 [0.19; 0.53]
Oliveira LC *et al*	66	83	0.80 [0.69; 0.88]

I^2 – Heterogeneity statistic. 95% CI – 95% confidence interval. τ^2 – Between-study variance. p – Cochran Q Test.95% CI – 95% confidence interval. Source: research data, 2021.

Table 4. Evaluation of the mortality rate in the studies after index sensitivity from heterogeneity of the studies

Study	Events	Total	Proportion 95%-CI
Álvarez MAL *et al*	15	36	0.42 [0.26; 0.59]
Elkrief A *et al*	71	252	0.28 [0.23; 0.34]
Fu C *et al*	70	233	0.30 [0.24; 0.36]
Garassino MC *et al*	66	200	0.33 [0.27; 0.40]
García-Suárez JG *et al*	227	697	0.33 [0.29; 0.36]
Guarneri V *et al*	57	170	0.34 [0.26; 0.41]
Joode K *et al*	114	351	0.32 [0.28; 0.38]
Martin S *et al*	63	212	0.30 [0.24; 0.36]
Nakamura S *et al*	11	32	0.34 [0.19; 0.53]
Provencio M *et al*	146	447	0.33 [0.28; 0.37]
Segura PP *et al*	258	770	0.34 [0.30; 0.37]
Smith M *et al*	25	89	0.28 [0.19; 0.39]

In addition, active cancer increased the risk of mortality by approximately 2 times (95%CI: [1.363-2.643]; P<0.001; I^2=0%; p=0.93). It is noteworthy that patients in palliative care (CI95%: [3.441-16,639]; P<0.001; p=0.172) and Cancer in the lung site (CI95%: [1.272-5.248]; P=0.009; p=0.174) presented an intermediate inconsistency (I2 = 46%), although the first one was responsible for increasing the risk of About smoking, from Table 6, it is possible to observe that it did not increase the mortality risk of cancer patients with SARS-CoV-2 infection, as it presented significant heterogeneity (I^2= 80.4%; p=0.024). Mortality by up to 7.5 times, while the second one by up to 2.5 times. Over the time that cancer patients with SARS-CoV-2 infection were observed, it was possible to analyze that Age > 65 years and advanced stage (AS) cancer were associated with a 2 times increased mortality.

When evaluating males, it was observed that this risk factor over time there was no interference in the risk of mortality, as it showed high heterogeneity (I^2= 88.7%; p= <0.001).

DISCUSSION

Cancer patients are routinely considered more vulnerable than the general population. However, there is still no consensus in the literature regarding the susceptibility of these patients to Sars-Cov-2 infection, especially due the severity and mortality in this population. This study approached some of these issues, having been able to estimate the influence of some additional risk factors on the survival of cancer patients. The overall mortality rate found in this meta-

analysis was 32%. The studies carried out by ElGohary et al[35] and Salunke et al[36] found mortality rates of 21 and 20.83%, respectively. The difference between the value found in the present study and those reported in the literature can be attributed to the sample size and, in part, to the correction performed to reduce the heterogeneity of the initial data. In this meta-analysis, age was a determining factor for mortality, since cancer patients over 60 years of age had their risk increased by 2.4 times. Although there are studies that corroborate this finding, it is an important point of debate in the literature, for example, in the meta-analysis performed by Giannakoulis et al, patients over 65 years of age with and without cancer had a similar mortality rate.

cancerpatients by 1.2 times. In the study carried out by Kaur et al[39], the relation between diabetes mellitus and mortality in cancer patients was also significant, and it was observed that even in non-cancer patients, diabetes is an important risk factor forseverity and mortality from Sars-Cov-2 infection. Regarding the presence of active cancer, it was found that the risk of mortality increased by 2.0 times. In a study carried out by Chen et al[19] using data from the Langone Medical Center at New York University, it was possible to prove, through medical records reviews and also with the aim of establishing descriptive statistics, logistic regression and quantifying the results, that patients with active cancer had probability of progressing to

Table 5. Overview of risk factors for mortality in cancer patients with COVID-19

Variables	Factor	Studies	Measure	AdjustedEstimate	95% CI
Age	Age ≥ 65	"Oliveira et al 2021 (28)"	HR	2.03	1.09–3.78
		"Sharafeldin et al 2021 (32)"	HR	1.99	1.27–3.10
	Age ≥ 60	"Ferrari et al 2021 (18)"	OR	3.1	1.1–9.7
		"Ramaswamy et al 2020 (30)"	OR	1.9	0.66–5.65
Gender	Male	"Assaad et al 2020 (16)"	HR	2.75	1.91–3.59
		"Elkrief et al 2020 (17)"	HR	1.04	0.84–1.29
		"García–Suárez et al 2020 (22)"	HR	1.13	0.85–1.51
		"Sharafeldin et al 2021 (32)"	HR	1.05	1.01–1.08
		"Fu et al 2021 (19)"	OR	1.17	1.08–1.27
		"Garassino et al 2020 (21)"	OR	1.17	0.85–1.62
		"Joode et al 2020 (24)"	OR	1.84	1.04–3.23
		"Ramaswamy et al 2020 (30)"	OR	1.12	0.47–2.68
CCI Stage	IV	"Elkrief et al 2020 (17)"	HR	2.49	1.30–4.74
		"Sharafeldin et al 2021 (32)"	HR	2.04	1.79–2.33
Smoking	Yes	"Ferrari et al 2021 (18)"	OR	3.4	1.3–8.6
		"Ramaswamy et al 2020 (30)"	OR	1.12	1.07–1.18
Treatment intent	Noncurative	"Ferrari et al 2021 (18)"	OR	20.6	4.0–378.5
		"Ramaswamy et al 2020 (30)"	OR	5.6	2.28–13.78
Diabetes Mellitus	Yes	"Fu et al 2021 (19)"	OR	1.26	1.04–1.53
		"Ramaswamy et al 2020 (30)"	OR	2.02	0.69–5.91
Active Cancer	Yes	"Fu et al 2021 (19)"	OR	1.89	1.34–2.67
		"Ramaswamy et al 2020 (30)"	OR	2.0	0.59–6.81
Lung Cancer	Yes	"Joode et al 2020 (24)"	OR	3.40	1.51–7.64
		"Martin et al 2021 (26)"	OR	1.07	0.25–4.60

Legend: HR – Hazard Ratio. OR – Odds Ratio. 95% CI – 95% confidence interval. **Fonte:** dados da pesquisa, 2021.

Table 6. Risk factors associated with increased mortality in cancer patients with COVID-19

Factors	**Studies**	N	P	I2	P	Adjusted Estimate (95% CI)
Odds Ratio Age > 60 Male	(3) (15)	428	0.018	0	0.517	2.439 (1.164 to 5.112)
Smoker	(4) (6) (9)	265	< 0.001	0	0.496	1.179 (1.092 to 1.273)
Non-curative	-15					
DM	(3) (15)	428	0.303	0.8044	0.024	1.751 (0.602 to 5.093)
A c t i v e Cancer						7.567 (3.441 to
Lung Cancer *Hazard Ratio* Age > 65	(3) (15)	428	< 0.001	0.4639	0.172	16.639)
Male	(4) (15)	463	0.011	0	0.397	1.279 (1.058 to 1.544)
	(4) (15)	463	< 0.001	0	0.93	1.898 (1.363 to 2.643)
Stage 4						
	(9) (11)	563	0.009	0.46	0.174	2.583 (1.272 to 5.248)
		38697	< 0.001	0	0.959	2.004 (1.392 to 2.884)
	(13) (17)					
	(1) (2) (7)	39865	0.084	0.8877	<0.001	1.301 (0.965 to 1.752)
	-17					
	(2) (17)	38666	< 0.001	0	0.556	2.056 (1.809 to 2.337)

DM - Diabetes Mellitus. I² - Heterogeneity. P – adjusted factor significance. p – Cochran Q Test. 95% CI – 95% confidence interval. **Source:** research data, 2021

This similarity is believed to be due to the possibility that increasing age is an independent prognostic worsening factor. Another important aspect analyzed concerns about the advanced stage of the neoplasm, resulting in an increase by 2.0 times in the risk of mortality, however, further studies are still needed to better understand this scenario38. The presence of diabetes mellitus increased the risk of mortality in

death increased by 34.3% and those with a history of cancer by 27.6%, while in patients without a history this percentage was 20%. Thus, itis concluded that patients with active oncological disease are more likely to die and it is also added that the highest mortality rate among this group is from hematological malignancy. Furthermore, it was observed that patients with lung cancer had a 2.5-fold increased

risk of mortality, the study by Lei et al[40] did not identify a significant difference between the mortality rate of patients with lung cancer and other tumor subgroups. Peravali et al[41], on the other hand, found an odds ratio of 1.62 for the mortality of these patients, having also found greater disease severity and higher rates ofhospitalization in the Intensive Care Unit. It is also noteworthy that lung cancer is associated with a greater predisposition to respiratory infections, which are also able to increase morbidity and mortality.

CONCLUSION

It was observed that there are several risk factors associated with the increased mortality of cancer patients, including advancing age, presence of comorbidities such asdiabetes mellitus, active cancer and a higher stage of neoplasia. The results obtained in this review can significantly help clinical practice, providing an evidence base on the prognosis in different profiles of cancer patients. They can also contribute to directing public health policies towards target populations in the current pandemic context.

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