





## MINI REVIEW

# Susceptibility of lung cancer patients to COVID-19: A review of the pandemic data from multiple nationalities

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## Funding information

Brazilian Ministry of Health; CAPES; CNPq; FAPERJ; Oswaldo Cruz Institute/ FIOCRUZ; Proppi/ UFF

## Abstract

Several studies have highlighted that cancer patients tend to be more susceptible to develop severe infection and to die from COVID-19. Certain medical conditions such as immunosuppression, presence of comorbidities, and underlying pulmonary damage are possible determinants of disease severity, especially in lung cancer patients. While recent studies have shown that lung cancer is one of the most prevalent tumor types among COVID-19 cancer patients, we still have an incomplete view of how data from several countries work as a whole. The aim of this review was to investigate COVID-19 prevalence in lung cancer patient cohorts and their probability to develop severe illness and death when compared to nonlung cancer patients from multiple nationalities, including countries that have been the epicenters of the pandemic. We also focus on some intrinsic lung cancer features that might influence COVID-19 outcomes. An integrative view of the susceptibility of lung cancer patients might be especially relevant to assist physicians in evaluating the risks of COVID-19 in these patients, and to foster better decisions on treatment delay.

## KEYWORDS

COVID-19, lung cancer, mortality, SARS-CoV-2, severity

## INTRODUCTION

The first cases of coronavirus disease 2019 (COVID-19) were described in late December 2019. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was defined as the etiological agent of the ongoing pandemic in March 2020 by the World Health Organization (WHO).<sup>1</sup>

Until mid-March 2021, WHO reported 120 million cases of COVID-19, including 2.6 million deaths. Some of its risk factors are shared with cancer patients, including age > 65 years old and comorbidities.<sup>1,2</sup> Notably, oncological patients present a higher risk of contracting and developing severe illness from COVID-19,<sup>3</sup> as well as higher mortality rates than noncancer patients,<sup>4,5</sup> due to their weakened

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immune system, by the malignancy itself and to oncological interventions.<sup>6</sup> The follow-up routine also impacts social isolation measures for the containment of COVID-19, increasing the risk of exposure to pathogens.<sup>7</sup> Despite that, labeling all patients with cancer as susceptible to COVID-19 is probably neither reasonable nor effective from a public health standpoint. Cancer encompasses a diverse array of primary tumor subtypes and stages, affecting a heterogeneous group of patients with diverse prognoses and outcomes.

Among all types of cancers, lung cancer patients (LCPs) are of particular interest in this pandemic because the main primary site of infection by the virus, the respiratory tract, is already compromised by the presence of the tumor.<sup>8</sup> Previous respiratory virus outbreaks<sup>9–12</sup> have shown that LCPs are more vulnerable than other cancer patients because their abnormal respiratory epithelium is probably more prone to rapid virus entry into the lungs. In fact, lung cancer (LC) is one of the most frequent types of cancer among COVID-19 cancer patients.<sup>5,13,14</sup> However, an integrative view of the worldwide data regarding the novel coronavirus infection impact on LCPs has not yet been achieved. A possible limitation of studying single cohorts lies in the fact that it may not represent the cancer population of one country as a whole; as such, we hope to increase this by analyzing several cohorts from countries with diverse numbers of cases of SARS-CoV-2 infection. The comparison between COVID-19 LCPs and NLCPs (nonlung cancer patients) described in each cohort could provide data regarding the susceptibility of LCPs to develop severe COVID-19 outcomes.

Therefore, the aim of this mini review was to gather the prevalence of COVID-19 in LCP cohorts and their probability to develop severe outcomes (intensive care unit [ICU] admission, intubation, invasive mechanical ventilation and/or deaths) when compared to NLCPs from multiple nationalities, including countries that have been the epicenters of this pandemic. We also focus on some intrinsic LC features, including molecular mechanisms and the host response to SARS-CoV-2 infection that might influence COVID-19 outcomes. It is hoped that this integrative view might assist physicians in evaluating the risks of COVID-19 in LCPs, and foster better decisions on treatment delay and/ or vaccination.

## COVID-19 LUNG CANCER PATIENTS: PREVALENCE AND OUTCOMES

There are currently 21 studies which have estimated COVID-19 prevalence and outcomes among LCPs in China,<sup>4,5,7,14–19</sup> Italy,<sup>20,21</sup> France,<sup>22</sup> Spain,<sup>23–25</sup> United Kingdom (UK),<sup>26</sup> United States of America (USA),<sup>13,27,28</sup> Iran,<sup>29</sup> and Brazil<sup>30</sup> (Figure 1 (a)). Here, we present an analysis of 2195 COVID-19 cancer patients from these countries admitted to hospitals, of which 274 were LCPs and 1921 were NLCPs (Figure 1(b)). Among COVID-19 cancer patients, LC has been the most frequently detected type of cancer (12 of 21),<sup>4,7,14–18,21,23–25,29</sup> followed by breast cancer (4 of 12)<sup>5,13,28,30</sup> and others (Table 1).

Six of the 21 studies analyzed the risk of LCPs contracting SARS-CoV-2 infection and all of them showed an

increased risk in this cohort compared to NLCPs.<sup>4,16–18,25,27</sup> Regarding COVID-19 outcomes, the Chinese cohorts have shown that LC is not associated with severe outcomes (Figure 2(a)). Despite that, LCPs from several countries showed a higher probability of death from COVID-19 than NLCPs in almost all studies,<sup>4,5,7,13–15,17–19,22–30</sup> except for one Chinese report<sup>16</sup> and one Italian report<sup>21</sup> (Figure 2(b)). LCP showed higher morbidity and lower survival than NLCPs in almost all studies analyzed (Table 2).

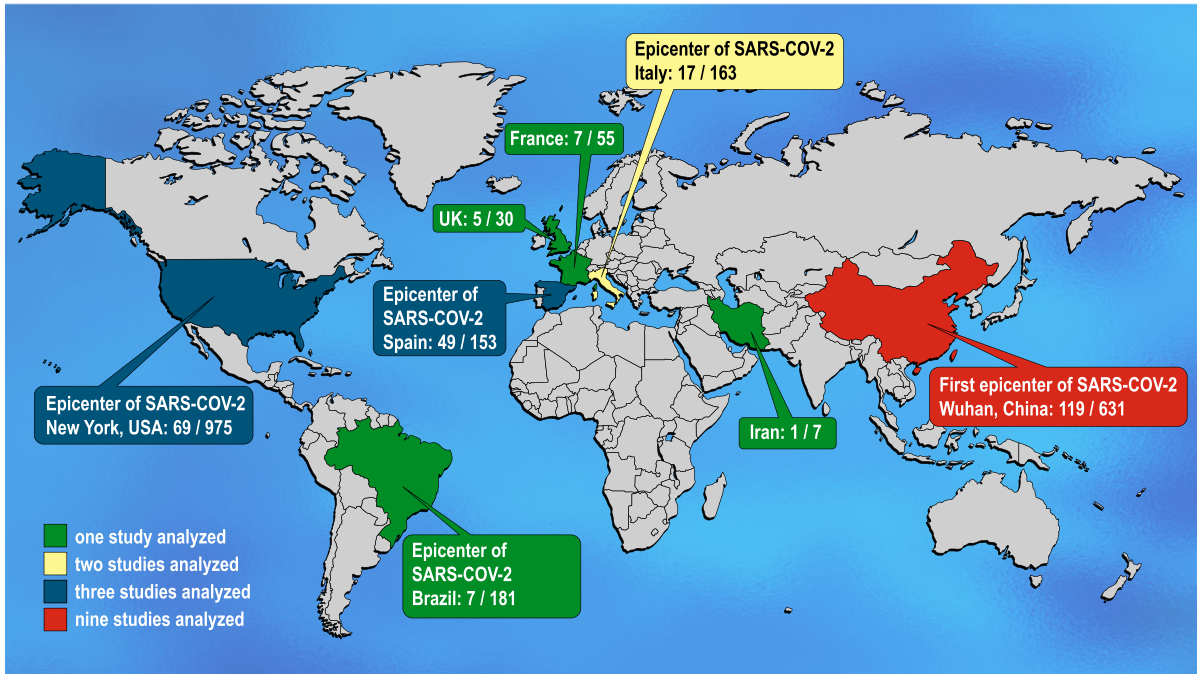
Regarding the sources of SARS-CoV-2 infection in cancer patients, only one Chinese study investigated this subject and showed that infection was greater in the community than in hospitals.<sup>7</sup>

Different types of cancer treatment and schedules might impact on the severity of COVID-19. Four Chinese studies and the one from the UK reported that patients who received some type of antitumor treatment presented worse COVID-19 prognoses compared to those on follow-up.<sup>5,15,17,18,26</sup> The Spanish study corroborated this data, demonstrating that cancer patients under active oncological therapy showed a higher mortality rate due to COVID-19.<sup>25</sup> Patients who received surgery demonstrated higher rates of death, chances of ICU admission or of presenting severe or critical symptoms, and higher requirement of invasive ventilation than other treatments excluding immunotherapy.<sup>15</sup> However, a consistent impact on the severity of COVID-19 in patients who received targeted therapy, including tyrosine kinase inhibitors<sup>15,31</sup> or radiotherapy<sup>15</sup> was not observed. Noteworthy, patients under immunotherapy treatment had the highest death rate and severity of illness, in contrast to patients receiving other treatments.<sup>15</sup> It is possible that immunotherapy induces the release of large amounts of cytokines, which can be toxic to normal cells, including lung epithelial cells<sup>32</sup> and, therefore, contribute to higher mortality rates. Conversely, one Italian study showed that immunotherapy in LC seems to improve prognosis,<sup>21</sup> and a Chinese study reported that cancer treatment did not impact COVID-19 clinical outcomes.<sup>19</sup> Reinforcing this finding, the French, Brazilian, and one of the American studies revealed that none of the treatments given in the previous month for cancer patients showed any association with mortality.<sup>22,27,30</sup> Data from each specific country discussed below.

## China

As China was the first nation affected by COVID-19, there have been more published studies there than in any other country, which explains the greater number of cohorts evaluated in this work. Therefore, among the nine cohorts,<sup>4,5,7,14–19</sup> the prevalence of COVID-19 in LCPs ranged from 11.7%–58.3% (Table 1). These single or multicenter studies were heterogeneous and varied in sample sizes, ranging from 12 to 205 subjects. Interestingly, the prevalence of COVID-19 in LC showed an inverse correlation to the population size of two cohorts, as the highest (58.3%) was detected in the smallest COVID-19 cancer

a



b

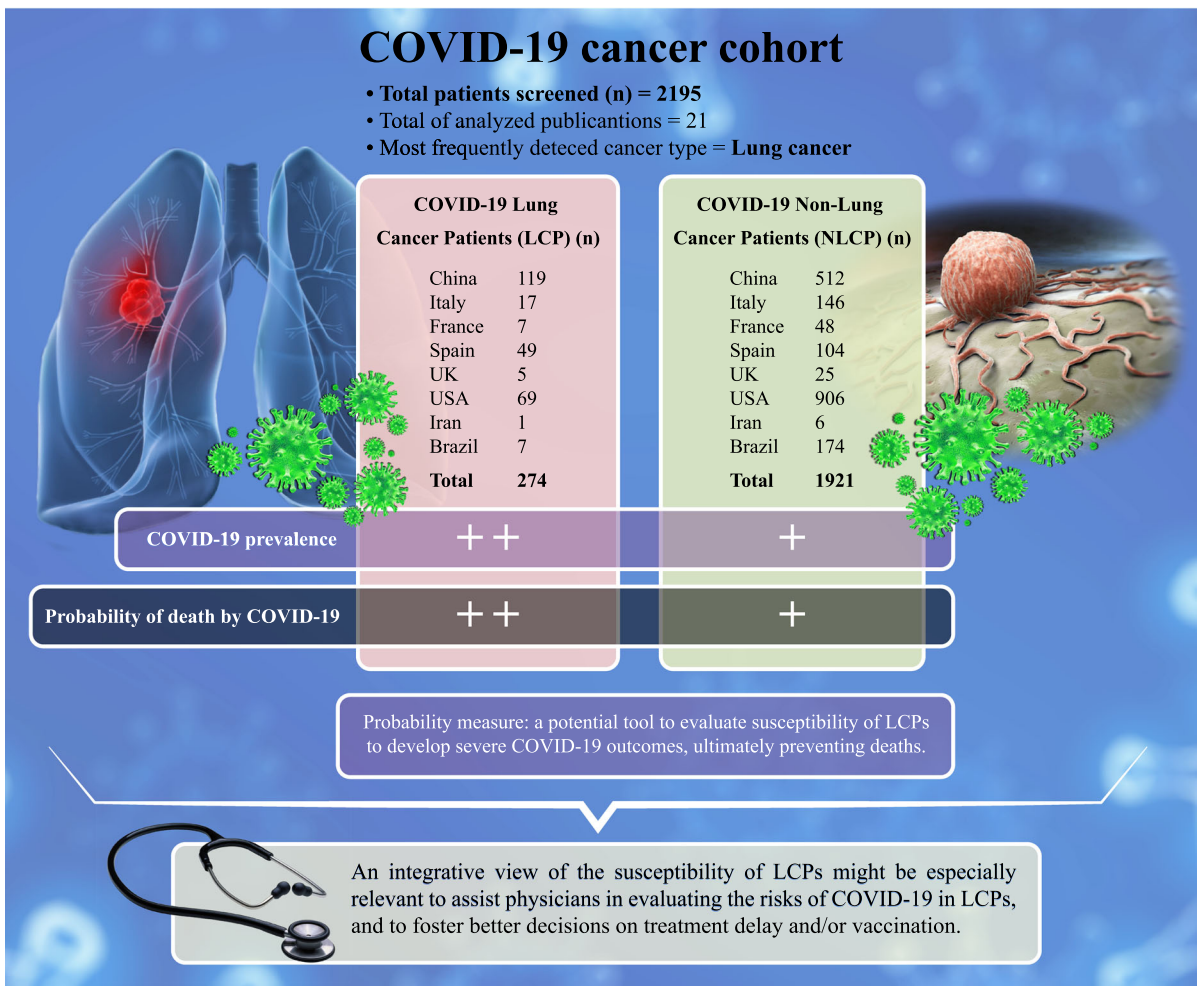


FIGURE 1 Legend on next page.

cohort ( $n = 12$ ). On the contrary, the study that showed the lowest COVID-19 LC frequency (11.7%) was assessed in the biggest COVID-19 cancer cohort ( $n = 205$ ).

Expectedly, given their inherent pulmonary fragility, LCPs were most frequently detected among cancer COVID-19 cases in most of the Chinese studies.<sup>4,7,14–18</sup> For other reports, LC was ranked as one of the top three most detected tumors.<sup>5,19</sup>

LC is not related to severe COVID-19 outcomes (Figure 2(a)), since three studies have shown that LCPs had a higher probability of developing severe illness in relation to NLCPs<sup>4,7,15</sup> while three others have shown the opposite.<sup>14,18,19</sup> This discrepancy regarding severe COVID-19 outcomes in LCPs could be related to the cohort sizes and to the kind of study; single institutional versus multicenter.

The probability of death among these Chinese COVID-19 LC cases ranged from 18.2% to 33.3%, while it ranged from 9.6% to 25.0% in COVID-19 NLCPs. Almost all reports showed that LCPs had a higher probability of death from COVID-19 when compared with NLCPs,<sup>4,5,7,14,15,17–19</sup> apart from one study that described that this probability was similar among LCPs and NLCPs<sup>16</sup> (Figure 2(b)).

## Italy

Among the two Italian articles analyzed in this mini review (Table 1), one evaluated a cohort of 25 COVID-19 cancer subjects and detected 32.0% LC frequency, corresponding to the highest type of cancer detected.<sup>21</sup> The other study evaluated a bigger cohort ( $n = 138$ ), which not only reported a lower frequency of LC (6.5%) but classified LC as the fifth most common cancer, after prostate, breast, colorectal, and bladder, respectively.<sup>20</sup> LCPs had a lower probability of death from COVID-19 than NLCPs (25.0% versus 41.2%, respectively)<sup>21</sup> (Figure 2(b)).

## France

A single French study reported a cohort that included 55 individuals, of which 12.7% were COVID-19 LCPs (Table 1), in which the probability of death from COVID-19 was almost three times higher than in NLCPs (42.9% versus 16.7%, respectively)<sup>22</sup> (Figure 2(b)).

## Spain

In Spain, three studies evaluated 1069,<sup>23</sup> 1878,<sup>24</sup> and 287<sup>25</sup> cases seen at hospitals from the region of Madrid. LC was

the most prevalent among SARS-CoV-2 confirmed cancer patients, presenting a frequency of 37.8%, 37.8%, and 27.0%, respectively (Table 1).<sup>23–25</sup> One of the reports showed that 64.7% of LC patients had severe COVID-19 infection, such as the presence of bilateral pneumonia, but none of these patients were admitted to the ICU.<sup>24</sup> The probability of death for LCPs from COVID-19 was higher than for NLCPs, exhibiting 40.0% versus 21.0%<sup>25</sup> and 52.9% versus 35.7%,<sup>24</sup> respectively (Table 1 and Figure 2(b)).

## United Kingdom (UK)

A multicenter study from five London hospitals reported that 17.0% of the 30 analyzed cancer patients presented with LC (Table 1), which together with colorectal cancer was the second most common tumor observed, with prostate cancer in first place. Despite the small cohort, probability of death from COVID-19 among LCPs was almost two times higher than NLCPs (60.0% versus 32.0%, respectively)<sup>26</sup> (Table 1 and Figure 2(b)).

## United States of America (USA)

The largest cohorts analyzed in this review were from the USA, including 218, 334 and 423 COVID-19 cancer patients, in which the prevalence of LC ranged from 5.1% to 8.3% (Table 1).<sup>13,27,28</sup> LC was the third<sup>13,28</sup> or fifth<sup>27</sup> most common tumor detected (Table 1). Despite that, the probability of death of LCPs from COVID-19 was two times higher than NLCPs (55.0% versus 26.6%, respectively)<sup>27</sup> (Table 1 and Figure 2(b)). Interestingly, the course of SARS-CoV-2 infection in LCPs was longer and more severe than in the general US population.<sup>31</sup> This report also showed that although the rates of severe COVID-19 appear to be increased in LCPs, recovery occurred in most of them (65.0% patients recovered or were improving at the time of writing this study, while the others 35.0% were pending or had died).<sup>31</sup> With regard to ICU admission, 21.0% of LC patients with COVID-19 needed ICU hospitalization.

## Iran

A small study conducted with seven Iranian COVID-19 cancer patients described that, among the cases that had solid tumors, lung, colon, ovarian, and glioblastoma multiform were detected in one patient each, representing a prevalence of 14.3% for each (Table 1). Concerning COVID-19

**FIGURE 1** Global map with the COVID-19 LCP and NLCP cohorts evaluated and study schematic. (a) Colored countries indicate the included nations in this study. The subtitle color indicates the number of studies analyzed from each nation, in which  $N =$  one study; green: Countries with 1 N (France, UK, Iran, Brazil); yellow: Countries with 2 N (Italy); blue: Countries with 3 N (Spain, USA); red: Countries with 9 N (China). The number of COVID-19 LCP and COVID-19 cancer patients are described inside the balloons, respectively. (b) A summary of the COVID-19 LCP and NLCP cohorts from each country studied, including the significant findings and the relevance of this work. COVID-19 prevalence and the probability of death by COVID-19 are summarized as follows: +: High; ++: Very high

**TABLE 1** Data of lung cancer patient (LCP) and nonlung cancer patient (NLCP) cohorts affected by COVID-19 from several countries

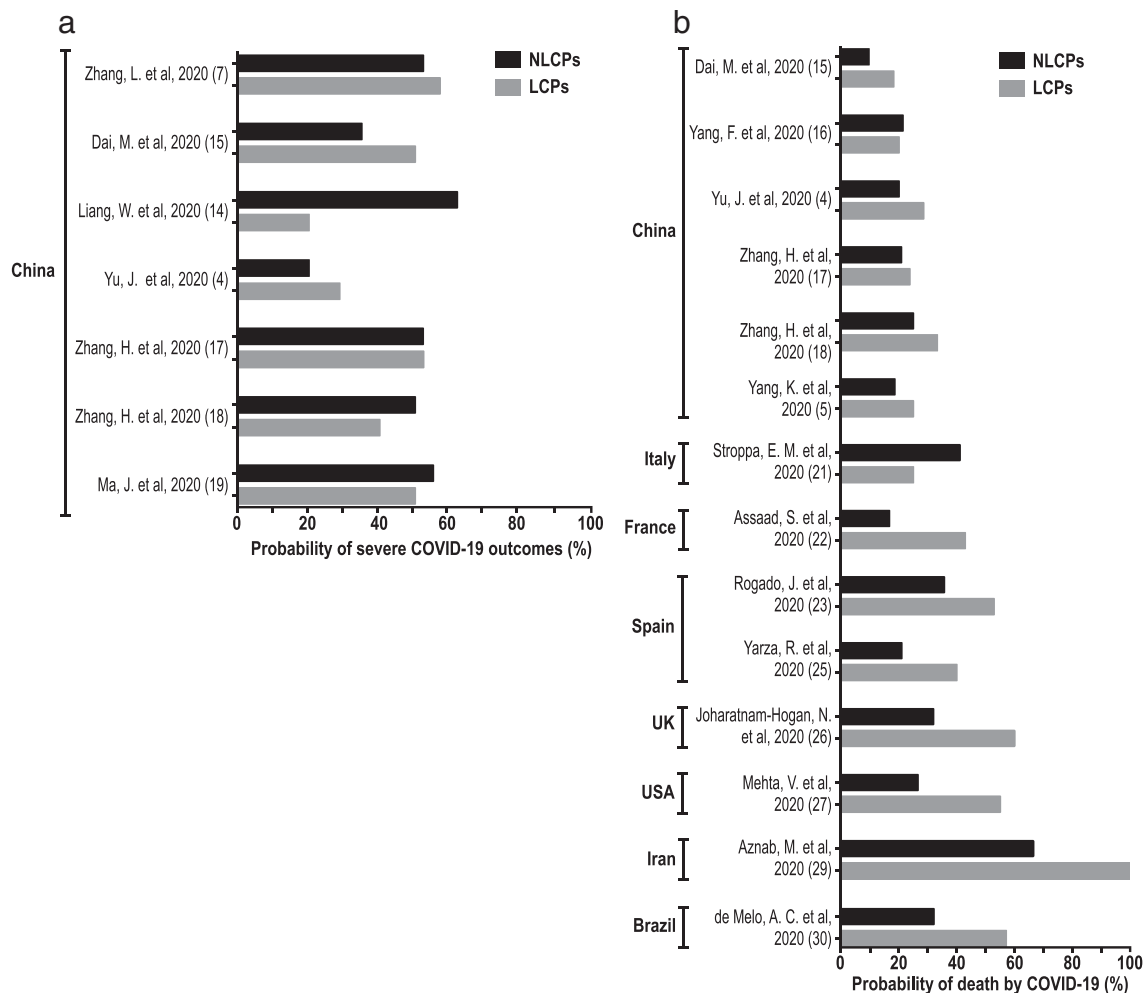
Country	Most frequently detected solid type of cancer	LC position within ranking of COVID-19 cancer patients	Single institutional or multicenter study	Total COVID-19 cancer patients - n	COVID-19 outcomes in LCPs			COVID-19 outcomes in NLCPs			Reference
					COVID-19 LCPs % (n)	Probability of severe outcomes % (n)	Probability of death % (n)	Probability of severe outcomes % (n)	Probability of death % (n)		
China	Lung	1	Multicenter	28	25.0% (7 of 28)	57.0% (4 of 7) <sup>a</sup>	N/A	52.4% (11 of 21) <sup>a</sup>	N/A	N/A	7
	Lung	1	Multicenter	105	20.9% (22 of 105)	50.0% (11 of 22) <sup>b</sup>	18.2% (4 of 22) <sup>b</sup>	35.0% (29 of 83) <sup>a</sup>	9.6% (8 of 83) <sup>a</sup>		15
	Lung	1	Single Institutional	52	19.2% (10 of 52)	N/A	20.0% (2 of 10) <sup>a</sup>	N/A	21.4% (9 of 42) <sup>a</sup>		16
	Lung	1	Multicenter	18	28.0% (5 of 18)	20.0% (1 of 5) <sup>b</sup>	N/A	62.0% (8 of 13) <sup>b</sup>	N/A		14
	Lung	1	Single Institutional	12	58.3% (7 of 12)	28.6% (2 of 7) <sup>a</sup>	28.6% (2 of 7) <sup>a</sup>	20.0% (1 of 5) <sup>a</sup>	20.0% (1 of 5) <sup>a</sup>		4
	Lung	1	Multicenter	107	19.6% (21 of 107)	52.4% (11 of 21) <sup>b</sup>	23.8% (5 of 21) <sup>a</sup>	52.3% (45 of 86) <sup>a</sup>	20.9% (18 of 86) <sup>a</sup>		17
	Lung	1	Multicenter	67	22.4% (15 of 67)	40.0% (6 of 15) <sup>a</sup>	33.3% (5 of 15) <sup>a</sup>	50.0% (26 of 52) <sup>a</sup>	25.0% (13 of 52) <sup>a</sup>		18
	Colorectal	2	Single Institutional	37	21.6% (8 of 37)	50.0% (4 of 8) <sup>a</sup>	N/A	55.2% (16 of 29) <sup>a</sup>	N/A		19
	Breast	3	Multicenter	205	11.7% (24 of 205)	N/A	25.0% (6 of 24) <sup>a</sup>	N/A	18.7% (34 of 181) <sup>a</sup>		5
Italy	Lung	1	Single Institutional	25	32.0% (8 of 25)	N/A	25.0% (2 of 8) <sup>b</sup>	N/A	41.2% (7 of 17) <sup>a</sup>		21
	Prostate	5	Single Institutional	138	6.5% (9 of 138)	N/A	N/A	N/A	N/A		20
France	N/A <sup>c</sup>	N/A	Multicenter	55	12.7% (7 of 55)	N/A	42.9% (3 of 7) <sup>b</sup>	N/A	16.7% (5 of 48) <sup>a</sup>		22
Spain	Lung	1	Single Institutional	45	37.8% (17 of 45)	N/A	52.9% (9 of 17) <sup>a</sup>	N/A	35.7% (10 of 28) <sup>a</sup>		23
	Lung	1	Single Institutional	45	37.8% (17 of 45)	64.7% (11 of 17) <sup>b</sup>	52.9% (9 of 17) <sup>b</sup>	N/A	N/A		24
	Lung	1	Single Institutional	63	27.0% (15 to 63)	N/A	40.0% (6 of 15) <sup>b</sup>	N/A	21.0% (10 of 48) <sup>b</sup>		25
UK	Prostate	2	Multicenter	30	17.0% (5 of 30)	N/A	60.0% (3 of 5) <sup>a</sup>	N/A	32.0% (8 of 25) <sup>b</sup>		26
USA	Breast	3	Single Institutional	334	6.9% (23 of 334)	N/A	N/A	N/A	N/A		13
	Breast	3	Single Institutional	423	8.3% (35 of 423)	N/A	N/A	N/A	N/A		28
	Genitourinary	5	Single Institutional	218	5.1% (11 of 218)	N/A	55.0% (6 of 11) <sup>b</sup>	N/A	26.6% (55 of 207) <sup>a</sup>		27
Iran	Colon, lung, ovarian and glioblastoma multiform	Similar frequency	N/A	7	14.3% (1 of 7)	N/A	100.0% (1 of 1) <sup>a</sup>	N/A	66.6% (4 of 6) <sup>a</sup>		29
Brazil	Breast	7	Single Institutional	181	3.9% (7 of 181)	N/A	57.1% (4 of 7) <sup>b</sup>	N/A	32.2% (56 of 174) <sup>a</sup>		30

Abbreviations: LC, lung cancer; LCPs, lung cancer patients; N/A, data not available; NLCP, nonlung cancer patients.

<sup>a</sup>Percentage calculated from the available data in the article.

<sup>b</sup>Percentage available in the article.

<sup>c</sup>No single solid tumor subtypes were overrepresented in the SARS-COV-2 RT-PCR positive subgroup.



**FIGURE 2** Probability of severe COVID-19 outcomes, including death for LCPs and NLCPs. (a) the probability of severe COVID-19 outcomes (%) is represented as the ratio of the number of LCPs or NLCPs with severe COVID-19 outcomes over the total number of COVID-19 LCPs or NLCPs, respectively. (b) The probability of death by COVID-19 (%) is represented as the ratio of the number of LCPs or NLCPs deaths by COVID-19 over the total number of COVID-19 LCPs or NLCPs, respectively. The probability measure has been calculated for this review when the original articles do not provide. The x-axis shows the probability of severe COVID-19 outcomes and death in LCPs versus NLCPs. The y-axis shows the studies/countries in which data were reported. LCPs, lung cancer patients; NLCPs, nonlung cancer patients

outcomes, the only COVID-19 LCP was a fatal case, yielding a fatality of 100.0% versus 66.6% of fatality among COVID-19 NLCPs<sup>29</sup> (Figure 2(b)). These high fatality rates were observed due to the small size of the cohorts.

## Brazil

Recently, a Brazilian report conducted in 181 COVID-19 cancer cases described that only 3.9% of them were classified as LC. This represented the lowest prevalence of LC cases among all the studies discussed herein, as it ranked as the seventh most detected type of cancer<sup>30</sup> (Table 1). Despite that, the probability of death from COVID-19 in LCPs was much higher than that observed in NLCPs (57.1% versus 32.2%, respectively)<sup>30</sup> (Table 1 and Figure 2(b)). This study also highlighted the importance of metastasis among the fatalities of COVID-19 cancer patients, as this condition was

identified in almost half of the total fatal cases (49.7%). Lung metastasis was especially relevant, as it accounted for 17.7% of the fatalities and was the third most prevalent, following bone and lymph nodes. Moreover, in line with Consortium data from the USA, Canada, and Spain,<sup>33</sup> the Brazilian report showed that pulmonary metastasis was significantly associated with a higher risk of death from COVID-19.<sup>30</sup>

Remarkably, the prevalence and mortality patterns observed in this report reflected the typical epidemiological data of LC in Brazil,<sup>34</sup> in which LC does not configure the most prevalent tumor<sup>34</sup> but is the one with the highest mortality rate among men and the second highest among women.<sup>35</sup> The prevalence was possibly reduced due to the Brazilian Tobacco Control Program implemented in the late 1980s,<sup>36</sup> which decreased by 46% the percentage of smokers in the country and avoided 420 000 deaths during the period from 1989 to 2010.<sup>37</sup> Almost half of that 46% reduction can be explained by large price increases, smoke-free air laws,

**TABLE 2** The number of dead and alive COVID-19 LCPs and NLCPs from each study analyzed

Country	Total COVID-19 cancer patients (n)	COVID-19 LCPs (n)	COVID-19 LCPs		COVID-19 NLCPs (n)	COVID-19 NLCPs		Reference
			Dead n (%)	Alive n (%)		Dead n (%)	Alive n (%)	
China	28	7	N/A	N/A	21	N/A	N/A	7
	105	22	4 (18.2%)	18 (81.8%)	83	8 (9.6%)	75 (90.4%)	15
	52	10	2 (20.0%)	8 (80.0%)	42	9 (21.4%)	33 (78.6%)	16
	18	5	N/A	N/A	13	N/A	N/A	14
	12	7	2 (28.6%)	5 (71.4%)	5	1 (20.0%)	4 (80.0%)	4
	107	21	5 (23.8%)	16 (76.2%)	86	18 (20.9%)	68 (79.1%)	17
	67	15	5 (33.3%)	10 (66.7%)	52	13 (25.0%)	39 (75.0%)	18
	37	8	N/A	N/A	29	N/A	N/A	19
	205	24	6 (25.0%)	18 (75.0%)	181	34 (18.7%)	147 (81.3%)	5
Italy	25	8	2 (25.0%)	6 (75.0%)	17	7 (41.2%)	10 (58.8%)	21
	138	9	N/A	N/A	129	N/A	N/A	20
France	55	7	3 (42.9%)	4 (57.1%)	48	5 (10.4%)	43 (89.6%)	22
Spain	45	17	9 (52.9%)	8 (47.1%)	28	10 (35.7%)	18 (64.3%)	23
	45	17	9 (52.9%)	8 (47.1%)	28	N/A	N/A	24
	63	15	6 (40.0%)	9 (60.0%)	48	10 (21.0%)	38 (79.0%)	25
UK	30	5	3 (60.0%)	2 (30.0%)	25	8 (32.0%)	17 (68.0%)	26
USA	334	23	N/A	N/A	311	N/A	N/A	13
	423	35	N/A	N/A	388	N/A	N/A	28
	218	11	6 (55.0%)	5 (45.0%)	207	55 (26.6%)	152 (73.4%)	27
Iran	7	1	1 (100.0%)	0 (0%)	6	4 (66.6%)	2 (33.4%)	29
Brazil	181	7	4 (57.1%)	3 (42.9%)	174	56 (32.2%)	118 (67.8%)	30

Abbreviations: LCPs, lung cancer patients; N/A, data not available; NLCPs, nonlung cancer patients.

marketing restrictions, health warnings, mass media campaigns, and cessation treatment programs.<sup>37</sup> Brazil provides one of the most successful public health interventions in reducing deaths due to smoking and serves as a model for other low- and middle-income nations.<sup>37</sup> However, a set of stricter policies could further reduce smoking and save many additional lives, as well as diagnosis at an early stage which could contribute to countering the increasing mortality rate during the pandemic.

## PATHOPHYSIOLOGICAL ASPECTS OF LUNG CANCER AND COVID-19 OUTCOMES

The presence of cancer itself and submission to antitumor therapies could predispose cancer patients to a higher susceptibility to COVID-19 and worse outcomes, including fatality from SARS-CoV-2 infection. Furthermore, as has been observed in most of the cohorts discussed, the relevant association of LC with these COVID-19 effects could be attributed to some possible pathophysiological features. Possible hypotheses include the role of a local disrupted immune response in the host, at the site of infection, as previously described for the development of long-term myelosuppression and impaired immunity after

chemotherapy.<sup>5</sup> Therefore, the destruction of lung cells caused by SARS-CoV-2 infection triggers a local immune response, recruiting macrophages and monocytes, releasing chemokines and proinflammatory cytokines, thus initiating the adaptive immune responses of T and B lymphocytes. SARS-CoV-2 infection is mediated by angiotensin-converting enzyme 2 (ACE2) expressed in the lungs, heart, intestines, kidneys, among other organs.<sup>38</sup> The infected cells trigger an innate immune response, corresponding to activation of the type I interferon (IFN-I) pathway.<sup>39</sup> At the end of this IFN activation cascade, the expression of hundreds of IFN-induced genes (ISGs) is induced,<sup>40</sup> which together with other IFN-controlled molecules, including proinflammatory cytokines, can act from direct inhibition of viral replication until the recruitment and activation of other cells of the immune system.<sup>41</sup> A robust, timely, and localized IFN-I response is necessary as the first line of defense against viral infection as it promotes the elimination of the virus, induces tissue repair, and triggers the consequent prolonged adaptive immune response.<sup>42</sup> However, the responses induced by IFN-I require fine adjustment, since exacerbated activation can be harmful to the host since the systemic, long-lasting, and uncontrolled production of IFN-I can lead to the onset of inflammatory diseases. In most individuals, the recruited cells clear the infection in the lung. The immune response

then decreases, and patients recover. However, in some cases, inefficient immune response and high replication of SARS-CoV-2 occurs, with excessive release of proinflammatory cytokines and chemokines, a phenomenon known as “cytokine storm”, mediating generalized lung inflammation.<sup>43</sup> This hyperinflammatory state involves major systemic perturbations, including dysregulation of iron metabolism that induces the production of reactive oxygen species (ROS) which is associated with disease severity. Mitochondria are the major sources of ROS and are the hub of cellular oxidative homeostasis. The intense inflammatory/pro-oxidative state may lead to mitochondrial dysfunction leading to platelet damage and apoptosis.<sup>44</sup> Moreover, one of the mechanisms for carcinogenesis is related to mitochondrial dysfunction, which increases mitochondrial-derived ROS.<sup>45</sup> Indeed, the mitochondrial function disorder is a hallmark of cancer;<sup>45,46</sup> of note, mutations in mitochondrial DNA can be used as a biomarker of lung cancer occurrence.<sup>45,47</sup> Thus, the various cellular and systemic incidents caused by SARS-CoV-2 critically impact the mitochondrial function, which may reflect on intra- and extracellular deregulation that ultimately contribute to the progression and severity of the disease in cancer patients. Further investigation on the role of mitochondrial dysfunction for COVID-19 outcomes in LCP should provide new insights on how to better manage those patients.

Another area that requires further investigation is the possibility of SARS-CoV-2 acting as an oncolytic virus and its effects on the disease-free survival rate of LCPs. The replication cycle of SARS-CoV-2 has recently been demonstrated to lead to oncolytic cell death and to play a crucial role in the transient remission of NK/T cell lymphoma.<sup>48</sup> In another study, infection led to the remission of one patient with Hodgkin's lymphoma.<sup>49</sup> Although there are no reports on lung cancer, for the time being, this is an interesting consequence of the infection, and one that might produce unexpected effects on cancer patients. The putative mechanisms of action include cross-reactivity of pathogen-specific T cells with tumor antigens and activation of natural killer cells mediated by the substantial release of proinflammatory cytokines, including IL-6, TNF- $\alpha$ , and IL-2, produced in response to infection.<sup>48,49</sup> However, further studies to investigate the molecular and cellular pathways role in such cases should be conducted before oncolysis can be directly associated with SARS-CoV-2 infection.

In addition to the cytokine storm, increased recruitment and infiltration of inflammatory cells into the airways might take place, leading to lymphopenia in patients with COVID-19.<sup>50,51</sup> Therefore, pulmonary immunopathology and diffuse alveolar damage can be generated, including desquamation of alveolar cells, formation of the hyaline membrane and pulmonary edema, which can result in damage to multiple organs, accounting for the increased probability of death for LCPs. Consequently, this inefficient immune response may contribute to development of severe lung disease and even systemic pathology.<sup>43</sup> In essence, a fine adjustment of

prompt and nonexaggerated inflammatory processes in the respiratory tract of COVID-19 patients would interfere with disease resolution, processes that are probably already compromised in LCPs.

The higher probability of death for LCPs from COVID-19 in cohorts from different nationalities possibly occurs due to some of their specific features, once they present a greater predisposition to respiratory infections,<sup>52</sup> higher rates of the previous diagnosis of chronic obstructive pulmonary disease (COPD), and smoking history.<sup>31</sup> Approximately 85% of LC cases result from smokers or secondary smoke exposure in nonsmokers.<sup>53</sup> Tobacco exposure is also responsible for modifying lung structure and immunology, as well as the expression of SARS-CoV-2 cellular receptor (ACE2).<sup>54–62</sup> Thereby, tobacco users have a worse prognosis for COVID-19 since smoking history has been shown to be associated with an increased risk of death in COVID-19 LCPs.<sup>59</sup> Conversely, LCPs who decreased their smoking activity have been associated with increased odds of recovery from COVID-19.<sup>31</sup> Thus, considering that smoking is the most common etiology of lung cancer, the putative association between chronic exposure to cigarette and ACE2 upregulation in the lungs might partially contribute to the increased probability of death for individuals with lung malignancies when infected by SARS-CoV-2.

## DISCUSSION

In the last year, an exciting boom of studies has brought to light the impact of the current pandemic on cancer patients. In this context, LC has been extensively studied since the respiratory tract is the SARS-CoV-2's main primary site of infection and it is already compromised by the presence of the tumor. After analysis of a collection of studies, it was possible to determine that LC is one of the most prevalent tumors among COVID-19 cancer patients and that LCPs are at increased risk of death from COVID-19 when compared to NLCPs in different countries, which supports the findings of a previous study.<sup>63</sup> However, there are still questions which remain unanswered in further understanding the susceptibility of LCPs to severe COVID-19 outcomes, in particular how intrinsic LC features, including molecular mechanisms, could contribute to the increased risk of COVID-19 mortality for LCPs and how host responses (or lack thereof, considering the immunocompromised state of patients) to SARS-CoV-2 infection could influence COVID-19 outcomes. Furthermore, other molecular and cellular interplays such as the role of mitochondrial dysfunction for COVID-19 and a possible oncolytic effect of SARS-CoV-2 might arise as interesting focal points of future studies. That notwithstanding, we must consider the significant impact on the diagnosis and prognosis of patients with all types of cancer during the pandemic.

LC may be one of the types of cancer most impacted due to overlapping symptoms with COVID-19 and to the



inevitable sharing of resources from respiratory medicine services. Furthermore, the interpretation of computed tomography chest findings and the distinction between features of COVID-19 and LC is also a challenge, in which both conditions may present the same features such as ground-glass opacities, nodules, and lymphadenopathy.<sup>64</sup> As a result, during the COVID-19 pandemic, LC has been severely underdiagnosed, and this has led to diagnosis at later stages and poorer median overall survival.<sup>65–67</sup> This could contribute to poor prognosis and subsequently to the increased probability of death of LCPs since the stage of cancer diagnosis plays a significant role in the severity and death rate from COVID-19.

This report is the first review on this subject to employ the probability of COVID-19 outcomes as a potentially more immediate measure and still underexplored to directly compare the susceptibility of LCPs and NLCPs to develop severe COVID-19 illness, including death. The integrative view of these data from multiple nationalities is especially relevant to guide clinicians in LCP risk evaluation, and to enable decisions on treatment and/or vaccination, ultimately preventing deaths.

## ACKNOWLEDGMENTS

We are especially grateful to Dr Geraldo Marcelo da Cunha from the National School of Public Health Sergio Arouca, FIOCRUZ, for his kind support with epidemiological analysis. We thank Carlos André Accacio Lemos from Bio-Manguinhos, FIOCRUZ, for support on figures design and edition. We also thank Oswaldo Cruz Institute from FIOCRUZ, CNPq, CAPES, FAPERJ, Proppi/ UFF, and the Brazilian Ministry of Health for financial support.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**How to cite this article:** Lemos AEG, Silva GR, Gimba ERP, Matos AR. Susceptibility of lung cancer patients to COVID-19: A review of the pandemic data from multiple nationalities. *Thorac Cancer*. 2021;12:2637–2647. <https://doi.org/10.1111/1759-7714.14067>