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Mortality of COVID-19 pneumonia during anticancer treatment in lung cancer patients

Stopa mortaliteta od COVID-19 pneumonije u toku onkološkog lečenja bolesnika sa karcinomom bronha

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Abstract

Background/Aim. The coronavirus disease 2019 (COVID-19) pandemic has multiple impacts on the management of cancer patients. Treatment of malignancies, including chemotherapy, targeted therapy, immunotherapy, and radiotherapy, can suppress the immune system and lead to the development of severe complications of COVID-19. The aim of this study was to determine the mortality of lung cancer (LC) patients in whom the COVID-19 was confirmed during active antitumor treatment. **Methods.** This retrospective study was conducted at the Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia. All patients included in the study underwent active anticancer treatment at the time of diagnosis of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was determined by a polymerase chain reaction (PCR) test. Patient data were collected using the institutional database and the observed period was from November 20, 2020, to June 5, 2021. Statistical analysis of the derived patient data used multivariate and univariate testing. **Results.** Out of 828 observed COVID-19 hospitalized patients, 81 were LC patients on active antitumor treatment. Patients were predominantly male (67.9%), smokers (55.6%), and with an average age of 66.5 years (range 43–83). The majority of patients (50.6%) had the Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1, and 83.9% had at least one comorbidity. The most common comorbidities were arterial hypertension (66.7%), chronic obstructive pulmonary disease (COPD) (28.4%), and diabetes mellitus (21%). Obesity, congestive heart failure, and other cardiovascular diseases were present in 11%, 6.2%, and 7.4% of patients, respectively. The most common was adenocarcinoma (33.3%), followed by squamous (30.9%) and small-cell LC (24.7%). Predominantly, 63% of the patients were in stage III of the disease, and 33.3% were in stage IV. Metastases were most commonly present in the contralateral lung/pleura (14.8%), brain (6.2%), bone (3.7%), and liver (3.7%). Systemic anticancer therapy was applied in 37 out of 81 patients (45.6%), chest radiotherapy in 35 (43.2%), concurrent chemoradiotherapy in 1 (1.2%), and other types of radiotherapy in 8 (9.87%) patients. The most common forms of systemic therapy were chemotherapy (35.8%), immunotherapy (7.4%), and targeted therapy (2.4%). The most common chemotherapy was a cisplatin-based regiment applied in 34.6% of patients. The mortality from COVID-19 was 19.8%. The statistical significance in relation to the type of treatment was not observed. Statistical significance was observed between mortality and the ECOG PS ($p = 0.011$). **Conclusion.** LC patients are dependent on antitumor treatment and, at the same time, highly susceptible to potential infection. In this study, we did not find statistically significant differences in mortality related to the type of antitumor treatment in COVID-19 positive LC patients. Further detailed research on a larger scale is needed in order to explore the effects of SARS-CoV-2 on cancer patients. All possible methods of protection against SARS-CoV-2 virus should be performed in order to minimize the risk of infection in all but especially in immunocompromised cancer patients.

Key words:
antineoplastic agents; comorbidity; covid-19; lung neoplasms; mortality; neoplasms staging.

Apstrakt

Uvod/Cilj. Pandemija *coronavirus disease* 2019 (COVID-19) ima višestruki uticaj na lečenje bolesnika obolelih od karcinoma. Lečenje malignih bolesti, uključujući hemioterapiju, ciljanu terapiju, imunoterapiju i radioterapiju može delovati supresivno na imunski sistem i dovesti do razvoja teških komplikacija COVID-19. Cilj ovog rada bio je da se utvrdi mortalitet bolesnika sa karcinomom bronha, kod kojih je prisustvo COVID-19 potvrđeno tokom aktivnog antitumorskog lečenja. **Metode.** Ova retrospektivna studija je sprovedena na Institutu za plućne bolesti Vojvodine u

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Sremskoj Kamenici, Srbija. Kod svih bolesnika sa karcinomom bronha obuhvaćenih studijom, u toku aktivnog antitumorskog lečenja je potvrđeno prisustvo COVID-19, testiranjem nazofaringealnog brisa lančanom reakcijom polimeraze. Podaci o bolesnicima prikupljeni su korišćenjem institucionalne baze podataka za period od 20. novembra 2020. do 5. juna 2021. Statistička analiza podataka je urađena korišćenjem multivarijatnog i univarijatnog testiranja. **Rezultati.** Od ukupno 828 hospitalizovanih bolesnika sa COVID-19, bilo je 81 sa karcinomom bronha u toku aktivnog antitumorskog lečenja. Bolesnici, tačnije njih 55 (67,9%), bili su muškarci, pušači (55,6%), prosečnog životnog doba od 66,47 godina (u rasponu od 43–83 godine). Najveći broj bolesnika (50,6%) imao je the *Eastern Cooperative Oncology Group Performance Status* (ECOG PS) 1, a 83,9% je imalo najmanje jedan komorbiditet. Najčešći komorbiditeti bili su arterijska hipertenzija (66,7%), hronična opstruktivna bolest pluća - HOBP (28,4%) i dijabetes (21%), dok je gojaznost, kongestivnu srčanu insuficijenciju i druge kardiovaskularne bolesti imalo 11%, 6,2% i 7,4%, redom. Najčešći je bio adenokarcinom (33,3%), zatim skvamozni karcinom (30,9%) i mikrocelularni karcinom bronha (24,7%). Većina bolesnika (63%) bila je u stadijumu III, dok je 33,3% bolesnika bilo u stadijumu IV. Metastaze su najčešće bile prisutne u kontralateralnom plućnom krilu/pleuri (14,8%), mozgu (6,2%), a u kostima i jetri su bile prisutne jednako (3,7%). Samostalna sistemska terapija primenjena je kod 37 od 81 (45,6%) bolesnika, radioterapija grudnog koša kod 35 (43,2%), konkurentna hemioradioterapija kod jednog (1,2%) i drugi vidovi radioterapije kod 8 (9,87%) bolesnika. Najčešći oblici sistemske terapije bili su hemioterapija kod 29 od 81 (35,8%) bolesnika, imunoterapija kod 6 (7,4%) i ciljana terapija kod 2 (2,4%) bolesnika. Najčešće (34,6%) su primenjivani protokoli na bazi cisplatina. Ustanovljena stopa mortaliteta od COVID-19 iznosila je 19,8%, bez statistički značajne razlike u odnosu na vrstu lečenja (p = 0,973). Utvrđena je statistička značajnost uticaja ECOG PS na porast mortaliteta (p = 0,011). **Zaključak.** Bolesnici sa karcinomom bronha su zavisni od antitumorskog lečenja, ali su istovremeno populacija koja je osetljiva na COVID-19. U našem istraživanju nisu pronađene razlike u mortalitetu u odnosu na vrstu antitumorskog lečenja. Potrebna su dalja istraživanja kako bi se bolje razumeli efekti infekcije SARS-CoV-2 na bolesnike sa karcinomom. Takođe, potrebno je sprovesti sve moguće metode zaštite od infekcije SARS-CoV-2, kako bi se rizik od infekcije sveo na minimum kod svih osoba, a posebno kod imunokompromitovanih bolesnika sa karcinomom.

Ključne reči:
antineoplastici; komorbiditeti; covid-19; pluća, neoplazme; mortalitet; neoplazme, određivanje stadijuma.

Introduction

Since December 2019, when a new virus appeared in Wuhan, China, the health care system around the globe has undergone significant changes. It is now well known that coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can occur in the form of asymptomatic infection but also as severe viral pneumonia, acute respiratory distress syndrome and lead to death [1, 2].

Patients with associated diseases, such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, and cardiovascular disease, may have a more severe form of COVID-19 and develop numerous complications. Therefore, their treatment more often requires hospitalization and respiratory support – from oxygen therapy to mechanical ventilation [3].

Cancer patients are an extremely sensitive subgroup in the COVID-19 pandemic. The pathway of patients with malignancy represents a major challenge for oncologists, from diagnosis to treatment and palliative care [1]. Several problems emerged in access to cancer patients during the COVID-19 pandemic. One of them is the possible overlap of symptoms between pneumonia caused by the SARS-CoV-2 virus and lung cancer (LC) such as shortness of breath, cough, and fatigue. Exposure of patients to infection during visits to health care facilities is another expected problem. Patients with LC are most often elderly smokers with already mentioned associated diseases. These factors increase the risk of COVID-19 [1, 4, 5].

Radiologically, COVID-19 can be presented in the same way as radiation pneumonitis, immunotherapy-associated pneumonitis, or other infections, which further complicates the assessment of patients with LC. In this situation, bronchoscopy plays an important role in the differential diagnosis, but it is relatively contraindicated in suspicion of COVID-19 [1].

Immunosuppressive antitumor drugs may increase the risk of viral infection, affecting neutrophil function and humoral immunity [6]. Most LC patients are current or former smokers, which can lead to further complications in possible COVID-19 [6, 7]. Multifactorial anemia and hypoproteinemia, often presented in these patients, further increase susceptibility to infectious pathogens [8]. As a result of previous thoracic surgery or radiation therapy, damage to the alveolar architecture and/or malignant airway obstruction may occur, which is another possible contributing factor to more severe infections [9].

In the last two years, the topic of SARS CoV2 infection has probably been the most current field of research in medicine. Several large meta-data research that analyzed COVID-19 mortality in patients with malignancies demonstrated an increased risk of death ranging from 1.66 to 3.16 [10–12]. Management of cancer patients undergoing active antitumor treatment is a particularly important issue. Immunosuppressive factors and susceptibility to SARS-CoV-2 infection differ between certain types of cancer and the type and duration of treatment. Kuderer et al. [13] demonstrated that patients who were in remission or without evidence of active disease had a lower risk of death from COVID-19 than patients with active diseases treated with some of the antitumor forms of treatment.

On the other hand, this area of interest has a lot of controversial results. Among recent research, a study by Wang et al. [14] showed that the use of radiotherapy, immunotherapy, or hormone therapy one month before SARS-CoV-2 infection was not associated with an increased risk of mortality among cancer patients.

The effect of chemotherapy on the outcome of cancer patients with COVID-19 may be different. Several studies have reported an increase in the mortality rate from COVID-19 in cancer patients previously treated with chemotherapy [15–17]. However, recent large observational studies have shown that there is no evidence of COVID-19 higher mortality rate associated with active chemotherapy [13, 18, 19].

An important factor in considering the outcome of treatment of patients with malignant disease is the possible negative impact of delays in the application of an anticancer treatment which allows the progression of cancer and certainly requires precise guidelines and recommendations.

The aim of this study was to determine the mortality of LC patients in whom the COVID-19 was confirmed during active antitumor treatment.

Methods

This retrospective study included data from LC patients diagnosed with COVID-19. This trial was conducted at the Institute of Lung Diseases of Vojvodina, Sremska Kamenica, Serbia, in the observed period from November 20, 2020, to June 5, 2021.

Inclusion criteria were the following: confirmed SARS-CoV-2 infection, radiologically confirmed pneumonia, cytologically/histologically confirmed LC, LC patients receiving at least one cycle of active antitumor treatment (chemotherapy, immunological or targeted therapy), and/or application of at least 2 radiotherapy fractions. COVID-19 was determined by reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 according to institutional guidelines based on the recommendations of the National Ministry of Health [20].

Patients were classified as active if less than 30 days had passed since the last dose of chemotherapy or immunotherapy, if targeted therapy was being actively taken, or if the time since the last fraction of radiotherapy was less than two weeks.

Data on demographic and clinical characteristics of patients, type of cancer, type of specific antitumor treatment, laboratory and radiological data, and treatment outcome were collected using the institutional database. COVID-19 treatment was performed according to institutional protocols based on the recommendations of the National Ministry of Health [21].

Results

Study population

In the period from November 20, 2020, to June 5, 2021, a total of 828 patients with COVID-19 were hospitalized at the Institute for Lung Diseases of Vojvodina (COVID-19 Clinical Department) in Sremska Kamenica, Serbia. Of these patients, 81 patients were on active cancer therapy and met the criteria for inclusion in this study.

The clinical characteristics of examined patients in this study corresponded to the average demographic data of patients with LC. Demographic and treatment characteristics of LC patients with COVID-19 are shown in Table 1.

The majority of patients were in stage III (63%), while the metastatic stage was present in 33.3% of patients (Table 1). The most common localizations of metastases

Table 1

Demographic and treatment characteristics of lung cancer (LC) patients with coronavirus disease 2019 (COVID-19) (n = 81)

Characteristics	Values
Age (years)	66.47 (43–83)
40–49	1 (1.2)
50–59	10 (12.3)
60–69	42 (51.9)
70–79	24 (29.7)
80–89	4 (4.9)
Gender	
male	55 (67.9)
female	26 (32.1)
Smoking status	
current	45 (55.6)
former	31 (38.3)
non-smoker	5 (6.2)
ECOG PS	
1	41 (50.6)
2	26 (32.1)
3	14 (17.3)
Comorbidities	
no	13 (16.0)
hypertension	54 (66.7)
COPD	23 (28.4)
diabetes mellitus	17 (21.0)
obesity	9 (11.1)
congestive heart failure	5 (6.2)
other cardiovascular diseases	6 (7.4)
others	8 (9.8)
Pathology	
adenocarcinoma	27 (33.3)
SqCC	25 (30.9)
SCLC	20 (24.7)
others	9 (11.1)
Stage	
I	1 (1.2)
II	2 (2.5)
III	51 (63.0)
IV	27 (33.3)
Metastasis-location	
lung/pleural	12 (14.8)
brain	5 (6.2)
bone	3 (3.7)
liver	3 (3.7)
others	4 (4.9)

All variables are expressed as numbers (%) except age, which is expressed as median (range).
COPD – chronic obstructive pulmonary disease; SqCC – squamous cell carcinoma; SCLC – small-cell LC; ECOG PS – Eastern Cooperative Oncology Group Performance Status.

were in the contralateral lung/pleura (14.8%), brain (6.2%), bone (3.7%), and liver (3.7%), and the median number of metastatic sites was 1 (range 1–3).

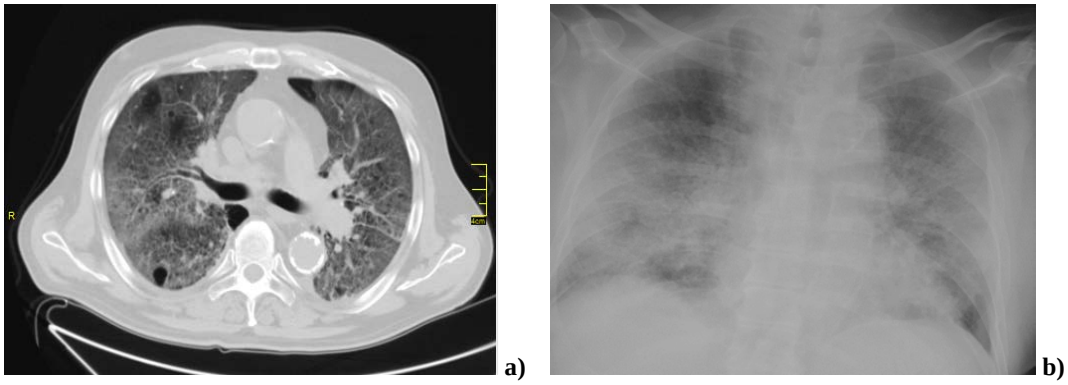
All included patients were treated with anticancer therapy, systemic therapy, and/or radiotherapy at the time of diagnosis of COVID-19 (Table 2). Regarding the type of therapy, out of 81 patients, 37 (45.6%) received systemic therapy, thoracic radiotherapy was applied in 35 (43.2%) patients, concurrent chemo-radiotherapy in one (1.2%) patient, and non-thoracic radiotherapy in 8 (9.87%) patients. The types of applied systemic therapy are shown in Table 2. In the observed study group, no patient with COVID-19 was treated with the combination of chemo- and immunotherapy. Non-thoracic radiotherapy was applied as palliative brain radiotherapy (whole-brain radiation therapy – WBRT or prophylactic cranial radiation – PCI). Chemotherapy was most often used as first-line chemotherapy (24.7%), followed by second-line chemotherapy (12.3%), neoadjuvant and adjuvant chemotherapy (2.5% and 1.2%, respectively). The most commonly used was cisplatin-based protocols in 34.6% of LC patients.

We observed high variability of computed tomography (CT) and radiological findings (Figures 1 and 2). On chest X-rays, the highest number of patients had bilateral pneumonia (33/81), and on CT examination, most patients had chest multilobar pneumonia (52/81). Overall, multilobar

Table 2

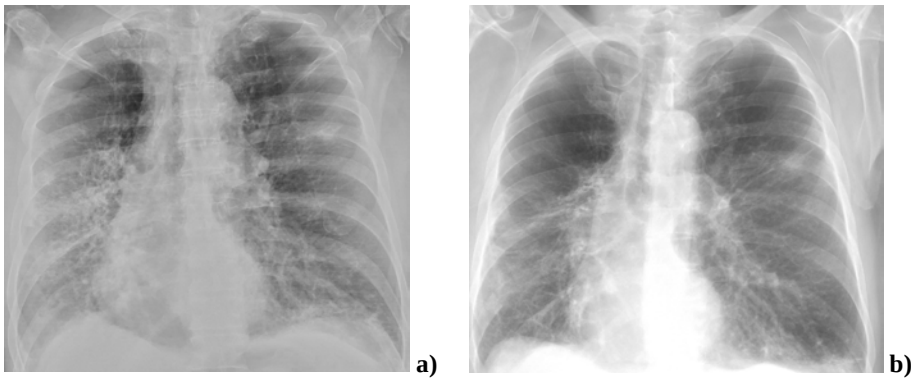
Anticancer treatment of lung cancer (LC) patients with coronavirus disease 2019 (COVID-19) (n = 81)

Treatment type	Number (%) of patients
Chemotherapy	29 (35.8)
Radiotherapy	43 (53.1)
Targeted therapy	2 (2.5)
Immunotherapy	6 (7.4)
Combined chemoradiotherapy	1 (1.2)



a) b)

Fig. 1 – a) Computed tomography (CT) findings and b) Radiological findings in patients with lung cancer (LC) at the time of diagnosis of coronavirus disease 2019 (COVID-19): bilateral pneumonia in a 71-year-old male with stage IV non-small-cell LC treated with first-line cisplatin-based chemotherapy.



a) b)

Fig. 2 – a) and b) Radiological findings in patients with lung cancer (LC) at the time of diagnosis of coronavirus disease 2019 (COVID-19): radiological regression of bilateral pneumonia in a 62-year-old male with stage III squamous cell carcinoma treated with chest radiotherapy.

pneumonia was the most common radiological presentation in 64.2% of patients.

Respiratory failure type 1 was registered in 76 (93.8%) patients and type 2 in 5 (6.2%) patients. Oxygen therapy was administered to all patients: in 69 (85.2%) patients with the regular cannula and in 9 (11.1%) with a high-flow nasal cannula. Non-invasive ventilation was performed in 2 (2.5%) patients, and one (1.2%) patient was treated in the Intensive Care Unit with invasive mechanical ventilation (Table 3).

Overall, 64 (79.0%) patients were treated with antibiotics, while antiviral drugs were administered to 3 (3.7%) patients. Anticoagulant therapy with nadroparin was introduced to 76 (93.8%) examined patients. In two (2.5%) patients, thromboembolic events were diagnosed during hospitalization (Table 3). Corticosteroid therapy was performed in 77 (95%) patients, while tocilizumab was not administered to any patients. Renal replacement therapy or extracorporeal membrane oxygenation has not been administered. Finally, our results showed that 16 (19.8%) patients with LC died from the COVID-19, while 65 (80.2%) patients survived the infection (Table 3).

Table 3

Outcomes of lung cancer (LC) patients with coronavirus disease 2019 (COVID-19) (n = 81)

Parameter	Number (%) of patients
Evolution	
alive	65 (80.2)
died	16 (19.8)
Antibiotics	64 (79.0)
Antiviral treatment	3 (3.7)
Corticosteroids	77 (95.1)
Anticoagulants	76 (93.8)
Oxygen support	
regular cannula	69 (85.2)
high-flow nasal cannula	9 (11.1)
NIV	2 (2.5)
IMV	1 (1.2)

NIV – noninvasive ventilation; IMV – invasive mechanical ventilation.

The mortality rate in a series of our patients was 19.8% (16/81 patients). Univariate analysis showed a statistically significant association between the ECOG PS and mortality rate ($p = 0.011$) (Table 4). The highest number of deaths was observed in patients treated with radiotherapy – 8 (9.8%) patients, followed by chemotherapy – 5 (6.17%) patients. We did not observe a statistically significant correlation between the type of antitumor therapy and mortality ($p = 0.973$) (Table 4).

Table 4

Predictive factors of mortality in lung cancer patients with coronavirus disease 2019 (COVID-19) (n = 81)

Variables	*p*
Treatment type	0.973
Stage	0.890
ECOG PS	0.011

ECOG PS – Eastern Cooperative Oncology Group Performance Status.

Discussion

One of the most important challenges for oncologists during the COVID-19 pandemic is the possible effect of applied specific anticancer treatment on morbidity and mortality of SARS-CoV2 infected cancer patients. This study highlights the importance of treating patients with LC, despite their high susceptibility to COVID-19.

Clinical characteristics and results of treatment in 81 patients with LC hospitalized due to confirmed SARS-CoV2 infection presented in our study showed that the majority of patients were men (67.9%), smokers (55.6%), and, in average, 66.47 years old (range 43–83). The largest number of patients had the ECOG PS 1 (50.6%). Most patients (83.9%) had at least one comorbidity (arterial hypertension in 66.7%, COPD in 8.4%, and diabetes mellitus in 21% of patients). According to the histopathological LC type, the most common were adenocarcinoma (33.3%), followed by squamous cell carcinoma (30.9%), and small-cell LC (24.7%). Regarding the stage of the disease, 63% of the patients were in stage III, while 33.3% were in stage IV at the time of the confirmed COVID-19. Metastases were most often localized in the contralateral lungs and pleura (14.8%), brain (6.2%), and the bones and liver (3.7% each). This result is comparable to the average demographic data of LC patients in the world [22].

In a study by Luo et al. [23] from the Memorial Sloan Kettering Cancer Center (MSKCC), which included 102 patients with diagnosed LC and COVID-19, 52% were women. The mean age was 68 years (range 31–91), 64% were smokers, and 72% had active or metastatic LC. The global registry for patients with LC and confirmed COVID-19 TERAVOLT (Thoracic Cancers International COVID-19 Collaboration) initially included a total of 200 patients from 21 countries [24] and is expanded to 1,012 patients [25]. The patients were predominantly men (70.5%), current or former smokers (81.1%), with NSCLC (non-small-cell LC) (75.5%) in the metastatic stage (73.5%) with comorbidities (83.8%) [24, 25].

The mortality rate in our study was 19.8%, which corresponds with most of the available results. Most of the available data suggest that mortality from COVID-19 in patients with malignancy is 25% to 30%, but not for all types of cancer equally [9, 16, 26, 27]. The results indicate that patients with LC and hematological malignancies have the highest risk of death from COVID-19 [28, 29]. According to data from Wuhan, China. [16], active anticancer treatment administered 14 days before SARS-CoV-2 infection in 28 cancer patients, statistically significantly increased the risk of severe COVID-19 outcomes (HR 4.079, $p = 0.037$), with a mortality rate of 28.6%. Dai et al. [30] presented the treatment results of immunotherapy-treated LC patients infected with SARS CoV2. Although the study had a small number of patients, the mortality rate was 66.7%. Luo et al. [23] observed a mortality rate of 25% and revealed that pulmonary comorbidities such as COPD or smoking history were most associated with poor disease outcomes. However, according to their results, anticancer treatment, radiotherapy, or surgery, as well as the presence of the active and metastatic

disease, did not affect the most severe outcome of COVID-19. However, some studies have shown significantly lower mortality in this population. Calles et al. [28] published the results of a study of 23 LC patients who received systemic anticancer therapy where the mortality rate of COVID-19 was 2.1%, with no difference concerning the type of oncological treatment.

All patients included in this study were treated with systemic anticancer therapy or radiotherapy at the time of diagnosis of COVID-19. The highest number of deaths was in patients treated with radiotherapy – 8 (9.8%) patients, followed by patients receiving chemotherapy – 5 (6.17%) patients, but no statistically significant correlation between the type of oncology therapy and mortality was observed ($p = 0.973$).

Results of the impact of the type of oncology treatment on the outcome of COVID-19 are diverse, and the approach to patients with a diagnosed malignant disease has changed under the influence of the ongoing pandemic. The results of the TERAVOLT study showed an increased risk of death from COVID-19 for patients with LC treated with chemotherapy (hazard ratio-HR 1.71) but not in patients treated with immunotherapy or targeted therapy (HR 1.04) [24, 25]. A retrospective study of Memorial Sloan Kettering conducted on LC patients and COVID-19 showed that, although mortality was 25%, anti-cancer therapy had no effect on poor outcomes [23]. Lee et al. [31] published the results of a large cohort study involving 800 patients. They reached a mortality rate of 27% in 281 patients with active cancer treated with chemotherapy one month before COVID-19. As the mortality rate in patients not treated with chemotherapy was 29%, the authors concluded that chemotherapy was not a significant risk factor for mortality from COVID-19.

These results suggest that anticancer treatment does not increase mortality from COVID-19. The study included patients with different types of cancer, a wide range of anticancer treatments, as well as the impact of comorbidities, which may be limiting factors in interpreting the results.

According to an analysis conducted by Luo et al. [23], which included only patients with LC, immunotherapy associated with smoking status was an independent predictor of poor outcomes of COVID-19. The study from the Gustave Roussy Center in Paris included 137 cancer patients with COVID-19. Among those patients, 12 (10.1%) had LC and, in univariate analysis, chemotherapy treatment in the last 3 months significantly increased the risk of clinical deterioration with HR 2.60 ($p = 0.006$), while chemotherapy or immunotherapy were without the effect [32].

In our study, univariate analysis showed a statistically significant correlation between mortality and the ECOG PS ($p = 0.011$). It is known that clinic characteristics of the patient certainly affect the outcome of the disease, and the ECOG PS is only one of them. In the study by Kuderer et al. [13], an increased risk of severe complications in patients with COVID-19 was associated with an ECOG higher than 2. In the largest multicenter retrospective cohort study from China, which included 13,077 patients with COVID-19, 23 were with LC. In this subgroup of patients, the mortality rate was 39%. This study also confirmed that the ECOG PS $\geq$ 2, metastatic stage of disease, and older age were associated with an increase in mortality rate [12]. In the already mentioned study by Barlesi et al. [32], conducted by the Gustave Roussy Center, multivariate analysis confirmed a statistically significant effect of the ECOG PS on the poor outcome with HR 3.9 ($p = 0.008$).

Treatment of patients with LC during the COVID-19 pandemic should include careful and regular monitoring of clinical and radiological changes, more so than in patients with other types of malignancies. It is recommended that cancer patients be tested for SARS-CoV-2 at the beginning of treatment and during therapy in case of clinical suspicion of COVID-19 [33].

Our study has several limitations. This trial was conducted in a single institution as a retrospective study with a limited follow-up period. A possible underestimation of the actual incidence of COVID-19 in our study population may be due to false-negative RT-PCR tests, as well as the inability to display patients diagnosed outside of our hospital system. We did not include patients with an active disease without specific cancer therapy (*eg*, patients receiving the best supportive care) in the definition of an "at-risk" population. The impact of COVID-19 on these patients is an important area for future research.

Conclusion

The COVID-19 pandemic affected all aspects of the management of LC patients. The diagnostic and therapeutic approach to patients with LC has been changed due to incoherent and insufficient data. The biological and clinical aggressiveness of this type of cancer generally does not allow discontinuation or delay of specific anticancer treatment. Careful monitoring of the clinical condition and radiological status of LC patients on active treatment during a pandemic is highly recommended. Research on a larger number of patients is needed to make recommendations for optimal measures to reduce patient exposure to COVID-19, best treatment strategies, and safe implementation of anticancer procedures.

REFERENCES

1. *Round T, L'Esperance V, Bayly J, Brain K, Dallas L, Edwards JG,* et al. COVID-19 and the multidisciplinary care of patients with lung cancer: an evidence-based review and commentary. Br J Cancer 2021; 125(5): 629–40.
2. *Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y,* et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497–506.
3. *Seth G, Sethi S, Bhattarai S, Saini G, Singh CB, Aneja R.* SARS-CoV-2 Infection in Cancer Patients: Effects on Disease Outcomes and Patient Prognosis. Cancers (Basel) 2020; 12(11): 3266.
4. *Liang W, Guan W, Chen R, Wang W, Li J, Xu K,* et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020; 21(3): 335–7.

5. *Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J,* et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect 2020; 81(2): e16–e25.
6. *D'Antiga L.* Coronaviruses and Immunosuppressed Patients: The Facts during the Third Epidemic. Liver Transpl 2020; 26(6): 832–4.
7. *Xia Y, Jin R, Zhao J, Li W, Shen H.* Risk of COVID-19 for patients with cancer. Lancet Oncol 2020; 21(4): e180.
8. Are Patients with Cancer at Higher Risk of COVID-19? Available online: https://www.oncnursingnews.com/web-exclusives/are-patients-with-cancer-at-higher-risk-of-covid-19 [accessed on 2020 April 21].
9. *Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S.* Severity of COVID-19 in patients with lung cancer: evidence and challenges. J Immunother Cancer 2021 9(3): e002266.
10. *Giannakoulis VG, Papoutsi E, Siempos II.* Effect of Cancer on Clinical Outcomes of Patients with COVID-19: A Meta-Analysis of Patient Data. JCO Glob Oncol 2020; 6: 799–808.
11. *Venkatesulu BP, Chandrasekar VT, Girdhar P, Advani P, Sharma A, Elumalai T,* et al. A Systematic Review and Meta-Analysis of Cancer Patients Affected by a Novel Coronavirus. JNCI Cancer Spectr 2021; 5(2): pkaa102.
12. *Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B,* et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020; 21(7): 893–903.
13. *Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR,* et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020; 395(10241): 1907–18.
14. *Wang Z, Wang J, He J.* Active and Effective Measures for the Care of Patients with Cancer during the COVID-19 Spread in China. JAMA Oncol 2020; 6(5): 631–2.
15. *Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K,* et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicenter, retrospective, cohort study. Lancet Oncol 2020; 21(7): 904–13.
16. *Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R,* et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. Ann Oncol 2020; 31(7): 894–901.
17. *Tian J, Miao X.* Challenges and recommendations for cancer care in the COVID-19 pandemic. Cancer Biol Med 2020; 17(3): 515–8.
18. *Jee J, Foote MB, Lumish M, Stonestrom AJ, Wills B, Narendra V,* et al. Chemotherapy and COVID-19 outcomes in patients with cancer. J Clin Oncol 2020; 38(30): 3538–46.
19. *Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M,* et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020; 26(8): 1218–23.
20. Republic Expert Commission for Supervision of Hospital Infections of the Ministry of Health of the Republic of Serbia. Guidelines on measures to prevent and control the spread of Sars-Cov-2 virus in health care facilities. Belgrade, March 12, 2020. Available from: https://www.batut.org.rs
21. Ministry of Health of the Republic of Serbia. Protocol of treatment of patients with COVID-19. v.8. Belgrade: Ministry of Health of the Republic of Serbia; 2020.
22. *Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A,* et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3):209-249.
23. *Luo J, Rizvi H, Egger JV, Preeshagul IR, Wolchok JD, Hellmann MD.* Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers. Cancer Discov 2020; 10(8): 1121–8.
24. *Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F,* et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 2020; 21(7): 914–22.
25. *Baena Espinar J, Torri V, Whisenant J, Hirsch FR, Rogado J, de Castro Carpeño J,* et al. LBA75 defining COVID-19 outcomes in thoracic cancer patients: TERAVOLT (thoracic cancERs international coVid 19 collaboration). Ann Oncol 2020; 31: S1204–5.
26. *Bakouny Z, Hawley JE, Choueiri TK, Peters S, Rini BI, Warner JL,* et al. COVID-19 and Cancer: Current Challenges and Perspectives. Cancer Cell 2020; 38(5): 629–46.
27. *Saini KS, Tagliamento M, Lambertini M, McNally R, Romano M, Leone M,* et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. Eur J Cancer 2020; 139: 43–50.
28. *Calles A, Aparicio MI, Alva M, Bringas M, Gutierrez N, Soto J,* et al. Outcomes of COVID-19 in Patients with Lung Cancer Treated in a Tertiary Hospital in Madrid. Front Oncol 2020; 10: 1777.
29. *Horn L, Garassino M.* COVID-19 in patients with cancer: managing a pandemic within a pandemic. Nat Rev Clin Oncol 2021; 18(1): 1–2.
30. *Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z,* et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multicenter study during the COVID-19 outbreak. Cancer Discov 2020; 10(6): 783–91.
31. *Lee LY, Cazier JB, Angelis V, Arnold R, Bisht V, Campton NA,* et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020; 395(10241): 1919–26.
32. *Barlesi F, Foulon S, Bayle A, Gachot B, Pommeret F, Willekens C,* et al. Abstract CT403: Outcome of cancer patients infected with COVID-19, including toxicity of cancer treatments. Cancer Res 2020; 80(16 Suppl): CT403.
33. *Calabrò L, Peters S, Soria JC, Di Giacomo AM, Barlesi F, Covre A,* et al. Challenges in lung cancer therapy during the COVID-19 pandemic. Lancet Respir Med 2020; 8(6): 542–4.

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