Abstract. COVID-19 reinfection, although a controversial issue, is an important clinical problem in cancer patients and beyond. The present study aimed to identify the risk factors associated with worse outcomes in cancer patients with Covid-19 in both first infection and reinfection and to describe the involvement of vaccines in reinfection outcome. The present study enrolled 85 patients with solid tumors who had Covid-19 infection and had not been previously vaccinated. Classical risk factors associated with worse outcomes in cancer patients with second SARS-CoV infection were considered. The patients were followed up retrospectively, measuring mortality at the first and second infection and the vaccination rate after the first infection. The factors associated with the highest risk of mortality at the first infection were, in order of importance: intensive care unit (ICU) admission, unfavorable performance status, radiologically quantifiable presence of oncological disease, and administration of cytotoxic chemotherapy in the period immediately before infection. The risk factors associated with higher mortality from reinfection were ECOG 3-4 performance status and administration of cytotoxic chemotherapy in the period immediately before infection. In the studied patients, mortality from reinfection was not affected by prior vaccination. Thus, bearing in mind all of these risk factors for poor outcomes in cancer patients with solid tumors presenting with Covid-19 can help the treating oncologists make personalized decisions about patient care during the pandemic.

Introduction

Globally, more than 275 million confirmed cases of COVID-19, including more than 5.3 million deaths, were registered by December 23, 2021, and over 8.3 billion vaccine doses have been administered (1). Research has shown that cancer is an important risk factor for COVID19-related morbidity and mortality. The mortality rates for COVID19-positive cancer patients widely range from 9 to 33%, with an Intensive Care Unit (ICU) mortality rate of over 41% (2,3). High mortality rates were observed in cancer patients with associated comorbidities such as diabetes, obesity, hypertension, cardiovascular or respiratory diseases (4,5). Moreover, among all solid cancers, pulmonary cancer patients had a particularly higher overall mortality rate (6).

Although the term reinfection is somewhat controversial, the recurrence of infection is an obvious clinical issue. After a search in the current literature, we found no trials addressing the question of the effect of COVID-19 vaccination after first infection on the mortality of cancer patients. Immunocompromised subjects are known to be more susceptible to COVID-19 reinfection but there is a lack of previous research studies on this topic.

The present study meets the need for these data. The present study aimed to assess the risk factors associated with worse outcomes, following first and second SARS-COV2 infection in cancer patients. We also highlight the interest to identify features of vulnerable COVID-19 reinfected patients. These risk factors may influence treatment decisions and require careful evaluation.
Patients and methods

The present study is retrospective, observational, and enrolled solid cancer patients diagnosed with COVID-19 by reverse transcription-polymerase chain reaction (RT-PCT) between November 2020 and September 2021. At Elias University Emergency Hospital (Bucharest, Romania), where this trial took place, all patients were tested before starting treatment as a precaution method for virus spreading in an exposed population. Signing the informed consent was mandatory for inclusion. Patients vaccinated before the first infection were excluded. The purpose of the present study was to establish whether vaccination after the first infection can reduce the mortality rate in the second one infection. Thus, we decided to exclude per primam vaccinated patients. Data related to general clinical features (age, sex, smoking status, cancer site, presence of quantifiable disease at first infection, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, types of comorbidities, and the type of systemic treatment during the first infection were recorded, and the patients were monitored for COVID-19 reinfection and secondary prophylaxis. Variables included: the number of days that the RT-PCR test remained positive, the SARS-CoV2 reinfection, the time in months until the reinfection, the fatality of the second infection, if the first or second infection required hospitalization in the intensive care unit (ICU) and vaccination after the first infection. None of the patients suffered from any conditions that might have impaired their immune response (complete blood counts had values in the normal ranges). Patients with hematological adverse effects to oncologic treatment were not included in the analysis. For a patient to be considered re-infected, an interval of at least 28 days was required between a negative RT-PCT test after the first infection and a positive one. Mortality in the patients studied was quantified if the death occurred within 30 days of SARS-CoV-2 infection and if the patient was still positive. This protocol was approved by the Elias Emergency University Hospital Ethics Committee.

Statistical analysis was performed using SPSS statistics version 20 (IBM Corp.). Non-parametric tests were used to compare the descriptive characteristics. The Fisher exact test was used due to the sample sizes. A result was considered statistically significant if the P-value was <0.05.

Results

A total of 85 patients who met the inclusion criteria were enrolled. However, 3 patients were lost to follow-up. The analysis was made for the 83 remaining patients. The clinical characteristics of the patients are included in Table I (sex, age, smoking status and comorbidities). Data related to the neoplastic disease are listed in Table II; details addressing cancer status, the treatment they underwent during infection and their performance status were considered most significant.

Of the total 83 infected patients, 15 (18.1%) required care in the ICU. The mortality in the first infection was 22.9% (19 patients of the total 83 died within 30 days of the first positive test). The average number of days of SARS-CoV-2 positivity at the first infection was 24.3 [4-90; Std. Dev. (SD) 14.7]. Of the patients studied, 9 out of 83 (10.8%) were reinfected. The average duration to reinfection measured in months was 0.4 months (1-10 months; SD, 1.61). 18 patients of the total 83 (21.7%) were vaccinated after the first infection. Of the reinfeected patients, 5 (6% of the total 83 included at first) were admitted to the ICU and all died, with a mortality of 6% compared to the initial number of patients studied, and 55.5% compared to the number of reinfeected patients (9 patients in total).

The univariate analysis of risk factors for death at first infection is summarized in Table III. With logistic regression analysis, independent factors associated with increased 30-day mortality, after partial adjustment, were smoker status (smokers had a 2-fold increase in the risk of death compared to non-smokers), cytotoxic chemotherapy (those who received cytotoxic chemotherapy during the time they tested positive had a 3.2-fold increase in the risk of death compared to those who received other therapies), patients admitted to the ICU had a 48.8-fold increase in the risk of death and finally, patients with detectable disease had a 9.1-fold increase in the risk of death compared to those who had no detectable cancer.

The univariate analysis of the risk factors for death from reinfection included the performance status reported as ECOG 1-2 and 3-4, whether cytotoxic chemotherapy was administered during reinfection and the vaccination status. The highest relative risk (OR=15.05; 95% CI, 1.28-24.57) was found to be an unfavorable performance status. The remaining values are documented in Table IV.

Discussion

Sex, smoking status and various comorbidities (discussed below) have been described in the literature as factors influencing the course of SARS-CoV-2 infection. Landmark studies consider that mortality and ICU admission rates are elevated for SARS-CoV-2 patients with obesity, hypertension, diabetes, chronic obstructive pulmonary disease, and former smokers. The risk of mortality was also found to be highly associated with lung cancer, recent surgery, age over 75 years, or poor ECOG performance status (4-8).

One trial suggests that cancer status, the oncological treatment during infection and the performance status are the most important in predicting patient outcome, and these
were our specific focus (5). In the present study, the factors that correlated the highest with mortality in the first infection were ECOG performance status 3–4 and ICU admission; these correlations were also statistically significant. The presence of detectable disease was also an important risk factor for death.

Whether or not the type or the time of administration of chemotherapy influences the mortality in COVID-19 positive cancer patients, is not fully understood. Early data suggest that different cancer treatments within 14 days of the COVID-19 diagnosis were associated with higher mortality and morbidity (9). However, recent studies have come to different conclusions. Patients who received cancer treatments in the last 30 days of the COVID-19 diagnosis were found to have an increased risk of death from SARS-Cov-2 infection (7,10,11).

Table II. Oncological characteristics of the patients.

| Variable                              | No. (%)    |
|---------------------------------------|------------|
| Cancer type                           |            |
| Other types of cancer                 | 71 (85.5%) |
| Lung cancer (both NSCLC and small cell lung cancer) | 12 (14.5%) |
| Cancer status                         |            |
| No detectable cancer                  | 3 (3.6%)   |
| Detectable cancer, but responding to treatment | 32 (38.6%) |
| Progressive disease                   | 48 (57.8%) |
| Cancer treatment during the infection period |          |
| Had NOT received oncological treatment in the last 4 weeks before COVID-19 | 34 (41%) |
| Had received oncological treatment in the last 4 weeks before COVID-19 | 49 (59%) |
| ECOG status                           |            |
| 1                                     | 39 (47%)   |
| 2                                     | 19 (22.9%) |
| 3                                     | 14 (16.9%) |
| 4                                     | 11 (13.3%) |

NSCLC, non-small cell carcinoma; ECOG, Eastern Cooperative Oncology Group.

Table III. Univariate analysis of risk factors for death at first infection.

| Variable                                           | OR         | 95% CI       | Statistical significance (P-value) |
|----------------------------------------------------|------------|--------------|-----------------------------------|
| Smoker patient                                     | 2.05       | (0.39-10.6)  | 0.380                             |
| Male sex                                           | 1.20       | (0.23-6.20)  | 0.080                             |
| Cytotoxic chemotherapy as treatment when infected  | 3.26       | (0.62-17.02) | 0.160                             |
| Admitted to the ICU                                 | 48.86      | (7.96-50.2)  | <0.001                            |
| Oncological disease present (radiologically)       | 9.12       | (1.04-12.34) | 0.040                             |
| ECOG 3-4                                            | 13.49      | (4.02-35.08) | <0.001                            |

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Table IV. Univariate analysis of the risk factors for death after reinfection with SARS-Cov2 in the studied population.

| Variable                                           | OR         | 95% CI       | Statistical significance (P-value) |
|----------------------------------------------------|------------|--------------|-----------------------------------|
| ECOG 3-4                                            | 15.05      | (1.28-24.57) | 0.050                             |
| Vaccinated                                         | 1.89       | (0.12-28.19) | 0.630                             |
| Cytotoxic chemotherapy as treatment when infected  | 9.53       | (0.92-98.6)  | 0.050                             |

OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.
Given the existing data, cancer treatment was reported in our study as sooner or later than a 4-week interval before COVID-19. Recent administration of cytotoxic chemotherapy before COVID-19 influenced the patient outcome. The COVID-19 and Cancer Consortium, suggest that chemotherapy treatments containing platinum salt plus etoposide, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), or DNA methyltransferase inhibitors, administered within 90 days of a COVID-19 diagnosis predispose to a worse outcome (12-14). Data regarding other types of systemic therapy is, however, controversial. One study raised the hypothesis that immune checkpoint inhibitors increase the risk of hospitalization and death (8). Yet, one systematic review reached the opposite conclusion (14).

With this in mind, our study focused on cytotoxic chemotherapy only and its impact on COVID-19 outcome. Mortality was high for the patients receiving this type of treatment before the first infection (OR=3.26; 95% CI, 0.62-17.02; P=0.160) and higher for the reinfection mortality (OR=9.53; 95% CI, 0.92-98.6; P=0.050).

To define second infection or SARS-COV-2 reinfection, we have to understand its replication and infectivity. Evidence suggests that the estimated time to recovery from SARS-COV-2 infection is between 2 to 6 weeks, given the viral load decrease 28 days after the onset of symptoms. Therefore, the definition of COVID-19 reinfection includes an initial positive PCR test result, a consecutive negative PCR test after clinical recovery, and a new confirmatory PCR-positive test at least 28 days after the last positive test (15-17).

In the present study, only 10.3% of the patients were reinfeected. This can both be explained by strict adherence of patients to preventive measures and by the protective natural immunity after the first infection.

The state of immunosuppression can be induced by hematological or solid malignancies, or by the cancer treatment itself. Researchers found that cancer patients with COVID-19 infection and suppressed immune function have a decline in circulating lymphocytes. In consequence, lymphopenia may jeopardize viral clearance. Throughout the SARS-Cov-2 infection, immunocompromised patients show prolonged viral shedding and persistent symptoms (18-22). The median duration of positivity in the first infection in our patients was longer than the one reported for non-cancer patients (24.3 days).

Real-world data concerning COVID-19 vaccination in cancer patients are limited. But researchers have investigated the willingness to take the COVID-19 vaccination in Korean, French, Polish, and Romanian cancer patients. Over 61.8% of cancer patients from Korea were willing to take the COVID-19 vaccination, which is higher than that in the French (53.7%), Polish (53.7%), and Romanian (55.5%) surveys (23-26).

The results of our study demonstrated that vaccination did not influence the mortality from reinfection in patients with solid tumors. This information is in no way intended to discourage vaccination in cancer patients. However, even though cancer patients are associated with poor COVID-19 clinical outcomes, the efficacy of anti-SARS-CoV-2 vaccines is unknown because they were largely excluded from vaccination trials. Previous studies have shown that patients with compromised immune systems do not develop a protective immune response to the flu vaccination (27). In the era of COVID-19, data suggest that cancer and cancer treatments can affect the immune system, which can diminish the efficacy of the vaccine (28).

A study evaluating the efficacy of the Pfizer vaccine showed that after one dose of vaccine, only 29% of the cancer patients developed antibodies, compared with 84% in the control immunocompetent group, and almost 86% do so after their second dose (29,30). Thus, what should patients who do not mount an effective immune response do? The answer to this question can probably be found in the data on booster doses and cancer patients should be considered first candidates for them (31).

In the patients enrolled in this study, the vaccination rate was low (only 21.7% decided to have the vaccine after the first infection). One reason for the low percentage could have been that patients relied on the resulting protective immunity. The vaccine, as commented before, did not prove to be a protective factor against death in the second reinfection. The number of the studied patients is not high enough for the correlation to have statistical significance, but the idea that prevention is not the same in cancer patients as in the general population has to be kept in mind. We plan another prospective trial that will compare outcomes in per primam vaccinated patients vs. non-vaccinated ones.

One possible limitation of the present trial was that the measurement of the COVID-19 antibody titer was not possible in our institution for all the enrolled patients. This was the reason why this information was not presented.

In conclusion, the present study found that ICU admission, unfavorable performance status, a radiologically quantifiable presence of oncological disease, and administration of cytotoxic chemotherapy in the period immediately before infection were important risk factors for mortality in first-infected COVID-19 solid cancer patients. The risk factors for reinfection included ECOG 3-4 performance status and the administration of cytotoxic chemotherapy. The vaccination status did not influence mortality in the second reinfection. All of these data can broaden the treating oncologists’ perspectives on their patients during the COVID-19 pandemic and can help them make decisions accordingly.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
CNi, COS and AIP made substantial contributions to the design, and acquisition, analysis and interpretation of data. AIP also agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MO, AMP, CP, CI, RV and MIS collected and analyzed the data. AMP, AOM and DB provided technical
support and contributed to the statistical analysis. CNE made substantial contributions to the analysis and interpretation of data and gave final approval for the version to be published. All authors confirm the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study received approval from Elias University Emergency Hospital Ethics Committee (approval no. 8767/22.12.2021). All patients provided written informed consent for participation.

Patient consent for publication

All patients provided written informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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