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COVID-19 in Patients with Active Cancer: Higher Inflammatory Activity Predicts Poor Outcome

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Keywords
Active cancer · COVID-19 · Inflammatory activity · Hyperinflammation

Abstract
Introduction: Active malignancies have been identified as an independent risk factor for severity and mortality in COVID-19. However, direct comparisons between SARS-CoV-

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2-infected patients with active (acP) and non-active cancers (n-acP) remain scarce. ***Patients and Methods:*** We retrospectively analyzed a cohort of cancer patients with PCR-confirmed SARS-CoV-2 infection, enrolled from March 16, 2020, to July 31, 2021. Data on demographics, cancer, and laboratory findings were collected. Descriptive and subsequent regression analyses were performed. Endpoints were "deterioration to severe COVID-19" and "infection-associated mortality." ***Results:*** In total, 987 cancer patients (510 acP vs. 477 n-acP) were included in our analysis. The majority was >55 years old, more men than women were included. At detection of SARS-CoV-2, 65.5% of patients had mild/moderate symptoms, while deterioration to severe COVID-19 was slightly more common in acP (19 vs. 16%; p = 0.284). COVID-19-associated mortality was significantly higher in acP (24 vs. 17.5%, $p < 0.001$). In terms of laboratory tests, severe cytopenia and elevated levels of inflammatory markers were common findings in acP at baseline, particularly in those who developed a severe infection or died. Multivariate analysis revealed that ferritin (HR 14.24 [2.1–96], p = 0.006) and CRP (HR 2.85 [1.02–8.02], p = 0.046) were associated with severity and mortality. In n-acP, association was seen for ferritin only (HR 4.1 [1.51–11.17], p = 0.006). ***Conclusion:*** Comparing patients with active and non-active cancer, the former showed higher mortality rates. Also, inflammatory markers were significantly increased, assuming higher levels of inflammation may play a role in the adverse outcome of COVID-19 in aCP. © 2023 S. Karger AG, Basel

Introduction

In December 2019, the first cases of respiratory tract infections caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in Wuhan, China [1]. After its initial description, it has rapidly spread throughout the world and reached a pandemic of global scale [2]. By now, more than 766 million confirmed cases and 6,900,000 deaths have been reported to the World Health Organization [3]. Over the years, the virus has rapidly evolved into a wide range of variants with different properties affecting transmissibility, immunity, and pathogenicity [4]. At the present, omicron is the dominant variant, being highly transmissible but less severe compared with previous variants [5, 6].

Although many individuals infected with SARS-CoV-2 remain asymptomatic, the virus can cause a variety of symptoms, ranging from mild flu-like symptoms to life-threatening respiratory insufficiency. Triggered by SARS-CoV-2 hyperinflammatory syndrome, severe courses with need for mechanical ventilation, hemodialysis, and extracorporeal perfusion procedures have been described [7, 8].

In addition to advanced age, male sex, and number of comorbidities, several studies identified active cancer as an independent risk factor for severe illness and increased mortality, with the highest rates observed in patients with advanced cancer not adequately controlled by therapy [9–11]. Notably, neither the duration of disease nor the type of anti-cancer treatment showed a significant correlation with an adverse clinical outcome [11–14]. However, direct comparisons between patients with active and non-active cancer are scarce. We therefore performed a follow-up analysis of SARS-CoV-2-infected patients with cancer from the Lean European Open Survey on SARS-CoV-2 (LEOSS) registry to compare epidemiologic, clinical, and laboratory characteristics of patients with active and non-active cancer and to identify parameters predicting a higher risk of severe infection course and COVID-19 mortality [15].

Materials and Methods

Patient Population and Data Collection

In March 2020, the multicenter LEOSS registry was established to rapidly gain insights into the epidemiology and clinical course of patients infected with SARS-CoV-2. Data collection was based on an electronic case report form (eCRF) hosted on ClinicalSurveys.net, a website developed by the University Hospital Cologne. The database contains data from patients with RT-PCR-confirmed SARS-CoV-2 infection who were treated as in- or outpatients at one of the LEOSS study sites. The clinical manifestation of COVID-19 has been described in four phases: (i) uncomplicated (oligo-/asymptomatic), (ii) complicated (need for oxygen supplementation), synonymous with non-severe COVID-19, (iii) critical (need for life-supporting therapy) synonymous with severe COVID-19, and (iv) recovery (clinical improvement/discharge). Cohort compilation and initial results have been previously reported [15, 16].

In our study, only patients with available data on cancer activity, follow-up, or last known status were included. The day of the first positive SARS-CoV-2 PCR was defined as baseline. Of 987 patients with a cancer diagnosis enrolled in the LEOSS registry between March 16th and July 11th, 2021, 510 patients were identified with active cancer. Data analyzed included demographics, comorbidity according to Charlson Comorbidity Index (CCI), and cancer-related features such as entity, disease status at detection of SARS-CoV-2 (e.g., active cancer, remission), and information about the anti-cancer treatment (e.g., chemotherapy, high-dose steroids, targeted therapy, other immunosuppressive medication). Outcomes, symptoms, vital signs, and laboratory values were analyzed at baseline and during all phases of SARS-CoV-2 infection. Primary endpoints were the deterioration to severe COVID-19 and the infection-associated mortality. Because of the retrospective and anonymous nature of the registry, the respective ethics committees waived the requirement for written informed consent.

Statistical Analysis

Categorical variables were described as counts and percentages; continuous variables were presented as mean with standard deviation (±SD) or as median with interquartile range (IQR). When appropriate, data were analyzed with χ^2 or Fisher's exact test. For comparison of continuous data, a two-sided t test was used. For every statistical test, a significance level of 0.05 was assumed.

Table 1. Patients' characteristics active cancer disease versus non-active cancer disease

	Active cancer disease (N = 510)	Non-active cancer disease (N = 477)	p value
Age categories, *n/N* (%)			<**0.001**
<18 years	6/510 (1)	0/477 (0)	
18–25 years	3/510 (0.5)	1/477 (0.5)	
26–35 years	12/510 (2.5)	6/477 (1.5)	
36–45 years	16/510 (3)	16/477 (3.5)	
46–55 years	47/510 (9)	35/477 (7.5)	
56–65 years	103/510 (20)	60/477 (12.5)	
66–75 years	126/510 (25)	97/477 (20.5)	
76–85 years	160/510 (31.5)	189/477 (39.5)	
>85 years	38/510 (7.5)	73/477 (15.5)	
Sex, *n/N* (%)			0.335
Female	228/510 (44.5)	198/477 (41.5)	
Male	282/510 (55.5)	279/477 (58.5)	
CCI (+/−SD)			
CCI	4.75 (+/−2.79)	3.85 (+/−2.16)	<**0.001**
Comorbidities, *n/N* (%)			
Hemiplegia	10/501 (2)	12/474 (2.5)	0.668
Dementia	28/499 (5.5)	66/473 (14)	<**0.001**
Cerebrovascular disease, stroke, TIA	48/500 (9.5)	64/470 (13.5)	0.056
Myocardial infarction	36/499 (7)	43/472 (9)	0.293
Chronic heart failure	47/495 (9.5)	59/468 (12.5)	0.149
Peripheral vascular disease	27/495 (5.5)	43/472 (9)	**0.034**
Hypertension	255/501 (51)	312/472 (66)	<**0.001**
Coronary artery disease	69/498 (14)	96/470 (20.5)	**0.008**
COPD	43/500 (8.5)	45/473 (9.5)	0.655
Asthma	16/501 (3)	19/474 (4)	0.606
Other chronic pulmonary disease	24/496 (4.5)	32/473 (7)	0.217
Connective tissue disease	2/501 (0.5)	3/475 (0.5)	0.679
Peptic ulcer disease	12/501 (2.5)	6/474 (1.5)	0.237
Chronic liver disease	11/500 (2)	3/475 (1)	0.057
Liver cirrhosis	18/501 (3.5)	15/474 (3)	0.727
Diabetes w/o end organ damage	52/499 (10.5)	80/475 (17)	**0.004**
Diabetes w end organ damage	43/498 (8.5)	43/474 (9)	0.822
Chronic kidney disease	95/501 (19)	115/475 (24)	0.051
Acute kidney injury	42/489 (8.5)	33/455 (7.5)	0.242
Organ transplantation	7/499 (1.5)	4/475 (1)	0.548
Rheumatic disease	12/497 (2.5)	18/471 (4)	0.266
Obesity, *n/N* (%)			
BMI >30 kg/m^2	220/510 (43)	251/477 (52.5)	**0.003**
Smoking, *n/N* (%)			**0.008**
Active smoking	71/247 (28.5)	36/215 (16.5)	
Non-smoking	129/247 (52.5)	126/215 (58.5)	
Former smoking	47/247 (19)	53/215 (25)	
Underlying cancer disease (according to CCI), *n/N* (%)			
Solid tumor	190/499 (38)	377/477 (79)	<**0.001**
Solid tumor, metastasized	185/496 (37.5)	26/472 (5.5)	<**0.001**
Lymphoma	75/501 (15)	44/475 (9.5)	**0.008**
Leukemia	60/502 (12)	24/475 (5)	<**0.001**
Stem cell transplantation	15/499 (3)	14/474 (3)	1.000
Other hematological disease	62/334 (18.5)	22/328 (6.5)	<**0.001**
Non-hematological disease	319/510 (62.5)	385/477 (80.5)	<**0.001**
Hematological disease	191/510 (37.5)	92/477 (19.5)	
Date of diagnosis hematological/ oncological disease, *n/N* (%)			<**0.001**
<3 months	128/377 (34)	10/310 (3)	
3–6 months	33/377 (8.5)	10/310 (3)	
7–11 months	34/377 (9)	14/310 (4.5)	
1–2 years	64/377 (17)	43/310 (14)	

Table 1 (continued)

	Active cancer disease (*N* = 510)	Non-active cancer disease (*N* = 477)	*p* value
3–5 years	56/377 (15)	58/310 (19)	
6–10 years	34/377 (9)	65/310 (21)	
>10 years	28/377 (7.5)	110/310 (35.5)	
Disease status at detection of SARS-CoV-2, *n/N* (%)			
Remission	17/376 (4.5)	266/342 (78)	<**0.001**
Anti-cancer therapy (≤1 month)	174/509 (34)	31/475 (6.5)	<**0.001**
Steroid treatment (≥10 mg)	93/510 (17.5)	18/477 (4)	<**0.001**

CCI, Charlson Comorbidity Index; w/o, without; BMI, body mass index.

To explore a predictive value of the laboratory findings at baseline uni- and multivariate logistic regression analyses were performed. All statistical analyses were conducted using SPSS software version 29.0 (IBM, Corp., Armonk, NY, USA).

Results

Baseline Characteristics

A total of 987 cancer patients (510 active vs. 477 non-active), of whom 979 (99%) were hospitalized, were included in our analysis. Detailed characteristics are shown in Table 1. The majority of patients included were older than 55 years, with a higher number of elderly individuals with non-active cancer. The proportion of women was 44.5% in patients with active and 41.5% in patients with non-active cancer, respectively. Mean CCI appeared to be higher in patients with active cancer as compared to those with non-active cancer (4.8 vs. 3.9, $p < 0.001$). In patients with active solid tumors, 38% showed a localized and 37.5% a metastasized tumor stage (multi-selection). Hematologic malignancies were observed in 37.5% of the patients. The most common entities summarized under active tumor disease were non-Hodgkin's lymphoma (19.0%), gastrointestinal cancer (14.5%), lung cancer (12.5%), prostate cancer (9.0%), and breast cancer (9.0%). In the cohort of patients with non-active cancer, 79% suffered from localized, 5.5% from metastasized solid tumors, 19.5% had a hematologic disease. In this group, the most frequent entities were prostate cancer (16.5%), breast (15.5%), gastrointestinal (13.5%), non-Hodgkin lymphoma (11%), and lung cancer (4.5%).

Thirty-four percent of patients with active cancer (vs. 6.5%, $p < 0.001$) received a specific anti-cancer treatment: cytotoxic agents were administered in 30% (139/465), targeted drugs in 21% (92/439), and immunosuppressants in 12.5% (55/442) of patients. Ninety-three patients with active (17.5%) and 18 patients with non-active cancer (4%, $p < 0.001$) were treated with steroids. Disease remission was observed in only 4.5% of patients with active cancer, compared with 78% of patients with non-active cancer ($p < 0.001$).

Clinical Course

At the time of the first SARS-CoV-2 positive PCR, the majority of patients in both cohorts had mild to moderate symptoms consistent with a non-severe stage of the disease (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000535267). Median lengths of hospital stay were 15 (IQR 8–26) days in patients with active cancer and 12 (6–22, $p = 0.007$) days in patients with non-active cancer, respectively. Although the majority required hospitalization, less than 5% showed signs of severe COVID-19 at baseline. The most common symptoms in patients with and without active cancer were fever in 33.5% versus 34.5% ($p = 0.779$), dry cough in 23.5% versus 28% ($p = 0.096$), and excessive tiredness in 17% versus 20% ($p = 0.232$). Progression to severe COVID-19 was observed in 19% (77/404) and 16% (63/394, $p = 0.284$), respectively. A total of 138 (27%) patients with active and 122 (25.5%, $p = 0.284$) patients with non-active cancer were admitted to an ICU. In critically ill patients, median time in the ICU was 11 (4–22.5) and 8 (4–18.75, $p = 0.172$) days, respectively. Mortality attributable to COVID-19 was between 24% and 17.5% ($p = 0.012$), with approximately half of all deaths occurring in ICUs. All-cause mortality was 1.7 times higher in patients with active cancer than in patients with non-active cancer (31 vs. 18.5%, $p < 0.001$).

Laboratory Findings

Laboratory Findings in Patients with Active and Non-Active Cancer at Baseline

In patients with non-severe COVID-19 at baseline, cytopenia occurred more frequently in patients with active cancer. Compared to patients with non-active cancer, they had significantly higher incidences of leukocyte levels (WBC) <4,000/μL (24.5 vs. 15.5%, $p = 0.009$) and absolute neutrophil (ANC) as well as lymphocyte

counts (ALC) < 500/μL (8.5 vs. 1.5%, $p = 0.002$ and 27 vs. 18%, $p = 0.002$). ANC >2,000/μL were documented for 38.5% and 36.5% ($p = 0.002$). Anemia with hemoglobin levels <8.0 g/dL was reported in 10% versus 6% ($p < 0.001$) and platelet counts <50,000/μL in 8.5% versus 0.5% ($p < 0.001$). Concomitantly, elevated inflammation markers were more common in patients with active cancer than in patients with non-active cancer. Here, CRP levels >120 mg/dL were seen in 21.5% versus 14.5% ($p = 0.017$), serum ferritin levels >500 ng/mL in 59% versus 47.5% ($p = 0.008$), IL-6 > 500 pg/mL in 2% versus 0% (0.332), and D-dimer levels more than twice the upper limit of normal in 74% versus 63% ($p = 0.176$). A detailed comparison of the laboratory findings of both groups is given in online supplementary Table S2.

Laboratory Findings in Patients with Active and Non-Active Cancer during Course of the Infection

During the infection, a higher rate of severe cytopenia was observed in patients with active cancer (online suppl. Table S3). Between UC/CO and CR, the relative frequency of leukopenia increased from 38.5% to 47.5%, neutropenia from 7% to 12.5%, lymphopenia from 28% to 53.5%, anemia from 19% to 49.5%, and thrombocytopenia from 12% to 30%. At the same time, the rate of patients with neutrophilia increased from 39% to 68%. In parallel, CRP (26–76%), IL-6 (1.5–46.5%), ferritin (9.5–38.5%), and D-dimers (15–53%) were also observed to increase.

In patients with non-active cancer, the incidence of neutrophilia increased from 34.5% to 75%, lymphopenia from 18.5% to 45%, anemia from 10% to 31%, and thrombocytopenia from 0.5% to 8%. In parallel, higher concentrations of CRP (18 vs. 72%), IL-6 (1 vs. 37.5%), ferritin (1 vs. 20%), and D-dimers (8 vs. 42%) were more frequently found in later stages of the infection (online suppl. Table S3).

Outcome

Outcome in Patients with Active Cancer

Patients with active cancer who developed a severe infection or died from COVID-19 were significantly more likely to show ANC <500/μL (death attributed to COVID-19: 6.5 vs. 18%, $p = 0.017$) and platelet count <50,000/μL (severe infection: 7.5 vs. 16.5%, $p = 0.045$; death attributed to COVID-19: 6.5 vs. 17.5%, $p = 0.004$) at baseline (online suppl. Table S4). Similar results were seen for Il-6 (severe infection: 0 vs. 13.5%, $p = 0.003$; death attributed to COVID-19: 0 vs. 10.5%, $p = 0.012$), CRP (death attributed to COVID-19: 19 vs. 32%, $p = 0.020$), and ferritin (severe infection: 54.5 vs. 90%, $p = 0.002$; death attributed to COVID-19: 51.5 vs. 89.5%, $p < 0.001$).

In a subsequent bivariate regression analysis, elevated CRP >120 mg/dL (HR 2.38, 95% CI [1.43–3.99], $p = 0.001$) and ferritin levels >500 ng/mL (HR 6.06, 95% CI [2.84–12.97], $p < 0.001$), as well as low platelets (HR 0.732, 95% CI [0.59–0.91], $p = 0.004$) appeared to be associated with severe COVID-19 or death attributed to COVID-19 (online suppl. Table S5). In multivariate analyses, CRP >120 mg/dL (HR 2.85, 95% CI [1.02–8.02], $p = 0.046$) and ferritin >4,000 ng/mL (HR 14.24, 95% CI [2.1–96], $p = 0.006$) were significantly associated with a severe course of infection and death due to COVID-19 (Table 2).

Outcome in Patients with Non-Active Cancer

Patients with non-active cancer who developed a severe infection or died from COVID-19 were significantly more likely to show WBC >12,000/μL (death attributed to COVID-19: 5 vs. 11%, $p = 0.015$), ALC <500/μL (severe infection: 15.5 vs. 40%, $p = 0.011$; death attributed to COVID-19: 15.5 vs. 34.5%, $p = 0.020$), and hemoglobin levels <12.0 g/dL (death attributed to COVID-19: 39.5 vs. 63%, $p = 0.006$) at baseline than patients with mild to moderate stages of infection (online suppl. Table S6). Similar was seen for CRP (severe infection: 12.5 vs. 29%, $p = 0.011$; death attributed to COVID-19: 9.5 vs. 38.5%, $p \leq 0.001$) and ferritin (severe infection: 43 vs. 75%, $p = 0.019$; death attributed to COVID-19: 40.5 vs. 78.5%, $p < 0.004$).

Univariate regression analysis revealed that WBC counts >12,000/μL (HR 2.36, 95% CI [1.19–4.67], $p = 0.014$), hemoglobin levels <12 g/dL (HR 0.62, 95% CI [0.41–0.96, $p = 0.032$), and an increase in CRP (HR 4.94, 95% CI [2.52–9.6], $p < 0.001$) and ferritin (HR 3.69, 95% CI [1.68–8.26], $p = 0.001$) were associated with severe infection or death from COVID-19 (online suppl. Table S5). In a subsequent multivariate analysis, only ferritin (HR 4.1, 95% CI [1.51–11.17], $p = 0.006$) was identified as being independently associated with severity and COVID-19-associated mortality (Table 2).

Discussion

This multicenter cohort study provides detailed information on clinical and laboratory findings in patients with active cancer infected with SARS-CoV-2 as compared to those with non-active cancer. Differences between the cohorts, possible reasons for an adverse clinical course, and factors relevant to the outcome were identified. All patients were enrolled in the LEOSS registry, an open, collaborative approach with more than 135 active European and non-European study sites launched during the early phase of the pandemic [17].

Our cohort consists of 987, mainly hospitalized cancer patients, and is characterized by an advanced age and a male predominance. Half of our patients had active cancer, and about one-third were under specific anticancer treatment, mirroring previously published data [12, 13, 15]. Noteworthy, patients with active cancer were

Table 2. Multivariate analysis (logistic regression model) identifying laboratory markers independently associated with mortality/severe COVID-19 in patients with active cancer and non-active cancer

	Hazard ratio (HR) [95% CI]	*p* value
Patients with active cancer		
Platelets		
<50,000/µL versus 50,000–119,000/µL	0.52 [1–2.7]	0.440
<50,000/µL versus 120,000–449,000/µL	0.7 [0.15–3.2]	0.642
<50,000/µL versus ≥450,000/µL	0.000	0.999
CRP (< vs. ≥ 120 mg/L)	2.85 [1.02–8.02]	**0.046**
Ferritin		
<500 versus 500–4,000 ng/mL	3.3 [0.99–11.26]	0.056
<500 versus >4,000 ng/mL	14.24 [2.1–96]	**0.006**
Patients with active cancer and non-active cancer		
CRP (< vs. ≥120 mg/L	1.93 [0.58–6.45]	0.288
Ferritin (<500 vs. 500–4,000 ng/mL)	4.1 [1.51–11.17]	**0.006**
WBC		
<4,000 versus 4,000–11,999/µL	7.9 [1–68.34]	0.061
<4,000 versus ≥ 12,000/µL	8.3 [0.59–115.1]	0.117
Hemoglobin		
<8 versus 8–11.9 g/dL	$1.079E^{+9}$	0.999
<8 versus ≥12 g/dL	$5.14E^{+9}$	0.999

a little younger, less multimorbid, and had a higher burden of metastasized solid tumors and hematological cancer. In both cohorts, most patients presented with non-severe COVID-19. However, infection- and all-cause mortality was higher in patients with active cancer and exceeded mortality in patients with non-active cancer by 1.5- to 1.7-fold. Similar findings have been reported elsewhere [11, 15, 18, 19]. Of 580 cancer patients, positively tested for SARS-CoV-2 at New York University Langone Hospital, for example, 221 had active cancer. Latter were younger and had a higher proportion of hematological cancer. Progression to complicated or critical phases of infection was comparable between both groups (59.3 vs. 62.4%, $p = 0.18$), as was the rate of ICU admissions (18.1 vs. 20%, $p = 0.305$). Here again, all-cause mortality was significantly higher in patients with active cancer (40.7 vs. 31.8%, $p = 0.035$) [19]. Data from the UK Coronavirus Cancer Monitoring Project (UKKCMP) demonstrated similar results: 1 in 4 patients with active cancer was critically ill, 7% were admitted to the ICU, and 28% died caused by COVID-19 [20]. On a global scale, the number of patients admitted to ICUs ranged from 7% to 32%, which is explained by differences in the pandemic timeline, different capacities of ICU beds, and changes to DNR/DNI during hospitalization [12, 15, 19–21].

In terms of laboratory tests, patients with active cancer often revealed severe cytopenia and elevated serum levels of inflammatory markers at baseline. This occurred particularly in those, who developed a severe viral infection or died from COVID-19. Lymphopenia, mild thrombopenia, anemia, and neutrophilia are well-described findings in patients infected with SARS-CoV-2 and more pronounced in those with severe COVID-19 [22, 23]. Similar blood results were found in patients with active cancer [24, 25]. A correlation between preexisting blood count changes and adverse clinical outcomes has not been demonstrated so far [24]. With progression of COVID-19, the proportion of lymphopenia, thrombopenia, and anemia increased substantially in patients with active cancer as compared to patients with non-active cancer. Similar results were observed for inflammatory markers. Consistent with the literature, neutrophilia was a common finding in patients in the critical phase of infection [23, 26]. A subsequent analysis of ANC at baseline did not show a predictive value regarding severity or mortality, which was contrary to data published by Zhang et al. [27]: here, the ANC showed an overall higher level in patients who died and was found to be an independent predictor for severity and outcome. Comparable was seen for high CRP levels [27]. In addition, worse outcomes were reported for neutropenic cancer patients receiving G-CSF with an even more adverse clinical outcome in those who respond to G-CSF (OR 7.78, 95% CI: 2.05–27.9; $p = 0.004$) [28].

Pathologic findings from patients who died due to COVID-19 revealed neutrophil infiltration, particularly in the alveolar spaces as potential driver of further cytokine release, respiratory failure, and death [29, 30]. Alongside neutrophilia and lymphopenia, high levels of ferritin, IL-6, CRP, and D-dimer are predictive biomarkers of severity and mortality, suggesting virally driven hyperinflammation and coagulopathy [26, 31, 32]. Consistent with previous reports, an increase in inflammatory markers at baseline, including ferritin, CRP, IL-6, and D-dimer, was more common in patients who developed severe COVID-19 or died within disease

progression [13, 25, 27, 33]. Our data confirm worse outcomes in patients with active cancer compared with patients with non-active cancer, suggesting that patients with active cancer are more likely to experience hyperinflammatory immune response. In subsequent regression analyses, hyperferritinemia and CRP were identified to be associated with severity and mortality attributed to COVID-19 in patients with active cancer. In line with our findings, Zhou et al. [1] showed that an increase in ferritin levels at baseline and throughout the following days of infection is associated with an adverse clinical outcome. Furthermore, Cheng et al. [34] demonstrated that multimorbid patients, particularly those with diabetes or cancer had significantly higher levels of ferritin, indicating a more severe inflammation and an associated adverse outcome. Additionally, a study by Meng et al. [35] reported higher CRP and IL-6 levels in patients with cancer compared to a matched cohort of non-cancer patients, suggesting an aggravation of the inflammatory response in patients with cancer. A further analysis characterizing cytokine profiles in 107 cancer patients and 57 health care workers with and without exposure to SARS-CoV-2 showed a significant upregulation of inflammatory markers, e.g., CRP and G-CSF in unexposed cancer patients compared with healthy controls. After viral exposure, IL-6 and CRP were significantly increased in patients with active cancer. Again IL-6 and CRP, both common inflammatory biomarkers in COVID-19, were associated with subsequent organ failure and an increase in mortality [36].

Our data support the hypothesis that cytokines essential for cancer dissemination and progression promote COVID-19-induced mortality, particularly in patients with active cancer, higher tumor burden, progressive disease, or hematologic malignancies. Despite our findings that further explain excess mortality in cancer patients with COVID-19, the study also has some limitations: most recruitments were performed by universities and tertiary care hospitals in larger cities. Therefore, rural areas and community practices are underrepresented, which naturally creates a bias towards severe cases. Due to its open design and varying standards of care for patients infected with SARS-CoV-2, not all investigations, e.g., more special laboratory tests, were performed on all patients. And although eCRFs have been regularly updated to reflect rapidly growing medical knowledge, patients' data may be incomplete, and the number of cases analyzed may vary.

Conclusion

To the best of our knowledge, the current analysis is unique, performing a comparison of clinic demographics and associated laboratory findings in a large cohort of patients with active and non-active cancer with COVID-19. While the severity of infection did not differ significantly between both cohorts, mortality rates were higher in patients with active cancer. Also, inflammatory markers were significantly increased, assuming higher levels of inflammation may play a role in the adverse outcome of COVID-19 in patients with active cancer.

Appendix

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Statement of Ethics

This study protocol was reviewed and approved by Ethics Commission, Faculty of Medicine, Goethe University Frankfurt, approval/reference number: 20-600. It was performed in line with the principles of the Declaration of Helsinki. Approval for LEOSS was obtained by the applicable local ethics committees of all participating centers. This study is registered at the German Clinical Trials Register (DRSK) (trial registration ID: S00021145; date of registration: April 8, 2020). Data were recorded anonymous, and no patient-identifying data were stored. Written patient informed consent was waived – the need for informed consent was waived by the Ethics Commission, Faculty of Medicine, Goethe University Frankfurt.

Conflict of Interest Statement

Y.K. received speaker fees/travel grants and fees for participation in Advisory Boards from Merck/MSD, Gilead Sciences, and ViiV Healthcare, all outside of the submitted work. C.G.-J. reported honoraria and travel accommodation expense from Roche, Gruenenthal, Falk Foundation, and Lilly Oncology, all outside of the submitted work. M.M.R. has received honoraria from Janssen and AstraZeneca, outside the submitted work. All other authors have no conflicts of interest to declare.

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Author Contributions

J.J. Vehreschild: initiation and leading of LEOSS. J.J. Vehreschild, C.E.M. Koll, M. Stecher, M. Schons, and A.Y. Classen: developing and maintaining LEOSS. M. Stecher, C. Jakob S. Nunes de Miranda: data management and extraction. M.M. Rüthrich: statistical analysis, data interpretation, and manuscript preparation. Y. Khodamoradi: revision of the manuscript. M. von Lilienfeld-Toal and G. Beutel: supervision, conceptual advice, and critical revision of the manuscript. K. Wille, C. Giessen-Jung, and L. Tometten: critical revision of the manuscript. M.M. Rüthrich, Y. Khodamoradi, K. Wille, C. Giessen-Jung, L. Tometten, J. Lanznaster, F. Volt, S. Borgmann, B.O. Jensen, and F. Hanses: acquisition of data. All authors revised and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary.

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