

Outcome of oncological patients admitted with COVID-19: experience of a hospital center in northern Italy

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Abstract

Background: Recent literature regarding the outcome of cancer patients infected with COVID-19 are not encouraging. Nevertheless, current evidence on the risk and benefits of continuing oncological treatment of cancer patients during the pandemic remains insufficient. We provide our experience in a center with high access for patients with COVID-19-associated pneumonia in Lombardy, Italy. We conducted a retrospective study using a prospectively maintained database of patients admitted to our hospital between 25 February 2020 and 9 April 2020 with a confirmed diagnosis of COVID-19 pneumonia.

Results: A total of 53 patients with a history or current oncological disease were included in this study. Sixteen oncological patients (30.2%) died during hospitalization. Multivariable logistic regression analysis found that age (Odds ratio [OR]: 1.17, $p=0.009$), diabetes (OR: 15.05, $p=0.028$) and active oncological disease (OR 13.60, $p=0.015$) were independently associated with in-hospital mortality. The mortality rate of the total number of cancer patients is about twice as high as that of non-oncological patients admitted to our hospital with a diagnosis of COVID-19.

Conclusion: The presence of active oncological disease is independently related to mortality as well as age and diabetes. The majority of patients who died were frail. Careful evaluation of the risks and benefits of treatment in frail patients is needed, considering that difficult access to intensive care may have affected the mortality rate.

Keywords: cancer, chemotherapy, COVID-19, immunodeficiency, SARS-CoV-2

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Introduction

The first cases of infection with severe acute respiratory coronavirus 2 (SARS-CoV-2) were reported in December 2019 in Wuhan, China, leading to a fast international spread, with the first Italian infection reported on 21 February 2020.¹ Eventually, the World Health Organization (WHO) declared the COVID-19 outbreak to be a pandemic on 12 March 2020.²

At the time of writing (22 May 2020), in Italy alone, 228,006 persons were tested positive for COVID-19, making it the country with the fourth most COVID-19 positively tested inhabitants worldwide. Moreover, 32,486 COVID-19-related deaths were reported.³

Lombardy was the most affected Italian region both in terms of infected patients and COVID-19-related mortality. This made a significant impact on the healthcare system, and oncological units, which had to consider this risk of infection in oncological patients receiving urgent treatment, the risk of tumor progression when suspending chemotherapy and the potential severe complications related to the potential state of immunodeficiency.⁴

Oncological patients have a complex immunological profile, which largely depends on previous and active treatments.⁵ Moreover, oncological patients can develop immunosuppression even in the absence of active treatments due to the tumor biology itself.⁶

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Recent studies on COVID-19 infection in oncological patients describe a greater susceptibility to COVID-19 infection, and a worse outcome in patients with active or a history of oncological disease.^{7,8} In particular, as reported by Liang *et al.*, patients who received any type of oncological treatment (chemotherapy, immunotherapy or radiotherapy) 2 weeks prior to infection with COVID-19, were at increased risk for mortality.⁸

On the contrary, several studies have questioned the assumption that immunosuppressed patients are at higher risk of acute respiratory disease syndrome (ARDS) secondary to COVID-19.^{9,10} The role of the cytokine storm secondary to COVID-19 infection is well known in the genesis of acute respiratory complications. Multiple ongoing clinical trials for the treatment of COVID-19 are based on targeting cytokines and other molecules involved in the cytokine cascade, such as Janus kinases.¹¹ Some studies have speculated that patients with immunosuppression might have a milder cytokine cascade in relation to lymphopenia, which would protect them from severe intravascular pulmonary coagulopathy, linked to extensive pulmonary immuno-thrombosis.¹²

A better understanding of the risk of COVID-19 infection and complications could provide oncologists with an additional tool to weigh the risks and benefits of starting or continuing oncological treatment during the pandemic.¹³

Therefore, the aim of this study was to determine the mortality rate in COVID-19-positive patients with current or previous oncological disease. In addition, we assessed patient and COVID-19-related factors which may be associated with an increased mortality rate.

Patients and methods

Study design and participants

The referral ethics committee approved a waiver of consent from individual patients due to the retrospective nature of the study. Data were retrieved from a prospectively maintained database of all patients admitted to our hospital between 25 February 2020 and 9 April 2020. Patients with a positive real time reverse transcriptase polymerase chain reaction (RT-PCR) test for SARS-CoV-2 on biological samples or with a suspicious clinical history and a highly suggestive chest computed tomography (CT) scan were considered as COVID-19

positive. Inclusion criteria were: (a) adult patients (18 years or older); and (b) oncological patients (i.e. patients with active or previous oncological disease). A total of 2039 patients were considered. Fifty-three patients (2.5%) were included for this study.

Outcome measures and variables

The outcome variable was the incidence of mortality. Response variables were age, gender, body mass index (BMI), smoking, comorbidities, active oncological treatment in the previous 3 months, type of oncological treatment, type of cancer, medication usage, acute respiratory distress syndrome (ARDS) (severe, moderate, mild), medical treatments for COVID-19, inflammatory markers (white blood cell [WBC], lymphocytes, neutrophil, platelets, c-reactive protein [CRP], lactic acid dehydrogenase [LDH], erythrocyte sedimentation rate [ESR]) and eventual intensive care unit [ICU] admission along with hospitalization outcome (healed, deceased, transferred to rehabilitation structures).

Statistical analysis

Variables were presented with frequencies and percentages for categorical variables and as median with interquartile range (IQR) for non-normal distributed continuous variables. The difference in explanatory variables were assessed using a chi-square test for dichotomous and categorical variables, *t*-test for normally distributed continuous variables and a Mann–Whitney U test for non-normal distributed continuous variables. The incidence of mortality was determined. Odds ratios (ORs) with 95% confidence intervals (CIs) were presented to quantify the association between risk factors and the outcome variables without controlling for other explanatory variables. Multivariable logistic regression analyses were used to assess if risk factors separately associate with mortality after accounting for explanatory variables. Vittinghoff and McCulloch¹⁴ described that the rule of thumb in which logistic and Cox models should be used with a minimum of 10 outcome events per predictor variable (EPV), based on two simulation studies, may be too conservative. Therefore, considering the total number of deaths in our study ($n = 16$), five variables were chosen for multivariable analysis on the basis of clinical constraints. All analyses were performed using SPSS 26.0 software (SPSS, Chicago, IL, USA) and two-tailed *p*-values less than 0.05 were considered significant.

Results

Baseline characteristics

Of all 2039 patients, 1237 (60%) were men. The median age was 64 years, 178 (8%) were admitted to the intensive care unit and 345 (17%) patients died during their hospital stay (Table 1).

Of the 53 patients with active or a history of oncological disease, there were 32 (60.4%) men, the

median age was 75 years (IQR 68–83), the mean BMI was 26.3 (standard deviation [SD] 4.6), 19 (35.8%) patients had hypertension, 15 (28.3%) patients had diabetes type one or two, and 20 (37.7%) patients were known with cardiomyopathy (Table 2). The different types of cancers are shown in Table 3. Twenty-five (47.2%) patients had active disease, of which 23 (92%) had metastatic disease. In this population, 18 (32.1%) patients were on active treatment, of which 16 (64%) were on chemo,

Table 1. Mortality rate and admission in intensive care unit (ICU) adjusted for sex and median age of patients hospitalized for COVID-19 in Fondazione Poliambulanza from 25 February to 9 April 2020.

Variables	Total patients (n = 2039)		Oncological patients (n = 53)		Non-cancer patients (n = 1986)		RR
Age, median	64		75		67		
Male sex	1237	60.7%	32	60.4%	1204	60.6%	
ICU admittance	178	8.7%	0	0%	178	8.9%	RR=0 IC=95% p=0.0219
Mortality	333	16%	16	30%	317	16.7%	RR=2.22 IC=95% 1.25–3.94 p=0.0057

Table 2. Baseline characteristics oncological patients with COVID-19.

Variables	Total (n = 53)		Survivors (n = 37)		Non-survivors (n = 16)		p-value
Age (years), median IQR	75	68–83	72	63–80	82	77–89	0.001
Male sex	32	60.4%	21	56.8%	11	68.8%	0.412
BMI, mean SD	26.3	4.6	25.5	4.1	28.2	5.2	0.050
Smoking	12	22.6%	8	21.6%	4	25.0%	0.629
Diabetes mellitus	16	28.3%	7	18.9%	8	50.0%	0.021
Hypertension	19	35.8%	12	32.4%	7	43.8%	0.43
Cardiopathy	20	37.7%	10	27.0%	10	62.5%	0.014
Coronary heart disease	1	1.9%	1	2.7%	0	0.0%	0.507
ARDS							
Not severe (pO ₂ /fiO ₂ 200–300)	36	67.9%	28	75.7%	8	50.0%	0.003
Moderate (pO ₂ /fiO ₂ 100–200)	7	13.2%	1	2.7%	6	37.5%	0.003
Severe (pO ₂ /fiO ₂ <100)	3	5.7%	1	2.7%	2	12.5%	0.003
Active oncological disease	25	47.2%	14	37.8%	11	68.8%	0.038
Localized disease	2						
Metastatic disease	23						
Active oncological treatment	18	32.1%	14	37.8%	4	25%	0.051

(Continued)

Table 2. (Continued)

Variables	Total (n=53)		Survivors (n=37)		Non-survivors (n=16)		p-value
Type of oncological treatment							
Immunotherapy	1	1.9%	1	2.7%	0	0.0%	0.507
Radiotherapy	2	3.8%	1	2.7%	1	6.3%	0.252
Hormone therapy	3	5.7%	1	2.7%	2	12.5%	0.075
Chemotherapy	16	30.0%	14	37.8%	2	12.6%	0.080
Adjuvant/neoadjuvant	4						
Palliative treatment	12						
First line	4						
Second line	3						
Third line and beyond	5						
Medication							
ACE inhibitors	6	11.3%	4	10.8%	2	12.5%	0.885
Anti-anxiety medication	11	20.8%	8.0	21.6%	3	18.8%	0.813
Antibiotics	39	73.6%	27	73.0%	12	75.0%	0.878
Anti-diabetics	17	32.1%	10	27.0%	7	43.8%	0.231
Anti-hypertensives	21	39.6%	15	40.9%	6	37.5%	0.835
Cortisones	19	35.8%	13	35.1%	6	37.5%	0.869
Heparins	22	41.5%	15	40.5%	7	43.8%	0.888
Sartans	8	15.1%	6	16.2%	2	12.5%	0.701
COVID-19-specific medication	12	22.6%	10	27.0%	2	12.5%	0.246
Hydrochloroquine	8	15.1%	7	18.9%	1	6.3%	0.584
Lopinavir/ritonavir	9	17.0%	7	18.9%	2	12.5%	0.371
Laboratory findings							
White blood cell count (10 ⁹ /L), mean SD	6.52	3.0	6.3	2.7	6.9	3.8	0.473
Lymphocytes (10 ⁹ /L), mean SD	0.98	0.47	1.1	0.37	0.81	0.64	0.011
Platelets (10 ⁹ /L), median IQR	174	130–233	160	134–258	179	109–214	0.275
CRP (mg/L), median IQR	92	42–161	75	34–118	134	87–190	0.012
LDH U/L, median IQR	342	264–479	305	242–362	518	475–582	<0.001
ESR (mm/hour), mean SD	60	23.1	56.9	22.9	67.1	22.6	0.172
Hemoglobin mmol/L, median IQR	12	10–13	13	10–14	11	11–13	0.148
Red blood cell count (cells/μL), mean SD	3.83	0.65	3.9	0.62	3.6	3.16	0.052
BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LDH, lactate dehydrogenase; SD, standard deviation; ARDS, acute respiratory distress syndrome; ACE, angiotensin-converting enzyme.							

Table 3. Types of cancer.

	Total (n=53)	%
Urological	15	28%
Prostate	8	15%
Gynecological	3	6%
Gastrointestinal	14	26%
Lung	5	9%
Breast	8	15%
Hepatic–pancreatic–biliary	5	9%
Skin	1	2%
Head and neck	4	4%

and two (8%) with hormonal therapy. The remaining patients were entrusted to palliative care. Of the 16 patients receiving active treatment with chemotherapy, five were in the third line of treatment (Table 2). The median length of hospital stay for patients with an active oncological disease was 3 days (IQR 1–8), and for patients with a history of oncological disease it was 6 days (IQR 4–9) (Table 2).

In-hospital medication

During their admission for COVID-19, six (11.3%) patients were on angiotensin-converting enzyme (ACE) inhibitors, 39 (73.6%) on antibiotics, 19 (35.8%) on corticosteroids, 22 (41.5%) on heparins, and eight (15.1%) were on sartans. Twelve patients (22.6%) were prescribed COVID-19-specific treatment including eight (15.1%) hydroxychloroquine, six (11.3%) and nine (17.0%) lopinavir/ritonavir (Table 2).

In-hospital mortality

Sixteen of the 53 patients (30.2%) died during their hospital admission for COVID-19. There were 11 (68.8%) men, the median age was 82 years (IQR 77–89), the mean BMI was 28.2 (SD 5.2), seven (43.8%) patients had hypertension, eight (50.0%) patients had diabetes type 1 or 2, and 10 (62.5%) patients were known with cardiomyopathy (Table 2). Multivariable logistic regression analysis found that age (OR 1.17, $p=0.009$), diabetes (OR 15.05, $p=0.028$) and active oncological disease (OR 13.60, $p=0.015$)

Table 4. Multivariable logistic regression analysis risk factors associated with mortality in oncological patients with COVID-19 ($n=52$).

Variables	Odds ratio	95% CI		p-value
Age	1.17	1.04	1.31	0.009
BMI	1.08	0.90	1.29	0.411
Diabetes	15.05	1.34	168.87	0.028
Cardiopathy	1.15	0.187	7.13	0.878
Active oncological disease	13.60	1.68	110.38	0.015

CI, confidence interval; IQR, interquartile range.

were independently associated with in-hospital mortality (Table 4). No patients with active or a history of oncological disease were admitted to the intensive care unit.

Discussion

This retrospective study identified several risk factors associated with mortality in oncological patients admitted with COVID-19. Age, diabetes type 1 or 2, and having an active oncological disease were independently associated with a higher risk of mortality. Scarce data are available on the trend of SARS-CoV-2 infection in oncological patients. The study by Wang and Zhang identified 28 oncological patients among 1276 COVID-19-positive patients who were admitted to three hospitals in Wuhan, China, between January and February 2020.⁷ The prevalence of cancer in the study cohort of Wang and Zhang (2.2%) was 1.7 times higher compared to the non-COVID-19 Chinese population with oncological disease and a similar age. In addition, the authors reported that the recent use of oncological treatment (chemo, immune or radiotherapy) within 14 days of hospitalization was an independent predictor of mortality or other serious adverse events with a risk ratio greater than 4. Our analysis indicates that 2.5% of patients admitted to our hospital were patients with active or a history of oncological disease. The prevalence of oncological disease in the Italian population is 5.3%. Therefore, considering that 25 patients out of 2039 (1.2%) had active oncological disease, we recorded a higher incidence of cancer in patients with COVID-19 than that of cancer in the general population in Italy (562.54 per 100,000 people).¹⁵ Moreover, the mortality percentage of cancer patients with COVID-19 is higher than that of non-cancer patients, which is in line with what Wang and Zhang postulated (Table 1).

A second study, published by Liang *et al.*⁸ identified a higher risk of both infection and complications in oncological patients with COVID-19. They advised to pay extra attention to patients with oncological disease in case of rapid deterioration. This study recommends to postpone adjuvant chemotherapy and elective surgery in endemic areas, to provide stricter provisions on individual protection of oncological patients and finally, to give more COVID-19-specific intensive treatments in oncological patients with COVID-19 when these patients have multiple comorbidities and higher age. As highlighted by Xia *et al.*,¹⁶ half of the patients in the study of Liang *et al.*⁸ had a disease history of more than 4 years, indicating that a substantial proportion of these patients might be clinically cured from their oncological disease. For a better understanding of the characteristics of our deceased patients, we divided the cohort into two distinct groups: patients with active oncological disease and patients in follow-up for previous cancer (Table 2). Interestingly, in multivariable logistic regression analysis, active oncological disease was independently associated with in-hospital mortality (OR 13.60, $p=0.015$). We defined active oncological treatment as treatment within the past 3 months with either chemotherapy, immunotherapy, hormone therapy and radiotherapy. The vast majority of our patients (88%) was treated with chemotherapy, in 75% of cases for palliative purposes, and in a high percentage (41%) as third-line treatment, reflecting the advanced disease status of these patients.

Most patients who died were octogenarian (median age 82 years) with significant comorbidities (i.e. heart disease, diabetes and hypertension). Pre-existing cardiovascular diseases were reported to be associated with worse outcomes among patients with COVID-19.¹⁷ Similarly, diabetes and hypertension may also represent risk factors for adverse outcomes as well.^{18,19} In our analysis, diabetes and age were confirmed to be independently associated with mortality.

One of the most recent autaptic findings about COVID-19 is the association with severe intravascular pulmonary coagulopathies.²⁰ Laboratory data might indicate an early pulmonary intravascular coagulopathy showing an increase in the circulating D-dimer and cardiac enzymes. Those are an indirect sign of pulmonary vascular bed thrombosis resulting in fibrinolysis and a manifestation of ventricular stress induced by pulmonary hypertension, respectively. This could explain the negative impact

of male sex, hypertension, obesity and diabetes on the prognosis of patients with COVID-19.

When focusing on the non-surviving population from our study (Table 2), our study confirms that in oncological patients, the majority of the patients with fatal outcomes were frail. Frailty is a distinct biological syndrome defined as a state of decreased reserve and resistance to stressors, resulting from cumulative deterioration across multiple physiological systems, and causing vulnerability to adverse outcomes.²¹ Frail patients are a central concern in emergency management. Physicians have been warned that a first cure is not giving harm, the so-called *primum non nocere* assumption. However, the ethical issue remains crucial in this category of patients having on one hand the risk of infection, and on the other hand the risk of undertreatment of their oncological disease. Although the *modus operandi* for this category of patients differs between countries, we agree with the Société Francophone d'Onco-Gériatrie (SoFOG), and the French cooperative group for clinical research in geriatric oncology DIALOG (GERICO-UCOG). They have stated that the decision-making process should take into account cancer type, disease extent, prognosis and treatment opportunities irrespective of a patient's age, but acknowledge the excess risks associated with viral infection in older patients along with life expectancy.^{22,23} This assumption has even more significance in a country like Italy, where the average age is high.²⁴ Several authors have reported on the age difference in the Italian population, which is on average higher than in China.^{25,26}

During the COVID-19 pandemic, it was difficult to offer the high standard of intensive care support normally available for frail patients. This was due to the sudden increase of patients in need of intensive care support and the limited number of available beds. This has had a serious impact on the oncological management of frail patients. In our center, ICU beds have quadrupled from 20 to 80 beds in a timely fashion. However, despite this immense effort, patient selection and triage for eligibility for invasive treatments were needed during this crisis. The first report on the prognosis of COVID-19 patients and cancer in the United States disclosed that patients with cancer were intubated more frequently compared to the others [relative risk (RR) 1.89, 95% confidence interval (CI) 1.37–2.61]; however, without a difference in mortality.²⁷ In our study population, due to different factors including our triage policy, none of the

patients with a history or active oncological disease were admitted to the ICU. This might partially explain the higher mortality rate of our cohort compared to the data reported by Miyashita *et al.*²⁷ The shortage of ICU beds in pandemic outbreaks is well known. For example, a quarter of patients who died early in Wuhan did not receive invasive mechanical ventilation.²⁸ Yet, not all critically ill patients in the hospital are eligible for ICU admittance during the pandemic, because the chances of survival for some will be viewed as too low.²⁹ Some authors suggested a maximization of benefits by giving priority to patients likely to survive longest after treatment.³⁰ However, exclusion criteria are unlikely to have been validated for patients during the pandemic, also it is unknown if they can accurately predict which patients have the lowest potential to survive with intensive care. For these reasons, it is uncertain if the lack of access to intensive care had a significant impact on mortality.

This study has a number of limitations inherent in the retrospective nature of the study and the small number of included patients. However, data were retrieved from a prospective maintained central electronic database of our center. Considering the short interval between the crisis, our study, and the urgent need for data to build the body of evidence in this field, our cohort, coming from one of the regions with the highest incidence of COVID-19 infection after Wuhan is quietly representative. Finally, this analysis cannot offer a holistic overview on the outcomes of all oncological patients infected with COVID-19. In fact, these data may give a good reflection only on oncological patients who required hospitalization. This leaves unknown numbers and characteristics of a potential large pole of patients treated or deceased in the community.

Conclusion

The mortality rate of oncological patients can be significantly high. The presence of active oncological disease is independently related to mortality, as are age and diabetes. The majority of patients who died from COVID-19 were frail. Careful evaluation of the risks and benefits of treatment in frail patients is needed, considering that the difficult access to intensive care may have partially affected the mortality rate.

Author contributions

SC had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Each author has contributed significantly to, and is willing to take public responsibility for, the following aspects of the study:

Study concept and design: SC, DHLL

Acquisition, analysis, or interpretation of data: SC, DHLL

Drafting of the manuscript: SC, DHLL, SN

Critical revision of the manuscript for important intellectual content: MAH, AZ, SN

Statistical analysis: DHLL, SN

Administrative, technical, or material support: SN

Study supervision: AZ, MAH

Availability of data and materials

All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Data for this study are available on request from the corresponding author.

Conflict of interest statement

Each author certifies that he or she, or a member of his or her immediate family, has no funding or commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Ethics statement

The Comitato Etico di Brescia has approved a waiver of consent for this study because of its retrospective nature. Protocol number: NP 4198.

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