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Original Research

Epidemiology and clinical course of severe acute respiratory syndrome coronavirus 2 infection in cancer patients in the Veneto Oncology Network: The Rete Oncologica Veneta covID19 study

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Abstract ***Introduction:*** Coronavirus disease 2019 (COVID-19) pandemic started in Italy with clusters identified in Northern Italy. The Veneto Oncology Network (Rete Oncologica Veneta) licenced dedicated guidelines to ensure proper care minimising the risk of infection in patients with cancer. Rete Oncologica Veneta covID19 (ROVID) is a regional registry aimed at describing epidemiology and clinical course of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cancer.
Materials and methods: Patients with cancer diagnosis and documented SARS-CoV-2 infection are eligible. Data on cancer diagnosis, comorbidities, anticancer treatments, as well as details on SARS-CoV-2 infection (hospitalisation, treatments, fate of the infection), have been recorded. Logistic regression analysis was applied to calculate the association between clinical/laboratory variables and death from any cause.
Results: One hundred seventy patients have been enrolled. The median age at time of the SARS-CoV infection was 70 years (25–92). The most common cancer type was breast cancer (n = 40). The majority of the patients had stage IV disease. Half of the patients had two or more comorbidities. The majority of the patients (78%) presented with COVID-19 symptoms. More than 77% of the patients were hospitalized and 6% were admitted to intensive care units. Overall, 104 patients have documented resolution of the infection. Fifty-seven patients (33%) have died. In 29 cases (17%), the cause of death was directly correlated to SARS-CoV-2 infection. Factors significantly correlated with the risk of death were the following: Eastern Cooperative Oncology Group performance status (PS), age, presence of two or more comorbidities, presence of dyspnoea, COVID-19 phenotype $\geq$ 3, hospitalisation, intensive care unit admission, neutrophil/lymphocyte ratio and thrombocytopenia.
Conclusions: The mortality rate reported in this confirms the frailty of this population. These data reinforce the need to protect patients with cancer from SARS-CoV-2 infection.

1. Introduction

On February 21, 2020, in the Veneto region, the country's first death from coronavirus disease 2019 (COVID-19) occurred. In early March 2020, the rapid global spread of the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection led the World Health Organisation to declare a pandemic [1]. Since the beginning of COVID-19 outbreak, the Veneto region started a proactive approach, including testing for SARS-CoV-2 infection the population living in area of the initial outbreak as well as healthcare providers even in the absence of symptoms suspicious on COVID 19 [2].

To face the emergency of the first weeks, the national health system was reorganised to implement wards dedicated to patients with COVID-19 and to potentiate intensive care units. In this context, maintaining oncology care was considered one of the priorities of the regional health system. To ensure proper cancer care minimising the risk of infection, the Veneto Oncology Network (Rete Oncologica Veneta [ROV]) licenced a dedicated diagnostic-therapeutic pathway (PDTA), a workflow harmonising protective measures for oncologic patients and staff members across the 26 medical oncology units operating in the Veneto region [3]. Indeed, it was immediately clear since the very beginning of the pandemic that patients with cancer and SARS-CoV-2 infection might be at higher risk of developing severe complications and death [4]. Patients with cancer are usually susceptible to infectious disease, and infections are a leading cause of death among this patient population. This vulnerability is related to the immunosuppressive state caused by underlying malignancy

and anticancer treatments and also to comorbidities. Starting from the first retrospective cohort in China, describing a higher risk of severe events for patients with and without cancer, data from several multicentric registries including hundreds of patients with cancer reported a mortality rate in the range of 10–33% [5–17]. It is important to note, however, the huge heterogeneity of the clinical course of SARS-CoV-2 infection across different countries. Mortality, the most important measure of COVID-19 disease burden, largely differs across countries. As of December 2020, the case fatality ratio ranges from 0.2% to 9.7%. In Europe, Italy has one of the highest case fatality ratios (3.5%) [18]. Differences in demographics, availability of personal protective equipment, testing strategy and characteristics of healthcare systems might account for this variability in mortality. In this framework, a regional registry [Rete Oncologica Veneta covID19 (ROVID)] has been set up with the aim of describing epidemiology and clinical course of SARS-CoV-2 infection in patients with cancer treated following shared guidelines and in services relying on the same resources.

2. Methods

The ROVID (**ROV** COV**ID**19) study is an observational study including patients with cancer diagnosis and documented SARS-CoV-2 infection (positive nasopharyngeal swab). Under the coordination of the ROV, 26 medical oncology units participate to this project. The set of variables focused on SARS-CoV-2 infection diagnosis (nasopharyngeal swabs, serological tests) and of COVID-19 treatments were discussed with infection disease specialists and pneumologists. The following data are recorded: age, cancer diagnosis, stage, tumour biology, presence of comorbidities, presence of COVID-19 symptoms, anticancer treatment at time of infection (type, aim, line of therapy, discontinuation, recovery), other medical treatments, hospitalisation, treatments for SARS-CoV-2 infection, fate of the infection.

Nasopharyngeal swabs were performed by using flocked swabs in liquid-based collection and transport systems. All nasopharyngeal swab samples were processed with an in-house real-time polymerase chain reaction method [2]. Samples were initially collected and analysed at the Clinical Microbiology and Virology Unit of Padova University Hospital, which is the regional reference laboratory for emerging viral infections and received accreditation as a reference laboratory for SARS-CoV-2 testing. With the growing of the pandemic, other laboratories using the same methodology were subsequently certified by the regional government.

According to the Italian Society of Emergency and Urgency Medicine recommendations, patients have been classified into 5 COVID-19 phenotypes: type 1: presence of fever, no hypoxaemia at arterial blood gas analysis (BGA), normal chest radiograph; type 2: fever and pulmonary consolidation area at chest radiograph or

Table 1
Patient demographic, clinical and tumour characteristics.

N (%)	170 (100)
Sex	
Male	78 (46)
Female	92 (54)
Age	
Minimum	25
Median	70
Maximum	92
ECOG performance status	
0	50 (34)
1	54 (36.7)
2	22 (15)
3	15 (10.2)
4	6 (4.1)
Cancer diagnosis	
Breast cancer	40 (23.7)
Gastrointestinal tumours	38 (22.5)
Genitourinary tract tumours	22 (13)
Lung cancer	18 (10.6)
Haematologic malignancies	14 (8.3)
Melanoma	9 (5.3)
Gynaecologic cancers	7 (4.1)
Head and neck	5 (3)
Other	17 (10)
Stage	
I	32 (19.2)
II	15 (9.1)
III	21 (12.6)
IV	99 (59.3)
Documented lung metastases	
Yes	27 (16)
No	143 (84)
Smoking status	
Smoker	27 (15.9)
Former smoker	37 (21.7)
Non-smoker	89 (52.3)
NA	17 (10)
Comorbidities	
Hypertension	72 (42.4)
Cardiac comorbidities	51 (30)
Diabetes	30 (17.6)
Obesity	23 (13.5)
Pulmonary comorbidities	16 (9.4)
Autoimmune disorders	12 (7.1)
Chronic renal failure	12 (7.1)
Other	70 (41.2)
Presence of at least 1 comorbidities	135 (79.4)
Presence of 2 or more comorbidities	85 (50)
Active anticancer therapy*	
Any	89 (52.4)
Chemotherapy	46 (27)
Targeted therapy	24 (14)
Endocrine therapy	19 (11.2)
Immunotherapy	9 (5.3)

ECOG, Eastern Cooperative Oncology Group.
* Multiple choice allowed.

mild hypoxia at BGA; type 3: fever associated with moderate-severe respiratory insufficiency and bilateral pulmonary consolidation area at chest X-ray (XR); type 4: patients requiring mechanical ventilation but not yet diagnosed with adult respiratory distress syndrome (ARDS); type 5: subjects with ARDS [19].

The complete set of variables is listed in supplemental appendix 1. The data extracted from electronical medical records are entered into a de-identified Research Electronic Data Capture database. Each participating institution is assigned a unique number, and access to the database is password protected. To study the association between clinical/laboratory variables and outcomes (death from any cause), odds ratios and their 95% confidence intervals (95% CIs) were calculated by logistic regression analysis. Statistical analyses were performed by using IBM® SPSS® Statistics (version 26). The protocol was approved by the institutional review board of participating centres. All study procedures were in accordance with the precepts of Good Clinical Practice and the Declaration of Helsinki.

3. Results

3.1. Patients

One hundred seventy-eight patients have been registered so far. Eight patients were excluded (n = 6 no laboratory confirmation of SARS-CoV-2 infection, n = 1 diagnosis of monoclonal gammopathy of undetermined significance (MGUS), n = 1 diagnosis of non-melanoma skin cancer), leaving for the present analysis 170 patients with cancer diagnosed with SARS-CoV-2 infection between February 2020 and September 2020. The median age at time of the SARS-CoV infection was 70 years (25–92). The most common cancer diagnosis was breast cancer (n = 40). Of all, 70.7% of the patients had Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1. The majority of the patients had stage IV disease. Lung metastases were documented in 16% of the patients. The presence of at least one comorbidity was reported for 79% of the cases, with two or more reported in 50% of the patients. Patient characteristics are summarised in Table 1.

Consistently with pandemic evolution in the Veneto region, the vast majority (96%) of our patients were diagnosed between February and April 2020.

3.2. Anticancer treatment

Active anticancer therapy was reported for 89 patients (52%), with curative intent (adjuvant or neoadjuvant) in 22 cases and with palliative intent in 67 cases (first line n = 40, second line n = 11, third or more n = 16). Chemotherapy was the most frequent anticancer therapy (n = 46), followed by targeted therapy (n = 24), endocrine therapy (n = 19) and immunotherapy (n = 9).

Treatment was discontinued because of SARS-CoV-2 infection in 68% of the cases.

Interruptions of specific treatments were as follows: chemotherapy 80.4% (37/46), immunotherapy 77.8% (7/9), targeted therapy 68.8% (44/64) and endocrine therapy 26.3% (5/19). The rate of interruption of anticancer therapy did not differ according to severity of SARS-CoV-2 infection (75.0% of patients with clinical phenotype 1–2 and 71.4% of patients with clinical phenotype ≥3, p = 0.743) and in hospitalised vs non-hospitalised patients (71.2% vs 59.1%, p = 0.290). Anticancer therapy was resumed in 24 of 60 patients (40.0%).

Table 2
Univariate regression analysis and odds of death based on clinical and laboratory variables.

	OR	95% CI	p value
Sex (M vs F)	0.713	0.374–1.360	0.305
ECOG PS (>=/2 vs 0–1)	4.286	2.001–9.183	0.000
Age (per 1 year increment)	1.030	1.003–1.057	0.030
Current or former smoker (vs no smoker)	0.750	0.295–1.906	0.545
At least one comorbidity (vs none)	1.594	0.691–3.677	0.274
Two or more comorbidities (vs 0–1)	2.005	1.047–3.839	0.036
Hypertension	1.686	0.886–3.208	0.11
Stage (IV vs I-III)	1.658	0.844–3.257	0.142
Treatment setting (curative vs palliative)	1.705	0.878–3.310	0.115
Presence of lung metastases (yes vs no)	1.435	0.617–3.338	0.402
Active anticancer therapy (yes vs no)	1.131	0.597–2.141	0.706
Chemotherapy (yes vs no)	1.401	0.694–2.830	0.347
Presence of symptoms (any vs no)	2.166	0.918–5.114	0.078
Fever (yes vs no)	1.516	0.759–3.029	0.239
Dyspnoea (yes vs no)	5.956	2.959–11.989	0.000
Clinical phenotype (>/03 vs 1–2)	6.006	2.793–12.915	0.000
Hospitalisation (yes vs no)	4.290	1.573–11.700	0.004
Intensive care unit admission (yes vs no)	9.061	1.856–44.236	0.006
Lymphopenia	2.259	0.873–5.845	0.093
Neutrophil/lymphocyte ratio (>/=7 vs < 7)	7.669	3.097–18.990	0.000
Thrombocytopenia (<150.000 vs >/= 150.000)	2.770	1.306–5.876	0.008
LDH (>250 vs </=250)	1.889	0.652–5.476	0.242
PCR (>50 vs </0 50)	1.637	0.707–3.790	0.250

CI, confidence interval; OR, odds ratio; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PCR, C-reactive protein. Bold font indicate the variables with statistical significance.

3.3. SARS-CoV-2 infection

At the time of SARS-COV-2 infection diagnosis, 78% of the patients presented with COVID-19 symptoms, while 37 patients were asymptomatic. Among them, 32 performed a nasopharyngeal swab as part of a tracing procedure, 5 patients presented radiological findings suspicious for SARS-CoV-2 pneumonia on CT scan planned as part of routine diagnostic workup, confirmed by a positive nasopharingeal swab. A potential source of infection was identified as an in-hospital contact in 24% of the cases and as an extra-hospital contact in 26% of the cases.

The most frequently reported symptoms were fever (66%), dyspnoea (43,5%), cough (38%) (Table 2). Among symptomatic patients, the distribution of clinical phenotype was as follows: type 1, 25%; type 2, 36%; type 3, 24%; type 4, 12%; type 5, 3%.

More than 77% of the patients were hospitalised and 6% were admitted to intensive care units. The median in-hospital stay was 13 days (min 1, max 97 days). Thirty-five percent of the patients received low flow oxygen support and 17% received non-invasive mechanical ventilation, high flow nasal cannula or endotracheal intubation. The most commonly reported treatment was hydroxychloroquine (40% of the cases), azythromicine (29%), low-molecular-weight heparin (20%), lopinavir/ritonavir (15%), steroids (11%). The use of remdesivir, tocilizumab, hyper immune serum was anecdotic.

Overall, 104 patients have documented resolution of the infection (two consecutive negative nasopharyngeal swabs). The median time to nasopharyngeal swab negativity was 23 days (1–128 days). There was no difference in time to nasopharyngeal swab negativisation according to cancer stage: the median was 23 days (95% CI: 20–26) for stage IV and 22 days (95% CI: 13–31) for stage I-III, log-rank $p = 0.188$. No difference was also observed according to disease setting: the median was 21 days (95% CI: 12–30) for curative setting and 25 days (95% CI: 21–29) for palliative setting, log-rank $p = 0.079$.

Overall, 57 patients (33%) have died (in 3 cases, after documented infection resolution); in 29 cases (17%), the cause of death was directly correlated to SARS-CoV-2 infection.

Factors significantly correlated with risk of death (any cause) were as follows: ECOG PS, age, presence of two or more comorbidities, presence of dyspnoea, COVID-19 phenotype ≥ 3, hospitalisation, intensive care unit admission, neutrophil/lymphocyte ratio and thrombocytopenia (Table 2). Chemotherapy use at the time of the infection was not associated with increased mortality. Regarding treatment for SARS-CoV-2 infection, we found no association with hydroxychloroquine and azythromicine use and mortality.

4. Discussion

ROVID is a regional registry aimed at collecting data on the clinical course of SARS-CoV-2 infection in patients with cancer treated in the Veneto region. In this analysis, we report on the first 170 patients enrolled. The majority of the patients were diagnosed with breast, gastrointestinal, genitourinary or lung cancer, consistently with the prevalence of these cancer types. Therefore, our patient sample reflects the cancer population routinely referring to medical oncology units. The rate of patients presenting with symptoms at time of SARS-CoV-2 infection in our registry is coherent with the initial recommendations for SARS-CoV-2 testing licenced by the Italian Ministry of Health. According to these guidelines, nasopharyngeal swabs for SARS-CoV-2 infection documentation were limited to patients with symptoms suspicious for COVID-19 disease and a direct contact with a positive case [20]. Indeed, 96% of our patients have been diagnosed from February to April 2010. Afterwards, also thanks to a larger availability of diagnostic tests, criteria for nasopharyngeal swabs were expanded. According to the recommendation licenced by ROV, screening nasopharyngeal swab are now routinely applied to asymptomatic cancer patients candidates to invasive diagnostic procedures or to anticancer treatments associated with a high risk of myelosuppression, or for admission in the inpatient clinic [3].

Systemic treatment for COVID-19 in the ROVID study was largely empirical, with hydroxychloroquine being the most frequently administered drug. The rate of admission in intensive care unit in our study was 6%, the same as reported in the UK Coronavirus Cancer Monitoring Program (UKCCMP), a prospective observational study including 800 cancer patients presenting with symptomatic COVID-19, and also in line with the rate of admission observed in non-cancer patients in the Veneto region [7,21].

In Italy, on April 4 2020, which represented the peak of hospitalisation due to COVID-19 during the first wave of the pandemic, patients hospitalised in intensive care units represented 4.4% of the total positive cases [22]. The referral of critically ill cancer patients to intensive care units is often challenging and requires a case-by-case evaluation weighting the benefit of treating a potentially reversible condition against a futile care. It is therefore important to highlight that in these circumstances, cancer patients were offered the same opportunities as compared non-cancer patients.

We report a median time to negativity of nasopharyngeal swab of 23 days. Our results are in line with those reported in a study conducted in more than 530,000 inhabitants in the northeastern Italian province of Udine. In the 974 subjects diagnosed with SARS-

CoV-2 infection, the median time to negativity was 23.3 days [23]. Therefore, the kinetic of virus clearance is not negatively affected in patients with cancer.

In our study, the overall mortality rate is of 33%, with COVID-19 as the primary cause of death in 17% of the cases. We identified several factors significantly correlated with the risk of death. As reported in the vast majority of studies, we confirmed the association of age and comorbidities with an increased risk of death [14,16,24]. Poor PS was also associated with an increased risk of death. The association of PS $\geq$ 2 with increased risk of death has been already described by the CCC19 cohort study including 928 patients, by the French nationwide cohort study (GCO-002 CACOVID-19) including 1289 patients and by the Gustave Roussy cohort of 178 patients [6,9,16].

In our study, presence of dyspnoea, COVID-19 phenotype $\geq$ 3, hospitalisation and intensive care unit admission were all significant predictors of increased risk of death. Because of the relatively limited sample size, we did not perform a multivariate analysis. However, it is important to highlight that patients suffering from symptoms are those more likely to experience a fatal outcome. In particular, the presence of dyspnoea has been confirmed as a predictor of a fatal outcome also in the TERAVOLT study, which included only patients with thoracic malignancies, and in the UKCCMP study [7,8]. Interestingly, we describe a significant association of neutrophil/lymphocyte ratio and thrombocytopenia with the risk of death. These are simple and easily reproducible tests that might be helpful for an early identification of patients at higher risk for an adverse outcome.

Conflicting data on the association between chemotherapy use and increased risk of death have been reported so far. With the growing of the pandemic, the majority of international societies made recommendations on the basis of the general principle of the risk-to-benefit ratio, recognising the need to protect a vulnerable population from a potentially fatal infection, alongside with the potential harms of delaying diagnostic procedures and treatments in patients with cancer [25–28]. Therefore, data on the impact of anticancer treatments on the COVID-19 trajectory are largely awaited. The UKCCMP and the CCC19 cohort found no association of increased mortality with recent chemotherapy administration. A recent study from Memorial Sloan Kettering Cancer Center including more than 300 patients found no association between chemotherapy use and adverse COVID-19 outcome [5]. In an observational study of 890 European patients with cancer, chemotherapy use was not associated with increased mortality [14]. Interestingly, provision of active anticancer therapy was found to be protective. In the French GCO-002 CACOVID-19, none of the anticancer treatments administered within the previous three months significantly affect mortality or COVID-19 severity [16]. In our ROVID study, we found no association between chemotherapy use and increased risk of death. On the other hand, in the TERAVOLT study, chemotherapy use was associated with an increased risk of death [8].

More recent data from the Gustave Roussy cohort described a significant association between chemotherapy use in the past 3 months and clinical worsening and death [9]. A recent meta-analysis including 16 studies concluded for an increased risk of death for chemotherapy administered within the last 30 days before COVID-19 diagnosis [29].

It is important to note, however, that all these studies vary in design, end-points, statistical methods, patient composition, and so comparisons are challenging. In our study, active anticancer treatments were discontinued due to SARS-CoV-2 infection diagnosis in two third of the patients. Notably, a decrease in cancer diagnosis and access to cancer facilities have been reported, and some screening services have been temporarily interrupted, raising the concern on a potential increase in cancer mortality overtime due to underdiagnoses or under treatment [30,31]. In our view, the high mortality rate reported in our and other studies largely overcome these concerns, and in the absence of an effective vaccine and treatment, preventing transmission of SARS-CoV-2 remains the goal. Cancer patients are a fragile population, and maximum effort should be made to ensure proper care in a safe environment [32]. In the ROVID study, disease stage and disease setting (curative vs palliative) were not associated with the risk of death, reinforcing the importance of maintaining protective measures for all these patients. Triage procedures to identify patients at risk for having COVID-19 infection before access to cancer care facilities, the use of telemedicine for follow-up visits, where possible prescribing oral drugs can be helpful to protect this vulnerable population.

At the time of this report, we are at the beginning of the second wave of the pandemic, with an extremely rapid spread of the contagion worldwide. We acknowledge the limited sample size of this study and the heterogeneity of the population in terms of cancer diagnosis, disease stage, anticancer treatments. However, these data are generated starting from an homogeneous environment in terms of healthcare resources, with shared guidelines for cancer patients treatment during the pandemic discussed and licenced since the beginning [3]. Our data contribute to the knowledge of the trajectory of the disease course in cancer patients

and can helpful for proper cancer care planning at regional and national levels.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.01.021.

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