RESEARCH BRIEF

Clinical Portrait of the SARS-CoV-2 Epidemic in European Patients with Cancer

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ABSTRACT

The SARS-CoV-2 pandemic significantly affected oncology practice across the globe. There is uncertainty as to the contribution of patients' demographics and oncologic features to severity and mortality from COVID-19 and little guidance as to the role of anticancer and anti–COVID-19 therapy in this population. In a multicenter study of 890 patients with cancer with confirmed COVID-19, we demonstrated a worsening gradient of mortality from breast cancer to hematologic malignancies and showed that male gender, older age, and number of comorbidities identify a subset of patients with significantly worse mortality rates from COVID-19. Provision of chemotherapy, targeted therapy, or immunotherapy did not worsen mortality. Exposure to antimalarials was associated with improved mortality rates independent of baseline prognostic factors. This study highlights the clinical utility of demographic factors for individualized risk stratification of patients and supports further research into emerging anti–COVID-19 therapeutics in SARS-CoV-2–infected patients with cancer.

SIGNIFICANCE: In this observational study of 890 patients with cancer diagnosed with SARS-CoV-2, mortality was 33.6% and predicted by male gender, age ≥65, and comorbidity burden. Delivery of cancer therapy was not detrimental to severity or mortality from COVID-19. These patients should be the focus of shielding efforts during the SARS-CoV-2 pandemic.

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INTRODUCTION

The pandemic spread of SARS-CoV-2, a novel *Betacoronavirus* first isolated in Wuhan, China (1), has been responsible, as of May 15, 2020, for >300,000 deaths globally, half of which occurred in Europe. Mortality from coronavirus disease 2019 (COVID-19) is linked to advanced age and comorbidity burden (2). There is consensus that patients with cancer represent a particularly vulnerable population in the context of the COVID-19 pandemic. Early data from the Hubei province outbreak highlighted a 6.2-fold difference in mortality for patients with cancer compared with previously healthy SARS-CoV-2–infected patients (5.6% vs. 0.9%; ref. 3). This observation has been more recently corroborated by a multicenter case–control study which suggested a higher rate of complications and mortality in patients with cancer compared with noncancer SARS-CoV-2–infected controls, with poorer outcomes observed in hematologic malignancies and lung cancer (4).

Most of the available evidence describing the outlook of patients with cancer infected by COVID-19 has so far been drawn from relatively small case series with unbalanced representation of key oncologic features including primary tumor site, stage, and prior therapy. As a result, a number of open questions still exist as to whether, within the broader population of patients with cancer, outcome of COVID-19 is more strongly related to patients' demographic factors such as age and comorbidities rather than oncologic features.

In the first quarter of the year 2020, cancer care has been profoundly challenged by the unfolding of the SARS-CoV-2 pandemic: limitation of hospital attendance and deferral or interruption of interventions characterized by higher risk of COVID-19–related morbidity or limited survival benefit have been common practice in most healthcare systems (5). The majority of precautionary measures implemented so far rest on expert opinions or evidence extrapolated from other infectious diseases (6).

An accurate portrait of severity, early mortality, and long-term survival following COVID-19 infection across tumor sites, stages of cancer, and therapeutic modality is urgently needed to redesign the provision of cancer services during and beyond the pandemic on the basis of solid clinical evidence (7).

OnCovid is the first multicenter observational study aimed at describing natural history and outcomes from SARS-CoV-2 infection in European patients with cancer.

In this report, we sought to explore clinical factors that are associated with severe SARS-CoV-2 infection in patients with cancer and study baseline demographic factors that relate to mortality following SARS-CoV-2 infection. As an additional aim, we tested whether type of anticancer therapy received prior to COVID-19 and provision of SARS-CoV-2–specific therapy influenced patients' mortality from COVID-19.

RESULTS

Demographics and Oncologic Features

Between February 26 and April 1, 2020, we identified 890 patients with confirmed SARS-CoV-2 infection and cancer at the 19 centers surveyed in the United Kingdom (n = 218, 24.5%), Italy (n = 343, 38.5%), Spain (n = 323, 36.3%), and Germany (n = 6, 0.7%; Supplementary Table S1). This patient pool represents all the consecutive referrals received by acute oncology and/or emergency/internal medicine services during the accrual period. Demographic and clinical features of the patient population are described in Supplementary Table S2. The majority of patients were men (n = 503, 56.5%) with a mean (±SD) age of 68.0 (±13) years (range, 21–99). Most patients (n = 753, 84.6%) carried a diagnosis of solid malignancy, with advanced stage occurring in 330 patients (43.8%); breast cancers represented the most common primary site (n = 162, 18.2%). The median interval from first diagnosis of cancer to COVID-19 diagnosis was 17 months [interquartile range (IQR), 54]. Comorbid conditions were documented in 670 patients (75.2%), the most prevalent being hypertension (n = 386, 43.4%), cardiovascular diseases (n = 190, 21.3%), and diabetes mellitus (n = 181, 20.3%). In total, 411 patients (46.2%) had >1 comorbidity.

Prior oncologic therapies are summarized in Supplementary Table S2. Forty-two patients (4.7%) were assuming corticosteroids at the dose of >10 mg of prednisone equivalent.

Anticancer Therapy at COVID-19 Diagnosis

At COVID-19 diagnosis, 556 patients (62.5%) had evidence of active malignancy, and 479 (53.8%) were on systemic anticancer therapy, mostly with palliative intent (n = 276, 31.0%), whereas 403 patients (45.3%) were not on treatment. The mean interval between the last dose of systemic anticancer treatment was 19.3 days (SD 33.3). Patients on active anticancer therapy were more likely females, of younger age, with inferior comorbidity burden and lower proportion of active disease (P < 0.001; Supplementary Table S3). When stratified across therapeutic modality irrespective of indication, 206 were on chemotherapy (23.1%), 92 on endocrine therapy (10.3%), 93 on targeted therapies (10.4%), and 56 on immunotherapy (6.3%; Supplementary Fig. S1A–S1C). In total, 128 (26.7%) patients were receiving treatment with radical/curative intent including 59 patients undergoing primary curative chemotherapy for a hematologic malignancy (6.6%), 26 patients (2.6%) on

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Note: Supplementary data for this article are available at Cancer Discovery Online (http://cancerdiscovery.aacrjournals.org/).

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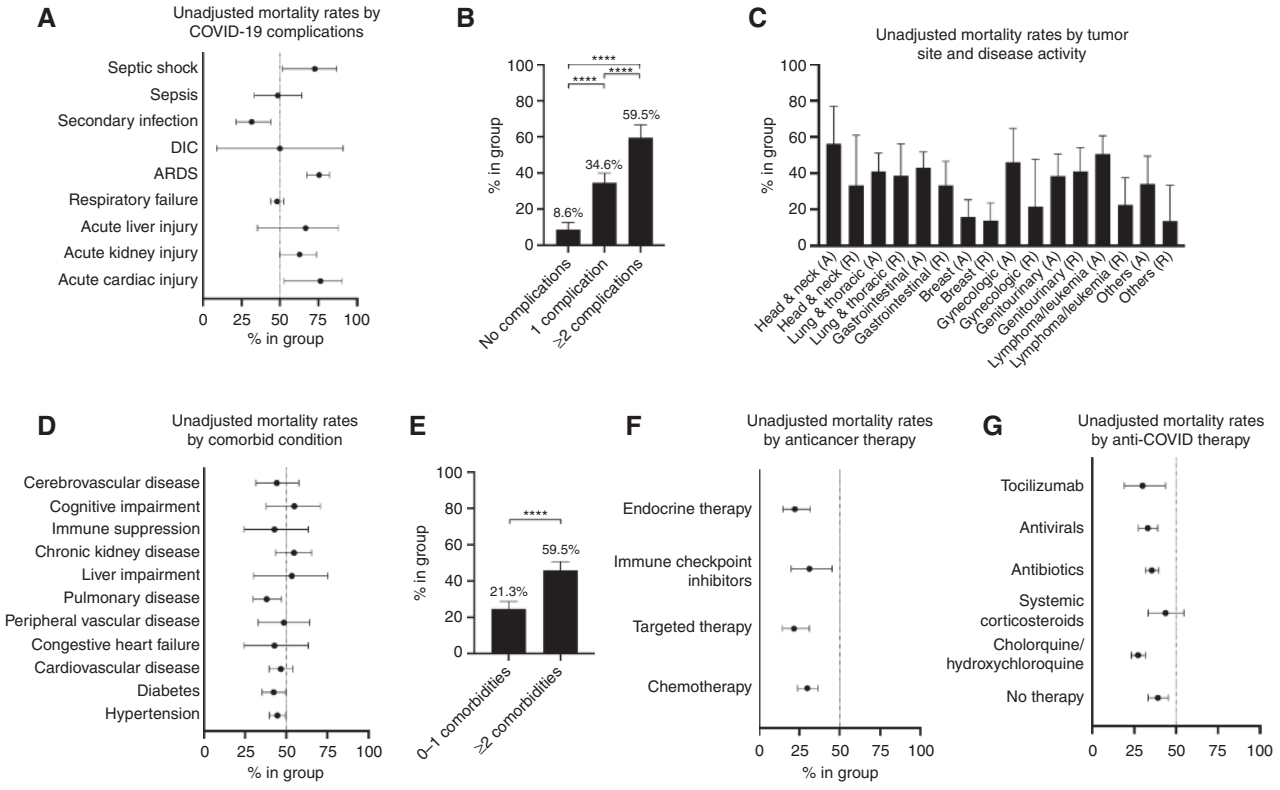

Figure 1. The relationship between mortality from COVID-19 and clinicopathologic features of patients with cancer. Unadjusted mortality rates stratified by type (**A**) and number (**B**) of complications from COVID-19, primary tumor site (**C**), type (**D**) and number (**E**) of comorbid conditions, and anticancer therapy (**F**) and anti–COVID-19 therapy (**G**) received. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$. DIC, disseminated intravascular coagulation.

neoadjuvant chemotherapy, and 43 patients treated with adjuvant therapy (4.8%), most commonly chemotherapy ($n = 37$, 4.2%). Thirty-three patients (3.7%) were receiving radiotherapy, mostly with radical intent ($n = 25$, 75.8%).

Features of COVID-19 Disease

The most common presenting symptoms of SARS-CoV-2 infection were fever ($n = 569$, 63.9%), cough ($n = 448$, 50.3%), and dyspnea ($n = 340$, 38.2%). Mean body temperature at presentation was 37.4°C (SD ± 0.5). SARS-CoV-2 was community-acquired in 708 patients (79.5%) and complicated a preexisting hospital admission in another 182 (20.4%). Mean time from onset of symptoms to presentation was 6.3 days (SD ± 9.5). Radiologic investigations including a chest X-ray (CXR) and/or CT were performed at the discretion of the treating physician in 811 (91.1%) patients. Acute abnormalities were found in 445 of 842 patients with a baseline CXR available (53.0%) and in 224 of 234 patients with a baseline CT (95.7%). Bilateral ground-glass/reticulo-nodular changes were the most commonly observed pattern on CXR ($n = 253$, 39.5%) and on CT ($n = 174$, 74.7%).

The majority of patients were treated in the context of ward-based care ($n = 760$, 85.4%). One hundred ten (14.5%) required escalation to intensive/subintensive care. In 120 cases (13.6%), admission to hospital was not deemed necessary, and patients were managed with domiciliary self-isolation. The median length of hospitalization in admitted patients was 10 days (IQR, 5–18), and median permanence in intensive/subintensive care unit was 6 days (IQR, 3–12). Oxygen therapy was administered to 527 patients (59.2%), including high-flow delivery in 244 (27.4%). Mechanical ventilation was initiated in 97 patients (10.9%), including noninvasive ventilation ($n = 67$, 69.0%) and endotracheal intubation ($n = 35$, 36.0%). None of the patients received extracorporeal membrane oxygenation.

Factors Associated with Complicated COVID-19 Disease in Patients with Cancer

Throughout the observation period, the majority of patients ($n = 565$, 63.5%) developed at least 1 complication from COVID-19, the most common being acute respiratory failure ($n = 527$, 59.2%) followed by acute respiratory distress syndrome (ARDS; $n = 127$, 22.5%). In total, 274 patients (30.8%) had evidence of an uncomplicated illness. We evaluated the association between baseline clinical and demographic features and the emergence of complicated COVID-19 disease, defined as the presence of at least 1 complication from SARS-CoV-2 infection throughout the observation period. Figure 1A highlights the unadjusted mortality rates stratified by type of COVID-19–related complication. Number of COVID-19–related complications was significantly associated with increasing mortality rates, ranging from 8.6% in patients with uncomplicated disease to 59.5% in those with ≥2 complications (Fig. 1B, $P < 0.001$) and with shorter survival times (Supplementary Fig. S2, $P < 0.001$). As shown in Table 1, male gender, age ≥65, and presence of ≥2 comorbidities

Table 1. Univariable and multivariable logistic regression models evaluating the relationship between patient characteristics and the development of complicated COVID-19 disease

Characteristic	Univariable OR	95% CI	*P* value	Multivariable OR	95% CI	*P* value
Sex, M/F	2.41	1.80–3.24	<0.0001	2.01	1.46–2.77	<0.0001
Age, <65/≥65	2.44	1.81–3.28	<0.0001	1.90	1.37–2.65	<0.0001
Comorbidities, 0–1/≥2	2.47	1.83–3.35	<0.0001	1.75	1.24–2.46	0.001
Tumor stage, nonadvanced/advanced	0.84	0.62–1.12	0.23	1.24	0.85–1.81	0.26
Tumor status Remission/no measurable disease Active malignancy	0.67	0.49–0.92	0.012	0.69	0.46–1.03	0.07
Anticancer therapy, no/yes	0.52	0.39–0.70	<0.0001	0.68	0.48–1.00	*P* = 0.03
Immunotherapy ongoing, no/yes	1.12	0.59–2.14	0.73			
Chemotherapy ongoing, no/yes	1.15	0.78–1.68	0.47			
Targeted therapy ongoing, no/yes	0.65	0.40–1.05	0.08			

prior to SARS-CoV-2 infection were significantly associated with the development of a complicated disease course irrespective of oncologic features such as tumor stage or presence of measurable disease at COVID-19 diagnosis. Receipt of active anticancer therapy at the moment of COVID-19 diagnosis was associated with lower risk of complicated disease; however, type of systemic anticancer therapy, including cytotoxic chemotherapy ($P = 0.47$), targeted therapy ($P = 0.08$), or immunotherapy ($P = 0.73$), was not associated with COVID-19 severity. Multivariable logistic regression models confirmed male gender, age ≥65 ($P < 0.0001$), presence of ≥2 comorbidities ($P = 0.001$), presence of active malignancy ($P = 0.07$), and active anticancer therapy ($P = 0.03$) as independent predictors of complicated COVID-19.

Factors Associated with Mortality from COVID-19 in Patients with Cancer

At time of censoring on May 11, 2020, of the 890 patients accrued, 299 had died (33.6%), 22 (2.5%) were hospital survivors, and 569 (63.9%) were discharged from hospital. The mortality rate stratified by country was 33.2% for Italian ($n = 112/337$), 29.6% for Spanish ($n = 95/321$), and 44.4% for UK centers ($n = 91/205$). After a mean follow-up time of 19.0 ± 16.3 days, the median overall survival (OS) calculated as time from COVID-19 diagnosis was not reached [mean, 86.0; 95% confidence interval (CI), 78.7–93.1; range, 0–155 days]. The mean duration of follow-up was 19.0 ± 16.3 days. First, we evaluated clinical predictors of patients' mortality following COVID-19. When categorized according to tumor site of origin, unadjusted mortality rates were highest in head and neck cancer ($n = 13/29$, 44.8%) and lowest in breast cancer ($n = 24/258$, 15.2%; Fig. 1C). The Kaplan–Meier analysis of OS revealed genitourinary (median, 22.0; 95% CI, 5.3–36.6 days) and hematologic malignancies (median, 24.0; 95% CI, 8.8–39.1 days) to be characterized by worse outcome (Supplementary Table S4 and Supplementary Fig. S3). We then evaluated the impact of baseline clinicopathologic features on patients' mortality. In Fig. 1D, unadjusted analysis of mortality rates stratified by comorbid condition demonstrated cognitive impairment ($n = 17/32$, 54.8%) and chronic kidney disease ($n = 41/75$, 54.6%) to be characterized by higher mortality rates. Significantly higher mortality rates were observed for male patients (40.8 vs. 26.3%, $P < 0.001$), for those aged ≥65 years (43.8 vs. 19.3%, $P < 0.001$), in those with ≥2 preexisting comorbidities (45.9 vs. 24.7%, $P < 0.001$; Fig. 1E). Nosocomial transmission of SARS-CoV-2 was also associated with higher mortality rates (47.5% vs. 36.7%, $P = 0.01$) in hospitalized patients ($n = 760$). Active malignancy ($P < 0.0001$) emerged as the only oncologic feature predictive of higher mortality rates in multivariable Cox regression models alongside age ≥65 ($P < 0.0001$) and comorbidities ($P = 0.002$), whereas provision of active anticancer therapy was protective ($P = 0.003$; Table 2). Restricted mean survival time (RMST) analysis reproduced findings from the Cox regression model (Supplementary Table S5). Figure 1F illustrates unadjusted mortality rates in association with exposure to chemotherapy, targeted therapy, endocrine therapy, and immunotherapy.

In a subset of patients with routine laboratory parameters obtained at COVID-19 diagnosis, we observed differential distribution of hematologic and biochemical parameters in relationship with patients' mortality (8). As shown in Supplementary Fig. S4, the presence of an acute phase reaction evidenced by hypoalbuminemia, anemia, leukocytosis, increased C-reactive protein, and ferritin was associated with patients' mortality together with biomarkers of tissue turnover such as lactate dehydrogenase, D-dimer, and troponin levels.

Treatment of COVID-19

Empirical therapy for COVID-19 was initiated in 629 patients (70.7%) and included broad-spectrum antibiotics ($n = 516$, 58.0%), chloroquine/hydroxychloroquine ($n = 423$, 47.5%), and antivirals including lopinavir/ritonavir ($n = 186$, 20.9%), darunavir/cobicistat ($n = 53$, 6%), and remdesivir ($n = 19$, 2.1%). Eighty patients received systemic corticosteroids (9.0%), and 51 received tocilizumab (5.7%). Other therapies ($n = 37$, 5.8%) included heparin ($n = 21$, 3.3%), oseltamivir

Table 2. Univariable and multivariable Cox regression models evaluating the relationship between patient characteristics and mortality from COVID-19

Characteristic	Univariable HR (95% CI)	95% CI	*P* value	Multivariable HR (95% CI)	95% CI	*P* value
Sex, M/F	1.37	1.07–1.77	0.013			
Age, <65/≥ 65	2.71	1.99–3.70	<0.0001	2.37	1.71–3.30	<0.0001
Comorbidities, 0–1/≥2	1.83	1.42–2.35	<0.0001	1.47	1.13–1.92	0.004
Tumor stage, nonadvanced/advanced	1.36	1.06–1.76	0.019			
Tumor status Remission/no measurable disease Active malignancy	1.55	1.18–2.03	0.003	1.81	1.35–2.44	<0.0001
Anticancer therapy, no/yes	0.77	0.60–1.00	0.10	0.71	0.53–0.95	0.019
Immunotherapy ongoing, no/yes	0.80	0.46–1.40	0.43			
Chemotherapy ongoing, no/yes	0.78	0.57–1.07	0.12			
Targeted therapy ongoing, no/yes	0.80	0.47–1.39	0.44			
Endocrine therapy ongoing, no/yes	1.20	0.71–2.04	0.48			
Intensive/high dependency care unit admission, no/yes	1.14	0.82–1.60	0.41			

(n = 10, 1.5%), and IFNα (n = 6, 0.9%). Unadjusted mortality rates across major classes of COVID-19 therapy are presented in Fig. 1G. Exposure to any type of empirical therapy against COVID-19 (antibiotics, antimalarials, corticosteroids, tocilizumab, or others) was not associated with patients' mortality in univariable Cox regression models (HR, 1.0; 95% CI, 0.7–1.4). We subsequently categorized patients according to exposure to any of the following classes of COVID-19–specific therapies, antimalarials, antivirals, and tocilizumab (n = 444), and compared them with patients who did not receive any of these therapies (n = 446). Exposure to therapy was associated with lower mortality rate (HR, 0.53; 95% CI, 0.38–0.75; P < 0.0001). Because 256 patients (28.7%) received >1 treatment for COVID-19 in association (Supplementary Table S6), we elected to categorize exposure to different classes of COVID-19–specific therapies by evaluating each drug class separately, including patients who received antimalarials alone (n = 182), antivirals (n = 16), and those who received tocilizumab either alone or in association with antimalarials and/or antivirals (n = 51), and compared patients in these categories against patients who did not receive any of these therapies (n = 446). Distribution of demographic and clinicopathologic features of the various treatment groups is illustrated in Supplementary Table S7. In multivariable Cox regression models and in RMST analyses, exposure to antimalarials alone was associated with a significant reduction in mortality from COVID-19 (P < 0.001) compared with patients who did not receive any anti–COVID-19 therapy, after adjusting for patients' gender, age, and tumor stage. Exposure to antivirals alone and to tocilizumab was not associated with mortality, although sample size was significantly smaller for these categories of exposure (n = 16 for antivirals alone and n = 51 for tocilizumab; Table 3). We explored the interaction between classes of therapies using antimalarial and antiviral exposure as interaction terms in

Table 3. Model-adjusted risk of mortality complemented by restricted mean survival time analysis according to type of anti–COVID-19 therapy in patients with cancer and SARS-CoV-2 infection

Therapy	Cox proportional model HR (95% CI) *P* value	Covariates: Sex (M/F)	Covariates: Age (<65/≥65 years)	Covariates: Tumor stage (advanced/nonadvanced)	RMST difference (95% CI) *P* value
Antimalarials only (n = 182) vs. no drug (n = 446)	0.41 (0.26–0.66) P < 0.0001	1.20 (0.89–1.63) P = 0.23	2.81 (1.90–4.17) P < 0.0001	1.20 (0.87–1.66) P = 0.27	8.00 (5.50–10.52) P < 0.0001
Antivirals only (n = 16) vs. no drug (n = 446)	0.75 (0.32–1.79) P = 0.52	1.35 (1.00–1.89) P = 0.08	2.96 (1.90–4.62) P < 0.0001	1.13 (0.78–1.63) P = 0.51	0.29 (–0.19–0.77) P = 0.23
Tocilizumab (n = 51) vs. no drug (n = 446)	0.80 (0.37–1.74) P = 0.57	1.43 (1.03–2.00) P = 0.03	2.61 (1.74–3.92) P < 0.0001	1.28 (0.90–1.82) P = 0.16	2.64 (0.90–4.38) P = 0.003

separate Cox regression models for mortality, having excluded tocilizumab exposure in view of low numerosity of the group and because 50 of 51 patients (98%) received tocilizumab with at least 1 other therapy (Supplementary Table S6). The relationship between antimalarials and mortality was independent of antiviral exposure following adjustment for age, sex, and tumor stage (Supplementary Table S8).

DISCUSSION

The rapid dissemination of SARS-CoV-2 has imposed an unprecedented toll on the quality of cancer care across the globe. Prioritization of oncologic care has followed a delicate balance between expected therapeutic benefit and risk of harm secondary to viral transmission, responding to the need for caution in the context of uncertainty (9). Patients with cancer are at risk of high mortality rates from COVID-19 (up to 28.6%; ref. 10), a 3-fold increase compared with noncancer controls (4).

Our study contributes to delineate the natural history of COVID-19 by reporting outcomes from the largest European series of consecutive SARS-CoV-2–infected oncologic patients to date, lending credence to the view that COVID-19 is a severe, life-threatening disease leading to mortality in 1:3 patients with cancer. Despite shorter duration of symptoms (6.3 days) and largely similar presenting features compared with cancer-unselected populations (11), more than half of our patients developed or presented with complications from COVID-19, some of which were associated with mortality rate in excess of 70%, including acute cardiac injury, ARDS, and septic shock. Because of the strong impact of COVID-19–related complications on mortality, we sought to identify clinical predictors of severe COVID-19 disease, defined as the occurrence of ≥1 complication from COVID-19. Interestingly, we found a lower but still significant rate of mortality (8.6%) in patients who did not develop complications from COVID-19. Because our study recorded all-cause mortality and lacks COVID-19–negative cancer controls, it is difficult to conclude whether uncomplicated COVID-19 might have led to premature mortality in patients with cancer, a point that should be explored in future studies. Unlike other studies, we excluded escalation to intensive care as a marker of disease severity given its reliance on oncologic prognosis and intensive-care capacity. We found that complicated COVID-19 disease was significantly associated with male gender, more advanced age, and higher comorbidity burden, prognostic features that are known to adversely influence the course of COVID-19 irrespective of cancer. The same demographic features emerged as strong, independent predictors of patients' mortality, to underscore their central role in dictating the pathophysiology of SARS-CoV-2 infection in the context of malignancy.

In our study, provision of active anticancer treatment was not associated with worse mortality. Recent exposure to anticancer therapy was initially found to increase mortality in a case series of only 28 patients (10). Subsequent studies have however challenged this view, having shown for instance that exposure to immunotherapy does not affect severity or mortality from COVID-19 in lung cancer (12), whereas androgen deprivation therapy may potentially improve survival from COVID-19 due to postulated inhibition of TMPRSS2, an androgen-regulated serine protease involved in viral replication (13). In line with recent evidence, data from the OnCovid registry suggest for the first time that recent exposure to any of the individual classes of systemic anticancer therapy, including cytotoxics, endocrine therapy, molecularly targeted therapies, and immunotherapy, does not adversely influence mortality from COVID-19 across a wide range of tumors. Although patients on treatment had lower mortality in our study, these were also generally younger, less comorbid, and more likely to be female (Supplementary Table S2), suggesting the protective effect we observed for exposure to any anticancer therapy to be associative rather than causative. This finding is of utmost clinical importance in delineating evidence-based treatment strategies for patients with cancer during the COVID-19 pandemic, as it suggests that continued use of systemic anticancer therapies may be safe and should be guided by an individualized risk-stratification process on the basis of demographic features of patients with cancer. Based on our data, younger patients without comorbidities are characterized by lower complications and mortality and should be prioritized for anticancer therapy on the basis of the expected therapeutic benefit of the regimen of choice. On the other hand, in elderly and multiple-comorbidity patients, survival benefit from cancer therapy may be outweighed by COVID-19–related morbidity and mortality, warranting deferral or de-escalation of treatment (9). The importance of limitation of hospital attendance emerges even more strongly from the notion that 1:5 patients in our study acquired SARS-CoV-2 via nosocomial transmission. The higher mortality rates observed in these patients, approaching 50%, underscores the need to create and maintain COVID-19–free pathways for patients with cancer in order to limit nosocomial spread to the most vulnerable (10).

Interestingly, our study shows that mortality from COVID-19 is not uniformly distributed across the various types of malignancy. Here, we reproduce the observation made by Dai and colleagues in reporting significantly inferior survival of patients with hematologic malignancies, a finding that might be explained by the intrinsic impairment in innate and adaptive immunity that is typical of patients with leukemia, lymphoma, and myeloma (14). Surprisingly, patients with breast cancer experienced the lowest mortality rates compared with other malignancies (15.2%), a finding that may not be fully explained by the protective effect of female gender in dictating the severity of COVID-19, given the higher rates of mortality seen in gynecologic cancers (37.5%). More detailed analyses of clinical and biological features of this patient subset are ongoing.

Therapeutic targeting of SARS-CoV-2 infection has been dominated by the lack of clear prospective evidence and extensive empirical attempts at COVID-19–specific pharmacotherapy (15). In our study, we performed detailed analyses of exposure to COVID-19–specific therapies in relationship with patients' mortality, an aspect that has not been addressed by any of the other studies specifically in patients with cancer. Due to the retrospective nature of our study and the discretionary use of the diverse classes of pharmacologic agents either as monotherapies or in combination, we focused our attention on antimalarials, antivirals, and the anti-IL6

antagonist tocilizumab as broad categories of anti–COVID-19 therapy. We found that combined exposure to these selected classes of COVID-19 therapies was associated with improvement in mortality compared with unexposed controls. Acknowledging the imbalance of prognostic features across treatment groups, we adjusted our estimates for key confounders including age, gender, and comorbidity burden. Using multivariate Cox regression models and restricted mean survival time analyses, exposure to antimalarials emerged as an independent predictor of patients' survival compared with untreated controls. It should be emphasized that a direct cause–effect relationship between exposure to each agent and mortality from COVID-19 cannot be inferred due to the observational, retrospective nature of our study and the high proportion of patients treated with concomitant therapies. This is particularly true for antivirals and tocilizumab. However, the association we observed is highly provocative, as it supports ongoing clinical research focusing on COVID-19–specific therapies in patients with cancer, a population where mortality from COVID-19 is particularly high and influenced by a number of competing factors, including high comorbidity burden and active malignancy. Evolving clinical data have shown promising evidence of efficacy for some of these therapies including remdesivir (16), whereas data on other agents such as lopinavir/ritonavir have been less convincing (17). Although supported by initial evidence of potential efficacy against COVID-19 (18), antimalarials have been at the focus of intense debate following publication and subsequent retraction of poorly conducted observational studies (19, 20). Definitive reports from prospective, randomized controlled clinical studies are eagerly awaited in this therapeutic area (21).

Our study acknowledges a number of limitations. In view of the retrospective, observational design of this study, diagnostic pathways and therapeutic decisions were not standardized *a priori* across centers. This point should be carefully considered when interpreting data on the association between therapies and clinical outcomes, which might be influenced by unmeasured confounders, including patients' oncologic prognosis, which might have guided prescription of anti–COVID-19 therapy. Incomplete documentation or missing laboratory/radiologic data are another important limitation of retrospective research. In addition, our decision to focus on outcomes of patients with confirmed SARS-CoV-2 infection is likely to have skewed our observation toward the more severe cases of COVID-19 disease, excluding those cases with asymptomatic or mildly symptomatic disease, for which RT-PCR testing may not have been available at the beginning of the outbreak. In addition, although healthcare authorities published data on incidence, prevalence, and mortality in real time during the COVID-19 outbreak in Europe, we lack a precise estimate of incidence of COVID-19 infection in patients with cancer. This is a point that should be explored in future population-based epidemiologic studies.

Although outcomes from COVID-19 are influenced by ceilings of care, mortality rates can be as high as 50% (22) even in selected patients treated within intensive care units (11). Escalation beyond ward-based care is the subject of careful case-by-case evaluation in patients with cancer, the majority of whom may not be appropriate for resuscitation (23). Such balance is made even harder in the context of a global pandemic, where saturation of clinical services imposes an often difficult prioritization of critical care resources in favor of younger and less comorbid critically ill patients (24). In our study, a minority of patients were admitted to intensive/subintensive care units, and an even smaller proportion were intubated and ventilated. Although admission to intensive/high-dependency care was not associated with mortality in our study, we cannot draw definitive conclusions as to prognostic outlook and outcomes in this subpopulation, a point that should be investigated in future studies.

Despite the acknowledged limitations, our study is the largest and most geographically diverse European study to document outcomes of COVID-19 in patients with cancer, factors that broaden the generalizability of our results to the wider population of oncologic patients requiring hospital assessment for COVID-19.

In a context of continuing threat from SARS-CoV-2 infection, our data argue against a detrimental influence of active anticancer therapy in determining outcome from COVID-19 and open important questions as to the role of COVID-19–specific therapy in the management of SARS-CoV-2–infected patients with cancer. The combination of simple tumor type– and stage-independent demographic features such as gender, age, and number of comorbidities should be used in the clinic to support comprehensive clinical risk stratification during the COVID-19 pandemic in an attempt to avoid indiscriminate deferral of anticancer therapy and preserve oncologic outcomes.

METHODS

Study Population, Setting, and Data Collection

The OnCovid registry (NCT04393974) includes patients ≥18 years of age with diagnosis of SARS-CoV-2 infection confirmed by RT-PCR of a nasopharyngeal swab and history of solid or hematologic malignancy, at any time during the patients' past medical history, either active or in remission at the time of COVID-19 diagnosis. Patients with a history noninvasive/premalignant lesions or with low malignant potential (i.e., basal cell carcinoma of the skin, noninvasive carcinoma *in situ* of the cervix, ductal carcinoma *in situ*) were excluded. For hematologic malignancies, only patients with a history of oncologic diseases with defined malignant behavior (lymphoma, leukemia, multiple myeloma) were included. At database lock (May 11, 2020), the registry included 890 patients consecutively diagnosed with COVID-19 in 19 academic centers between February 26 and May 7, 2020. A list of participating centers is provided in Supplementary Table S1. OnCovid was granted central approval by the United Kingdom Health Research Authority (20/HRA/1608) and by the corresponding research ethics committees at each participating institution outside the UK. Waiver of prospective informed consent was granted due to the retrospective nature of the study and anonymized use of data collected as per standard of care. Clinical data including patients' demographics, laboratory results, and radiologic results were collated from electronic medical records into a case report form designed using the Research Electronic Data Capture software (REDCap, Vanderbilt University). Features of SARS-CoV-2 infection include presenting symptomatology, severity, requirement for and length of hospitalization, and emergence of secondary complications. Outcomes from COVID-19 including recovery and mortality rates were documented. Multisite access and data curation were coordinated by the Medical Statistics Unit in Novara, Italy.

Study Endpoints and Definitions

The clinical definition of the symptoms, clinical syndromes, and complications associated with COVID-19, including ARDS, followed criteria published by the World Health Organization. Eligibility for the study required a diagnosis of SARS-CoV-2 based on real-time RT-PCR testing of nasopharyngeal swab sample (25). Nosocomial SARS-CoV-2 transmission was defined in patients who developed symptoms and tested positive for COVID-19 while being admitted for other reasons (26). Patients with active malignancy were defined as those who, at the time of COVID-19 diagnosis, presented with measurable oncologic disease defined by radiologic, clinical, and hematologic criteria routinely employed for clinical monitoring of the reference tumor type. Treatment-naïve patients were defined as those with a diagnosis of cancer who did not receive any treatment for their malignancy at the time of COVID-19 diagnosis (surgery, radiotherapy, and systemic therapy). For the purpose of analyzing the interplay between active anticancer therapy and outcomes form COVID-19, patients were defined as receiving active cancer therapy if they were receiving systemic anticancer agents (i.e., chemotherapy, immunotherapy, targeted therapy, endocrine therapy, or combinations) with an interval between last dose and COVID-19 diagnosis within 4 weeks. Patients were classified as being on treatment if actively receiving systemic anticancer therapy. There were two primary outcomes of this study: death and occurrence of complicated SARS-CoV-2 infection, defined as the presence of at least one complication from SARS-CoV-2 infection identified from the moment of clinical diagnosis throughout the observation period. Patients' OS was computed from the date of SARS-CoV-2 swab positivity to the date of death or last follow-up. In evaluating the relationship between exposure to anti–COVID-19 therapy and mortality, we categorized treatment groups based on having received at any time during hospitalization: any antimalarial (hydroxychloroquine or chloroquine), any antiviral (lopinavir/ritonavir, darunavir/cobicistat, remdesivir), tocilizumab either alone or in association with antimalarials and/or antivirals; neither drug defined as no receipt of either antimalarials, antivirals, or tocilizumab.

Statistical Analysis

Normally distributed data were presented as mean and SD, whereas data following a non-normal distribution were presented as median and IQR. Categorical variables were summarized as counts and percentages. Differences in medians were evaluated using Mann–Whitney *U* test and Wilcoxon Rank signed-rank test for pairwise comparisons. Associations between categorical variables were tested using Pearson χ^2 test or Fisher exact test as appropriate.

Univariable and multivariable Cox proportional hazards models stratified by center were used to assess the impact of the factors on risk of death. The proportionality of hazards assumption was tested by visual inspection of the scaled Schoenfeld residuals plot and by the Grambsch and Therneau nonproportionality test. Multivariable Cox proportional hazards model was applied using stepwise selection. Results of Cox analysis were presented as HR with a 95% CI and corresponding *P* value. Cox regression models were complemented by RMST analyses.

A two-sided P value < 0.05 was considered statistically significant. Analyses of patients' survival followed Kaplan–Meier methodology and log-rank test.

We examined the association between the study variables and complications using univariable and multivariable logistic regression model. The predictors were incorporated into a multivariable logistic regression model using a stepwise selection process. OR and 95% CIs were calculated.

Analyses were performed using STATA software, version 14 (StataCorp. 2015. Statistical Software: Release 14.0. College Station, TX: Stata Corporation) and SPSS version 25 (IBM Inc.).

Disclosure of Potential Conflicts of Interest

D.J. Pinato reports personal fees from ViiV Healthcare (Lecture Fees), personal fees from Bayer Healthcare (Lecture Fees), other from BMS (Travel Fees), other from Bayer Healthcare (Travel Fees), personal fees from Mina Therapeutics (Consultancy), personal fees from EISAI (Consultancy), personal fees from Roche (Consultancy), personal fees from AstraZeneca (Consultancy), grants from MSD (Grant to institution), and grants from BMS (Grant to institution) outside the submitted work. A. Zambelli reports personal fees from Roche (For occasional advisory board), personal fees from Pfizer (For occasional advisory board), personal fees from Novartis (For occasional advisory board), personal fees from Lilly (For occasional advisory board), personal fees from AstraZeneca (For occasional advisory board), personal fees from Merck (For occasional advisory board), and personal fees from Exact Science GH (For occasional advisory board) outside the submitted work. M. Bower reports Speaker honoraria received from ViiV, Gilead Sciences, BMS, Janssen, and MSD. R. Mesia reports grants and personal fees from Merck KgA, personal fees from MSD, personal fees from BMS, personal fees from AstraZeneca, personal fees from Nanobiotics, personal fees from Seattle Genetics, and personal fees from Roche outside the submitted work. D. Generali reports personal fees from Novartis, personal fees from Pfizer, and personal fees from Lilly outside the submitted work. R. Bertulli reports other from Advenchen Laboratories (research funding), other from Amgen Dompe (research funding), other from AROG Pharmaceuticals (research funding), other from Bayer (research funding), other from Blueprint Medicine (research funding), other from Daiichi Sankyo (research funding), other from Deciphera (research funding), other from Eisai (research funding), other from Eli Lilly (research funding), other from Epizime Inc. (research funding), other from Glaxo (research funding), other from Karyopharm Pharmaceuticals (research funding), other from Novartis (research funding), other from Pfizer (research funding), and other from Pharmamar (research funding) outside the submitted work. C. Tondini reports grants from Roche (clinical trial), grants from Novartis (clinical trial), grants from BMS (clinical trial), personal fees from Myriad Genetics (Consulting or Advisory Role), personal fees from Amgen (Speakers' Bureau), personal fees from Celgene (Travel/Accommodations, Expenses), personal fees from Novartis (Travel/Accommodations, Expenses), and personal fees from Roche/Genentech (Travel/Accommodations, Expenses) outside the submitted work. O. Mirallas reports personal fees from Kyowa Kirin (Travel) outside the submitted work. S. Provenzano reports other from Eli Lilly (research funding), other from Novartis (research funding), other from Pfizer (research funding), other from Pharmamar (research funding), other from Karyopharm (research funding), other from GSK (research funding), other from Epizime (research funding), and other from Eisai (research funding) outside the submitted work; and spouse working for AstraZeneca. J.S. Evans reports grants from Takeda and personal fees from Roche outside the submitted work. T. Newsom-Davis reports personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Amgen, personal fees and non-financial support from BMS, personal fees and non-financial support from MSD, personal fees and non-financial support from Eli Lilly, personal fees from Novartis, personal fees and non-financial support from Roche, personal fees from Bayer, personal fees from Pfizer, and personal fees and non-financial support from Takeda outside the submitted work. A. Sureda reports personal fees from Takeda, personal fees from Celgene-BMS, personal fees from Novartis, personal fees from Kite Gilead, personal fees from Sanofi, personal fees from Janssen, and personal fees from Roche outside the submitted work. G. Gaidano reports personal fees from Janssen (Advisory Board, Speaker' Bureau), personal fees from AbbVie (Advisory Board, Speakers' Bureau), personal fees from Sunesys (Advisory Board), and personal fees from AstraZeneca (Advisory Board)

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Authors' Contributions

D.J. Pinato: Conceptualization, Resources, Data Curation, Software, Formal Analysis, Supervision, Funding Acquisition, Validation, Investigation, Visualization, Methodology, Writing-Original Draft, Project Administration, Writing-Review and Editing. **A. Zambelli:** Investigation. **J. Aguilar-Company:** Data Curation, Investigation. **M. Bower:** Data Curation, Investigation. **C.C.T. Sng:** Data Curation, Investigation. **R. Salazar:** Data Curation, Investigation. **A. Bertuzzi:** Data Curation, Investigation. **J. Brunet:** Data Curation, Investigation. **R. Mesia:** Data Curation, Investigation. **E. Seguí:** Data Curation, Investigation. **F. Biello:** Data Curation, Investigation. **D. Generali:** Data Curation, Investigation. **S. Grisanti:** Data Curation, Investigation. **G. Rizzo:** Data Curation, Investigation. **M. Libertini:** Data Curation, Investigation. **A. Maconi:** Data Curation, Investigation. **N. Harbeck:** Data Curation, Investigation. **B. Vincenzi:** Data Curation, Investigation. **R. Bertulli:** Data Curation, Investigation. **D. Ottaviani:** Data Curation, Investigation. **A. Carbó:** Data Curation, Investigation. **R. Bruna:** Data Curation, Investigation. **S. Benafif:** Data Curation, Investigation. **A. Marrari:** Data Curation, Investigation. **R. Wuerstlein:** Data Curation, Investigation. **M.C. Carmona-Garcia:** Data Curation, Investigation. **N. Chopra:** Data Curation, Investigation. **C. Tondini:** Data Curation, Investigation. **O. Mirallas:** Data Curation, Investigation. **V. Tovazzi:** Data Curation, Investigation. **M. Betti:** Data Curation, Investigation. **S. Provenzano:** Data Curation, Investigation. **V. Fotia:** Data Curation, Investigation. **C.A. Cruz:** Data Curation, Investigation. **A. Dalla Pria:** Data Curation, Investigation. **F. D'Avanzo:** Data Curation, Investigation. **J.S. Evans:** Data Curation, Investigation. **N. Saoudi-Gonzalez:** Data Curation, Investigation. **E. Felip:** Data Curation, Investigation. **M. Galazi:** Data Curation, Investigation. **I. Garcia-Fructuoso:** Data Curation, Investigation. **A.J.X. Lee:** Data Curation, Investigation. **T. Newsom-Davis:** Data Curation, Investigation. **A. Patriarca:** Data Curation, Investigation. **D. García-Illescas:** Data Curation, Investigation. **R. Reyes:** Data Curation, Investigation. **P. Dileo:** Data Curation, Investigation. **R. Sharkey:** Data Curation, Investigation. **Y.N.S. Wong:** Data Curation, Investigation. **D. Ferrante:** Data Curation, Software, Formal Analysis, Investigation, Writing-Original Draft, Writing-Review and Editing. **J. Marco-Hernandez:** Data Curation, Investigation. **A. Sureda:** Data Curation, Investigation. **C. Maluquer:** Data Curation, Investigation. **I. Ruiz-Camps:** Data Curation, Investigation. **G. Gaidano:** Data Curation, Investigation. **L. Rimassa:** Data Curation, Investigation. **L. Chiudinelli:** Data Curation, Investigation. **M. Izuzquiza:** Data Curation, Investigation. **A. Cabirta:** Data Curation, Investigation. **M. Franchi:** Data Curation, Investigation. **A. Santoro:** Data Curation, Investigation. **A. Prat:** Data Curation, Investigation. **J. Tabernero:** Data Curation, Investigation. **A. Gennari:** Conceptualization, Data Curation, Supervision, Investigation, Writing-Review and Editing.

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