Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients.

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Abstract.

The SARS-Cov-2 pandemic significantly impacted on oncology practice across the globe. There is uncertainty as to the contribution of patients' demographics and oncological features on severity and mortality from Covid-19 and little guidance as to the role of anti-cancer and anti-Covid-19 therapy in this population. In a multi-center study of 890 cancer patients with confirmed Covid-19 we demonstrated a worsening gradient of mortality from breast cancer to haematological malignancies and showed that male gender, older age, and number of co-morbidities identifies a subset of patients with significantly worse mortality rates from Covid-19. Provision of chemotherapy, targeted therapy and 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 support further research into emerging anti-Covid-19 therapeutics in SARS-Cov-2 infected cancer patients.

Statement of Significance.

In this observational study of 890 cancer patients diagnosed with SARS-CoV-2, mortality was 33.6% and predicted by male gender, age $\geq$65 and co-morbid 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.

Introduction.

The pandemic spread of SARS-CoV-2, a novel *Betacoronavirus* first isolated in Wuhan, China(1) has been responsible, as of the 15th May 2020, of >300.000 deaths globally, half of which occurred in Europe. Mortality from Coronavirus disease 2019 (Covid-19) is linked to advanced age and co-morbid burden(2). There is consensus that patients with cancer represent a particularly vulnerable population in the context of the SARS-CoV-2 pandemic. Early data from the Hubei province outbreak highlighted a 6.2-fold difference in mortality for cancer patients compared to previously healthy Covid-19 infected patients (5.6% versus 0.9%)(3). This observation has been more recently corroborated by a multi-centre case-control study which suggested a higher rate of complications and mortality in cancer patients compared to non-cancer Covid-19 infected controls, with poorer outcomes observed in haematologic malignancies and lung cancer(4).

Most of the available evidence describing the outlook of cancer patients infected by Covid-19 has so far been drawn from relatively small case series with unbalanced representation of key oncological features including primary tumour 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 from Covid-19 is more strongly related to patients' demographic factors such as age and co-morbidities over oncological features.

In the first quarter of year 2020, cancer care has been profoundly challenged by the unfolding of the SARS-CoV-2 pandemic: limitation of hospital attendance, deferral or interruption of interventions characterised 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 rests on expert opinions or evidence extrapolated from other infectious diseases(6).

An accurate portrait of severity, early mortality and long-term survival from Covid-19

infection across tumour 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 cancer patients.

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

Results.

Demographics and oncological features.

Between February 26th to April 1st 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 1**). 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 2**. 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 (47.2%); breast cancers represented the commonest primary site (n=162, 18.2%). The median interval from first diagnosis of cancer to Covid-19 diagnosis was 17 months (IQR 54). Co-morbid 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 co-morbidity.

Prior oncological therapies are summarized in **Supplementary Table 2**. Forty-two patients (4.7%) were assuming corticosteroids at the dose of >10 mg of prednisone equivalent.

Anti-cancer 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 anti-cancer 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 anti-cancer treatment was 19.3 days (SD 33.3). Patients on active anti-cancer therapy were more likely females, of younger age, with inferior co-morbid burden and lower proportion of active disease (p<0.001 **Supplementary Table 2**). 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%), 56 on immunotherapy (6.3% **Supplementary Figure 1**). In total, 128 (26.7%) patients were receiving treatment with radical/curative intent including 59 patients were undergoing primary curative chemotherapy for a haematological malignancy (6.6%), 26 patients (2.6%) on 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 pre-existing 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 computerized tomography (CT) were performed at the discretion of the treating physician in 811 (91.1%) patients. Acute abnormalities were found in 445 out of 842 patients with a baseline CXR available (53.0%) and in 224 out 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, 86.4%). One hundred and ten (14.5%) required escalation to intensive / sub-intensive 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-sub/intensive 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 non-invasive 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 cancer patients.

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 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 (**Figure 1B,** p<0.001) and with shorter survival times (**Supplementary Figure 2**, p<0.001). As shown in **Table 1**, male gender, age ≥65 and presence of ≥2 comorbidities prior to SARS-Cov-2 infection were significantly associated with the development of a complicated disease course irrespective of oncological features such as tumour stage or presence of measurable disease at Covid-19 diagnosis. Receipt of active anti-cancer therapy at the moment of Covid-19 was associated with lower risk of complicated disease, however type of systemic anti-cancer therapy including cytotoxic chemotherapy (p=0.47), targeted therapy (p=0.08) or immunotherapy (p=0.73) were not associated with Covid-19 severity. Multivariable logistic regression models confirmed male gender, age ≥65 (p<0.0001), presence of ≥2 co-morbidities (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 cancer patients.

At time of censoring on May 11th 2020, of the 890 patients accrued, 299 had died (33.6%), 22 (2.5%) were in 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 centres (n= 91/205). After a mean follow up time of 19.0±16.3 days, the median OS calculated from time to Covid-19 diagnosis was not reached (mean 86.0, 95%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 tumour site of origin, unadjusted mortality rates were highest in head & neck (n=13/29, 44.8%) and lowest in breast cancer (n=24/258, 15.2%, **Figure 1C**). Kaplan-Meier analysis of OS revealed genitourinary (median 22.0 95%CI 5.3-36.6

days) haematological malignancies (median 24.0 95%CI 8.8-39.1 days) to be characterized by worse outcome (**Supplementary Table 4 and Supplementary Figure 3**). We then evaluated the impact of a baseline clinico-pathologic features of on patients' mortality. In **Figure 1D** unadjusted analysis of mortality rates stratified by co-morbid 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 versus 26.3%, p<0.001) for those aged ≥65 years (43.8 versus 19.3%, p<0.001), in those with ≥2 pre-existing comorbidities (45.9 versus 24.7%, p<0.001; **Figure 1E**). Nosocomial transmission of SARS-Cov-2 was also associated with higher mortality rates (47.5% versus 36.7% p=0.01) in hospitalized patients (n=760). Active malignancy (p<0.0001) emerged as the only oncological feature predictive of higher mortality rates in multivariable Cox regression models alongside age ≥65 (p<0.0001) and co-morbidities (p=0.002), whereas provision of active anti-cancer therapy was protective (p=0.003, **Table 2**). RMST analysis reproduced findings from the Cox regression model (**Supplementary Table 5**). **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 haematological and biochemical parameters in relationship with patient's mortality(8). As shown in **Supplementary Figure 4**, the presence of an acute phase reaction evidenced by hypoalbuminemia, anaemia, leukocytosis, increased CRP, ferritin, was associated with patients' mortality together with biomarker of tissue turnover such as LDH, 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, 60.9%) and anti-virals 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 (n=10, 1.5%), interferon alpha (n=6, 0.9%). Unadjusted mortality rates across major classes of Covid-19-therapy is presented in **Figure 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 categorised patients according exposure to any of the following classes of Covid-19-specific therapies: antimalarials, anti-virals 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 rates (HR 0.40 95% CI 0.30-0.56, p<0.001). Because, 256 patients (28.7%) received >1 treatment for Covid-19 in association (**Supplementary Table 6**), 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), anti-virals (n=16) and those who received tocilizumab either alone or in association with anti-malarials and/or antivirals (n=51) and compared 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 7**. In multivariable Cox regression models and in RMST analyses, exposure to anti-malarials alone was associated with a significant reduction in mortality from Covid-19 (p<0.001) compared to patients who did not receive any anti-Covid-19 therapy, after adjusting for patients' gender, age, tumour stage. Exposure to anti-virals alone and to tocilizumab was not associated with mortality, although sample size was significantly smaller for these

categories of exposure (n=16 for anti-virals alone and n=51 for tocilizumab, **Table 3**). We explored the interaction between classes of therapies using anti-malarials and anti-virals exposure as interaction terms in separate Cox regression models for mortality having excluded tocilizumab exposure in view of low numerosity of the group and because 50/51 patients (98%) received tocilizumab with at least 1 other therapy (**Supplementary Table 6**). The relationship between anti-malarials and mortality was independent of anti-viral exposure following adjustment for age, sex and tumour stage (**Supplementary Table 8**).

Discussion.

The rapid dissemination of SARS-Cov-2 has imposed an unprecedented toll on the quality of cancer care across the globe. Prioritization of oncological 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). Cancer patients are at risk of high mortality rates from Covid-19 (up to 28.6%)(10), a three-fold increase compared to non-cancer 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 oncological 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 to 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 in influencing 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 cancer patients: 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 oncological prognosis and intensive care capacity. We found that complicated Covid-19 disease was significantly associated with male gender, more advanced age and higher co-morbid 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, tofc underscore their central role in dictating the pathophysiology of SARS-Cov-2 infection in the context of malignancy.

In our study provision of active anti-cancer treatment was not associated with worse mortality. Recent exposure to anti-cancer 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 anti-cancer therapy including cytotoxics, endocrine, molecularly targeted therapies and immunotherapy does not adversely influence mortality from SARS-Cov-2 across a wide range of tumours. Whilst patients on treatment had lower mortality in our study, these were also generally younger, less comorbid and more

likely to be of female gender (**Supplementary Table 2**), suggesting the protective effect we observed for exposure to any anti-cancer therapy to be associative rather than causative. This finding is of utmost clinical importance in delineating evidence-based treatment strategies for cancer patients during the Covid-19 pandemic as it suggests that continued use of systemic anti-cancer therapies may be safe and should be guided by an individualised risk-stratification process on the basis of demographic features of patients with cancer. Based on our data, younger patients without co-morbidities are characterised by lower complications and mortality and should be prioritised for anti-cancer therapy on the basis of the expected therapeutic benefit of the regimen of choice. On the other hand, in elderly and multiply co-morbid patients survival benefit from cancer therapy may be outweighed by Covid-19-related morbidity and mortality, warranting deferral or de-escalation of treatment(14). 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 cancer patients 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 et al. in reporting significantly inferior survival of patients with haematologic malignancies, a finding that might be explained by the intrinsic impairment in innate and adaptive immunity that is typical of patients with leukaemia, lymphoma and myeloma(15). Surprisingly, patients with breast cancer experienced the lowest mortality rates compared to 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 gynaecological cancers (37.5%). More detailed analyses of clinical and biologic 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(16). 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 pharmacological agents either as monotherapies or in combination, we focused our attention on antimalarials, antivirals and the anti-interleukin-6 antagonist tocilizumab as broad categories of anti-SARS-Cov-2 therapy. We found that combined exposure to these selected classes of Covid-19 therapies was associated with improvement in mortality compared to unexposed controls. Acknowledging the imbalance of prognostic features across treatment groups, we adjusted our estimates for key confounders including age, gender and co-morbid burden. Using multivariate Cox regression models and restricted mean survival time analyses, exposure of antimalarials emerged as an independent predictor of patients' survival compared to untreated controls. It should be emphasised 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 anti-virals and tocilizumab. However, the association we observed is highly provocative, as it supports ongoing clinical research focusing on Covid-19 specific therapies in cancer patients, a population where mortality from SARS-Cov-2 is particularly high and influenced by a number of competing factors including high co-morbid burden and active malignancy. Evolving clinical data have shown promising evidence of efficacy for some of these therapies including remdesivir(17), whereas data on other agents such as lopinavir/ritonavir have been less convincing(18). Whilst supported by initial

evidence of potential efficacy against Covid-19(19), antimalarials have been at the focus of intense debate following publication and subsequent retraction of poorly conducted observational studies(20, 21). Definitive reports from prospective, randomised controlled clinical studies are eagerly awaited in this therapeutic area(22).

Our study acknowledges a number of limitations. In view of the retrospective, observational design of this study, diagnostic pathways and therapeutic decisions were not standardised a priori across centres. 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' oncological prognosis, which might have guided prescription of anti-covid therapy. Incomplete documentation or missing laboratory/radiologic data is 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 towards 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, whilst 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 cancer patients. This is a point that should be explored in future population-based epidemiological studies.

Whilst outcomes from SARS-Cov-2 are influenced by ceilings of care, mortality rates can be as high as 50%(23) 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 cancer patients, the majority of whom may not be appropriate for resuscitation(24). Such balance is made even harder in the context of a global pandemic, where saturation of clinical services imposes an often difficult prioritisation

of critical care resources in favour of younger and less co-morbid critically ill patients(25). In our study, a minority of patients were admitted to intensive/sub-intensive care units and an even smaller proportion were intubated and ventilated. Whilst admission to intensive/high dependency care was not associated with mortality in our study, future This precludes us from drawing 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 cancer patients: factors that broaden the generalisability of our results to the wider population of oncological 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 anti-cancer 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 cancer patients. Combination of simple, tumour and stage-independent demographic features such as gender, age and number of co-morbidities 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 anti-cancer therapy and preserve oncological 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 reverse-transcriptase polymerase chain reaction (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 non-

invasive / pre-malignant lesions or with low malignant potential (i.e. basal cell carcinoma of the skin, non-invasive carcinoma in situ of the cervix, ductal carcinoma in situ) were excluded. For haematological malignancies only patients with a history of oncological diseases with defined malignant behaviour (lymphoma, leukemia, multiple myeloma) were included. At database lock (11th May 2020) the registry included 890 patients consecutively diagnosed with Covid-19 in 19 academic centres between February 26th and May 7th, 2020. A list of participating centres is provided in **Supplementary Table 1**. 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 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 including presenting symptomatology, severity, requirement for and length of hospitalization, emergence of secondary complications. Outcomes from Covid-19 including recovery and mortality rates were documented. Multi-site access and data curation was 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 Acute Respiratory Distress Syndrome (ARDS), followed criteria published by the World Health Organisation(26). Eligibility to the study required a diagnosis of SARS-CoV-2 based on Real-time RT-PCR testing of nasopharyngeal swab sample(27). Nosocomial SARS-CoV-2 transmission was defined in patients who developed symptoms and tested positive for Covid-19 whilst admitted for other reasons(28). Patients with active malignancy were defined as

those who, at the time of Covid-19, presented with measurable oncological disease defined by radiologic, clinical, haematological criteria routinely employed for clinical monitoring of the reference tumour 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 (surgery, radiotherapy, systemic therapy). For the purpose of analysing the interplay between active-anticancer therapy and outcomes form Covid-19, patients were defined as receiving active cancer therapy if they were receiving systemic anti-cancer 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 anti-cancer 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' overall survival (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 categorised treatment groups based on having received at any time during hospitalisation: any antimalarial (hydroxycholoroquine 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 standard deviation (SD), whereas data following a non-normal distribution were presented as median and interquartile range (IQR). Categorical variables were summarized as counts and percentages. Differences in medians were evaluated using Mann Whitney's U test and Wilcoxon Rank signed-rank test for pairwise comparisons. Associations between

categorical variables were tested using Pearson's Chi-square test or Fisher's 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 Shoenfeld residuals plot and by the Grambsch and Therneau non-proportionality test. Multivariable Cox proportional hazards model was applied using stepwise selection. Results of Cox analysis were presented as hazard rate (HR) with a 95% confidence interval and corresponding p value. Cox regression models were complemented by restricted mean survival time (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. Odds ratio and 95% confidence intervals 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., Armonk, NY).

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Figure Legends.

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 of complications from Covid-19 (**B**), primary tumour site (**C**), type (**D**) and number of co-morbid conditions (**E**), anti-cancer therapy (**F**) and anti-Covid-19 therapy received (**G**). **** = p<0.0001, *** = p<0.001, ** = p<0.01, * = p<0.05

Authors Contribution.

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

Study concept and design: DJP, AG.

Acquisition of data: DJP, AZ, JAC, MB, CS, RS, AB, JB, RM, ES, FB, DG, SG, GR, ML, AM, NH, BB, RB, DO, AC, RB, SB, AM, RW, CC, NC, CT, OM, VT, MB, SP, VF, CAC, FD, JSE, NS, EF, MG, IGF, AJXL, TND, AP, DGI, RR, PD, RS, YNSW, DF, JMH, AS, CM, IRC, GG, LR, LC, MI, AC, MF, AS, AP, JT, AG.

Analysis and interpretation of data: DJP, AG, DF.

Drafting of the manuscript: DJP.

Critical revision of the manuscript for important intellectual content: All the authors.

Statistical analysis: DJP, DF, AG.

Obtained funding: DJP.

Administrative, technical, or material support: DJP, AG.

Study supervision: DJP, AG.

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Figure 1.

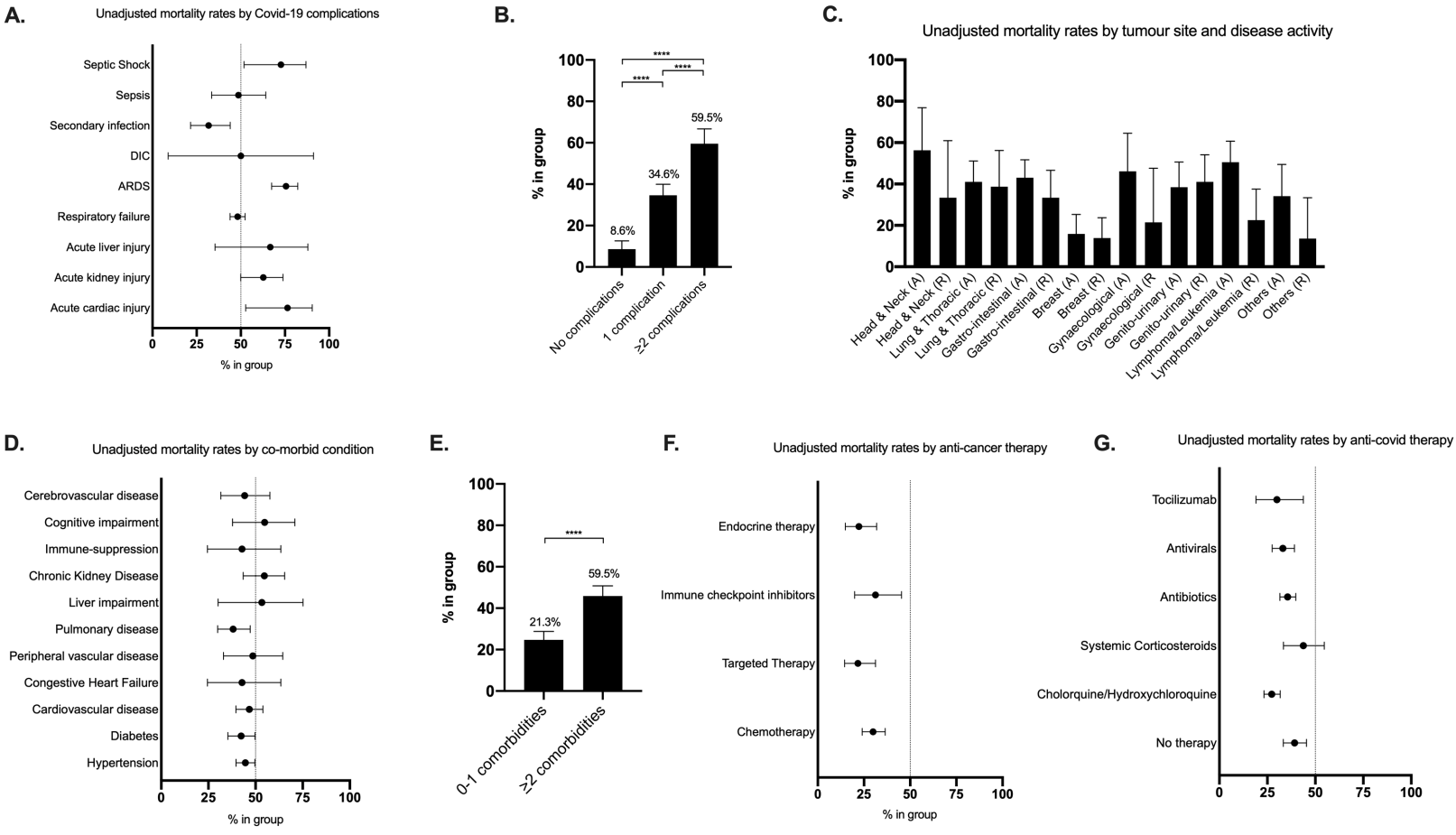
A.
Unadjusted mortality rates by Covid-19 complications
Septic Shock
Sepsis
Secondary infection
DIC
ARDS
Respiratory failure
Acute liver injury
Acute kidney injury
Acute cardiac injury
0
25
50
75
100
% in group
B.
% in group
8.6%
34.6%
59.5%
****
****
****
No complications
1 complication
≥2 complications
C.
Unadjusted mortality rates by tumour site and disease activity
% in group
Head & Neck (A)
Head & Neck (R)
Lung & Thoracic (A)
Lung & Thoracic (R)
Gastro-intestinal (A)
Gastro-intestinal (R)
Breast (A)
Breast (R)
Gynaecological (A)
Gynaecological (R
Genito-urinary (A)
Genito-urinary (R)
Lymphoma/Leukemia (A)
Lymphoma/Leukemia (R)
Others (A)
Others (R)
D.
Unadjusted mortality rates by co-morbid condition
Cerebrovascular disease
Cognitive impairment
Immune-suppression
Chronic Kidney Disease
Liver impairment
Pulmonary disease
Peripheral vascular disease
Congestive Heart Failure
Cardiovascular disease
Diabetes
Hypertension
% in group
E.
% in group
21.3%
59.5%
****
0-1 comorbidities
≥2 comorbidities
F.
Unadjusted mortality rates by anti-cancer therapy
Endocrine therapy
Immune checkpoint inhibitors
Targeted Therapy
Chemotherapy
% in group
G.
Unadjusted mortality rates by anti-covid therapy
Tocilizumab
Antivirals
Antibiotics
Systemic Corticosteroids
Cholorquine/Hydroxychloroquine
No therapy

Table 1. Uni and multi-variable 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	p<0.0001	2.01	1.46-2.77	p<0.0001
Age, <65/ ≥65	2.44	1.81-3.28	p<0.0001	1.90	1.37-2.65	p<0.0001
Comorbidities, 0-1/≥2	2.47	1.83-3.35	p<0.0001	1.75	1.24-2.46	p=0.001
Tumor Stage, Non advanced/Advanced	0.84	0.62-1.12	p=0.23	1.24	0.85-1.81	p=0.26
Tumour Status Remission/No measurable disease Active Malignancy	0.67	0.49-0.92	p=0.012	0.69	0.46-1.03	p=0.07
Anti-cancer therapy, No/Yes	0.52	0.39-0.70	p<0.0001	0.68	0.48-1.00	p=0.03
Immunotherapy ongoing, No/Yes	1.12	0.59-2.14	p=0.73			
Chemotherapy ongoing, No/Yes	1.15	0.78-1.68	p=0.47			
Targeted therapy ongoing, No/Yes	0.65	0.40-1.05	p=0.08			

Table 2. Uni and multi-variable 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	p=0.013			
Age, <65/ ≥ 65	2.71	1.99-3.70	p<0.0001	2.37	1.71-3.30	p<0.0001
Comorbidities, 0-1/≥2	1.83	1.42-2.35	p<0.0001	1.47	1.13-1.92	p=0.004
Tumor Stage, Non advanced/Advanced	1.36	1.06-1.76	p=0.019			
Tumour Status, Remission/No measurable disease Active Malignancy	1.55	1.18-2.03	p=0.003	1.81	1.35-2.44	p<0.0001
Anti-cancer therapy, No/Yes	0.77	0.60-1.00	p=0.10	0.71	0.53-0.95	p=0.019
Immunotherapy ongoing, No/Yes	0.80	0.46-1.40	p=0.43			
Chemotherapy ongoing, No/Yes	0.78	0.57-1.07	p=0.12			
Targeted therapy ongoing, No/Yes	0.80	0.47-1.39	p=0.44			
Endocrine therapy ongoing, No/Yes	1.20	0.71-2.04	p=0.48			
Intensive / high dependency care unit admission, No/Yes	1.14	0.82-1.60	p=0.41			

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*	***Co-variates***			***RMST difference*** *(CI95%) p value*
		Sex (M/F)	**Age** (<65/≥65 years)	**Tumour Stage** (Advanced/non-advanced)	
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