Determinants of enhanced vulnerability to COVID-19 in UK cancer patients: a European Study

David J. Pinato, Lorenza Scotti, Alessandra Gennari, Emeline Colomba-Blameble, Saoirse Dolly, Angela Loizidou, John Chester, Uma Mukherjee, Alberto Zambelli, Juan Aguilar-Company, Mark Bower, Myria Galazi, Ramon Salazar, Alexia Bertuzzi, Joan Brunet, Ricard Mesia, Ailsa Sita-Lumsden, Johann Colomba, Fanny Pommeret, Elia Seguí, Federica Biello, Daniele Generali, Salvatore Grisanti, Gianpiero Rizzo, Michela Libertini, Charlotte Moss, Joanne S. Evans, Beth Russell, Rachel Wuerstlein, Bruno Vincenzi, Rossella Bertulli, Diego Ottaviani, Raquel Liñan, Andrea Marrari, M. Carmen Carmona-García, Christopher CT. Sng, Carlo Tondini, Oriol Mirallas, Valeria Tovazzi, Vittoria Fotia, Claudia Andrea Cruz, Nadia Saoudi-Gonzalez, Eudald Felip, Ariadna Roqué Lloveras, Alvin J.X. Lee, Thomas Newsom-Davis, Rachel Sharkey, Chris Chung, David García-Illescas, Roxana Reyes, Yien Ning Sophia Wong, Daniela Ferrante, Javier Marco-Hernández, Isabel Ruiz-Camps, Gianluca Gaidano, Andrea Patriarca, Anna Sureda, Clara Martinez-Vila, Ana Sanchez de Torre, Lorenza Rimassa, Lorenzo Chiudinelli, Michela Franchi, Marco Krengli, Armando Santoro, Aleix Prat, Josep Tabernero, Mieke Van Hemelrijck, Nikolaos Diamantis, Alessio Cortellini, on behalf of the OnCovid study group

PII: S0959-8049(21)00202-1

DOI: https://doi.org/10.1016/j.ejca.2021.03.035

Reference: EJC 11878

To appear in: *European Journal of Cancer*

Received Date: 6 March 2021

Revised Date: 14 March 2021

Accepted Date: 16 March 2021

Please cite this article as: Pinato DJ, Scotti L, Gennari A, Colomba-Blameble E, Dolly S, Loizidou A, Chester J, Mukherjee U, Zambelli A, Aguilar-Company J, Bower M, Galazi M, Salazar R, Bertuzzi A, Brunet J, Mesia R, Sita-Lumsden A, Colomba J, Pommeret F, Seguí E, Biello F, Generali D, Grisanti S, Rizzo G, Libertini M, Moss C, Evans JS, Russell B, Wuerstlein R, Vincenzi B, Bertulli R, Ottaviani D, Liñan R, Marrari A, Carmona-García MC, Sng CC, Tondini C, Mirallas O, Tovazzi V, Fotia V, Cruz CA, Saoudi-Gonzalez N, Felip E, Roqué Lloveras A, Lee AJX, Newsom-Davis T, Sharkey R, Chung C,

García-Illescas D, Reyes R, Sophia Wong YN, Ferrante D, Marco-Hernández J, Ruiz-Camps I, Gaidano G, Patriarca A, Sureda A, Martinez-Vila C, Sanchez de Torre A, Rimassa L, Chiudinelli L, Franchi M, Krengli M, Santoro A, Prat A, Tabernero J, Van Hemelrijck M, Diamantis N, Cortellini A, on behalf of the OnCovid study group, Determinants of enhanced vulnerability to COVID-19 in UK cancer patients: a European Study, *European Journal of Cancer*, https://doi.org/10.1016/j.ejca.2021.03.035.

Determinants of enhanced vulnerability to COVID-19 in UK cancer patients: a European Study.

David J. Pinato[1,2], Lorenza Scotti[3], Alessandra Gennari[2], Emeline Colomba-Blameble[4], Saoirse Dolly[5], Angela Loizidou[6], John Chester[7,8], Uma Mukherjee[9], Alberto Zambelli[10], Juan Aguilar-Company[11,12], Mark Bower[13], Myria Galazi[14], Ramon Salazar[15], Alexia Bertuzzi[16], Joan Brunet[17], Ricard Mesia[18], Ailsa Sita-Lumsden[5], Johann Colomba[4], Fanny Pommeret[4], Elia Seguí[19], Federica Biello[2], Daniele Generali[20,21], Salvatore Grisanti[22], Gianpiero Rizzo[23], Michela Libertini[24], Charlotte Moss[26], Joanne S. Evans[1], Beth Russell[26], Rachel Wuerstlein[27], Bruno Vincenzi[28], Rossella Bertulli[29], Diego Ottaviani[14], Raquel Liñan[17], Andrea Marrari[16], M. Carmen Carmona-García[17], Christopher CT Sng[14], Carlo Tondini[10], Oriol Mirallas[11], Valeria Tovazzi[22], Vittoria Fotia[10], Claudia Andrea Cruz[19], Nadia Saoudi-Gonzalez[11], Eudald Felip[18], Ariadna Roqué Lloveras[17], Alvin J X Lee[14], Thomas Newsom-Davis[13], Rachel Sharkey[13], Chris Chung[1], David García-Illescas[11], Roxana Reyes[19], Yien Ning Sophia Wong[14], Daniela Ferrante[3], Javier Marco-Hernández[30], Isabel Ruiz-Camps[12], Gianluca Gaidano[31], Andrea Patriarca[31], Anna Sureda[32], Clara Martinez-Vila[33], Ana Sanchez de Torre[34], Lorenza Rimassa[16,35], Lorenzo Chiudinelli[10], Michela Franchi[10], Marco Krengli[36], Armando Santoro[16,35], Aleix Prat[18,37], Josep Tabernero[38], Mieke Van Hemelrijck[5,26], Nikolaos Diamantis[9], Alessio Cortellini[1,39*] on behalf of the OnCovid study group.

1. Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, London, UK
2. Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy
3. Unit of Cancer Epidemiology, Department of Translational Medicine, CPO-Piemonte, University of Piemonte Orientale, Novara, Italy.
4. Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, 114 rue Edouard Vaillant, 94800 Villejuif, France
5. Medical Oncology, Guy's and St Thomas' NHS Foundation Trust (GSTT), London, UK
6. Department of Infectious Diseases, Internal Medicine, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
7. Medical Oncology, School of Medicine, Cardiff University, Cardiff, UK
8. Medical Oncology, Velindre Cancer Centre, Cardiff, UK
9. Medical Oncology, Barts Health NHS Trust, London, UK
10. Oncology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy
11. Medical Oncology, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain
12. Infectious Diseases, Vall d'Hebron University Hospital, Barcelona, Spain
13. Department of Oncology and National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London, UK
14. Cancer Division, University College London Hospitals, London, UK
15. Department of Medical Oncology, ICO L'Hospitalet, Oncobell Program (IDIBELL), CIBERONC, Hospitalet de Llobregat, Spain
16. Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, 20090 Pieve Emanuele, Milan, Italy.
17. Department of Medical Oncology, Catalan Institute of Oncology, University Hospital Josep Trueta, Girona, Spain
18. Department of Medical Oncology, Catalan Institute of Oncology, Badalona, Spain.
19. Department of Medical Oncology, Hospital Clinic, Barcelona, Spain.
20. Multidisciplinary Breast Pathology and Translational Research Unit, ASST Cremona, Italy
21. Department of Medical, Surgical and Health Sciences, University of Trieste, Italy
22. Medical Oncology Unit, Spedali Civili, Brescia, Italy
23. Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
24. Medical Oncology Unit, Fondazione Poliambulanza Istituto Ospedaliero, Brescia, Italy
25. Infrastruttura Ricerca Formazione Innovazione, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
26. Translational Oncology and Urology Research (TOUR), School of Cancer and Pharmaceutical Sciences, King's College London, London, UK
27. Department of Gynecology and Obstetrics, Breast Center and Gynecological Cancer Center and CCC Munich, University Hospital Munich, Munich, Germany
28. Policlinico Universitario Campus Bio-Medico, Rome, Italy
29. Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
30. Department of Internal Medicine, Hospital Clinic, Barcelona, Spain
31. Division of Haematology, Department of Translational Medicine, University of Piemonte Orientale and Maggiore della Carità Hospital, Novara, Italy
32. Haematology Department, ICO Hospitalet, Hospitalet de Llobregat, IDIBELL, Universitat de Barcelona, Barcelona, Spain.
33. Fundació Althaia Manresa, Manresa, Spain.
34. Hospital Universitario XII de Octubre Madrid, Spain.
35. Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy.

36. Division of Radiotherapy, Department of Translational Medicine, University of Piemonte Orientale and Azienda Ospedaliera Maggiore Della Carita, Novara, Italy
37. Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain
38. Medical Oncology, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain
39. Department of Biotechnology and Applied Clinical Sciences, University of L'Aquila, Via Vetoio, 67100, L'Aquila, Italy

Word Count: 3215 **Tables:** 3 **Figures:** 3

Running Head: COVID-19 in UK Cancer patients

Keywords: COVID-19, SARS-CoV-2, cancer, UK, Europe, Mortality.

To whom correspondence should be addressed:

Dr David J. Pinato, MD MRes MRCP PhD
Clinical Senior Lecturer and Consultant in Medical Oncology
Imperial College London Hammersmith Campus,
Du Cane Road, W12 0HS, London (UK)
Tel: +44 020 83833720 E-mail: david.pinato@imperial.ac.uk

Abstract

Background: Despite high contagiousness and rapid spread, SARS-CoV-2 has led to heterogeneous outcomes across affected nations. Within Europe, the United Kingdom (UK) is the most severely affected country, with a death toll in excess of 100.000 as of January 2021. We aimed to compare the national impact of COVID-19 on the risk of death in UK cancer patients versus those in continental Europe (EU).

Methods: We performed a retrospective analysis of the OnCovid study database, a European registry of cancer patients consecutively diagnosed with COVID-19 in 27 centres from February 27 to September 10, 2020. We analysed case fatality rates and risk of death at 30 days and 6 months stratified by region of origin (UK versus EU). We compared patient characteristics at baseline, including oncological and COVID-19 specific therapy across UK and EU cohorts and evaluated the association of these factors with the risk adverse outcome in multivariable Cox regression models.

Findings: Compared to EU (n=924), UK patients (n=468) were characterised by higher case fatality rates (40.38% versus 26.5%, p<0.0001), higher risk of death at 30 days (hazard ratio, HR 1.64 [95%CI 1.36-1.99]) and 6 months after COVID-19 diagnosis (47.64% versus 33.33%, p<0.0001, HR 1.59 [95%CI 1.33-1.88]). UK patients were more often males, of older age and more co-morbid than EU counterparts (p<0.01). Receipt of anticancer therapy was lower in UK versus EU patients (p<0.001). Despite equal proportions of complicated COVID-19, rates of intensive care admission and use of mechanical ventilation, UK cancer patients were less likely to receive anti-COVID-19 therapies including corticosteroids, anti-virals and interleukin-6 antagonists (p<0.0001). Multivariable analyses adjusted for imbalanced prognostic factors confirmed the UK cohort to be characterised by worse risk of death at 30 days and 6 months, independent of patient's age, gender, tumour stage and status, number of co-morbidities, COVID-19 severity, receipt of anticancer and anti-COVID-19 therapy. Rates of permanent cessation of anticancer therapy post COVID-19 were similar in UK versus EU.

Interpretation: UK cancer patients have been more severely impacted by the unfolding of the COVID-19 pandemic despite societal risk mitigation factors and rapid deferral of anticancer therapy. The increased frailty of UK cancer patients highlights high-risk groups that should be prioritised for anti-SARS-CoV-2 vaccination. Continued evaluation of long-term outcomes is warranted.

INTRODUCTION.

Coronavirus Disease 2019 (COVID-19) has, since its emergence in late 2019[1], claimed the life of nearly 2 million people worldwide as of January 2021. The response of healthcare services to the escalating threat posed by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has led to significant changes in the practice of medicine including re-organisation and redeployment of workforce, modification to emergency and elective services and expansion of community and in hospital SARS-CoV-2 testing to facilitate early recognition of the disease and reduce risk of mortality to patients and healthcare workers.

In over a year of rapidly accumulating observational evidence, it is now clear that COVID-19 disproportionally affects the elderly and those with comorbidities[2-5]. Cancer patients are inherently susceptible to severe SARS-CoV-2 and determinants of mortality such as age, co-morbid burden, and presence of active malignancy have been reproducibly documented as drivers of adverse disease course across studies[6-10].

Despite some evidence regarding the negative role of previous chemotherapy[11,12], anticancer therapy does not appear to worsen the prognosis from COVID-19. However, the immunosuppressive nature of most systemic anticancer therapies (SACT), the requirement for regular hospital attendance and the risk of morbidity and hospitalisation from treatment-related adverse events have induced a more cautious delivery of oncological therapies in an attempt to prevent harm and avoid SARS-CoV-2 exposure.

Despite national lockdowns, social distancing measures, broad reaching precautionary attempts and early dissemination of clinical practice guidelines, the United Kingdom (UK) has registered the highest number of SARS-CoV-2 related deaths in Europe (EU), with a death toll in excess of 100.000 patients as of January 2021[13].

It is unknown whether the higher mortality observed in the general UK population translates into worse outcomes from COVID-19-infected cancer patients. Previous results from the OnCovid study have revealed a higher case-fatality rate in the UK (44.4%) compared to Italy (33.2%) and Spain (29.6%)[6]. Understanding whether there is regional variation in the natural course of COVID-19 is of utmost importance in the context of a still unresolved healthcare crisis. Such effort not only helps portraying the healthcare system response to COVID-19 but can also aid characterisation of geographical heterogeneity in the clinical characteristics underlying the vulnerability of cancer patients to SARS-CoV-2 infection.

In addition to regional differences to case fatality rates from COVID-19, it is important to understand whether deferral and discontinuation of SACT recommended at the onset of the pandemic[14] might have impacted on the overall survival of patients with cancer in the UK, a population that is already characterised by poorer 5-year survival outcomes in a number of solid tumours[15].

In an attempt to prevent indiscriminate deferral of therapy, which is known to affect oncological outcomes in cancer[16-18], in March 2020 the UK National Health Service identified 6 priority levels for SACT based on treatment intent and expected efficacy so that treatment can proceed for those where benefits clearly outweigh risks[19].

In this ad-hoc analysis of the OnCovid registry, we aimed to compare and contrast the risk of death following diagnosis of COVID-19 in cancer patients diagnosed in the UK versus those diagnosed in continental Europe.

STUDY DESIGN AND OUTCOMES.

OnCovid (NCT04393974) is an active European registry study that has collected, since the beginning of the pandemic, consecutive patients fulfilling the following inclusion criteria: 1) age ≥18 years; 2) diagnosis of SARS-CoV-2 infection confirmed by RT-PCR of a nasopharyngeal swab[20]; 3) 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 of non-invasive/premalignant 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 hematologic malignancies, only patients with a history of oncologic diseases with defined malignant behavior (lymphoma, leukemia, multiple myeloma) were included.

As primary endpoint of our study we elected the all-cause 30-days risk of death, a measure that mirrors endpoints utilized in clinical trials of COVID-19 therapeutics[21]. In view of the extended length of follow up of our cohort compared to earlier studies reporting case fatality rates censored at 14 days of observation[6-9,22,23], we reported, as additional study endpoint, all-cause risk of death at 6 months following COVID-19 diagnosis. The choice of this additional endpoint allowed us to preliminary investigate determinants of longer-term prognosis in COVID-19 survivors[24-26].

In comparing outcomes from UK and EU patients, we evaluated the distribution of baseline characteristics already known to be major determinants of mortality[6-8,22,23]. These included gender, age, number of co-morbidities, smoking history, tumour type (clustered as: breast, gastro-intestinal, gynecological/genito-urinary, hematological, thoracic, and others)[7-9,27], tumour stage (defined as advanced versus non-advanced

according to disease-specific criteria), tumour status (presence of active versus non-measurable disease), receipt of anticancer or anti-COVID-19 therapy, and occurrence of complicated COVID-19 as described before[6]. The role of each determinant of mortality was explored across the two cohorts using univariable analysis. Accounting for their unbalanced distribution across cohorts, a fixed multivariable regression analysis model was adopted to verify their independent prognostic role.

The differential distribution across UK and EU patients of other characteristics of interest including hospitalization and intensive care unit (ICU) admission rates, need for supplemental oxygen therapy and assisted ventilation, emergence of COVID-19 related complications and receipt of COVID-19-specific therapy were also reported as described previously[6,23]. In addition, we reported rates of permanent discontinuation of anticancer therapy among those patients who were listed as receiving anticancer therapy at COVID-19 diagnosis, including only patients alive after 30 days since COVID-19 diagnosis.

STUDY PROCEDURES.

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. Core study data were collated from electronic medical records into a case report form designed using the Research Electronic Data Capture software (REDCap, Vanderbilt University, Nashville, TN, USA). Multi-site access and data curation was coordinated by the Medical Statistics Unit in Novara, Italy. A list of participating centers is provided in **Supplementary Table 1.** Six institution were from the UK and 21 institutions were from continental EU. The data cut-off for the present analysis was 1 November 2020.

STATISTICAL ANALYSIS.

Key baseline characteristics were summarized as categorical variables and reported as counts and percentages. Associations between categorical variables were tested using Pearson $\chi 2$ test. Overall survival (OS) and all-cause 30-days and 6-months survival curves for the two cohorts of interest were also reported according to the Kaplan–Meier method and compared with the log-rank test. OS was defined as the survival interval from COVID-19 diagnosis to death and/or last follow-up. Univariable and multivariable Cox proportional hazards models were used to assess the impact of the factors as well as the geographical area (UK vs EU) on risk of death from all causes at 30 days and 6 months landmark timepoints. All the explored baseline

characteristics have been included in the multivariable model, in view of their strong linkage with mortality within the study population[6,23] and because of their differential distribution across the UK and EU cohorts. Results of Cox regression analysis were presented as hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) . A p-value of <0.05 was considered statistically significant. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS version 25 (IBM Inc.).

FUNDING SOURCE.

OnCovid acknowledges infrastructural support from the Imperial College Biomedical Research Centre. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS.

Demographic Features of UK and EU cancer patients with COVID-19.

At database lock, the registry included 1559 patients consecutively diagnosed with COVID-19. A total of 167 patients were excluded due to missing outcome data (n=23) or loss to follow-up (n=144). The final population consisted of 1392 patients accrued from 27 institutions across 6 countries (UK, Italy, Spain, France, Belgium and Germany) and diagnosed with COVID-19 between the 27th of February and the 10th of September 2020 (**Figure 1**). Patient distribution across participating centers is provided in **Supplementary Table 1**.

The UK cohort included 468 patients (33.6%) whereas the continental EU cohort included 924 patients (66.4%). The distribution of baseline patient characteristics across cohorts is summarized **Table 1**.

The distribution of primary tumors between the two cohorts was significantly different across cohorts (p<0.0001): the UK cohort had a lower proportion of breast cancer patients (12.39% vs 23.70%) and hematological malignancies (11.32% vs 18.61%) and a higher proportion of gynecological/genito-urinary cancer patients (31.20% vs 14.29%) compared to the continental EU cohort.

Compared to the rest of Europe, the UK cohort included a significantly higher proportion of patients with adverse baseline features with respect to COVID-19 related outcome, including male gender (61.72% vs 48.86%, p < 0.0001), age $\geq$65 (67.74% vs 58.25%, p=0.0006) and $\geq$2 comorbidities (62.61% vs 54.5%, p=0.0041). Conversely, UK patients were less likely to have advanced stage cancer (32.26% vs 41.13%, p<0.0001) and to be receiving active anticancer therapy within 4 weeks

before COVID-19 diagnosis (60.53% vs 74.69%, p<0.0001). No difference between the cohorts was found with respect to smoking status (former/current smokers: 37.85% vs 42.32%, p=0.8355) and presence of active malignancy (67.03% vs 67.03%, p=0.9996) and rates of complicated COVID-19 (61.75% vs 60.28%, p=0.5955). However, UK patients were less likely to have received COVID-19 specific therapies of any kind (60.53% vs 74.69%, p<0.0001).

Supplementary table 2 provides the detailed distribution across the cohorts of patients' comorbidities, specific anticancer therapy, COVID-19 symptoms at diagnosis, complications and provision of COVID-19 specific therapy. It also summarizes hospitalization and ICU admission rates across the cohorts. Even though a higher proportion of hospitalizations was reported for the UK cohort (87.39% vs 82.47%, p=0.0175), there was no significant difference regarding ICU admission rates (14.14% vs 13.77%, p=0.6919), requirement for oxygen therapy (57.91% vs 57.86%, p=0.9868) and mechanical ventilation (12.29% vs 10.30%, p=0.8630). However, a higher proportion of patients requiring non-invasive ventilation (NIV) was reported in the UK cohort (71.15% vs 36.78%, p<0.0001). Among patients who were on anticancer therapy at the moment of COVID-19 diagnosis and were alive at 30 days (n=406), no significant difference was found in the rates of permanent cessation of anticancer therapy post COVID-19 between the UK (n=10/94, 10.6%) and the EU (n=32/312, 10.3%, p=0.9152).

Clinical Outcomes.

The median follow-up interval for the entire population was 2.2 months (95%CI: 2.1-7.1) and similar for the UK (2.2 months [95%CI: 2.1-6-7]) and EU cohort (2.2 months [95%CI: 2.0-7.1]). When considering the entire population (n=1392), the overall all-cause case-fatality rates at 30 days and 6 months were 31.17% (434 events) and 38.14% (531 events) respectively. As shown in **Figure 2A** case fatality rates were higher in UK versus EU patients both at 30 days (40.38%, 189 events versus 26.5%, 245 events; p<0.0001) and at 6 months (47.64%, 223 events versus 33.33%, 308 events; p<0.0001).

At time of censoring, the median survival time of the overall OnCovid population was 6.3 months (95%CI: 4.4-6.3) with 532 recorded deaths. **Figure 2B** and **2C** illustrate the Kaplan-Meier estimation of OS for the entire population and following stratification into UK and EU cohorts. Univariable analyses revealed patients from the UK cohort to have experienced a significantly higher risk of death at 30 days (HR = 1.64 [95%CI: 1-36-1.99)] and 6 months (HR = 1.58 [95%CI: 1.33-1.88]) compared to patients from the EU cohort. **Figure 3A** and **3B** illustrate the significant difference in

patients' OS at 30 days and 6 months landmark timepoints for UK versus EU patients.

Risk factors of Outcome in UK versus EU cancer patients with COVID-19.

To evaluate clinical determinants of worse outcome in UK cancer patients with COVID-19, we initially performed univariable analyses to identify the factors associated with the risk of death at 30 days and 6 months in the whole population (**Table 2**). Alongside a significant increase in the risk of death at 30 days (HR 1.64, 95%CI 1.36-1.99) and 6 months (HR 1.58, 95% 1.333-1.881) documented for UK patients, we confirmed patients' gender, age, number of comorbidities, smoking status, tumor stage, status and occurrence of complicated COVID-19 were to be significantly associated with an increased risk of death at 30 days and 6 months, in line with previously published reports[6,22,23]. Receipt of anticancer therapy at COVID-19 diagnosis was significantly associated with improved risk of death at both the 30-days and 6-months landmarks, a finding that mirrors previously published evidence from the OnCovid study[6]. With the exception of patients with breast cancer and those in the other malignancy subgroup, who were characterized by a decreased risk of death at 30 days and at 6 months compared to lung cancer patients, no other significant differences were found with respect to clinical outcome regarding primary tumors subgroups.

To evaluate whether UK origin was independently associated with outcome, we designed a multivariable Cox regression model adjusted for all the prognostic covariates tested in univariable models. As shown in **Table 3**, following adjustment for all the included covariates, patients from the UK cohort were confirmed to have a significantly higher risk of death at 30 days (HR = 1.52 [95%CI: 1.17-1.99]) and at 6 months (HR = 1.41 [95%CI: 1.10-1-80]) compared to patients from the rest of Europe. Multivariable analysis confirmed receipt of anticancer therapy not to influence the risk of death at 30 days mortality but to exert a protective effect at 6 months (HR = 0.72 [95%CI: 0.57-0.92]). Exposure to any COVID-19-specific therapy was be associated to a decreased risk of death at 30 days (HR = 0.72 [95%CI: 0.59-0.87]) and at 6 months (HR = 0.73 [95%CI: 0.61-0.87]), whereas the occurrence of complicated COVID-19 was confirmed to be associated with an increased risk of death at both 30 days (HR = 5.10 [95%CI: 3.86-6.72]) and 6 months (HR = 3.53 [95%CI: 2.84-4.38]).

DISCUSSION.

The high proportion of asymptomatic transmission has made SARS-CoV-2 a rapidly escalating global threat. However, mortality from COVID-19 is unevenly distributed across affected countries[28]. A number of factors play a role in determining this heterogeneity including differences in infection control policies, healthcare systems, racial disparity and diverse distribution of age and co-morbidities. Whilst a number of studies have evaluated severity of COVID-19 in cancer versus non-cancer patients[29], little effort has been dedicated to understanding whether the mortality of cancer patients with COVID-19 is geographically influenced. The UK has reported one of the highest number of deaths per capita from COVID-19 in Europe and it detained the global primate before SARS-CoV-2 infections peaked in the Americas[28].

Our *ad hoc* analysis of the OnCovid registry confirms that UK cancer patients were 1.5 times more likely to die from COVID-19 compared to patients enrolled from EU countries. In line with many other studies, our analysis confirms that exposure to anticancer therapy plays no role on the 30-days risk of death from COVID-19[6,9,23,30]. Interestingly, UK patients were less likely to be receiving anticancer therapy at the moment of COVID-19 diagnosis. This is likely to reflect, at least in part, the rapid diffusion of the National Institute of Clinical Excellence guidelines on SACT prioritisation and deferral in the UK on the 20th of March 2020[31].

Previously published evidence from the OnCovid registry had shown that patients on active anticancer therapy achieved better outcomes from COVID-19 as they were more likely younger, of female gender, with less comorbidities and lower proportion of active disease[6]. Consistent with this view, in this updated analysis of the OnCovid registry data, recent exposure to anticancer therapy was protective for the risk of mortality at 6 months in the UK and EU cohorts, suggesting the survival disadvantage seen in UK patients to independent from the delivery of anticancer therapy *per se* and reflect different degrees of patient fitness, for which candidacy to SACT may act as a proxy.

Interestingly, the significantly higher risk of death of UK patients was not restricted to estimates at 30 days post COVID-19 diagnosis but persisted in the evaluation of mortality at 6 months post infection. Whilst there are no high-quality data to characterise excess risk of long-term mortality attributable to COVID-19, recent studies have demonstrated the considerable long-term impact of SARS-CoV-2 on respiratory function, fatigue and psychological wellbeing in patients without cancer[32,33]. We hypothesized that an imbalance in the resumption of anticancer therapies in the UK versus EU cohort might be contributory to the differential risk of

death. Our results, however, argue against that interpretation, given the rates of permanent discontinuation of therapy were similar across UK and EU cohorts.

Careful evaluation of baseline patient characteristics gives important insight as to the geographical difference in outcomes from COVID-19, highlighting a number of vulnerabilities that are typical of cancer patients in the UK. In particular, the higher proportion of male, elderly patients with higher co-morbid burden and highlights a higher degree of frailty in UK patients.

The constellation of clinical features enriched in the UK cohort have been long time characterised as adverse prognostic traits in patients with cancer, capable of defining a state of intrinsic vulnerability and poor return to physiologic homeostasis following a stressor event[34].

Recognition of these adverse prognostic factors from the patient's medical and oncological history should continue to inform the basis of an individualised risk assessment in planning hospital attendance, delivery of cancer care and in prioritising the delivery of immunisation against SARS-CoV-2 in a context of scarce vaccinal resources[35].

Baseline patient features are not the sole determinants of outcome to COVID-19 and despite the unfavourable imbalance in prognostic factors for UK patients our multivariate analyses of survival were adjusted for all the available key confounders present at baseline and during the course of the observation including the emergence of COVID-19 complications and receipt of anti-COVID-19 therapy[6,7,9,22,23]. Interestingly, patients in the UK cohort were less likely to have received specific anti-COVID-19 therapy, a factor that emerged to be protective for 30-days and 6-months risk of death following adjustment for COVID-19 severity.

When considering anti-COVID-19 therapies in detail (**Supplementary Table 2**), it should be emphasised that the majority of agents listed were utilised off-label or on compassionate grounds on the basis of the opinion of the treating physician. Whilst some agents including hydroxychloroquine were later on judged ineffective in reducing mortality[36], others such as interleukin-6 inhibitors, corticosteroids and remdesivir were subsequently shown to improve some COVID-19 related outcomes in different stages of disease[21,37-40]. A direct cause-effect relationship between exposure to each agent and mortality from COVID-19 across UK and EU cohorts cannot be inferred due to the observational, retrospective nature of our study, where most patients were treated with varying combinations of agents and in response to different levels of severity of the disease. However, the lower level of exposure to anti-COVID-19 therapies that have been proven effective such as corticosteroids and

tocilizumab cannot be discounted as a potential factor influencing the worse outcome of patients belonging to the UK cohort.

Another important aspect that should be considered in interpreting our results is hospital capacity, one of the determining factor for the overall COVID-19 mortality in UK during the first wave[28]. In our study, we report a higher hospitalization rate for UK compared to EU patients, despite equal proportion of complicated COVID-19 and no differences with regards to the intensive care admission rates and mechanical ventilation. Whilst a registry study such as OnCovid cannot claim to be fully illustrative of the countrywide hospital capacity, the lack of difference in key measures of severity and treatment escalation aids us in addressing hospital capacity and escalation of treatment beyond ward-based care as important confounders in our estimates of mortality. To this end, we believe the higher hospitalization rate of UK patients to be an imperfect indicator of capacity or severity of COVID-19, being more likely to reflect the scarcity of community testing observed at the early beginning of the pandemic in the UK, when SARS-CoV-2 PCR testing capacity was limited to hospitalized patients and in those with more severe forms of COVID-19.

Whilst many studies have described outcomes from SARS-CoV-2 infected cancer patients in the UK[8,22], this is the first study to perform a comparative assessment of outcomes taking advantage of a large cohort of European patients. Our study is largely an account of the first wave of the pandemic and pre-dates the widespread diffusion of the Variant of Concern B.1.1.7, for which increased lethality has been postulated[41], but not definitively proven. With increased physician experience, resilience of healthcare services and widespread use of active anti-COVID-19 therapies, infections diagnosed in the so-called “second wave” might be characterized by improved outcomes: a hypothesis that we aim to test when clinical data from our registry are fully mature. Similarly, whilst our study relies on significantly longer follow-up time compared to earlier reports, more mature survival data will allow us to provide further insight on the topic of long-term outcomes from COVID-19.

Despite attempting to control for key clinicopathologic factors, our analyses might still be affected by unmeasured bias. For instance, we lack data on quantitative estimation of SARS-CoV-2 viral load, a parameter associated to disease severity and mortality from COVID-19[42] and that might have given us insight into severity of community exposure or underlying immune dysfunction in our study participants[43-45].

Notwithstanding the acknowledged limitations, this study provides a comprehensive, comparative assessment of the impact of the SARS-CoV-2 pandemic in UK cancer

patients, a population already characterized by intrinsically poorer survival outcomes from cancer compared to many other industrialized countries[15]. We highlight key areas of vulnerability to COVID-19 in UK cancer patients, in particular higher co-morbid burden and age, which, in a healthcare system characterised by the highest overall mortality from COVID-19 in Europe, calls for the rapid implementation of protective strategies against SARS-CoV-2 in this exquisitely vulnerable patient cohort.

Rapid and widespread vaccination of cancer patients should be advocated as a priority in UK cancer patients. Secondly, clinical use of anti-COVID-19 therapies with proven benefit against SARS-CoV-2 should be facilitated in UK cancer patients, a population that is underrepresented in clinical trials of vaccines and therapeutics against SARS-CoV-2[46]. Whilst the UK is at the forefront of drug development in COVID-19[47], concerted efforts should continue to be aimed at maintaining the ever so delicate balance between protection from harm due to the pandemic and preservation of oncological outcomes in patients at risk of cancer relapse or progression.

Authors' Contributions

AC and DJP had full access to all data in the study and take responsibility for data integrity and analysis.

Study concept and design: Pinato, Cortellini, Scotti, Ferrante.
Acquisition of data: All authors.
Analysis and interpretation of data: Pinato, Cortellini, Scotti, Ferrante.
Drafting of the manuscript: Pinato, Cortellini.
Manuscript revision and input: All authors.
Statistical analysis: Scotti, Cortellini, Ferrante.
Obtained funding: Pinato
Study supervision: Pinato

Acknowledgements

D.J. Pinato is supported by grant funding from the Wellcome Trust Strategic Fund (PS3416) and acknowledges grant support from the Cancer Treatment and Research Trust (CTRT) and infrastructural support by the Cancer Research UK Imperial Centre and the NIHR Imperial Biomedical Research Centre. G. Gaidano is supported by the AIRC 5 × 1000 Grant, No. 21198, Associazione Italiana per la Ricerca sul Cancro Foundation, Milan, Italy. A. Gennari is supported by the AIRC IG Grant, No. 14230, Associazione Italiana per la Ricerca sul Cancro Foundation, Milan, Italy. A. Gennari and G. Gaidano from the University of Piemonte Orientale (Novara, Italy) acknowledge support from the UPO Aging Project.

Consent for Publication
Informed consent was waived by competent authorities due to anonymized nature of patient data and retrospective design of the study.

Availability of Data and Material
Study data made available upon reasonable request.

Competing Interests

DJP received lecture fees from ViiV Healthcare and Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, and Astra Zeneca; received research funding (to institution) from MSD and BMS. AP has declared personal honoraria from Pfizer, Roche, MSD Oncology, Eli Lilly, and Daiichi Sankyo; travel, accommodations, and expenses paid by Daiichi Sankyo; research funding from Roche and Novartis; and consulting/advisory role for NanoString Technologies, Amgen, Roche, Novartis, Pfizer and Bristol-Myers Squibb. TND has declared consulting/advisory role for Amgen, Bayer, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Otsuka, Pfizer, Roche, and Takeda; speakers fees from AstraZeneca, MSD, Roche, Takeda and travel, accommodations and expenses paid by AstraZenca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, and Takeda. JB has declared consulting/advisory role for MSD and Astra Zeneca. PPS has declared consulting/advisory role for Sanofi and Abbvie. AP has declared consulting/advisory role for Takeda and Sanofi. MP has declared consulting/advisory role for Gilead and Bayer. AG has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, EISAI, and Daichii Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, Astra Zeneca, Celgene, and Daichii Sankyo; research funds: EISAI, Eli Lilly, and Roche. CMV has received travel grants and other honoraria from BMS, MSD, Novartis and Roche. LR received consulting fees from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi; travel expenses from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. JT reports personal financial interest in form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech, Inc, HalioDX SAS, Ikena Oncology, IQVIA, Imedex, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Seattle Genetics, Servier, Taiho, Tessa Therapeutics and TheraMyc. AC received consulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Astellas. All remaining authors have declared no conflicts of interest.

References.

1. Pan A, Liu L, Wang C, et al. Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. *Jama.* 2020.
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020;395(10223):507-513.
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *Jama.* 2020.
4. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama.* 2020.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.
6. Pinato DJ, Zambelli A, Aguilar-Company J, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. *Cancer Discov.* 2020.
7. Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. *Lancet Oncol.* 2020;21(7):914-922.
8. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 prevalence and mortality in patients with cancer and the effect of primary tumour subtype and patient demographics: a prospective cohort study. *Lancet Oncol.* 2020;21(10):1309-1316.
9. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet.* 2020;395(10241):1907-1918.
10. Saini KS, Tagliamento M, Lambertini M, et al. Mortality in patients with cancer and coronavirus disease 2019: A systematic review and pooled analysis of 52 studies. *Eur J Cancer.* 2020;139:43-50.
11. Yekeduz E, Utkan G, Urun Y. A systematic review and meta-analysis: the effect of active cancer treatment on severity of COVID-19. *Eur J Cancer.* 2020;141:92-104.
12. Lievre A, Turpin A, Ray-Coquard I, et al. Risk factors for Coronavirus Disease 2019 (COVID-19) severity and mortality among solid cancer patients and impact of the disease on anticancer treatment: A French nationwide cohort study (GCO-002 CACOVID-19). *Eur J Cancer.* 2020;141:62-81.
13. UK Government Office of National Statistics. Number of Coronavirus (COVID-19) cases and risk in the UK. In:2020.
14. Ueda M, Martins R, Hendrie PC, et al. Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal. *J Natl Compr Canc Netw.* 2020:1-4.
15. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014

(ICBP SURVMARK-2): a population-based study. *Lancet Oncol.* 2019;20(11):1493-1505.
16. Raphael MJ, Biagi JJ, Kong W, Mates M, Booth CM, Mackillop WJ. The relationship between time to initiation of adjuvant chemotherapy and survival in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2016;160(1):17-28.
17. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *Jama.* 2011;305(22):2335-2342.
18. Chen Z, King W, Pearcey R, Kerba M, Mackillop WJ. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. *Radiother Oncol.* 2008;87(1):3-16.
19. National Health Service England. Clinical guide for the management of noncoronavirus patients requiring acute treatment:
Cancer,. https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/specialty-guide-acute-treatment-cancer-23-march-2020.pdf. Published 2020. Accessed.
20. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro Surveill.* 2020;25(3).
21. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med.* 2021;384(1):20-30.
22. Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet.* 2020;395(10241):1919-1926.
23. Pinato DJ, Lee AJX, Biello F, et al. Presenting Features and Early Mortality from SARS-CoV-2 Infection in Cancer Patients during the Initial Stage of the COVID-19 Pandemic in Europe. *Cancers (Basel).* 2020;12(7).
24. Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. *Lancet Infect Dis.* 2020;20(7):773.
25. Ellul M, Varatharaj A, Nicholson TR, et al. Defining causality in COVID-19 and neurological disorders. *J Neurol Neurosurg Psychiatry.* 2020;91(8):811-812.
26. Statistics OfN. Measuring pre-existing health conditions in death certification – deaths involving COVID- 19: March 2020. A method for deciding which pre-existing condition mentioned on death certificates is the main pre-existing condition. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/measuringpreexistinghealthconditionsindeathcertificationdeathsinvolvingcovid19march2020. . Published 2020. Accessed 15/01/2021, 2021.
27. de Joode K, Dumoulin DW, Tol J, et al. Dutch Oncology COVID-19 consortium: Outcome of COVID-19 in patients with cancer in a nationwide cohort study. *Eur J Cancer.* 2020;141:171-184.
28. Stephen Rocks OI. Did hospital capacity affect mortality during the pandemic's first wave? https://www.health.org.uk/news-and-

comment/charts-and-infographics/did-hospital-capacity-affect-mortality-during-the-pandemic. Published 2020. Accessed 23th Jan 2021.
29. Dai M, Liu D, Liu M, et al. Patients with Cancer Appear More Vulnerable to SARS-COV-2: A Multicenter Study during the COVID-19 Outbreak. *Cancer Discov.* 2020.
30. Brar G, Pinheiro LC, Shusterman M, et al. COVID-19 Severity and Outcomes in Patients With Cancer: A Matched Cohort Study. *J Clin Oncol.* 2020;38(33):3914-3924.
31. Clark JJ, Dwyer D, Pinwill N, Clark P, Johnson P, Hackshaw A. The effect of clinical decision making for initiation of systemic anticancer treatments in response to the COVID-19 pandemic in England: a retrospective analysis. *Lancet Oncol.* 2021;22(1):66-73.
32. Bellan M, Soddu D, Balbo PE, et al. Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge. *JAMA Netw Open.* 2021;4(1):e2036142.
33. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;397(10270):220-232.
34. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol.* 2015;26(6):1091-1101.
35. Emanuel EJ, Persad G, Upshur R, et al. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. *N Engl J Med.* 2020;382(21):2049-2055.
36. Group RC, Horby P, Mafham M, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020;383(21):2030-2040.
37. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
38. Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. *Lancet Rheumatol.* 2020;2(10):e603-e612.
39. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA.* 2020;324(13):1307-1316.
40. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med.* 2020.
41. Iacobucci G. Covid-19: New UK variant may be linked to increased death rate, early data indicate. *BMJ.* 2021;372:n230.
42. Fajnzylber J, Regan J, Coxen K, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun.* 2020;11(1):5493.
43. Xu T, Chen C, Zhu Z, et al. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. *Int J Infect Dis.* 2020;94:68-71.
44. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* 2020;20(5):565-574.

45. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ.* 2020;369:m1443.
46. Marina Chiara Garassino NG, Petros Grivas, Karin Jordan, Francesca Lucibello, Olivier Mir, George Pentheroudakis, Florian Scotté, Marie von Lilienfeld-Toal, Giuseppe Curigliano, John Haanen, Uwe Gerd Liebert, Florian Lordick, Ignacio Melero, Corinna Pietsch, and Solange Peters. ESMO STATEMENTS FOR VACCINATION AGAINST COVID-19 IN PATIENTS WITH CANCER. https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination. Published 2021. Accessed 28/01/2021.
47. Guidance on shielding and protecting people who are clinically extremely vulnerable from COVID-19. GOV.UK. https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#cev. Published 2021. Accessed 28/01/2021.

Figure Legends.

Figure 1: Study diagram.

Figure 2: Histograms illustrating the case fatality rates at 30 days and 6 months for the cohorts of interest (A). Kaplan-Meier survival curves. Overall Survival for the entire study population; (B) 6.3 months (95%CI: 4.4-6.3; 532 events). Overall survival for the cohorts of interest; (C) UK cohort: 2.7 months (95%CI: 1.5-4.3; 223 events); EU cohort: 6.3 months (95%CI: 6.3-6-3; 309 events). Log-rank: p<0.0001.

Figure 3: Kaplan-Meier survival curves. 30-days survival for the cohorts of interest; (A) UK cohort: not reached (189 events); EU cohort: not reached (245 events). Log-rank: p < 0.0001. 6-month survival for the cohorts of interest; (B) UK cohort: 2.7 months (95%CI: 1.5-4.3; 223 events); EU cohort: not reached (208 events). Log-rank: p<0.0001.

TABLE 1: Patient characteristics of the cohorts of interest.

	EU cohort N=924 (%)	**UK cohort N=468 (%)**	χ^2 test **p-value**
Gender			
Male	451 (48.86)	287 (61.72)	<0.0001
Female	472 (51.14)	1778 (38.28)	
Missing	4		
Age			
<65 yo	382 (41.75)	151 (32.26)	0.0006
≥65 yo	533 (58.25)	317 (67.74)	
Missing	9		
Number of comorbidities			
0-1	420 (45.45)	175 (37.39)	0.0041
≥2	504 (54.55)	293 (62.61)	
Missing	0		
Smoking history			
Never-smokers	407 (44.97)	192 (41.29)	0.8355
Former/current smokers	383 (42.32)	176 (37.85)	
Missing	234		
Cancer site			
Breast	219 (23.70)	58 (12.39)	<0.0001
Gastrointestinal	167 (18.07)	92 (19.66)	
Gynaecological/Genito-Urinary	132 (14.29)	146 (31.20)	
Hematological	172 (18.61)	53 (11.32)	
Lung	118 (12.77)	58 (12.64)	
Other	116 (12.55)	61 (13.03)	
Missing	0		
Tumour stage			
Local/loco-regional	390 (42.21)	294 (62.82)	<0.0001
Advanced	380 (41.13)	151 (32.26)	
Missing	177		
Tumour status			
Remission/non measurable diease	299 (32.97)	150 (32.97)	0.9996
Active malignancy	608 (67.03)	305 (67.03)	
Missing	30		
Anti-cancer therapy at Covid-19			
No	371 (40.55)	278 (61.64)	<0.0001
Yes	544 (59.55)	173 (38.36)	
Missing	26		
Covid-19 therapy (any)			
No	224 (25.31)	163 (39.47)	<0.0001
Yes	661 (74.69)	250 (60.53)	
Missing	94		
Complicated Covid-19			
No	367 (39.72)	179 (8.25)	0.5955
Yes	557 (60.28)	289 (61.75)	
Missing	0		

TABLE 2: Univariable analysis of factors predictive for the risk of death at 30-days and 6-months.

	30 days			6 months		
	Alive N=958 (%)	**Death N=434 (%)**	**HR (95%CI)**	**Alive N=861 (%)**	**Death N=531 (%)**	**(HR 95%CI)**
Area						
Other EU	679 (70.88)	245 (56.45)	1	616 (71.54)	308 (58.00)	1
UK	279 (29.12)	189 (43.55)	1.64 (1.36-1.99)	245 (28.46)	223 (42.00)	1.58 (1.333-1.881)
Gender						
Male	474 (49.63)	264 (60.97)	1	414 (48.25)	324 (61.13)	1
Female	481 (50.37)	169 (39.03)	0.68 (0.56-0.83)	444 (51.75)	206 (38.87)	0.68 (0.573-0.813)
Missing	4			4		
Age						
<65 y	438 (46.01)	95 (22.04)	1	407 (47.49)	126 (23.95)	1
≥65 y	514 (53.99)	336 (77.96)	2.53 (2.01-3.18)	450 (52.51)	400 (76.05)	2.39 (1.963-2.932)
Missing	9			9		
Number of comorbidities						
0-1	457 (47.70)	138 (31.80)	1	428 (49.71)	167 (31.45)	1
≥2	501 (52.30)	296 (68.20)	1.78 (1.45-2.18)	433 (50.29)	364 (68.55)	1.89 (1.574-2.272)
Missing	0			0		
Smoking history						
Never smokers	431 (53.74)	168 (47.19)	1	395 (54.33)	204 (47.33)	1
Former/current smokers	371 (46.26)	188 (52.81)	1.25 (1.01-1.54)	332 (45.67)	227 (52.67)	1.24 (1.031-1.504)
Missing	234			234		
Cancer site						
Breast	226 (23.90)	48 (11.06)	0.35 (0.25-0.51)	216 (25.09)	61 (11.49)	0.39 (0.28-0.55)
Gastrointestinal	172 (17.95)	87 (20.05)	0.76 (0.55-1.03)	147 (17.07)	112 (21.09)	0.85 (0.64-1.1)
Gynaecological/Genito-Urinary	184 (19.21)	94 (21.66)	0.76 (0.56-1.03)	166 (19.28)	112 (21.09)	0.80 (0.60-1.06)
Hematological	142 (14.82)	83 (19.12)	0.78 (0.57-1.07)	121 (14.05)	104 (19.59)	0.79 (0.59-1.06)
Lung	102 (10.65)	74 (17.05)	1	92 (10.69)	84 (15.82)	1
Other	129 (13.47)	48 (11.06)	0.58 (0.40-0.84)	119 (13.82)	58 (10.92)	0.59 (0.42-0.83)
Missing	0			0		
Tumour stage						
Local/loco-regional	501 (59.71)	183 (48.67)	1	467 (61.94)	217 (47.07)	1
Advanced	338 (40.29)	193 (51.33)	1.42 (1.16-1.74)	287 (38.06)	244 (52.93)	1.58 (1.32-1.90)
Missing	177			177		
Tumour status						
Remission/non measurable diease	342 (36.62)	107 (25.00)	1	332 (38.57)	117 (22.37)	1
Active malignancy	592 (63.38)	321 (75.00)	1.55 (1.24-1.93)	507 (60.43)	406 (77.63)	1.85 (1.51-2.28)
Missing	30			30		
Anti-cancer therapy at Covid-19						
No	419 (44.62)	230 (53.86)	1	371 (43.96)	278 (53.26)	1
Yes	520 (55.38)	197 (46.14)	0.72 (0.59-0.87)	473 (56.04)	244 (46.74)	0.73 (0.61-0.87)
Missing	26			26		

Figure 1.

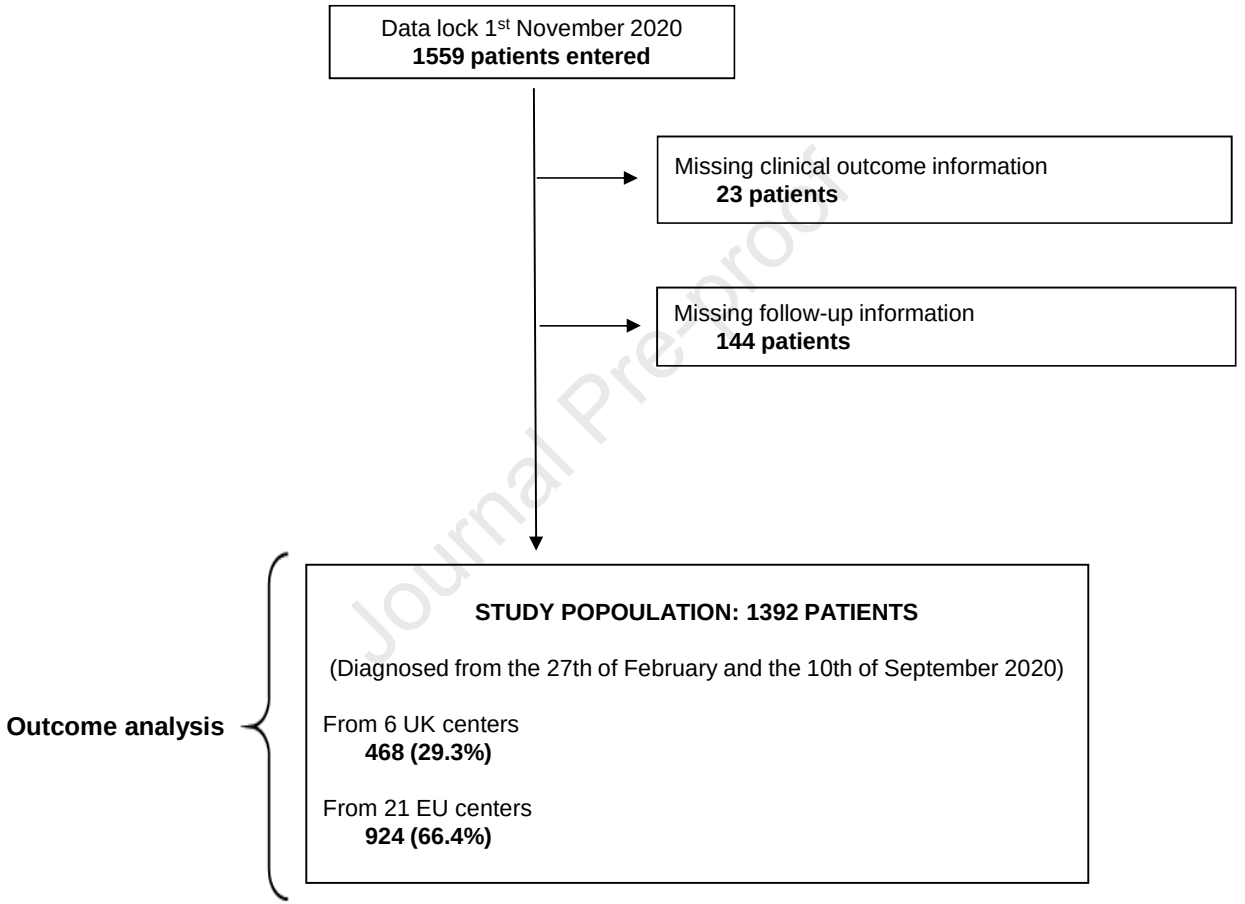


Figure 2.

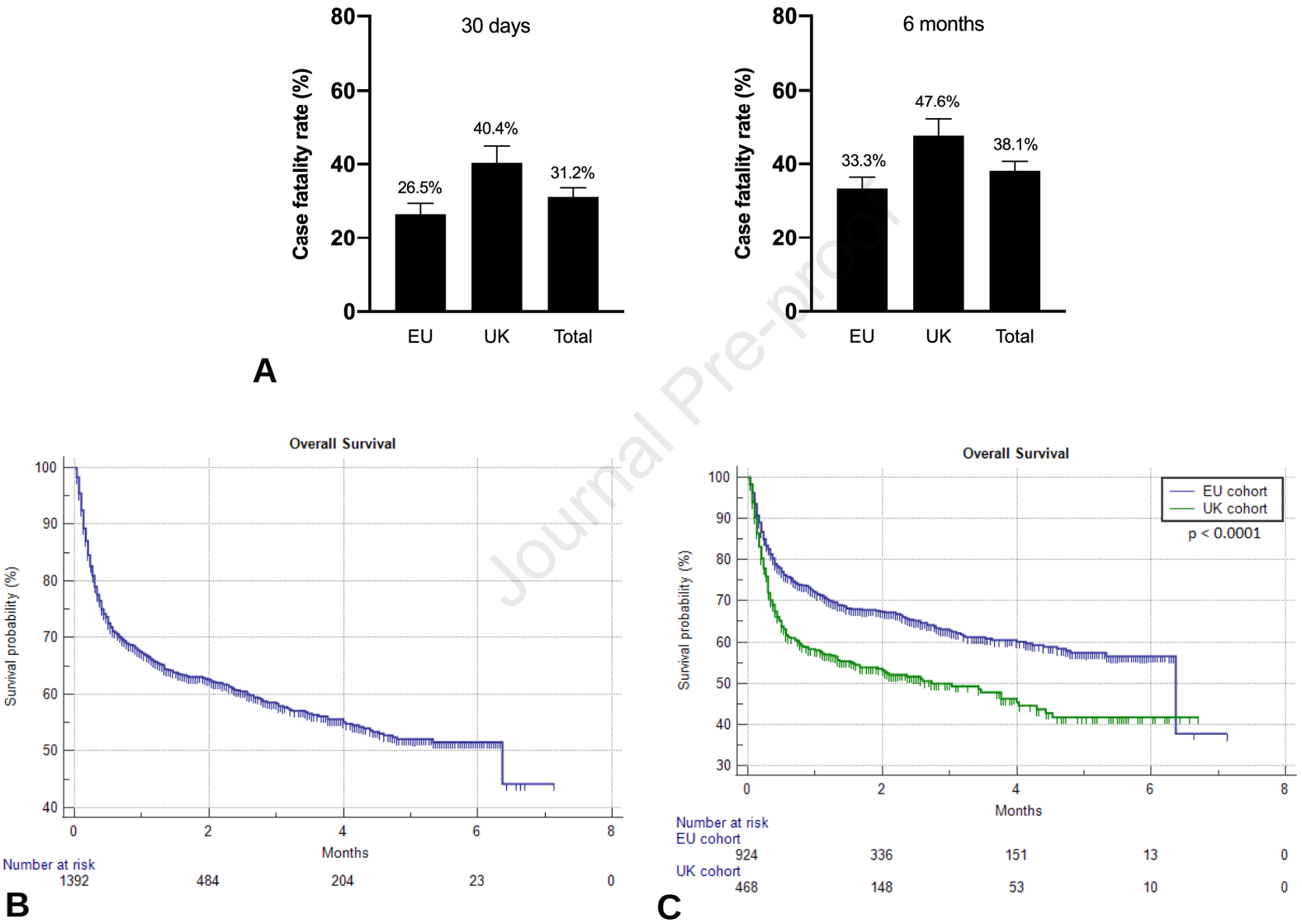
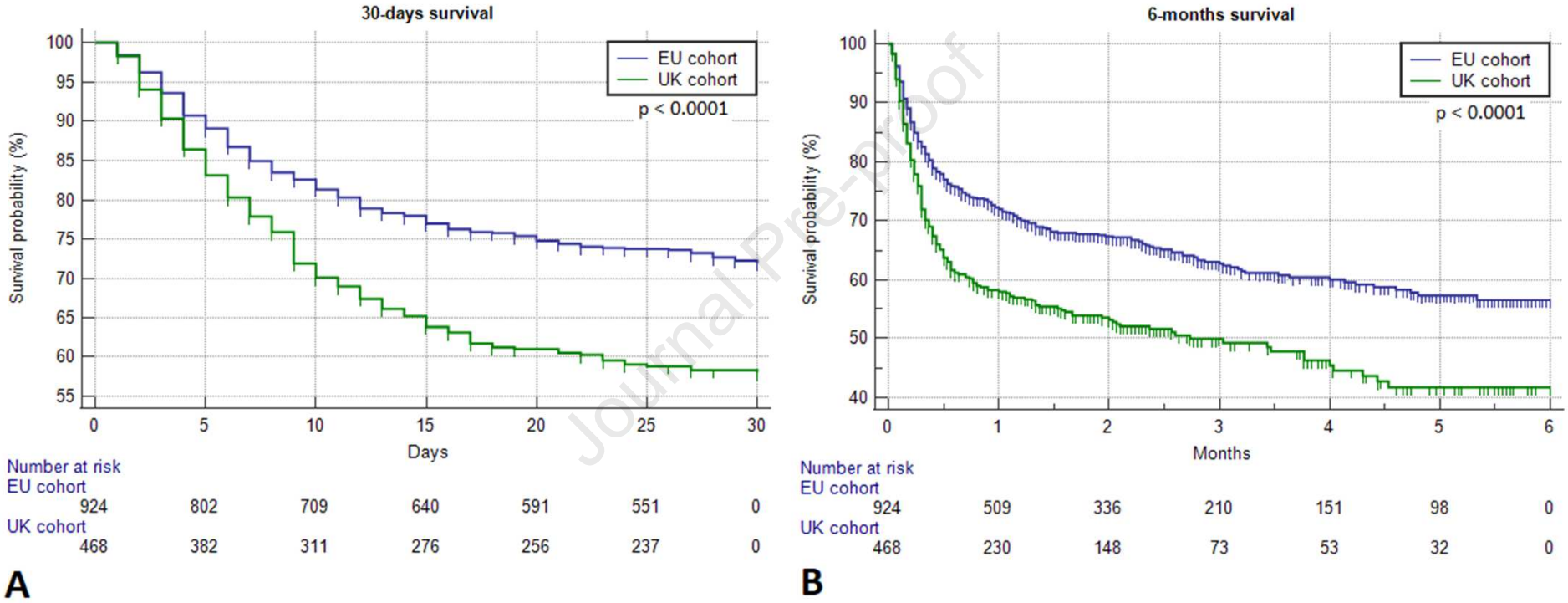


Figure 3.



Highlights

COVID-19 mortality in the UK has exceeded that of all other European countries

UK cancer patient outcomes with COVID-19 may compare unfavourably with EU countries

This is the first study to report detrimental outcomes for UK cancer patients

UK patients older, more co-morbid & less likely to have received COVID-19 therapy

Considering our results rapid vaccination against SARS-CoV-2 should be recommended

CONFLICT OF INTEREST STATEMENT

Determinants of enhanced vulnerability to COVID-19 in UK cancer patients: a European Study.

As corresponding author of the abovementioned manuscript, I declare on behalf of my co-authors the following conflict of interests:

DJP received lecture fees from ViiV Healthcare and Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, and Astra Zeneca; received research funding (to institution) from MSD and BMS. AP has declared personal honoraria from Pfizer, Roche, MSD Oncology, Eli Lilly, and Daiichi Sankyo; travel, accommodations, and expenses paid by Daiichi Sankyo; research funding from Roche and Novartis; and consulting/advisory role for NanoString Technologies, Amgen, Roche, Novartis, Pfizer and Bristol-Myers Squibb. TND has declared consulting/advisory role for Amgen, Bayer, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Otsuka, Pfizer, Roche, and Takeda; speakers fees from AstraZeneca, MSD, Roche, Takeda and travel, accommodations and expenses paid by AstraZenca, BMS, Boehringer Ingelheim, Lilly, MSD, Otsuka, Roche, and Takeda. JB has declared consulting/advisory role for MSD and Astra Zeneca. PPS has declared consulting/advisory role for Sanofi and Abbvie. AP has declared consulting/advisory role for Takeda and Sanofi. MP has declared consulting/advisory role for Gilead and Bayer. AG has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, EISAI, and Daichii Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, Astra Zeneca, Celgene, and Daichii Sankyo; research funds: EISAI, Eli Lilly, and Roche. CMV has received travel grants and other honoraria from BMS, MSD, Novartis and Roche. LR received consulting fees from Amgen, ArQule, AstraZeneca, Basilea, Bayer, BMS, Celgene, Eisai, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Lilly, MSD, Nerviano Medical Sciences, Roche, Sanofi, Zymeworks; lecture fees from AbbVie, Amgen, Bayer, Eisai, Gilead, Incyte, Ipsen, Lilly, Merck Serono, Roche, Sanofi; travel expenses from Ipsen; and institutional research funding from Agios, ARMO BioSciences, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Zymeworks. JT reports personal financial interest in form of scientific consultancy role for Array Biopharma, AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, F. Hoffmann-La Roche Ltd, Genentech, Inc, HalioDX SAS, Ikena Oncology, IQVIA, Imedex, Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Seattle Genetics, Servier, Taiho, Tessa Therapeutics and TheraMyc. AC received consulting fees from MSD, BMS, AstraZeneca, Roche; speakers' fee from AstraZeneca, MSD, Novartis and Astellas. All remaining authors have declared no conflicts of interest.

London, March 4th, 2020