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ORIGINAL RESEARCH

## COVID-19 in patients with cancer: first report of the ESMO international, registry-based, cohort study (ESMO-CoCARE)

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**Background:** ESMO COVID-19 and Cancer REgistry (ESMO-CoCARE) is an international collaborative registry-based, cohort study gathering real-world data from Europe, Asia/Oceania and Africa on the natural history, management and outcomes of patients with cancer infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

**Patients and methods:** ESMO-CoCARE captures information on patients with solid/haematological malignancies, diagnosed with coronavirus disease 2019 (COVID-19). Data collected since June 2020 include demographics, comorbidities, laboratory measurements, cancer characteristics, COVID-19 clinical features, management and outcome. Parameters influencing COVID-19 severity/recovery were investigated as well as factors associated with overall survival (OS) upon SARS-CoV-2 infection.

**Results:** This analysis includes 1626 patients from 20 countries (87% from 24 European, 7% from 5 North African, 6% from 8 Asian/Oceanian centres), with COVID-19 diagnosis from January 2020 to May 2021. Median age was 64 years, with 52% of female, 57% of cancer stage III/IV and 65% receiving active cancer treatment. Nearly 64% patients required hospitalization due to COVID-19 diagnosis, with 11% receiving intensive care. In multivariable analysis, male sex, older age, Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$ , body mass index (BMI)  $< 25 \text{ kg/m}^2$ , presence of comorbidities, symptomatic disease, as well as haematological malignancies, active/progressive cancer, neutrophil-to-lymphocyte ratio (NLR)  $\geq 6$  and OnCovid Inflammatory Score  $\leq 40$  were associated with COVID-19 severity (i.e. severe/moderate disease requiring hospitalization). About 98% of patients with mild COVID-19 recovered, as opposed to 71% with severe/moderate disease. Advanced cancer stage was an additional adverse prognostic factor for recovery. At data cut-off, and with median follow-up of 3 months, the COVID-19-related death rate was 24.5% (297/1212), with 380 deaths recorded in total. Almost all factors associated with COVID-19 severity, except for BMI and NLR, were also predictive of inferior OS, along with smoking and non-Asian ethnicity.

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**Conclusions:** Selected patient and cancer characteristics related to sex, ethnicity, poor fitness, comorbidities, inflammation and active malignancy predict for severe/moderate disease and adverse outcomes from COVID-19 in patients with cancer.

**Key words:** COVID-19, SARS-CoV-2, oncology, cancer

## INTRODUCTION

In the beginning of 2020, a striking increase in cases and deaths from a new virus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and its disease [coronavirus disease 2019 (COVID-19)], startled the worldwide community. Clinical features associated with COVID-19 included fever, fatigue, dry cough, acute respiratory distress syndrome, blood test abnormalities or ground-glass opacity in the lungs.<sup>1,2</sup> In addition, analysis from initial studies identified older age, diabetes, cardiovascular, cerebrovascular and malignant disease as risk factors for COVID-19 severity.<sup>1,2</sup>

Patients with cancer commonly have an immune dysfunction due to the use of immunosuppressive medicines (e.g. cytotoxic drugs, corticosteroids), poor nutritional status or direct effects of the tumour on the fitness of the immune system.<sup>3,4</sup> They also represent an older population frequently with severe comorbidities. It was, thus, hypothesized that patients with cancer would be at higher risk of experiencing severe COVID-19.<sup>3-5</sup> Rapid changes in cancer care and research were implemented globally,<sup>6-8</sup> while screening and diagnostic programmes were severely affected, with subsequent higher prevalence of more advanced-stage presentation.<sup>7,9,10</sup> To mitigate these evolving issues, several cancer societies developed and regularly updated specific guidelines for cancer care, despite the limited availability of data-driven evidence.<sup>11</sup> An urgent need to study the effects of COVID-19 in patients with cancer emerged and several international groups started to collaborate worldwide, with a swift set up of dedicated clinically oriented databases to address this new priority and unmet need.<sup>12-14</sup>

Several publications reported on the deleterious effects of COVID-19 in specific subgroups of patients with cancer<sup>1,2,15-17</sup>; however, the heterogeneous data collection and lack of statistical power were important limitations leading, in some cases, to contradictory results.<sup>16</sup> It became, therefore, essential to gather larger and more robust datasets powered to study the effects of COVID-19 in different subgroups of patients with cancer (i.e. histology, staging, treatments) from various geographic areas.

The ESMO COVID-19 and CANcer REgistry (ESMO-CoCARE) was initiated to meet this goal and was designed as a large, observational multicentre, transnational database, including centres from Europe, Africa and Asia/Oceania to study the effects of COVID-19 in patients with hematologic or solid tumours. Herein, we present the first ESMO-CoCARE results with data collected until May 2021. We report on risk factors for severity and mortality from COVID-19 in patients with cancer integrating data from

centres in Europe, Asia/Oceania and Africa, and we independently validate observations from similar registries, in an effort to contribute to a better understanding of COVID-19 disease in people with cancer, informing clinicians and regulatory bodies on optimal management.

## METHODOLOGY

### *Study design and participants*

The ESMO-CoCARE is an observational prospective study, based on a longitudinal multicentre survey of patients with cancer with any solid or haematological malignancy who were diagnosed with COVID-19. The data reside in the ESMO-CoCARE registry, developed and maintained as an electronic REDCap (Research Electronic Data Capture) database housed at Centre Hospitalier Universitaire Vaudois (CHUV) in Lausanne, Switzerland. Active data collection is planned until the end of the pandemic as declared by the World Health Organization (WHO), or the end of epidemic situation in each region, with subsequent follow-up as needed.

Data on clinical features, course of the disease, management and outcomes are collected for both cancer and COVID-19 disease. The aim of the study is primarily descriptive of the characteristics of COVID-19 in patients with cancer, exploring associations with both cancer and COVID-19 outcomes. Data reported here were extracted from medical records of consecutive patients diagnosed with COVID-19 from 1 January 2020 up to 18 May 2021. COVID-19 diagnosis included both laboratory-confirmed COVID-19 cases (irrespective of symptoms and clinical presentation) and cases with only clinical diagnosis of COVID-19, based on signs such as fever  $>38^{\circ}\text{C}$ , cough, diarrhoea, otitis, dysgeusia, anosmia, myalgia, arthralgia, conjunctivitis and rhinorrhoea, lymphocyte count  $<1.0 \times 10^9/\text{l}$ , and/or chest radiographic or lung computed tomography imaging suggestive of SARS-CoV-2-19 pneumonia.

### *Study objectives and endpoints*

The objectives of this study included the identification of risk factors predictive of severity, in terms of hospitalization, or recovery from COVID-19 in patients with cancer, and overall survival (OS). In the current analysis, the following endpoints were considered as co-primary: COVID-19 severity was categorized based on hospitalization requirement and indication for intensive care unit (ICU) admission (mild: no hospitalization; moderate: hospitalization indicated/took place, without ICU admission; severe: ICU indication/admission). In the univariate/multivariable analyses performed the following grouping was used: moderate/severe (hospitalization required) versus mild (no hospitalization).

Recovery from COVID-19 illness was defined by the rate of patients with COVID-19 who survived the disease, having a date of recovery reported. OS was defined as the time from COVID-19 diagnosis to death from any cause. OS was assessed for patients with available follow-up information, that is, date of death for reported deaths or date of last follow-up for those alive.

### Statistical analysis

All the variables of interest were described overall and by the primary outcomes of COVID-19 severity/recovery and OS.

Mann–Whitney and Fisher’s exact tests were used for the associations of continuous and categorical variables, respectively, with COVID-19 severity and recovery, while the associations with OS were explored through log-rank test. Univariable logistic and Cox proportional hazards models were also fitted, for COVID-19 severity/recovery and OS, respectively. Of note, no adjustment of multiple comparisons was performed, and differences were primarily descriptive. Other associations of interest were assessed through Fisher’s exact test (e.g. treatment adjustment due to COVID-19 with type of cancer treatment, symptoms and COVID-19 complications with demographics, and others). OS was estimated by the Kaplan–Meier method for the whole analysis cohort with available follow-up information. In the frame of OS analysis, COVID-19-related mortality, that is, deaths reported for patients who did not recover, as well as deaths reported for patients who recovered but died later due to COVID-19 complications, was also assessed.

Multivariable models were also fitted: logistic for COVID-19 severity/recovery and Cox proportional hazards for OS. A preselection of baseline variables to be included in the multivariable models was processed to avoid overfitting. Variable selection was based on significance from the univariable analysis ( $P < 0.10$ ), clinical relevance, degree of factor missingness and possible correlation between candidate predictors. Of note, because almost all patients who were not hospitalized finally recovered, multivariable analysis for identifying risk factors for recovery focused only on the hospitalized patients (moderate/severe disease).

The variables initially included were gender, age, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status (PS), smoking status, BMI ( $<25 \text{ kg/m}^2$  versus  $\geq 25 \text{ kg/m}^2$ ), comorbidities, cancer type/stage/status at COVID-19 diagnosis, COVID-19 symptoms (symptomatic/asymptomatic) and the following inflammation-based biomarkers measured prior to COVID-19 diagnosis: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), OnCovid Inflammatory Score (OIS). The backward elimination method with removal criterion  $P > 0.10$  was utilized to obtain the factors with significant effects. Multicollinearity and proportionality assumption based on the Schoenfeld residuals were checked. Data were analysed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.0.0 (R Foundation, Vienna, Austria) software.

## RESULTS

### Cohort description and cancer disease characteristics

From January 2020 to May 2021, a total of 1626 eligible patients with COVID-19 diagnosis and a history of active malignancy or in remission were registered in the CoCARE database and comprised the analysis cohort. COVID-19 was diagnosed most often in March and April 2020 (16.6% and 16.1%, respectively), followed by December 2020 and January 2021 (12.2% and 11.8%, respectively; [Supplementary Figure S1](https://doi.org/10.1016/j.esmooop.2022.100499), available at <https://doi.org/10.1016/j.esmooop.2022.100499>).

Registration of patients was performed at 37 participating centres in 20 countries, from 6 June 2020 to 18 May 2021. United Kingdom (32%) and Spain (24%) contributed the highest proportion of patients, with 31% from other European countries; 7% and 6% were registered from African and Asian/Oceanian countries, respectively ([Supplementary Table S1](https://doi.org/10.1016/j.esmooop.2022.100499) and [Supplementary Figure S2](https://doi.org/10.1016/j.esmooop.2022.100499), available at <https://doi.org/10.1016/j.esmooop.2022.100499>).

Cohort demographics, clinical and cancer disease characteristics, are presented in [Table 1](#). Overall, approximately half of the patients were female (52%), with a median age of 64 years, including 563 patients (35%) older than 70 years. Most of the patients were Caucasian (58%). Almost 50% of the patients had ECOG PS = 1, while 41% were never smokers (never exposed to active smoking). BMI was recorded for 82% of patients, with 547 of them (41%) having BMI  $<25 \text{ kg/m}^2$  [most of whom ( $n = 490$ ) with  $18.5 \leq \text{BMI} < 25 \text{ kg/m}^2$ ], 502 (38%) being overweight ( $25 \leq \text{BMI} < 30 \text{ kg/m}^2$ ) and 280 (21%) obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ).

Regarding clinical characteristics, the majority of the patients had pre-existing comorbidities (70%), with the most common being cardiovascular (42%), metabolic (26%) and pulmonary co-morbidities (14% [Table 1](#), [Supplementary Table S2a](https://doi.org/10.1016/j.esmooop.2022.100499) and [b](https://doi.org/10.1016/j.esmooop.2022.100499), available at <https://doi.org/10.1016/j.esmooop.2022.100499>). Furthermore, almost 60% of the patients received at least one concomitant medication. With respect to cancer disease characteristics, 47% of patients were diagnosed with cancer within the past year. The majority (86%) were solid tumours (breast: 20%, colorectal: 14%, lung: 14%, other: 38%), with haematological malignancies reported only for 9% of the patients. Most patients had evidence of active disease at COVID-19 diagnosis (66%), with 21% having no evidence of disease. Over half of the patients had cancer stage III or IV (57%; [Table 1](#)).

A total of 1053 patients (65%) were receiving anticancer treatment. Among them, most were on cytotoxic chemotherapy (69%) or on targeted therapy (15%; [Supplementary Table S3](https://doi.org/10.1016/j.esmooop.2022.100499), available at <https://doi.org/10.1016/j.esmooop.2022.100499>). For 56% of the patients, the treatment plan was not adjusted due to COVID-19 ([Supplementary Table S3](https://doi.org/10.1016/j.esmooop.2022.100499), available at <https://doi.org/10.1016/j.esmooop.2022.100499>). Treatment adjustment was more often observed for patients on targeted therapy compared with treatments other than targeted (41% versus 29%), and less often for patients on radiotherapy compared with treatments other than radiotherapy (21% versus 32%;

Table 1. Cohort demographics, clinical and cancer disease characteristics (n = 1626)	
Characteristic	All patients (n = 1626)
<b>Demographics</b>	
<b>Sex, n (%)</b>	
Female	845 (52.0)
Male	757 (46.6)
Unknown/missing	24 (1.5)
<b>Age (years at COVID-19 diagnosis), n (%)</b>	
≤49	303 (18.6)
50-69	735 (45.2)
≥70	563 (34.6)
Unknown/missing	25 (1.5)
Median (Q1-Q3)	64 (53-73)
<b>Ethnicity, n (%)</b>	
Caucasian	942 (57.9)
Non-Caucasian	466 (28.7)
Asian	117 (7.2)
Other <sup>a</sup>	349 (21.5)
Unknown/missing	218 (13.4)
<b>ECOG performance status, n (%)</b>	
0	342 (21.0)
1	758 (46.6)
2	273 (16.8)
≥3	114 (7.0)
Unknown/missing	139 (8.5)
<b>Smoking history, n (%)</b>	
Current smoker	148 (9.1)
Former smoker	373 (22.9)
Never smoker	658 (40.5)
Unknown/missing	447 (27.5)
<b>BMI (kg/m<sup>2</sup>), n (%)</b>	
Underweight (<18.5)	57 (3.5)
Normal (18.5 ≤ BMI < 25)	490 (30.1)
Overweight (25 ≤ BMI < 30)	502 (30.9)
Obesity (≥30)	280 (17.2)
Unknown/missing	297 (18.3)
Median (Q1-Q3)	25 (22-29)
<b>Clinical characteristics</b>	
<b>Number of comorbidities, n (%)</b>	
0	447 (27.5)
1	510 (31.4)
>1	624 (38.4)
Unknown/missing	45 (2.8)
<b>Number of concomitant medications, n (%)</b>	
0	501 (30.8)
≥1	956 (58.8)
Unknown/missing	169 (10.4)
<b>Cancer disease characteristics</b>	
<b>Date of cancer diagnosis, n (%)</b>	
Within the past year	758 (46.6)
Within the past 5 years	552 (33.9)
More than 5 years ago	210 (12.9)
Unknown/missing	106 (6.5)
<b>Primary tumour type, n (%)</b>	
Breast	332 (20.4)
Colorectal	234 (14.4)
Lung	221 (13.6)
Other solid tumour	619 (38.1)
Haematological malignancy	151 (9.3)
Unknown/missing	69 (4.2)
<b>Cancer status at COVID-19 diagnosis, n (%)</b>	
Active disease, complete response	56 (3.4)
Active disease, partial response	129 (7.9)
Active disease, stable disease	519 (31.9)
Active disease, progressive disease	368 (22.6)
NED	335 (20.6)
Unknown/missing	219 (13.5)
<b>Cancer stage at COVID-19 diagnosis, n (%)</b>	
I	65 (4.0)

Continued

Table 1. Continued	
Characteristic	All patients (n = 1626)
II	162 (10.0)
III	242 (14.9)
IV	688 (42.3)
Not applicable <sup>b</sup>	395 (24.3)
Unknown/missing	74 (4.6)
<b>On anticancer treatment at COVID-19 diagnosis, n (%)</b>	
Yes (up to 3 months prior to COVID-19 diagnosis)	1053 (64.8)
No	424 (26.1)
Unknown/missing	149 (9.2)
<b>Past systemic treatment, n (%)</b>	
Yes	707 (43.5)
No	661 (40.7)
Unknown/missing	258 (15.9)

BMI, body mass index; COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; NED, no evidence of disease.

Current smoker: exposed to active smoking; Former smoker: previously exposed to active smoking; Never smoker: never exposed to active smoking.

<sup>a</sup>Including African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Māori and other.

<sup>b</sup>The 'not applicable' cancer stage category includes cases for which cancer stage could not be determined: due to patient's cancer type or because cancer restaging was not available.

Supplementary Table S4, available at <https://doi.org/10.1016/j.esmoop.2022.100499>. Of note, the association of BMI with specific cancer treatments and type/status/stage of cancer was also explored; it was significantly correlated only with cancer type ( $P = 0.0011$ ), with >60% of patients with breast or colorectal cancer being overweight/obese (Supplementary Table S5, available at <https://doi.org/10.1016/j.esmoop.2022.100499>).

### COVID-19 diagnosis and course of illness

Information on COVID-19 diagnosis, course of illness and recovery is provided in Table 2. COVID-19 was confirmed based on laboratory tests for the majority of the patients (76%), including 65% with RT-PCR and 9% with SARS-CoV-2 serologic test.

At initial presentation of COVID-19, 1167 patients (72%) had at least one symptom, with the most frequent being fever (49%), cough (including productive cough; 46%), dyspnoea (33%), severe fatigue (21%), myalgia (13%) and headache (11%; details in Supplementary Table S6a, available at <https://doi.org/10.1016/j.esmoop.2022.100499>).

Symptoms were reported more often by older patients, non-Caucasian, of higher ECOG PS, with pre-existing comorbidities or with lung cancer (Supplementary Table S6b-d, available at <https://doi.org/10.1016/j.esmoop.2022.100499>). Of note, patients with no evidence of malignant disease appeared more often to be symptomatic compared with those diagnosed in the presence of active cancer disease (87% versus 78%;  $P < 0.001$ ; Supplementary Table S6d, available at <https://doi.org/10.1016/j.esmoop.2022.100499>). Mild severity of COVID-19 was indicated for 562 patients (36%), moderate for 822 (53%) and severe for 168 (11%; Table 2).

Complications during COVID-19 illness occurred in 641 patients (39%), most frequently pulmonary (29%),



Table 2. COVID-19 diagnosis, course of illness and recovery (n = 1626)	
Characteristic	All patients (n = 1626)
<b>COVID-19 suspicion confirmed with laboratory tests, n (%)</b>	
RT-PCR	1050 (64.6)
SARS-CoV-2 serology	126 (7.7)
Serum Ig, Ig subtypes	21 (1.3)
Other (blood cultures/swab/vector-best system)	31 (1.9)
Not confirmed	175 (10.8)
Unknown/missing	223 (13.7)
<b>Symptoms, n (%)<sup>a</sup></b>	
Yes (symptomatic)	1167 (71.8)
Fever (>38°C)	797 (49.0)
Cough (including productive cough)	745 (45.8)
Dyspnoea	542 (33.3)
Severe fatigue	333 (20.5)
Myalgia	218 (13.4)
Headache	185 (11.4)
Other (including symptoms experienced by <10% of the patients)	638 (39.2)
No (asymptomatic)	280 (17.2)
Unknown/missing	179 (11.0)
<b>Primary endpoint: severity of COVID-19 illness, n (% excluding 'unknown/missing')</b>	
Mild (no hospitalization took place)	562 (36.2)
Moderate (hospitalization took place or indicated, but no ICU)	822 (53.0)
Severe (ICU admission or at least indication)	168 (10.8)
Unknown/missing	74
<b>Complications occurring during COVID-19, n (%)</b>	
At least one	641 (39.4)
Pulmonary	477 (29.3)
Cardiovascular	182 (11.2)
Systemic	156 (9.6)
Gastrointestinal	86 (5.3)
Other	260 (16.0)
None	917 (56.4)
Unknown/missing	68 (4.2)
<b>Requirement of oxygen during the illness, n (%)</b>	
Yes	609 (37.5)
No	821 (50.5)
Unknown/missing	196 (12.1)
<b>Receipt of any treatment for COVID-19 or its sequelae, n (%)</b>	
Yes	795 (48.9)
No	819 (50.4)
Unknown/missing	12 (0.7)
<b>Primary endpoint: recovery from COVID-19, n (% excluding 'unknown/missing')</b>	
Yes	1253 (80.5)
No (COVID-19 death <sup>b</sup> )	304 (19.5)
Unknown/missing	69
<b>Primary endpoint: overall survival status, n (% excluding 'unknown/missing')</b>	
Alive (at last follow-up)	832 (68.6)
Dead (with death date available)	380 (31.4)
Unknown/missing (nonavailable follow-up)	414

COVID-19, coronavirus disease 2019; Ig, immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

<sup>a</sup>A detailed table with all symptoms is provided in the supplement (Supplementary Table S6a, available at <https://doi.org/10.1016/j.esmooop.2022.100499>).

<sup>b</sup>Death date was not reported for 8 of the 304 patients that did not recover from COVID-19.

cardiovascular (11%) and systemic (10%; Table 2). Associations of the most common types of complications with cohort demographics, comorbidities and cancer disease characteristics are provided in Supplementary Table S7a-c, available at <https://doi.org/10.1016/j.esmooop.2022.100499>.

Overall, 609 patients (38%) required supplemental oxygen (Table 2). Treatment for COVID-19 or its sequelae was administered to almost half of the patients (49%), including azithromycin (23%), anticoagulation (23%), hydroxychloroquine (20%) and corticosteroids (16%; Supplementary Table S8, available at <https://doi.org/10.1016/j.esmooop.2022.100499>). Regarding the primary endpoint of recovery, of the 1557 patients with available data, 1253 (81%) recovered from COVID-19 (Table 2).

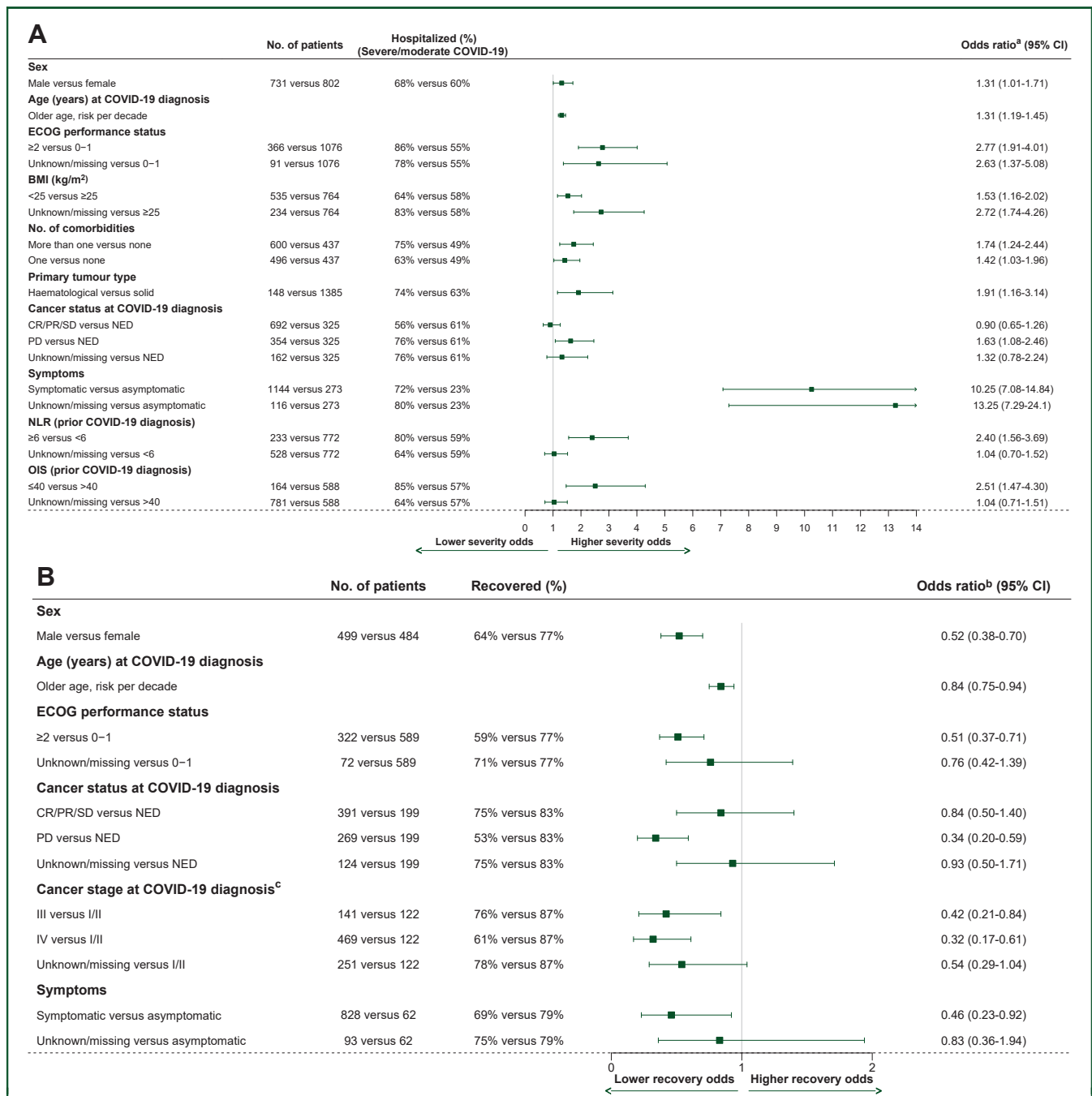
### Laboratory measurements and inflammatory-based biomarkers

Laboratory measurements were considered at three distinct timepoints: prior to COVID-19 diagnosis, during COVID-19 and at time of recovery, including white blood cell ( $\times 10^9/l$ ), neutrophil count ( $\times 10^9/l$ ), lymphocyte count ( $\times 10^9/l$ ), platelet count ( $\times 10^9/l$ ), albumin (g/dl), haemoglobin (mmol/l), creatinine (mg/dl), Na (mmol/l) and K (mmol/l) (Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmooop.2022.100499>, indicating differences over the different timepoints). C-reactive protein values were also collected but not included in the analysis, as many extreme values were reported, casting doubt on their validity.

Measurements prior to COVID-19 formed the basis of primary inference, as measurements at this timepoint were feasible for all patients and could also have predictive significance for the COVID-19 disease. Based on these, additional inflammatory-based biomarkers were calculated, according to the OnCovid dataset.<sup>18</sup> Two OnCovid inflammatory markers involved C-reactive protein, and thus were not analysed here. NLR, PLR and OIS, measured prior to COVID-19 for ESMO-CoCARE patients, are summarized in Supplementary Table S9, available at <https://doi.org/10.1016/j.esmooop.2022.100499>.

### COVID-19 severity (hospitalization): association with baseline factors

The severity rate of COVID-19 (severe/moderate disease, i.e. hospitalization) differentiated significantly according to each of several factors examined (Supplementary Table S10a, available at <https://doi.org/10.1016/j.esmooop.2022.100499>). The multivariable model is illustrated in Figure 1A. Severe/moderate COVID-19 disease was experienced more frequently in male patients, patients of older age, with worse ECOG PS ( $\geq 2$ ), BMI  $< 25$  kg/m<sup>2</sup> and a higher number of pre-existing comorbidities [odds ratio (OR) = 1.31-2.77]. Regarding cancer characteristics, patients with haematological malignancies developed severe/moderate disease more frequently than patients with solid tumours, as well as patients with progressive disease compared with those with no evidence of disease {OR = 1.91 [95% confidence interval (CI) 1.16-3.14] and 1.63 (95% CI 1.08-2.46), respectively}. Symptomatic patients at diagnosis subsequently developed severe/moderate COVID-19 [OR = 10.25 (95% CI



**Figure 1.** (A) Multivariable logistic model for COVID-19 severity. The model was based on 1533 patients, including 976 patients with hospitalization (severe/moderate COVID-19). (B) Multivariable logistic model for COVID-19 recovery, including only patients with hospitalization (severe/moderate COVID-19 disease). Among patients with available recovery information, 984 needed hospitalization. However, the model was based on 983 hospitalized patients (severe/moderate COVID-19), including 694 recovered patients, because there was 1 patient with missing age. BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; CR, complete response; ECOG, Eastern Cooperative Oncology Group; NED, no evidence of disease; NLR, neutrophil-to-lymphocyte ratio; OIS, OnCovInflammatory Score; PR, partial response; SD, stable disease. <sup>a</sup>Odds ratios (95% CI) for hospitalized (severe/moderate disease) versus nonhospitalized (mild disease). <sup>b</sup>Odds ratios (95% CI) for recovered versus nonrecovered. <sup>c</sup>The 'not applicable' category is also included in the 'unknown/missing' category.

7.08-14.84]] significantly more often. With respect to inflammatory-based biomarkers, patients with NLR ≥6 and patients with OIS ≤40 experienced severe/moderate COVID-19 more frequently [OR = 2.40 (95% CI 1.56-3.69) and 2.51 (95% CI 1.47-4.30), respectively].

**COVID-19 recovery: association with baseline factors**

Recovery from COVID-19 was found to be associated with several risk factors, mostly similar to the ones associated with COVID-19 severity (Supplementary Table S10a, available at <https://doi.org/10.1016/j.esmop.2022.100499> for

all patients). In addition, increased recovery rate was found in patients from participating countries in Asia/Oceania, as well as in countries with upper-middle income economies. Among patients with available severity and recovery information, the vast majority (98%) of patients with no need of hospitalization (mild disease) eventually recovered versus a 71% recovery rate among patients with severe/moderate COVID-19 ( $P < 0.001$ ; [Supplementary Table S11](https://doi.org/10.1016/j.esmoop.2022.100499), available at <https://doi.org/10.1016/j.esmoop.2022.100499>). Respective results for the hospitalized patients only are provided in [Supplementary Table S10b](https://doi.org/10.1016/j.esmoop.2022.100499), available at <https://doi.org/10.1016/j.esmoop.2022.100499>.

As illustrated in [Figure 1B](#), in the multivariable analysis, focusing on the group of patients who needed hospitalization, the odds of recovering from COVID-19 disease were lower for male patients [OR = 0.52 (95% CI 0.38-0.70)], for older patients [OR = 0.84 (95% CI 0.75-0.94)], with worse ECOG PS [ $\geq 2$ ; OR = 0.51 (95% CI 0.37-0.71)] and COVID-19 symptoms [OR = 0.46 (95% CI 0.23-0.92)]. Regarding cancer characteristics, patients with progressive disease compared with patients with no evidence of disease and patients in stage III or advanced (IV) stage compared with patients in stage I/II recovered less often [OR = 0.34 (95% CI 0.20-0.59), OR = 0.42 (95% CI 0.21-0.84) and OR = 0.32 (95% CI 0.17-0.61), respectively].

### All-cause survival analysis

Based on 1212 patients with follow-up information, the median follow-up time was 3.02 months from COVID-19 diagnosis (interquartile range 2.96-6.05), with 832 (69%) alive patients at last follow-up. Overall, a total of 380 (31%) deaths were recorded, with a 1-month OS rate of 78.4% (95% CI 76.0% to 80.6%) and a 3-month OS rate of 71.4% (95% CI 68.7% to 73.8%). The median OS time was not reached ([Figure 2A](#)). From all patients with available follow-up, a total of 297 deaths were reported as related to COVID-19 complications (24.5%); 256 up to 1 month (97.7% of 262 deaths up to 1 month) and 293 up to 3 months (84.7% of 346 deaths up to that timepoint). Hence, from the total of 380 deaths recorded, the majority (78.2%) were attributed to COVID-19 disease, while the remaining 83 deaths were caused by disease progression (12.6%), cancer treatment toxicity (0.3%), other reason (2.1%) or unknown reason (6.8%; [Supplementary Tables S12 and S13](https://doi.org/10.1016/j.esmoop.2022.100499) available at <https://doi.org/10.1016/j.esmoop.2022.100499>). As expected, all risk factors significantly associated with COVID-19 recovery also had a significant impact on OS ([Supplementary Table S10c](https://doi.org/10.1016/j.esmoop.2022.100499), available at <https://doi.org/10.1016/j.esmoop.2022.100499>).

In the final multivariable Cox model, a higher mortality risk was estimated for male sex, older age, Caucasian or other ethnicity as compared with Asian, worse ECOG PS, current/former smoking status and pre-existence of comorbidities [hazard risk (HR) ranged from 1.13 for risk per decade of older age to 3.75 for other versus Asian ethnicity].

Regarding cancer characteristics, mortality risk was higher for haematological malignancies compared with solid tumours [HR = 1.54 (95% CI 1.06-2.22)], while an almost threefold increase in risk was found for progressive disease compared with no evidence of disease [HR = 2.78 (95% CI 1.77-4.36)]. With respect to inflammatory-based biomarkers, patients with OIS  $\leq 40$  had a higher risk of death, although only at the 10% significance level. Cancer stage at COVID-19 diagnosis and symptoms were included in the model as stratification factors due to detected violation of the proportionality hazard assumption for their effect (explored by the Schoenfeld residuals).

### DISCUSSION

Overall, we independently validated previously published observations on variables associated with COVID-19 outcomes in patients with cancer. In addition, Asian ethnicity and higher BMI ( $\geq 25$  kg/m<sup>2</sup>) were associated with better COVID-19-related outcomes. Notably, in multivariable analysis most of the factors affecting severity appeared to have a significant impact on OS at 3-month median follow-up.

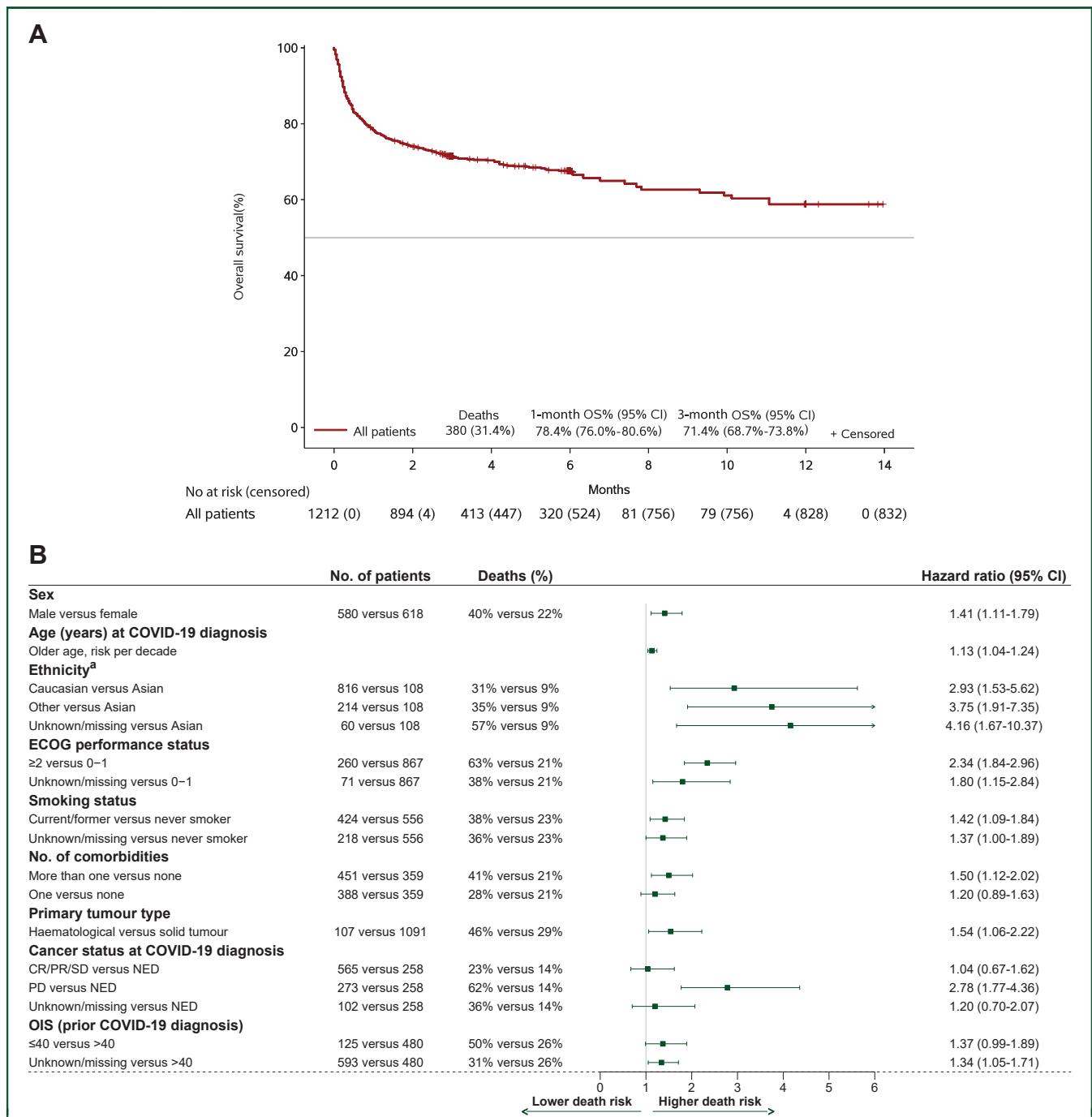
The COVID-19-related death in our cohort was 24.5%, which is higher than what has been reported for the general population infected with COVID-19.<sup>19-21</sup> In a retrospective case-control analysis from 15 510 patients, the COVID-19-related death for the overall population was 5.61%, compared with 14.93% (100/670) in patients with cancer.<sup>20</sup> A meta-analysis from 32 studies and 46 499 patients with COVID-19 (1776 patients with cancer) demonstrated a higher ICU admission (relative risk = 1.56; 95% CI 1.31-1.87) and mortality rate (relative risk = 1.66; 95% CI 1.33-2.07) for patients with cancer in comparison with the noncancer population.<sup>21</sup> Interestingly, for patients aged  $> 65$  years, the all-cause mortality was comparable between those with cancer versus those without cancer, suggesting the strong effect of age alone for COVID-19-related death.<sup>21</sup>

The mortality rate associated with COVID-19 for patients with cancer varies in different studies from 13% to 33.6%.<sup>16,17,20,22</sup> In a systematic review and meta-analysis, including 33 879 patients with cancer and SARS-CoV-2 infection, the overall case fatality rate was 25.4% (95% CI 22.9% to 28.2%), very similar to our findings.<sup>23</sup> In another systematic review and meta-analysis from 17 studies, the pooled in-hospital mortality for the 904 hospitalized patients with COVID-19 and cancer was 14.1%.<sup>24</sup>

Those different results might be explained by population heterogeneity and a selection bias towards the most severe cases in some studies. In addition, a higher mortality rate was reported in the beginning of the pandemic.<sup>25-28</sup> Indeed, in our cohort, 38% of cases were diagnosed between March and May 2020. Moreover, the high proportion of cases with advanced or progressive cancer may have influenced the mortality rate observed.

Older age, male sex, current/former smoking (patients exposed to active smoking) status have been consistently associated with worse COVID-19-related outcomes for the





**Figure 2.** (A) Overall survival ( $n = 1212$ ). Only patients with available follow-up information are included. (B) Multivariable Cox model for overall survival (stratified by cancer stage at COVID-19 diagnosis and symptoms). The model was based on 1198 patients, including 370 deaths. Cancer stage at COVID-19 diagnosis and symptoms were used as stratification factors due to violation of the proportionality hazard assumption.

CI, confidence interval; COVID-19, coronavirus disease 2019; CR, complete response; ECOG, Eastern Cooperative Oncology Group; NED, no evidence of disease; OIS, OnCovid Inflammatory Score; OS, overall survival; PR, partial response; SD, stable disease.

<sup>a</sup>In the 'other' category: African, Arab/Middle Eastern, Latino American, Mediterranean, Pacific Islander/Māori and others are included. The respective hazard ratio (95% CI) for 'other' versus 'Caucasian' is 1.28 (0.96-1.69).

general population, irrespective of a cancer diagnosis.<sup>29,30</sup> Unsurprisingly similar results were obtained not only in our cohort, but also in other studies in patients with cancer and COVID-19.<sup>16,22,26,31</sup> We were intrigued by a significantly lower mortality for the Asian population in our cohort. During the first wave, the pandemic affected more severely Europe than East Asian countries,<sup>32,33</sup> reflecting potentially higher social and health system epidemic preparedness in

the latter.<sup>33</sup> Importantly, the great majority of the Asian population in our cohort is from Asian cancer centres. Beyond clinical characteristics, it has been hypothesized that host genetics and human leukocyte antigen profiles may influence COVID-19 outcomes.<sup>34-38</sup> Notably, a strong correlation was found between ACE1 II genotype, more frequent in Asians, and lower severity or death from COVID-19.<sup>39</sup> All these factors may justify the favourable survival

from COVID-19 observed in our Asian population, which to the best of our knowledge was not previously reported in other studies on patients with cancer.<sup>20,27,40</sup> Nevertheless, considering the low sample size (117 Asians out of 1626 patients), further confirmative analysis in larger populations is needed.

Moreover, in our study, other ethnicities (mainly reported from European centres) tend to have higher, but not statistically significant, mortality rate compared with Caucasians. It has been consistently demonstrated that ethnic minorities in Europe and North America have been more severely affected by COVID-19,<sup>41-45</sup> including patients with cancer.<sup>20,27</sup> Social determinants of health, including poorer socioeconomic status, adverse working conditions, decreased access to healthcare or social exclusion may have contributed to these findings.<sup>46,47</sup>

The following clinical risk factors were associated with worst COVID-19 outcomes in CoCARE: ECOG PS  $\geq 2$ , pre-existing comorbidities, COVID-19-related symptoms, haematological malignancies and progressive disease. Although collectively these parameters are consistent with those reported in other studies,<sup>16,22,31</sup> intriguingly, we observed that overweight/obese patients (BMI  $\geq 25$  kg/m<sup>2</sup>) experienced less often infection requiring hospitalization compared with patients with BMI  $< 25$  kg/m<sup>2</sup>. In other series, obesity has been associated with worse outcomes from COVID-19, in the general population<sup>48-50</sup> and cancer,<sup>16</sup> whereas this correlation was not confirmed by others.<sup>51</sup> Overweight status has been associated with better survival in patients with advanced cancer.<sup>52-54</sup> This so-called obesity paradox may be justified by increased treatment tolerability and fitness status associated with higher BMI.<sup>52</sup> Besides, any correlation between obesity and clinical outcomes may be confounded by tumour characteristics and treatment (i.e. hormone therapy),<sup>52,53</sup> although we found no such association between obesity and confounders in our cohort, except for a higher prevalence of obesity in patients with colorectal and breast cancers (Supplementary Table S5, available at <https://doi.org/10.1016/j.esmoop.2022.100499>). Finally, the correlation between BMI and cancer outcomes can be impacted by inaccurate or evolving-over-time BMI measurements. Moreover, adiposity and muscle mass contribute to BMI, are more potent prognosticators and can vary from one patient to another.<sup>52,55,56</sup> Further studies are needed to better assess the influence of BMI, muscle mass and adiposity for patients with cancer and COVID-19.

In our multivariable analysis, no significant association was found between current administration of cancer treatment and COVID-19-related outcomes. Although in some studies cytotoxic chemotherapy was associated with worse outcomes,<sup>27,57</sup> that was not confirmed in other cohorts.<sup>22,31,58</sup> Heterogeneity related to the class of therapies, treatment intention (curative versus noncurative), time between treatment and COVID-19 diagnosis and type of disease may contribute to these apparently contradictory results. Hormone therapy, targeted therapy or immune checkpoint inhibitors have not been associated with worse outcomes from COVID-19 in recent literature.<sup>27,31,57,59</sup>

We independently validated NLR  $\geq 6$  and OIS  $\leq 40$  as prognosticators for COVID-19 severity and OIS  $\leq 40$  (at 10% significance level) for OS, following a previous publication by Dettorre et al.<sup>60,61</sup> Systemic inflammatory response and several alterations in inflammation-related parameters have been associated with worst COVID-19 outcomes in the overall population<sup>18,62,63</sup> and also in patients with cancer.<sup>27,60,64</sup> The NLR and OIS (or prognostic nutritional index) combine commonly used laboratory parameters (neutrophils, lymphocytes and albumin level), and represent easily accessible, inexpensive and valid scores that can be implemented in daily clinical practice. Among other available prognosticator algorithms, CORONET is a decision-support online tool focused on hospital admissions and recovery of patients with cancer and COVID-19,<sup>65,66</sup> which has been updated by integrating the ESMO-CoCARE data.<sup>66</sup>

There are limitations in our study. This is an observational registry study, with potential selection bias including missing values, the tendency to identify and report mainly the more severe cases, heterogeneity in patient management and data collection across institutions. We observed some differences in type and quality of data collected over time, in line with the increasing clinical experience and knowledge in managing patients with COVID-19. Finally, the quality of data depended on each centre, without the implementation of a centralized audit system. Despite these limitations, a unique electronic case report form and the multicentre, multicountry nature of the study with  $> 1500$  cases included empower a robust statistical analysis partly mitigating the selection bias.

In conclusion, in our study, male sex, older age, smokers, non-Asian ethnicity, poor ECOG PS, lower BMI, presence of comorbidities, symptomatic COVID-19, higher NLR, lower OIS, haematological malignancies, more advanced disease stage and progressive cancer status were identified as risk factors for COVID-19 adverse outcomes in patients with cancer. We are now facing another phase of the pandemic with a significant proportion of patients with cancer vaccinated against COVID-19 across countries, many already receiving a vaccination boost and new SARS-CoV-2 variants of concern with different transmissibility and morbidity rates. In this rapidly evolving context, ESMO-CoCARE is committed to strengthen a worldwide network tackling unmet needs for people with cancer and COVID-19 with the long-term goal to support clinicians and regulatory bodies on the optimal management of patients with cancer.

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