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ORIGINAL RESEARCH

COVID-19 in cancer patients: update from the joint analysis of the ESMO-CoCARE, BSMO, and PSMO international databases

P. Martin[1†], Z. Tsourti[2†], J. Ribeiro[3†], L. Castelo-Branco[4,5], E. de Azambuja[6], S. Gennatas[7], J. Rogado[8], M. Sekacheva[9], S. Šušnjar[10], D. Viñal[11], R. Lee[12,13], S. Khallaf[14], G. Dimopoulou[2], S. Pradervand[15], J. Whisenant[16], T. K. Choueiri[17,18], D. Arnold[19], K. Harrington[20], K. Punie[21], J. Oliveira[22], O. Michielin[15], U. Dafni[23], S. Peters[15‡], G. Pentheroudakis[5‡] & E. Romano[1‡*]

[1]Department of Oncology, Institut Curie, Paris, France; [2]Frontier Science Foundation-Hellas, Athens, Greece; [3]Gustave Roussy, Department of Cancer Medicine, Villejuif, France; [4]NOVA National School of Public Health, NOVA University, Lisbon, Portugal; [5]Scientific and Medical Division, ESMO (European Society for Medical Oncology), Lugano, Switzerland; [6]Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium; [7]Medical Oncology Department, The Royal Marsden Hospital — NHS Foundation Trust, London, UK; [8]Medical Oncology Department, Hospital Universitario Infanta Leonor, Madrid, Spain; [9]World-Class Research Center 'Digital Biodesign and Personalized Healthcare', Sechenov First Moscow State Medical University, Moscow, Russia; [10]Department of Medical Oncology, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [11]Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain; [12]Faculty of Biology, Medicine and Health, The University of Manchester, Manchester; [13]Medical Oncology Department, The Christie NHS Foundation Trust, Manchester, UK; [14]Medical Oncology Department, South Egypt Cancer Institute (SECI), Assiut University, Assiut, Egypt; [15]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [16]Vanderbilt University Medical Center, Nashville; [17]The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston; [18]Harvard Medical School, Boston, USA; [19]Asklepios Tumorzentrum Hamburg, AK Altona, Department of Oncology, Haematology and Palliative Care, Hamburg, Germany; [20]Division of Radiotherapy and Imaging, The Royal Marsden/The Institute of Cancer Research NIHR Biomedical Research Centre, London, UK; [21]Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [22]Department of Medicine, Instituto Português de Oncologia, Porto, Portugal; [23]Laboratory of Biostatistics, School of Health Sciences, National and Kapodistrian University of Athens, Athens Frontier Science Foundation-Hellas, Athens, Greece

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Background: COVID-19 has significantly affected patients with cancer and revealed unanticipated challenges in securing optimal cancer care across different disciplines. The European Society for Medical Oncology COVID-19 and CAncer REgistry (ESMO-CoCARE) is an international, real-world database, collecting data on the natural history, management, and outcomes of patients with cancer and SARS-CoV-2 infection.

Methods: This is the 2nd CoCARE analysis, jointly with Belgian (Belgian Society of Medical Oncology, BSMO) and Portuguese (Portuguese Society of Medical Oncology, PSMO) registries, with data from January 2020 to December 2021. The aim is to identify significant prognostic factors for COVID-19 hospitalization and mortality (primary outcomes), as well as intensive care unit admission and overall survival (OS) (secondary outcomes). Subgroup analyses by pandemic phase and vaccination status were carried out.

Results: The cohort includes 3294 patients (CoCARE: 2049; BSMO: 928, all hospitalized by eligibility criteria; PSMO: 317), diagnosed in four distinct pandemic phases (January to May 2020: 36%; June to September 2020: 9%; October 2020 to February 2021: 41%; March to December 2021: 12%). COVID-19 hospitalization rate was 54% (CoCARE/PSMO), ICU admission 14%, and COVID-19 mortality 22% (all data). At a 6-month median follow-up, 1013 deaths were recorded with 73% 3-month OS rate. No significant change was observed in COVID-19 mortality among hospitalized patients across the four pandemic phases (30%-33%). Hospitalizations and ICU admission decreased significantly (from 78% to 34% and 16% to 10%, respectively). Among 1522 patients with known vaccination status at COVID-19 diagnosis, 70% were non-vaccinated, 24% had incomplete vaccination, and 7% complete vaccination. Complete vaccination had a protective effect on hospitalization (odds ratio = 0.24; 95% confidence interval [0.14-0.38]), ICU admission (odds ratio = 0.29 [0.09-0.94]), and OS (hazard ratio = 0.39 [0.20-0.76]). In multivariable analyses, COVID-19 hospitalization was associated with patient/cancer characteristics, the first pandemic phase, the presence of COVID-19-related symptoms or inflammatory biomarkers, whereas COVID-19 mortality was significantly

*Correspondence to: Dr Emanuela Romano, Institut Curie, 26, rue d'Ulm, Paris 75005, France. Tel + 33-(0)-1-56-24-64-37
E-mail: Emanuela.Romano@curie.fr (E. Romano).

†Equal contributors.
‡Co-last authors.

higher in symptomatic patients, males, older age, ethnicity other than Asian/Caucasian, Eastern Cooperative Oncology Group performance status ≥2, body mass index <25, hematological malignancy, progressive disease versus no evident disease, and advanced cancer stage.

Conclusions: The updated CoCARE analysis, jointly with BSMO and PSMO, highlights factors that significantly affect COVID-19 outcomes, providing actionable clues for further reducing mortality.

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

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARs-CoV-2) emerged in December 2019, infecting more than 645 million people and resulting in >6 million deaths from the coronavirus disease (COVID-19).[1] COVID-19 has had important consequences on health systems across the world,[2] with cancer patients especially vulnerable given the increased risk of SARS-CoV2 infection, morbidity, and mortality,[3-6] and also given the global disruption of cancer care from early detection and diagnosis to optimal care.[7-9] In January 2020, the European Society for Medical Oncology (ESMO) initiated the ESMO COVID-19 and CAncer REgistry (ESMO-CoCARE) in order to study the effects of COVID-19 in patients with cancer and propose approaches to mitigate the risks related to COVID-19 and cancer diagnosis/treatment, as well as the evolution of both diseases.[10] ESMO-CoCARE was amongst the largest, observational, multicenter registries, including centers from Europe, Africa, and Asia/Oceania.

The first analysis of the ESMO-CoCARE registry showed that patient/cancer characteristics related to gender, ethnicity, poor fitness, comorbidities, systemic inflammation, and the presence of an active malignancy were associated with moderate/severe disease and adverse outcomes from COVID-19. These initial findings highlighted the need to adapt the daily practice in oncology.[10,11] With the evolution of the pandemic, prevention of infection and subsequent severe COVID-19 appeared to be crucial for patients with cancer, with vaccination being the most effective method of achieving this goal. Fortunately, owing to a massive global effort, several highly effective vaccines, particularly messenger RNA (mRNA)-based (BNT162b2 and mRNA-1273) and adenovirus-vectored vaccines (ChAdOx1 nCoV19, Ad26.COV2-S, and Gam-COVID-Vac), have been developed at an unprecedented speed.[12-15] These vaccines were safe and effective in patients with cancer.[13,16-18] Moreover, several patients experienced natural SARS-CoV2 infection and acquired immune protection.[11,13]

As the pandemic has progressed, the availability of effective vaccines and therapeutics as well as the development of new variants could influence the severity of COVID-19 in cancer patients, hence we proceeded to the second analysis of ESMO-CoCARE data, jointly with BSMO (Belgian Society of Medical Oncology)[19] and PSMO (Portuguese Society of Medical Oncology) registries. Herein, we report on the results of this updated analysis, which aimed at assessing significant prognostic factors for the COVID-19 outcomes of hospitalization, mortality, intensive care unit (ICU) admission, and overall survival (OS). In addition, subgroup analyses by pandemic phase and vaccination status were carried out.

METHODOLOGY

Study design and participants

This is an observational prospective study, based on longitudinal multicenter surveys of cancer patients diagnosed with COVID-19. The aim of the study is primarily to describe the characteristics of COVID-19 in patients with cancer, exploring associations with both cancer and COVID-19 outcomes. The current analysis cohort includes cancer patients with COVID-19, registered in CoCARE, BSMO, and PSMO. In the BSMO registry, only hospitalized patients with cancer and COVID-19 were included. All three registries collected data on clinical features, course of disease, management, and outcomes for both cancer and COVID-19 disease. Data reported here were extracted from medical records of consecutive patients diagnosed with COVID-19 from 1 January 2020.

Study objectives and endpoints

The present analysis focuses on the identification of factors potentially associated with COVID-19 hospitalization and mortality over the different pandemic phases (also named waves) and subgroups of special interest. The primary endpoints were (i) COVID-19 hospitalization, categorized based on hospitalization requirement and indication for ICU admission (no hospitalization versus hospitalization indicated/took place, with or without ICU indication/admission) and (ii) COVID-19 mortality, including deaths reported for patients who did not recover from COVID-19, as well as deaths reported for patients who recovered but died later due to COVID-19 complications. Secondary endpoints included admission to ICU (ICU indication/admission versus no hospitalization or hospitalization indicated/took place, without ICU) and OS (time-to-event endpoint), defined as time from the date of formal COVID-19 diagnosis until death from any cause. Of note, the analysis of COVID-19 hospitalization did not include BSMO, since all patients from BSMO were hospitalized, while COVID-19 mortality was analyzed for hospitalized patients only (among non-hospitalized only 2.8% died due to COVID-19).

Statistical analysis

Significant risk factors for COVID-19 hospitalization, COVID-19 mortality, and admission to ICU were examined through multivariable logistic regression models, stratified by registry, odds ratios (OR) are provided (multicollinearity also checked).

Multivariable Cox proportional hazards models, stratified by registry, were fitted for OS, hazard ratios (HR) are provided (proportionality was explored by Schoenfeld's residuals).

For the multivariable analyses, a pre-selection of explanatory variables was made to avoid overfitting of the model. Initial variable selection was based on significance from univariable analysis stratified by registry ($P < 0.10$), possible correlation between variables, importance of factors, and data availability. For all the multivariable models, the factors with significant effects were derived based on the backward elimination method (removal criterion $P >$ 10%). Several important factors were further explored, including (i) phase of the pandemic [phase I (January to May 2020); phase II (June to September 2020); phase III (October 2020 to February 2021); phase IV (March to December 2021)], (ii) vaccination status at COVID-19 diagnosis [no vaccination/vaccination not completed; vaccination completed (at least 2 weeks)], (iii) age at COVID-19 diagnosis (<50; 50-69; ≥70 years), and (iv) ethnicity (Caucasian; Asian; other). The association of these factors with patient/clinical/cancer/COVID-19 characteristics was explored through Fisher's exact test. Subgroup analyses for the primary outcomes of COVID-19 hospitalization/mortality were carried out to determine whether the effect of these characteristics of interest was consistent across the various subgroups. Separate multivariable logistic regression analyses were carried out for each subgroup.

For the subgroup analysis by vaccination status, the propensity score matching method was used to create two cohorts of the same size and similar characteristics, adjusting for confounding factors and reducing potential bias resulting from factors' inequalities between the two cohorts ('1 to 1 Greedy Matching' algorithm).

All P values are two-sided and considered statistically significant if ≤0.05. Due to the exploratory setting of this analysis, multiplicity adjustment is not applied.

Data were analyzed using SAS v9.4 and R v4.0.5 software.

RESULTS

Cohort description

The overall analysis cohort includes 3294 patients with cancer history and COVID-19 diagnosis from January 2020 to February 2022: 2049 (62%) from CoCARE (23 countries, with the UK (31%) and Spain (20%) contributing most, database cut-off date: 17 May 2022), 928 (28%) from Belgian centers (BSMO), and 317 (10%) from Portuguese centers (PSMO) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101566). Overall, 36% of the analysis cases were diagnoses from the first phase of the pandemic, 9% from phase II, 41% from phase III, and 12% from phase IV (Figure 1A). This time distribution holds also for CoCARE, whereas in BSMO, most of the cases were from phase I (54%), and in PSMO from phase III (62%). Of note, in BSMO registry, there is available information only until January 2021 (i.e. until phase III of the pandemic).

A flow chart of the analysis for the overall population and by registry is presented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101566. Cohort demographics, clinical, and cancer disease characteristics are provided in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101566. Median age of the overall cohort was 66 years (interquartile range 55-75 years), with half of the patients being females. Among patients with known ethnicity, 68% were Caucasian and 8% Asian. Almost equal were the never smokers (38%) with the former/current smokers (37%), while 60% had Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1. Most of the patients had pre-existing co-morbidities (74%), with cardiovascular (49%) and metabolic (33%) the most common ones, while 69% received at least one concomitant medication (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101566).

The vast majority (88%) of patients had solid tumors (breast: 21%, colorectal: 13%, lung: 13%, prostate: 7%; other: 34%), with hematological malignancies reported for 9%. Most of the patients had evidence of active cancer at COVID-19 diagnosis (62%) with 21% having no evidence of disease (excluding BSMO with non-available cancer status), whereas half (50%) had cancer stage III/IV. Some 60% were on cancer treatment (including any antineoplastic therapies within 3 months before COVID-19 diagnosis). For 31% of the patients, the cancer treatment plan was adjusted due to COVID-19 (25% delay, 3% cancellation).

Table 1 summarizes the vaccination status of patients. Among the 2366 CoCARE/PSMO patients, 534 (23%) had an initial vaccination and 186 (8%) had also received a booster dose. At COVID-19 diagnosis, 103 patients (4%) had completed vaccination (last dose at least 2 weeks before COVID-19 diagnosis) and 1419 (60%) were either not vaccinated (1058; 45%) or vaccination was not completed (361; 15%).

COVID-19 diagnosis, course of illness, and outcome

Details on COVID-19 diagnosis and course of illness are provided in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101566. COVID-19 hospitalization was reported for 65% of the patients, including 14% with ICU admission. Of note, the COVID-19 hospitalization rate (excluding BSMO who were all hospitalized) was 54%. At initial presentation of COVID-19, 76% had at least one symptom, most commonly fever (46%), cough (41%), and dyspnea (31%). Complications occurred to 35% of the patients, most frequently pulmonary (24%), cardiovascular (7%), and systemic (6%). Furthermore, based on CoCARE/PSMO, 13% experienced serious complications, 32% required supplemental oxygen, whereas treatment of COVID-19 or its sequelae was administered to 42%, including azithromycin (19%), anticoagulation (18%), hydroxychloroquine (15%), and corticosteroids (15%).

Regarding clinical outcome (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101566), among 2809 patients with available follow-up, 622 (22%) died due to COVID-19. Overall, 1031 (37%)

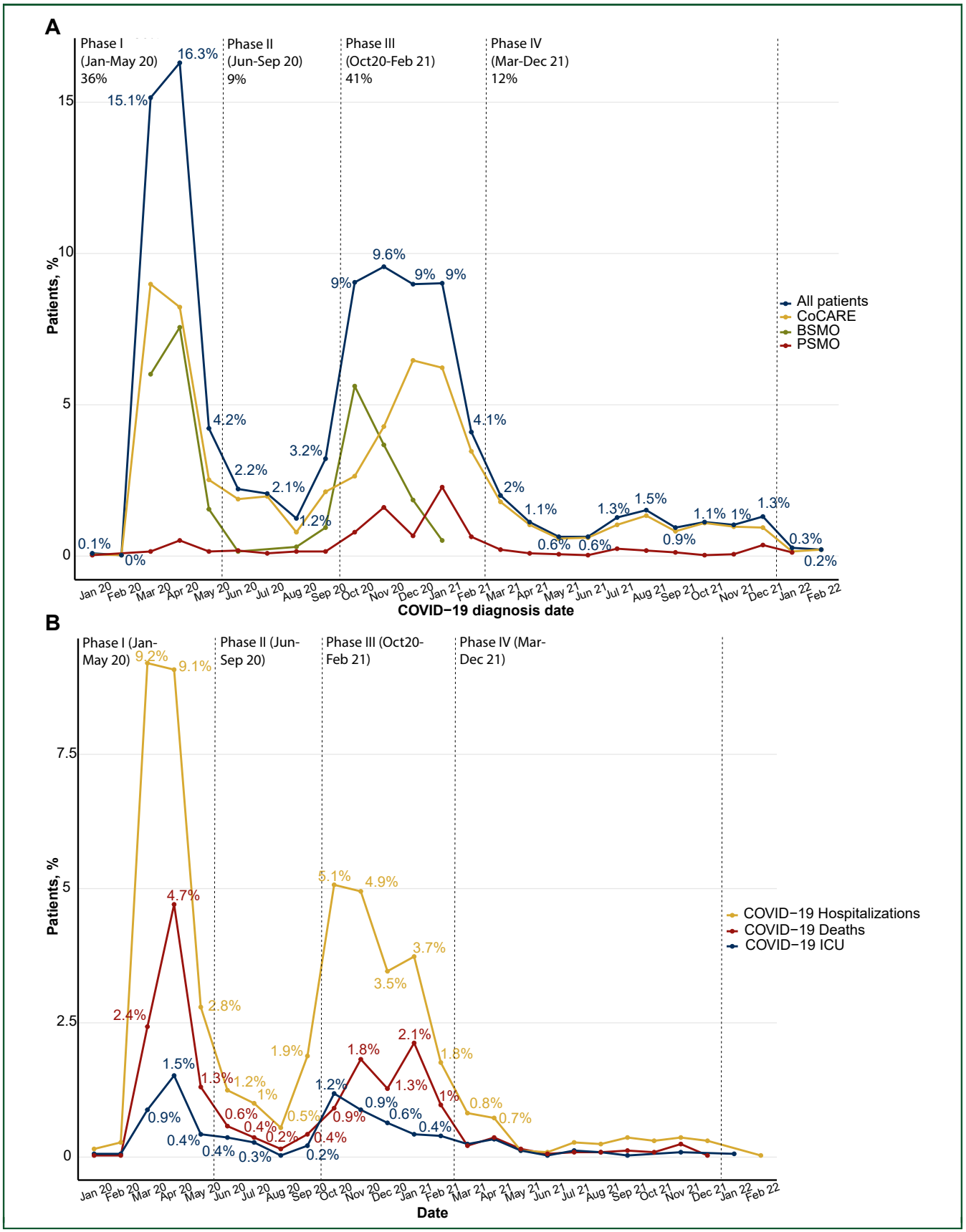

Figure 1. COVID-19 infection across pandemic phases. (A) Patients with COVID-19 infection over time, overall, and by registry ($N = 3294$). (B) Patients with COVID-19-related hospitalization, ICU admission and death due to COVID-19 across pandemic phases, overall ($N = 3294$).
CoCARE, COVID-19 and CAncer REgistry; BSMO, Belgian Society of Medical Oncology; ICU, intensive care unit; PSMO, Portuguese Society of Medical Oncology.

Table 1. Vaccination status, overall and by registry

Vaccination	CoCARE (n = 2049)	PSMO (n = 317)	All patients (N = 2366)
Initial vaccination, *n* (%)			
Yes	451 (22.0)	83 (26.2)	534 (22.6)
Modified virus	220 (10.7)	15 (4.7)	235 (9.9)
RNA	169 (8.2)	45 (14.2)	214 (9.0)
Peptide	4 (0.2)		4 (0.2)
Other	10 (0.5)		10 (0.4)
Non-available	48 (2.3)	23 (7.3)	71 (3.0)
No	976 (47.6)	82 (25.9)	1058 (44.7)
Unknown/missing	622 (30.4)	152 (47.9)	774 (32.7)
Booster vaccination, *n* (%)			
Yes	183 (8.9)	3 (0.9)	186 (7.9)
Modified virus	24 (1.2)	—	24 (1.0)
RNA	144 (7.0)	2 (0.6)	146 (6.2)
Peptide	2 (0.1)	—	2 (0.1)
Other	—	—	—
Non-available	13 (0.6)	1 (0.3)	14 (0.6)
No	241 (11.8)	69 (21.8)	310 (13.1)
No initial vaccination	976 (47.6)	82 (25.9)	1058 (44.7)
Unknown/missing	649 (31.7)	163 (51.4)	812 (34.3)
Vaccination status at COVID-19 diagnosis, *n* (%)			
No vaccination/ vaccination not completed before infection	1273 (62.1)	146 (46.1)	1419 (60.0)
No vaccination	976 (47.6)	82 (25.9)	1058 (44.7)
Vaccination not completed	297 (14.5)	64 (20.2)	361 (15.3)
Vaccination completed before infection (at least 2 weeks)	97 (4.7)	6 (1.9)	103 (4.4)
Initial vaccination	83 (4.1)	6 (1.9)	89 (3.8)
Booster dose	14 (0.7)		14 (0.6)
Unknown/missing	679 (33.1)	165 (52.1)	844 (35.7)

BSMO had no available information regarding vaccination.
Percentages are calculated within column.
BSMO, Belgian Society of Medical Oncology; CoCARE, COVID-19 and CAncer REgistry; PSMO, Portuguese Society of Medical Oncology.

deaths were recorded, with the most common reasons being COVID-19 complications (60%) and progressive disease (PD) (cancer) (18%). Among patients who recovered (n = 2437), 7% had major complications, including lung function (3%), pneumonitis (3%), and fatigue (2%). Thirty patients had been re-infected or COVID-19 was re-activated (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101566).

Association with baseline factors—multivariable analysis and temporal trends

COVID-19 hospitalization. According to the multivariable logistic model (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101566), COVID-19 hospitalization rate was higher in older patients, with Asian/other ethnicity compared with Caucasian, worse ECOG PS (≥2) and a higher number of co-morbidities (OR range 1.26-2.90). Patients with breast, colorectal, or other solid tumors had lower hospitalization rate than patients with hematological malignancies (OR = 0.34, 0.48, and 0.59, respectively) whereas patients with PD (cancer) needed to be hospitalized more often compared with those with no evidence of disease (NED) (OR = 1.67). During the second, third, and fourth phases, lower hospitalization rates were observed compared with the first phase (OR = 0.26, 0.36, and 0.19, respectively). Asymptomatic patients were hospitalized less often, as expected (OR = 0.13), whereas, patients in the poorer risk category of neutrophil-lymphocyte ratio (NLR) (≥6), platelet-lymphocyte ratio (PLR) (≥270), OnCOVID inflammatory score (OIS) (≤40), and prognostic index (PI) had higher hospitalization rates (OR range 1.60-5.48).

COVID-19 mortality (among hospitalized patients). COVID-19 mortality among hospitalized patients (multivariable model; Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2023.101566) was higher in male patients, older, with ethnicity other than Asian/Caucasian, worse ECOG PS (≥2), and BMI < 25 (OR range 1.34-2.14). Patients with prostate or other solid tumors had fewer COVID-19-related deaths than patients with hematological malignancies (OR = 0.37 and 0.55, respectively). Patients with progressive tumor, however, died more often due to COVID-19 compared with those with NED (OR = 2.50). Finally, as expected, patients with stage I/II or III, had lower COVID-19 mortality rates than patients with stage IV (OR = 0.40 and 0.62, respectively). This held also for asymptomatic patients (OR = 0.43).

COVID-19 ICU admission. ICU admission (Supplementary Table S7A, available at https://doi.org/10.1016/j.esmoop.2023.101566) was higher in patients with worse ECOG PS (≥2), coming from centers in lower-middle-income countries compared with high-income (OR = 1.87 and 2.02, respectively), whereas, older age patients had a lower ICU admission rate (OR = 0.89). Patients with solid tumors were admitted to ICU less frequently than patients with hematological malignancies (OR range 0.31-0.63). Patients with PD, however, had higher ICU admission rates compared with those with NED (OR = 1.70) as well as patients in the poorer risk category of OIS (≤40) (OR = 1.71). Asymptomatic patients were admitted to ICU less often (OR = 0.19).

Due to the unexpected finding regarding age, a sensitivity analysis was conducted excluding BSMO (with only hospitalized patients). In this case, the pandemic phase was found significant and remained in the model instead of age (all other variables and their effect were the same) (Supplementary Table S7A, available at https://doi.org/10.1016/j.esmoop.2023.101566).

OS. Among 2791 patients with available information, median follow-up was 6.05 months (interquartile range 5.95-11.99). A total of 1013 (36%) deaths were recorded, with 58.8% [95% confidence interval (CI) 56.6% to 61.0%] 1-year OS rate and median OS 13.6 months (95% CI 12.6-16.5 months) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101566). According to the final stratified multivariable Cox model (Supplementary Table S8A, available at https://doi.org/10.1016/j.esmoop.2023.101566), males showed a higher mortality risk

(HR = 1.40). The risk of death was lower for Asians in comparison with Caucasians (HR = 0.55), whereas higher for other ethnicity (HR = 1.31). Worse ECOG PS and lower BMI were also associated with increased risk of death (HR = 2.09 and 1.32, respectively). Patients with breast and prostate tumors had lower mortality risk compared with those with hematological malignancies (HR = 0.63 and 0.55, respectively), as well as patients with stage I/II and III compared with IV (HR = 0.38 and 0.62, respectively). Immunotherapy/targeted therapy (alone or with chemotherapy) and other cancer treatment or no treatment, were also associated with lower risk of death compared with chemotherapy (HR range 0.70-0.79). Finally, patients in the NLR poorer risk category displayed higher mortality risk (HR = 1.44). In sensitivity analysis excluding BSMO, only BMI (compared with the above model) was not found to be significant and thus not included in the corresponding final model (Supplementary Table S8B, available at https://doi.org/10.1016/j.esmoop.2023.101566).

Subgroup analysis by pandemic phase

Hospitalization, ICU admission, and all-cause death rates decreased significantly across the four pandemic phases (hospitalization from 78% in January to May 2020 to 34% in March to December 2021, ICU from 16% to 10%, all-cause death from 41% to 19%). Among hospitalized patients, no significant change was observed for COVID-19 mortality, as opposed to COVID-19 mortality for the overall cohort (Table 2). Respective rates for the overall cohort are presented in Figure 1B.

Most of the patient/clinical/cancer/COVID-19 characteristics differed significantly among the different pandemic phases (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2023.101566). According to multivariable models for COVID-19 hospitalization and COVID-19 mortality (among hospitalized), by pandemic phase (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2023.101566), age, ECOG PS, cancer status, tumor type were significant prognostic factors for both endpoints, in most of the phases. Symptoms were also significant for COVID-19 hospitalization in all phases, as well as in phase I for COVID-19 mortality. The effect of gender was significant only in phase I. Ethnicity and BMI exhibited a significant effect only on the hospitalization rate in phase III. The effect of country's income level on hospitalization was significant in phases I and III, but in the opposite direction: in phase I, hospitalization rate was higher in upper-middle-income countries (95%) compared with high-income economies (75%), whilst in phase III the opposite association was detected (22% versus 46%).

Subgroup analysis by vaccination status

Vaccination had a protective effect in COVID-19 hospitalization (OR = 0.24), ICU admission (OR = 0.29), and OS (HR = 0.39), whereas no difference was shown in COVID-19 mortality rate among hospitalized patients (Table 3). The association of vaccination status with variables of interest is presented in Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2023.101566, with a significantly higher vaccination rate for Caucasians (9%), patients with ECOG PS 0 (9%), centers in Northern/Western Europe (10%), and upper-middle-income economies (13%). Breast (10%) and prostate (9%) cancer patients had the highest vaccination rates, as well as patients on active cancer treatment at COVID-19 diagnosis (8%). The vaccination rate, however, was significantly lower among symptomatic patients (6%), with pulmonary/cardiovascular/systemic complications (2%/1%/2%), requiring O_2 (2%), as well as those requiring COVID-19 treatment (5%). In Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2023.101566, the multivariable logistic models for COVID-19 hospitalization are presented for each vaccination subgroup, after matching for baseline characteristics. For non-completely vaccinated patients, less hospitalizations occurred in the upper-middle economies compared with high-income countries, possibly due to health system capacity saturation. Age, symptoms and PLR were significant factors in the vaccination group, whereas ethnicity, ECOG PS, BMI, and cancer status were significant factors in the non-vaccinated one. No model was fitted for COVID-19 mortality due to the small number of patients and events in each subgroup.

Subgroup analyses by age group and ethnicity

Subgroup analysis by age is based on the following grouping: 543 (17%) '<50 years', 1379 (42%) '50-69 years', and 1324 (41%) '≥70 years'. Older patients had significantly higher rates of hospitalization (70%), COVID-19 death among hospitalized (37%), and all-cause death (45%) (Table 4). Age was significantly associated with most of the factors examined (Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2023.101566). In Supplementary Table S14, available at https://doi.org/10.1016/j.esmoop.2023.101566, results from the multivariable models for COVID-19 hospitalization and COVID-19 mortality (among hospitalized) are presented for each age subgroup. ECOG PS was a significant prognostic factor for both endpoints, in all subgroups, with stronger effect for younger patients. Cancer status (PD versus NED) was significant for COVID-19 hospitalization and mortality in the <50 and 50-69 groups, whereas cancer stage had a significant effect on the mortality of patients >50 years old. Symptoms had a significant effect (increasing with age) on hospitalization for all age groups, and for mortality of older patients (≥70). PI significantly affected the hospitalization of younger patients, and PLR and OIS the hospitalization of middle-age patients, whereas modified Glasgow prognostic score (mGPS) affected older patients. Ethnicity was found to be significant for COVID-19 hospitalization only, in the groups of <50 years and 50-69 years (with Caucasian having lower hospitalization rate), whereas gender, co-morbidities, and vaccination status were significant prognostic factors for hospitalization in the <50 years age group. The pandemic phase was significant for COVID-19 hospitalization, for all age groups (with less hospitalizations during phases II/III/IV

Table 2. Univariable association of pandemic phase with the primary/secondary outcomes, overall

Characteristic	COVID-19 hospitalization			COVID-19 mortality				COVID-19 ICU admission			Overall survival		
	(All pts excl. BSMO)			(Hospitalized pts)			(All pts excl. BSMO)	(All pts)			(All pts)		
	% Hospital ($n = 1148$)	Total ($n = 2143$)	Odds ratio[a] (95% CI)	% COVID-19 deaths ($n = 520$)	Total ($n = 1639$)	Odds ratio[a] (95% CI)	% COVID-19 deaths ($n = 379$)	% ICU ($n = 379$)	Total ($n = 2818$)	Odds ratio[a] (95% CI)	% Deaths ($n = 1013$)	Total ($n = 2791$)	Hazard ratio[a] (95% CI)
Pandemic phase	***P* < 0.001**[b]			***P* = 0.62**[b]			***P* < 0.001**[b]	***P* = 0.010**[b]			***P* < 0.001**[c]		
Phase I (Jan-May 2020)	78.0	642	Reference	33.1	785	Reference	28.9	16.1	1008	Reference	41.0	1052	Reference
Phase II (Jun-Sept 2020)	51.5	231	0.3 (0.22-0.42)	30.7	114	0.81 (0.53-1.25)	17.2	10.9	266	0.84 (0.54-1.29)	31.2	237	0.70 (0.55-0.90)
Phase III (Oct 2020-Feb 2021)	45.4	873	0.26 (0.2-0.32)	29.9	635	0.81 (0.64-1.02)	17.5	13.0	1147	0.92 (0.72-1.18)	37.7	1197	0.87 (0.76-0.99)
Phase IV (Mar-Dec 2021)	34.1	381	0.15 (0.11-0.2)	32.7	104	0.75 (0.48-1.17)	12.8	10.0	381	0.92 (0.62-1.37)	18.9	302	0.53 (0.40-0.71)
(Jan 2022 +)	6.7	15	—	—	—	—	—	—	15	—	—	3	—
Unknown/missing	100.0	1	—	100.0	1	—	100.0	100.0	1	—	—	—	—

Non-significant associations are presented in gray.
Percentages are calculated within row for each outcome.
BSMO, Belgian Society of Medical Oncology; CI, confidence interval; ICU, intensive care unit.
[a]Stratified by registry, excluding categories 'unknown/missing' and '(Jan 2022 +)'.
[b]Fisher's exact test excluding categories 'unknown/missing' and '(Jan 2022 +)'.
[c]Log-rank test excluding categories 'unknown/missing' and '(Jan 2022 +)'.

compared with I), as well as for older patients (≥70 years) for COVID-19 mortality (with less COVID-19 deaths for phase II only compared with I).

Subgroup analysis by ethnicity was based on 2036 patients with known ethnicity: 1390 (68%) Caucasian, 163 (8%) Asian, and 483 (24%) other ethnicities. Patients with ethnicity other than Asian/Caucasian had significantly higher rates of COVID-19 hospitalization (62%), COVID-19-related deaths among hospitalized (47%), ICU admission (17%), and all-cause death (41%) (Table 4). Ethnicity was also significantly associated with most of the factors examined (Supplementary Table S15, available at https://doi.org/10.1016/j.esmoop.2023.101566). In Supplementary Table S16, available at https://doi.org/10.1016/j.esmoop.2023.101566, the multivariable logistic models for COVID-19 hospitalization and COVID-19 mortality among hospitalized are presented for each ethnicity subgroup. Results for the Asian subgroup are mainly descriptive due to the small number of patients.

DISCUSSION

This updated analysis showed a significant decrease across the four pandemic phases in COVID-19-related hospitalization, ICU admissions, and overall COVID-19-mortality; however, no significant change was reported in COVID-19-related mortality among hospitalized patients, which remained relatively stable across pandemic phases. At the time of analysis, the COVID-19-related death rate in our cohort was 22% with 622 deaths. This result was similar to that of 24.5%, reported in the first analysis of ESMO-CoCARE[10] but higher compared with the mortality rates in the general population.[20-22] Although, these results were better than those reported initially in COVID-19 patients with cancer,[21,23] a great variability was observed across studies in the literature, with a mortality rate between 13% and 33%.[23-26] A meta-analysis of 110 studies showed a pooled mortality rate of 14.1% in patients with cancer and COVID-19.[27] On the contrary, a different meta-analysis on 33 879 patients yielded a mortality rate of 25.4%, in line with the first CoCARE analysis.[10,28] This heterogeneity could be explained by geographic location, pandemic phases, as well as access to cancer treatment and COVID-19 care.

Regarding the stability in COVID-19-related mortality among hospitalized patients across the pandemic phases, this could be due to the increased risk of infection after the first lockdown, a negative selection bias for the high-risk population, and ineffective antiviral treatments for severe COVID-19. Indeed, modalities of viral transmission have changed[29] and some patients might have had more advanced and severe cancers during phases III and IV of the pandemic owing to a disrupted access to care. A study showed a decrease in mortality between the first and the second outbreaks,[30] and this finding was also present in our analysis when evaluating COVID-19 mortality over all CoCARE/PSMO patients, but stability was observed for COVID-19 mortality over hospitalized patients in our cohort (primary endpoint). The hospitalization rate was 54%, close

Table 3. Univariable association of vaccination status with the primary/secondary outcomes, overall

Characteristic	COVID-19 hospitalization (All pts excl. BSMO)			COVID-19 mortality (Hospitalized pts)			COVID-19 ICU admission (All pts)			Overall survival (All pts)		
	% Hospital ($n = 1148$)	Total ($n = 2143$)	Odds ratio[a] (95% CI)	% COVID-19 deaths ($n = 520$)	Total ($n = 1639$)	Odds ratio[a] (95% CI)	% ICU ($n = 379$)	Total ($n = 2818$)	Odds ratio[a] (95% CI)	% Deaths ($n = 1013$)	Total ($n = 2791$)	Hazard ratio[a] (95% CI)
Vaccination at COVID	***P* < 0.001**[b]			$P = 0.78$[b]			***P* = 0.029**[b]			***P* = 0.0039**[c]		
Incomplete/no vaccination	51.4	1343	Reference	33.6	660	Reference	9.4	1343	Reference	33.1	1281	Reference
Vaccination completed	20.4	103	0.24 (0.14-0.38)	28.6	14	0.83 (0.26-2.67)	2.9	103	0.29 (0.09-0.94)	11.0	82	0.39 (0.20-0.76)
Unknown/missing	62.7	697	—	30.5	965	—	18.2	1372	—	40.6	1428	—

Non-significant associations are presented in gray.
Percentages are calculated within row for each outcome.
BSMO, Belgian Society of Medical Oncology; CI, confidence interval; ICU, intensive care unit.
[a]Stratified by registry, excluding category 'unknown/missing'.
[b]Fisher's exact test excluding category 'unknown/missing'.
[c]Log-rank test excluding category 'unknown/missing'.

Table 4. Univariable associations of age and ethnicity with the primary/secondary outcomes, overall

Characteristic	COVID-19 hospitalization (All pts excl. BSMO)			COVID-19 mortality (Hospitalized pts)			COVID-19 ICU admission (All pts)			Overall survival (All pts)		
	% Hospital ($n = 1148$)	Total ($n = 2143$)	Odds ratio[a] (95% CI)	% COVID-19 deaths ($n = 520$)	Total ($n = 1639$)	Odds ratio[a] (95% CI)	% ICU ($n = 379$)	Total ($n = 2818$)	Odds ratio[a] (95% CI)	% Deaths ($n = 1013$)	Total ($n = 2791$)	Hazard ratio[a] (95% CI)
Age at COVID	$P < 0.001$[b]			$P < 0.001$[b]			$P = 0.30$[b]			***P* < 0.001**[c]		
<50 years	36.6	467	0.22 (0.17-0.29)	24.2	178	0.43 (0.3-0.63)	11.3	495	1.21 (0.86-1.72)	21.0	461	0.38 (0.31-0.48)
50-69 years	49.4	968	0.4 (0.32-0.49)	26.6	646	0.56 (0.44-0.7)	14.1	1216	1.27 (0.99-1.62)	33.2	1158	0.63 (0.55-0.73)
≥70 years	70.4	707	Reference	37.3	814	Reference	13.7	1106	Reference	45.3	1171	Reference
Unknown/missing	100.0	1	—	100.0	1	—	100.0	1	—	100	1	—
Ethnicity	$P < 0.001$[b]			$P < 0.001$[b]			$P < 0.001$[b]			***P* < 0.001**[c]		
Caucasian	51.4	1351	Reference	36.0	644	Reference	7.2	1351	Reference	35.2	1240	Reference
Asian	54.4	160	1 (0.72-1.4)	17.3	81	0.39 (0.21-0.71)	10.0	160	1.41 (0.81-2.48)	13.7	146	0.40 (0.26-0.63)
Other	62.0	471	1.43 (1.15-1.78)	46.9	192	1.6 (1.15-2.22)	16.8	471	2.58 (1.87-3.55)	40.5	346	1.28 (1.05-1.55)
Unknown/missing	46.6	161	—	25.5	722	—	22.4	836	—	39.3	1059	—

Non-significant associations are presented in gray.
Percentages are calculated within row for each outcome.
BSMO, Belgian Society of Medical Oncology; CI, confidence interval; ICU, intensive care unit.
[a]Stratified by registry, excluding categories 'unknown/missing'.
[b]Fisher's exact test excluding categories 'unknown/missing'.
[c]Log-rank test excluding categories 'unknown/missing'.

to that of 58% reported by Grivas et al.[26] The actual number of patients with cancer and COVID-19 may have not been accurate, with some patients having asymptomatic or minimally symptomatic COVID-19 not being tested and consequently not being included in the studies.[31-33] Another study showed a decrease in mortality across the wave during the acute phase of COVID-19 infection with a possible benefit of steroids.[34] Possible explanations were the difference of duration of follow-up or the fewer number of different countries with less heterogeneity in the management of COVID infection and therefore a better management of patients and their complications.

The factors associated with increased COVID-19-related risk of mortality in hospitalized patients were male gender, older age, ethnicity other than Caucasian/Asian, worse ECOG PS, BMI $<$ 25, and an active malignancy—in line with published studies[24,26,35] and the first CoCARE analysis.[10] Hematological malignancy had significantly higher risk of death than prostate cancer or other solid tumors. Hematological malignancies had already been associated with worst COVID-19 outcome[36,37] and reduced immune responses to the vaccination contributing to ongoing unfavorable COVID-19 outcomes.[13,18,38] The HR for 'no treatment' versus chemotherapy with regard to hospitalization was 2.81; this result is consistent with those of CCC19,[24] which suggested that cancer treatment could be continued during the pandemic in view of the benefit-risk ratio, even for cytotoxic chemotherapy if clinically indicated.

Interestingly, in our study COVID-19 hospitalizations and ICU admissions decreased across the four pandemic phases. The OR between the first phase (January to May 2020) compared with the subsequent pandemic phases ranged from 0.15 to 0.30. This result could be explained by better management of COVID-19, acquired anti-SARS-Cov2 immunity either naturally or through vaccination, early diagnosis and supportive therapy, the presence of less aggressive SARS-Cov2 variants, and a lower tendency to hospitalize minimally symptomatic patients.[39] Indeed, avoiding hospitalization could also decrease the risk of nosocomial transmission and complication. Our observation that older age patients had a lower ICU admission rate could reflect an age limit of ICU admissions during the highest peaks of the COVID-19 pandemic.

Because of the effectiveness of COVID-19 vaccines in patients with cancer, we carried out a subgroup analysis in patients with complete vaccination and found—in univariate analysis—a significant decrease in COVID-19 hospitalization, ICU admission, along with an increased OS. Of note, complete vaccination rate in our cohort was only 7%, which did not allow the assessment of the effect of vaccination on COVID-19 mortality. Our findings are consistent with previous studies that showed the effect of vaccination on humoral and T-cell-mediated responses[16,40] or on COVID-19 infection41-43; however, clinical outcome was explored on limited numbers of vaccinated patients.[44] Vaccination against COVID-19 proves to be an effective strategy in protecting vulnerable populations, including patients with cancer, and boosters could further increase its benefit.[45] The study OnCovid recently showed a reduction of infection's morbidity and mortality in patients with breast cancer with complete vaccination.[46]

It is important to highlight that in our study complete vaccination had a significantly protective effect against COVID-19 hospitalization, ICU admission, and OS only in univariable analysis; this effect, however, was lost when adjusting for socioeconomic and demographic parameters. In this respect, we report that complete vaccination rates were significantly higher in Northern/Western Europe and in upper-middle-income level countries, which confirms previous observations in the health care utilization and health outcomes of populations during the COVID-19 pandemic, especially in terms of morbidity and mortality.[47,48] Indeed, gross disparities in hospitalization rates and mortality between racial/ethnic groups and geographical locations in the context of COVID-19 highlighted the shortcomings of public health strategies in achieving best health for all. For instance, several studies have shown disproportionate adverse effects of COVID-19 on African Americans.[49,50] Progressive pandemic planning in the next decade must be inclusive, aware of the social gradient of risk, and reflecting a whole-of-society approach to risk reduction. In addition, our results support the importance of SARS-CoV-2 vaccination in cancer patients. Indeed, vaccine hesitancy was present in all populations, including patients with cancer,[51-53] as demonstrated by a large meta-analysis that found only 59% vaccine acceptance.[53]

Limitations to our study include the potential selection bias due to the observational nature of our registries; the presence of missing values, the enrichment with mainly severe COVID-19 cases, the heterogeneity in patient management, and data collection across individual registries and institutions. Despite these limitations, with $>$3000 cases from real-world electronic health record data included, our study allowed for a robust statistical analysis partly mitigating its intrinsic selection bias.

In conclusion, we showed a decrease in COVID-19 hospitalization and ICU admission rates across the pandemic phases. Complete vaccination had a protective effect against severe COVID-19 but did not remain significant when adjusting for other socioeconomic and demographic parameters. Our study highlights factors that significantly affect COVID-19 outcomes, providing actionable clues for further reducing mortality. Collectively, our results have risk stratification and resource use implications that may be informative for future public health challenges experienced by patients, clinicians, and health care systems.

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