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Time-Dependent COVID-19 Mortality in Patients With Cancer
An Updated Analysis of the OnCovid Registry

OnCovid Study Group

IMPORTANCE Whether the severity and mortality of COVID-19 in patients with cancer have improved in terms of disease management and capacity is yet to be defined.

OBJECTIVE To test whether severity and mortality from COVID-19 among patients with cancer have improved during the course of the pandemic.

DESIGN, SETTING, AND PARTICIPANTS OnCovid is a European registry that collects data on consecutive patients with solid or hematologic cancer and COVID-19. This multicenter case series study included real-world data from 35 institutions across 6 countries (UK, Italy, Spain, France, Belgium, and Germany). This update included patients diagnosed between February 27, 2020, and February, 14, 2021. Inclusion criteria were confirmed diagnosis of SARS-CoV-2 infection and a history of solid or hematologic cancer.

EXPOSURES SARS-CoV-2 infection.

MAIN OUTCOMES AND MEASURES Deaths were differentiated at 14 days and 3 months as the 2 landmark end points. Patient characteristics and outcomes were compared by stratifying patients across 5 phases (February to March 2020, April to June 2020, July to September 2020, October to December 2020, and January to February 2021) and across 2 major outbreaks (February to June 2020 and July 2020 to February 2021).

RESULTS At data cutoff, 2795 consecutive patients were included, with 2634 patients eligible for analysis (median [IQR] age, 68 [18-77] years ; 52.8% men). Eligible patients demonstrated significant time-dependent improvement in 14-day case-fatality rate (CFR) with estimates of 29.8% (95% CI, 0.26-0.33) for February to March 2020; 20.3% (95% CI, 0.17-0.23) for April to June 2020; 12.5% (95% CI, 0.06-22.90) for July to September 2020; 17.2% (95% CI, 0.15-0.21) for October to December 2020; and 14.5% (95% CI, 0.09-0.21) for January to February 2021 (all $P < .001$) across the predefined phases. Compared with the second major outbreak, patients diagnosed in the first outbreak were more likely to be 65 years or older (974 of 1626 [60.3%] vs 564 of 1008 [56.1%]; $P = .03$), have at least 2 comorbidities (793 of 1626 [48.8%] vs 427 of 1008 [42.4%]; $P = .001$), and have advanced tumors (708 of 1626 [46.4%] vs 536 of 1008 [56.1%]; $P < .001$). Complications of COVID-19 were more likely to be seen (738 of 1626 [45.4%] vs 342 of 1008 [33.9%]; $P < .001$) and require hospitalization (969 of 1626 [59.8%] vs 418 of 1008 [42.1%]; $P < .001$) and anti–COVID-19 therapy (1004 of 1626 [61.7%] vs 501 of 1008 [49.7%]; $P < .001$) during the first major outbreak. The 14-day CFRs for the first and second major outbreaks were 25.6% (95% CI, 0.23-0.28) vs 16.2% (95% CI, 0.13-0.19; $P < .001$), respectively. After adjusting for country, sex, age, comorbidities, tumor stage and status, anti–COVID-19 and anticancer therapy, and COVID-19 complications, patients diagnosed in the first outbreak had an increased risk of death at 14 days (hazard ratio [HR], 1.85; 95% CI, 1.47-2.32) and 3 months (HR, 1.28; 95% CI, 1.08-1.51) compared with those diagnosed in the second outbreak.

CONCLUSIONS AND RELEVANCE The findings of this registry-based study suggest that mortality in patients with cancer diagnosed with COVID-19 has improved in Europe; this improvement may be associated with earlier diagnosis, improved management, and dynamic changes in community transmission over time.

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Supplemental content

Group Information: The members of the OnCovid Study Group appear at the end of the article.

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Despite inherent geographic differences, all registry studies documenting the effect of SARS-CoV-2 in patients with cancer have consistently reported case-fatality rates (CFRs) from COVID-19 ranging from 13% to 41%.[1-7] However, these data are deeply influenced by the lack of preparedness toward an unprecedented and rapidly expanding health care threat alongside inadequate testing and reduced hospital capacity.

The past year has seen unprecedented improvements in the understanding of SARS-CoV-2 biology and clinical management of COVID-19. Compared with the early phases of the pandemic, several COVID-19–directed therapies shown to improve outcomes[8-14] are now routinely used, whereas off-label treatments lacking evidence of efficacy have progressively fallen into disuse.[15,16] In addition, SARS-CoV-2 testing capacity has increased over time, and strict infection control policies are in place to reduce nosocomial and community transmission.[17-19]

As a result of this rapidly evolving landscape, the initial evidence surrounding the effect of COVID-19 on patients with cancer has become outdated, leaving a need to understand whether the adapting response of health care systems and the improved medical management of COVID-19 have exerted a positive effect on mortality of patients with cancer.

Key Points

Question Has COVID-19 mortality in patients with cancer improved during the course of the pandemic in Europe?

Findings In this registry-based study of 2634 patients in 6 European countries with COVID-19 and cancer, there was significant time-dependent improvement in the risk of death at 14 days and at 3 months.

Meaning Mortality from COVID-19 has improved; this improvement may be associated with earlier diagnosis and improved disease management.

Methods

The OnCovid Registry[20] has collected consecutive patients fulfilling the following inclusion criteria: (1) age 18 years or older, (2) diagnosis of SARS-CoV-2 infection confirmed by reverse transcription–polymerase chain reaction of a nasopharyngeal swab,[21] and (3) history of solid or hematologic cancer at any time during the patient's past medical history, either active or in remission at the time of COVID-19 diagnosis.

OnCovid was granted central approval by the UK Health Research Authority and by the corresponding research ethics committees at each participating institution; informed consent was waived because of the anonymized nature of the patient data and retrospective design of the study. Patients could be entered in the registry by investigators at any time of their history after COVID-19 diagnosis, with further periodic updates as necessary. The data lock for the present analysis was March 1, 2021, and included patients diagnosed with COVID-19 between February 27, 2020, and February 14, 2021, from 35 institutions across 6 countries (UK, Italy, Spain, France, Belgium, and Germany). A list of participating centers is provided in eTable 1 in the Supplement. Information on patient race and ethnicity was collected and included Asian, Black, White, mixed race, and other race, but the distribution revealed a majority White population. Therefore, we did not include this information in the analyses; it did not have any relevance in our investigation.

Oncologic and disease-specific variables were collected at baseline, defined at the moment of diagnosis of SARS-CoV-2 by polymerase chain reaction testing. Characteristics of severity, complications, and therapy against COVID-19 were collected throughout the observation period until full clinical resolution of COVID-19 or the patient's death, irrespective of setting (home, hospital, intensive care unit); resuscitation status information was not available.

Acknowledging the competing influence of underlying cancer in determining mortality in patients with cancer, we elected all-cause CFR as the major clinical end point of interest. Additionally, considering the extended follow-up times now available for OnCovid study participants and with the intent to characterize early (likely COVID-19–related) from later (likely cancer-related) mortality, we differentiated the risk of death at 14 days and 3 months as the 2 landmark end points for survival analysis.

We hypothesized that the severity of and mortality from COVID-19 varied during the course of the pandemic. We then analyzed tumor and COVID-19 characteristics associated with mortality[1-4,6] and evaluated them by clustering patients into 5 groups, depending on the period of SARS-CoV-2 infection diagnosis: (1) February to March 2020, (2) April to June 2020, (3) July to September 2020, (4) October to December 2020, and (5) January to February 2021. Variables of interest included have already been described elsewhere.[6,22,23] To ascertain whether SARS-CoV-2 testing capacity might be associated with an improvement in outcomes, we presented time-dependent changes in the median ratio between confirmed cases and number of SARS-CoV-2 tests performed. The daily ratio between confirmed cases and number of SARS-CoV-2 tests performed across the UK, Italy, Spain, Belgium, and Germany from February 24, 2020, to February 28, 2021, was retrieved from the Our World in Data website, a freely and publicly available open source.[17,24] Information about daily ratios in France was not available.

To provide a more detailed estimate of the risk of death at 14 days and 3 months, we then grouped patients in 2 major outbreaks (February to June 2020 and July 2020 to February 2021) following the bimodal spread of SARS-CoV-2 in European countries across 2020 and 2021.

We did not account for immunization campaigns, which by the data lock (February 2021) were still limited, and less than 2% of patients had received a full course of SARS-CoV-2 vaccination after the previous infection. A detailed description of study methodology and statistical analysis is provided in the eMethods in the Supplement. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Statistical Analysis

Baseline characteristics were summarized as categorical variables and reported using descriptive statistics. We tested

associations between categorical variables using Pearson χ^2 test and the Kruskal-Wallis test to compare the median times from symptoms to SARS-CoV-2 infection diagnosis. We reported overall survival and all-cause mortality at 14 days and 3 months according to the Kaplan-Meier method. Survival intervals were computed from COVID-19 diagnosis to death or last follow-up. We used univariable and multivariable Cox proportional-hazards models to investigate the associations and evaluate the differential outcome of the time of diagnosis (first vs second outbreak) on the 14 days and 3 months risk of death. Results of Cox regression analysis were presented as hazard ratios (HRs) and 95% CIs. A 2-sided *P* value <.05 was considered statistically significant. Analyses were performed using the MedCalc software, version 20 (MedCalc Software Ltd), STATA software, version 14 (StataCorp), and SPSS, version 25 (IBM Inc). More detailed information on the analyses performed can be found in the eMethods in the Supplement.

Results

Time-Dependent Changes in Clinical, Oncologic, and SARS-CoV-2 Infection Features in the Evolving Phases of the Pandemic

At the time of database lock, the registry included 2795 patients (median [IQR] age, 68 [18-77] years; 52.8% men). Patient race included 7.9% Asian, 3.6% Black, 77.9% White, 1.3% mixed, and 9.4% other race or ethnicity. A total of 161 patients were excluded owing to unconfirmed date of COVID-19 diagnosis, and the final study population consisted of 2634 patients; a further 211 patients were excluded from survival analysis owing to missing outcome data (eFigure 1 in the Supplement). Patient distribution across participating centers is provided in eTable 1 in the Supplement.

In total, 906 patients (34.4%) were diagnosed between February and March 2020, 720 (27.3%) between April and June 2020, 90 (3.4%) between July and September 2020, 696 (26.4%) between October and December 2020, and 222 (8.4%) between January 2021 and February 2021.

eTable 2 in the Supplement gives the detailed distribution of patients and disease characteristics across the subgroups. From the early phases of the pandemic, we described significantly increasing proportions of patients younger than 65 years (1083 of 2634 [41.3%]; *P* = .02), with lower comorbid burden (1414 of 2634 [53.7%]; *P* = .01) but with advanced tumor stage (1244 of 2634 [46.0%]; *P* < .001). Receipt of anticancer therapy within 4 weeks of COVID-19 diagnosis was also significantly different across the phases (1305 of 2634 [51.8%]; *P* = .01), as was the distribution of primary tumor site (breast, 493 of 2634 [18.9%]; gastrointestinal, 476 [18.2%]; gynecologic/genitourinary, 530 [20.3%], hematologic, 357 [13.7%]; *P* = .01). No variation in sex, smoking history, and tumor status was found.

Changes in Management and Improving Fatality From COVID-19 in Patients With Cancer

Rates of complicated COVID-19 were significantly reduced across the 5 phases (phase 1, 465 of 906 [51.3%] to phase 5, 86 of 222 [38.7%]; *P* < .001), a finding mirrored by a concordant reduction in the prescription of COVID-19–specific treatments (phase 1, 598 of 906 [66.0%] to phase 5, 110 of 222 [49.5%]; *P* < .001), with corticosteroid therapy significantly increasing over time (phase 1, 79 of 906 [8.7%] to phase 5, 79 of 222 [35.6%]; *P* < .001). We observed a significant reduction in patients requiring hospitalization due to COVID-19 (phase 1, 583 of 906 [64.7%] to phase 5, 94 of 222 [42.7%]; *P* < .01) with a slight increase in the proportion of patients who acquired COVID-19 during a preexisting hospitalization (phase 1, 202 of 906 [22.4%] to phase 5, 73 of 222 [33.2%]; *P* < .001). The proportion of patients who required oxygen therapy (phase 1, 532 of 906 [62.6%] to phase 5, 99 of 222 [46.0%]; *P* < .001) and mechanical ventilation (phase 1, 99 of 906 [12.1%] to phase 5, 25 of 222 [11.8%]; *P* = .01) significantly decreased over time, whereas admission to intensive care showed stability from phase 1 (123 of 906 [16.0%]) to phase 5 (27 of 222 [16.9%]), although with a significant variation (*P* = .01) (eTable 2 in the Supplement).

Analysis of CFRs at 14 days demonstrated a significant time-dependent improvement throughout the 5 predefined time periods, reducing from 29.8% (258 of 867 events; 95% CI, 0.26-0.33) for February to March 2020 to 20.3% (141 of 694 events; 95% CI, 0.17-0.23) for April to June 2020, 12.5% (10 of 80 events; 95% CI, 0.06-22.90) for July to September 2020, 17.2% (104 of 603 events; 95% CI, 0.15-0.21) for October to December 2020, and 14.5% (26 of 179 events; 95% CI, 0.09-0.21; *P* < .001) for January to February 2021. The median time from symptom onset to COVID-19 diagnosis significantly improved over time, ranging from 4 days (April to June 2020) to 1 day (October to December 2020) (*P* < .001).

Using publicly available data, we found an increase in the number of SARS-CoV-2 tests performed over time, leading to the ratio between confirmed cases and number of SARS-CoV-2 tests performed in the UK, Italy, Spain, Belgium, and Germany to follow a similar trend toward improvement across the 5 phases from 9.2% to 21.8%.

eFigure 2 in the Supplement shows the paired 14-day CFRs, with the proportion of complicated COVID-19 cases presented alongside the median time from symptoms to COVID-19 diagnosis, and the median ratio between confirmed cases per number of SARS-CoV-2 tests performed across the 5 time intervals. A country-level breakdown is reported in eFigure 3 in the Supplement.

After adjusting for country, sex, age, comorbidities, primary tumor, tumor stage and status, receipt of anticancer therapy within 4 weeks of COVID-19 diagnosis, COVID-19 complications, and COVID-19–specific therapy and hospitalization, we reported a significant, progressive, time-dependent reduction of the risk of death at 14 days (HR, 0.79; 95% CI, 0.74-0.86). When compared with phase 1, patients diagnosed in later phases also experienced a concordantly reduced risk of death (eTable 3 in the Supplement).

Evaluation of Short- and Medium-term Outcomes in Patients Diagnosed With Cancer and COVID-19 in the Early vs Later Stages of the Pandemic

Collectively, 1626 of 2634 patients (61.7%) were diagnosed with COVID-19 from February to June 2020, whereas another 1008

Table 1. Distribution of Baseline Characteristics of Patients, Tumor Stage, and COVID-19 Variables by Major Outbreak Grouping

Characteristic	Outbreak, No. (%)		*P* value[c]
	1st (n = 1626)[a]	2nd (n = 1008)[b]	
Country			
United Kingdom	552 (33.9)	393 (39.0)	<.001
Spain	464 (28.5)	175 (17.4)	
Italy	418 (25.7)	396 (39.3)	
Germany, Belgium, and France	192 (11.8)	44 (4.4)	
Sex			
Male	849 (52.3)	541 (53.7)	.51
Female	773 (47.7)	467 (46.3)	
Missing[d]	4	0	
Age, y			
<65	641 (39.7)	442 (43.9)	.03
≥65	974 (60.3)	564 (56.1)	
Missing[d]	11	2	
Comorbidities			
0-1	833 (51.2)	581 (57.6)	.001
≥2	793 (48.8)	427 (42.4)	
Tumor stage			
Local/locoregional	817 (53.6)	420 (43.9)	<.001
Advanced	708 (46.4)	536 (56.1)	
Missing[d]	101	52	
Tumor status			
Remission/nonmeasurable disease	521 (32.8)	339 (34.1)	.47
Active cancer	1069 (67.2)	654 (65.9)	
Missing	36	15	
Anticancer therapy			
No	775 (48.7)	438 (47.2)	.48
Yes	816 (51.3)	489 (52.8)	
Missing[d]	35	81	
COVID-19 complications			
No	888 (54.6)	666 (66.1)	<.001
Yes	738 (45.4)	342 (33.9)	
COVID-19 therapy			
No	622 (38.3)	507 (50.3)	<.001
Yes	1004 (61.7)	501 (49.7)	
Hospitalization			
Not required	290 (17.9)	303 (30.5)	<.001
Required	969 (59.8)	418 (42.1)	
Preexisting	361 (22.3)	272 (27.4)	
Missing[d]	6	15	

[a] The first outbreak occurred from February to June 2020.

[b] The second outbreak occurred from July 2020 to February 2021.

[c] Values obtained via χ^2 test for the comparison across the 2 major outbreaks; missing data were excluded from the proportions' estimation. Primary tumor information according to the 2 major outbreaks is available in eTable 5 in the Supplement.

[d] Proportions have been computed after the exclusion of missing data from the denominator.

of 2634 patients (38.3%) were diagnosed between July 2020 and February 2021. **Table 1** reports the distribution of clinical, tumor, and COVID-19–related characteristics divided according to the 2 major outbreaks in Europe.

Patients in the first outbreak were more likely to be 65 years or older (974 of 1626 [60.3%] vs 564 of 1008 [56.1%]; *P* = .03), have at least 2 comorbidities (793 of 1626 [48.8%] vs 427 of 1008]; *P* = .001), and have advanced tumors (708 of 1626 [46.4%] vs 536 of 1008 [56.1%]; *P* < .001) compared with those diagnosed in the second phase. Similarly, patients diagnosed in the first outbreak were more likely to experience complications of COVID-19 (738 of 1626 [45.4%] vs 342 of 1008 [33.9%]; *P* < .001) and require hospitalization (969 of 1626 [59.8%] vs 418 of 1008 [42.1%]; *P* < .001) and COVID-19–specific therapy (1004 of 1626 [61.7%] vs 501 of 1008 [49.7%]; *P* < .001). A significant variation in the distribution of primary tumors was also reported across the 2 major outbreaks (breast, 333 of 1626 [20.5%] vs 160 of 987 [16.2%]; gastrointestinal, 299 of 1626 [18.4%] vs 177 of 987 [17.9%]; gynecologic/genitourinary, 329 of 1626 [20.2%] vs 201 of 987 [20.4%]; hematologic, 227 of 1626 [14.0%] vs 130 of 987 [13.2%]; thoracic, 210 of 1626 [12.9%] vs 165 of 987 [16.7%]; other, 228 of 1626

Table 2. Fixed Multivariable Analyses for the Risk of Death at 14 Days and 3 Months According to the Two Major Outbreaks Grouping[a]

Variable	Multivariable, HR (95% CI)	
	14 d	3 mo
Outbreak		
2nd (July 2020 to February 2021)	1 [Reference]	1 [Reference]
1st (February to June 2020)	1.85 (1.47-2.32)	1.28 (1.08-1.51)
Country		
United Kingdom	1 [Reference]	1 [Reference]
Spain	0.55 (0.43-0.71)	0.57 (0.47-0.69)
Germany, Belgium, and France	0.60 (0.40-0.89)	0.64 (0.48-0.86)
Italy	1.02 (0.81-1.29)	0.89 (0.73-1.08)
Sex		
Male	1 [Reference]	1 [Reference]
Female	0.91 (0.74-1.12)	0.92 (0.78-1.09)
Age, y		
<65	1 [Reference]	1 [Reference]
≥65	1.67 (1.33-2.11)	1.58 (1.33-1.89)
Comorbidities		
0-1	1 [Reference]	1 [Reference]
≥2	1.24 (1.01-1.51)	1.25 (1.06-1.46)
Primary tumor		
Breast	1 [Reference]	1 [Reference]
Gastrointestinal	1.04 (0.72-1.51)	1.21 (0.90-1.63)
Gynecologic/genitourinary	0.79 (0.54-1.15)	0.94 (0.71-1.27)
Hematologic	0.91 (0.61-1.37)	0.98 (0.71-1.36)
Thoracic	1.15 (0.79-1.67)	1.29 (0.95-1.75)
Other	1.14 (0.76-1.71)	1.30 (0.94-1.79)
Tumor stage		
Local/locoregional	1 [Reference]	1 [Reference]
Advanced	1.38 (1.09-1.75)	1.64 (1.36-1.99)
Tumor status		
Remission/nonmeasurable disease	1 [Reference]	1 [Reference]
Active cancer	1.62 (1.23-2.13)	1.56 (1.25-1.95)
Anticancer therapy		
No	1 [Reference]	1 [Reference]
Yes	1.21 (0.99-1.47)	1.33 (1.13-1.56)
COVID-19 complications		
0	1 [Reference]	1 [Reference]
≥1	5.51 (4.27-7.11)	3.79 (3.19-4.51)
COVID-19 therapy		
No	1 [Reference]	1 [Reference]
Yes	0.99 (0.81-1.19)	1.07 (0.92-1.25)
Hospitalization		
Not required	1 [Reference]	1 [Reference]
Required	4.44 (2.30-8.57)	4.25 (2.76-6.54)
Preexisting	4.63 (2.37-9.02)	5.01 (3.23-7.74)

Abbreviation: HR, hazard ratio.

[a] A total of 2154 patients were included; hazard ratios for each covariate describe independent associations with mortality in a model designed to assess the causal association between outbreaks and mortality. Univariable analysis information according to the 14-day and 3-month risk of death is available in eTable 6 in the Supplement.

[14.0%] vs 154 of 987 [15.6%]; $P = .02$). The 14-day CFRs for the first and second outbreaks were 25.6% (399 of 1561 events; 95% CI, 0.23-0.28) and 16.2% (140 of 862 events; 95% CI, 0.13-0.19) ($P < .001$), respectively, whereas the 3-month CFRs were 37.5% (585 of 1561 events; 95% CI, 34.5-40.6) and 32.1% (276 of 862 events; 95% CI, 28.3-36.0) ($P = .01$), respectively.

With a median follow-up of 2.9 months (IQR, 1.4-8.4 months), the median overall survival for the whole study population was 9.7 months (95% CI, 7.3-10.4 months; 950 events) (eFigure 4A in the Supplement). The median follow-up period for the first and second outbreaks was 5.8 months (IQR, 1.6-10.1 months) and 2.0 months (IQR, 1.2-2.9 months), respectively, whereas the median overall survival was 8.3 months (95% CI, 6.2-10.4 months; 670 events) and not reached (280 events), respectively (eFigure 4B in the Supplement). Univariable analysis revealed patients diagnosed with COVID-19 during the first outbreak have an increased risk of death at 14 days (HR, 1.69; 95% CI, 1.40-2.06; $P < .001$) (eFigure 5A in the Supplement) and 3 months after SARS-CoV-2 infection (HR, 1.20; 95% CI, 1.04-1.39; $P = .01$) (eFigure 5B in the Supplement).

After adjusting for country, sex, age, comorbidities, primary tumor, tumor stage and status, receipt of anticancer therapy within 4 weeks of COVID-19 diagnosis, COVID-19 complications, and COVID-19–specific therapy and hospitalization, patients diagnosed with COVID-19 during the first outbreak had a significantly higher risk of death at 14 days (HR, 1.85; 95% CI, 1.47-2.32) and 3 months (HR, 1.28; 95% CI, 1.08-1.51) than patients diagnosed during the second outbreak (**Table 2**). The restricted mean survival time analysis reported in eTable 4 in the Supplement supports the findings from the Cox regression model with a significant difference in mean survival at 14 days and 3 months for patients diagnosed with COVID-19 between the 2 major outbreaks.

An ancillary analysis providing a comparison of the 14-day CFRs between patients diagnosed in the 2 major outbreaks according to primary tumor site is summarized in eFigure 6 in the Supplement, with a consistent decrease in mortality reported across tumor types.

An improved risk of death at 14 days was observed across the 5 phases and between the second and the first major outbreaks when categorizing patients in those with nonmeasurable disease or in remission (HR, 0.81; 95% CI, 0.71-0.93 and HR, 0.60; 95% CI, 0.40-0.88, respectively; 818 patients included) and those with active cancer (HR, 0.79; 95% CI, 0.74-0.86 and HR, 0.58; 95% CI, 0.46-0.72, respectively; 1605 patients included) separately.

Discussion

Whether improvements in the diagnosis and treatment of COVID-19 and infection control policies adopted since March 2020 have changed the outlook for patients with cancer and COVID-19 has been an ongoing question. Capitalizing on the resources of the OnCovid study, in this case series, we found a significant, time-dependent improvement in the mortality and severity of COVID-19.

Patients diagnosed at the peak of the first COVID-19 outbreak were characterized by a 30% unadjusted CFR at 14 days, a figure that mirrors widely published data across COVID and

cancer registries.[2,4-7,22,25] We documented a downward trend in mortality reaching a nadir of 12.5% in July to September 2020, when community transmission of SARS-CoV-2 was at its lowest in Europe, with estimates of mortality remaining below 20% in the subsequent time periods. This downward trend was observed across tumor sites and countries, a point of greater consequence given the tumor-specific and geographic heterogeneity in outcomes from COVID-19.

Despite a slight increase in overall and complicated COVID-19 cases reported from late 2020, as a consequence of the pan-European COVID-19 surge likely related to the new emerging variants (eg, the B.1.1.7 lineage),[26,27] CFRs at 14 days and case-test ratios did not increase meaningfully, a finding that suggests enhanced capacity of health care systems.

The progressive reduction in acute, COVID-19–related mortality over time is likely multifactorial. In the first outbreak, we saw a higher proportion of older patients and patients with more comorbidities, characterized by a greater than 50% rate of complicated COVID-19 leading to high mortality—figures that strongly resonate with data published from other registries.[2,5] In interpreting these results, we should remember that SARS-CoV-2 testing was restricted to hospitalized patients in the first trimester of 2020.[17] Although it is reasonable to presume that early diffusion of SARS-CoV-2 in Europe proved most lethal to higher-risk patients in the first outbreak, our data suggest an inversely proportional relationship between testing capacity and adverse outcomes. The diminishing fatality and complicated disease rates in the context of increasing case and test ratios suggest that early reports on SARS-CoV-2 and cancer might have been skewed toward more severely ill patients and have overestimated fatality from infection as a result of underreporting of uncomplicated cases. With the diffusion of routine testing in mid-2020,[17] to include patients visiting the hospital and receiving active treatment, it has become possible to demonstrate that uncomplicated disease not warranting hospital admission increased from 12.9% in February to March 2020 to 33.4% in October to December 2020.

We found a reduction in median interval from symptomatic presentation to molecular diagnosis of SARS-CoV-2 with time; this reduction was likely associated with greater testing availability and introduction of asymptomatic screening adopted by many participating institutions[28] as a measure to contain SARS-CoV-2 spread.[29-33] In our study, the association between case and test ratios and improved outcomes from COVID-19 support the role of the enhanced testing capacity as a measure to minimize the impact of COVID-19 in patients with cancer, although it could be at the same time a proxy of reduced community transmission.

Another important finding from our study is the documentation of significant changes in the prescribing of anti-COVID-19 therapeutics, following discussions about their use in patients with cancer[6,34] and the evolving evidence about COVID-19–specific therapy overall.[35] The early phases of the pandemic were in fact dominated by off-label prescribing of drugs in the absence of clear evidence of benefit and the simultaneous withholding of therapies such as corticosteroids that would eventually be found to change the natural history of severe COVID-19.[11,13] Our data suggest that changes in COVID-19 management were associated with the dissemination of level-I evidence, with a complete disappearance in the use of antimalarials and a more judicious use of empirical antibiotics, antivirals, and tocilizumab, mirrored by an increase in the use of systemic corticosteroid therapy for the treatment of severe COVID-19. These trends are important in explaining the difference in mortality and suggest that active management of COVID-19 should be pursued in patients with cancer.[36]

Last, in addition to a reduction of hospitalization due to COVID-19, we also reported an increasing trend of preexisting hospitalization at the moment of SARS-CoV-2 infection diagnosis. Although this trend is likely associated with the increase of in-hospital screening campaigns, it may account at least partially for hospital-acquired transmissions. These are informative findings to guide future policies, which support the maintenance of safety measures (social distancing rules, mandatory masks, etc) in hospitals, all while several countries in Europe have undergone progressive easing of social restrictions.

Limitations

This study had several limitations. Observations from OnCovid cannot substitute evidence from large-scale population-based studies, a more ideal setting to evaluate the association between government policies and mortality across geographic regions as well as to measure the success of improved therapies and vaccination campaigns. Country-level changes in the incidence of COVID-19 during the pandemic might have affected data reporting and clinical outcomes, with a trend toward improvement during low incidence phases. In addition, our ability to capture the beneficial outcomes from ongoing immunization efforts was largely limited. Last, we were not able to produce evidence concerning the differential role of emerging SARS-CoV-2 variants, such as the B.1.1.7 and B.1.617 lineages, and the retrospective design and the lack of centralized data review exposed us to several selection biases.

Conclusions

Improved testing capacity, clinical management, and outcomes of health care policies and guidelines are difficult, if not impossible, to directly measure in a multinational registry study. Despite the acknowledged limitations, this case series provides an important contemporary portrait of the evolving outcomes of COVID-19 in patients with cancer, highlighting the importance of widespread SARS-CoV-2 testing as a strategy to facilitate early diagnosis of COVID-19 and maintain the appropriate therapeutic pathway for patients with cancer despite the ongoing threat of an unresolved global pandemic.

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