original reports

Pandemic Phase-Adjusted Analysis of COVID-19 Outcomes Reveals Reduced Intrinsic Vulnerability and Substantial Vaccine Protection From Severe Acute Respiratory Syndrome Coronavirus 2 in Patients With Breast Cancer

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abstract

PURPOSE Although representing the majority of newly diagnosed cancers, patients with breast cancer appear less vulnerable to COVID-19 mortality compared with other malignancies. In the absence of patients on active cancer therapy included in vaccination trials, a contemporary real-world evaluation of outcomes during the various pandemic phases, as well as of the impact of vaccination, is needed to better inform clinical practice.

METHODS We compared COVID-19 morbidity and mortality among patients with breast cancer across prevaccination (February 27, 2020-November 30, 2020), Alpha-Delta (December 1, 2020-December 14, 2021), and Omicron (December 15, 2021-January 31, 2022) phases using OnCovid registry participants (ClinicalTrials.gov identifier: NCT04393974). Twenty-eight-day case fatality rate (CFR_{28}) and COVID-19 severity were compared in unvaccinated versus double-dosed/boosted patients (vaccinated) with inverse probability of treatment weighting models adjusted for country of origin, age, number of comorbidities, tumor stage, and receipt of systemic anticancer therapy within 1 month of COVID-19 diagnosis.

RESULTS By the data lock of February 4, 2022, the registry counted 613 eligible patients with breast cancer: 60.1% (n = 312) hormone receptor–positive, 25.2% (n = 131) human epidermal growth factor receptor 2–positive, and 14.6% (n = 76) triple-negative. The majority (61%; n = 374) had localized/locally advanced disease. Median age was 62 years (interquartile range, 51-74 years). A total of 193 patients (31.5%) presented ≥ 2 comorbidities and 69% (n = 330) were never smokers. In total, 392 (63.9%), 164 (26.8%), and 57 (9.3%) were diagnosed during the prevaccination, Alpha-Delta, and Omicron phases, respectively. Analysis of CFR_{28} demonstrates comparable estimates of mortality across the three pandemic phases (13.9%, 12.2%, 5.3%, respectively; $P = .182$). Nevertheless, a significant improvement in outcome measures of COVID-19 severity across the three pandemic time periods was observed. Importantly, when reported separately, unvaccinated patients from the Alpha-Delta and Omicron phases achieved comparable outcomes to those from the prevaccination phase. Of 566 patients eligible for the vaccination analysis, 72 (12.7%) were fully vaccinated and 494 (87.3%) were unvaccinated. We confirmed with inverse probability of treatment weighting multivariable analysis and following a clustered robust correction for participating center that vaccinated patients achieved improved CFR_{28} (odds ratio [OR], 0.19; 95% CI, 0.09 to 0.40), hospitalization (OR, 0.28; 95% CI, 0.11 to 0.69), COVID-19 complications (OR, 0.16; 95% CI, 0.06 to 0.45), and reduced requirement of COVID-19–specific therapy (OR, 0.24; 95% CI, 0.09 to 0.63) and oxygen therapy (OR, 0.24; 95% CI, 0.09 to 0.67) compared with unvaccinated controls.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

In this comprehensive phase-adjusted analysis of the OnCovid registry (ClinicalTrials.gov identifier: NCT04393974), we sought to provide a contemporary portrait of the impact of COVID-19 in patients with breast cancer.

Knowledge Generated

We reported a consistent reduction in all surrogates of COVID-19 severity during the Omicron outbreak in Europe in comparison with prior phases of the pandemic in patients with breast cancer, including hospitalizations due to COVID-19, COVID-19 complications, and oxygen therapy requirement. However, we did not confirm a time-dependent decrease in COVID-19 mortality. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, including booster doses, was independently associated with improved outcomes. Unvaccinated patients from the Omicron phase experience similar outcomes to those from prevaccination phase, suggesting that a complete SARS-CoV-2 vaccination course is the strongest determinant of improved morbidity and mortality during the evolving phases of the pandemic.

Relevance

Patients with breast cancer should be encouraged to receive SARS-CoV-2 vaccination to reduce the risk of severe illness, hospitalization, and death.

CONCLUSION Our findings highlight a consistent reduction of COVID-19 severity in patients with breast cancer during the Omicron outbreak in Europe. We also demonstrate that even in this population, a complete severe acute respiratory syndrome coronavirus 2 vaccination course is a strong determinant of improved morbidity and mortality from COVID-19.

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INTRODUCTION

Registry studies on COVID-19 and cancer have provided important evidence in support of stratification strategies according to the risk of morbidity and mortality from COVID-19 by cancer type.[1-7] Primary tumor type influences lethality of infection and host capacity to elicit natural and vaccinal immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3,8-10] Overall, breast cancer accounts for the largest proportion of new oncologic diagnoses as well as patients on active treatment and surveillance for malignancy.[11] This specific population experiences lower complications rates and mortality from COVID-19 compared with other cancer types. Similarly, the putative detrimental effect of recent exposure to active anticancer therapy before the infection appears to be attenuated in this patient population.[12]

Outcomes from COVID-19 in patients with cancer have also considerably evolved over time. Enhanced health care system capacity and improved management of COVID-19,[13] widespread immunization campaigns,[14] shifting changes in community transmission, and the emergence of new SARS-CoV-2 variants[15] have dramatically changed the clinical impact of SARS-CoV-2 infection since declaration of the pandemic in March 2020.

In the absence of patients on active cancer therapy included in vaccination trials, a contemporary, real-world evaluation of outcomes during the various pandemic phases, as well as of the impact of vaccination, is needed to better inform clinical practice. With the aim of defining the overall improvement in COVID-19 outcomes over time as well as vaccine effectiveness in patients with breast cancer, we sought to provide a contemporary portrait of the impact of COVID-19 in this population, to inform as carefully as possible clinical practice and outcomes during the progressive resumption of normal oncologic continuity of care.

METHODS

This is a breast cancer specific subanalysis of the OnCovid registry (ClinicalTrials.gov identifier: NCT04393974) focusing on patients with invasive breast cancer. A full description of inclusion criteria and methodology of data collection is available in the Data Supplement (online only).

This analysis of outcomes from COVID-19 in patients with breast cancer recognizes the following aims: (1) to demonstrate time-dependent changes in the estimates of morbidity and mortality from COVID-19; (2) to describe COVID-19 outcomes according to SARS-CoV-2 vaccination status; and (3) to evaluate COVID-19 outcomes in relationship to recent exposure to different systemic anticancer therapy (SACT) regimens within the four weeks preceding the COVID-19 diagnosis.

By the previous data lock of February 4, 2022, the registry included 3,820 patients diagnosed with COVID-19 between February 27, 2020, and January 31, 2022. We subsequently launched a follow-up update of previously entered patients with a new data-lock of June 30, 2022, to reach the minimum observation period in all subgroups. To ensure consecutive accrual and comparability of outcomes, we

excluded data from centers that did not actively enter new information from the March 2021 and February 2022 data locks.

We elected the all-cause 28-day case fatality rate (CFR_{28}) as the major clinical end point of interest, to document COVID-19–related mortality.[13] As measures of COVID-19 severity, we included rates of hospitalization and intensive care unit admission, rate of complications from COVID-19, requirement for supplemental oxygen therapy, and receipt of COVID-19–specific therapy as previously described.[1-5]

Patients were grouped by date of COVID-19 diagnosis into prevaccination phase (from February 27, 2020, to November 30, 2020), Alpha-Delta phase (from December 1, 2020, to December 14, 2021),[16] and Omicron phase (from December 15, 2021, to January 31, 2022)[17] to describe time-dependent changes in clinical characteristics and outcomes.

To provide additional insight on the role of SARS-CoV-2 vaccination on the evolution of the pandemic, we described COVID-19 morbidity and mortality among unvaccinated (including partially vaccinated patients who were incompletely immunized before COVID-19, given the limited sample size of subgroups) and vaccinated patients across the predefined time phases after the exclusion of patients with unknown vaccination status.

Subsequently, we categorized patients according to SARS-CoV-2 vaccination status as unvaccinated, partially vaccinated, double-dosed, and boosted. After the exclusion of patients who received a partial vaccination course before COVID-19, COVID-19 outcomes were evaluated with univariable and multivariable comparison following inverse probability of treatment weighting (IPTW) between fully vaccinated patients (ie, double dosed or boosted) and unvaccinated patients. We additionally performed exploratory comparative analyses of the CFR_{28} between boosted and partially/unvaccinated patients, and double-dose and partially/unvaccinated patients.

Receipt of SACT at COVID-19 was defined as the receipt of treatment within 4 weeks before SARS-CoV-2 infection as per appendix. SACT regimens were categorized as chemotherapy (either alone or in combination with other agents), endocrine therapy (excluding any combination therapy), anti–human epidermal growth factor receptor 2 (HER2)–targeted therapy (excluding combinations with chemotherapy), cyclin-dependent kinase (CDK) inhibitor–based regimens, and others. A detailed description of vaccination categories and statistical methodology is reported in the Data Supplement.

OnCovid was granted central approval by the UK Health Research Authority (20/HRA/1608) and by the corresponding research ethics committees at each participating center. Informed consent was waived by competent authorities because of the anonymized nature of patient data and retrospective design of the study.

RESULTS

Improved Morbidity From COVID-19 Across the Evolving Phases of the Pandemic Is Driven by Prior SARS-CoV-2 Vaccination

Out of a total of 3,820 patients, the registry included 613 eligible patients with breast cancer, of whom 14 (2.3%) were male (Data Supplement). Distribution of patients across participating centers is provided in the Data Supplement.

The median age at COVID-19 diagnosis was 62 years (interquartile range, 51-74 years). A total of 193 patients (31.5%) presented ≥ 2 comorbidities and 69% (n = 330) were never smokers. Regarding tumor characteristics, 61% (n = 374) had localized/locally advanced disease, whereas in 56.9% (n = 346) breast cancer was nonmeasurable/in remission. Hormone receptor only positive disease was the most common breast cancer subtype, accounting for 60.1% of cases (n = 312), while 25.2% of cases (n = 131) had HER2-positive disease and 14.6% (n = 76) triple-negative tumors. Among patients with advanced-stage disease, 21.8% (n = 52) had bone-only metastases. Table 1 provides a complete description of patient characteristics.

In total, 392 patients (63.9%) were diagnosed with SARS-CoV-2 infection during the prevaccination phase, while 164 (26.8%) and 57 (9.3%) during the Alpha-Delta and Omicron phases, respectively. There was an increased proportion of patients with HER2-positive disease across the subgroups (from 81 of 340 [23.8%] in prevaccination phase to 19 of 53 [35.8%] in the Omicron phase), and a reduction of those with triple-negative tumors (from 60 of 340 [17.6%] in the prevaccination phase to five of 53 [9.4%] in the Omicron phase; $P = .039$). As expected, SARS-CoV-2 vaccination was restricted to patients diagnosed during the Alpha-Delta and Omicron phases ($P < .0001$). No other differences in patient, disease, or treatment characteristics were observed.

The median observation period for the entire population was 265 days (95% CI, 203 to 305), with a median follow-up for patients in the prevaccination, Alpha-Delta, and Omicron groups of 335 (95% CI, 270 to 382), 279 (95% CI, 205 to 323), and 149 (95% CI, 36 to 165) days, respectively.

Analysis of CFR_{28} demonstrates comparable estimates of mortality across the three pandemic phases. A total of 54 events of 388 patients (13.9%; 95% CI, 10.8 to 17.7) were registered in the prevaccination phase, 20 of 164 patients (12.2%; 95% CI, 8.0 to 18.1) in the Alpha-Delta period, and three of 57 patients (5.3%; 95% CI, 1.1 to 15.4) during the Omicron phase ($P = .182$). Nevertheless, a significant improvement, mostly driven by patients from the Omicron phase, in measures of COVID-19 severity across the three subgroups was observed, consisting in reduced rates of COVID-19 complications, hospitalization due to COVID-19, receipt of COVID-19–specific therapy, and oxygen therapy (Fig 1).

TABLE 1. Patient Characteristics of the Overall Population and According to the Pandemic Phase

Characteristic	Overall Population (N = 613), No. (%)	Prevaccination (n = 392), No. (%)	Alpha-Delta (n = 164), No. (%)	Omicron (n = 57), No. (%)	*P*
Country					
United Kingdom	179 (29.0)	92 (23.5)	77 (47.0)	9 (15.8)	< .0001
Spain	206 (33.6)	148 (37.8)	36 (22.0)	22 (38.6)	
Italy	229 (37.4)	152 (38.8)	51 (31.1)	26 (45.6)	
Sex					
Female	599 (97.7)	382 (97.4)	160 (97.6)	57 (100.0)	.4782
Male	14 (2.3)	10 (2.6)	4 (2.4)	—	
Age, years					
< 60	281 (46.3)	176 (45.2)	72 (44.4)	33 (58.9)	.1360
≥ 60	326 (53.7)	213 (54.8)	90 (55.6)	23 (41.1)	
Missing	6	3	2	1	
Comorbidities					
0-1	420 (68.5)	271 (69.1)	109 (66.5)	40 (70.2)	.7937
≥ 2	193 (31.5)	121 (30.9)	55 (33.5)	17 (29.8)	
Hypertension	200 (32.6)	136 (34.7)	49 (29.9)	15 (26.3)	.3075
Cardiovascular comorbidities	73 (11.9)	48 (12.2)	22 (13.4)	3 (5.3)	.2470
COPD/others	64 (10.4)	38 (9.7)	21 (12.8)	5 (8.8)	.5006
Diabetes	89 (14.5)	52 (13.3)	25 (15.2)	12 (21.1)	.2827
Obesity	29 (4.7)	14 (3.6)	12 (7.3)	3 (5.3)	.1621
Smoking history					
Never smokers	330 (69.0)	218 (70.8)	85 (64.9)	27 (69.2)	.4737
Former/current smokers	148 (31.0)	90 (29.2)	46 (35.1)	12 (30.8)	
Missing	135	84	33	18	
HR status (either ER or PgR)					
Negative	114 (20.7)	84 (23.4)	21 (15.0)	9 (17.0)	.0899
Positive	438 (79.3)	275 (76.6)	119 (85.0)	44 (83.0)	
Missing	61	33	24	4	
HER2 status					
Negative	392 (75.0)	260 (76.2)	97 (75.8)	35 (64.8)	.1914
Positive	131 (25.0)	81 (23.8)	31 (24.2)	19 (35.2)	
Missing	90	51	36	3	
Tumor subtype					
Hormone receptor–positive only	312 (60.1)	199 (58.5)	84 (66.7)	29 (54.7)	.0398
HER2-positive	131 (25.2)	81 (23.8)	31 (24.6)	19 (35.8)	
Triple-negative	76 (14.6)	60 (17.6)	11 (8.7)	5 (9.4)	

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TABLE 1. Patient Characteristics of the Overall Population and According to the Pandemic Phase (continued)

Characteristic	Overall Population (N = 613), No. (%)	Prevaccination (n = 392), No. (%)	Alpha-Delta (n = 164), No. (%)	Omicron (n = 57), No. (%)	*P*
Missing	94	52	38	4	
ECOG PS at COVID-19					
0-1	335 (80.9)	169 (82.0)	125 (78.6)	41 (83.7)	.6206
≥ 2	79 (19.1)	37 (18.0)	34 (21.4)	8 (16.3)	
Missing	199	186	2	9	
Tumor status					
In remission or radiologic response/nonmeasurable	346 (56.9)	218 (56.2)	100 (61.0)	28 (50.0)	.3200
Active or progressive disease	262 (43.1)	170 (43.8)	64 (39.0)	28 (50.0)	
Missing	5	4	—	1	
Tumor stage					
Nonadvanced	374 (61.0)	244 (62.2)	100 (61.0)	30 (52.6)	.3803
Advanced	239 (39.0)	148 (37.8)	64 (39.0)	27 (47.4)	
Bone-only disease					
No	187 (78.2)	116 (78.4)	49 (76.6)	22 (81.5)	.8719
Yes	52 (21.8)	32 (21.6)	15 (23.4)	5 (18.5)	
SACT at COVID-19 diagnosis[a]					
No	224 (38.0)	148 (38.7)	63 (40.6)	13 (24.5)	.0986
Yes	366 (62.0)	234 (61.3)	92 (59.4)	40 (75.5)	
Chemotherapy (± combos)	151 (25.6)	97 (25.4)	40 (25.8)	14 (26.4)	.9848
Chemo-free HER2 regimens	32 (5.4)	19 (5.0)	4 (2.6)	9 (17.0)	.0003
CDK4/6 inhibitors regimens	50 (8.5)	28 (7.3)	15 (9.7)	7 (13.2)	.2915
Endocrine therapy only	124 (21.0)	83 (21.7)	31 (20.0)	10 (18.9)	.8352
Others	9 (1.5)	7 (1.8)	2 (1.3)	—	.5718
Missing	23	10	9	4	
Median No. of treatment lines[b] (IQR)	2 (1-3)	2 (1-3)	1 (1-2)	1 (1-3)	.2322
Missing	65	35	20	10	
Median time from cancer diagnosis to COVID-19, months (IQR)	37 (8.0-98.5)	35 (8.0-99.0)	40 (7.0-92.5)	33 (8.5-129.0)	.8361
Missing	24	13	11	0	
SARS-CoV-2 vaccination status					
Unvaccinated	494 (84.6)	392 (100.0)	99 (71.2)	3 (5.7)	< .0001
Partially vaccinated	18 (3.1)	—	13 (9.4)	5 (9.4)	
Fully vaccinated	42 (7.2)	—	23 (16.5)	19 (35.8)	
Boosted	30 (5.1)	—	4 (2.9)	26 (49.1)	
Unknown	29	—	25	4	

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TABLE 1. Patient Characteristics of the Overall Population and According to the Pandemic Phase (continued)

Characteristic	Overall Population (N = 613), No. (%)	Prevaccination (n = 392), No. (%)	Alpha-Delta (n = 164), No. (%)	Omicron (n = 57), No. (%)	*P*
COVID-19 therapy					
No	269 (48.0)	148 (40.8)	85 (55.9)	36 (80.0)	< .0001
Yes	291 (52.0)	215 (59.2)	67 (44.1)	9 (20.0)	
Missing	53	29	12	12	
Antibiotics	228 (40.7)	178 (49.0)	46 (30.3)	4 (8.9)	< .0001
Antimalarials	131 (23.4)	131 (36.1)	—	—	< .0001
Antivirals	73 (13.0)	60 (16.5)	11 (7.2)	2 (4.4)	.0034
IL-6 inhibitors	19 (3.4)	13 (3.6)	4 (2.6)	2 (4.4)	.7945
Corticosteroids	102 (18.2)	56 (15.4)	42 (27.6)	4 (8.9)	.0011
Others	55 (9.8)	41 (11.3)	11 (7.2)	3 (6.7)	.2808

Abbreviations: CDK, cyclin-dependent kinase; COPD, chronic obstructive pulmonary disease; ECOG PS, Easter Cooperative Oncology Group performance status; ER, estrogen receptors; HER2, human epidermal growth factor receptor 2; HR, hormone receptors; IL-6: interleukin 6; IQR, interquartile range; PgR, progesterone receptors; SACT, systemic anticancer therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Defined as within 4 weeks before COVID-19 diagnosis.

[b]In the advanced setting, including patients with advanced disease only.

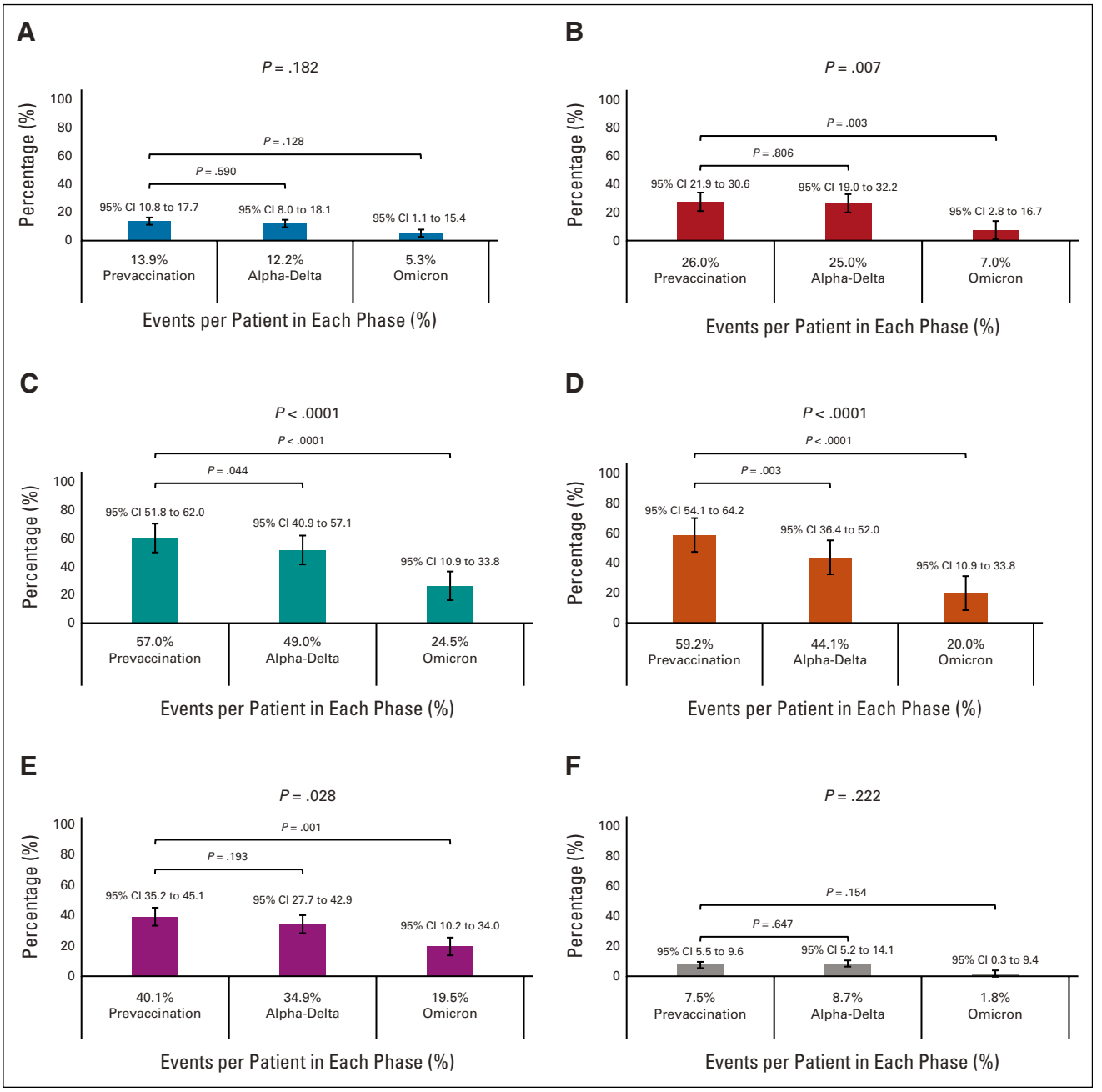

FIG 1. Measures of COVID-19 severity across different pandemic phases (prevaccination, Alpha-Delta, and Omicron). Rates of COVID-19 outcomes are calculated with 95% Wilson CIs, as events occurred for each outcome per number of patients observed in each phase, excluding missing data. Cross-groups comparison *P* value is provided as subheadings. Intergroup comparison *P* values with prevaccination phase as reference term and events/patients ratio are also provided. Overall missing/excluded events were: 4 CFR_{28}, 5 ICU admission, 63 hospitalization (5 missing/58 pre-existing), 56 oxygen therapy requirement, 53 COVID-19 specific therapy. (A) CFR_{28}: prevaccination (54/388), Alpha-Delta (20/164), and Omicron (3/57). (B) COVID-19 complications: prevaccination (102/392), Alpha-Delta (41/164), and Omicron (4/57). (C) Hospitalization due to COVID-19: prevaccination (204/358), Alpha-Delta (70/143), and Omicron (12/49). (D) COVID-19–specific therapy: prevaccination (215/363), Alpha-Delta (67/152), and Omicron (9/45). (E) Oxygen therapy requirement: prevaccination (147/367), Alpha-Delta (52/149), and Omicron (8/41). (F) ICU admission: prevaccination (29/391), Alpha-Delta (14/161), and Omicron (1/56). CFR_{28}, 28-day case fatality rate; ICU, intensive care unit.

After the exclusion of 29 patients with unknown vaccination status, we included in the descriptive analysis of COVID-19 outcomes according to the vaccination status across the pandemic phases, eight (14%) and 113 (68.9%) unvaccinated, and 46 (80.7%) and 26 (15.8%) vaccinated patients from the Omicron and Alpha-Delta phases, respectively. As reported in Figure 2, unvaccinated patients from the Omicron and Alpha-Delta phases experienced a CFR_{28} of 25% (95% CI, 7.2 to 59.1) and 13.3% (95% CI, 8.2 to 20.8), respectively, which was comparable with the

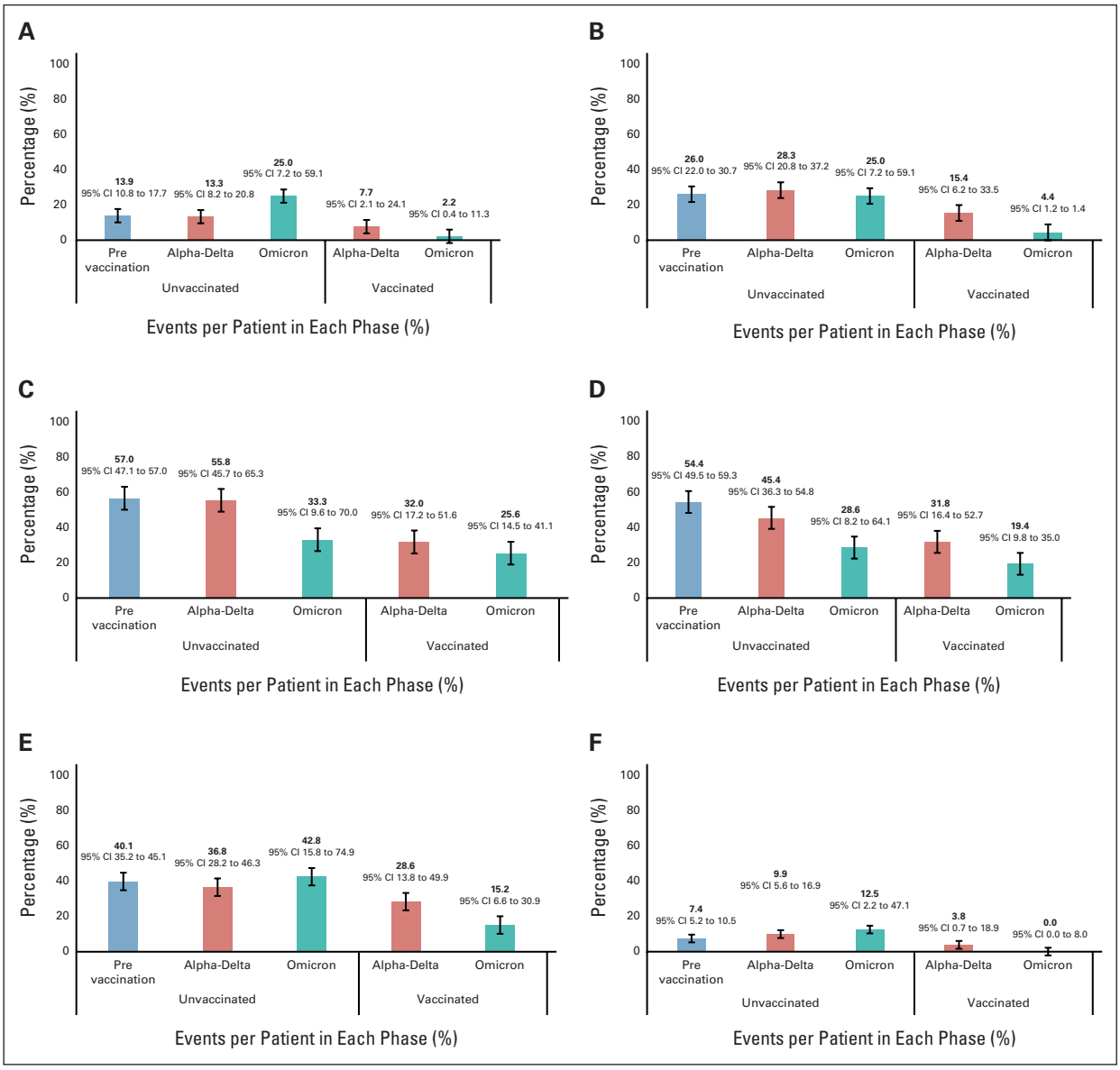

FIG 2. Measures of COVID-19 severity across different pandemic phases (prevaccination, Alpha-Delta, and Omicron) according to the vaccination status. Partially vaccinated patients were included among unvaccinated patients to increase the sample size of subgroups. Rates of COVID-19 outcomes are calculated with 95% Wilson CIs, as events occurred for each outcome per number of patients observed in each phase, excluding missing data. Events/patients ratio is also provided. Overall missing/excluded events were: 4 CFR_{28}, 3 ICU admission, 57 hospitalization, 48 oxygen therapy requirement, 46 COVID-19 specific therapy. (A) CFR_{28}: prevaccination (54/388), Alpha-Delta unvaccinated (15/113), Omicron unvaccinated (2/8), Alpha-Delta vaccinated (2/26), and Omicron vaccinated (1/46). (B) COVID-19 complications: prevaccination (102/392), Alpha-Delta unvaccinated (32/113), Omicron unvaccinated (2/8), Alpha-Delta vaccinated (4/26), and Omicron vaccinated (2/46). (C) Hospitalization due to COVID-19: prevaccination (204/358), Alpha-Delta (53/95), Omicron (2/6), Alpha-Delta vaccinated (8/25), and Omicron vaccinated (10/39). (D) COVID-19–specific therapy: prevaccination (215/363), Alpha-Delta unvaccinated (49/108), Omicron unvaccinated (2/7), Alpha-Delta vaccinated (7/22), and Omicron vaccinated (7/36). (E) Oxygen therapy requirement: prevaccination (147/367), Alpha-Delta vaccinated (39/106), Omicron vaccinated (3/7), Alpha-Delta unvaccinated (6/21), and Omicron unvaccinated (5/33). (F) ICU admission: prevaccination (29/391), Alpha-Delta unvaccinated (11/111), Omicron unvaccinated (1/8), Alpha-Delta vaccinated (1/26), and Omicron vaccinated (0/44). CFR_{28}, 28-day case fatality rate; ICU, intensive care unit.

13.9% experienced by patients diagnosed during the prevaccination phase. However, vaccinated patients from the Omicron phase experienced a markedly lower CFR_{28} of 2.2% (95% CI, 0.4 to 11.3). Similar trends of more comparable outcomes with prior phases in unvaccinated patients from the Omicron phase aligned with markedly improved outcomes restricted to vaccinated patients were reported in all the included surrogates of COVID-19 severity.

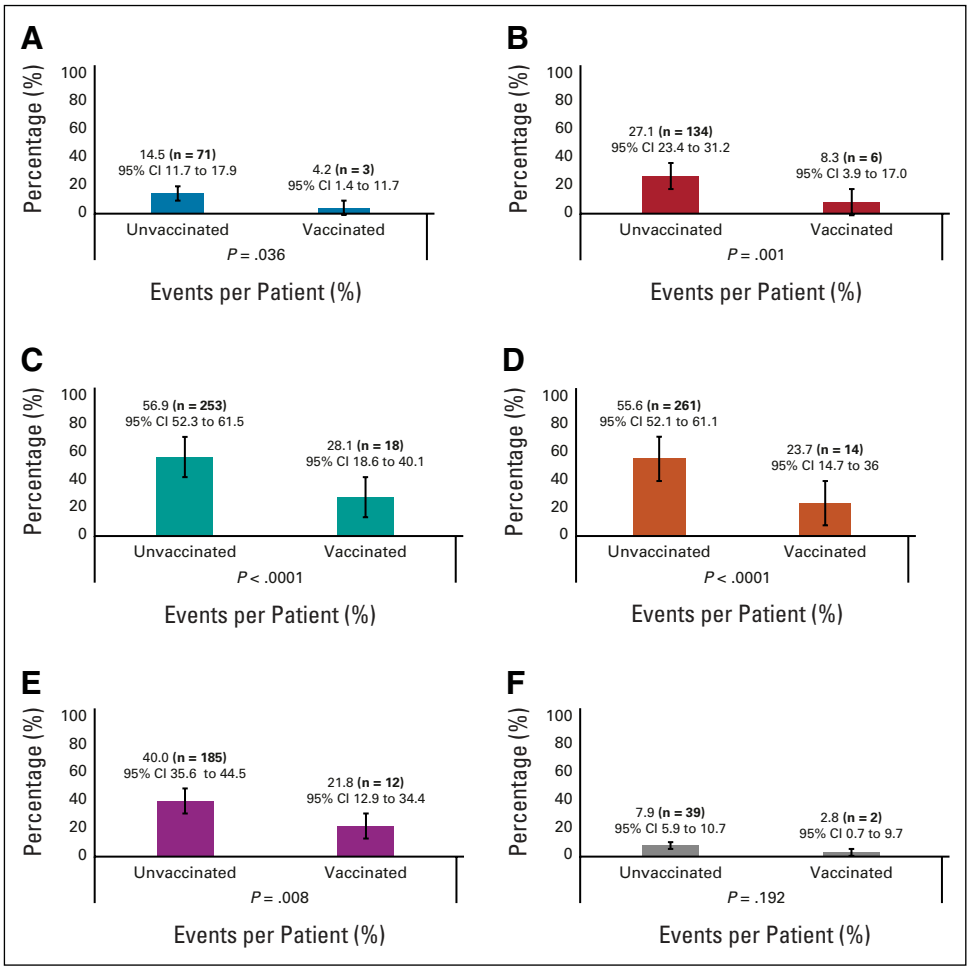

FIG 3. Measures of COVID-19 severity according to the vaccination status. Partially vaccinated patients were excluded. Rates of COVID-19 outcomes are calculated with 95% Wilson CIs, as events occurred for each outcome per number of patients observed in each phase, excluding missing data. Events/patients ratio is also provided. Overall missing/excluded events were: 4 CFR_{28}, 4 ICU admission, 61 hospitalization, 49 oxygen therapy requirement, 47 COVID-19 specific therapy. (A) CFR_{28}: unvaccinated patients (71/490) and vaccinated patients (3/71). (B) COVID-19 complications: unvaccinated patients (134/494) and vaccinated patients (6/72). (C) Hospitalization due to COVID-19: unvaccinated patients (253/444) and vaccinated patients (18/64). (D) COVID-19–specific therapy: unvaccinated patients (261/461) and vaccinated patients (14/59). (E) Oxygen therapy requirement: unvaccinated patients (185/463) and vaccinated patients (12/55). (F) ICU admission: unvaccinated patients (39/492) and vaccinated patients (2/71). CFR_{28}, 28-day case fatality rate; ICU, intensive care unit.

Receipt of SARS-CoV-2 Vaccination Is Independently Associated With Improved Morbidity and Mortality Outcomes From COVID-19 in Patients With Breast Cancer

After exclusion of patients with unknown vaccination status and those who received a partial vaccination course before COVID-19, 566 patients were eligible for this analysis, of whom 72 (12.7%) were vaccinated (ie, double-dosed or boosted) and 494 (87.3%) were unvaccinated. Among vaccinated patients, 31 (43.1%) received the BNT162b2 vaccine (double-dosed: 19, boosted: 12), 18 (25.0%) received the mRNA-1273 vaccine (double-dosed: 8, boosted: 10), 12 (16.7%) received the ChAdOx1-S vaccine (double-dosed: 7, boosted: 5), and two (2.8%) received the Ad.26.COV2.S vaccine (both double-dosed). Distribution of vaccination status across subgroups is reported in the Data Supplement. No significant difference was observed between vaccinated and unvaccinated patients in terms of patient, tumor, and treatment characteristics with the exception of the Easter Cooperative Oncology Group—Performance Status (ECOG-PS; Data Supplement).

CFR_{28} was significantly lower in fully vaccinated patients compared with unvaccinated patients (three events of 71 patients events [4.2%; 95% CI, 1.4 to 11.7] *v* 71 events of 490 patients [14.5%; 95% CI, 11.7 to 17.9]; $P = .036$). When compared with controls, fully vaccinated patients had a significantly improvement in indices of morbidity from

TABLE 2. Summary of Main Results of the Inverse Probability of Treatment Weighting Fitted Multivariable Logistic Regression Analyses Comparing Outcomes of Vaccinated and Unvaccinated Patients

CFR_{28}	Patients Included	aOR	95% CI
Vaccinated (double dosed or boosted) *v* unvaccinated (unvaccinated patients only)			
Vaccination yes *v* no	562	0.19	0.09 to 0.40
ICU admission			
Vaccination yes *v* no	563	0.12	0.02 to 1.05
Hospitalization due to COVID-19			
Vaccination yes *v* no	509	0.28	0.11 to 0.69
Complications from COVID-19			
Vaccination yes *v* no	566	0.16	0.06 to 0.45
Oxygen therapy requirement			
Vaccination yes *v* no	518	0.24	0.09 to 0.67
COVID-19 specific therapy requirement			
Vaccination yes *v* no	520	0.24	0.09 to 0.63
Vaccinated (boosted) *v* unvaccinated (unvaccinated patients only)			
Vaccination yes *v* no	520	0.04	0.01 to 0.17
Vaccinated (double dosed) *v* unvaccinated (unvaccinated patients only)			
Vaccination yes *v* no	531	0.27	0.09 to 0.80

NOTE. Partially vaccinated patients were excluded. The reported aOR and 95% CIs are corrected according to the clustered-robust adjustment for participating centers. Full multivariable models are presented in the Data Supplement.

Abbreviations: aOR, adjusted odds ratio; CFR_{28}, 28-day case fatality rate; ICU, intensive care unit.

COVID-19, as demonstrated by reduced rates of hospitalization (28.1% [18/64] *v* 56.9% [253/444]; $P < .0001$), complications from COVID-19 (8.3% [6/72] *v* 27.1% [134/494]; $P = .001$), and need for COVID-19–specific therapy (23.7% [14/59] *v* 56.6% [261/461]; $P < .0001$) and for oxygen therapy (21.8% [12/55] *v* 40.0% [185/463]; $P = .008$). Figure 3 provides a summary of these COVID-19–related outcomes according to the vaccination status.

The balancing ability of the IPTW procedure between vaccinated and unvaccinated patients is displayed in the Data Supplement, which reports the distribution of weighted characteristics. After double adjustment for tumor stage, the receipt of SACT at COVID-19, ECOG-PS, tumor status, and age, and following the cluster correction for participating center, vaccinated patients were confirmed to achieve improved CFR_{28} (adjusted odds ratio [aOR], 0.19; 95% CI, 0.09 to 0.40), hospitalization due to COVID-19 rate (aOR, 0.28; 95% CI, 0.11 to 0.69), as well as improved rate of COVID-19 complications (aOR, 0.16; 95% CI, 0.06 to 0.45), and reduced requirement of COVID-19–specific therapy (aOR, 0.24; 95% CI, 0.09 to 0.63) and oxygen therapy (aOR, 0.24; 95% CI, 0.09 to 0.67) in comparison with unvaccinated patients (results reassumed in Table 2, and multivariable fitted logistic regression models provided in the Data Supplement).

The IPTW balancing ability for the comparisons between boosted and unvaccinated and between double-dosed and unvaccinated is summarized in the Data Supplement. After double adjustment for country of origin, number of comorbidities, the receipt of SACT, tumor stage, ECOG-PS and age, and following the cluster correction of participating center, both boosted (aOR, 0.04; 95% CI, 0.01 to 0.17) and double-dose patients (aOR, 0.27; 95% CI, 0.09 to 0.80) were confirmed to achieve improved CFR_{28} in comparison with unvaccinated patients (Table 2; respective full multivariable fitted models are summarized in the Data Supplement).

Influence of SACT on COVID-19 Outcomes in Patients With Breast Cancer

Overall, 62% of the patients (n = 366) had received SACT within 4 weeks before COVID-19 diagnosis; 192 of them (52.5%) had nonadvanced disease (44 of 192 [22.9%] treated in the neoadjuvant setting, 143 of 192 [74.5%] in the adjuvant setting), whereas 174 (47.5%) had advanced disease. SACT recipients were more frequently entered from Italian centers (162 of 366 [44.3%] *v* 64 of 224 [28.1%]), and less frequently from UK centers (83 of 366 [22.7%] *v* 86 of 224 [38.4%]; $P < .0001$), and presented more frequently advanced-stage tumors (174 of 366 [47.4%] *v* 58 of 224 [25.9%]; $P < .0001$). No other associations were observed between subgroups (Data Supplement).

The descriptive analysis of the CFR_{28} among SACT recipients according to the vaccination status and tumor stage is summarized in the Data Supplement. Patients with nonadvanced disease experienced decreased COVID-19 mortality in comparison with patients with advanced-stage disease. However, fully vaccinated patients were those experiencing the lowest CFR_{28} across different SACT

regimens including chemotherapy and endocrine therapy independently of tumor stage.

The Data Supplement summarizes the balancing ability of the propensity score–matching procedures between patients not on SACT at COVID-19 and patients on SACT (as a whole), on chemotherapy, and on endocrine therapy only.

After double adjustment for the selected variables and following cluster correction for the participating center, patients on endocrine therapy only (aOR, 0.44; 95% CI, 0.21 to 0.90), but not those on SACT as a whole category (aOR, 0.52; 95% CI, 0.26 to 1.07) and those on chemotherapy (aOR, 0.59; 95% CI, 0.26 to 1.36), were confirmed to experience reduced CFR_{28} in comparison with patients who were not on SACT at COVID-19 (Data Supplement).

DISCUSSION

To the best of our knowledge, this is the first study assessing SARS-CoV-2 vaccination and clinical outcomes in patients with breast cancer. In contrast to previous studies assessing SARS-CoV-2 vaccinations across all cancer types,[14] our analysis of outcomes in patients with breast cancer found that CFR_{28} did not significantly change across pandemic phases, although all measures of COVID-19 severity showed a significant and clinically meaningful improvement over time. However, prior vaccination is a time-dependent variable by definition and our data suggest that SARS-CoV-2 vaccines are the strongest driver of improved outcomes across the pandemic phases. In fact, when describing COVID-19 outcomes in unvaccinated patients from the Omicron and Alpha-Delta phases, we reported similar estimates to those of patients from the prevaccination phase.

A full course of vaccination dramatically decreased the mortality at 28 days by 81% compared with unvaccinated patients, even after adjustment for major prognostic confounders and cluster correction for participating center. Vaccination also substantially improved other prespecified outcomes, including hospitalizations, COVID-19 complications, and need for oxygen or for COVID-19–specific therapy.

Patients with breast cancer appear less vulnerable to SARS-CoV-2 infection and COVID-19 severity in comparison with patients with other malignancies. The lower mortality rates observed in this population since the beginning of the pandemic, when effective therapies or vaccines were not available, raises important questions as to whether diversity in comorbid burden, age, sex, and perhaps in a direct immune-modulating potential of certain anticancer therapies[18] or supportive care might underlie the differential vulnerability of these patients compared with other tumor types. Our patient population has a very small proportion of obese patients ($< 5\%$), which also may point toward the fact that patients were more highly selected for undergoing systemic therapy during the COVID-19 pandemic. In addition, the improvement in COVID-19 outcomes over time in Europe[13] begs the question of whether this positively evolving scenario applies to patients with breast cancer, who revealed to have peculiar and yet not fully understood features in response to COVID-19.

With CFRs for unselected patients with cancer reported to be 25% to 30%[3,7,9,19,20] in the prevaccination phase, our study complements previous evidence showing patients with breast cancer achieve better outcomes compared with other malignancies, by reporting a CFR_{28} consistently $< 15\%$ throughout the pandemic phases. The attenuated vulnerability to COVID-19 of patients with breast cancer can be easily traced to the distribution of patient and disease characteristics within our cohort. In our study, we observed an enrichment in features that carry a reduced risk for poor COVID-19 outcomes: more than half of the patients surveyed had evidence of localized cancer and nonactive oncologic disease at COVID-19 diagnosis, a preserved performance status, were age < 60 years, and nonsmokers. We should also acknowledge that female sex is an intrinsic protective factor from severe COVID-19, as a likely consequence of both biological and behavioral factors, such as but not limited to reduced tobacco consumption, and reduced prevalence of comorbidities.[21,22]

Sex-related differences in susceptibility to SARS-CoV-2 infection have also been hypothesized because of the possible immune-enhancing effects of estrogens, as documented by the correlation between immune-cell infiltration and estrogen receptor level in normal and SARS-CoV-2–infected human tissues, alongside the estrogen-inducted decline in angiotensin-converting enzyme 2 activity.[23,24] Nevertheless, despite 60% of the patients in our study having a hormone receptor–positive tumor, only approximately 30% of those on active oncologic treatment at COVID-19 diagnosis were receiving endocrine therapy with or without CDK 4/6 inhibitors. In addition, 31.5% of the patients had ≥ 2 comorbidities known to negatively influence COVID-19 outcomes, particularly hypertension, cardiovascular diseases, and pulmonary diseases.[25,26]

As mentioned, our study highlights that patients with breast cancer have also substantially benefitted from immunization campaigns with SARS-CoV-2 vaccines. IPTW fitted models clearly showed a significant improvement in all measures of COVID-19 severity for vaccinated patients. In addition, we reported a substantial reduction in the risk of death at 28 days for boosted compared with unvaccinated patients.

Seroconversion rates in patients with cancer do not always mirror the serologic response obtained among the general population[27,28]; therefore, patients with cancer have been prioritized for a booster strategy along with the continued application of shielding measures against the transmission.[28] Along the same lines, large cancer SARS-CoV-2 studies report a progressive waning of antibody responses to SARS-CoV-2 vaccination with time, especially in patients with cancer on active chemotherapy, with a subsequent risk

of breakthrough infections.[7,29-31] However, studies demonstrated that patients with solid tumors, and breast cancer in particular, achieve an improved immunologic response to SARS-CoV-2 vaccination compared with patients with hematologic malignancies,[27,32,33] while some evidence reported similar levels of postvaccination neutralizing antibodies in patients with breast cancer receiving CDK4/6 inhibitor treatment in comparison with matched healthy subjects.[34]

In view of published evidence supporting a nonuniversally consistent negative prognostic value of recent SACT, and particularly of chemotherapy,[3,4,13,18,35-37] our propensity score–matched analysis showed no detrimental effect for the recent receipt of SACT and chemotherapy on COVID-19–related outcomes. Hormonal therapy appeared associated with reduced mortality, partially aligning our results to those reported from the COVID-19 and Cancer Consortium registry.[38] Limitations related to SACT data completeness, including lack of information on prior toxicity and dose intensity, call for caution in interpreting strength and direction of associations with anticancer therapy. In addition, clinical risk factors for mortality may be underestimated in multivariable analyses that include interventions used specifically in patients with severe COVID-19.[39]

Interestingly, patients on SACT achieved lower CFR_{28} compared with the whole study population irrespective of therapeutic modality, suggesting patients on treatment to represent a more favorable prognostic group overall, perhaps related, in part, to known physician treatment selection criteria for cancer therapy. Clinicians may avoid more intense chemotherapy regimens in the most vulnerable, which may result for the frail, nursing home patients, as well as end-of-life and socioeconomically deprived individuals to be more likely represented among the untreated comparator group.[40-42] Studies capable of looking at treatment 3 months before COVID-19, and adjusting for some of these additional poor prognostic factors associated with progressive disease, have reported chemotherapy as an adverse risk factor.[38,43] In a study of insured and mostly employed individuals, data providing detailed drug information together with nursing home status reported odds ratios of 1.8 across all chemotherapies and 2.3 for chemoimmunotherapy-associated COVID-19 mortality.[43] With the ability to make adjustments for detailed comorbid as well as immunosuppressive conditions, nursing home status, and detailed social deprivation indices, Clift et al[44] found a striking dose response with increasing levels of immunosuppression and intensity of chemotherapy for COVID-19 hospitalization and mortality. Coinfections can also complicate cancer and severe COVID-19, especially in patients with comorbidities, neutropenia, and/or receipt of chemotherapy, with reported all-cause mortality of 25%-35%.[39,45-47] Descriptive analysis of outcomes in SACT recipients shows higher CFR_{28} in patients with advanced versus nonadvanced malignancy, with lowest mortality rates reported for vaccinated patients across all different SACT modalities, including chemotherapy and endocrine therapy, independently of tumor stage. Although an approximately 4% mortality rate still meaningfully outpaces figures observed among the general population and needs to be cautiously considered, these results further corroborate the protective role of SARS-CoV-2 vaccination, supporting the importance of maintaining the oncologic continuity of care outside the acute phase of SARS-CoV-2 infection in patients with breast cancer.[48-50]

This study has some limitations that should be acknowledged, mainly deriving from its retrospective design and the unavoidable unbalanced sample size of patients across the different pandemic phases, although our vaccine efficacy estimates resemble those from large UK population-wide cancer database on breakthrough infections.[29] All-cause mortality was retrieved and validated by investigators at each center by accessing patients' electronic medical records and death certificates. Of note, we used the reduction in use of COVID-19–specific treatments as a surrogate of disease severity in the pandemic phases and vaccination analysis. While reporting significant changes in COVID-19 management with reduced use of empirical antibiotics and antimalarials, mirrored by an increase in the use of systemic corticosteroids,[13] our database was not designed to collect data on anti–SARS-CoV-2 antivirals and monoclonal antibodies. Importantly, viral genomes were not routinely characterized in Europe. Despite adopting validated epidemiologic criteria to define pandemic phases,[14] the lack of viral genomic sequences to define SARS-CoV-2 variants stands as a major limitation. In addition, residual unmeasured confounding cannot be controlled for despite robust IPTW models.

In conclusion, our comprehensive phase-adjusted analysis of SARS-CoV-2 vaccination status and adverse COVID-19 outcomes in patients with breast cancer highlights no statistically significant decrease in COVID-19 mortality over time, as a likely result of the lower pathogenicity of SARS-CoV-2 in these patients and still limited vaccination rates, despite the consistent reduction in all surrogates of COVID-19 severity during the Omicron outbreak in Europe. Comparable COVID-19 severity in unvaccinated patients diagnosed across Omicron to the prevaccination phase emphasizes the strong protective role of a complete SARS-CoV-2 vaccination course as the most likely factor to be associated with improved morbidity and mortality, irrespective of patient and tumor characteristics. By including patients diagnosed during the Omicron phase, we provide contemporary clinical data to inform current clinical practice. In patients with breast cancer, promotion of widespread vaccination, ideally with boosters for immunocompromised individuals, and stringent infection control policies are essential for the preservation of oncologic continuity of care.

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DISCLAIMER

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EQUAL CONTRIBUTION

N.M.K., D.J.P., and A.C. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Individual, deidentified participant data and data dictionary may be made available at the request of investigators whose proposed use of the data has been approved by the OnCovid consortium investigators following review of a methodologically sound research proposal.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pandemic Phase-Adjusted Analysis of COVID-19 Outcomes Reveals Reduced Intrinsic Vulnerability and Substantial Vaccine Protection From Severe Acute Respiratory Syndrome Coronavirus 2 in Patients With Breast Cancer

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