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Interplay of Immunosuppression and Immunotherapy Among Patients With Cancer and COVID-19

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IMPORTANCE Cytokine storm due to COVID-19 can cause high morbidity and mortality and may be more common in patients with cancer treated with immunotherapy (IO) due to immune system activation.

OBJECTIVE To determine the association of baseline immunosuppression and/or IO-based therapies with COVID-19 severity and cytokine storm in patients with cancer.

DESIGN, SETTING, AND PARTICIPANTS This registry-based retrospective cohort study included 12 046 patients reported to the COVID-19 and Cancer Consortium (CCC19) registry from March 2020 to May 2022. The CCC19 registry is a centralized international multi-institutional registry of patients with COVID-19 with a current or past diagnosis of cancer. Records analyzed included patients with active or previous cancer who had a laboratory-confirmed infection with SARS-CoV-2 by polymerase chain reaction and/or serologic findings.

EXPOSURES Immunosuppression due to therapy; systemic anticancer therapy (IO or non-IO).

MAIN OUTCOMES AND MEASURES The primary outcome was a 5-level ordinal scale of COVID-19 severity: no complications; hospitalized without requiring oxygen; hospitalized and required oxygen; intensive care unit admission and/or mechanical ventilation; death. The secondary outcome was the occurrence of cytokine storm.

RESULTS The median age of the entire cohort was 65 years (interquartile range [IQR], 54-74) years and 6359 patients were female (52.8%) and 6598 (54.8%) were non-Hispanic White. A total of 599 (5.0%) patients received IO, whereas 4327 (35.9%) received non-IO systemic anticancer therapies, and 7120 (59.1%) did not receive any antineoplastic regimen within 3 months prior to COVID-19 diagnosis. Although no difference in COVID-19 severity and cytokine storm was found in the IO group compared with the untreated group in the total cohort (adjusted odds ratio [aOR], 0.80; 95% CI, 0.56-1.13, and aOR, 0.89; 95% CI, 0.41-1.93, respectively), patients with baseline immunosuppression treated with IO (vs untreated) had worse COVID-19 severity and cytokine storm (aOR, 3.33; 95% CI, 1.38-8.01, and aOR, 4.41; 95% CI, 1.71-11.38, respectively). Patients with immunosuppression receiving non-IO therapies (vs untreated) also had worse COVID-19 severity (aOR, 1.79; 95% CI, 1.36-2.35) and cytokine storm (aOR, 2.32; 95% CI, 1.42-3.79).

CONCLUSIONS AND RELEVANCE This cohort study found that in patients with cancer and COVID-19, administration of systemic anticancer therapies, especially IO, in the context of baseline immunosuppression was associated with severe clinical outcomes and the development of cytokine storm.

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Supplemental content

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COVID-19 disproportionately affects patients with cancer, with high rates of hospitalization and death.[1] Both patient- and cancer-specific factors have emerged as predictors of poor outcomes.[1] Among anti-neoplastic agents, cytotoxic chemotherapy, which is immunosuppressive, has been linked to worse outcomes.[2] However, the effect of additional therapies that influence the immune system such as immunotherapy (IO) or immunosuppressive agents on COVID-19 severity has not been fully established.

It has been hypothesized that immune checkpoint inhibitors (ICIs) could have a beneficial association with COVID-19 outcomes. Severe COVID-19 is characterized by lymphopenia with markedly reduced CD8-positive T-cells, and an upregulation of exhaustion markers (eg, PD-1).[3,4] Given that blocking immune checkpoints can reverse T-cell exhaustion, multiple clinical trials are evaluating anti-PD-1 antibodies in patients with COVID-19 to test their potential to decrease COVID-19 severity (NCT04413838, NCT04268537, NCT04356508). Conversely, IO could disrupt the balance of the immune system and potentially exacerbate widespread immune-mediated injury observed with severe COVID-19.[5] Similarly, immunosuppression has been hypothesized to limit antiviral responses and consequently lead to poor outcomes.

To date, there have been conflicting studies regarding immune-stimulating and immunosuppressive therapies on COVID-19 outcomes, possibly owing to modest sample sizes and potential confounding factors.[6-9] Given the unclear influence of IO on patients with cancer and COVID-19 outcomes and immune-mediated inflammation, we aimed to evaluate the association between baseline immunosuppression and/or IO-based therapies on COVID-19 severity and incidence of cytokine storm using data from the COVID-19 and Cancer Consortium (CCC19, ccc19.org), while accounting for relevant demographic and clinical covariates and adjusting for effect modification.

Key Points

Question Are immunotherapy (IO) drugs and/or baseline immunosuppression associated with cytokine storm and worse clinical outcomes in patients with cancer and COVID-19 disease?

Findings This cohort study of 12 046 patients with cancer and COVID-19 found that treatment with IO and other systemic anticancer therapies in the context of baseline immunosuppression was associated with an increased incidence of cytokine storm and worse outcomes in patients with cancer infected with SARS-CoV-2.

Meaning These findings suggest that patients with cancer with baseline immunosuppression and COVID-19 may experience worse outcomes when treated with IO or non-IO systemic anticancer therapy, whereas those without any preexisting immune suppression can safely receive anticancer therapeutic regimens.

Methods

Study Design

The CCC19 maintains an international multi-institution registry of patients with COVID-19 with a current or past invasive cancer diagnosis.[10] Data are collected and managed using REDCap at Vanderbilt University Medical Center.[10,11] The trial protocol is available in Supplement 1.

Reports were accrued from March 17, 2020, to May 12, 2022, and included patients with laboratory-confirmed SARS-CoV-2 infection (eFigure 1 in Supplement 2). Patients were divided into 3 groups: those who received IO, defined as PD-(L)1 and/or CTLA-4 inhibitors, bispecific T-cell engagers (BiTE), or chimeric antigen receptor (CAR) T-cell therapies, during the 3 months before COVID-19 diagnosis (IO group); those who received non-IO antineoplastic regimens (non-IO group), defined as cytotoxic chemotherapy, targeted therapies, or endocrine therapies; and those who did not receive any systemic therapy (untreated group). Patients were also divided by baseline immunosuppression status. Complete inclusion and exclusion criteria are provided in the eMethods in Supplement 2.

The Vanderbilt University institutional review board determined that informed consent was not required, and all data were deidentified (VUMC IRB#200467). The study was approved by institutional review boards at participating sites. This ongoing study is registered on ClinicalTrials.gov (NCT04354701).

Outcome Definitions

The primary outcome was a 5-level ordinal scale of COVID-19 severity based on the most severe disease status: no complications; hospitalized without requiring oxygen; hospitalized and required oxygen; intensive care unit admission and/or mechanical ventilation; death. In the event of mortality, causes of death were determined as part of data curation in the CCC19 registry.

The secondary outcome was the incidence of a cytokine storm among patients, defined as biological and clinical evidence of severe inflammation, with end-organ dysfunction (eMethods in Supplement 2), based on a previously suggested definition of cytokine storm.[12]

Statistical Analysis

To evaluate the association of IO or immunosuppression with the primary and secondary outcomes, we conducted a multivariable logistic regression balanced for covariate distributions through inverse probability of treatment weighting (IPTW), and adjusted for variables (Supplement 2) selected based on a priori decisions.

Because baseline immunosuppression might modify the effect of anticancer systemic therapies, we included the interaction terms of cancer treatment and immunosuppression in the regression models to account for different effects between the strata by immunosuppression status. A full description of the statistical plan is available in eFigure 2, and eTable 2, and eMethods in Supplement 2.

Results

A total of 12 046 patients were included (eFigure 1 in Supplement 2). Overall, 6359 (53.0%) were women and 6598 (55%) were non-Hispanic White. The median IQR) age was 65 (54-74) years. The median (IQR) follow-up was 90 (30-180) days (**Table**).

Table. Descriptive Statistics for Outcome Variables and Clinical Features Stratified by 3 Treatment Groups

Characteristic	No. (%)		
	No systemic treatment (n = 7120)	Systemic anticancer therapy other than IO[a] 3 mo prior to COVID-19 diagnosis (n = 4327)	IO within 3 mo prior to COVID-19 diagnosis (n = 599)
COVID-19 severity			
Not hospitalized	3368 (47)	1902 (44)	260 (43)
Hospitalized and did not require supplemental oxygen	966 (14)	682 (16)	81 (14)
Hospitalized and required supplemental oxygen	1147 (16)	638 (15)	87 (15)
Intensive care unit and/or mechanical ventilation	515 (7)	249 (6)	33 (6)
Death	1124 (16)	856 (20)	138 (23)
Cytokine storm[b]			
Absent	2354 (33)	1268 (29)	186 (31)
Present	860 (12)	533 (12)	68 (11)
Age (25th/50th/75th percentile), y	56/66/76	52/62/72	57/65/73
Sex			
Female	3575 (50)	2527 (58)	257 (43)
Male	3539 (50)	1798 (42)	342 (57)
Race and ethnicity			
Hispanic	958 (13)	855 (20)	85 (14)
Non-Hispanic Black	1256 (18)	761 (18)	75 (13)
Non-Hispanic White	4050 (57)	2192 (51)	356 (59)
Other	728 (10)	441 (10)	69 (12)
Smoking status			
Never	3650 (52)	2429 (56)	227 (38)
Current or former	3233 (45)	1743 (40)	356 (59)
ECOG performance status			
0	2251 (32)	1467 (34)	157 (26)
1	1438 (20)	1544 (36)	272 (45)
2 or higher	842 (12)	701 (16)	117 (20)
Type of malignant abnormality[c]			
Solid tumor	5901 (83)	3182 (74)	567 (95)
Hematological neoplasm	1415 (20)	1360 (31)	52 (9)
Cancer status			
Remission or no evidence of disease	4562 (64)	930 (21)	33 (6)
Active and progressing	606 (9)	900 (21)	175 (29)
Active and responding	233 (3)	1086 (25)	147 (25)
Active and stable	919 (13)	945 (22)	176 (29)
Immunosuppression[d]			
Absent	6489 (91)	3410 (79)	517 (86)
Present	631 (9)	917 (21)	82 (14)
Previous receipt of COVID-19 vaccines			
Yes	584 (8)	538 (12)	90 (15)
No	6241 (88)	3608 (83)	477 (80)
Follow-up (25th/50th/75th percentile), d	30/90/180	24/70/180	30/70/135

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[a] Immunotherapy (IO) was defined as the receipt of PD-(L)1 and/or CTLA-4 inhibitors, bispecific T-cell engagers (BiTE) or chimeric antigen receptor T-cell therapies within 3 months before COVID-19 diagnosis

[b] Cytokine storm was defined by presence of 3 criteria: (1) an elevated marker of inflammation (IL-6, CRP, or D-dimer), (2) a severe systemic clinical manifestation (ie, hypotension, need for vasopressors, or sepsis) or severe lung injury (ie, pneumonitis or acute respiratory distress syndrome), and (3) a secondary organ dysfunction (ie, elevated alanine transaminase; aspartate transaminase, or elevated creatinine levels) or fever.

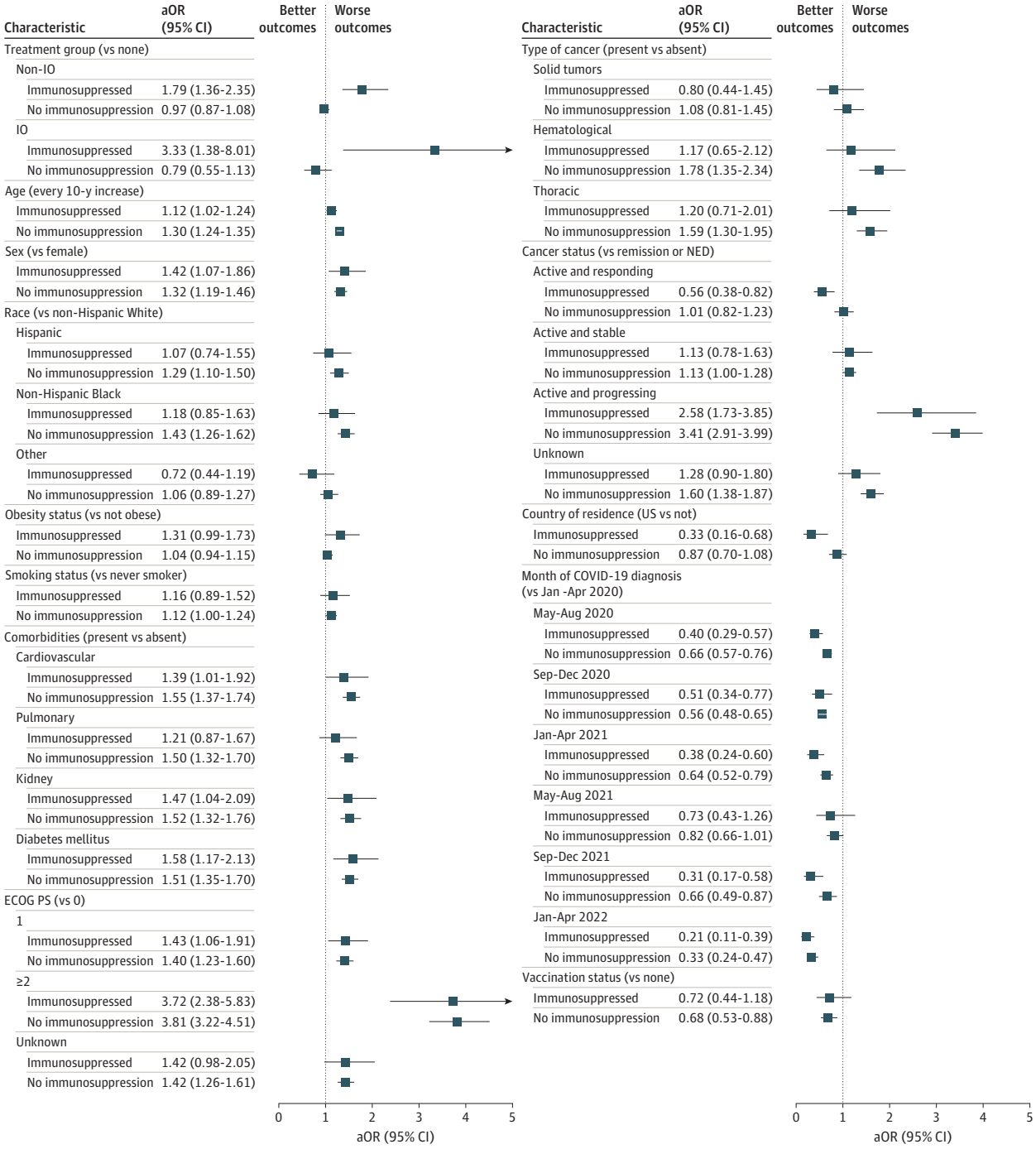
[c] Percentages could sum to greater than 100% because categories are not mutually exclusive.

[d] Immunosuppression was defined as (1) baseline administration of more than 20 mg/d of prednisone equivalent, (2) baseline administration of other immunosuppressive medications, (3) receipt of Bruton tyrosine kinase inhibitors (BTKi) within 3 months from COVID-19 diagnosis, (4) receipt of anti-CD20 therapy within 12 months from COVID-19 diagnosis, or (5) stem cell therapy within 12 months from COVID-19 diagnosis.

Overall, 599 (5.0%) patients received IO within 3 months before COVID-19 diagnosis (IO group; eTable 1 and eFigure 3 in Supplement 2), whereas 4327 (35.9%) received non-IO therapies (non-IO group), and 7120 (59.1%) received no antineoplastic regimen (untreated group). In the IO group, 138 (23%) patients died, compared with 856 (20%) in the non-IO group, and 1124 (16%) in the untreated group. The raw incidence of cytokine storm was comparable across all groups at 12% with 684, 533, and 860 for the IO, non-IO, and untreated groups, respectively (eTable 5 in Supplement 2). The standardized mean differences (SMDs) pre- and post-IPTW are shown in eTables 3 and 4 in Supplement 2.

No difference was found for COVID-19 severity or cytokine storm in the IO and non-IO groups vs untreated group (**Figure 1**; eTables 6 and 8 in Supplement 2). Baseline immunosuppression was also not associated with higher incidence

Figure 1. Forest Plot of Adjusted Odds Ratios for COVID-19 Severity, Stratified by Immunosuppression Status

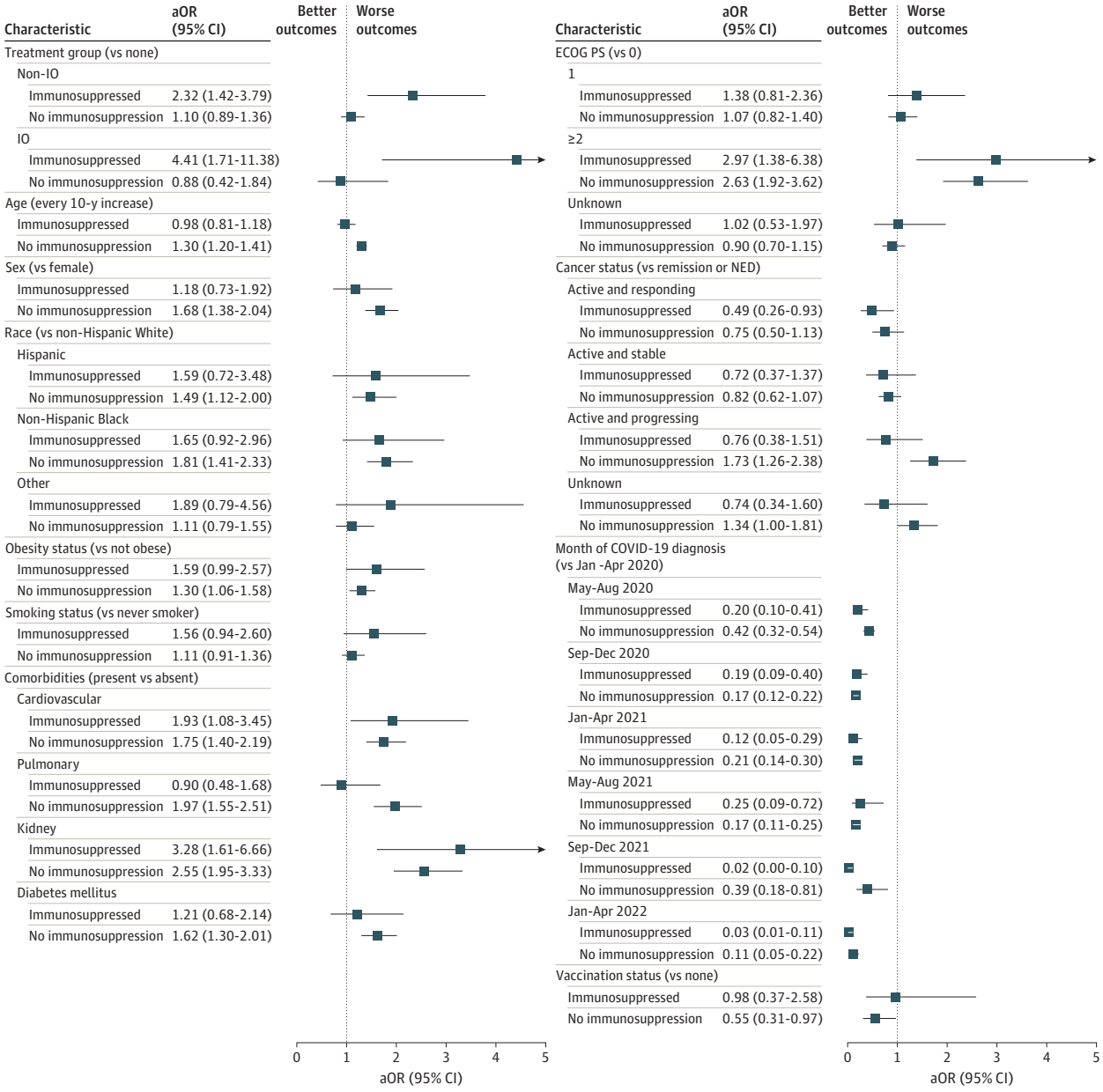


aOR indicates adjusted odds ratio; ECOG PS, Eastern Cooperative Oncology Group performance score; IO, immunotherapy.

of severe COVID-19 or cytokine storm in the total cohort (eTables 6 and 8 in Supplement 2).

In the multivariate regression analysis, the interaction term of IO (vs untreated) group and baseline immunosuppression presented a nonsignificant trend toward worse clinical outcomes and was significantly associated with cytokine storm. In addition, the interaction term of the non-IO (vs untreated) group and baseline immunosuppression was significantly associated with more severe COVID-19 and cytokine storm (eTables 6 and 8 in Supplement 2). Based on these results, multivariable analyses stratified by baseline immunosuppression demonstrated both the IO and non-IO (vs untreated) groups were associated with worse COVID-19 outcomes in the context of preexisting immunosuppression (aOR,

Figure 2. Forest Plot of Adjusted Odds Ratios for Cytokine Storm, Stratified by Immunosuppression Status



aOR indicates adjusted odds ratio; ECOG PS, Eastern Cooperative Oncology Group performance score; IO, immunotherapy.

3.33; 95% CI, 1.38-8.01, and aOR, 1.79; 95% CI, 1.36-2.35, respectively, Figure 1; eTable 7 in Supplement 2). Higher risk of cytokine storm was also identified in both the IO and non-IO (vs untreated) groups among patients with baseline immunosuppression (aOR, 4.41; 95% CI, 1.71-11.38, and aOR, 2.32; 95% CI, 1.42-3.79, respectively, **Figure 2**; eTable 9 in Supplement 2). Similar results were seen in the subgroup analysis of patients with active cancer (eTables 10-13 in Supplement 2), and in the sensitivity analysis after the exclusion of patients who received a combination of cytotoxic chemotherapy and PD-(L)1 inhibitors in the IO group (eTables 14-18 in Supplement 2).

Discussion

Among patients with baseline immunosuppression, administration of IO and, to a lesser extent, non-IO systemic anticancer therapy prior to SARS-CoV-2 infection was associated with worse disease severity and higher risk of cytokine storm.

The findings of this study help better characterize the association of IO with poor COVID-19 outcomes in relation to immunosuppression among patients with cancer, and also suggest that these agents are relatively safe to use among immunocompetent patients even during peaks of the pandemic.

We also found that patients with cancer diagnosed with COVID-19 across all time periods from May 2020 to April 2022 presented better outcomes compared with the first pandemic peak (January 2020-April 2020), indicating that the management of COVID-19 improved over time (Figure 1). Moreover, vaccination against SARS-CoV-2 was independently associated with less severe COVID-19 and a lower incidence of cytokine storm.

Limitations

This study has some limitations, including its retrospective nature, limited power to evaluate patient outcomes according to the specific types of immunosuppression and IO used and therapeutic combinations. Nevertheless, this represents the largest cohort with comprehensive clinical and biological data of patients with cancer and COVID-19 treated with IO reported so far, helping to evaluate the influence of IO and immunosuppression on patient outcomes and cytokine storm.

Conclusions

This cohort study found that in patients with cancer diagnosed with COVID-19, IO and immunosuppression alone did not increase the risk of severe infection or cytokine storm. However, IO given in patients with cancer with baseline immunosuppression was associated with cytokine storm and worse clinical outcomes.

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