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MAJOR ARTICLE

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Background. The frequency of coinfections and their association with outcomes have not been adequately studied among patients with cancer and coronavirus disease 2019 (COVID-19), a high-risk group for coinfection.

Methods. We included adult (≥18 years) patients with active or prior hematologic or invasive solid malignancies and laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection, using data from the COVID-19 and Cancer Consortium (CCC19, NCT04354701). We captured coinfections within ±2 weeks from diagnosis of COVID-19, identified factors cross-sectionally associated with risk of coinfection, and quantified the association of coinfections with 30-day mortality.

Results. Among 8765 patients (hospitalized or not; median age, 65 years; 47.4% male), 16.6% developed coinfections: 12.1% bacterial, 2.1% viral, 0.9% fungal. An additional 6.4% only had clinical diagnosis of a coinfection. The adjusted risk of any coinfection was positively associated with age >50 years, male sex, cardiovascular, pulmonary, and renal comorbidities, diabetes, hematologic malignancy, multiple malignancies, Eastern Cooperative Oncology Group Performance Status, progressing cancer, recent cytotoxic chemotherapy, and baseline corticosteroids; the adjusted risk of superinfection was positively associated with tocilizumab administration. Among hospitalized patients, high neutrophil count and C-reactive protein were positively associated with bacterial coinfection risk, and high or low neutrophil count with fungal coinfection risk. Adjusted mortality rates were significantly higher among patients with bacterial (odds ratio [OR], 1.61; 95% CI, 1.33–1.95) and fungal (OR, 2.20; 95% CI, 1.28–3.76) coinfections.

Conclusions. Viral and fungal coinfections are infrequent among patients with cancer and COVID-19, with the latter associated with very high mortality rates. Clinical and laboratory parameters can be used to guide early empiric antimicrobial therapy, which may improve clinical outcomes.

Keywords. bacterial infections; CAPA (COVID-19-associated pulmonary aspergillosis); COVID-19; mucormycoses; viral infections.

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the etiologic agent of coronavirus disease 2019 (COVID-19), has infected >288 million people and contributed to >5.4 million deaths globally [1]. Among patients with confirmed COVID-19, the frequency of cancer diagnosis has been reported to be 2% [2]. Nevertheless, large meta-analyses of patients with cancer and COVID-19 have described mortality rates of 19%–23% and a case fatality rate (CFR) of 23% [2, 3]. Conversely, patients without cancer with COVID-19 had 3-fold lower odds of mortality and a CFR of only 6% [2, 3]. Patients

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with cancer hospitalized for management of COVID-19 have a >40% risk of developing severe illness [2].

Critical illness with interventions such as the placement of central venous access catheters and endotracheal tubes and shifts in the immune profile during COVID-19 might lead to the development of a coinfection [4]. Treatment modalities for COVID-19, including steroids and other immune-modulating therapies, such as interleukin 6 (IL6) inhibitors (eg, tocilizumab), can increase the risk of development of secondary infections. Several studies have described coinfections among patients with COVID-19. Meta-analyses have found bacterial infection rates of 3.5%–7% on initial presentation and 14.3% for secondary bacterial infection [5, 6]. A systematic review of 9 studies reporting coinfections among patients with COVID-19 showed that 8% of patients developed a bacterial or fungal coinfection [7].

Patients with cancer are vulnerable to infection due to myelosuppression and other forms of direct immune suppression caused by cytotoxic chemotherapy or chronic steroids, side effects of chemotherapy on mechanical barriers (eg, mucositis and skin ulceration), presence of indwelling central venous catheters, and increased exposure to health care facilities [8]. One study of 684 patients with cancer focused on coinfections showed higher incidence compared with the general population [5–7, 9].

In this study, we captured bacterial, fungal, and viral coinfections in a large multi-institutional cohort of patients with cancer and COVID-19, identified factors associated with an increased risk of such coinfections, and quantified the association of coinfections with 30-day all-cause mortality.

METHODS

Study Design

The COVID-19 and Cancer Consortium (CCC19) is an international registry that includes reports of >12 000 patients with current or historical cancer diagnoses who developed presumed or laboratory-confirmed COVID-19. The registry was built by and is maintained at Vanderbilt University Medical Center (VUMC) [10]. One hundred twenty-nine participating sites from the United States, Mexico, and Canada independently identify patients and report data through electronic REDCap survey instruments developed by CCC19. The mechanism of data collection can be retrospective (after the course of COVID-19) or concurrent at the discretion of the respondent. To ensure that data are high quality, each report is reviewed centrally and assigned a quality score, as previously described [10].

This was a retrospective cohort study with cross-sectional analyses (except for mortality analysis). We included adult (≥18 years) patients with a laboratory-confirmed diagnosis of SARS-CoV-2 infection, regardless of hospitalization status. We excluded reports with inadequate data quality (>4 according to our previously published metric), those with noninvasive cancers, premalignant conditions, nonmelanoma skin cancers, and those with unknown coinfection status or 30-day mortality [10]. Patients who were not admitted to the hospital were excluded from analyses that included laboratory values, because laboratory values were uncommonly reported among outpatients.

Procedures and Outcome Definitions

Day of COVID-19 diagnosis (baseline) was defined as the day the first positive PCR test was collected. The primary end point was any non-SARS-CoV-2 infection diagnosed with positive microbiological tests and/or compatible clinical picture (eg, chest imaging with superimposed pneumonia, not due to COVID-19 alone per clinician assessment), as explained below. All coinfections studied within this cohort were reported to have been within ±2 weeks of COVID-19 diagnosis. Coinfection data were either reported via a structured data field or interpreted from de-identified free-text responses provided by sites for each patient at the time of data entry, with queries sent to individual sites for clarification when appropriate (full data dictionary available at: https://github.com/covidncancer/CCC19_dictionary).

Secondary end points were bacterial, viral, and fungal coinfections. In a separate outcome analysis, we evaluated the association between coinfection and all-cause mortality within 30-days after COVID-19 diagnosis.

Covariates

Clinically relevant variables included in this study were age, sex, race and ethnicity, time of COVID-19 diagnosis, geographical region of patient residence, smoking status, obesity, comorbid conditions (cardiovascular, pulmonary, renal disease, diabetes), Eastern Cooperative Oncology Group (ECOG) Performance Status, type of malignancy (solid or hematological), cancer status (remission or active [measurable] disease, with active further classified as stable, responding to treatment, or progressing), anticancer therapy, and COVID-19 treatments. Active anticancer therapy was classified as either cytotoxic chemotherapy or all other therapies except surgery (targeted drugs, endocrine therapy, immunotherapy, radiotherapy) given before COVID-19 diagnosis [10].

We could not determine whether corticosteroids initiated after diagnosis of COVID-19 for treatment of COVID-19 were administered before or after coinfection onset. Therefore, we only studied baseline corticosteroids (preceding COVID-19 diagnosis, which the patients were taking for reasons other than COVID-19). Nevertheless, we examined the cross-sectional association between tocilizumab use as treatment for COVID-19 and superinfections, given that active infection is a contraindication to tocilizumab administration [11]. Therefore, it is highly unlikely that tocilizumab was administered after diagnosis of an infection other than COVID-19, and any coinfections were in all likelihood diagnosed after administration of tocilizumab.

Statistical Methods

All analysis methods were prespecified in a statistical analysis plan before initiation of the analysis (included with variable list as Supplementary Data). We used descriptive statistics to compare baseline characteristics between patients with and without any coinfection, both overall and among patients who were hospitalized for any reason at the time of COVID-19 diagnosis. Adjusted cross-sectional associations between these characteristics and the odds of any coinfection, as well as bacterial, viral, and fungal coinfections, were estimated from multivariable logistic regression models and represented as odds ratios (ORs) and 95% CIs. Logistic regression models also quantified the adjusted association of coinfection (any, bacterial, viral, fungal, and not classified [clinical only diagnosis]) with 30-day mortality. Adjustment variables were selected a priori based on clinical knowledge (Table 2; Supplementary Table 2); no statistical model selection procedures were used.

Exploratory analyses with smoothing splines were used to determine the association of age (as a continuous variable) with outcomes; regression splines were used to model apparent nonlinear associations. For analyses of any coinfection and bacterial coinfections, there were sufficient degrees of freedom to include all prespecified variables. For analyses of viral and fungal coinfections, model degrees of freedom were limited by the low number of events. We therefore used a reduced set of variables considered to be most clinically relevant (Table 1; Supplementary Table 1). Model stability was assessed by comparing adjusted and unadjusted regression coefficients and their standard errors, as well as variance inflation factors.

Multiple imputation (10 iterations) using additive regression, bootstrapping, and predictive mean matching was used to impute missing and unknown data, except unknown ECOG Performance Status and unknown cancer status, which were not imputed and included as "unknown" categories. Imputation was performed on the full data set (n = 8765). A separate imputation model (20 iterations) was developed for laboratory values among hospitalized patients (n = 4508). All analyses were performed in R, version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria), including the rms extension package.

Role of the Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or manuscript preparation. The corresponding author had full access to aggregate data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Patient Cohort

Of 12 034 reports in the registry at the time of data lock (6/6/2021), 8765 patients met inclusion criteria (Figure 1).

Table 1. Baseline Demographic and Clinical Characteristics Stratified by Diagnosis of any Coinfection

	Any Coinfection (n = 1459), No. (%)	No Coinfection (n = 7306), No. (%)
Age[a]		
Median [IQR], y	69.0 [60.0–78.0]	64.0 [54.0–74.0]
Sex		
Female	676 (46.3)	3925 (53.7)
Male	781 (53.5)	3376 (46.2)
Missing/unknown	2 (0.1)	5 (0.1)
Race/ethnicity		
Non-Hispanic White	791 (54.2)	3866 (52.9)
Non-Hispanic Black	276 (18.9)	1340 (18.3)
Hispanic	232 (15.9)	1150 (15.7)
Other	144 (9.9)	827 (11.3)
Missing/unknown	16 (1.1)	123 (1.7)
Region		
Northeast	685 (46.9)	2465 (33.7)
Midwest	332 (22.8)	2033 (27.8)
South	177 (12.1)	1120 (15.3)
West	185 (12.7)	1393 (19.1)
Undesignated	10 (0.7)	0 (0.0)
Non-US	70 (4.8)	295 (4.0)
Smoking status		
Never smoked	688 (47.2)	3964 (54.3)
Former smoker	659 (45.2)	2693 (36.9)
Current smoker	54 (3.7)	438 (6.0)
Missing/unknown	58 (4.0)	211 (2.9)
Obesity		
No	932 (63.9)	4471 (61.2)
Yes	526 (36.1)	2796 (38.3)
Missing/unknown	1 (0.1)	39 (0.5)
Comorbid conditions[b]		
Diabetes	502 (34.4)	1830 (25.0)
Pulmonary disease	376 (25.8)	1364 (18.7)
Cardiovascular disease	582 (39.9)	1956 (26.8)
Renal disease	320 (21.9)	942 (12.9)
Missing/unknown	4 (0.3)	62 (0.8)
ECOG Performance Status		
0	310 (21.2)	2579 (35.3)
1	378 (25.9)	1871 (25.6)
2+	324 (22.2)	894 (12.2)
Unknown	445 (30.5)	1955 (26.8)
Missing	2 (0.1)	7 (0.1)
Type of malignancy[b]		
Solid tumor	1113 (76.3)	5973 (81.8)
Hematological neoplasm	417 (28.6)	1567 (21.4)
Cancer status		
Remission/NED	640 (43.9)	3522 (48.2)
Stable/responding	370 (25.4)	2218 (30.4)
Progressing	264 (18.1)	918 (12.6)
Unknown	185 (12.7)	645 (8.8)
Missing	0 (0.0)	3 (0.0)
HCT		
No	1449 (99.3)	7267 (99.5)
Yes	10 (0.7)	38 (0.5)
Missing/unknown	0 (0.0)	1 (0.0)
Recent cytotoxic chemotherapy		
Never/beyond 12 mo	1015 (69.6)	5453 (74.6)
Within 4 wk	275 (18.8)	1129 (15.5)

Table 1. Continued

	Any Coinfection (n = 1459), No. (%)	No Coinfection (n = 7306), No. (%)
4 wk to 3 mo	64 (4.4)	252 (3.4)
3 to 12 mo	40 (2.7)	247 (3.4)
Missing/unknown	65 (4.5)	225 (3.1)
Baseline corticosteroids		
No	1102 (75.5)	6152 (84.2)
Yes	325 (22.3)	1012 (13.9)
Missing/unknown	32 (2.2)	142 (1.9)
Tocilizumab		
No	1326 (90.9)	6971 (95.4)
Yes	99 (6.8)	121 (1.7)
Missing/unknown	34 (2.3)	214 (2.9)
Period of COVID-19 diagnosis		
Jan–Apr 2020	385 (26.4)	1697 (23.2)
May–Aug 2020	689 (47.2)	2870 (39.3)
Sept–Dec 2020	226 (15.5)	1562 (21.4)
Jan–Apr 2021	142 (9.7)	1114 (15.2)
May–June 2021	11 (0.8)	45 (0.6)
Missing/unknown	6 (0.4)	18 (0.2)

Abbreviations: COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; HCT, hematopoietic cell transplant; NED, no evidence of disease.

[a]Age was truncated at 90 years.

[b]Percentages could sum to >100% because categories are not mutually exclusive.

The median age (interquartile range) was 65 (55–75) years; 47.4% were male, 53.1% were non-Hispanic White, 18.4% were non-Hispanic Black, and 15.8% were Hispanic. Most patients (80.8%) had solid tumors; 22.6% had hematologic malignancies; approximately half (51.4%) were hospitalized at the time of COVID-19 diagnosis; 11.8% died within 30 days after diagnosis of COVID-19. Patient characteristics are summarized in Table 1 for all patients and in Supplementary Table 1 for those who were hospitalized.

Factors Associated With Coinfections

A total of 1459 patients (16.6%) developed any coinfection, with 1059 (12.1%) bacterial, 188 (2.1%) viral, 79 (0.9%) fungal, and 560 (6.4%) coinfections that were diagnosed clinically. Adjusted cross-sectional associations of clinical or treatment factors and coinfections are summarized in Table 2 and Figure 2 for all patients and in Supplementary Table 2 for hospitalized patients only. Clinical types of coinfections are summarized in Supplementary Table 3.

Risk of any coinfection was positively associated with age among patients >50 years, male sex, cardiovascular, pulmonary, or renal comorbid conditions, diabetes, ECOG Performance Status, hematologic malignancy, multiple malignancies, progressing or unknown cancer status, cytotoxic chemotherapy within 4 weeks before COVID-19 diagnosis, baseline corticosteroids, tocilizumab administration, and COVID-19 diagnosis between May and August 2020.

A majority of the above factors showed strong associations of similar magnitude with the risk of bacterial coinfections. The risk for viral coinfection was positively associated with pulmonary disease, diabetes, hematologic malignancy, multiple malignancies, baseline corticosteroids, and diagnosis of COVID-19 between May and August 2020. Fungal coinfections were associated with cytotoxic chemotherapy last given between 3 months and 4 weeks before COVID-19 diagnosis and tocilizumab administration.

Among hospitalized patients, high C-reactive protein (CRP) was associated with higher risk of any coinfection, and high neutrophil count was associated with higher risk of bacterial or fungal coinfection. Neutropenia was associated with higher risk of fungal coinfection. Lymphopenia was not associated with risk of coinfection.

Mortality

All-cause 30-day mortality was significantly higher among patients with any (23.8%), bacterial (24.6%), and viral (22.9%) coinfections compared with all other patients (9.4%, 10.1%, and 11.6%, respectively) and >2-fold higher among patients with fungal coinfections (34.2%), compared with all other patients (11.6%) (Figure 3). Adjusted 30-day all-cause mortality rates were markedly higher among patients with any, bacterial, and especially fungal coinfections, compared with those without the respective coinfections (Table 3).

DISCUSSION

We identified factors associated with coinfection among 8765 patients with cancer and COVID-19. Laboratory values such as high neutrophil count may be useful in differentiating bacterial or fungal coinfection from COVID-19 alone. Neutropenia was associated with fungal coinfections, which were overall rare. Development of any, but especially fungal coinfection, was associated with higher adjusted all-cause mortality compared with patients without coinfection. Tocilizumab administration exhibited a strong association with development of bacterial and fungal superinfection.

Infection remains a leading cause of mortality among immunocompromised patients, including those with malignancies [8]. Many more patients with cancer die from infection, compared with the general population [12]. Patients with cancer and COVID-19 are subject to immune modulation through treatments for cancer (eg, chemotherapy-induced myelosuppression, administration of corticosteroids for antineoplastic or supportive purposes) and for COVID-19 infection (eg, corticosteroids, IL6 inhibitors). Furthermore, SARS-CoV-2 has been implicated as an immunomodulating virus, causing a maladaptive immune response [4].

The percentage of coinfections in immunocompromised patients with COVID-19 has been previously reported to be as high as 60% among transplant recipients [13]. In another recent study of patients with underlying malignancies or organ

Table 2. Adjusted Associations of Baseline Factors With Concomitant Infection Among all Patients

	Any Coinfection Odds Ratio (95% CI)	Bacterial Coinfection Odds Ratio (95% CI)	Viral Coinfection Odds Ratio (95% CI)	Fungal Coinfection Odds Ratio (95% CI)
Age			0.94 (0.85–1.05)[a]	1.00 (0.85–1.18)[a]
≤50 (per decade increase)	1.02 (0.88–1.18)	0.99 (0.83–1.18)	-	-
>50 (per decade increase)	1.14 (1.07–1.21)	1.18 (1.10–1.27)	-	-
Sex				
Female	Ref	Ref	-	-
Male	1.23 (1.08–1.38)	1.21 (1.05–1.38)	-	-
Race/ethnicity				
Non-Hispanic White	Ref	Ref	-	-
Non-Hispanic Black	0.97 (0.82–1.14)	1.02 (0.85–1.23)	-	-
Hispanic	1.09 (0.91–1.31)	1.29 (1.06–1.58)	-	-
Other	0.83 (0.67–1.03)	0.75 (0.58–0.97)	-	-
Region				
Northeast	Ref	Ref	Ref	-
Midwest	0.68 (0.58–0.79)	0.92 (0.77–1.09)	0.40 (0.26–0.60)	-
South	0.71 (0.58–0.86)	0.86 (0.69–1.08)	0.26 (0.14–0.48)	-
West	0.60 (0.50–0.73)	0.92 (0.75–1.13)	0.34 (0.20–0.58)	-
Non-US	1.12 (0.82–1.53)	1.70 (1.21–2.39)	0.18 (0.04–0.72)	-
Smoking status				
Never smoked	Ref	Ref	-	-
Former smoker	1.08 (0.95–1.23)	1.02 (0.88–1.18)	-	-
Current smoker	0.65 (0.48–0.89)	0.67 (0.47–0.96)	-	-
Obesity				
No	Ref	Ref	Ref	Ref
Yes	0.97 (0.85–1.10)	1.04 (0.90–1.20)	0.87 (0.64–1.20)	0.67 (0.41–1.11)
Diabetes				
No	Ref	Ref	Ref	Ref
Yes	1.35 (1.18–1.54)	1.36 (1.17–1.57)	1.51 (1.09–2.08)	1.16 (0.70–1.91)
Pulmonary disease				
No	Ref	Ref	Ref	Ref
Yes	1.27 (1.10–1.47)	1.32 (1.12–1.55)	1.69 (1.22–2.35)	1.39 (0.83–2.33)
Cardiovascular disease				
No	Ref	Ref	-	-
Yes	1.22 (1.06–1.40)	1.27 (1.09–1.48)	-	-
Renal disease				
No	Ref	Ref	-	-
Yes	1.31 (1.12–1.53)	1.35 (1.14–1.61)	-	-
ECOG Performance Status				
0	Ref	Ref	-	-
1	1.30 (1.10–1.55)	1.45 (1.19–1.76)	-	-
2+	1.95 (1.61–2.37)	2.33 (1.88–2.89)	-	-
Unknown	1.60 (1.36–1.90)	1.50 (1.23–1.82)	-	-
Type of malignancy				
Solid tumor	Ref	Ref	Ref	Ref
Hematological neoplasm	1.41 (1.21–1.64)	1.39 (1.17–1.66)	1.85 (1.31–2.62)	1.57 (0.93–2.65)
Multiple tumors	1.34 (1.12–1.59)	1.40 (1.16–1.70)	1.60 (1.05–2.42)	1.27 (0.65–2.49)
Cancer status				
Remission/NED	Ref	Ref	-	-
Stable/responding	0.78 (0.67–0.91)	0.80 (0.67–0.95)	-	-
Progressing	1.26 (1.05–1.51)	1.13 (0.92–1.40)	-	-
Unknown	1.25 (1.03–1.53)	1.13 (0.90–1.43)	-	-
HCT				
No	Ref	Ref	Ref	-
Yes	1.22 (0.58–2.57)	1.18 (0.50–2.75)	1.66 (0.37–7.37)	-
Recent cytotoxic chemotherapy				
Never/beyond 12 mo	Ref	Ref	Ref	Ref
Within 4 wk	1.35 (1.13–1.60)	1.16 (0.95–1.42)	0.89 (0.60–1.31)	1.54 (0.86–2.74)

Table 2. Continued

	Any Coinfection Odds Ratio (95% CI)	Bacterial Coinfection Odds Ratio (95% CI)	Viral Coinfection Odds Ratio (95% CI)	Fungal Coinfection Odds Ratio (95% CI)
4 wk to 3 mo	1.28 (0.94–1.73)	1.19 (0.84–1.69)	0.79 (0.37–1.66)	3.08 (1.41–6.70)
3 to 12 mo	0.90 (0.62–1.29)	0.75 (0.49–1.16)	0.55 (0.20–1.54)	0.93 (0.21–4.03)
Baseline corticosteroids				
No	Ref	Ref	Ref	Ref
Yes	1.39 (1.19–1.62)	1.23 (1.02–1.47)	2.42 (1.75–3.35)	1.40 (0.82–2.40)
Tocilizumab				
No	Ref	Ref	Ref	Ref
Yes	3.32 (2.48–4.44)	3.61 (2.67–4.87)	1.78 (0.98–3.21)	5.48 (2.72–11.04)
Period of COVID-19 diagnosis				
Jan–Apr 2020	Ref	Ref	Ref	-
May–Aug 2020	1.21 (1.04–1.40)	1.07 (0.90–1.27)	1.62 (1.15–2.29)	-
Sept–Dec 2020	0.87 (0.72–1.05)	1.04 (0.85–1.29)	0.33 (0.17–0.67)	-
Jan–Apr 2021	0.67 (0.54–0.83)	0.73 (0.58–0.93)	0.32 (0.15–0.69)[b]	-
May–Jun 2021	0.96 (0.48–1.93)	1.05 (0.48–2.29)	-	-

Abbreviations: COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplant; NED, no evidence of disease.

[a]Only linear term is included in the multivariable model.

[b]Comparison group: Jan–Jun 2021 vs Jan–Apr 2020.

transplantation, the cumulative incidence of coinfections was 27% [14]. Most immunosuppressed patients receive empiric antibacterial or antifungal agents, which can lead to high costs, side effects, drug–drug interactions, and development of resistance. In a previous report from Europe, North America, and South America, >80% of patients with cancer and COVID-19 received empiric antimicrobials, although only 8% had another infection at the time of COVID-19 diagnosis, and 19% developed secondary infections [9].

To our knowledge, this is the largest study of coinfections among patients with cancer and COVID-19 to date. Coinfections were reported in 17% of patients with cancer and COVID-19. This proportion is higher than that captured in the general population [7], but still relatively low, and similar to that of a previous report [9]. In that series, most coinfections were bacterial and associated with high CRP levels and increased mortality, in agreement with our results.

Our findings and those of Gudiol et al. indicate that most patients with cancer and COVID-19 do not develop coinfections [9]. However, the high mortality rates associated with coinfections in both reports call for early diagnosis and treatment. Also, like COVID-19 itself, bacterial and fungal infections can add indirectly to cancer-attributable morbidity and mortality by delaying the administration of potentially lifesaving chemotherapy [8]. Thus, we identified clinical parameters (older age, male sex, diabetes, pulmonary, cardiovascular, or renal comorbid conditions, baseline corticosteroids, cytotoxic chemotherapy, performance status, hematologic or multiple malignancies, progressing cancer) and laboratory values (CRP, neutrophil count) that could be useful for risk stratification. For example, neutropenic patients who have received recent cytotoxic chemotherapy or tocilizumab could benefit from preemptive protocols including serial (eg, weekly or twice weekly) testing of fungal markers and early administration of antifungal agents in the setting of worsening pneumonia or sepsis, taking into account regional and institutional epidemiological data.

Given that many factors associated with coinfection were also associated with adverse COVID-19 outcomes in prior studies (eg, older age, male sex, comorbidities), it is likely that coinfections are an important mediator of adverse outcome [15, 16]. However, lymphopenia was not associated with risk of coinfection, although it was strongly associated with severe illness and mortality in previous CCC19 studies [15, 16]. The results of this report merit further external validation and may help develop predictive models to guide timely and appropriate use of antibiotics and promote effective antimicrobial stewardship.

With the large number of mucormycosis cases observed during the SARS-CoV-2 surge in India, post-COVID-19 fungal infections have emerged as an important category of highly lethal coinfections [17]. The fungal syndrome that has been best described is COVID-19-associated pulmonary aspergillosis (CAPA), with small case series reporting frequencies of 20%–30% among patients with severe COVID-19 [18–20]. Unlike post-COVID-19 mucormycosis, where >90% of cases are proven, most cases of CAPA are classified as probable/putative [17, 18]. Notably, a series of postmortem cases and 1 recent systematic review of autopsy data indicate that many cases classified as CAPA reflect colonization with *Aspergillus*, as proven invasive mold disease was rare (0%–2%), even when studied only among patients with severe COVID-19 who died [21, 22].

Our results support the notion that COVID-19-associated fungal coinfections are rare, as their prevalence was only 0.9%. Likewise, Saade et al. reported only 1 fungal infection among

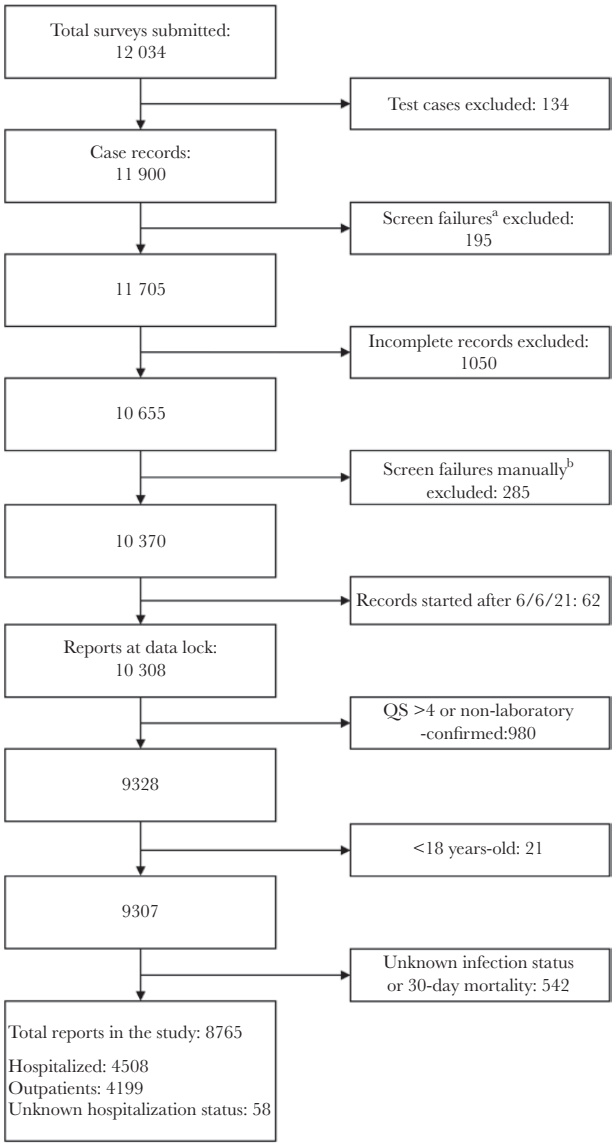

Figure 1. Descriptive flowchart of patients included in the study. [a]Nonmelanoma skin cancers, in situ malignancies, or premalignant conditions. [b]Duplicate records, noninvasive malignancies, precursor or benign hematologic conditions, presumed false-positive SARS-CoV-2 test results, low QS from a non-CCC19 site. Abbreviations: CCC19, COVID-19 and Cancer Consortium; QS, quality score; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

100 patients with cancer or organ transplantation and COVID-19, and Gudiol et al. found that only 1% of all patients with cancer and COVID-19 developed opportunistic infections; fungal pneumonia was the only fungal infection reported in 3 patients (<0.5%) [9, 14]. We acknowledge that diagnosis of invasive fungal infections is elusive, and some cases may not have been captured, especially given the 2-week time frame and long incubation times of mold infections [23]. Unlike some other cohorts, we do not know of standardized diagnostic protocols and surveillance for CAPA across different centers participating in CCC19 [24, 25]. However, these caveats could have been offset by the significant number of patients at risk for invasive fungal infections in our report, such as those with neutropenia (8.7% of patients with coinfections) (Supplementary Table 1) or receiving corticosteroids (36.3% of patients with coinfections) (Table 1).

Neutropenia exhibited a strong association with elevated risk of fungal infections, although it has been suggested that CAPA frequently occurs in atypical, immunocompetent (before diagnosis of SARS-CoV-2 infection) hosts with critical COVID-19 [18–20]. Interestingly, the strong association between fungal coinfection and receipt of cytotoxic chemotherapy within 4 weeks to 3 months before diagnosis of COVID-19 is aligned with the incubation period for most invasive fungal infections. Overall, our results further highlight the need for antifungal stewardship and prospective, carefully designed studies with tissue diagnoses to better define the epidemiology and clinical features of CAPA and other post-COVID-19 fungal infections [18].

The role of immunomodulating treatments among patients with COVID-19 who already have impaired immune systems remains controversial. Corticosteroids are currently the standard of care for hospitalized patients who require O_2 supplementation based on the results from the RECOVERY trial, which showed mortality benefit from dexamethasone, compared with controls [26]. In a previous observational study of patients with cancer, we did not find a significant 30-day mortality benefit from corticosteroids, which, nonetheless, were often administered to severely ill patients and combined with other treatments [27]. Broad use of corticosteroids has been implicated in outbreaks of post-COVID-19 mucormycosis: in 1 systematic review, 88% of patients with mucormycosis were receiving systemic steroids [17]. In another recent study, dexamethasone use was significantly associated with coinfections [14]. We found that patients receiving baseline corticosteroids (at the time of COVID-19 diagnosis, previously prescribed for reasons other than COVID-19 treatment) were at higher risk of coinfection after adjustment for other factors. Therefore, in such patients, early administration of antimicrobials, along with a thorough diagnostic workup and ongoing assessment for infection, is advisable.

We did not study the potential association of corticosteroid use as treatment for COVID-19 with coinfection, as we did not have event dates. However, we analyzed the relationship between administration of tocilizumab and presumably superinfection, as clinical suspicion of an active, preexisting bacterial, viral, or fungal coinfection precludes tocilizumab administration [11]. We found a strong association between tocilizumab use and development of any, bacterial, or fungal superinfections. Although residual confounding from unmeasured factors associated with critical illness and high oxygen requirements among patients who received tocilizumab is possible, our findings support the

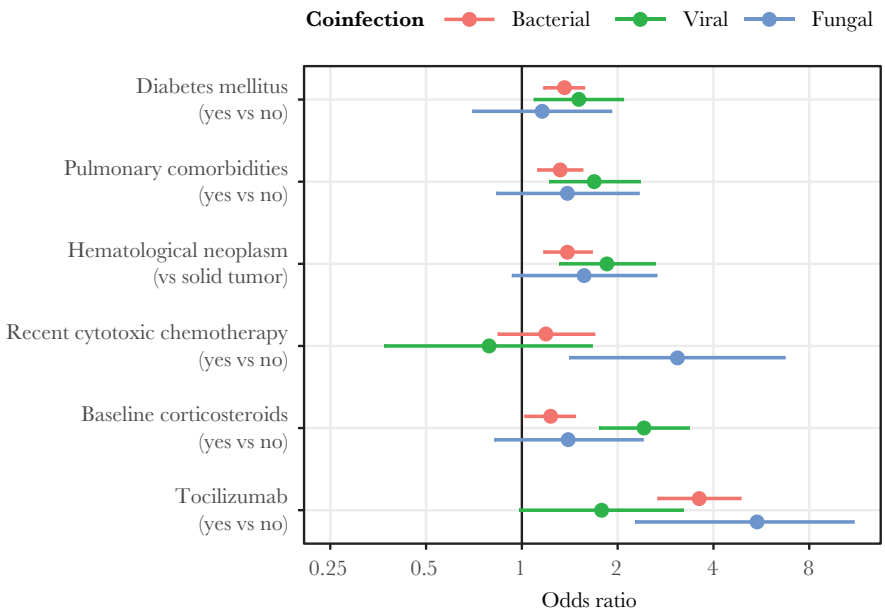

Figure 2. Forest plot of categorical clinical variables significantly associated with at least ≥1 coinfection category (bacterial, viral, or fungal). Recent cytotoxic chemotherapy is that received between 4 weeks and 3 months from the date of COVID-19 diagnosis. Abbreviation: COVID-19, coronavirus disease 2019.

current recommendation that IL6 inhibitors should be used with caution in immunocompromised patients [28].

Limitations of this study include retrospective data collection in many cases, potential ascertainment bias, limited granularity for specific pathogens and comorbid conditions, dependence on clinically annotated data with reliance on abstractor judgment, and use of time intervals rather than specific dates to ensure de-identified data. Also, we could not differentiate infections present at the time of COVID-19 diagnosis from nosocomial superinfections, which likely represent most coinfections among patients with COVID-19. We had no information regarding timing of corticosteroid administration as treatment for COVID-19 due to the survey design. Last, different and evolving institutional standards in diagnosing and reporting bacterial, viral, or fungal infections may account for the observed associations of coinfections with specific geographic regions and time periods.

While the above can be considered important limitations, this study represents a large multi-institutional effort subject to the realistic constraints of voluntary data reporting. Its strengths include the large number of patient records, allowing adjustments for multiple confounders, a comprehensive list of demographic, clinical, and laboratory variables, and a robust quality assurance process.

In conclusion, the frequency of coinfections among patients with cancer and COVID-19 in our study was relatively low but not trivial. Viral and fungal coinfections were uncommon. Coinfections were associated with high mortality rates. The use of tocilizumab in immunocompromised patients with cancer and COVID-19 may increase their risk of developing secondary infections. Several clinical and laboratory parameters could guide early empiric antimicrobial agent selection, which may improve clinical outcomes. These data could inform antimicrobial stewardship interventions in this tenuous patient population.

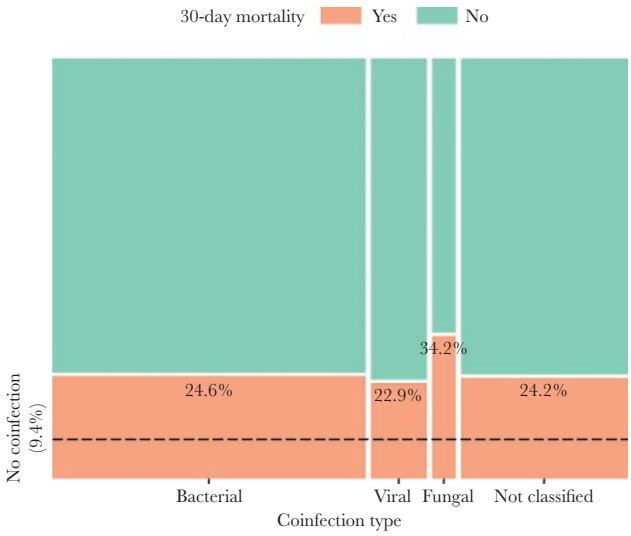

Figure 3. Thirty-day all-cause mortality by coinfection type. The width of the boxes is proportional to the number of coinfections; the height of the boxes is proportional to the number of patients who died or did not die within 30 days.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Table 3. Univariable and Adjusted Associations Between Coinfections and Mortality

	Unadjusted 30-Day Mortality[a]			
	Coinfection, No. (%)	No Coinfection, No. (%)	Adjusted[b] OR (95% CI)	*P* Value
Any[c]	347/1459 (23.8)	689/7306 (9.4)	1.77 (1.50–2.08)	<.001
Bacterial	261/1062 (24.6)	775/7703 (10.1)	1.61 (1.33–1.95)	<.001
Viral	43/188 (22.9)	993/8577 (11.6)	1.48 (0.99–2.21)	.058
Fungal	27/79 (34.2)	1009/8686 (11.6)	2.20 (1.28–3.76)	.004
Not classified	136/563 (24.2)	900/8202 (11.0)	1.14 (0.89–1.47)	.293

Abbreviations: COVID-19, coronavirus disease 2019; ECOG, Eastern Cooperative Oncology Group; HCT, hematopoietic cell transplant; OR, odds ratio.

[a]Number with 30-day mortality/No. with (yes/no) coinfection (%).

[b]For age, sex, race, region, comorbidities (cardiovascular, pulmonary, renal disease, diabetes), ECOG Performance Status, type of malignancy, cancer status, HCT, recent cytotoxic chemotherapy, corticosteroids at any time, tocilizumab, period of COVID-19 diagnosis.

[c]The C-statistic of the model with any concomitant infection is 0.834.

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Patient consent. This study was considered exempt from institutional review board (IRB) review at Vanderbilt University Medical Center (VUMC IRB 200467) and was approved by local IRBs at participating sites per institutional policy, according to the principles of the Declaration of Helsinki.

Trial registration. This study is registered on ClinicalTrials.gov, NCT04354701, and is ongoing.

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