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Co-infections and superinfections complicating COVID-19 in cancer patients: A multicentre, international study ☆

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SUMMARY

Background: We aimed to describe the epidemiology, risk factors, and clinical outcomes of co-infections and superinfections in onco-hematological patients with COVID-19.
Methods: International, multicentre cohort study of cancer patients with COVID-19. All patients were included in the analysis of co-infections at diagnosis, while only patients admitted at least 48 h were included in the analysis of superinfections.
Results: 684 patients were included (384 with solid tumors and 300 with hematological malignancies). Co-infections and superinfections were documented in 7.8% (54/684) and 19.1% (113/590) of patients, respectively. Lower respiratory tract infections were the most frequent infectious complications, most often caused by *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. Only seven patients developed opportunistic infections. Compared to patients without infectious complications, those with infections had worse outcomes, with high rates of acute respiratory distress syndrome, intensive care unit (ICU) admission, and case-fatality rates. Neutropenia, ICU admission and high levels of C-reactive protein (CRP) were independent risk factors for infections.
Conclusions: Infectious complications in cancer patients with COVID-19 were lower than expected, affecting mainly neutropenic patients with high levels of CRP and/or ICU admission. The rate of opportunistic infections was unexpectedly low. The use of empiric antimicrobials in cancer patients with COVID-19 needs to be optimized.

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Introduction

Bacterial and fungal infections represent a significant complication in some viral diseases, such as influenza. [1] Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, several studies have been published describing the epidemiology of infectious complications of COVID-19. Co-infections, diagnosed around the time of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, appear to be uncommon occurring in 0.6 to 3.2% of patients. [2–5] Bacterial respiratory co-infections with *Streptococcus pneumoniae* or *Staphylococcus aureus* are the most common causes of coinfections, whereas respiratory viral co-infections appear to be relatively rare.[4,6]

In contrast, nosocomial superinfections appear to be more frequent than co-infections, particularly among patients admitted to the intensive care unit (ICU) and those receiving high doses of corticosteroids[4,6–9]. These patients develop high rates of bloodstream infections and ventilator-associated pneumonia. Additionally, emerging data have demonstrated unexpectedly high rates of fungal infections, such as candidemia and invasive aspergillosis, particularly among mechanically ventilated patients.[4,5,7–10] Infections due to multidrug-resistant (MDR) organisms have been reported some series.[9] Importantly, outcomes of patients with superinfections are likely to be poor, with prolonged hospital stay[6,7,9] and higher mortality.[4,6]

Onco-hematological patients, including hematopoietic stem cell transplant (HSCT) recipients are at a higher risk of acquiring COVID-19,[11,12] with the associated mortality reported to be higher than that in the general population.[12,13] Yet, there is scarce information regarding infectious complications in cancer patients with COVID-19. Cancer as a comorbidity has been reported to be higher in patients with superinfections than in those without these complications.[4,9] However, there are only two studies that mention very briefly the incidence and types of infectious complications. In a series of 536 patients with hematologic malignancies, of whom 82 were allogeneic HSCT recipients, the only information provided was that 187 patients (34.8%) presented additional infections.[14] In another series involving 77 HSCT recipients (37 allogeneic, 37 autologous, and five CAR T-cell recipients), ten patients developed infections (13%), caused by multiple organisms in some patients.[15] The infections reported were bloodstream infections (BSIs) ($n = 3$), fungal pneumonia ($n = 3$), urinary tract infections (UTIs) ($n = 2$), *Clostridioides difficile* colitis ($n = 2$), bacterial pneumonia ($n = 1$) and Epstein-Barr virus reactivation ($n = 1$). Given these knowledge gaps, we designed an international multicenter cohort study of oncology patients with COVID-19. Our objectives were to define the epidemiology, risk factors and outcomes of infectious complications in these individuals, with a focus on co-infections present at the time of COVID-19 diagnosis and superinfections developing within 48 h of admission.

Methods

Study design and patients

The COVICAN registry was an international, multicenter, combined prospective/retrospective, observational cohort study of adult patients with cancer and COVID-19, across 28 hospitals from 9 countries in Europe, North America and South America from 1 March 2020 to 30 June 2020 (COVICAN registry). A list of the participating centers is provided in the Supplementary Material. All

Table 1
Baseline characteristics of patients with co-infections at COVID-19 diagnosis.

Characteristic	No co-infection $N = 630$ (%)	Co-infection $N = 54$ (%)	P value	Adjusted OR (95% CI)	P value
Age, years (median, IQR)	67 (18–95)	67.5 (20–88)	0.42	0.98 (0.93–1.02)	0.40
Male sex	364 (57.8)	31 (57.4)	1.00	1.52 (0.39–5.91)	0.54
Hematological malignancy	276 (43.8)	24 (44.4)	1.00		
Lymphoma	88 (14)	10 (18.5)			
Multiple myeloma	58 (9.2)	5 (9.3)			
Acute leukemia	40 (6.3)	3 (5.6)			
Myelodysplastic syndrome	21 (3.3)	2 (3.7)			
Chronic lymphocytic leukemia	48 (7.6)	3 (5.6)			
Hematopoietic stem cell transplant	54 (19.6)	2 (8.3)			
Solid tumor	354 (56.2)	30 (56.6)	1.00		
Lung cancer	82 (23.2)	3 (10)			
Breast cancer	60 (17)	5 (16.7)			
Colorectal cancer	58 (16.4)	2 (6.7)			
Upper GI tract cancer	24 (6.8)	2 (6.7)			
Urinary tract cancer	21 (5.9)	2 (6.7)			
Gynecological cancer	14 (4)	5 (16.7)			
Prostate cancer	29 (8.2)	3 (10)			
Head and neck cancer	16 (4.5)	3 (10)			
Hepatobiliary tumor	22 (6.2)	2 (6.7)			
Others	19 (3.01)	3 (5.5)			
Comorbidities					
Hypertension	290 (46.1)	28 (51.9)	0.47		
Diabetes mellitus	127 (20.3)	10 (18.9)	1.00		
COPD	52 (60.5)	4 (44.4)	0.48		
Chronic heart disease	23 (3.7)	2 (3.7)	1.00		
Chronic renal disease	21 (3.3)	1 (1.9)	1.00		
Immunosuppressive therapy					
Previous corticosteroids (1 month)	155 (24.8)	18 (33.3)	0.15		
Prednisone > 10 mg/day	91 (59.9)	8 (44.4)	0.21		
Immunotherapy/targeted therapies	130 (20.6)	10 (18.5)	0.86		
Monoclonal antibodies	35 (5.6)	4 (7.4)	0.53		
Neutropenia (< 500 cells/mm^3)	25 (4.3)	9 (18)	0.001	2.99 (0.99–9.06)	0.052
Inflammatory biomarkers (median, IQR)					
C-reactive protein (mg/L)	77.4 (0.08–580)	129 (3–629)	0.019	1.00 (1.00–1.02)	0.022
Procalcitonin (μg/L)	0.14 (0.0–105)	0.19 (0.03–80.9)	0.2		
Ferritin (μg/L)	831 (2.4–35,854)	1.343 (12.4–36.079)	0.22		
Creatine kinase (U/L)	56 (0.94–1.549)	56.5 (9–2.344)	0.31		
Antibacterial therapy	480 (78.4)	45 (88.2)	0.098		
Amoxicillin-clavulanate	58 (12.1)	6 (13.3)	0.81		
Broad-spectrum cephalosporins	64 (13.3)	3 (6.7)	0.24		
Carbapenems	91 (19)	17 (37.8)	0.006		
Quinolones	33 (6.9)	2 (4.4)	0.75		
Piperacillin-tazobactam	111 (23.1)	17 (37.8)	0.044		
Antifungal therapy	12 (2)	3 (5.9)	0.10		
Acute respiratory distress syndrome	185 (30.7)	29 (56.9)	<0.001		
Intensive care unit admission	77 (12.7)	8 (15.7)	0.51		
Overall in-hospital case fatality rate	187 (30.6)	28 (53.8)	<0.001		

COPD, Chronic obstructive pulmonary disease; Broad-spectrum cephalosporins: cefepime, ceftazidime, ceftolozane-tazobactam and ceftazidime-avibactam; Antifungal therapy (more than one antifungal was administered in some patients): fluconazole ($n = 5$), anidulafungin ($n = 3$), voriconazole ($n = 3$), micafungin ($n = 3$), caspofungin ($N = 2$), posaconazole ($n = 1$), Amfotericin B ($n = 1$).

patients had an active malignancy or were HSCT recipients with COVID-19, defined as symptoms of COVID-19 with a positive real-time reverse transcription PCR (RT-PCR) nasopharyngeal or oropharyngeal swab test. Active cancer was defined as metastatic cancer or anticancer treatment in any setting (curative, radical, adjuvant, or neoadjuvant) or administration of with cytotoxic chemotherapy or radiotherapy within the past 6 months. The COVICAN registry was built and maintained as an electronic REDCap database housed at Bellvitge University Hospital. Data collection was either retrospective or prospective. All patients were included in the analysis of co-infections at diagnosis, while only patients admitted for at least 48 h were included in the analysis of superinfections that developed during hospitalization. The study was approved by the Institutional Review Board of Bellvitge University Hospital (reference number PR133/20) and by the research ethics committees of the participating centers. Furthermore, it was conducted according to the guidelines of the Declaration of Helsinki. The need for informed consent was waived for retrospective cases by the clinical research ethics committees.

Data collection and procedures

We collected data on demographics, comorbidities, cancer status and therapy, laboratory tests, microbiological results (cultures and non-culture diagnostics such as fungal biomarkers and viral PCR results), treatment, and outcomes. All testing and treatment was conducted as routine care by the individual centers.

Definitions

Co-infections or nosocomial superinfections were defined as infections occurring at COVID-19 diagnosis or after 48 h of hospital admission for COVID-19, respectively. Neutropenia was defined as an absolute neutrophil count < 500 per mm^3.

Infectious were defined using the Centers for Disease Control National Healthcare and Safety Network[16]. A bloodstream infection (BSI) was defined as the growth of bacteria or fungi in at least one blood culture. BSIs caused by skin colonizers such as coagulase-negative staphylococci (CoNS) were considered to be significant

when the pathogens grew in two or more blood cultures drawn from different sites. Catheter-related BSIs were diagnosed in patients using at least one of the following criteria: (1) positive peripherally drawn blood cultures and positive blood cultures drawn from any of the catheter lumens; (2) time to positivity of at least 120 min for catheter-drawn blood cultures; or (3) positive culture of the same microorganism as that isolated from the catheter tip. Episodes of polymicrobial BSIs were those in which more than one type of organism was isolated from one or more blood cultures within a 72 h period. Bacterial respiratory infections were diagnosed in patients with one or more positive cultures of respiratory pathogens obtained from the blood, pleural fluids, sputum, bronchoalveolar lavage, and tracheal aspirate and/or a positive urinary *S. pneumoniae* antigen test. Other respiratory pathogens such as influenza A and B viruses, respiratory syncytial virus, parainfluenza virus and metapneumovirus were also studied in respiratory samples, based on the requests of the attending physician. Respiratory infections without microbiological diagnosis were considered in patients with the following criteria: (1) fever; (2) respiratory symptoms; (3) new pulmonary infiltrates; (4) exclusion of other non-infectious causes of pulmonary infiltrates. A urinary infection was defined as the growth of bacteria or fungi in a cultured urine sample from a patient with clinical symptoms and/or when a urinary infection was considered to be clinically significant by the researchers.

Aspergillus spp. tracheobronchitis was indicated by the isolation of *Aspergillus* species from respiratory samples of patients with purulent secretions and no radiological images. Invasive aspergillosis was diagnosed as possible, probable or proven according to EORCT/MSGERC criteria.[17]

Statistical analysis

Descriptive statistics were used to determine characteristics of patients and infections. To compare the characteristics, risk factors and outcomes between infected and non-infected patients, the Mann-Whitney U Fisher test, chi-square and Fisher exact tests were used for categorical and continuous variables, as appropriate. Patients with and without co-infections were compared in a univariate analysis in order to identify potential risk factors for co-infection at COVID-19 diagnosis. Similarly, patients with and without superinfections were compared in a univariate analysis in order to identify potential risk factors for superinfections during hospitalization. Multivariate logistic regression analyses were performed to identify independent risk factors for co-infections and superinfections, using variables that achieved statistical significance in the univariate analysis. *P*-values < 0.05 were considered significant.

Results

A total of 684 patients were included, all of whom had data available about co-infections with COVID-19; 590 of these patients also had follow-up data for nosocomial superinfections. Three hundred patients had an underlying hematological malignancy; lymphoma (32.6%, 98/300) and multiple myeloma (20.6%, 62/300) were the most common conditions (Table 1). Among the 384 patients with solid tumors, lung (22.1%, 85/384) and breast cancer (16.9%, 62/384) were the most frequent malignancies (Table 1).

Co-infections at COVID-19 diagnosis

Overall, 7.8% (54/684) of patients presented with co-infections. The characteristics of patients with and without co-infections are shown in Table 1. There were no relevant differences in the baseline characteristics of the patients. However, higher levels of C-reactive protein (CRP) and the presence of neutropenia at diagnosis were more frequently reported in patients with co-infections. Antibiotic therapy was more frequently administered in this group of patients, particularly carbapenems (37.8% vs 19%, $p = 0.006$) and piperacillin-tazobactam (37.8% vs 23.1%, p=0.044). Patients with co-infections were more likely to present worse outcomes, with higher rates of acute respiratory distress syndrome (56.9% vs 30.7%, $p < 0.001$) and a higher overall in-hospital case-fatality rate (53.8% vs 30.6%, $p = 0.001$).

Table 2 details the types and etiologies of the 54 co-infections identified at COVID-19 diagnosis. All co-infections were bacterial. Respiratory tract infections were the most common (38.8%), followed by BSIs (33.3%). *Streptococcus pneumoniae* and Gram-negative bacilli (which included three cases of *Pseudomonas aeruginosa*) were the most common causes of respiratory tract infections (42.8% (9/21) and 33.3% (7/21), respectively). Eighty nine percent of *S. pneumoniae* pneumonias were diagnosed by urinary antigen test. Three episodes were associated with BSI (*Haemophilus influenzae* ($n = 2$) and *Escherichia coli* ($n = 1$)), and two episodes were polymicrobial. Among BSI episodes, catheter-related BSIs due to CoNS were the most common cause (33.3%, 6/18), followed by

Table 2
Type and microbiological etiology of 54 co-infections occurring in 54 cancer patients at COVID-19 diagnosis.

Co-infections at COVID-19 diagnosis	N (54/684 (7.8%))
Respiratory tract infections[a]	21 (38.8%)
Streptococcus pneumoniae[b]	9
Moraxella catarrhalis	3
Haemophilus influenzae[c]	3
Pseudomonas aeruginosa	3
E. coli[d]	1
Klebsiella pneumoniae	1
Enterobacter cloacae	1
Serratia marcescens	1
Staphylococcus aureus[e]	1
Bacteremia[f]	18 (33.3%)
E. coli	5
Viridans group streptococci	3
Enterococcus faecium	2
P. aeruginosa	1
Listeria monocytogenes	1
Capnocytophaga sputigena	1
S. aureus	1
Catheter-related bacteremia	6
Coagulase-negative staphylococci	6
Micrococcus letis	1
Urinary tract infection[g]	15 (27.7%)
E. coli[h]	9
K. pneumoniae	2
Enterococcus faecalis	2
Klebsiella oxytoca	1
Proteus mirabilis	1
P. aeruginosa	1
Enterobacter aerogenes	1
Enterococcus faecium	1

[a] Two episodes were polymicrobial: *E. coli* + *Streptococcus pneumoniae* ($n = 1$), and *Serratia marcescens* + *Enterobacter cloacae* ($n = 1$).
[b] Eight episodes were diagnosed by the pneumococcal urinary antigen test.
[c] Two episodes were diagnosed by positive blood cultures.
[d] This episode was associated with bacteremia.
[e] Positive culture from pleural effusion.
[f] Three episodes were polymicrobial: *E. coli* + viridans group streptococci ($n = 1$), *E. coli* + *Enterococcus faecium* ($n = 1$), and *Pseudomonas aeruginosa* + *Staphylococcus aureus* ($n = 1$).
[g] Three episodes were polymicrobial: *Klebsiella oxytoca* + *E. faecium* ($n = 1$), *E. coli* + *E. faecalis* ($n = 1$), and *P. aeruginosa* + *Proteus mirabilis* ($n = 1$).
[h] One episode was associated with bacteremia.

E. coli (27.7%, 5/18) and viridans group streptococci (VGS) (16.6%, 3/18). Three episodes of BSI were polymicrobial. Among the UTIs, *E. coli* was the most common pathogen (60%), and three episodes were polymicrobial.

The risk factors for co-infections at COVID-19 diagnosis are also shown in Table 1. By univariate analysis, higher levels of CRP and the presence of neutropenia at COVID-19 diagnosis were more frequently seen in patients with co-infections. In multivariate logistic regression, neutropenia was found to be the only significant independent risk factor for co-infections at COVID-19 diagnosis.

Superinfections during hospitalization

Overall, 82 patients developed 113 superinfections during hospitalization (19.1%). Table 3 outlines the characteristics, outcomes and risk factors of patients with and without superinfections during hospitalization. Patients with hematologic malignancies, particularly those with lymphoma, were more likely to develop superinfections than those with solid tumors (57.3% vs. 42.7%, $p = 0.023$). Patients treated with immunotherapy or targeted therapies in the previous 3 months were less likely to present superinfections than those were not (11% vs. 22.4%, $p = 0.018$). In contrast, neutropenia (10.8% vs. 4.2%, $p = 0.04$), and the use of corticosteroids for the treatment of COVID-19 (48.1% vs. 36.9%, $P = 0.049$), were significantly more common in patients presenting with superinfections. In multivariate analysis, only neutropenia and ICU admission were found to be independent risk factors for developing a superinfection during hospitalization. Antibiotic and antifungal therapies were more frequently administered in this group of patients, particularly carbapenems (44.3% vs. 16.2%, $p < 0.001$) and piperacillin-tazobactam (36.7% vs. 22.2%, $p = 0.010$). Patients with superinfections had poorer outcome than those without superinfections, with higher rates of acute respiratory distress syndrome (44.3% vs. 31.3%, $p = 0.028$), ICU admission (35% vs. 10.1%, $p < .001$), and invasive mechanical ventilation (33.8% vs. 5.9%, $p < 0.001$), as well as higher ICU-associated case-fatality rates (14.1% vs 4.7%, $p = 0.003$).

The types and etiologies of the 113 episodes of superinfections occurring in 82 cancer patients are detailed in Table 4. Respiratory tract infections were the most frequent infectious complications (46/113, 40.7%). In 17 cases (36.9%), no microorganisms were identified. Gram-negative bacteria accounted for more than half of the cases (52.1%), with *P. aeruginosa* being the most common (34.7%). *Aspergillus fumigatus* was the etiological agent in three cases of tracheobronchitis (one polymicrobial with *P. aeruginosa*). Only seven cases of opportunistic infections developed, including five cases of cytomegalovirus viremia, one case of probable invasive pulmonary aspergillosis (IPA) and one case of BK polyomavirus-associated hemorrhagic cystitis. Only six infections were caused by MDR organisms: three due to MDR *P. aeruginosa*, two due to methicillin-resistant *S. aureus* and one caused by extended-spectrum ß-lactamase-producing *Enterobacter* spp.

Discussion

In our large multinational cohort of onco-hematological patients with COVID-19, we found that the rate of co-infections at the time of diagnosis was more than double the rate reported in the general population[2–5] but the rate of superinfections was comparable to those observed in previous reports in the general population.[6–9] Neutropenia was a major risk factor for both co-infections and superinfections, whereas ICU admission was also a risk factor for superinfections. Surprisingly, no respiratory viral co-infections were encountered, and the rate of opportunistic infections, particularly IPA, was unexpectedly low. Nevertheless, patients with co-infections and/or superinfections presented worse outcomes, with higher case fatality rates. Taken together, our data highlight the need for improved diagnostics to identify patients at highest risk for infections following COVID-19, in order to prioritize these patients for antimicrobial therapy.

Although there are some published studies involving large cohorts of onco-hematological patients with COVID-19, data on the rates, characteristics and outcomes of infectious complications in this population are lacking.[14, 15, 18–21] This is of special concern since cancer patients are at a higher risk of acquiring COVID-19.[11,12] Due to their often severely impaired immune system, it has been widely assumed that the risk of developing additional infectious complications is high. As a consequence, it has been reported that the number of antimicrobial prescriptions in cancer patients with COVID-19 has been high,[18–21] even in patients showing no evidence of infectious complications during hospitalization, which reached 81.5% in our study. This is of special concern in the current era of emerging antimicrobial resistance, since a reduction of antibiotic consumption is a cornerstone in the fight against the development of resistance.

In our series, co-infections mainly occurred in patients with neutropenia and high levels of CRP. These included both bacterial co-infections commonly encountered in cancer patients (*S. pneumoniae, P. aeruginosa*), as well as BSIs, which are common in cancer patients due to the presence of indwelling catheters, mucositis, and neutropenia.[22,23] These findings suggest that antibiotics may not need to be administered to all cancer patients who present with COVID-19, but may instead be targeted more to those with neutropenia and elevated CRP levels. No other respiratory viruses were identified, although this may have been a result of limited diagnostic testing in 2020, due to swab and PCR reagent shortages.

Nearly 20% of patients developed nosocomial superinfections, which was lower than we had originally expected, as many patients had previously received immunosuppressive therapies and/or immunomodulatory treatments for COVID-19. This finding may be a result of limitations in diagnostic testing in patients who are under COVID-19 transmission-based precautions. ICU stay and neutropenia were risk factors for superinfections, further suggesting that even among hospitalized patients, empiric antibiotics may potentially be withheld for most individuals, except for critically ill patients and those with neutropenia. Additional studies are needed to help optimize antibiotic use in critically ill neutropenic cancer patients, in whom distinguishing between respiratory failure and fever from COVID-19 versus an underlying bacterial infection can be difficult.

Interestingly, opportunistic infections were unexpectedly rare, with only one case of documented IPA, although three patients were diagnosed with *Aspergillus* tracheobronchitis. The rates of COVID-19-associated pulmonary aspergillosis (CAPA) reported in the literature vary greatly, ranging from 0.1 to 47.4%.[24–28] We hypothesize that these findings may be explained by the challenges encountered in diagnosing CAPA: diagnostic criteria are poorly-defined, the radiological findings are often non-specific in individuals with concurrent COVID-19 pneumonia, testing may be infrequently sent due to lack of clinician awareness, the performance of fungal biomarkers assays in CAPA is unknown (although the galactomannan assay is expected to have a good performance in neutropenia), and it is difficult to distinguish colonization from infection. Nonetheless, the rate of IPA observed in patients with COVID-19, even when they carry a baseline immunosuppressive condition (such as our patients), appears to be much lower than that observed in patients with influenza.[12–13] Other invasive fungal infections, such as *Candida*, were not observed in our cohort compared to other reports.[29–30]

The in-hospital case-fatality rate in our cohort was 32.4% (215/664), which is significantly higher than that reported for the general population, but in line with several other reports involving cancer patients.[18–21] Patients with infectious complications in

Table 3
Main characteristics of 82 patients with superinfections after 48 h of hospitalization for COVID-19.

Characteristic	Patients without a superinfection $N = 508$ (%)	Patients with a superinfection $N = 82$ (%)	P value	Adjusted* OR (95% CI)	P value
Age, years (median, IQR)	67 (40–84)	47 (22–72)	0.084	0.98 (0.95–1.00)	0.011
Male sex	278 (54.7)	55 (67.1)	0.041	0.93 (0.45–1.92)	0.85
Hematological malignancy	219 (43.1)	47 (57.3)	0.023	1.07 (0.49–2.31)	0.85
Lymphoma	66 (13)	19 (23.2)			
Acute leukemia	29 (5.7)	9 (11)			
Multiple myeloma	52 (10.2)	6 (7.3)			
Myelodysplastic syndrome	15 (3)	1 (1.2)			
Chronic lymphocytic leukemia	40 (7.9)	7 (8.5)			
Hematopoietic stem cell transplant	44 (20.1)	6 (12.8)			
Solid tumor	289 (57)	35 (42.7)	0.023		
Lung cancer	56 (19.4)	7 (20)			
Breast cancer	60 (20.8)	0			
Colorectal cancer	53 (18.4)	4 (11.4)			
Prostate cancer	22(7.6)	6 (17.1)			
Upper GI tract cancer	19 (6.6)	1 (2.9)			
Urinary tract cancer	16 (5.6)	3 (8.6)			
Gynecological cancer	13 (4.5)	5 (16.7)			
Head and neck cancer	9 (3.1)	4 (11.4)			
Hepatobiliary tumor	15 (5.1)	5 (14.3)			
Other	15 (5.1)	0			
Comorbidities					
Hypertension	241 (47.5)	39 (47.6)	1.00		
Diabetes mellitus	99 (19.6)	15 (18.3)	0.88		
COPD	37 (57.8)	10 (55.6)	1.00		
Chronic heart disease	19 (3.7)	4 (4.9)	0.54		
Chronic renal disease	14 (2.8)	4 (4.9)	0.30		
Immunosuppressive therapy					
Previous corticosteroids (1 m)	130 (25.7)	23 (28)	0.68		
-Prednisone > 10 mg/day	75 (58.6)	13 (59.1)	1.00		
Immunotherapy/targeted therapies	114 (22.4)	9 (11)	0.018	0.50 (0.17–1.43)	0.20
Monoclonal antibodies	29 (5.7)	7 (8.5)	0.32		
Neutropenia (< 500 cells/mm^3)	20 (4.2)	8 (10.8)	0.040	4.88 (1.35–17.5)	0.015
Inflammatory biomarkers (median, IQR)					
C-reactive protein (mg/L)	65 (12–250)	79.4 (13–381)	0.16	1.00 (1.00–1.00)	0.12
Procalcitonin (μg/L)	0.10 (0.02–3.94)	0.24 (0.11–2.00)	0.94		
Ferritin (μg/L))	1.247 (30–12.474)	654 (466–11,330)	<0.001		
Creatine kinase (U/L)	66 (16–296)	85 (16–185)	0.54		
Therapy					
Hydroxychloroquine	375 (92.4)	60 (83.3)	0.023		
Lopinavir/ritonavir	222 (54.7)	44 (61.1)	0.36		
Remdesivir	15 (3.7)	6 (8.2)	0.11		
Tocilizumab	75 (18.5)	18 (25)	0.20		
Corticosteroids	185 (36.4)	39 (48.1)	0.049	2.03 (0.96–4.30)	0.062
Corticosteroids and/or immunomodulators	204 (40.2)	42 (51.9)	0.053		
Antibacterial therapy	414 (81.5)	79 (97.5)	<0.001		
Amoxicillin-clavulanate	52 (12.6)	9 (11.4)	0.85		
Broad-spectrum cephalosporins	51 (12.3)	16 (20.3)	0.059		
Carbapenems	67 (16.2)	35 (44.3)	<0.001		
Quinolones	25 (6)	8 (10.1)	0.21		
Piperacillin-tazobactam	92 (22.2)	29 (36.7)	0.010		
Antifungal therapy	9 (1.8)	5 (6.2)	0.032		
Acute respiratory distress syndrome	158 (31.3)	35 (44.3)	0.028		
ICU admission	51 (10.1)	28 (35)	<0.001	4.98 (2.26–10.9)	<0.001
Invasive mechanical ventilation	30 (5.9)	27 (33.8)	<0.001		
Overall in-hospital case-fatality rate	157 (31.3)	26 (32.5)	0.89		
ICU-associated case-fatality rate	23 (4.7)	11 (14.1)	0.003		

ICU, intensive care unit. COPD, Chronic obstructive pulmonary disease; Broad-spectrum cephalosporins: cefepime, ceftazidime, ceftolozane-tazobactam and ceftazidime-avibactam; Antifungal therapy (more than one antifungal was administered in some patients): fluconazole ($n = 5$), voriconazole ($n = 3$), micafungin ($n = 3$), caspofungin ($n = 2$), anidulafungin ($n = 2$) posaconazole ($n = 1$), Amfotericin B ($n = 1$).

our study had worse outcomes, higher rates of acute respiratory distress syndrome, ICU admission, and increased mortality. These findings are consistent with those of previous reports of oncology patients with respiratory viral infections.[4,6,7,9] However, there are several variables that may influence the outcomes of cancer patients with COVID-19, particularly the presence of uncontrolled underlying malignancy. Thus, these worse outcomes cannot be entirely attributed to the development of infectious complications.

Limitations of the study include its partial retrospective design and the fact that diagnostic testing was performed according to the discretion of the individual sites. Our rate of infection may be falsely low, particularly in the setting of enhance COVID-19 transmission-based precautions limiting the ability of clinicians to perform diagnostic tests for infection. Additionally, systematic testing for viral co-infections was not performed by all participating centers. Despite these limitations, ours is the first published report addressing infectious complications in immunocompromised cancer patients with COVID-19. We include data for a large number of patients from 28 centers located in nine countries around the world, thereby improving the generalizability of our results.

In conclusion, in our large multinational cohort of cancer patients with COVID-19, co-infections were higher than in the gen-

Table 4
Detailed microbiological etiology of 113 superinfections occurring in 82 cancer patients after 48 of hospitalization for COVID-19.

Superinfections during hospitalization for COVID-19	113/590 (19.1%)
Ventilator-associated pneumonia	10 (8.8%)
Pseudomonas aeruginosa	5
Enterobacter aerogenes + *Burkholderia cepacia*	1
Not identified	4
Non-ventilator-associated pneumonia[a]	18 (15.9%)
Streptococcus pneumoniae	3
Pseudomonas aeruginosa	2
Haemophilus influenzae	1
E. coli	1
Stenotrophomonas maltophilia	1
Not identified	11
Nosocomial tracheobronchitis[b]	18 (15.9%)
P. aeruginosa	9
Aspergillus fumigatus	3
Staphylococcus aureus	2
Enterobacter aerogenes	2
E. coli	1
S. maltophilia	1
Acinetobacter baumannii	1
Not identified	2
Bacteremia[c]	31 (27.4%)
E. coli	4
P. aeruginosa	3
Enterococcus faecalis	2
Enterococcus faecium	1
Viridans group streptococci	1
Candida albicans	1
Catheter-related bacteremia	20
Coagulase-negative staphylococci	16
E. faecium	3
E. faecalis	2
P. aeruginosa	1
Candida parapsilosis	1
Urinary tract infection[d]	17 (12.7%)
E. faecium	4
E. faecalis	3
E. coli	3
P. aeruginosa	3
Proteus mirabilis[e]	2
Staphylococcus aureus	1
Citrobacter koseri	1
Candida krusei	1
Candida glabrata	1
Candida parapsilosis[f]	1
***Clostridium difficile* colitis**	6 (5.3%)
Other bacterial infections	4 (3.5%)
Biliary tract infections[g]	3
Peritonitis	1
Opportunistic infections	7 (6.1%)
Invasive pulmonary aspergillosis	1
Cytomegalovirus viremia	5
BK polyomavirus-associated hemorrhagic cystitis	1

[a] One episode was polymicrobial: *E. coli* + *Streptococcus pneumoniae* ($n = 1$).
[b] Three episodes were polymicrobial: *E. coli* + *Pseudomonas aeruginosa* ($n = 1$), *P. aeruginosa* + *Aspergillus fumigatus* ($n = 1$), and *Staphylococcus aureus* + *Enterobacter aerogenes* ($n = 1$).
[c] Four episodes were polymicrobial: *Enterococcus faecium* + *P. aeruginosa* ($n = 1$), *Enterococcus faecalis* + *Candida parapsilosis* ($n = 2$), and *E. faecalis* + *Staphylococcus haemolyticus* ($n = 1$).
[d] Two episodes were polymicrobial: *E. faecium* + *P. aeruginosa* ($n = 1$), and *E. faecalis* + *P. aeruginosa* ($n = 1$).
[e] This episode was bacteremic.
[f] This was an episode of candidemia.
[g] One episode was caused by *E. coli* + *Candida tropicalis*.

eral population, mainly affected neutropenic patients and critically ill ICU patients, and were associated with severe disease and poor outcomes. Further studies are needed to define the risk factors for bacterial and fungal infections in oncology patients with COVID-19 to better optimize antimicrobial use in these vulnerable individuals, and avoid unnecessary antibiotic exposure.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.07.014.

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