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Coronavirus Pandemic

Bacterial co-infections in cancer patients with COVID-19: predictors and antimicrobial resistance trends

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Abstract

Introduction: Within the context of the coronavirus disease 2019 (COVID-19) pandemic, this study investigated the multifaceted challenges of bacterial infections in cancer patients with COVID-19. It focuses on clinical predictors, resistance patterns, and microbiological characteristics.
Methodology: Over 18 months, 112 adult cancer patients with coronavirus infection confirmed by reverse transcription polymerase chain reaction (RT-PCR) were enrolled. Bloodstream and respiratory samples were evaluated for bacterial infection using the Phoenix automation system for definitive species identification. In vitro susceptibility testing followed the Clinical Laboratory Standards Institute (CLSI) M100-Ed30 guidelines.
Results: Bacterial infections affected 25.0% of patients, encompassing bacteremia (21.4%) and respiratory tract infections (8.0%). Multivariable analysis identified hypertension, age < 60, and critical COVID-19 as significant predictors for bacterial infections (p-values = 0.024, 0.029, and 0.039, respectively). Most patients received antimicrobial therapy (93.8%), including last-resort carbapenems (52.7%) and colistin (8.9%). Thirty-three bacterial isolates were identified, with secondary infections doubling co-infection rates. *Escherichia coli*, *Klebsiella* species, and *Staphylococcus aureus* were the most common co-infecting species, while *Klebsiella*, *Acinetobacter*, and *Pseudomonas* species were more frequently associated with secondary infections. Alarmingly, 84.8% of isolates displayed high resistance patterns. All isolated *S. aureus* species were methicillin-resistant, and 62.5% of Gram-negative bacteria were exclusively sensitive to colistin.
Conclusions: The dominance of highly transmissible hospital-acquired bacterial species, with increased resistance and extensive antibiotic use in COVID-19 patients, necessitates strict infection control and antimicrobial stewardship. Developing customized antimicrobial strategies for cancer patients with COVID-19 is crucial to managing bacterial infections effectively and improving patient outcomes.

Key words: Critical and severe COVID-19; multidrug-resistant; co-infections; secondary infections; cancer patients.

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Introduction

Coronavirus disease 2019 (COVID-19) is a coronavirus infection discovered in December 2019 in China. Later, this virus was recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Cancer patients are more susceptible to severe COVID-19 infection, which is exacerbated by factors such as chemotherapy [2]. Identifying patients' clinical criteria and risk variables linked to COVID-19 severity is crucial for prompt and appropriate management, especially considering the absence of targeted therapies [3]. Moreover, respiratory viral epidemics and pandemics have long been linked to an increased incidence of associated bacterial infections, further complicating the primary clinical course and prognosis [4]. Numerous studies have found strong correlations between bacterial co-infections or secondary infections and increased morbidity and mortality rates among COVID-19 patients [4-7].

On the other hand, the overuse of antibiotics during the COVID-19 pandemic and the disparity between confirmed bacterial infection rates and antibiotic use have raised concerns about increasing antimicrobial resistance (AMR). This, in turn, can lead to the reappearance of previously controlled pathogens and the emergence of new, more pathogenic and resistant variants. Even before the pandemic, developing countries reported high levels of resistance. According to World Health Organization (WHO) guidelines, antibiotics should be reserved for more severe,

complicated COVID cases, particularly those with a higher prevalence of bacterial infections, including multidrug-resistant (MDR) pathogens [8]. This situation necessitates immediate action, such as antimicrobial stewardship, to ensure efficient antibiotic usage, limit the risk of AMR, and prevent further deterioration of the patient [9].

Even though some studies found that COVID-19 patients had fewer bacterial co-infections than those with influenza and respiratory syncytial virus (RSV) [9,10], characterizing bacterial infections in COVID-19 patients is still essential since this will alter the patients' care and prognosis and might save lives, especially among those with severe illness [4]. Understanding bacterial infection determinants in COVID-19 patients can reveal antibiotic-benefit circumstances and antimicrobial stewardship opportunities [9]. Moreover, recognizing bacterial species' diversity and susceptibility patterns is crucial for designing effective policies for the global AMR crisis. Thus, we aimed to assess the landscape of bacterial infection in cancer patients with COVID-19, shedding light on antimicrobial resistance trends, microbiological characteristics, and clinical predictors for these infections.

Methodology

Study design and patients

This was an observational cohort study of cancer patients who received care at the National Cancer Institute (NCI) – Cairo University, Egypt. NCI is the largest comprehensive cancer facility in Egypt and North Africa, serving over 250,000 oncology patients annually. All adult cancer patients (> 18 years old) diagnosed with hematological and solid organ tumors and confirmed positive for coronavirus infection by RT-PCR between June 2020 and December 2021 were included. The severity of the patient's illnesses was evaluated according to WHO criteria: those with mild COVID-19 displayed non-specific symptoms and normal chest computed tomography (CT) findings. Patients with a moderate infection exhibited mild pneumonia on CT scans and did not need supplemental oxygen. Patients with severe disease experienced severe respiratory symptoms, a respiratory rate exceeding 30 breaths per minute, or oxygen saturation below 93% at rest. Patients with critical illness presented with sepsis and acute organ dysfunction or acute respiratory distress syndrome (ARDS) or sepsis with acute organ dysfunction [11].

Detection of bloodstream and respiratory co-infections and secondary infections

The prevalence of bloodstream and respiratory co-infections and secondary infections was estimated. Co-infection is the simultaneous presence of another pathogen, such as bacterial isolates, alongside a coronavirus infection. Conversely, a secondary infection follows coronavirus infection and is identified 48 hours after the initial COVID-19 diagnosis [4,9]. Blood isolates were included in the case of coagulase-negative *staphylococci* (CoNS) if at least two or more patient bottles revealed the same species. Sputum specimens were included if they exhibited a count of at least 25 polymorphonuclear leukocytes (PMNs) and less than ten epithelial cells per low-power field (10×) [12]. Samples showing only normal flora were excluded.

Blood culture bottles were analyzed using a Becton Dickinson BACTEC fluorescent series 9120 analyzer. Positive vials were then subcultured on blood, chocolate, and MacConkey agar plates for bacteria isolation. Blood, chocolate, and MacConkey agar plates were also used for respiratory specimens. Mueller–Hinton agar media was used for antimicrobial susceptibility testing (AST) via the disk diffusion method. The isolated colonies were identified primarily through microscopic examination and cultural characteristics. The Phoenix automation system was employed for definitive bacterial species identification and additional AST. The antibiotics tested for Gram-negative bacteria included amikacin, cefepime, cefoxitin, cefotaxime, imipenem, meropenem, levofloxacin, ciprofloxacin, piperacillin/tazobactam, and colistin. For Gram-positive bacteria, oxacillin, cefoxitin, gentamicin, clindamycin, erythromycin, azithromycin, ciprofloxacin, linezolid, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin antibiotics were tested. The CLSI (M100-Ed30) were followed to interpret the AST results of the disk diffusion method and the automation system [13].

Multidrug-resistant (MDR) bacteria were defined as having acquired resistance to at least a single antibiotic in three or more classes. However, extensively drug-resistant (XDR) bacteria were defined as being resistant to at least one drug in all but two or fewer antibiotic classes, making the bacteria susceptible to only one or two categories. Methicillin-resistant *S. aureus* (MRSA) was considered when oxacillin and cefoxitin resistance were present [14]. MDR was assigned to all MRSA isolates since this phenotype predicts resistance to β-lactam antimicrobials such as penicillins, cephalosporins, and carbapenems [15].

Follow-up and data collection

The patients' demographic and clinical characteristics, underlying malignancy, and comorbidities were collected. We evaluated patients' complete blood count (CBC), kidney and liver function tests, and chest CT findings at the initial diagnosis of COVID-19 infection. Follow-up chest CT scans were also performed and evaluated between 10 and 30 days later. Additionally, management, complications, and patient survival outcomes were assessed.

Statistical analysis

The data were statistically analyzed using version 25 of IBM SPSS. Median and interquartile range, or mean and standard deviation, were expressed for quantitative data, as appropriate, whereas frequency and percentage were provided for qualitative data. Shapiro–Wilk and Kolmogorov–Smirnov tests were utilized to check the normality of numerical variables. Kruskal–Wallis or Mann–Whitney tests were used when comparing non-normally distributed numerical variables. However, for comparison between qualitative variables, the Chi-square test (χ^2 test) or Fisher's exact test were utilized. The risk factors linked to COVID-19 severity were identified using the odds ratio and 95% confidence interval. Multivariable logistic regression analysis detected variables linked to bacterial infections, with the final model including variables of a p-value of ≤ 0.2 in the univariate analysis. A p-value of < 0.05 was considered significant.

Results

Clinical characteristics of COVID-19 patients

The study included 112 adult oncology patients confirmed to have COVID-19 infection during the study period. The severity of infection was assessed, revealing that 34.8% of patients had asymptomatic to mild infection, 36.6% had moderate, 19.6% had severe, and 8.9% had critical symptoms. Supplementary Table 1 presents the four groups' demographics,

Table 1. Risk variables and outcomes associated with severe and critical COVID-19 in cancer patients.

Risk factor	No. cases (%) or median (IQR)		Odds ratio	95% CI	*p*-value
	Severe COVID (n = 32)	Moderate COVID (n = 80)			
Demographic characteristic					
Age (years)	51 (31-64)	50 (33-59)			0.505
19-39 years (n = 43)	13 (40.6)	30 (37.5)	1.140	0.493-2.637	0.759
40-59 years (n = 41)	7 (21.9)	34 (42.5)	0.379	0.147-0.978	0.041*
≥60 years (n = 28)	12 (37.5)	16 (20.0)	2.400	0.975-5.911	0.053
Male gender (n = 65)	20 (62.5)	45 (56.3)	1.296	0.559-3.006	0.545
Medical oncology department (n = 73)	22 (68.8)	51 (63.8)	1.251	0.521-3.003	0.616
Underlying malignancy					
Acute leukemia (n = 49)	16 (50.0)	33 (41.3)	1.424	0.625-3.245	0.399
Chronic leukemia (n = 4)	0 (0.0)	4 (5.0)	NC	NC	0.577
Lymphoma (n = 20)	6 (18.8)	14 (17.5)	1.088	0.377-3.136	0.876
Gastrointestinal tract tumors (n = 22)	7 (21.9)	15 (18.8)	1.213	0.442-3.327	0.707
Genitourinary tract tumors (n = 11)	1 (3.1)	10 (12.5)	0.226	0.028-1.842	0.174
Other solid tumors (n = 6)	2 (6.3)	4 (5.0)	1.267	0.220-7.283	1.000
Prior chemotherapy or surgery (n = 95)	24 (75.0)	71 (88.8)	0.380	0.132-1.096	0.083
Stage of cancer					
Disease (n = 55)	17 (53.1)	38 (47.5)	1.253	0.551-2.848	0.591
Relapse (n = 2)	1 (3.1)	1 (1.3)	2.548	0.155-42.023	0.492
Remission (n = 55)	14 (43.8)	41 (51.3)	0.740	0.324-1.688	0.473
Comorbidity					
Any comorbidity[a] (n = 24)	10 (31.3)	14 (17.5)	2.143	0.834-5.508	0.109
Hypertension (n = 7)	4 (12.5)	3 (3.8)	3.667	0.772-17.417	0.101
Diabetes mellitus (n = 12)	4 (12.5)	8 (10.0)	1.286	0.358-4.611	0.740
Congestive heart failure (n = 2)	2 (6.3)	0 (0.0)	NC	NC	0.080
COPD (n = 4)	4 (12.5)	0 (0.0)	NC	NC	0.006*
HCV (n = 4)	1 (3.1)	3 (3.8)	0.828	0.083-8.269	1.000
Fever (n = 89)	32 (100.0)	57 (71.3)	NC	NC	0.001*
Associated bacterial infection (n = 28)	9 (28.1)	19 (23.8)	1.256	0.497-3.174	0.629
Hospitalization					
Hospitalized (n = 107)	32 (100.0)	75 (93.8)	NC	NC	0.319
Duration of stay (days)	15 (9-19)	7 (0-14)			< 0.001*
ICU (n = 35)	32 (100.0)	3 (3.8)	NC	NC	< 0.001*
Fatal outcome (n = 19)	16 (50.0)	3 (3.8)	25.667	6.683-98.570	< 0.001*

The severe group includes patients with severe or critical disease, and the moderate group includes those with mild to moderate illness. Numerical data are presented as the median and interquartile range (IQR), while frequency and percentages are provided for all other variables [No. (percent)]. Any comorbidity[a]: Patients have at least one comorbid condition in addition to cancer. A patient might have many comorbidities, COVID complications, or treatments simultaneously. * indicates significant *p*-value. SD: standard deviation; CI: confidence interval; NC: non-calculable; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus; ICU: intensive care unit.

comorbidities, risk factors, patient outcomes, COVID-related complications, and treatments. The median age of patients was 50 years, ranging from 19 to 79 years, with males accounting for 58.0% of the cases. Seventy-three patients had hematological malignancies (at the Medical Oncology Department), whereas 39 patients had solid organ tumors (at the Surgical Oncology Department) (65.2% and 34.8%, respectively). Acute leukemia was the most prevalent underlying malignancy among the patients, accounting for 43.8% of cases. At the time of initial diagnosis, 95.5% of patients required hospitalization or were already hospitalized, with the median duration of hospital stay being 9 days. Furthermore, 31.3% of COVID-19-infected patients necessitated intensive care unit (ICU) admission, and 21.4% showed vital instability.

Antibiotics were administered to 93.8% of the 112 patients, with 26.8% receiving a single antibiotic and 67.0% receiving a combination of two or more antibiotics. The prescribed antibiotics included azithromycin, vancomycin, tigecycline, piperacillin-tazobactam, cephalosporins, amikacin, meropenem, and colistin. Azithromycin was the most commonly prescribed antibiotic received by 90.1% of all patients (n = 101). Moreover, meropenem and colistin were administered to 59 and 10 patients (52.7% and 8.9%, respectively), often in combination with other antibiotics, except for two patients who received only meropenem. Initial chest CTs indicated radiological abnormalities in 79 patients (70.5%), the most prevalent of which was ground-glass opacity (GGO) with the consolidation of the lungs, followed by GGO alone and consolidation alone (35.7%, 23.2%, and 11.6%, respectively). On follow-up (10 days to 1 month later), 26.8% of patients had regressive or free findings, while 9.8% revealed progressive results. The progressive findings included advanced GGO, pneumothorax, lung nodules, cavitations, or atelectasis.

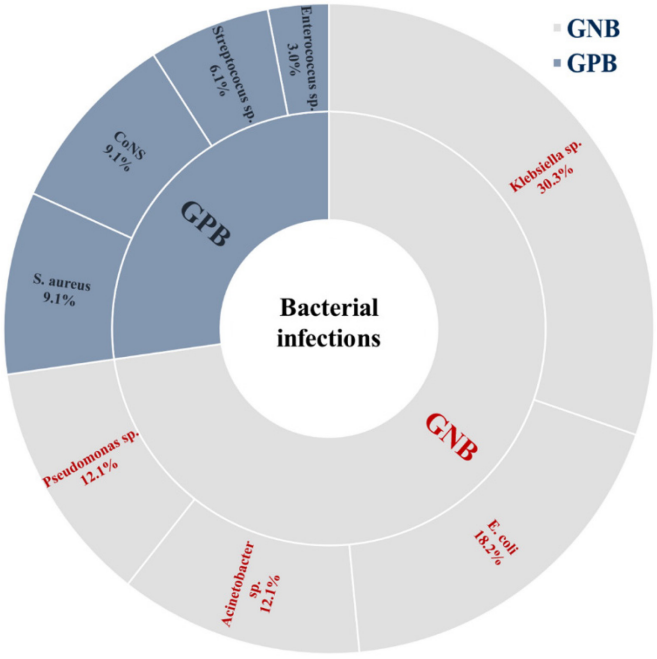
Risk factors for severe and critical COVID-19 infection

The patients were categorized into two groups: those with mild to moderate sickness (the moderate group) and those with severe or critical disease (the severe group) to investigate the risk variables and outcomes associated with severe COVID-19 infections (Table 1). Although elderly patients (≥ 60 years) had a higher risk of severe COVID-19 infection, the difference was statistically insignificant (p-value = 0.053). On the other hand, patients aged 40 to 59 were significantly less likely to suffer a severe illness (p-value = 0.041). Moreover, chronic obstructive pulmonary disease (COPD) was significantly associated with severe conditions (p-value = 0.006). All patients (100.0%) in the severe group were hospitalized and needed ICU admission; their median hospital stay duration was significantly longer compared to the moderate group (15 versus 7 days, p-value < 0.001). Patients in the severe group significantly encountered all complications compared to those in the moderate group (p-value < 0.001). All patients (100.0%) in the severe category received antibiotics, 87.5% intravenously. Furthermore, steroids, anticoagulants, and oxygen therapy were taken by 75.0%, 62.5%, and 90.6% of the patients in the severe group, respectively. The overall mortality was 17.0%, which was significantly higher among the severe group than the moderate group (50.0% versus 3.8%, p-value < 0.001).

Microbiological spectrum of bacterial pathogens in COVID-19 patients

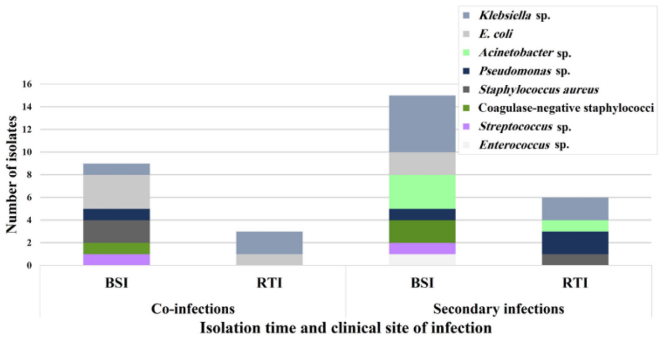
In our study, 28 out of 112 COVID-19-infected patients (25.0%) also had bacterial infections. Bacteremia was found in 17.0% of COVID-19 patients (n = 19/112), respiratory tract infections in 3.6% (4 patients), and both bloodstream and respiratory tract bacterial infections in 4.5% (5 patients). Thirty-three

Figure 1. Frequency of bacterial species causing infections in COVID-19 patients.



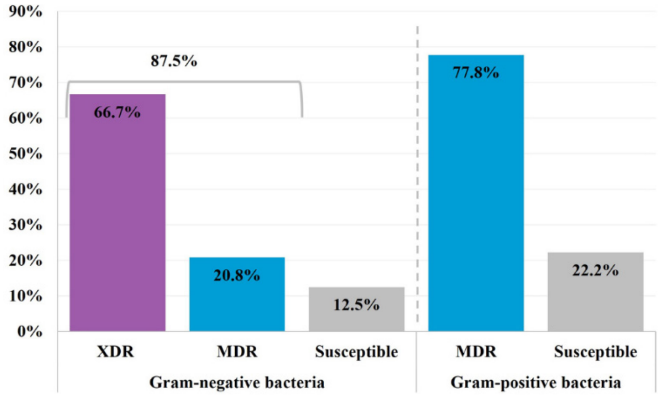
Gram-negative bacteria accounted for 72.7% (n = 24/33) of the bacterial isolates, with *Klebsiella* species being the most frequently isolated, followed by *Escherichia coli*, *Acinetobacter*, and *Pseudomonas* species. Gram-positive bacteria (n = 9, 27.3%), on the other hand, included *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Streptococcus*, and *Enterococcus* species. GNB: Gram-negative bacteria; GPB: Gram-positive bacteria; CoNS: coagulase-negative *staphylococci*.

Figure 2. Frequency of bacterial species based on isolation time and clinical site of infection.



The majority of bacterial isolates caused secondary infections > 48 hours after the initial coronavirus diagnosis (63.6%, 21/33), with *Klebsiella* species being the most frequently isolated, followed by *Acinetobacter*, *Pseudomonas*, *E. coli*, coagulase-negative *staphylococci* (CoNS), *Staphylococcus aureus*, *Streptococcus*, and *Enterococcus* species (n = 7, 4, 3, 2, 2, 1, 1, and 1, respectively). However, 36.4% of isolates (n = 12) caused COVID-19 co-infections within the first 48 hours, with *E. coli* being the most frequent, followed by *Klebsiella*, *S. aureus*, *Pseudomonas*, CoNS, and *Streptococcus* species. (n = 4, 3, 2, 1, 1, 1, respectively). BSI, bloodstream infection; RTI, respiratory tract infections.

Figure 3. Patterns of antimicrobial susceptibility of bacterial isolates causing infections in COVID-19 patients.



Among the 24 Gram-negative bacterial isolates, 87.5% exhibited either extensively drug-resistant (XDR) or multidrug-resistant (MDR) profiles (n = 16, 66.7%, and n = 5, 20.8%, respectively). The MDR pattern was also observed in 77.8% of the nine Gram-positive bacteria isolates (n = 7). MDR bacteria were those that acquired resistance to at least one drug from three or more antibiotic classes, while XDR bacteria were resistant to at least one drug in all but two or fewer antibiotic categories, making them susceptible to one or two classes only. XDR: extensively drug-resistant, MDR: multidrug-resistant.

bacterial isolates were revealed, of which Gram-negative bacteria accounted for 72.7% (n = 24/33) and Gram-positive bacteria for 27.3% (n = 9). Figure 1 depicts the prevalence and distribution of the overall isolated species causing bacterial infections in cancer patients with COVID-19. *Klebsiella* species were the most frequently revealed species, accounting for 30.3% of all bacterial isolates. Most bacterial isolates caused secondary infections > 48 hours after the initial coronavirus diagnosis (63.6%, 21 isolates), whereas 36.4% of isolates caused COVID-19 co-infections within the first 48 hours. Figure 2 and Table 2 illustrate the bacterial species according to isolation time and clinical site of infection. Twenty-eight (84.8%) of the total isolated bacteria exhibited considerable resistance, with 16 (48.5%) having XDR and 12 (36.4%) having MDR. Within the Gram-negative bacteria, 87.5% exhibited either XDR or MDR profiles, as shown in Figure 3. Carbapenem resistance was identified in 20 out of 24 (83.3%) of the Gram-negative isolates. Of the nine Gram-positive bacterial isolates, 77.8% displayed MDR. All identified *S. aureus* isolates were MRSA, representing 33.3% of Gram-positive isolates. Results of in vitro AST to various antibiotic classes are presented in Figure 4. Colistin was the most effective antibiotic against Gram-negative bacteria, with a sensitivity rate of 91.7%. However, the other antibiotic categories revealed substantial resistance rates, including carbapenems, with 83.3% for imipenem and 79.2% for meropenem. Although Gram-positive bacteria showed high sensitivity to vancomycin, linezolid, and teicoplanin (100.0%, 100.0%, and

Table 2. Bacterial species according to isolation time and clinical site of infections.

Species	Co-infection (N)		Secondary infection (N)		Total N (%)
	BSI	RTI	BSI	RTI	
Klebsiella sp.	1	2	5	2	10 (30.3)
Escherichia coli	3	1	2	0	6 (18.2)
Acinetobacter sp.	0	0	3	1	4 (12.1)
Pseudomonas sp.	1	0	1	2	4 (12.1)
Staphylococcus aureus	2	0	0	1	3 (9.1)
Coagulase-negative *staphylococci*	1	0	2	0	3 (9.1)
Streptococcus sp.	1	0	1	0	2 (6.1)
Enterococcus sp.	0	0	1	0	1(3.0)
Total bacterial isolates	**9**	**3**	**15**	**6**	**33 (100.0)**

Co-infections are infections revealed within 48 hours of the initial coronavirus diagnosis, whereas secondary infections are those revealed after 48 hours. BSI: bloodstream infection; RTI: respiratory tract infection.

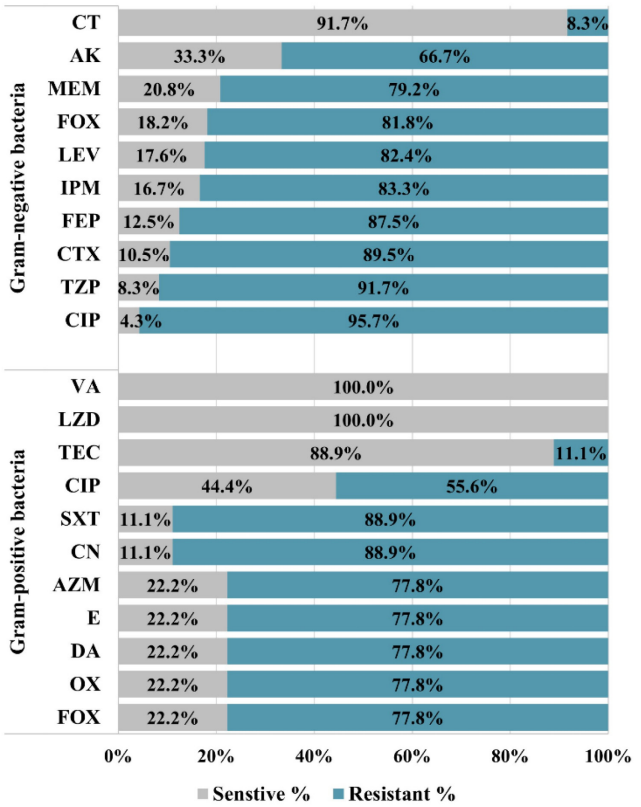
88.9%), the rest of the antibiotic classes exhibited high resistance rates.

Predictors of bacterial infections in COVID-19 patients

Patient demographics and risk variables linked to bacterial infections are illustrated in Table 3. Significantly more COVID-19 patients with bacterial infections had acute leukemia, were under 60 years of age, had hypertension, and prior chemotherapy or surgery (*p*-values = 0.037, 0.012, 0.010, and 0.006, respectively). Notably, all bacterial infections were detected in hospitalized patients; nonetheless, there was no statistically significant difference between hospitalized patients with and without bacterial infection (100.0% versus 94.0%; *p*-value = 0.329). Although univariate analysis found no significant correlation between critical COVID-19 disease and the presence of bacterial infection, multivariable logistic regression analysis with patients' departments as a control variable revealed a significant association (*p*-values = 0.056 and 0.039 for univariate and multivariable analysis, respectively). In addition, the multivariable analysis also showed that being under 60 years old and having hypertension were also significant risk factors for bacterial infection (adjusted *p*-values of 0.029 and 0.024, respectively), as indicated in Table 3.

Laboratory findings for both groups (patients with and without bacterial infections) are shown in Supplementary Table 2. Patients with elevated C-reactive protein (CRP) (> 6 mg/L), anemia (hemoglobin < 12 g/dL), and thrombocytopenia (platelets $<150\times10^3$/µl) had significantly more bacterial infections than those without bacterial infections (*p*-values = 0.008, 0.011, and 0.010, respectively). Moreover, COVID-19 patients with bacterial infections had significantly higher median CRP levels but significantly lower median platelet counts and mean hemoglobin values than those without bacterial co-infections (*p*-values < 0.001, 0.006, and 0.001, respectively). COVID-19 patients with bacterial infections had a higher mortality rate, although this difference was not statistically significant (25.0% versus 14.3%, *p*-value = 0.244).

Figure 4. In vitro antimicrobial susceptibility testing for bacterial isolates infecting COVID-19 patients.



Results were evaluated using Clinical Laboratory Standards Institute (CLSI) guidelines (M100-Ed30) [13]. CT: colistin; AK: amikacin; MEM: meropenem; FOX: cefoxitin; LEV: levofloxacin; IPM: imipenem; FEP: cefepime; CTX: cefotaxime; TZP: piperacillin/tazobactam; CIP: ciprofloxacin; VA: vancomycin; LZD: linezolid; TEC: teicoplanin; SXT: trimethoprim/sulfamethoxazole; CN: gentamycin; AZM: azithromycin; E: erythromycin; DA: clindamycin; OX: oxacillin.

Discussion

Cancer patients are believed to have a greater risk of severe morbidity and death due to COVID-19 [2,16]. Despite limited data in Egypt, our study confirmed similar trends, with advanced age, male gender, and underlying hematological malignancies, notably acute leukemia, associated with higher susceptibility to SARS-CoV-2 infection. Moreover, comorbidities, particularly diabetes mellitus, compounded these risks. A retrospective study of 19,219 hospitalized patients in the United States demonstrated a significant association between COVID-19 and advanced age, male gender, and ICU admission (*p*-value < 0.001) compared with non-coronavirus patients [10]. Other studies have also found comparable risk factors for COVID-19 to ours [7,17]. A UK study on adult oncology patients revealed hematological cancers as a significant risk factor for COVID-19 (*p*-value < 0.001) [16]. Host-related variables, such as old age and different comorbidities, substantially impact disease progression [3].

In our cohort, the severity of COVID-19 disease was linked with old age (≥ 60 years), COPD, prolonged hospitalization, and ICU admission (*p*-values = 0.053, 0.006, < 0.001, and < 0.001, respectively). Others also reported a significant association between COPD and COVID-19 severity and worse outcomes [18,19]. Our study's overall mortality rate was 17.0%, significantly

higher among the severe group than the moderate group (50.0% versus 3.8%, *p*-value < 0.001). A nearly comparable overall fatality rate of 19.6% was reported in a multicenter study on COVID-19 patients in Italy [20]. Nevertheless, some studies revealed lower rates of 13% in Germany [21] and 11% and 8% in two Chinese studies [17,22]. The death rate variability could be attributed to patients' spatiotemporal variances, comorbidities, and disease severity. This is obvious as mortality rates increase in COVID-19 studies conducted only on severe or critical cases. In a French study on ICU patients with severe and critical COVID-19, the death rate was 49% [23]. In addition, two Chinese studies reported 61.5% and 41.4% mortality rates among critical COVID-19 patients [17,24]. A prior Egyptian study at Zagazig University Hospitals also showed a more significant death rate among severely diseased COVID-19 patients than those with moderate illness (33.3% versus 0.6%, *p*-value < 0.001) [3]. Although many studies have linked the mortality of COVID-19 patients to associated bacterial infections [6, 25], other variables may contribute to mortality risk in cancer patients [2]. Furthermore, we found no statistically significant link between the death rate and bacterial infections (*p*-value = 0.244).

The prevalence of bacterial infection in COVID-19 patients varies considerably across published studies, mainly due to differences in illness severity, patient comorbidities, treatment disparities, or other variables [26]. Aside from variations in the specimen types, the pathogen panels and the assessment methodologies contributed to this heterogeneity [4]. A total bacterial

Table 3. Univariate and multivariable analysis of risk variables for bacterial infections in COVID-19 patients.

Risk factors (No.)	No. cases (%) or median (IQR)		Univariate analysis		Multivariable logistic regression analysis	
	Bacterial infection		Unadjusted		Adjusted	
	Yes (n = 28)	No (n = 84)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographic characteristic						
Age (years)	41 ± 13	49 ± 16		0.022*		
19-39 years (n = 43)	15 (53.6)	28 (33.3)	2.308 (0.967-5.510)	0.057		
40-59 years (n = 41)	11 (39.3)	30 (35.7)	1.165 (0.483-2.808)	0.734		
≥60 years (n = 28)	2 (7.1)	26 (31.0)	0.172 (0.038-0.777)	0.012*	0.134 (0.022-0.817)	0.029*
Male gender (n = 65)	18 (64.3)	47 (56.0)	1.417 (0.585-3.433)	0.439		
Medical Oncology Department (n = 73)	20 (71.4)	53 (63.1)	1.462 (0.576-3.714)	0.423	1.411 (0.301-6.612)	0.662
Underlying malignancy						
Acute leukemia (n = 49)	17 (60.7)	32 (38.1)	2.511 (1.045-6.036)	0.037*	2.411 (0.576-10.088)	0.228
Chronic leukemia (n = 4)	0 (0.0)	4 (4.8)	NC	0.570		
Lymphoma (n = 20)	3 (10.7)	17 (20.2)	0.473 (0.128-1.754)	0.254		
Gastrointestinal tract tumors (n = 22)	5 (17.9)	17 (20.2)	0.857 (0.284-2.584)	0.784		
Genitourinary tract tumors (n = 11)	3 (10.7)	8 (9.5)	1.140 (0.281-4.631)	1.000		
Other solid tumors (n = 6)	0 (0.0)	6 (7.1)	NC	0.334		
Prior chemotherapy or surgery (n = 95)	28 (100.0)	67 (79.8)	NC	0.006*		
Stage of cancer						
Disease (n = 55)	14 (50.0)	41 (48.8)	1.049 (0.446-2.467)	0.913		
Relapse (n = 2)	0 (0.0)	2 (2.4)	NC	1.000		
Remission (n = 55)	14 (50.0)	41 (48.8)	1.049 (0.446-2.467)	0.913		
Comorbidity						
Any comorbidity[a] (n = 24)	7 (25.0)	17 (20.2)	1.314 (0.480-3.598)	0.595		
Hypertension (n = 7)	5 (17.9)	2 (2.4)	8.913 (1.622-48.975)	0.010*	7.476 (1.304-42.850)	0.024*
Diabetes mellitus (n = 12)	2 (7.1)	10 (11.9)	0.569 (0.117-2.771)	0.727		
Congestive heart failure (n = 2)	1 (3.6)	1 (1.2)	3.074 (0.186-50.837)	0.439		
COPD (n = 4)	1 (3.6)	3 (3.6)	1.000 (0.100-10.021)	1.000		
HCV (n = 4)	1 (3.6)	3 (3.6)	1.000 (0.100-10.021)	1.000		
Fever (n = 89)	23 (82.1)	66 (78.6)	1.255 (0.418-3.764)	0.685		
Severity of COVID-19						
Mild (n = 39)	9 (32.1)	30 (35.7)	0.853 (0.343-2.118)	0.731		
Moderate (n = 41)	10 (35.7)	31 (36.9)	0.950 (0.390-2.315)	0.910		
Severe (n = 22)	4 (14.3)	18 (21.4)	0.611 (0.188-1.988)	0.410		
Critical (n = 10)	5 (17.9)	5 (6.0)	3.435 (0.914-12.906)	0.056	5.217 (1.083-25.140)	0.039*
Hospitalization						
Hospitalized (n = 107)	28 (100.0)	79 (94.0)	NC	0.329		
Duration of stay (days)	13 (0-18)	8 (0-15)		0.099		
ICU (n = 35)	10 (35.7)	25 (29.8)	1.311 (0.531-3.236)	0.556		
Fatal outcome (n = 19)	7 (25.0)	12 (14.3)	2.000 (0.699-5.723)	0.244		

Numerical data are presented as the median and interquartile range, while frequency and percentages are provided for all other variables [No. (percent)]. Any comorbiditya: Patients have at least one comorbid condition in addition to cancer. A patient might have many comorbidities, COVID complications, or treatments simultaneously. * indicates significant *p*-value. IQR: interquartile range; SD: standard deviation; CI: confidence interval; NC: non-calculable; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus; ICU: intensive care unit.

infection rate of 25.0% was detected in our study, with a rate of 28.1% versus 23.8% in the severe and moderate groups, respectively. This rate was comparable to a United States study, where 21.7% of COVID-19 patients had bacterial infections [5]. Another French study found that 28% of severe and critical COVID-19 patients admitted to the ICU were co-infected with pathogenic bacteria [23].

In our cohort, we conducted a multivariable analysis to identify predictors of bacterial infection. It showed that hypertension, age < 60 years, and critical COVID-19 were all significant risk factors for bacterial infection. These results supported several previous studies that showed that the severity of COVID-19 and ICU admission significantly increased the incidence of bacterial infection [9,17,27]. Furthermore, an interesting Iranian study on critically ill COVID-19 patients admitted to the ICU tested sputum cultures from all patients and demonstrated bacterial infection in 100% of them. Additionally, 84% of patients had underlying comorbidities, and 95% died [6]. Another study also identified hypertension as a significant risk factor for bacterial infection in COVID-19 patients [28]. Numerous variables may thus contribute to bacterial infection development in COVID-19 patients, primarily dependent on the underlying comorbidities and COVID-19 severity.

Physicians' awareness of the predicted spectrum of co-infections and secondary bacterial infections in a COVID-19 patient is necessary for optimal care, especially if empiric therapy is indicated. *Klebsiella*, *S. aureus*, and CoNS are the most frequently detected species in COVID-19 patients with bacterial co-infections or secondary infections. These bacteria correspond to those identified in bloodstream infections and hospital-acquired pneumonia that have also been observed outside of the COVID-19 setting [9]. In our cohort, 63.6% of detected bacterial infections occurred more than 48 hours after the initial COVID-19 diagnosis, aligning with findings from prior studies. The most common species causing secondary infections were *Klebsiella*, *Acinetobacter*, and *Pseudomonas*, while *E. coli*, *Klebsiella*, and *S. aureus* were the most common co-infecting species. Additionally, all bacterial infections were observed in hospitalized patients. Some studies reported higher isolation rates of *Acinetobacter* species and *S. aureus* from COVID-19 patients [6,29], while others found higher rates of *Klebsiella* species and *S. aureus* [7,23,30]. Weidmann et al. also observed a similar pattern of bacterial infections and reported a significantly lower percentage of hospitalized COVID-19 patients with community-acquired pneumonia compared to non-COVID-19 patients in the same clinical setting (p-value < 0.001) [10]. As a result of our findings and those of others, it appears that bacterial infections in COVID-19 patients are predominantly hospital-acquired, in contrast to influenza virus [4,9,10].

The increased AMR is a serious issue that might develop due to the extensive antimicrobial use during the COVID-19 pandemic [8]. Although only 25.0% of our COVID-19 patients had a proven bacterial infection, 93.8% received antibiotics. Previous studies have found comparable antimicrobial overuse [9,21,22,24]. On the other hand, antibiotics should be provided in compliance with local standards, with rapid de-escalation once culture or PCR results indicate no bacterial infection [4,7,9,31]. We found substantial resistance patterns in 84.8% of the isolates. All *S. aureus* species were methicillin-resistant, all *Acinetobacter* species were only susceptible to colistin (XDR), and all XDR-exhibiting isolates were exclusively susceptible to colistin except for one isolate. Therefore, our institute's high use of antibiotics might be explained by weak immunity and extensive resistance in those critical populations. Additionally, the potential exacerbation of COVID-19 outcomes by associated bacterial infections cannot be dismissed. Several studies have noted higher XDR, MDR, carbapenem resistance, and MRSA frequencies in COVID-19 patients [6,7,29]. Intriguingly, a previous study indicated that COVID-19 patients exhibited significantly more MRSA and antibiotic-resistant bacterial isolates than non-COVID-19 patients [10].

Consequently, antimicrobial stewardship, which ensures efficient antibiotic usage, patient isolation, and strict infection-control measures, may be beneficial in managing the spread of MDR organisms and solving this serious situation. Moreover, understanding these challenges in cancer patients with COVID-19 highlights the necessity for developing and implementing targeted antimicrobial approaches to address the specific dynamics of bacterial infections and guarantee optimal patient outcomes. Exploring additional biomarkers for bacterial infections and conducting further surveillance studies in COVID-19 patients could also provide valuable insights into the true impact of COVID-19 on the AMR problem and guide future interventions.

Despite being conducted in a single cancer facility, this study represents the national picture of Egyptian cancer patients with COVID-19 because the NCI admits patients from across Egypt. Moreover, we provided a comprehensive microbiological analysis of

bacterial infection trends linked to coronavirus in cancer patients, addressing a gap in prior research in our region, particularly in immunocompromised patients. Nevertheless, the study has some limitations. Cultures for microbiological workups were only performed for COVID-19 patients clinically suspected of having bacterial infections, potentially leading to underestimating the prevalence. However, most prior studies have had comparable approaches, infection rates, and spectra. In addition, we did not employ techniques such as multiplex PCR, which could have provided a more comprehensive panel of diagnoses, including the detection of other associated viral pathogens. We primarily focused on bacterial infections in cancer patients with COVID-19 and antimicrobial overuse during this pandemic.

Conclusions

Prolonged hospitalization, ICU admission, old age, and COPD were identified as significant risk factors for the severity of COVID-19. One-quarter of cancer patients with SARS-CoV-2 were found to have concurrent bacterial infections, primarily hospital-acquired. The severity of COVID-19 and the presence of comorbidities such as hypertension were revealed to be key determinants for bacterial infection in cancer patients. *Klebsiella* species were the predominant bacteria implicated in both co-infections and secondary infections alongside coronavirus. The relatively high incidence of bacterial infections with greatly elevated resistance rates in cancer patients despite the extensive use of antibiotics suggests a complex interplay, possibly linked to their immunocompromised status. This pandemic might exacerbate the already disastrous spread of AMR bacteria, especially in developing countries. These circumstances require an immediate and robust commitment to antimicrobial stewardship, infection-control measures, and designing new therapeutics. Furthermore, the call for continued surveillance studies is crucial to determine the true impact of the COVID-19 pandemic on the AMR problem.

Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The NCI ethics committee – Cairo University approved study protocol no. CP2212-503-036, and all participants provided informed consent.

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Annex – Supplementary items

Supplementary Table 1. Demographics, comorbidities, COVID-related complications, treatment, and outcomes of COVID-19-infected cancer patients.

Risk factors	No (%) or median (IQR) or mean ± SD					*p*-value
	Total (n = 112)	Clinical severity of COVID-19 infection				
		Mild (n = 39)	Moderate (n = 41)	Severe (n = 22)	Critical (n = 10)	
Demographic characteristics						
Age (years)	50 (32-60)	50 (33-59)	46 (33-58)	51 (29-65)	55 (37-64)	0.650
19-39 years	43 (38.4)	13 (33.3)	17 (41.5)	10 (45.5)	3 (30.0)	0.718
40-59 years	41 (36.6)	18 (46.2)	16 (39.0)	4 (18.2)	3 (30.0)	0.169
≥ 60 years	28 (25.0)	8 (20.5)	8 (19.5)	8 (36.4)	4 (40.0)	0.285
Male Gender	65 (58.0)	20 (51.3)	25 (61.0)	14 (63.6)	6 (60.0)	0.759
Medical Oncology Department	73 (65.2)	16 (41.0)	35 (85.4)	15 (68.2)	7 (70.0)	0.001*
Underlying malignancy						
Acute leukemia	49 (43.8)	9 (23.1)	24 (58.5)	11 (50.0)	5 (50.0)	0.012*
Chronic leukemia	4 (3.6)	3 (7.7)	1 (2.4)	0 (0.0)	0 (0.0)	0.614
Lymphoma	20 (17.9)	4 (10.3)	10 (24.4)	4 (18.2)	2 (20.0)	0.402
Gastrointestinal tract tumors	22 (19.6)	11 (28.2)	4 (9.8)	4 (18.2)	3 (30.0)	0.134
Genitourinary tract tumors	11 (9.8)	8 (20.5)	2 (4.9)	1 (4.5)	0 (0.0)	0.076
Other solid tumors	6 (5.4)	4 (10.3)	0 (0.0)	2 (9.1)	0 (0.0)	0.124
Cancer treatment						
Cytotoxic chemotherapy	69 (61.6)	15 (38.5)	33 (80.5)	15 (68.2)	6 (60.0)	0.001*
Surgery	36 (32.1)	21 (53.8)	6 (14.6)	6 (27.3)	3 (30.0)	0.002*
Others	7 (6.3)	3 (7.7)	2 (4.9)	1 (4.5)	1 (10.0)	0.749
Prior chemotherapy or surgery	95 (84.8)	36 (92.3)	35 (85.4)	17 (77.3)	7 (70.0)	0.177
Stage of cancer						
Disease	55 (49.1)	20 (51.3)	18 (43.9)	11 (50.0)	6 (60.0)	0.801
Relapse	2 (1.8)	0 (0.0)	1 (2.4)	1 (4.5)	0 (0.0)	0.743
Remission	55 (49.1)	19 (48.7)	22 (53.7)	10 (45.5)	4 (40.0)	0.851
Comorbidities						
Any comorbidity[a]	24 (21.4)	7 (17.9)	7 (17.1)	7 (31.8)	3 (30.0)	0.448
Hypertension	7 (6.3)	1 (2.6)	2 (4.9)	3 (13.6)	1 (10.0)	0.243
Diabetes mellitus	12 (10.7)	4 (10.3)	4 (9.8)	2 (9.1)	2 (20.0)	0.756
Congestive heart failure	2 (1.8)	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)	0.080
COPD	4 (3.6)	0 (0.0)	0 (0.0)	3 (13.6)	1 (10.0)	0.007*
HCV	4 (3.6)	2 (5.1)	1 (2.4)	1 (4.5)	0 (0.0)	0.887
Fever	89 (79.5)	16 (41.0)	41 (100.0)	22 (100.0)	10 (100.0)	< 0.001*
Associated infections						
Bacterial infection	28 (25.0)	9 (23.1)	10 (24.4)	4 (18.2)	5 (50.0)	0.265
Fungal infection	4 (3.6)	3 (7.7)	0 (0.0)	0 (0.0)	1 (10.0)	0.105
Hospitalization						
Hospitalized	107 (95.5)	34 (87.2)	41 (100.0)	22 (100.0)	10 (100.0)	0.028*
Duration of hospital stay (days)	9 (0-15)	0 (0-0)	13 (11-16)	16 (9-21)	14 (8-18)	< 0.001*
ICU	35 (31.3)	1 (2.6)	2 (4.9)	22 (100.0)	10 (100.0)	< 0.001*
COVID complications						
Vital instability	24 (21.4)	0 (0.0)	0 (0.0)	15 (68.2)	9 (90.0)	< 0.001*
Heart failure (or cardiac support)	17 (15.2)	0 (0.0)	0 (0.0)	9 (40.9)	8 (80.0)	< 0.001*
Respiratory failure (or MV)	12 (10.7)	0 (0.0)	0 (0.0)	3 (13.6)	9 (90.0)	< 0.001*
Renal impairment	12 (10.7)	0 (0.0)	1 (2.4)	6 (27.3)	5 (50.0)	< 0.001*
Other sequelae[b]	22 (19.6)	0 (0.0)	6 (14.6)	10 (45.5)	6 (60.0)	< 0.001*
Radiological chest findings						
Initial findings						
Free or NA	33 (29.5)	31 (79.5)	1 (2.4)	1 (4.5)	0 (0.0)	< 0.001*
GGO	26 (23.2)	1 (2.6)	19 (46.3)	5 (22.7)	1 (10.0)	< 0.001*
Consolidation	13 (11.6)	1 (2.6)	10 (24.4)	1 (4.5)	1 (10.0)	0.013*
GGO with consolidation	40 (35.7)	6 (15.4)	11 (26.8)	15 (68.2)	8 (80.0)	< 0.001*
Follow up findings						
ND or NA	71 (63.4)	35 (89.7)	15 (36.6)	13 (59.1)	8 (80.0)	< 0.001*
Free or Regressive	30 (26.8)	3 (7.7)	23 (56.1)	4 (18.2)	0 (0.0)	< 0.001*
Progressive	11 (9.8)	1 (2.6)	3 (7.3)	5 (22.7)	2 (20.0)	0.033*
COVID treatments						
Oral antibiotics	105 (93.8)	32 (82.1)	41 (100.0)	22 (100.0)	10 (100.0)	0.004*
IV antimicrobial	36 (32.1)	0 (0.0)	8 (19.5)	19 (86.4)	9 (90.0)	< 0.001*
Duration of IV antimicrobial (days)	7 ± 2		5 ± 1	8 ± 3	6 ± 1	0.018*
Steroids	31 (27.7)	0 (0.0)	7 (17.1)	17 (77.3)	7 (70.0)	< 0.001*
O2 therapy	31 (27.7)	0 (0.0)	2 (4.9)	19 (86.4)	10 (100.0)	< 0.001*
Anticoagulants	31 (27.7)	10 (25.6)	1 (2.4)	12 (54.5)	8 (80.0)	< 0.001*
Dead outcome	19 (17.0)	1 (2.6)	2 (4.9)	6 (27.3)	10 (100.0)	< 0.001*

Numerical data are presented as the median and interquartile range (IQR) or mean and standard deviation, as appropriate. Otherwise, frequency and percentages are provided for all other variables [No. (percent)]. Any comorbidity[a]: Patients have at least one comorbid condition in addition to cancer. Other sequelae[b]: include myocarditis, hepatic focal lesions, or neurological symptoms unrelated to underlying cancer or chemotherapy. A patient might have many comorbidities, COVID complications, or treatments simultaneously.* indicates significant *p*-value. SD: standard deviation; COPD: chronic obstructive pulmonary disease; HCV: hepatitis C virus; ICU: intensive care unit; MV: mechanical ventilation; NA: non-available; GGO: ground-glass opacity; ND: not done; IV: intravenous.

Supplementary Table 2. Laboratory findings of COVID-19-infected cancer patients.

Lab test (No tested)	Total	Clinical severity of COVID-19 infections			Presence of bacterial infections		
		Severe COVID	Moderate COVID	*p*-value	Yes	No	*p*-value
Hemoglobin (n = 106)	9.8 ± 2.5	9.8 ± 2.4	9.8 ± 2.6	0.961	8.4 ± 2.1	10.2 ± 2.5	0.001*
Abnormal Hb < 12 g/dL	84 (79.2)	23 (76.7)	61 (80.3)	0.681	26 (96.3)	58 (73.4)	0.011*
Platelets (n = 106)	192 (40-321)	231 (35-393)	163 (43-281)	0.254	45 (17-245)	222 (52-323)	0.006*
Platelets < 150×10^3/µl	48 (45.3)	11 (36.7)	37 (48.7)	0.263	18 (66.7)	30 (38.0)	0.010*
TLC (n = 106)	6.7 (1.8-12.5)	7.4 (4.8-11.4)	6.1 (1.4-12.7)	0.626	10.3 (0.5-16.7)	6.6 (2.9-11.2)	0.913
TLC > 11×10^9/L	31 (29.2)	7 (23.3)	24 (31.6)	0.401	11 (40.7)	20 (25.3)	0.128
ALC (n = 104)	0.9 (0.2-2.3)	1.3 (0.2-2.0)	0.9 (0.2-2.0)	0.731	0.8 (0.0-2.4)	1.1 (0.2-2.3)	0.417
ALC < 0.7×10^9/L	46 (44.2)	14 (46.7)	32 (43.2)	0.750	11 (42.3)	35 (44.9)	0.820
CRP (n = 81)	58 (11-156)	52 (14-120)	68 (9-167)	0.660	166 (70-278)	38 (6-106)	<0.001*
CRP > 6 mg/L	65 (80.2)	20 (87.0)	45 (77.6)	0.265	19 (100.0)	46 (74.2)	0.008*
ALT (n = 96)	23 (15-41)	19 (14-27)	23 (15-44)	0.244	23 (16-28)	22 (15-42)	0.877
ALT > 45 U/L	18 (18.8)	3 (11.1)	15 (21.7)	0.230	5 (20.0)	13 (18.3)	0.532
AST (n = 92)	24 (17-34)	19 (11-25)	26 (18-37)	0.020*	21 (15-27)	25 (17-36)	0.231
AST > 40 U/L	17 (18.5)	4 (15.4)	13 (19.7)	0.439	3 (12.5)	14 (20.6)	0.292
Urea (n = 81)	30 (24-43)	30 (24-47)	31 (25-42)	0.845	35 (26-56)	29 (22-41)	0.054
Urea > 45 mg/dL	18 (22.2)	7 (25.9)	11 (20.4)	0.571	7 (31.8)	11 (18.6)	0.166
Creatinine (n = 95)	0.8 (0.7-1.0)	0.9 (0.7-1.2)	0.8 (0.7-1.0)	0.910	0.9 (0.8-1.0)	0.8 (0.7-1.1)	0.831
Creatinine > 1.25 mg/dL	12 (12.6)	5 (18.5)	7 (10.3)	0.223	3 (12.0)	9 (12.9)	0.610

The severe group includes patients with severe or critical disease, and the moderate group includes those with mild to moderate illness. Numerical variables are presented as the median and interquartile range (IQR) or mean and standard deviation, as appropriate. Otherwise, frequency and percentages are provided for all other variables [No. (percent)]. The total number of patients for whom data was available is shown next to each laboratory test. Significant *p*-values are marked with asterisks. Hb: hemoglobin; TLC: total leucocyte count; ALC: absolute lymphocyte count; CRP: C-reactive protein; ALT: Alanine transaminase; AST: Aspartate transaminase.