Clinical and Virologic Characteristics and Outcomes of Coronavirus Disease 2019 at a Cancer Center

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**Background.** High morbidity and mortality have been observed in patients with cancer and coronavirus disease 2019 (COVID-19); however, there are limited data on antimicrobial use, coinfections, and viral shedding.

**Methods.** We conducted a retrospective cohort study of adult patients at the Seattle Cancer Care Alliance diagnosed with COVID-19 between February 28, 2020 and June 15, 2020 to characterize antimicrobial use, coinfections, viral shedding, and outcomes within 30 days after diagnosis. Cycle threshold values were used as a proxy for viral load. We determined viral clearance, defined as 2 consecutive negative results using severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction results through July 30, 2020.

**Results.** Seventy-one patients were included with a median age of 61 years; 59% had a solid tumor. Only 3 patients had documented respiratory bacterial coinfection. Empiric antibiotics for pneumonia were prescribed more frequently early in the study period (February 29–March 28, 2020; 12/34) compared to the later period (March 29–June 15, 2020; 2/36) (P = .002). The median number of days from symptom onset to viral clearance was 37 days with viral load rapidly declining in the first 7–10 days after symptom onset. Within 30 days of diagnosis, 29 (41%) patients were hospitalized and 12 (17%) died. Each additional comorbidity was associated with 45% lower odds of days alive and out of hospital in the month following diagnosis in adjusted models.

**Conclusions.** Patients at a cancer center, particularly those with multiple comorbidities, are at increased risk of poor outcomes from COVID-19. Prolonged viral shedding is frequently observed among cancer patients, and its implications on transmission and treatment strategies warrant further study.

**Keywords.** antimicrobial use; cancer; clinical outcomes; COVID-19; viral shedding.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic, leading to significant morbidity and mortality worldwide [1–4]. Earlier reports of coronavirus disease 2019 (COVID-19) demonstrate that cancer patients have worse outcomes compared to those without cancer [5–8]. Several large cohort studies demonstrated that older age, male sex, and underlying comorbidities are risk factors for severe disease and mortality in cancer patients [9–12]. However, important questions with regard to clinical and virologic characteristics of COVID-19 among cancer patients remain.

Limited data exist regarding symptom duration, viral shedding, and viral load trajectories among cancer patients [13, 14], leading to questions about the optimal approach to discontinuation of transmission-based precautions in this population. Additionally, coinfections and antibiotic use in immunocompromised populations are not well-described. Studies in other populations found high rates of empiric antibiotic use but relatively low rates of bacterial coinfections, raising concerns that the COVID-19 pandemic may further fuel antimicrobial resistance [15–17]. The above information is important to inform infection prevention strategies and clinical management in this vulnerable population. We aimed to characterize clinical and virologic features of COVID-19 infection among patients at a cancer center in Seattle, Washington, including viral shedding, antibiotic use, and respiratory coinfections.
METHODS

Setting and Study Population
We conducted a retrospective cohort study of patients at Seattle Cancer Care Alliance (SCCA) who had laboratory-confirmed SARS-CoV-2 infection between February 28, 2020 and June 15, 2020. The SCCA comprises a large ambulatory cancer center with inpatients cared for in a 20-bed inpatient hospital and at the affiliated teaching hospital of the University of Washington (UW). Some patients were admitted to other centers in the region. Patients eligible for inclusion were ≥18 years old with a diagnosis of cancer or hematologic disorder; to characterize the full spectrum of disease, symptomatic and asymptomatic individuals were included. Laboratory testing for SARS-CoV-2 polymerase chain reaction (PCR) evolved over the course of the pandemic and initially focused on symptomatic patients only. In late March to early April, testing expanded to include asymptomatic individuals on admission, pre-procedure as well as weekly testing of hematopoietic cell transplant (HCT) and cellular therapy patients. Frequency of PCR testing following a positive result varied according to the discretion of the treating physician, but often occurred weekly until 2 consecutive negative results were observed. From March 23, 2020 to April 21, 2020, symptomatic outpatients with SARS-CoV-2 infection received daily nurse monitoring phone calls until symptom resolution to evaluate need for higher levels of care.

Patient Consent Statement
The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board with a waiver of informed consent.

Laboratory Methods
Nasopharyngeal swabs were tested for SARS-CoV-2 RNA using a UW virology laboratory-developed real-time reverse-transcription polymerase chain reaction (RT-PCR) (limit of detection [LOD], cycle threshold [Ct] = 36.5) [18], Roche Cobas SARS-CoV-2 RT-PCR (LOD, Ct = 37.4), or Panther Fusion SARS-CoV-2 RT-PCR (LOD, Ct = 36.8) assay. Viral loads were measured through use of Ct as an inverse proxy, with lower Ct values indicating higher viral load.

Data Collection
We performed chart abstraction of clinical data including COVID-19 exposures, antimicrobial use and indications, microbiology data, and outcomes within 30 days after COVID-19 diagnosis. Among the subset of patients who had daily symptom monitoring, the duration of symptoms was captured. SARS-CoV-2 RT-PCR results including Ct values if available were extracted through July 30, 2020 from the UW Virology Laboratory or through chart review if performed outside of the system.

Definitions
The date of the first positive SARS-CoV-2 RT-PCR test served as day of COVID-19 diagnosis. COVID-19 exposures were based on documentation in the medical record. Household contact was defined as known exposure to a suspected or laboratory-confirmed COVID-19 case residing in the same household. Community contact was defined as known exposure to a person with suspected or laboratory-confirmed COVID-19 outside of the household in the community. A long-term care facility (LTCF) exposure was noted if the patient resided within an LTCF for the entire 2 weeks prior to COVID-19 diagnosis. A healthcare-associated exposure was defined if the patient was hospitalized for the entire 2 weeks prior to diagnosis or had known exposure to a laboratory-confirmed COVID-19 case in a healthcare facility. A travel-related exposure was defined based on a history of domestic or international travel in the 2 weeks prior to diagnosis. Lower respiratory tract infection (LRTI) was defined as new abnormal respiratory examination, radiographic findings, or new oxygen requirement in conjunction with a provider’s diagnosis of LRTI. A coinfection was defined as detection of pathogen by diagnostic tests including respiratory bacterial cultures (eg, sputum, endotracheal aspirate, bronchoalveolar lavage) and a laboratory-developed multiplex respiratory viral panel PCR that can detect 12 respiratory viruses [19]. To examine how antibiotic use varied throughout the study period, we divided patients equally into early (February 29–March 28, 2020) and late (March 29–June 15, 2020) periods. Viral shedding was defined as detection of viral RNA [20, 21].

Outcomes
We evaluated the following outcomes present at or within 30 days after COVID-19 diagnosis: all-cause mortality, LRTI, hospitalization, and intensive care unit (ICU) admission. Additionally, we evaluated a composite outcome of number of days alive and out of hospital in the 30 days after COVID-19 diagnosis, which was computed for each patient by subtracting the number of days spent in the hospital from the total number of days each patient was alive, in the 30-day period [19]. For the purpose of this outcome, hospital admission date, but not discharge date, was considered a day spent in the hospital.

Statistical Analysis
Among patients with at least 2 PCR tests performed, the duration of viral shedding, or time from symptom onset to viral clearance, was estimated using cumulative incidence methodology. Viral clearance was defined by 2 consecutive negative tests; date of viral clearance was defined as the date of the first of these 2 negative tests. Deaths occurring before 2 consecutive negatives were treated as a competing risk. Patients without 2 consecutive negatives and who did not die within 2 weeks of their last PCR test were censored at 2 weeks after the last test.
Median and interquartile (IQR) range for duration of shedding were then estimated from the cumulative incidence curve. To test for associations between baseline variables and our composite outcome, we used generalized estimating equations (GEEs) with the binomial distribution and logit link, treating the number of days alive and out of the hospital as the number of successes out of 30 days. GEE accommodates overdispersion that arises from the correlation among days in the same patient. Model estimates are presented as odds ratios (ORs) with 95% confidence intervals (CIs). We prespecified the following candidate explanatory variables: age (continuous), sex, race (nonwhite vs white), obesity (body mass index ≥30 vs <30), smoking (past/current vs never), number of comorbidities (continuous), primary disease (hematological malignancy vs solid tumor/other), statin use at the time of COVID-19 diagnosis, steroid use in the 2 weeks before COVID-19 diagnosis, and chemotherapy in the 30 days before COVID-19 diagnosis. For each candidate explanatory variable, we reported unadjusted ORs from univariable models and adjusted ORs from multivariable models that were adjusted for the following prespecified variables: age, sex, and number of comorbidities [9–12]. SAS version 9.4 software (SAS Institute, Cary, North Carolina) was used for all analyses.

RESULTS

Cohort Description
We identified 71 patients for inclusion during the study period. Baseline characteristics are summarized in Table 1. Median age was 61 years (range, 22–98 years) with 32 (45%) male patients and 9 (13%) Hispanic. Thirty-five (49%) had ≥2 identified comorbidities with hypertension, chronic kidney disease, and coronary artery disease as the most common. Forty-two (59%) patients had a solid tumor malignancy, with breast cancer being the most prevalent diagnosis. No patients in the cohort were recipients of HCT or cellular therapy. Nineteen (27%) patients received chemotherapy in the 30 days prior to COVID-19 diagnosis. Eleven (15%) patients received systemic steroids in the 2 weeks prior to COVID-19 diagnosis.

The most commonly reported known exposures included household contact (27%) and LTCF residence (24%). There were no known healthcare-associated exposures (Supplementary Figure 1).

Clinical Presentation and Management
Sixty-five (92%) patients had symptoms that prompted testing, with cough (68%), fever/chills (58%), and shortness of breath (37%) reported most often (Supplementary Figure 2). Among 64 patients with known symptom onset, the median number of days from symptom onset to laboratory-confirmed COVID-19 diagnosis was 4 days (range, 0–26 days). Among 23 (32%) symptomatic outpatients who underwent daily telephone examinations, the most commonly reported exposures included household contact (27%) and LTCF residence (24%). There were no known healthcare-associated exposures (Supplementary Figure 1).
monitoring until symptom resolution, the median number of days from symptom onset until resolution was 17 days (range, 3–55 days); 2 were subsequently admitted to the hospital.

Of the 13 patients who received therapy for COVID-19, the most commonly used treatments either alone or in combination with another agent were hydroxychloroquine, given in 9 patients while 6 received remdesivir. One patient received prednisone.

### Antibiotic Use and Coinfections

Among 70 patients with complete antibiotic information, 22 (31%) received antibiotics either at the time of COVID-19 diagnosis or within 48 hours after diagnosis, including 15 of 29 (54%) hospitalized patients and 7 of 42 (17%) outpatients. Among the 15 hospitalized patients prescribed antibiotics, 11 (73%) received empiric treatment for pneumonia; 3 (43%) of the 7 outpatients prescribed antibiotics were treated empirically for pneumonia. Empiric antibiotics for pneumonia were prescribed more frequently early in the study period (February 29–March 28, 2020) compared to the later period (March 29–June 15, 2020) \( (P = .002; \text{Figure } 1) \). Three patients had a microbiologically confirmed respiratory coinfection by sputum culture (Moraxella catarrhalis, Pseudomonas aeruginosa, and Staphylococcus aureus). Early in the study period, when access to SARS-CoV-2 testing was limited, 1 patient was diagnosed with parainfluenza virus a week prior to COVID-19 diagnosis; it was unclear whether the parainfluenza virus or SARS-CoV-2 infection came first. No fungal coinfections were identified.

### Duration of Viral Shedding

Of 50 patients with \( \geq 2 \) RT-PCR tests, the median duration between consecutive tests was 7 days (IQR, 3–15 days). The percentage of patients with positive follow-up RT-PCR test results was 83% at week 2, 56% at week 4, and 27% at 6 weeks following symptom onset (Figure 2A). The cumulative incidence of viral clearance from days of symptom onset is shown in Figure 2B; the median number of days from symptom onset to viral clearance was 37 days (IQR, 23–48 days). Individual patient patterns in PCR positivity are shown in Supplementary Figure 3. The median initial Ct value was 24.9 (range, 13.2–40.1). Trajectories of Ct values generally showed a rapid decline in viral load in the first 7–10 days following symptom onset, followed by more prolonged low-level viral shedding (Figure 2C).

### Clinical Outcomes

Twelve-nine (41%) patients were hospitalized; 9 (13%) required ICU-level care (Supplementary Table 1). LRTI was diagnosed in 27 (39%) patients. The most common abnormal findings on chest imaging were multifocal or patchy opacities (18/27 [67%]), followed by lobar consolidation (8/27 [30%]).

Twelve of 70 (17%) patients died within 30 days of diagnosis with the highest mortality observed among those \( \geq 70 \) years of age (Figure 3); 8 of the 12 died during the first month of the pandemic. Among 16 patients with LTCF exposure, 11 (69%) had LRTI and 8 (50%) died.

Thirty-nine (56%) patients were alive and out of the hospital for all 30 days after COVID diagnosis; the remaining patients had a median of 18 days alive and out of the hospital (range, 0–29 days; Supplementary Figure 4). Figure 4 shows model estimates for associations of baseline variables with this composite outcome. In unadjusted models, older age, male sex, greater number of comorbidities, statin use at diagnosis, and steroid use in the 2 weeks prior to diagnosis were all associated with lower odds of days alive and out of the hospital. However, after adjusting for age, sex, and number of comorbidities, only number of comorbidities remained significant, with a 45% reduction in the odds of days alive and out of the hospital with each additional comorbidity.
DISCUSSION

In this study, we observed high rates of hospitalization and significant morbidity and mortality in patients with COVID-19 who were seen at a cancer center. Empiric antibiotic use for pneumonia was common early in the study period despite few documented bacterial coinfections. Although we saw a rapid decline in viral load in the first 7–10 days following symptom onset, RT-PCR results remained positive at low viral loads in a substantial proportion of patients over a month following symptom onset.

Among baseline factors associated with the composite outcome of days alive and out of the hospital in univariable models, only number of comorbidities remained significant in multivariable models. This is consistent with other studies suggesting the importance of underlying comorbidities on outcomes among cancer patients [4, 7, 9, 22]. A trend was observed between systemic steroid use in the 2 weeks before COVID-19 diagnosis and worse clinical outcomes, an intriguing finding as clinical trials of steroid administration demonstrated a therapeutic benefit among those mechanically ventilated or requiring supplemental oxygen but a trend toward harm among those not requiring oxygen [23, 24]. Steroid exposure is a known risk factor for LRTI or death for other respiratory viruses in a dose-dependent fashion in immunocompromised hosts [25, 26]. This suggests the complex effect of steroids for SARS-CoV-2, potentially deleterious during the early viral replication phase with benefit later targeting an excessive host immune response.

Early reports from China as well as from New York City suggest that healthcare acquisition is an important source of exposure among cancer patients [7, 27], and a nosocomial outbreak of SARS-CoV-2 infection has been described in a hematology unit [28]. While we did not observe any cases of healthcare-associated infection, more than half of cases appeared to acquire SARS-CoV-2 from LTFC or household exposures. Notably, patients with LTFC exposure had high rates of LRTI and mortality, most likely reflecting a population of older individuals with multiple comorbidities, who are at high risk for severe disease and death [29, 30]. These observations indicate the importance of targeting vaccine distribution and other prevention efforts to congregate settings and to household members and caregivers in order to reduce risk of transmission to vulnerable populations.

Our cohort exhibited a longer median duration of viral shedding of 37 days when compared to findings from a recent meta-analysis that reported a mean duration of viral shedding of 17 days [20]. These differences may reflect the immunocompromised state, severity of illness, or older age in our cohort, which have been associated with delayed viral clearance [28]. Although prolonged viral shedding was observed in our cohort, viral loads declined rapidly in the first 7–10 days from symptom onset, similar to findings reported in the general population and in patients with renal transplantation [20, 31, 32]. While we were unable to directly assess for the presence of replication-competent virus through culture, studies suggest an inverse relationship between Ct value and quantity of viable virus, with low likelihood of infectivity with high Ct value [33].

Notably, our study had no HCT recipients and a smaller proportion of patients with hematologic malignancies than with solid tumors, which may reflect more stringent efforts among the most highly immunosuppressed patients to limit exposures. Prolonged and persistent shedding of infectious virus among patients with hematologic malignancy and HCT
recipients has been described in a few cases. In a report of a patient with chronic lymphocytic leukemia and acquired hypogammaglobulinemia, shedding of infectious virus was observed up to 70 days after diagnosis [34]. In another report, a patient with mantle cell lymphoma and treatment-associated B-cell deficiency shed replication-competent virus for at least 119 days [35]. In a study that included 18 recipients of HCT or CAR T-cell therapy and 2 patients with lymphoma, 3 patients had viable virus cultured beyond 20 days; 1 patient had viable virus detected at 61 days [36]. The Centers for Disease Control and Prevention currently recommends either a time/symptom-based or test-based approach to guide discontinuation of isolation precautions among severely immunosuppressed patients [37]. Further study is needed to characterize viral shedding dynamics among cancer patients and in particular those who are at increased risk for prolonged shedding of infectious virus.

Though several studies have noted significant use of empiric antibiotics despite low prevalence of coinfections, immunocompromised patients were not specifically identified in these studies [15, 16, 38]. In our cohort of patients at a cancer center, empiric antibiotic use for pneumonia within 30 days of diagnosis was common, despite few documented bacterial coinfections. Empiric antibiotic use decreased over the study period in the absence of targeted stewardship interventions, likely reflecting improved understanding of the clinical manifestations, course, and new therapeutic options for COVID-19 disease [16]. Although others have detected fungal coinfections in both immunocompetent and immunocompromised COVID-19 patients, we did not identify any in our cohort [39].

We acknowledge several limitations to our study including its retrospective study design in a single geographic region with less ethnic diversity. Less than one-third of our cohort had hematologic malignancies and there were no HCT recipients; it
Figure 3. Thirty-day all-cause mortality by age group at coronavirus disease 2019 (COVID-19) diagnosis. Total height of the bars represents the number of patients in each age category, shaded portion represents the number of patients who died within 30 days after COVID-19 diagnosis, and unshaded portion represents patients who survived at least 30 days after COVID-19 diagnosis. Percentages shown on top of bars represent the percentage of patients who died within each age category as indicated by the brackets. Of the 12 total deaths, 10 were attributable to COVID-19 and 2 (one 24-year-old, one 72-year-old) were thought to be most likely related to the patient’s underlying disease but could not exclude COVID-19 as a contributing factor.

Figure 4. Model estimates for associations of baseline characteristics with days alive and out of hospital. Filled squares represent the odds ratio (OR) and bars connect the lower confidence limit (LCL) and the upper confidence limit (UCL) of the 95% confidence interval for each baseline variable. Worse outcomes (lower odds of days alive and out of the hospital) are shown by estimates to the left of the vertical reference line and better outcomes (greater odds of days alive and out of the hospital) are shown to the right. Gray estimates are unadjusted and black estimates are adjusted for age, sex, and number of comorbidities. Estimates shown for comorbidities represent the OR for each additional comorbidity.
is unknown whether our findings—in particular, the data regarding viral shedding—are generalizable to these highly immunosuppressed populations. The frequency of PCR testing used to measure duration of viral shedding in this observational study was not standardized and varied by physician discretion; this may have impacted the precision of our estimates of shedding duration. However, in most cases, testing occurred at least every 1–2 weeks after initial positive result. As Ct values were only available in a subset of patients with variable timing of diagnosis relative to symptom onset, we were unable to assess for any association between initial Ct value and mortality as described in other studies [40]. Limited use of diagnostic studies early in the pandemic, such as bronchoscopy, may have underestimated the true incidence of bacterial or fungal coinfections.

In conclusion, patients at a cancer center, in particular those with multiple comorbidities, are at increased risk for poor outcomes associated with COVID-19. Opportunities exist to target prevention efforts including LTCF and household contacts, particularly as vaccines become available. Further studies on viral shedding dynamics in cancer patients are warranted to guide infection prevention and therapeutic management strategies for this vulnerable population.

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.

Notes
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