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MAJOR ARTICLE

Outcomes of Cytomegalovirus Viremia Treatment in Critically Ill Patients With COVID-19 Infection

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Background. Patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU) have poor outcomes and frequently develop comorbid conditions, including cytomegalovirus (CMV) reactivation. The implications of CMV reactivation in this setting are unknown. We aimed to investigate if treatment of CMV viremia improved in-hospital mortality in ICU patients with COVID-19.

Methods. In this single-center retrospective study, we analyzed clinical outcomes in patients diagnosed with COVID-19 pneumonia and CMV viremia admitted to an ICU from March 1, 2020, to April 30, 2021, who either received treatment (ganciclovir and/or valganciclovir) or received no treatment. The primary outcome was all-cause in-hospital mortality. Secondary outcomes were total hospital length of stay (LOS), ICU LOS, requirement for extracorporeal membrane oxygenation (ECMO) support, duration of mechanical ventilation (MV), and predictors of in-hospital mortality.

Results. A total of 80 patients were included, 43 patients in the treatment group and 37 in the control group. Baseline characteristics were similar in both groups. CMV-treated patients were more likely to test positive for CMV earlier in their course, more likely to be on ECMO, and received higher total steroid doses on average. In-hospital mortality was similar between the 2 groups (37.2% vs 43.2.0%; $P = .749$). There was no significant difference in hospital LOS, though CMV-treated patients had a longer ICU LOS.

Conclusions. Treatment of CMV viremia did not decrease in-hospital mortality in ICU patients with COVID-19, but the sample size was limited. CMV viremia was significantly associated with total steroid dose received and longer ICU stay.

Keywords. COVID-19; CMV; COVID; cytomegalovirus; critical care.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic, with infection resulting in a wide range of clinical presentations, from asymptomatic or mild coronavirus disease 2019 (COVID-19) pneumonia to severe disease requiring intensive care unit (ICU)–level care. Many patients with severe disease have prolonged ICU courses, resulting in a multitude of secondary disease processes, which have a significant impact on morbidity and mortality, as well as increased strain on the health care system. While many of these complications are inherent to ICU care or critical illness, such as ventilator- and catheter-associated infections, others may have a specific relationship to COVID-19. This may be due to immunologic or prothrombotic effects of the infection or sequelae of pharmacologic treatment of COVID-19, which now frequently includes glucocorticoids and other immunosuppressive agents [1–3]. Given that these secondary complications may significantly contribute to the overall morbidity and mortality in critically ill COVID-19 patients, improved understanding of their natural histories and effects of treatment offers the potential to improve outcomes for these patients.

Cytomegalovirus (CMV) is a herpesvirus that causes lifelong infection. After acute infection, latent infection rarely causes symptomatic disease in immunocompetent hosts but can reactivate and cause systemic or tissue-invasive disease in immunocompromised or otherwise critically ill patients. CMV reactivation in critically ill patients is frequently encountered and is associated with a significant increase in mortality in some studies, though no causal relationship has been established [4]. While there are strong data to support treatment of CMV viremia in immunocompromised hosts, such data are lacking for immunocompetent individuals and those with critical illness. COVID-19 and many of the medications used

Received 18 January 2022; editorial decision 27 May 2022; accepted 08 June 2022; published online 10 June 2022

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https://doi.org/10.1093/ofid/ofac286

to treat it can cause immune dysregulation and suppression, suggesting that findings from research on CMV in other critically ill patient populations may differ from CMV in patients with COVID-19.

At New York University Langone Health (NYULH), CMV viremia is sometimes monitored in patients with COVID-19 requiring ICU-level care, and a subset of these patients receive antiviral therapy. Testing and treatment for CMV viremia practice vary between providers. The testing and treatment of CMV viremia can be costly and expose patients to adverse effects from antiviral therapy. It is not known whether this practice improves patient outcomes such as LOS, duration of mechanical ventilation (MV), or mortality. Therefore, we investigated whether treatment of CMV viremia in critically ill patients with COVID-19 pneumonia was associated with improved mortality.

METHODS

Study Design and Population

This study was an institutional review board–approved, retrospective cohort study performed at NYULH (Tisch Hospital/Kimmel Pavilion, Brooklyn and Long Island campuses). The study included all patients aged 18 and older diagnosed with COVID-19 pneumonia (confirmed by positive SARS-CoV-2 reverse transcriptase polymerase chain reaction [RT-PCR] test result) who were found to have any level of CMV viremia and were admitted to medical ICUs (MICUs) from March 1, 2020, to April 30, 2021. Patients were excluded if they had received a solid organ or hematopoietic stem cell transplant, had CMV viremia detected before COVID-19 diagnosis, or remained hospitalized after the end of the study period. The treatment group included patients who were treated with ganciclovir and/or valganciclovir for at least 5 days, with the rationale that patients would need to participate in at least some conclusive part of the treatment period to see an effect. The control group included patients who were not treated with ganciclovir or valganciclovir. At the time of the study, there were no hospital guidelines on testing or treating CMV viremia in non–previously immunocompromised ICU patients, including for those with COVID-19. Based on individual experience, some providers were testing, and sometimes treating, CMV viremia in critically ill COVID-19 patients.

Study Variables

Patient-specific data on antimicrobial usage were obtained using Epic medication administration reports, and CMV viral load data were obtained from microbiology laboratory reports. Data obtained included patient demographics, admitting diagnosis, comorbidities, laboratory values, antimicrobial treatment, clinical outcomes, and discharge disposition. Data were validated via chart review. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included hospital and ICU LOS, requirement for ECMO support, duration of MV, and predictors of in-hospital mortality.

Study Definitions

The presence of CMV viral proteins or nucleic acid in the tissue, blood, or other bodily fluid, even in the absence of symptoms, is considered CMV infection [5]. CMV viremia is defined as the detection of CMV DNA in samples of plasma, serum, or whole blood. Isolation of virus in tissue, in conjunction with signs and symptoms of end-organ involvement, is defined as CMV disease.

In our study, CMV viremia was defined as any detected CMV viral load using the Roche CMV assay on the cobas 6800 instrument. Low positivity was defined as CMV viral load <1000 copies/mL. CMV positivity was defined as CMV viral load ≥1000 copies/mL. Glucocorticoid use was expressed as dexamethasone dose equivalents in milligrams, using the following conversions: hydrocortisone 20 mg = prednisone/prednisolone 5 mg = methylprednisolone 4 mg = dexamethasone 0.75 mg. Myelosuppression was defined as absolute neutrophil count (ANC) <1000 cells/μL (neutropenia) or <500 cells/μL (severe neutropenia) during the time period in which ganciclovir or valganciclovir was administered in a patient who previously had an ANC above these values before the start of ganciclovir or valganciclovir.

Statistical Analysis

Baseline demographics and outcomes were compared between the treatment group and the control group. No a priori power calculations were conducted. All patients satisfying the inclusion/exclusion criteria who were admitted to the MICU during the intervention period were included in the statistical analysis. Categorical variables were compared between the 2 groups using chi-square or Fisher exact tests (expressed as frequency and percentage), and continuous variables were compared using the Mann-Whitney *U* test (expressed as median and interquartile range [IQR]). A 2-sided alpha of .05 was used to determine statistical significance. A univariate analysis was conducted to identify predictors of mortality. Analyses were conducted using SPSS, version 25 (IBM, Armonk, New York, NY, USA).

RESULTS

Patient Characteristics

Of 107 MICU-admitted patients with COVID-19 and detected CMV viremia, a total of 80 patients were included in the study (treatment group n = 43, control group n = 37). Reasons for exclusion included transplant (n = 13), receipt of <5 days of ganciclovir treatment (n = 8), CMV viremia before COVID-19 diagnosis (n = 5), and continued hospitalization at the end of the study time frame (n = 1). Baseline demographics were similar between the 2 groups (Table 1). The median age of the

Table 1. Baseline Characteristics

	All Patients (n = 80)	Treatment (n = 43)	Control (n = 37)	*P* Value
Age, median (IQR), y	66 (56–72)	66 (55–72)	65 (56–71)	.904
Male	54 (67.5)	29 (67.4)	25 (67.6)	.990
Race				.693
White	30 (37.5)	16 (37.2)	14 (37.8)	
Other	30 (37.5)	15 (34.9)	13 (35.1)	
Asian	17 (21.3)	8 (18.6)	9 (24.3)	
African American	3 (3.8)	2 (4.7)	1 (2.7)	
Unknown	2 (2.5)	2 (4.7)	0	
CCI, median (IQR)	4 (2–6)	4 (2–5)	4 (2–6)	.329
Medical history				
DM	39 (48.8)	21 (48.8)	18 (48.6)	.987
MI	21 (26.3)	10 (23.3)	11 (29.7)	.688
Renal disease	15 (18.8)	7 (16.3)	8 (21.6)	.747
Smoking[a]	11 (13.8)	6 (14)	5 (13.5)	.955
Liver disease	10 (12.5)	5 (11.6)	5 (13.5)	1
Asthma	9 (11.3)	3 (7.0)	6 (16.2)	.290
COPD	9 (11.3)	4 (9.3)	5 (13.5)	.726
Cancer	9 (11.3)	4 (9.3)	5 (13.5)	.726
Metastatic solid malignancy	1 (1.3)	0	1 (2.7)	.462
Cerebrovascular disease	8 (10)	4 (9.3)	4 (10.8)	1
Pulm circ disorders[b]	6 (7.5)	1 (2.3)	5 (13.5)	.09
PVD	5 (6.3)	1 (2.3)	4 (10.8)	.176
CHF	2 (2.5)	1 (2.3)	1 (2.7)	1
Admission to ICU from ED	27 (33.8)	16 (37.2)	11 (29.7)	.640
Time from admission to first CMV test, median (IQR), d	13 (8–29)	10 (8–22)	20 (11–35)	**.037**
Time from admission to CMV viremia, median (IQR), d	27 (18–39)	25 (18–38)	30 (20–42)	.145
Time from ICU admission to first CMV test, median (IQR), d	22 (14–32)	7 (1–22)	13 (4–27)	.086
Time from ICU admission to CMV viremia, median (IQR), d	22 (14–32)	20 (12–32)	24 (15–32)	.478
Time from MV to CMV pos (n = 70)	19 (11–32)	19 (10–33) n = 36	22 (11–31) n = 34	.672

All data are expressed as No. (%) unless otherwise specified.

Abbreviations: CCI, Charlson comorbidity index; CHF, congestive heart failure; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; MI, myocardial infarction; MV, mechanical ventilation; PVD, peripheral vascular disease.

[a]Smoking status is unreliably documented in our computerized order entry system.

[b]Pulm circ disorders includes pulmonary embolism, pulmonary heart diseases (ie, pulmonary hypertension), and diseases of pulmonary vessels.

cohort (IQR) was 66 (56–72) years, 54 (67.5%) patients were male, and the median Charlson comorbidity index score (IQR) was 4 (2–6). Patients in the treatment group were more likely to be tested for CMV earlier in the hospital stay than patients in the control group (10 [8–22] vs 20 [11–35] days; $P = .037$). However, time from admission to CMV viremia was similar between groups (25 [18–38] vs 30 [20–42] days; $P = .145$). There was no significant difference between groups with regards to time from ICU admission to CMV viremia or time from initiation of MV to CMV viremia (Table 1). Patients who were treated for CMV viremia were more likely to receive glucocorticoids and/or tocilizumab and received higher dexamethasone dose equivalents than patients in the control arm, though only the latter was statistically significant.

Laboratory Results

The median highest value for CMV viral load in the treatment group and control group was 932 (394–6158) copies/mL and 535 (125–2236) copies/mL, respectively ($P = .061$). More patients in the treatment group had a CMV viral load ≥1000 copies/mL compared with the control group (25 [58.1%] vs 12 [32.4%]; $P = .038$). Baseline laboratory values indicated that patients in the treatment group had higher levels of alanine aminotransferase (ALT; 44 [30–69] vs 32 [22–49] U/L; $P = .017$), aspartate aminotransferase (AST; 59 [43–81] vs 43 [34–61] U/L; $P = .013$), and ferritin (1311 [840–3006] vs 913 [430–2170] ng/mL; $P = .049$) upon initial presentation compared with the control group (Table 2). Patients in the treatment group also had a higher peak ferritin level (4221 [2270–6840] vs 2732 [1700–4489] ng/mL; $P = .013$) compared with the control group. No patients in the treatment group developed myelosuppression.

Treatment Characteristics

Treatment for COVID-19 was compared between the 2 groups, with no statistically significant difference in use of remdesivir

Table 2. Laboratory Values

	All Patients (n = 80)	Treatment (n = 43)	Control (n = 37)	*P* Value
Maximum CMV viral load, copies/mL	731 (249–2991)	932 (394–6158)	535 (125–2236)	.061
Positive CMV, No. (%)	37 (46.3)	25 (58.1)	12 (32.4)	0.038
Baseline				
Alkaline phosphatase, U/L	67 (56.5–88) n = 73	67 (56–92) n = 39	68 (57–82) n = 34	.699
ALT, U/L	39 (23.5–61) n = 73	44 (30–69) n = 39	32 (22–49) n = 34	.017
AST, U/L	55 (36.5–72) n = 73	59 (43–81) n = 39	43 (34–61) n = 34	.013
Bilirubin, mg/dL	0.6 (0.4–0.8) n = 73	0.6 (0.4–0.7) n = 39	0.6 (0.4–0.9) n = 34	.807
CRP, mg/L	131 (82–228.2) n = 63	131 (80–265) n = 36	137 (86–171) n = 27	.311
D-dimer, ng/mL	349 (225–645) n = 63	376 (217–682) n = 35	326 (262–625) n = 28	.967
Ferritin, ng/mL	1130 (682–2436.8) n = 61	1311 (840–3006) n = 33	913 (430–2170) n = 28	.049
IL-6, pg/mL	13 (6.2–54) n = 9	39.5 (7.8–71.3) n = 4	13 (5.7–28.5) n = 5	.413
Procalcitonin, ng/mL	0.165 (0.08–0.395) n = 62	0.22 (0.09–0.48) n = 35	0.13 (0.08–0.24) n = 27	.078
WBC, $10^3/\mu L$	7.3 (5.3–9.9) n = 77	7.5 (5.4–10.2) n = 41	7.3 (5.1–9.5) n = 36	.520
Platelets, $10^3/\mu L$	194 (147–248) n = 75	195 (143–311) n = 39	187 (147–226) n = 36	.314
Maximum				
Alkaline phosphatase, U/L	220 (128.5–339.8) n = 80	227 (139–348) n = 43	169 (108–335) n = 37	.300
ALT, U/L	142 (79.8–365.3) n = 80	153 (106–385) n = 43	120 (66–333) n = 37	.103
AST, U/L	144.5 (80–365.3) n = 80	164 (99–380) n = 43	119 (66–346) n = 37	.072
Bilirubin, mg/dL	1.4 (0.8–2.3) n = 80	1.6 (0.9–2.3) n = 43	1.1 (0.8–1.9) n = 37	.114
CRP, mg/L	261.4 (200.7–365) n = 80	300 (209–380) n = 43	238 (195–315) n = 37	.085
D-dimer, ng/mL	5242 (2995–8653) n = 77	6641 (3099–8962) n = 43	4500 (2314–7958) n = 34	.125
Ferritin, ng/mL	3225 (1994–5843.8) n = 78	4221 (2270–6840) n = 42	2732 (1700–4489) n = 36	.013
IL-6, pg/mL	49.0 (20–148.6) n = 53	60 (15–164) n = 32	39.7 (21–132.5) n = 21	.928
Procalcitonin, ng/mL	1.7 (0.58–6.1) n = 80	1.41 (0.56–6.1) n = 43	1.7 (0.58–5.85) n = 37	.772
WBC, $10^3/\mu L$	25.7 (21.2–33.4) n = 80	26.5 (21.3–35.3) n = 43	25.3 (20.7–30.8) n = 37	.291
Platelets, $10^3/\mu L$	425 (341.8–538.5) n = 80	424 (350–540) n = 43	426 (337–550) n = 37	.946

All values are presented as median (IQR) unless otherwise specified.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CRP, C-reactive protein; IL-6, interleukin-6; IQR, interquartile range; WBC, white blood cell.

(28 [65.1%] vs 24 [64.9%]; $P = .981$), tocilizumab (22 [51.2%] vs 14 [37.8%]; $P = .333$), or glucocorticoids (43 [100%] vs 36 [97%]; $P = .462$) (Table 3). Patients in the treatment group received a higher total dexamethasone dose equivalent compared with the control group (309 [186–543] vs 188 [138–313] mg; $P = .017$). In the treatment group, the median duration of ganciclovir (IQR) was 15 (8–27) days, the median duration of valganciclovir (IQR) was 11 (7–15) days, and the median duration of ganciclovir plus valganciclovir (IQR) was 19 (9–30) days.

Primary Outcome: Mortality

There was no statistically significant difference between the treatment and control groups for overall in-hospital mortality (16 [37.2%] vs 16 [43.2%]; $P = .749$) or ICU mortality (16 [37.2%] vs 14 [37.8%]; $P = .954$) (Table 4). The median time from hospital admission to death (IQR) was 40 (30–69) days and from ICU admission to death (IQR) was 35 (25–61) days, with no significant difference between groups ($P = .752$ and $P = .696$, respectively) (Figure 1). Additionally, there was no difference in time from CMV viremia to death between

Table 3. COVID-19 and CMV Treatment Characteristics

	All Patients (n = 80)	Treatment (n = 43)	Control (n = 37)	*P* Value
Remdesivir	52 (65)	28 (65.1)	24 (64.9)	.981
Days of therapy, median (IQR)	10 (5–10)	10 (6–10)	6 (5–10)	.066
Tocilizumab	36 (45.0)	22 (51.2)	14 (37.8)	.333
Glucocorticoid use	79 (99)	43 (100)	36 (97)	.462
Dexamethasone	58	33 (76.7)	25 (67.6)	.506
Methylprednisolone	38	18 (41.9)	20 (54.1)	.387
Prednisone	13	7 (16.3)	6 (16.2)	.994
Hydrocortisone	39	21(48.8)	18 (47.6)	.987
Total dexamethasone dose equivalents, median (IQR), mg	254 (160–432)	309 (186–543)	188 (138–313)	.017
Ganciclovir duration, median (IQR), d (n = 40[a])	–	15 (8–27)	–	–
Time from CMV viremia to start of treatment, median (IQR), d (n = 40)	–	3 (2–7)	–	–
Valganciclovir duration, median (IQR), d (n = 17[a])	–	11 (7–15)	–	–
Total duration CMV viremia treatment, median (IQR), d	–	19 (9–30)	–	–
Infectious diseases consult	62 (77.5)	34 (79.1)	28 (75.7)	.925

All values presented as No. (%) unless otherwise specified.

Abbreviations: CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; IQR, interquartile range.

[a]Three patients received valganciclovir only.

the treatment and control groups (15 [8–31] days vs 13 [7–20] days; $P = .564$) (Figure 2). Similar results were obtained when the treatment group was adjusted to include all patients who received any dose of ganciclovir (Supplementary Table 1).

Secondary Outcomes

There was no difference in hospital LOS between the 2 groups (63 [40–88] vs 49 [34–74] days; $P = .121$) (Table 4). However, patients in the treatment group had a longer ICU LOS compared with the control group (51 [33–79] vs 38 [22–52] days; $P = .014$) and were more likely to require ECMO (12/36 MV patients [33.3%] vs 2/34 MV patients [5.9%]; $P = .010$). There was no difference in need for MV (36 patients [84%] in the treatment group and 34 patients [92%] in the control group; $P = .446$), no difference in time from ICU admission to MV (1 [0–3] vs 1 [0–3] day; $P = .723$), and no difference in duration

Table 4. Primary and Secondary Outcomes

	All Patients (n = 80)	Treatment (n = 43)	Control (n = 37)	*P* Value
Mortality, No. (%)				
In-hospital overall	32 (40)	16 (37.2)	16 (43.2)	.749
Max CMV viral load ≥1000 copies/mL (positive)	19/37 (51.4)	11/25 (44)	8/12 (66.7)	.347
Max CMV viral load <1000 copies/mL (low)	13/43 (30.2)	5/18 (27.8)	8/25 (32)	.766
ICU	30 (37.5)	16 (37.2)	14 (37.8)	.954
Time from hospital admission to death, d (n = 32)	40 (30–69)	39 (27–82) n = 16	21 (40–57) n = 16	.752
Time from ICU admission to death, d (n = 32)	35 (25–61)	32 (21–76) n = 16	38 (27–47) n = 16	.696
Time from CMV viremia to death, d (n = 32)	14 (8–26)	15 (8–31) n = 16	13 (7–20) n = 16	.564
Hospital LOS, d	56 (38–81)	63 (40–88)	49 (34–74)	.121
Hospital LOS from CMV viremia, d	26 (13–42)	33 (16–53)	16 (10–31)	.006
ICU LOS, d	43 (29–67)	51 (33–79)	38 (22–52)	.014
ICU LOS from CMV viremia, d	19 (7–39)	27 (13–44)	11 (4–26)	.001
ICU LOS from CMV viremia in ICU, d (n = 74[a])	22 (9–41)	27 (13–44) n = 43	14 (6–32) n = 31	.015
Required MV, No. (%)	70 (87.5)	36 (83.7)	34 (91.9)	.446
Required ECMO	14/70 (20.0)	12/36 (33)	2/34 (5.9)	.010
Time from ICU admission to MV, d (n = 70)	1 (0–3)	1 (0–3)	1 (0–3)	.723
MV duration, d	38 (24–68)	45 (27–77)	37 (18–59)	.176
MV duration from first CMV viremia, d	18 (8–36)	26 (13–50)	15 (6–27)	.019
Patients on MV at time of CMV viremia,[b] No. (%) (n = 64)	64 (80)	34 (79.1)	30 (81.1)	.823

All values presented as median (IQR) unless otherwise specified.

Abbreviations: CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MICU, medical intensive care unit; MV, mechanical ventilation.

[a]Six of 80 patients were discharged from the MICU before CMV was detected.

[b]Six patients were extubated before CMV viremia was detected (5 in no ganc group and 1 in ganc group).

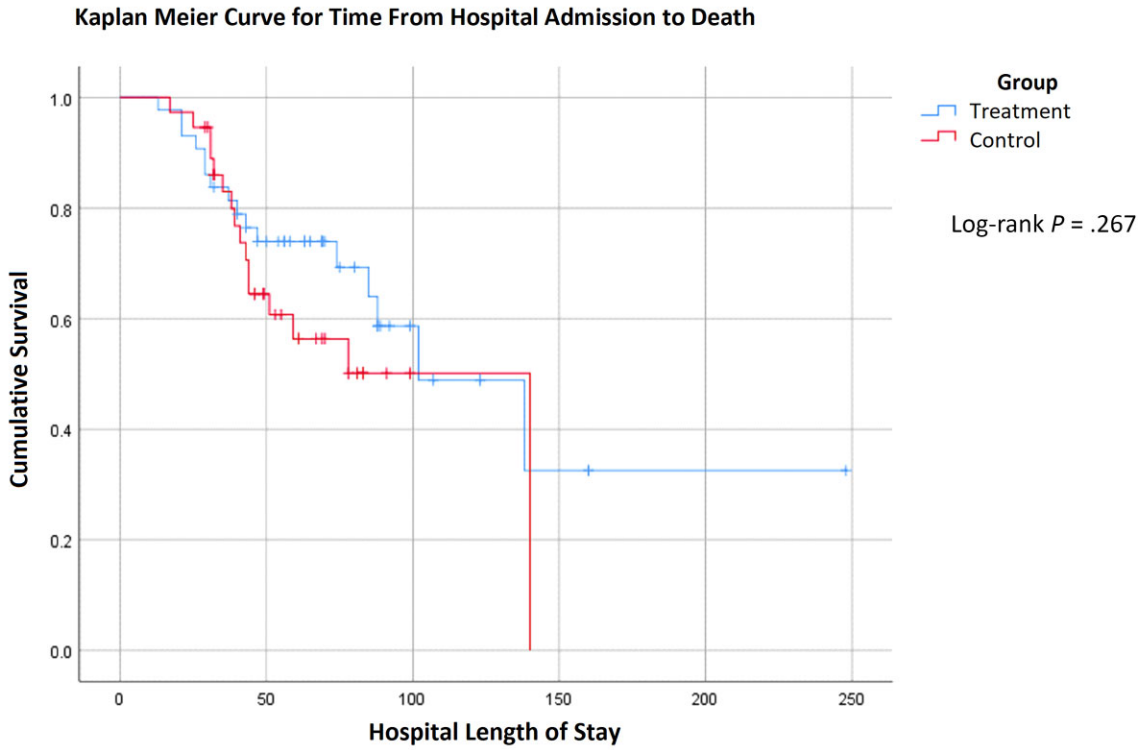

Figure 1. Kaplan-Meier curve comparing survival in the treatment and control groups from the time of hospital admission. All points of censorship represent patients who were discharged from the hospital alive. Patients were not followed after discharge. There was no statistically significant difference between groups. Log-rank $P = .267$.

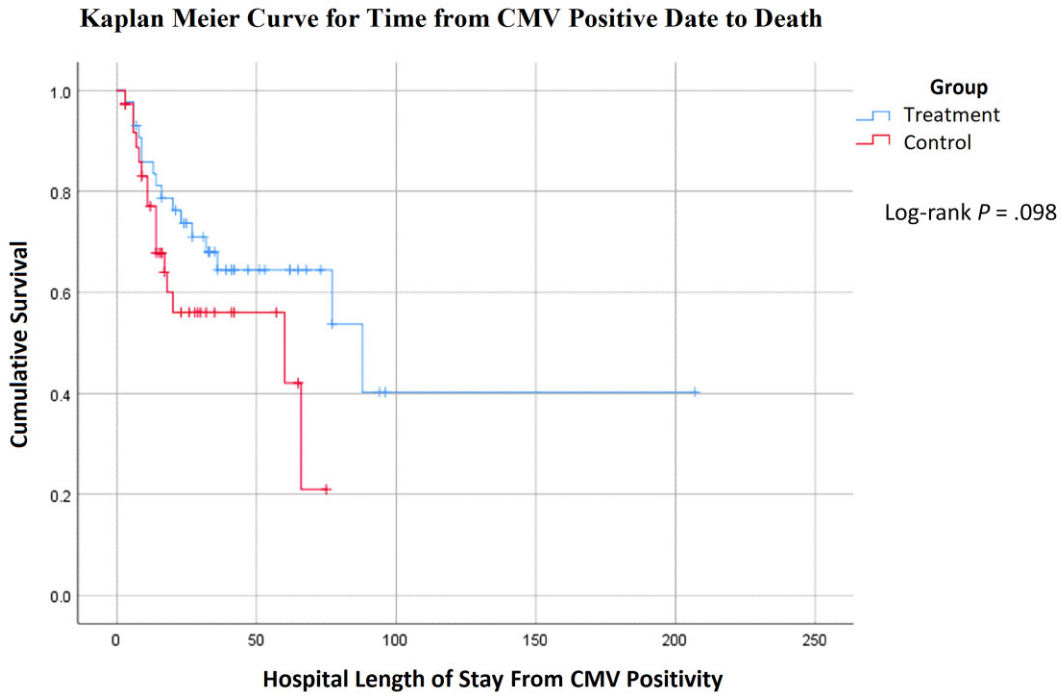

Figure 2. Kaplan-Meier curve comparing survival in the treatment and control groups from the time of the first positive CMV viral load. All points of censorship represent patients who were discharged from the hospital alive. Patients were not followed after discharge. There was no statistically significant difference between groups. Log-rank $P = .098$. Abbreviation: CMV, cytomegalovirus.

Table 5. Univariate Analysis—Predictors of Mortality

	Mortality (n = 32)	Survived (n = 48)	*P* Value	Odds Ratio (95% CI)
Treatment	16 (50)	21 (43.8)	.749	1.3 (0.524–3.154)
CMV viral load ≥1000 copies/mL	19 (59.4)	18 (37.5)	.090	2.4 (0.975–6.088)
Maximum CMV viral load, median (IQR), copies/mL	1741 (308–8260)	613 (183–1243)	.059	
Positive CMV viral load and received treatment	11 (34.4)	14 (29.2)	.806	1.3 (0.488–3.319)
Low CMV viral load and received treatment	5 (15.6)	13 (27.1)	.353	0.5 (0.158–1.570)
Required MV	31 (96.9)	39 (77.1)	.045	7.2 (0.859–59.548)
ICU admission from ED	9 (28.1)	18 (37.5)	.530	0.7 (0.248–1.715)
Dexamethasone	25 (78.1)	33 (68.8)	.506	1.6 (0.576–4.578)
Total dexamethasone dose equivalents, median (IQR), mg	257 (163–478)	254 (160–432)	.889	
Remdesivir	22 (68.8)	30 (62.5)	.738	1.3 (0.511–3.409)
Tocilizumab	12 (37.5)	24 (50)	.383	0.6 (0.241–1.494)
Male	21 (65.6)	33 (68.8)	.961	0.9 (0.335–2.246)
Smoker	2 (6.3)	9 (18.8)	.185	0.3 (0.058–1.437)
MI	10 (31.3)	11 (22.9)	.568	1.5 (0.559–4.181)
DM	19 (59.4)	20 (41.7)	.185	2.1 (0.824–5.080)
COPD and/or asthma	3 (9.4)	7 (14.6)	.732	0.6 (0.144–2.541)
Age, median (IQR), y	69 (57–73)	64 (53–68)	.064	N/A
CCI, median (IQR)	5 (3–7)	3 (2–4)	.004	N/A
Renal disease	10 (31.3)	5 (10.4)	.041	3.9 (1.189–12.851)
Cerebrovascular disease	5 (15.6)	3 (6.3)	.256	2.8 (0.614–12.559)
Liver disease	7 (21.9)	3 (6.9)	.080	4.2 (0.997–17.694)
ID consult	24 (75)	38 (79.2)	.870	0.8 (0.273–2.281)

All values are presented as No. (%) unless otherwise specified.

Abbreviations: CCI, Charlson comorbidity index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ED, emergency department; ICU, intensive care unit; ID, infectious diseases; IQR, interquartile range; MI, myocardial infarction; MV, mechanical ventilation.

of MV (45 [27–77] vs 37 [18–59] days; $P = .176$). Of note, once CMV viremia was detected, patients in the treatment group had a longer duration of MV (26 [13–50] vs 15 [6–27] days; $P = .019$). Based on univariate analysis, patients who died were more likely to have a higher Charlson comorbidity index ($P = .004$) and renal disease (OR, 2.8; 95% CI, 1.189–12.851; $P = .041$) (Table 5) as compared with patients who survived.

DISCUSSION

Our study serves as the first longitudinal study to investigate the treatment of CMV viremia in critically ill patients with COVID-19 pneumonia. We found no significant difference in in-hospital mortality between patients who received CMV treatment and those who did not. Prior data on COVID-19 and CMV coinfection are limited to case reports and series and are largely focused on patients with proven invasive CMV disease, which included myocarditis, hemorrhagic enteritis and/or colitis, CMV pneumonia, and pancreatitis [6–16]. While these cases suggest that CMV reactivation and invasive disease do occur in COVID-19 patients, the specific role of COVID-19 infection is difficult to assess, as critical illness itself is a risk factor for reactivation of CMV [4, 17].

The management of CMV reactivation in critically ill patients has been the subject of much debate [4]. One recent randomized controlled trial compared treatment with 14 days of ganciclovir vs placebo in 76 adults who developed CMV reactivation while on MV [18], but it was stopped early because it was underpowered to detect a difference. The mean duration of MV before randomization was 14–15 days, suggesting that CMV reactivation was a delayed event. Furthermore, >95% of patients screened for the study were ineligible, either due to death or extubation before receiving CMV test results. Two additional randomized controlled trials evaluated CMV prophylaxis in seropositive MV patients in the ICU. Limaye et al. found no difference in IL-6 levels, duration of MV, or mortality in the ganciclovir vs placebo groups, although ganciclovir prophylaxis was associated with lower incidence of CMV reactivation and a higher number of ventilator-free days [19]. Cowley et al. randomized patients to valacyclovir, valganciclovir, or placebo and found that while prophylaxis with either antiviral agent was associated with a lower incidence of CMV reactivation compared with placebo, valacyclovir prophylaxis was associated with higher mortality compared with valganciclovir and placebo. These studies suggest that strategies to offer prophylaxis to CMV-seropositive patients or to treat CMV reactivation are unlikely to offer significant benefits to immunocompetent patients.

The extrapolation of data from all critically ill and MV patients to COVID-19 patients is complicated by immune dysregulation due to COVID-19 as well as the immunosuppressive agents used to treat it [2, 20, 21]. Three studies have retrospectively tested patients with COVID-19 for CMV reactivation. Two of these studies found CMV reactivation in 23% of patients [22, 23]. The third study by Simonnet et al.

found CMV reactivation in only 15% of patients but also identified Epstein-Barr virus (EBV) reactivation in 82% [24]. Paolucci et al. prospectively tested 104 patients hospitalized with COVID-19 in an ICU or step-down unit of an Italian hospital for reactivation of herpes family viruses and only found reactivation of EBV in 88.3% of patients [25]. None of the 104 patients had CMV viremia detected by PCR, although it is not clear at what time during hospitalization the samples were taken. One systematic review of critically ill patients without COVID-19 found CMV reactivation in 25% of patients, although there was substantial heterogeneity across studies and a wide range of CMV reactivation reported (0%–38%). Thus it is not clear if COVID-19 increases the rate of reactivation independent of critical illness [26].

The practice of surveilling for CMV viremia and providing treatment if detected implies that COVID-19 is the inciting event causing CMV reactivation, which contributes to additional morbidity and mortality. However, there are mechanistic reasons to hypothesize that latent CMV infection may make patients more vulnerable to SARS-CoV-2. These mechanisms include increased immune senescence, decreased numbers of antigen-naïve T cells, and chronic vascular injury from CMV [27, 28]. The presence of CMV immunoglobulin G has been associated with increased mortality in the elderly, and it is also associated with lower socioeconomic status [29]. Furthermore, CMV and SARS-CoV-2 may have synergistic pathologic effects on tissues such as in the bowel or endothelium due to SARS-CoV-2 tropism for angiotensin-converting enzyme 2 (ACE-2) receptors [15].

Our study fills a gap in the current knowledge regarding the effects of treatment for CMV viremia in critically ill patients with COVID-19. Similar to studies in other critically ill patients, the results suggest that treatment of CMV viremia is unlikely to be beneficial for most patients on a nondiscriminatory basis. Specifically, we found that, among COVID-19 patients with CMV viremia, CMV treatment had no significant effect on the primary outcomes of in-hospital mortality and ICU-specific mortality. There are several possible reasons for this. First, it is not clear if CMV plays a pathogenic role in these patients or if it is merely a bystander and marker of critical illness. Second, the majority of our patients had low-level CMV viremia (<1000 copies/mL), where historical data indicate suppressive therapy may not improve outcomes. There was a trend toward decreased mortality with treatment in patients with positive CMV viremia (>1000 copies/mL), but it did not reach statistical significance. Third, any potential benefit of treatment may be offset by drug toxicity. Lastly, a history of CMV infection may predispose patients to severe COVID-19 but play less of a role during the acute course of COVID-19 illness.

With regards to the secondary outcomes, there was no significant difference in total LOS; however, CMV-treated patients had a longer ICU LOS and were more likely to receive ECMO. Our findings suggest that either ICU physicians treated CMV more frequently in patients they deemed sicker and therefore more likely to have longer ICU stays or to require ECMO or CMV treatment prolonged the ICU course. The total proportion of patients requiring MV and the time from ICU admission to MV were similar in the 2 groups, although treated patients had a longer duration of MV after detection of CMV viremia than nontreated patients. Whether this is due to treatment preferences, the underlying disease, or the sequelae of treatment is not known.

Our study has several important limitations. First, it is retrospective, and while the baseline characteristics of the groups were similar, there were differences in baseline transaminase levels, baseline and peak ferritin levels, and total dexamethasone-equivalent doses, suggesting that patients treated with ganciclovir may have been sicker. Due to the observational nature of the study, there may be clinical factors not captured that influenced physicians' decisions regarding CMV testing and treatment. Thus, COVID-19 patients not tested for CMV may differ from those tested. Additionally, due to infection control measures, patients with COVID-19 may undergo procedures less frequently for evaluation of tissue-invasive CMV disease, resulting in more frequent empiric treatment. Most ICU patients have other reasons for end-organ dysfunction, making it difficult to attribute causation to CMV without a tissue diagnosis. Lastly, most of our patients had low-level CMV viremia (<1000 copies/mL serum), which is below the threshold that shows treatment benefit in most studies. The strengths of our study include the relatively large sample size compared with similar studies, overall similar baseline characteristics of the 2 groups, and robust follow-up data. Larger studies are needed to determine whether preexisting positive CMV serology or the development of CMV viremia is associated with poor outcomes in COVID-19. If so, a large randomized controlled trial could then ascertain whether treatment has benefit, leading to a biomarker or algorithm to stratify patients into the groups most likely to derive benefit.

In summary, we found that among COVID-19 patients tested for CMV viremia, there was no mortality or other clear clinical benefit to treating CMV. Practices of empiric CMV testing and treatment of CMV in COVID-19 patients without suspected CMV organ disease should be reassessed. Prospective clinical trials on the significance of CMV viremia in COVID-19 patients, as well as the benefit of treatment, are needed.

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.

Acknowledgments

Financial support. The authors received no financial support for the research, authorship, and/or publication of this article.

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. This study does not include factors necessitating patient consent.

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