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Age and Comorbidities Predict COVID-19 Outcome, Regardless of Innate Immune Response Severity: A Single Institutional Cohort Study

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OBJECTIVES: The COVID-19 pandemic has claimed over eight hundred thousand lives in the United States alone, with older individuals and those with comorbidities being at higher risk of severe disease and death. Although severe acute respiratory syndrome coronavirus 2–induced hyperinflammation is one of the mechanisms underlying the high mortality, the association between age and innate immune responses in COVID-19 mortality remains unclear.

DESIGN: Flow cytometry of fresh blood and multiplexed inflammatory chemokine measurements of sera were performed on samples collected longitudinally from our cohort. Aggregate impact of comorbid conditions was calculated with the Charlson Comorbidity Index, and association between patient factors and outcomes was calculated via Cox proportional hazard analysis and repeated measures analysis of variance.

SETTING: A cohort of severely ill COVID-19 patients requiring ICU admission was followed prospectively.

PATIENTS: In total, 67 patients (46 male, age 59 ± 14 yr) were included in the study.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Mortality in our cohort was 41.8%. We identified older age (hazard ratio [HR] 1.09 [95% CI 1.07–1.11]; $p = 0.001$), higher comorbidity index (HR 1.24 [95% CI 1.14–1.35]; $p = 0.039$), and hyponatremia (HR 0.90 [95% CI 0.82–0.99]; $p = 0.026$) to each independently increase risk for death in COVID-19. We also found that neutrophilia ($R = 0.2$; $p = 0.017$), chemokine C-C motif ligand (CCL) 2 ($R = 0.3$; $p = 0.043$), and C-X-C motif chemokine ligand 9 (CXCL9) ($R = 0.3$; $p = 0.050$) were weakly but significantly correlated with mortality. Older age was associated with lower monocyte ($R = -0.2$; $p = 0.006$) and cluster of differentiation (CD) 16+ cell counts ($R = -0.2$; $p = 0.002$) and increased CCL11 concentration ($R = 0.3$; $p = 0.050$). Similarly, younger patients (< 65 yr) demonstrated a rise in CD4 (b-coefficient = 0.02; $p = 0.036$) and CD8 (0.01; $p = 0.001$) counts, as well as CCL20 (b-coefficient = 6.8; $p = 0.036$) during their ICU stay. This CD8 count rise was also associated with survival (b-coefficient = 0.01; $p = 0.023$).

CONCLUSIONS: Age, comorbidities, and hyponatremia independently predict mortality in severe COVID-19. Neutrophilia and higher CCL2 and CXCL9 levels are also associated with higher mortality, while independent of age.

KEY WORDS: age; comorbidities; COVID-19; immune; outcomes

The COVID-19 pandemic has claimed nearly eight hundred thousand lives in the United States alone and threatens to claim more given the rise of novel variants such as B.1.617.2 (Delta) and B.1.1.529 (Omicron). Despite significant advances in helping control the pandemic with preventative

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KEY POINTS

Question: The purpose of this study was to understand the association between age, comorbidities, and innate immune responses in COVID-19 mortality.

Findings: We found age, comorbidities, and hyponatremia to each independently increase risk for COVID-19–related mortality. Neutrophilia, CCL2, and CXCL9 concentrations were significantly correlated with mortality. Younger patients were able to demonstrate a rise in CD8+ and CD4+ T-cell counts over time after severe acute respiratory syndrome coronavirus 2 infection. Notably, the rise in CD8+ T cells was associated with survival.

Meaning: This study identifies unique markers and variables which may be used to indicate patient prognoses.

measures (social distancing, masking, and vaccines), as well as therapies aimed at shortening disease duration (remdesivir [1]) and improving mortality (dexamethasone [2], and in certain cases interleukin [IL]-6 inhibitors [3]), the pathophysiology of severe acute respiratory syndrome coronavirus (SARS-CoV)–2 and what makes it unique from other coronaviruses remain poorly understood.

One of the phenomena that has been most characterized, however, is the dysregulation of the immune system in patients with acute SARS-CoV-2 infection. Like SARS-CoV and Middle East respiratory syndrome–related coronavirus, SARS-CoV-2 infection induces a cytokine storm, which leads to activation and recruitment of a number of immune cells, most notably neutrophils, which perpetuates cytokine and chemokine secretion (4). This cytokine storm is at least partly mediated through damage-associated molecular patterns and pathogen-associated molecular patterns–induced monocytic Toll-like receptor activation, as we have recently demonstrated (5). As such, in patients with COVID-19, serum concentration of proinflammatory cytokines such as tumor necrosis factor (TNF)–α, IL-6, IL-8, and IL-10 has been shown to correlate with increased clinical severity and mortality (6). It is believed that this immune dysregulation in COVID-19 is indeed implicated in acute respiratory distress syndrome secondary to mononuclear inflammatory cell infiltration, septic shock, multiple organ failure, and in some cases death (7).

Intriguingly, the immune response triggered by SARS-CoV-2 is unique from those triggered by other upper respiratory viral infections, such as the influenza virus. Compared with the pathogenicity of influenza viruses, acute SARS-CoV-2 infections are marked by delayed interferon (IFN) responses (8), neutrophilia (9), impaired T-cell function (10), and atypical cytokine storms (11). It is believed that SARS-CoV-2 proteins, coronavirus nonstructural protein 14, open reading frame 3, open reading frame 6, and membrane protein protein, are able to inhibit IFN-β promoter activation within cells and impair intercellular antiviral responses (12). Impaired IFN responses during early infection facilitates viral replication, high viral loads, and myeloid driven innate hyperinflammation secondary to injury and death of viral infected cells (13). As such, compared with other upper respiratory viral infections, SARS-CoV-2 is associated with neutrophilia that is driven by immature neutrophils which are able to form neutrophil extracellular traps and myeloid-derived stem cells-like programmed death-ligand 1+ neutrophils that inhibit T-cell activity (9, 14). T-cell dysfunction, along with increased expression of IL-6, IL-6R, and IL-6ST, is just one of the characteristics that render the SARS-CoV-2–associated cytokine storm "atypical" (15).

Although SARS-CoV-2 infection undoubtedly leads to a starkly dysregulated immune response across all age ranges, older and more comorbid patients appear to be impacted the most, and it is this group that is chiefly burdened with excess disease severity and mortality (16–18). Older age and comorbidities, as predictive factors of COVID-19 disease severity and mortality, are not dissimilar from other pulmonary infectious processes (19). Similarly, comorbidities such as diabetes and HIV may also contribute to COVID-19 immune dysregulation and are believed to be associated with greater COVID-19 severity and mortality (20). It remains unclear, however, if the association between age, comorbidities, immune profiling, and COVID-19 mortality is a result of immune or extraimmune factors, such as angiotensin-converting enzyme 2 expression (21), or a combination of both.

In this study, we sought to determine the independent effect of age, comorbidities, and the immune response on SARS-CoV-2 mortality in a consecutive cohort of critically ill patients with COVID-19 admitted to a large tertiary academic referral center.

METHODS

Patient Population

Over the course of 9 months, consecutive COVID-19–positive patients requiring ICU admission at a tertiary academic medical center were enrolled in the study. Collection of data under protocol "ICU Biospecimen and Data Repository" was approved by the Duke University Institutional Review Board (IRB) (Pro 00101196) on June 19, 2020. This study was conducted in accordance with the ethical standards of the Duke IRB and the Helsinki Declaration of 1975. Eligible patients were adults (>18 yr old) of either gender who were admitted to an ICU with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) testing, and evidence of acute respiratory failure and/or multiple organ failure deemed to be a result of the SARS-CoV-2 infection. Written informed consent was obtained from the patients themselves, or their Legally Authorized Representatives, if they lacked decision-making capacity. Patients were excluded if they were enrolled in a blood conservation program or were pregnant or incarcerated.

Sample and Data Collection

EDTA whole blood and serum tubes were collected on days 1, 3, 7, 14, and 21 following enrollment or until discharge from ICU or death until day 21. In addition to biological samples, clinical data on these patients were also collected including baseline demographics, comorbidities, common laboratory panels, and clinically relevant outcomes. A modified Charlson Comorbidity Index (CCI) (22, 23) (age-excluding CCI) that did not include age was calculated for each patient (24). Similarly, to quantify the severity of a patient's COVID-19–related symptoms, a World Health Organization (WHO) ordinal scale ranging from 0 to 10 was calculated for each patient per recommendations outlined by the WHO Working Group on the Clinical Characterization and Management of COVID-19 Infection (25). To stratify patients by age, we used the age threshold of 65 years, to follow the Centers for Disease Control and Prevention COVID-19 Response Team guideline (26).

Whole Blood Flow Cytometry

To identify immune cells mobilized in the peripheral blood of our cohort, immune subset profiling antibody panels were obtained from Beckman-Coulter (Brea, CA). One basic immune subset panel tube (B53309) and one granulocyte panel tube (B88651) were used per patient at each time point per the manufacturer's instructions. The fixed and stained cells were acquired within 2 days of collection in accordance with biosafety level 2+ practices. Data were analyzed using FlowJo (Ashland, OR).

Chemokine Analysis

To study the mobilization of the innate immune response, human inflammatory chemokine LEGENDplex kits were obtained from BioLegend (Catalog Number 740985, San Diego, CA) to assess for serum chemokine concentrations. Assays were performed with serum at multiple timepoints as described earlier per the manufacturer's instructions. Data acquisition was performed using a Beckman Coulter CytoFLEX (Beckman Coulter, Brea, CA) flow cytometer and data processing performed using BioLegend's Bio-Bits (BioLegend, San Diego, CA) cloud-based software platform. Each sample was tested in triplicate, and results are reported as a mean value ± SD of these triplicates.

Statistical Analysis

Data analysis (unpaired *t* tests, univariate regression analysis, one-way repeated measures analysis of variance, and multiple unpaired *t* test analysis) and visualization were performed in IBM SPSS (IBM, Armonk, NY) and GraphPad Prism 9 (GraphPad Software, San Diego, CA). A Kaplan-Meier analysis of mortality in patients under and over 65 (Yanez et al [27]) was also performed. Univariate analyses for death were performed examining age, gender, age-excluding CCI, race, body mass index, and presence of comorbidities and common laboratory variables as outlined in **Supplementary Table 1** (http://links.lww.com/CCX/B91). The age-excluding CCI was calculated from the traditional CCI subtracting the points assigned for age (28). Cox proportional hazards regression analysis was conducted including the variables that were found to be statistically significant on univariate analysis. Regression analysis was conducted with Stata 15.1 (StataCorp, College Station, TX). Continuous variables are summarized as mean ± SDs or medians and 25–75% quartiles, depending on data distribution normality. Binary variables are summarized as counts (%). Statistical significance was declared at *p* value of less than 0.05.

RESULTS

Patient Characteristics and Comorbidities

Sixty-seven patients were enrolled in the study at the start of the COVID-19 pandemic. Of those, 38 had blood samples drawn at multiple timepoints. Mean age was 59.3 ± 14.3 years, and 69% of the cohort comprised males (Supplementary Table 1, http://links.lww.com/CCX/B91). Thirty-seven percent of the cohort were African American, 34% Caucasian, and 24% Hispanic. The most common comorbidities were obesity (body mass index [BMI] 33.1 ± 8.6) and type 2 diabetes mellitus (37%). Notably, patients who presented to the ICU on average had admission values indicating hyperglycemia (216 ± 138 mg/dL), elevated creatinine (2.4 ± 2.7 mg/dL), and elevated international normalized ratio (1.3 ± 0.4). 66.7% of patients were admitted directly to the ICU. Additionally, the average number of days to intubation was 3.9 ± 3.8, the average time from the first PCR positive test to day 1 of study was 8 days, and the average time from entry to ICU to day 1 of study was 3 days. Last, in this cohort, multiple organ failure was found to be the cause of death in 80% of patients, whereas acute respiratory failure and severe hypoxia made up the remaining 20%.

Age, Comorbidities, and Mortality

In the study cohort, mortality was 41.8%. Compared with survivors, nonsurvivors had higher age-excluding CCI (Supplementary Table 1, http://links.lww.com/CCX/B91) (2.3 ± 2.3 nonsurvivors vs 1.3 ± 1.5; $p < 0.001$). Nonsurvivors were also older than survivors (66 ± 12.4 vs 54.5 ± 13.8 yr; $p < 0.001$). Comorbidities such as chronic kidney disease (CKD) (21.4% vs 10.3%; $p = 0.010$) and solid tumors (14.3% vs 5.1%; $p = 0.008$) were more common among nonsurvivors compared with survivors.

On univariate analysis, older age (as a linear variable), age-excluding CCI, and lower sodium levels at admission were identified as being significantly associated with mortality in COVID-19. CKD and solid tumors were not significant, likely due to their inclusion in the CCI. History of myocardial infarction (10.7% vs 0 %; $p < 0.001$), liver disease (3.6% vs 0 %; $p = 0.010$), CKD, HIV/AIDS (3.6% vs 0 %; $p = 0.010$), and lower sodium at admission were seen with higher frequency in nonsurvivors. Interestingly, survivors had a higher BMI (34.4 ± 8.9 vs 31.2 ± 7.8; $p < 0.001$).

Older Age and Comorbidities Independently Increase Mortality Risk

The results of the Cox Proportional Hazards analysis are summarized in **Table 1**. Older age, higher age-excluding CCI, and hyponatremia were each identified to independently increase risk for death in COVID-19. Quantifying the effect of each of these variables, each 1-year increase in age was associated with a 10% increase in mortality in COVID-19, and each point decrease in admission serum sodium raised mortality risk by 10%. More notably, each point increase in the age-excluding CCI raised the risk for mortality by approximately 33%. Based on the model's dependence on CCI, certain comorbidities such as CKD and solid tumors do not contribute to mortality further than they already do as components of the CCI. Similarly, BMI was not identified to be an independent factor for mortality in our cohort.

Patients greater than 65 years were less likely to survive compared with patients less than 65 (**Fig. 1*A***) ($p = 0.004$; HR 4.2; CI 1.4–12.5), even though there was no statistically significant difference in disease severity per the WHO ordinal scores (25) between the two age groups (**Fig. 1*B***). Patients greater than 65 were more

TABLE 1.
Cox Proportional Hazard Regression Analysis

Variable	Hazard Ratio (95% CI)	*p*
Age	1.10 (1.05–1.15)	**< 0.001**
Age-excluding Charlson Comorbidity Index	1.33 (1.01–1.74)	**0.039**
Body mass index	1.01 (0.95–1.06)	0.957
Chronic kidney disease	0.52 (0.13–2.16)	0.370
Solid tumor	1.09 (0.25–4.69)	0.905
Sodium	0.90 (0.82–0.99)	**0.026**

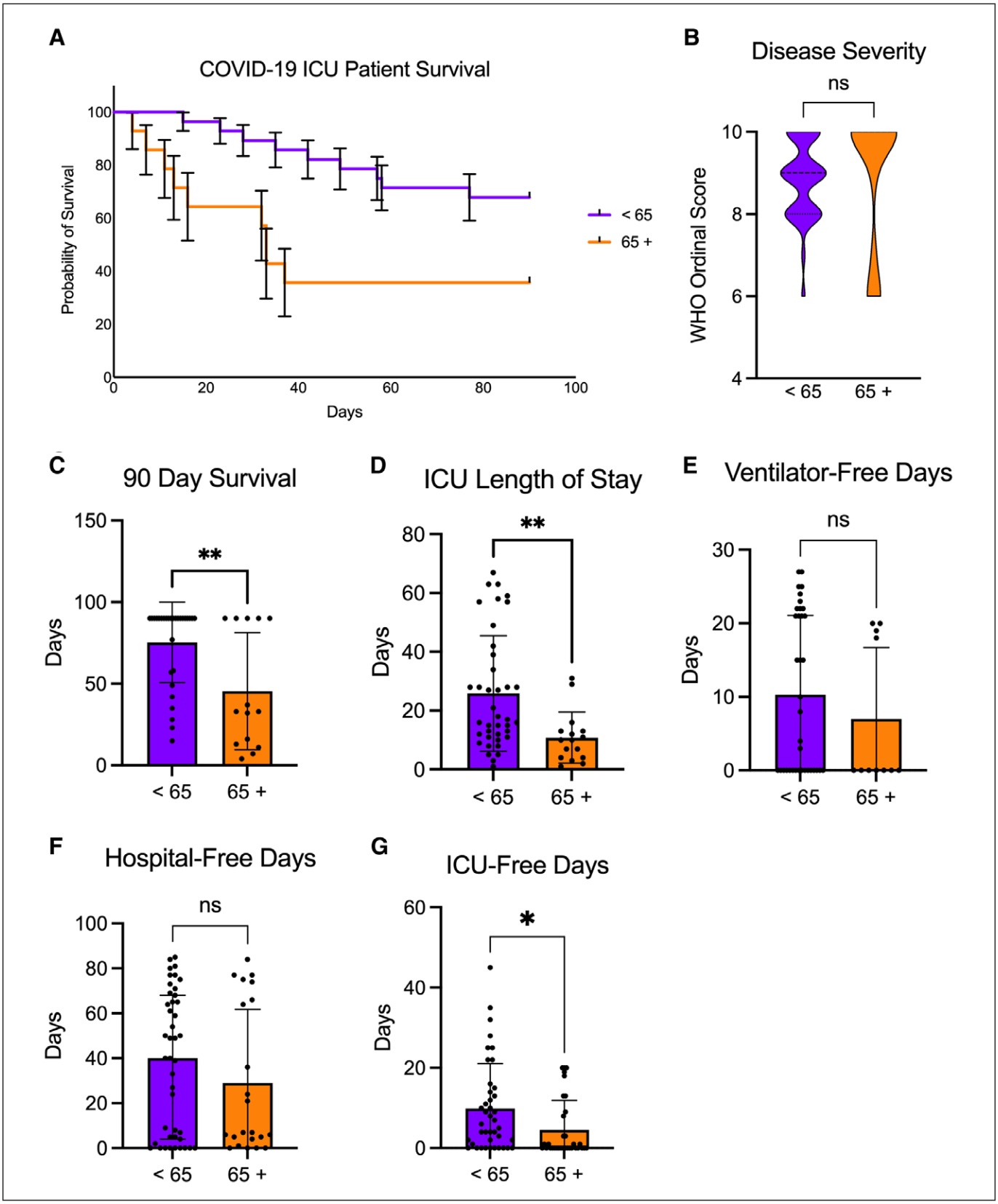

Figure 1. Outcomes by age. **A**, Patients above the age of 65 had worse survival compared to patients under the age of 65. **B**, The was no difference in World Health Organization (WHO) ordinal scores between patients above and below the age of 65. **C**, Patients above the age of 65 had worse 90-d survival compared with patients under the age of 65. **D** and **G**, Patients above the age of 65 had shorter stays in the ICU, as a result of worse survival. **E** and **F**, There was no difference in the number of ventilator-free days or hospital-free days between those above and below the age of 65. ns = not significant.

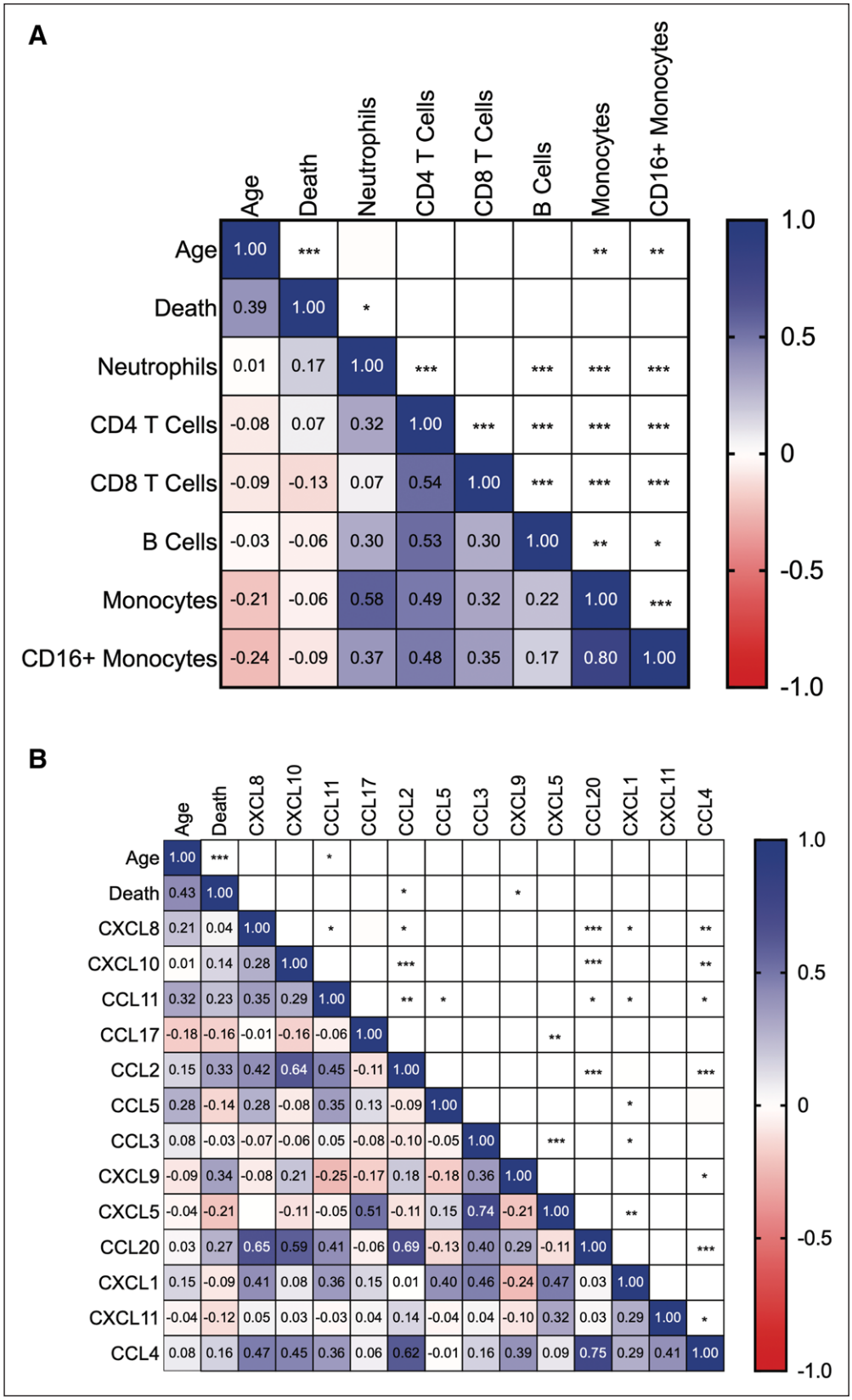

Figure 2. Correlational matrix of age and death with immune populations (**A**) and correlational matrix of age and death with serum CC chemokine family (CCL) and chemokine (C-X-C motif) ligand (CXCL) family chemokine concentrations (**B**). CD = cluster of differentiation.

likely to have a higher 90-day mortality than their younger counterparts (**Fig. 1*C***) (p = 0.003; 75.3 ± 24.6 d in patients < 65 vs 45.4 ± 35.9 d in patients 65+). Additionally, patients greater than 65 also had fewer ventilator-free days (**Fig. 1*E***) (10.3 ± 10.8 d in patients < 65 vs 7.0 ± 9.7 d in patients > 65; $p < 0.001$), hospital-free days (**Fig. 1*F***) (38.4 ± 31.3 d in patients < 65 vs 29.1 ± 32.7 d in patients > 65; $p < 0.001$), and stay in ICU (**Fig. 1*D***) and ICU-free days (**Fig. 1*G***) (9.9 ± 11.2 d in patients < 65 vs 4.5 ± 7.3 d in patients > 65; $p < 0.001$).

Immune Function and Mortality

Absolute T-cell counts, B-cell counts, and monocyte counts did not correlate with mortality; however neutrophil counts did (**Fig. 2*A***) (Pearson R = 0.2; p = 0.017). Interestingly, however, survivors demonstrated a greater rise in cluster of differentiation (CD) 8 T-cell counts over time (b-coefficient = 0.01; p = 0.023), unlike nonsurvivors (**Supplementary Fig. 3*I***, http://links.lww.com/CCX/B91).

The only chemokines that statistically, but weakly, significantly correlated with mortality were chemokine C-C motif ligand (CCL) 2 (**Fig. 2*B***)

(R = 0.3; p = 0.043) and C-X-C motif chemokine ligand (CXCL) 9 (Fig. 2*B*) (R = 0.3; p = 0.050).

The trends in all other chemokine concentrations over the course of COVID-19 are summarized in Supplementary Figure 3 (http://links.lww.com/CCX/B91).

Effect of Age on Immune Function

Lower absolute monocytes counts (Fig. 2*A*) (R = –0.2; p = 0.006) and CD16+ counts (Fig. 2*A*; and **Supplementary Fig. 1**, http://links.lww.com/CCX/B91) (R = –0.2; p = 0.002) were seen in older age patients. There was no correlation between absolute T-cell, B-cell, or neutrophil counts and age in our cohort. Interestingly, however, younger patients (< 65) demonstrated a rise in their CD4 T cell counts over time (b-coefficient = 0.02; p = 0.036), whereas their older counterparts did not. Similarly, we found that patients less than 65 exhibited a rise in their CD8 T cells over time (b-coefficient = 0.01; p = 0.001), whereas patients greater than 65 did not (**Supplementary Fig. 3*B***, http://links.lww.com/CCX/B91). No trends or differences in absolute neutrophil counts were noted between the two age groups (**Supplementary Fig. 3*C***, http://links.lww.com/CCX/B91).

Of all the chemokines measured in this study, the only chemokine which was weakly but positively correlated with age was CCL11 (**Supplementary Fig. 2**, http://links.lww.com/CCX/B91; Supplementary Fig. 3, http://links.lww.com/CCX/B91) (R = 0.3; p = 0.050). There were no notable trends in CCL11 concentrations during the course of COVID-19.

Last, younger patients (< 65) demonstrated a rising trend in CCL20 over the course of disease (b-coefficient = 6.8, p = 0.036), whereas their older counterparts did not (**Supplementary Fig. 3*G***, http://links.lww.com/CCX/B91).

DISCUSSION

In this study, we were able to follow a cohort of 67 patients and demonstrated that age, comorbidity burden, and hyponatremia were independently associated with mortality in COVID-19. Additionally, we demonstrated that neutrophilia, CCL2, and CXCL9 (both potent chemoattractants)—all markers of the innate immune response—correlated with mortality. Conversely, we demonstrated that lower monocyte and CD16+ counts, as well as higher CCL11 concentrations, were seen in older patients, without a notable association on survival. Similarly, younger patients demonstrated a rise in CD8 and CD4 cell counts, as well as their CCL20 levels during their ICU stay, and the former was also associated with survival. These observations may prove useful in mortality prediction in COVID-19 and in providing insights in the immune response triggered by SARS-CoV-2.

As has been described by others (27, 29–32), we also found that in our cohort of patients, patients who survived COVID-19 were generally younger than those who did not survive. We additionally found that patients greater than 65 had fewer ventilator-, ICU-, and hospital-free days. Similarly, in agreement with other groups (33–36), we found that those patients in our cohort with increased number of comorbidities were less likely survive. To better compare patients with multiple comorbidities, we employed the use of an age-excluding CCI to quantify comorbidity burden. Although previous studies have demonstrated that CCI commonly predicts survival (37–39), we demonstrate that an age-excluding CCI can also be predictive of mortality. Based on the how CCI is calculated, certain comorbidities such as diabetes and CKD are weighted more than other factors such as coronary heart disease and are predicted to have a greater influence on mortality. Interestingly, based on our analysis, we found that in addition to age, and age-excluding CCI, a lower sodium level at admission was also shown to independently decreased risk of mortality.

We also sought to determine whether there were immune response patterns that were associated with either participant age or mortality, by examining a wide number of chemokines and cell populations. Notably, Naqvi et al (5) did not find there to be any treatment effect of dexamethasone on cell populations other than CD16+ monocytes. Although we did not find correlations within lymphocytic populations, we found that older age was correlated with lower monocyte and CD16+ cell populations, which produce TNFa, IL6, macrophage inflammatory protein (MIP) 1a, MIP1B, and IFNg among other proinflammatory cytokines (40). This is in contrast with previous findings that CD16+ cell counts rise in older healthy adults (41). Although the etiology of this observation is unclear, a plausible explanation is that younger monocytes more rapidly proliferate in response to an acute innate immune cytokine storm, as commonly seen in severe infections (42). This may be supported by Naqvi et al (5) who also found

that younger patients were more likely to increase their CD4 and CD8 T cell populations, unlike their older counterparts. This finding is suggestive of the well-documented impaired age-related T-cell proliferation (43). Of the chemokines that we monitored in this study, we found that patients less than 65 also raised their CCL2 concentrations over time, unlike their greater than 65 counterparts. This is consistent with studies suggesting that younger patients with severe COVID-19 infection have proinflammatory responses predominately driven by factors such as IL-1RA, IL-6, CCL2, and CXCL1, whereas older patients have responses driven by CXCL8, IL-10, IL-15, and IL-27 (44).

We also noted that CCL2 and CXCL9, chemokines whose concentration typically rises early in SARS-CoV-2 infection and again in late stages of terminal cases (45, 46), were correlated to patient survival. These findings are consistent with data from Abers et Al (47) which identified CCL2 and CXCL9 to be independent predictors of survival along with IL-15, IL-2, neutrophil gelatinase-associated lipocalin, matrix metalloproteinase-9, soluble tumor necrosis factor receptor 1, soluble suppression of tumorigenicity 2, IL-10, and lactoferrin. In addition to these chemokines, we also identified CCL20 as another potential predictive marker for mortality in COVID-19. There may be value in quantifying these chemokines at admission to the ICU in patients with COVID-19 to determine patients' likelihood of disease progression and mortality risk. In addition, CCL2 and CXCL9 might also represent important targets for pharmacologic intervention to mitigate COVID-19–related morbidity and mortality.

Although the association between age and mortality has been long documented in COVID-19, in this study, we demonstrate how an impaired adaptive immunity may explain worse outcomes, independent of comorbidities, which also commonly cluster in the elderly. Although the importance of CD8+ T cells on COVID-19–related mortality has been previously described (48, 49), the influence of age on CD8+ T cells in COVID-19 patients is largely unexplored (50). Nevertheless, our study is consistent with findings by Westmeier et al (51) who also found that patients greater than 80 exhibited diminished cytotoxic T cell potential in response to SARS-CoV-2.

This study had several limitations, including the small number of subjects enrolled. It is possible that our analyses may have missed statistical significance for certain comorbidities due to our small sample size. Additionally, due to the common delay from presentation to ICU admission, especially in the earlier stages of the pandemic, it is possible that earlier perhaps equally important aspects of the immune response may have been left unexplored due to limited ability to collect datapoints. Despite these limitations, our study is one of the few that longitudinally followed several patients and enabled associations between trends in chemokines and cell populations and clinically relevant outcomes.

CONCLUSIONS

In conclusion, we demonstrate that age and presence of comorbidities, as well as admission hyponatremia, are each independently associated with mortality in COVID-19. We also demonstrate that neutrophilia and higher levels of CCL2 and CXCL9 are associated with higher mortality, whereas unassociated with age. Additionally, we found that in patients with COVID-19, age was correlated with lower absolute monocyte counts and lower CD16+ monocyte counts. Age was also found be correlated with increased CCL11 concentration. Although the influence of age and immune function were largely independent of each other, a rise in CD8+ cell population over time was found in patients less than 65 with COVID-19, and this trend is associated with survival. A rise in CCL20 levels is also seen in younger patients.

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Drs. Naqvi, Nair, Sullenger, and Kasotakis contributed to conception. Mr. Mohan and Drs. Olson, Naqvi, Nair, Sullenger, and Kasotakis contributed to study design. Drs. Kraft, Chen, and Que contributed to clinical samples. Mr. Mohan, Dr. Olson, and Dr. Kasotakis contributed to data analysis, contributions and writing—original draft. All authors contributed to editing and review.

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