AGE AND COMORBIDITIES PREDICT COVID-19 OUTCOME REGARDLESS OF SEVERITY OF INNATE IMMUNE RESPONSE

Aditya A. Mohan, Lyra B. Olson, PhD, Ibtehaj A. Naqvi, MD, PhD, Sarah A. Morrison, PhD, Bryan D. Kraft, MD, Lingye Chen, MD, Loretta G. Que, MD, Smita K. Nair, PhD, Qing Ma, PhD, Allan Kirk, MD PhD, Bruce A. Sullenger, PhD, **George Kasotakis, MD MPH**

ABSTRACT

Objective:
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, SARS-CoV-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 (CCI), and association between patient factors and outcomes was calculated via Cox proportional hazard analysis and repeated measures ANOVA.
Setting: A cohort of severely ill COVID-19 patients requiring ICU admission was followed prospectively.
Patients: In total, 67 patients (46 male, aged 59±14) were included in the study.
Interventions: None
Measurements and Main Results:
Mortality in our cohort was 41.8%. We identified older age (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), CCL2 (R=0.3, p=0.043), and 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 CD16+ cell counts (R=-0.2, p=0.002), and increased CCL11 concentration (R=0.3, p=0.050). Similarly, younger patients (<65 years) 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.

INTRODUCTION

- SARS-COVID-19 has claimed approx. 900,000 lives in the US.
- CoV-2 pathophysiology remains poorly understood.
  - Dysregulation of immune function key.
- Older, comorbid patients affected the most
- **Is there an association between the effects of age, comorbidities, and immune profile on mortality?**

METHODS

- **Patient Population**
  - Consecutive COVID-19+ patients requiring ICU admission at Duke (N=67).
- **Sample and Data Collection**
  - Whole blood & serum collected (days 1, 3, 7, 14, 21) until discharge or death.
- **EHR Review**
  - Demographics, comorbidities, outcomes collected.
- **Immune & Statistical Analyses**
  - Whole blood → flow cytometry
  - Serum → chemokine LEGENDplex
  - Correlation & Cox PH Regression.

RESULTS

Characteristic	Overall Cohort (n=67)	Survivors (n=39)	Non-survivors (n=28)	Univariate Analysis of Death (p-value)
Age (mean, SD)	59.3 (14.3)	54.5 (13.8)	66 (12.4)	<0.001
Female, (%)	21 (31.3%)	13 (33.3%)	8 (28.6%)	0.325
Race/Ethnicity, (%)				
African American, (%)	25 (37.3%)	15 (38.5%)	10 (35.7%)	
Caucasian, (%)	23 (34.3%)	13 (33.3%)	10 (35.7%)	
Hispanic, (%)	16 (23.9%)	9 (23.1%)	7 (25%)	
Other/Unknown, (%)	3 (4.5%)	2 (5.1%)	1 (3.6%)	0.098
Comorbidities				
Charlson Comorbidity Index Score, SD	3.3 (2.6)	2.5 (2.1)	4.4 (2.9)	<0.001
Age-excluding Charlson Comorbidity Index Score, SD	1.7 (1.9)	1.3 (1.5)	2.3 (2.3)	<0.001
Myocardial Infarction, (%)	3 (4.5%)	0 (0%)	3 (10.7%)	<0.001
Congestive Heart Failure, (%)	9 (13.3%)	6 (15.4%)	3 (10.7%)	0.842
Peripheral Vascular Disease, (%)	7 (10.4%)	3 (7.7%)	4 (14.3%)	0.079
Cerebrovascular Accident/Transient Ischemic Attack, (%)	8 (11.9%)	5 (12.8%)	3 (10.7%)	0.448
Dementia, (%)	2 (3%)	1 (2.6%)	1 (3.6%)	0.654
Chronic Obstructive Pulmonary Disease, (%)	9 (13.4%)	5 (12.8%)	4 (14.3%)	0.071
Connective tissue disease, (%)	4 (6%)	2 (5.1%)	2 (7.1%)	0.520
Peptic Ulcer Disease, (%)	0 (0%)	0 (0%)	0 (0%)	NA
Liver disease, (%)	1 (1.5%)	0 (0%)	1 (3.6%)	0.010
Diabetes Mellitus, (%)	25 (37.3%)	13 (33.3%)	12 (42.9%)	0.443
Hemiplegia, (%)	0 (0%)	0 (0%)	0 (0%)	NA
Chronic Kidney Disease, (%)	10 (14.9%)	4 (10.3%)	6 (21.4%)	0.010
Solid Tumor, (%)	6 (9%)	2 (5.1%)	4 (14.3%)	0.008
Leukemia, (%)	2 (3%)	1 (2.6%)	1 (3.6%)	0.654
Lymphoma, (%)	0 (0%)	0 (0%)	0 (0%)	NA
HIV/AIDS, (%)	1 (1.5%)	0 (0%)	1 (3.6%)	0.010
Body Mass Index (mean, SD)	33.1 (8.6)	34.4 (8.9)	31.2 (7.8)	0.001
Admission Lab Values				
White blood count, SD	12.9 (11.6)	13.9 (13.3)	11.7 (8.9)	0.398
Platelets, SD	221 (99)	243 (101)	192 (89)	0.060
Hemoglobin, SD	12.4 (2.4)	12.3 (2.4)	12 (2.5)	0.951
Sodium, SD	137 (5)	138 (6)	136 (4)	0.031
Bicarb, SD	24 (6)	25 (7)	23 (5)	0.295
Creatinine, SD	2.4 (2.7)	2.2 (2.5)	2.6 (3.0)	0.420
Glucose, SD	216 (138)	221 (156)	209 (109)	0.677
INR, SD	1.3 (0.4)	1.2 (0.5)	1.3 (0.4)	0.103
Clinical Outcomes				
Hospital Length of Stay (mean, SD)	29.1 (22.5)	33.3 (25.4)	23.2 (16.6)	<0.001
ICU Length of Stay (mean, SD)	21.4 (18.3)	21.3 (19.2)	21.4 (17.2)	0.830
90 – Days to Mortality (mean, SD)	65.0 (32.1)	90 (0)	30.1 (18.9)	<0.001
ICU Free Days (mean, SD)	7.7 (9.9)	12.0 (10.9)	1.8 (3.4)	<0.001
Hospital Free Days (mean, SD)	35.8 (31.9)	57.0 (24.5)	0	<0.001
Ventilator Free Days (mean, SD)	20.3 (18.8)	14.0 (10.0)	0.9 (0.9)	<0.001

Table 1: Clinical characteristics of ICU population.

Variable	Hazard ratio (95% Confidence Interval)	p-value
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

Table 2: Cox Proportional Hazard Regression analysis.

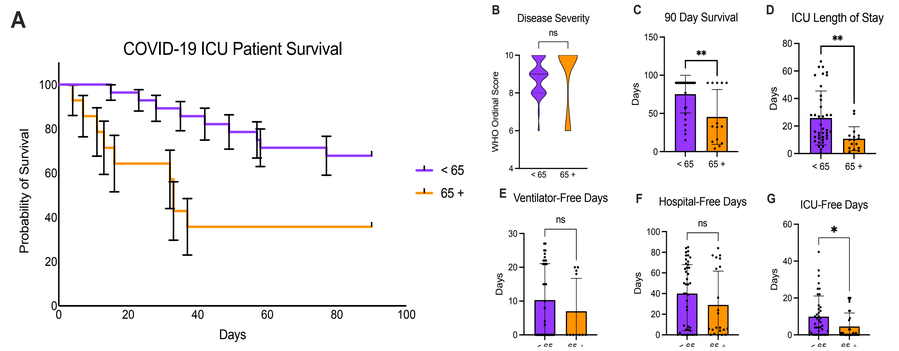

Figure 1: Outcomes by Age

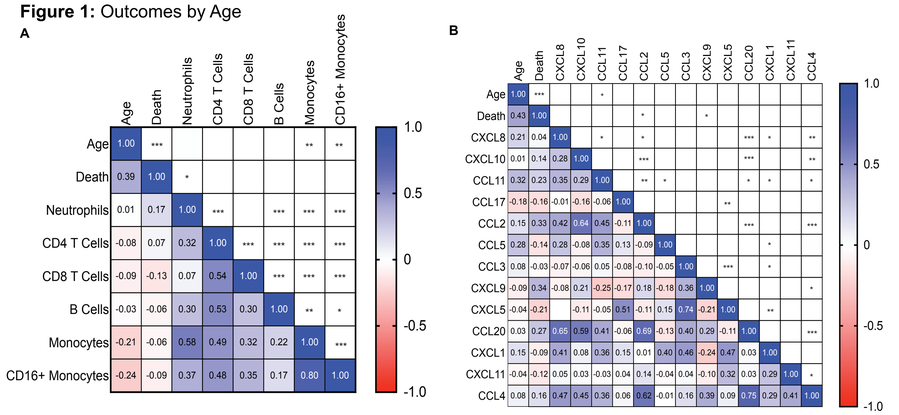

Figure 2: (A) Correlational Matrix of Age and Death with Immune Populations and **(B)** Correlational Matrix of Age and Death with Serum Chemokine Concentrations

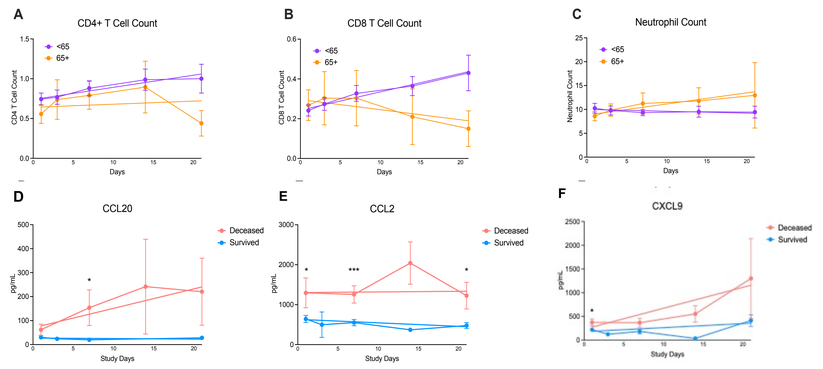

Figure 3: Longitudinal leukocyte and chemokine analysis stratified by mortality or age

CONCLUSIONS

- Age, comorbidities, hyponatremia independently predict mortality.
- Younger patients displayed increased CD4/CD8 T cell counts over time.
  Trends may be more important than single measurements.
- CCL2, CXCL9, CCL20 much higher in deceased patients.
- Age-related immunity changes do not correlate with mortality.