Predictors for Severe COVID-19 Infection

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Summary

Acute or pre-existing renal disease, oxygen requirement at the time of hospitalization and initial C-reactive protein were independent predictors for the development of severe COVID-19 infections. Every 1 unit increase in CRP increased the risk of severe disease by 0.06%.

Abstract

Background

COVID-19 is a pandemic disease caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Predictors for severe COVID-19 infection have not been well defined. Determination of risk factors for severe infection would enable identifying patients who may benefit from aggressive supportive care and early intervention.

Methods

We conducted a retrospective observational study of 197 patients with confirmed COVID-19 infection admitted to a tertiary academic medical center.

Results

Of 197 hospitalized patients, the mean (SD) age of the cohort was 60.6 (16.2) years, 103 (52.3%) were male and 156 (82.1%) were black. Severe COVID-19 infection was noted in 74 (37.6%) patients, requiring intubation. Patients aged above 60 were significantly more likely to have severe infection. Patients with severe infection were significantly more likely to have diabetes, renal disease, chronic pulmonary disease and had significantly higher white blood cell counts, lower lymphocyte counts, and increased C-reactive protein (CRP) compared to patients with non-severe infection. In multivariable logistic regression analysis, risk factors for severe infection included pre-existing renal disease (odds ratio [OR], 7.4; 95% CI 2.5-22.0), oxygen requirement at hospitalization (OR, 2.9; 95% CI, 1.3-6.7), acute renal injury (OR, 2.7; 95% CI 1.3-5.6) and initial CRP (OR,1.006; 95% CI, 1.001-1.01). Race, age and socioeconomic status were not identified as independent predictors.

Conclusions

Acute or pre-existing renal disease, supplemental oxygen at the time of hospitalization and initial CRP were independent predictors for the development of severe COVID-19 infections. Every 1 unit increase in CRP increased the risk of severe disease by 0.06%.

Keywords: Predictors, Risk factors, severe COVID-19

In December 2019, the first pneumonia cases of unknown origins were identified in Wuhan city, Hubei province, China[1]. The pathogen was identified as a novel coronavirus (nCoV), now called severe acute respiratory syndrome coronavirus (SARS-CoV), with the disease termed COVID-19[2]. Because of its rapid spread, the World Health Organization has declared 2019-nCoV as pandemic[3]. As of April 28, 2020, a total of 3, 090, 844 confirmed cases had been reported in at 184 countries[4]. SARS-CoV-2 infections have been described among asymptomatic (who never developed symptoms) as well as pre-symptomatic patients (who are not yet symptomatic)[5-10].

The clinical spectrum from the largest cohort of symptomatic COVID-19 patients from China ranged from mild to critically ill cases[11]. Age was described as a strong risk factor for severe disease, with the highest case fatalities occurring in those 80 years and older[11-13]. Preliminary data from the United States (U.S.) also suggested that adverse outcomes were most frequent among persons 85 years of age and older, but it also recognized that severe infections could occur in adults of any age group[14, 15]. Comorbid conditions of hypertension, diabetes, chronic lung and renal disease were also associated with severe infections and adverse outcomes[16-18]. Medications such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were suggested to increase the severity of infection[19], but currently there are no data to suggest a link between these medications and adverse outcomes. The determination of risk factors for severity in COVID-19 infection would enable identification of high-risk patients who may benefit from close monitoring, aggressive supportive care and early intervention.

To address this question, we collected clinical data from a cohort of hospitalized patients with the aim of identifying predictors for developing severe COVID-19 infections.

Study Setting and Design:

We conducted a single-center, retrospective observational study at a 776-bed tertiary care urban academic medical center. The study was approved by the Ascension St John Hospital Institutional Review Board. Patients with confirmed COVID-19 (positive real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab) from March 8th to April 8th, 2020 were included. COVID-19 testing for all patients under investigation (PUI) was done according to criteria, defined per the US Centers for Disease Control and Prevention (CDC)[20]. Patients' nasopharyngeal swab specimens were sent to the Michigan Department of Health and Human Services (MDHHS) Bureau of Laboratories (BOL) for RT-PCR testing after obtaining an nCoV identification number (ID) from the MDHHS Communicable Disease (CD) Division. These nCoV ID numbers were tracked by the institution's infection control database. All studied subjects were identified using this database.

Data collection

Data were collected from the electronic medical record (EMR) for all the patients meeting inclusion criteria. Clinical parameters included age; gender; ethnicity; residential zip code plus four; presence of comorbid conditions (according to the Charlson Comorbidity Index, a validated, weighted index scores that predict mortality); patient's home medications; vital signs on presentation; presenting symptoms; laboratory and radiological findings on admission; status on intubation and intensive care unit admission; hospital discharge or inpatient death[21]. Clinical outcomes will be addressed in another report.

Definitions

A COVID-19 infection was defined as "severe" if the patient required mechanical ventilation. Obesity and severe obesity were defined according to CDC definitions[22]. Fever was defined as an axillary temperature of 37.5°C or higher. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells per cubic millimeter. Thrombocytopenia was defined as a platelet count of less than 150,000 per cubic millimeter. Acute renal injury or elevated creatinine on admission was defined as increase in serum creatinine by ≥0.3mg/dL (≥26.5 micromol/L) within 48 hours or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior seven days[23]. Patients with pre-existing renal disease were on dialysis, had a history of renal transplant, had uremic syndrome, or had a creatinine > 3mg/dL in prior admissions. Using the nine-digit zip code, the area deprivation rank for each individual patient was also obtained. The Area Deprivation Index (ADI) is a measurement of healthcare deprivation based upon where a person lives; it correlates with socioeconomic status[24]. A higher ADI means more deprived. On a national level the ADIs are ranked from 1 to 100 (1 = least deprived, 100 = most deprived) and on a state level it is from 1 to 10 (1 = least deprived, 10 = most deprived).

Statistical Analysis

Statistical analysis was performed using SPSS v. 26.0 (Armonk, NY). Descriptive statistics were generated to characterize the study population. Continuous variables were described as the mean with standard deviation or median with interquartile range. Univariable analysis was done using Student's t-test, analysis of variance followed by multiple pairwise comparisons using the Bonferroni correction of the p-value, the Mann-Whitney U test and chi-squared analysis. Variables that were found to be significant (p <0.05) predictors of severity were then entered a multivariable logistic regression model using a forward likelihood ratio algorithm. When two variables were measuring the same underlying factor, the variable with the highest univariable measure of association was used in the model. Results from the regression are reported as odds ratios with 95% confidence intervals. All reported p values are two-sided.

Results

A total of 197 hospitalized patients with confirmed SARS-CoV-2 infections were included in the analysis. Mean (SD) age of the cohort was 60.6 (16.2) years, 103 (52.3%) were male and 156 (82.1%) were black. The mean body mass index of the cohort was 34.4 (9.0) kg/m^2. Of these patients, 161 (84.7%) had at least one comorbid condition listed. Hypertension was the most common underlying condition, present in 138 (70.1%) patients, followed by diabetes in 73 (37.1%) patients and chronic pulmonary diseases in 38 (19.3%) patients. History of sick contact was present in 60 (31.6%) patients. The mean duration of symptoms prior to hospitalization was 5.4 (3.8) days.

Severe COVID-19 infection was noted in 74 (37.6%) patients, requiring intubation. Average median time from the hospitalization to intubation was 10.9 hrs. (IQR: 0.0, 58.2). Time to

intubation from the time to hospital admission was < 2 hrs. in 22 (29.7%) patients and ≥ 2 hrs. in 52 (70.3%) patients. All 74 (100%) intubated patients with the severe infection were admitted to intensive care unit compared to 1 (0.8%) patient among the non-severe infection. The patients with severe infection tended to be older (mean [SD] age, 63.1 [13.9] years vs 59.1 [17.3] years; *p* – 0.08) than non-severe patients. Patients ages 60 years and older were significantly more likely to have severe infection (46 [62.2%] vs 58 [47.2%]; *p* – 0.04). Patients with severe infections were more likely to have at least one comorbid condition (64 ([91.4%] vs 97 [80.8%]; *p* – 0.05). Patients with severe infection were significantly more like to have diabetes (36 [48.6%] vs 37 [30.1%]; *p* – 0.009), renal disease (22 [29.7%] vs 12 [9.8%]; *p* - <0.0001) and chronic pulmonary diseases (20 [27.0%] vs 18 [14.6%]; *p* – 0.03). Patients with severe infections were significantly more likely to be tachypneic (breath/min [SD], 27.6 [10] vs 22.8 [6.6]; *p* - <0.0001) and had low oxygen saturation (percentage [SD] 91.4 [9.4] vs 94.7 [4.3]; *p* - 0.006) at the time of hospital admission.

There was no significant association found between race and severity (*p* - 0.4). To examine this further, we also assessed the association between the median state ADI rank with both race and severity of disease. Although there was a significant association between race and median state ADI rank (White median state rank 6.0 (IQR: 2.8,8) vs. Black median rank 9.0 (IQR: 7,9.75)), (*p* - <0.0001), there was no association between median state ADI rank and severity of disease.

The most common symptoms at the onset of illness in the studied cohort were cough (141 [73.1%]), shortness of breath (140 [71.1%]) and fever (116 [59.8%]). Among patients with severe disease, 28.4% were confused on presentation compared to 14.6% of those with non-severe disease (*p* – 0.02). History of sick contact, presence of sore throat and cough were

significantly less frequent in patients with severe disease compared to those non-severe disease. Patients with severe infection demonstrated an increased inflammatory response, including higher white blood cell counts, lower lymphocyte and platelet counts, and increased C-reactive protein (CRP) levels compared with those patients with non-severe infection. Although patients with severe infection had significantly elevated procalcitonin levels, which raises concern for the presence of secondary bacterial infection, these patients also had acute renal injury on admission which may have caused the elevated procalcitonin.

For all demographic data, clinical characteristics and laboratory findings in univariate analysis in table 1, we identified each variable that showed and/or reached statistical significance with $p<0.05$ between severe and non-severe infections. For multivariable logistic regression, variables initially entered the model included age, sex, chronic pulmonary disease, renal disease, altered mental status, fever within 24 hours of admission, respiratory rate on admission, oxygenation on admission, cough, shortness of breath, abnormal chest x-ray on admission, initial procalcitonin level, elevated creatinine from baseline and initial CRP level. After four iterations, the model with the lowest -2 log likelihood value included four variables that were independent predictors for severity of COVID-19 infection, including presence of preexisting renal disease, need for supplemental oxygen at the time of hospitalization, elevated creatinine and C-reactive protein (CRP) on admission laboratory findings.

Discussion

Unlike SARS-CoV and Middle Eastern respiratory syndrome (MERS-CoV), SARS-CoV-2 has become pandemic. While little has been reported regarding the predictors for severe COVID-19 infections, much is known regarding the risk factors and predictors for mortality[11, 25]. In our study we report pre-existing renal disease, supplemental oxygen requirement at admission, acute renal insufficiency, and initial CRP value as independent predictors of severe COVID-19 infections.

The kidneys play a key role in immune hemostasis. Reduced renal functions delays the clearance of circulating cytokines, leading to persistent inflammatory state[26]. Renal dysfunction causes reduced lymphocyte numbers and function, creating an immunodeficiency state, predisposing to severe infections[27]. Patients with renal disease often have the additional comorbidities of either diabetes or hypertension; yet interestingly, neither diabetes nor hypertension emerged as predictors of COVID-19 disease severity in the multivariable logistic regression analysis. Perhaps renal disease represents those patients with poorer control of either diabetes or hypertension (leading to the development of chronic kidney disease) and this explains why the latter two conditions fell out in multivariable analysis; well-controlled diabetes and hypertension may not portend the same risk as chronically-uncontrolled disease. Some patients also had end-stage renal disease (ESRD), which is a state of immune dysregulation in which buildup of uremic toxins and cytokines activates innate immune cells leading to a vicious cycle of further cytokine release and reactive oxygen species production[26]. Patients with kidney disease may also have received different antihypertensive or antihyperglycemic medications than those who did not have chronic kidney disease; we did not evaluate this specific potential in our study.

It is also interesting that acute renal insufficiency (whether in patients with chronic kidney disease or normal baseline renal function) was associated with adverse outcome. SARS-CoV-2 is strongly suspected to use angiotensin converting enzyme 2 (ACE2) as its receptor, and ACE2 binding affinity has been shown to be one of the most important determinants of SARS-CoV infectivity[28]. Perhaps acute renal insufficiency reflects more efficient binding of SARS-CoV-2 to ACE2 given the location of ACE2 expression. Interestingly, ACE inhibitors and angiotensin II type-1 receptor blockers (ARBs), increase ACE2 expression, yet our analysis did not detect an association between ACE or ARB use, or hypertension or diabetes, and disease severity. Persons taking ACE or ARB at home but presenting with renal insufficiency generally have those medications held upon admission. While SARS-CoV-2 enters cells by binding to ACE2, ACE2 also reduces inflammation[19]. If one hypothesizes that ACE2 expression decreases inflammation, and that withholding drugs that increase its expression was done mainly in patients with acute renal insufficiency, perhaps a proinflammatory reaction to drug withdrawal could contribute to unfavorable outcome in such patients.

The need for supplemental oxygen for baseline hypoxia was an independent factor for severe disease in our study. A recently published study showed oxygen saturation below 90% despite oxygen supplementation was a powerful predictor for fatal outcome[29]. Given that ACE2 is expressed in lung epithelium, hypoxia may represent more avid binding to SARS-CoV-2 in those hosts. Interestingly, ACE2 is also expressed by endothelial cells, which represent one third of lung cells[30]. The endothelium functions to promote vasodilation, fibrinolysis, and anti-aggregation; thus, endothelial damage may lead to a hypercoagulable state[31]. Accumulation of coagulation factors in lungs can drive ARDS through activation of

protease activated receptors. Microvascular permeability from endothelial injury can also facilitate viral invasion[31]. Thus, direct effect of viral invasion and indirect effects thorough endothelial damage lead to severe hypoxia.

Initial C-reactive protein (CRP) level also associated with severe infection. Every 1 unit increase in CRP increased the risk of severe disease by 0.06%. CRP is a homopentameric acute-phase inflammatory protein. Baseline CRP values are influenced by age, gender, smoking status, weight, lipid levels, and blood pressure, and by genetics[32]. Recent studies have reported that cases of sever COVID-19 exhibit increased plasma levels of interleukin (IL) 2, IL6, IL7, IL10, granulocyte colony- stimulating factor (GCSF), tumor necrosis factor (TNF) alpha, and others[33]. IL-6 is the main inducer of CRP gene expression, with IL-1 and TNF-alpha also playing a role[32]. Elevated CRP may reflect severe disease as an indirect marker of elevated IL-6 and TNF-alpha. CRP not only reflects inflammation, it also enhances the immune response. CRP can be irreversibly dissociated into monomeric subunits termed monomeric or modified CRP (mCRP) at either high concentrations of urea or elevated temperatures in the absence of calcium, and mCRP promotes monocyte chemotaxis and recruitment of circulating leukocytes to areas of inflammation. Modified CRP also binds immunoglobulin G (IgG) Fc receptors in an interaction leading to release of pro-inflammatory cytokines[32]. Thus, elevated CRP at admission may both reflect significant inflammation and itself drive further inflammation. And given that elevated levels of urea promote formation of mCRP, it fits that acute and chronic kidney disease may be associated with adverse outcomes.

In our data, having a known sick contact was associated with lower risk of severe disease. Perhaps some of those patients with a sick contact knew they were at risk of

exposure and therefore were already attempting to minimize that risk through hand-hygiene, masks, or physical isolation or using separate bathrooms, thus decreasing the potential amount of virus to which they were exposed. This would, however, only account for patients where someone else was symptomatic or exposed soon enough for the patient to be able to take precautions. Patients with known sick contacts may also have presented sooner due to a heightened suspicion of having contracted COVID-19, and thus received care more rapidly[34]. Recall bias may also have contributed. One other potential explanation is that the sickest patients were more confused or were intubated rapidly and therefore could not provide a history of sick contact, which would have impacted the recording of a sick contact in the electronic medical record and thus our results.

Patients over 60 years old were significantly more likely to have severe infection. In multivariable analysis, however, age, was not found to be an independent predicting factor for the severe infection. This may reflect that the occurrence of kidney disease tends to be higher in older people and kidney disease was the stronger predictor in the model. Older age has been significantly associated with death in previous studies[35, 36]. This might be related due to less robust immune responses as older age has been linked with declined immune competence[37]. On the contrary, older macaques had a stronger host innate immune responses to viral infection after inoculated with SARS-CoV than the younger ones due to differential expression of proinflammatory genes[38]. This proinflammatory state along with age-dependent functional deficits in T-cells and B-cells response could lead to poor outcomes.[39] This proinflammatory state is expressed by elevation in C-reactive protein. Elderly infected patients could be at risk for acute renal injury manifesting in elevation of serum creatinine on hospital admission. A study by Wang et al from China showed the patients admitted to intensive care unit (ICU) were older and had greater number

of comorbid conditions including significant elevation in creatinine on admission than those not admitted to ICU[13]. Thus, age in our studied cohort might have been a confounding factor to elevated serum creatinine and C-reactive protein.

During the COVID-19 pandemic, racial and ethnic minorities especially blacks, have been reported to be severely or disproportionately impacted. Our study did not show a disparity in severity by race, so we also investigated the relationship by ADI (as a proxy for socioeconomic status). No association was found between ADI and severity or between race and severity after controlling for ADI.

Our study has several limitations. This was a single institution study among all the admitted patients which makes generalization of interpretations difficult. Because of the retrospective nature of the study design, all variables in the studied patients were not available. Therefore, the role of some of these variables in predicting severity of the infection could have been underestimated. Last but not the least, the small sample size of our study and a predominantly black and overweight/obese cohort could have limited the generalizability of interpretation for some of the findings (for eg: race). Nonetheless our study did involve a population of black patients in the Detroit area and can provide valuable information on which factors are most significant predictors of severe disease in that population.

Conclusion

Our study identifies the presence of renal disease, elevated creatinine and C-reactive protein on hospital admission and requirement for the supplemental oxygen at the time of hospitalization as independent predictors for severe COVID-19 infection. Early identification of these risk factors can result in aggressive supportive care and prompt treatment intervention. Subsequent research involving multiple study sites and with larger database can further validate the findings of our study and help in early clinical decision making.

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References

1. Organization WH. Pneumonia of unknown cause – China. Available at: https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/.
2. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet **2020**; 395(10224): 565-74.
3. Organization WH. World Health Organization Home Page. Available at: https://www.who.int.
4. University JH. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University JHU). https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Date last accessed: April 28, 2020.
5. Hoehl S, Rabenau H, Berger A, et al. Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China. N Engl J Med **2020**; 382(13): 1278-80.
6. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci **2020**; 63(5): 706-11.
7. Wang Y, Liu Y, Liu L, Wang X, Luo N, Ling L. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. J Infect Dis **2020**.
8. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA **2020**.
9. Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King

County, Washington, March 2020. MMWR Morb Mortal Wkly Rep **2020**; 69(13): 377-81.

10. Roxby AC, Greninger AL, Hatfield KM, et al. Detection of SARS-CoV-2 Among Residents and Staff Members of an Independent and Assisted Living Community for Older Adults - Seattle, Washington, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69(14): 416-8.
11. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA **2020**.
12. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med **2020**.
13. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA **2020**.
14. Team CC-R. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69(12): 343-6.
15. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA **2020**.
16. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet **2020**; 395(10229): 1054-62.
17. Novel Coronavirus Pneumonia Emergency Response Epidemiology T. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi **2020**; 41(2): 145-51.

18. Team CC-R. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep **2020**; 69(13): 382-6.

19. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med **2020**; 8(4): e21.

20. Prevention CfDCa. Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19).

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40(5): 373-83.

22. Prevention CfDCa. Defining Adult Overweight and Obesity.

23. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract **2012**; 120(4): c179-84.

24. Knighton AJ, Savitz L, Belnap T, Stephenson B, VanDerslice J. Introduction of an Area Deprivation Index Measuring Patient Socioeconomic Status in an Integrated Health System: Implications for Population Health. EGEMS (Wash DC) **2016**; 4(3): 1238.

25. Grasselli G, Zangrillo A, Zanella A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA **2020**.

26. Tecklenborg J, Clayton D, Siebert S, Coley SM. The role of the immune system in kidney disease. Clin Exp Immunol **2018**; 192(2): 142-50.

27. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol **2008**; 3(5): 1526-33.

28. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol **2020**; 94(7).

29. Jiang Xie M, PhD, Naima Covassin, PhD, Zhengyang Fan, MD, Prachi Singh, PhD, Wei Gao, MD, Guangxi Li, MD, PhD, Tomas Kara, MD, PhD, Virend K. Somers, MD, PhD. Association Between Hypoxemia and Mortality in Patients With COVID-19. Mayo Clin Proc.

30. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol **2020**: 108427.

31. Whyte CS, Morrow GB, Mitchell JL, Chowdary P, Mutch NJ. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. J Thromb Haemost **2020**.

32. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol **2018**; 9: 754.

33. Xiong Y, Liu Y, Cao L, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect **2020**; 9(1): 761-70.

34. Pongpirul WA, Pongpirul K, Ratnarathon AC, Prasithsirikul W. Journey of a Thai Taxi Driver and Novel Coronavirus. N Engl J Med **2020**; 382(11): 1067-8.

35. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med **2020**.

36. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med **2020**.

37. Goronzy JJ, Fang F, Cavanagh MM, Qi Q, Weyand CM. Naive T cell maintenance and function in human aging. J Immunol **2015**; 194(9): 4073-80.

38. Smits SL, de Lang A, van den Brand JM, et al. Exacerbated innate host response to SARS-CoV in aged non-human primates. PLoS Pathog **2010**; 6(2): e1000756.

39. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis **2005**; 41 Suppl 7: S504-12.

Table 1. Univariate Analysis of Predictors for Severe COVID-19 Infection

Characteristic	**Non-severe (*n*=123) (%)**	**Severe (*n*=74) (%)**	**OR (95% CI)**	**P value**
Age groups, years				
<60	65 (52.8)	28 (37.8)	1.8 (1.02, 3.3)	0.04
>60	58 (47.2)	46 (62.2)		
Sex				
Male	58 (47.2)	45 (60.8)	0.6 (0.3, 1.03)	0.06
Female	65 (52.8)	29 (39.2)		
Race				
White	19 (15.8)	15 (21.4)	0.7 (0.3, 1.5)	0.38
Black	101 (84.2)	55 (78.6)		
Comorbidities, *n* (%)				
At least one comorbidity	97 (80.8)	64 (91.4)	2.32 (0.95, 5.69)	0.061
Myocardial infarction	5 (4.1)	4 (5.4)	1.34 (0.35, 5.19)	0.663
Congestive heart failure	10 (8.1)	10 (13.5)	1.76 (0.70, 4.47)	0.226
Peripheral vascular disease	0 (0.0)	5 (6.8)	- -	- -
Cerebrovascular disease	9 (7.3)	8 10.8)	1.53 (0.57, 4.17)	0.398
Dementia	16 (13.0)	5 (6.8)	0.49 (0.17, 1.38)	0.169
Chronic pulmonary disease	18 (14.6)	20 (27.0)	2.16 (1.06, 4.42)	0.03
Connective tissue disease	0 (0.0)	2 (2.7)	- -	- -
Peptic ulcer disease	3 (2.4)	2 (2.7)	1.11 (0.18, 6.81)	0.90
Diabetes	37 (30.1)	36 (48.6)	2.20 (1.21, 4.0)	0.009

Hemiplegia	5 (4.1)	4 (5.4)	1.35 (0.35, 5.19)	0.66
Renal disease	12 (9.8)	22 (29.7)	3.91 (1.80, 8.51)	<0.0001
Any malignancy	6 (4.9)	4 (5.4)	1.11 (0.30, 4.09)	0.87
Metastatic solid tumor	3 (2.4)	2 (2.7)	1.11 (0.18, 6.81)	0.91
Mild liver disease	2 (1.6)	3 (4.1)	2.56 (0.42, 15.67)	0.29
Moderate-severe liver disease	0 (0.0)	1 (1.4)	- -	- -
AIDS	1 (0.8)	0 (0.0)	- -	- -
Median CWIC (25^{th}, 75^{th})	0 (0,2)	1.5 (0,3)		0.001
Hypertension	82 (66.7)	56 (75.7)	1.56 (0.81, 2.98)	0.18
Current tobacco smoker	5 (4.1)	6 (8.3)	2.11 (0.62, 7.18)	0.22
Obesity	78 (64.5)	53 (71.6)	1.39 (0.74, 2.61)	0.30
Morbid obesity	29 (24.6)	19 (25.7)	1.06 (0.54, 2.07)	0.86
Home medications, n (%)				
Either ACEIs or ARBs	40 (32.5)	27 (36.5)	1.19 (0.65, 2.18)	0.57
Steroids	6 (4.9)	3 (4.1)	0.82 (0.20, 3.40)	0.79
History of sick contact	44 (37.0)	16 (22.5)	0.5 (0.3, 0.9)	0.03
Typical Symptoms, *n* (%)				
Fever	72 (58.5)	44 (62.0)	1.15 (0.63, 2.10)	0.63
Sore throat	18 (14.6)	2 (2.9)	0.17 (0.04, 0.78)	0.01
Headache	13 (10.6)	4 (5.8)	0.52 (0.16, 1.67)	0.264
Rhinorrhea	7 (5.7)	2 (2.9)	0.50 (0.10, 2.45)	0.38

Shortness of breath	83 (67.5)	57 (80.3)	1.96 (0.98, 3.94)	0.055
Cough	96 (78.0)	45 (64.3)	0.51 (0.27, 0.97)	0.038
Hemoptysis	1 (0.8)	1 (1.4)	1.77 (0.11, 28.71)	0.69
Fatigue	41 (33.3)	21 (30.0)	0.86 (0.46, 1.62)	0.63
Myalgia	29 (23.8)	16 (22.9)	0.95 (0.47, 1.91)	0.89
Nausea, vomiting	23 (18.7)	9 (12.9)	0.64 (0.28, 1.48)	0.29
Diarrhea	32 (26.0)	13 (18.3)	0.64 (0.31, 1.32)	0.22
Abdominal pain	11 (8.9)	2 (2.9)	0.30 (0.06, 1.39)	0.11
Altered mental status	18 (14.6)	21 (28.4)	2.31 (1.14, 4.71)	0.02
Vitals on admission				
Supplemental Oxygen required on hospitalization	33 (26.8)	44 (59.5)	4.0 (2.17, 7.38)	<0.0001
Vitals within first 24 hours				
Temperature, *n* (%)	74 (60.2)	52 (70.3)	1.57 (0.85, 2.90)	0.15
Abnormal Chest x-ray on admission	84 (68.9)	66 (90.4)	4.27 (1.79, 10.16)	0.001
Laboratory Findings on admission				
Leucopenia, *n* (%)	14 (11.4)	7 (9.5)	0.81 (0.31, 2.12)	0.67

Lymphocytopenia, *n* (%)	62 (50.8)	44 (60.3)	1.47 (0.82, 2.64)	0.20
Thrombocytopenia, *n* (%)	22 (17.9)	15 (20.3)	1.17 (0.56, 2.42)	0.68
Elevated Alanine aminotransferase, *n* (%)	43 (36.1)	24 (34.3)	0.92 (0.50, 1.71)	0.79
Elevated Aspartate aminotransferase, *n* (%)	67 (59.3)	46 (70.8)	1.66 (0.87, 3.19)	0.13
Elevated C-reactive protein, *n* (%)	105 (93.8)	63 (98.4)	4.20 (0.51, 34.94)	0.15
Elevated Procalcitonin, *n* (%)	84 (77.8)	60 (93.8)	4.29 (1.41, 12.99)	0.006
Elevated Creatinine, *n* (%)	45 (37.2)	38 (56.7)	2.21 (1.21, 4.06)	0.01

Abbreviations: *n*: Number, OR: Odds ratio, CI: Confidence interval, ACEI: Angiotensin converting enzyme inhibitor, ARBs: Angiotensin II receptor blockers

Table 2. Multivariate Logistic Regression Analysis of Predictors for severe COVID-19 Infection

Variables	**OR (95% CI)**	***P* value**
Pre-existing Renal Disease	7.4 (2.5, 22.0)	<0.0001
Oxygen required on admission	2.9 (1.3, 6.7)	0.01
Elevated creatinine from baseline	2.7 (1.3, 5.6)	0.01
Initial CRP value	1.006 (1.001, 1.01)	0.02

Abbreviations: OR: Odds ratio, CI: Confidence interval, CRP: C reactive protein