POST ACUTE COVID-19 SEQUELAE: MECHANISM AND MORTALITY

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DISCLOSURES/CONFLICTS

- None

LEARNING OBJECTIVES

- At the conclusion of the presentation, participants will:
  - 1) be able to identify post acute COVID-19 sequelae
  - 2) be able to discuss current theories of mechanisms for post acute COVID-19 sequelae
  - 3) be able to identify gaps in current knowledge for prevention of post acute COVID-19 sequelae

COVID-19

- COVID-19 has been global crisis and as of 5/17/22 has been the *identified* cause of >6.2 million deaths worldwide and >1,000,000 deaths in the US
  - https://coronavirus.jhu.edu/map.html
- Many people do recover from COVID-19
- Many patients complain of symptoms like anosmia and brain fog as part of "long COVID"
- Post-acute sequelae of COVID-19 is not well understood

POST ACUTE COVID-19

- After patients "recover" from an acute COVID-19 episode there are physical and mental health consequences that patients experience.
- This condition can affect different organs and body systems, with a wide range of signs and symptoms reported.
- There still is no consensus for a case definition of long COVID or Post Acute COVID-19 sequelae.
  - Munblit et al, *Lancet Respiratory Medicine*, May 4, 2022
- The patient community is very aware of this and has focused on persistent symptoms.
- Most of the identified complications are important but relatively mild.

HOSPITALIZATION AS A POST ACUTE SEQUELAE

- We undertook a study to examine if a COVID-19 episode was associated with a post-acute hospitalization.
  - Mainous AG 3rd, et al. Risk of New Hospitalization Post-COVID-19 Infection for Non-COVID-19 Conditions. *J Am Board Fam Med*. 2021 Sep-Oct;34(5):907-913. doi: 10.3122/jabfm.2021.05.210170.

COHORT

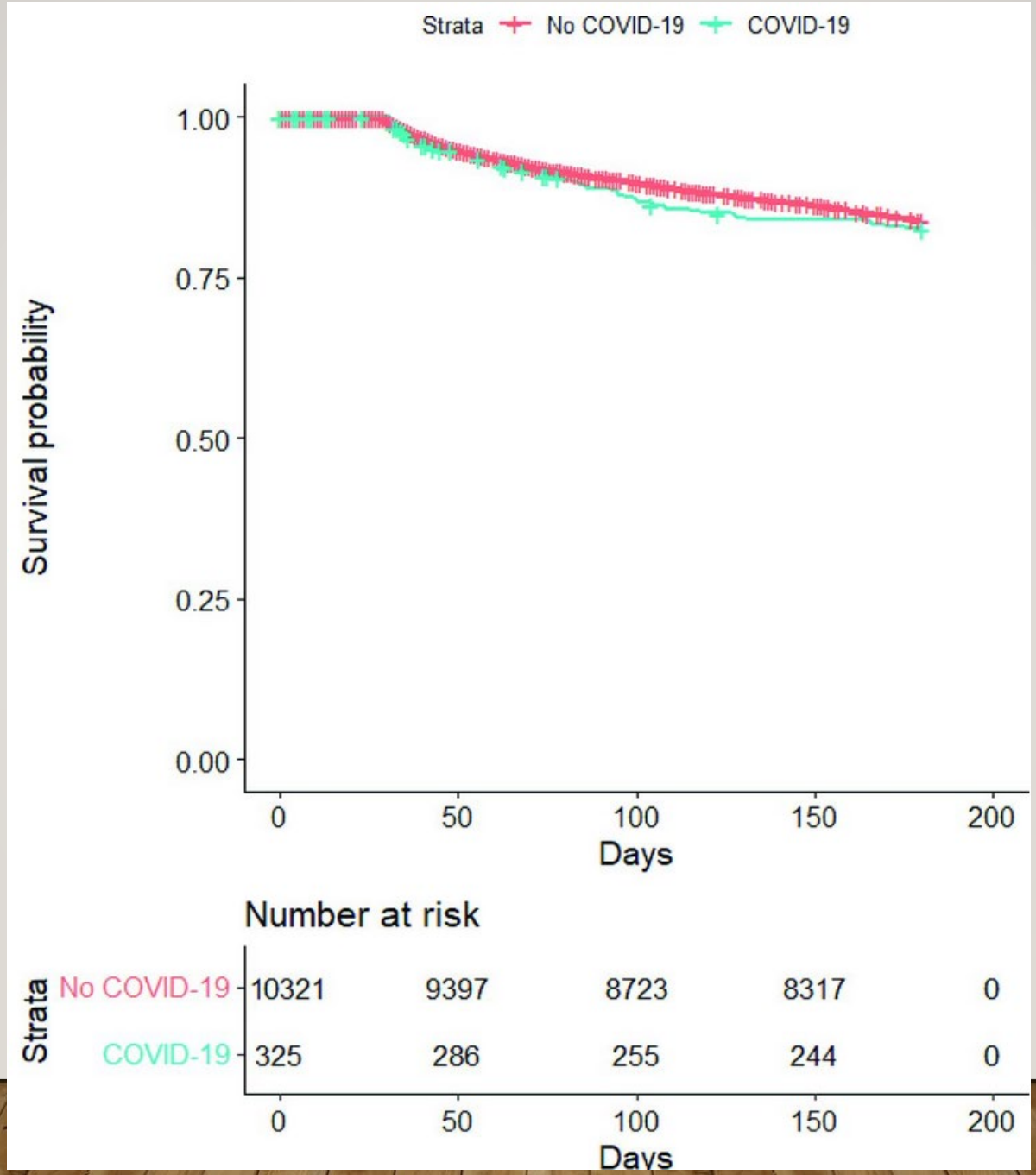
- We studied a longitudinal cohort of patients who tested either positive or negative for COVID-19 as determined by polymerase chain reaction (PCR) testing within a large health care system.
- Adult patients aged 18 years and older who were tested for COVID-19 between January 1, 2020, and July 5, 2020, within the UF Health system, in any encounter type (ambulatory, emergency department [ED], inpatient, etc).
- Only patients with at least 180 days of follow-up time after their baseline date were retained in the cohort. Mortality data were available in the databank, and patients who died within their 180-day window were included in the analysis and censored at the date of their recorded death. Mortality data were obtained from both patient electronic health records and the Social Security Death Index.
- The cohort was also censored for 30 days after baseline in the COVID-19 negative patients or until 30 days post-hospital discharge for the severe COVID-19 patients to ensure that health care utilization was post-acute and not part of the initial COVID-19 episode of care (eg, readmission).

COVID-19 DEFINITIONS

- For patients with multiple COVID-19 tests, if at least 1 test gave a positive result, the patient was classified as COVID-19 positive, and the date of their earliest positive COVID-19 test result was used as their baseline date.
- For patients with multiple COVID-19 tests that were all negative, the patient was classified as COVID-19 negative, and the date of their earliest negative COVID-19 test results was used as their baseline date.
- Patients were tested in the context of seeking care for COVID-19; the tests were not part of general screening and surveillance.

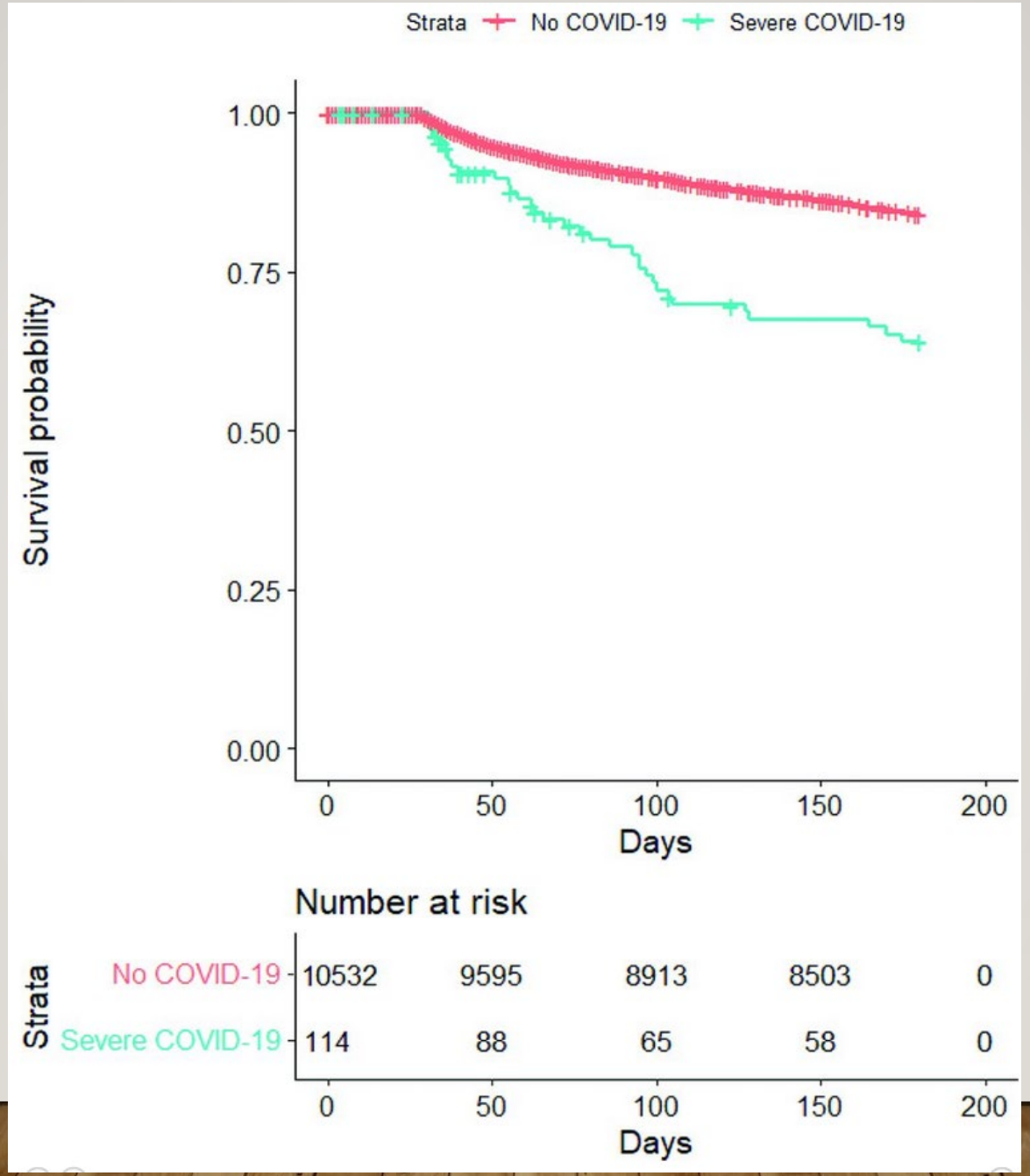
PRIMARY FINDINGS FOR COVID-19 AND DOWNSTREAM HOSPITALIZATION

- A total of 10,646 patients were included in the final cohort.
- First comparison was for COVID-19 positive versus COVID-19 negative
- The characteristics of the sample were split into the 3 groups of (a) mild/moderate COVID-19, (b) severe COVID-19, and (c) negative COVID-19.


Strata
No COVID-19
COVID-19
1.00
0.75
0.50
0.25
0.00
Survival probability
0
50
100
150
200
Days
Number at risk
Strata
No COVID-19
COVID-19
10321
9397
8723
8317
0
325
286
255
244
0
0
50
100
150
200
Days

REGRESSION RESULTS

- COVID-19 positive versus COVID-19 negative
  - Any cause hospitalization among those who were COVID-19 positive was not significantly increased in comparison to those who were COVID-19 negative (HR, 1.10; 95% CI, 0.84-1.45).
  - After adjustment for potential confounding variables, the results still indicated no significantly increased risk in future hospitalization for any condition for patients who were COVID-19 positive versus those who were COVID-19 negative (HR, 1.31; 95% CI, 0.98-1.74).


Strata
No COVID-19
Severe COVID-19
1.00
0.75
0.50
0.25
0.00
Survival probability
0
50
100
150
200
Days
Number at risk
Strata
No COVID-19
Severe COVID-19
10532
9595
8913
8503
0
114
88
65
58
0
0
50
100
150
200
Days

Risk of Future Hospitalization by COVID-19 Status for Conditions Other than COVID-19

	Hazard Ratios (95% CI)					
	Unadjusted			Adjusted*		
	Mild/Moderate versus No COVID-19	Severe versus No COVID-19	Severe versus Mild/Moderate COVID-19	Mild/Moderate versus No COVID-19	Severe versus No COVID-19	Severe versus Mild/Moderate COVID-19
Any hospitalization	0.53 (0.33-0.85)	2.55 (1.82-3.58)	4.80 (2.71-8.50)	0.71 (0.44-1.17)	2.16 (1.53-3.04)	3.01 (1.66-5.48)
Combined targeted hospitalizations†	0.78 (0.46-1.33)	3.73 (2.54-5.48)	4.76 (2.50-9.08)	1.02 (0.59-1.76)	2.24 (1.52-3.30)	2.20 (1.13-4.28)
Cardiovascular hospitalization	0.71 (0.37-1.37)	4.05 (2.62-6.25)	1.41 (0.73-2.72)	0.92 (0.46-1.86)	2.30 (1.48-3.57)	2.50 (1.10-5.66)
Respiratory hospitalization	0.72 (0.34-1.51)	4.09 (2.52-6.64)	5.72 (2.37-13.78)	1.05 (0.50-2.23)	2.64 (1.62-, 4.31)	2.51 (1.03-6.07)
Clotting hospitalization	0.52 (0.13-2.09)	4.86 (2.39-9.86)	9.36 (1.99-44.08)	0.64 (0.16-2.60)	3.32 (1.62-6.80)	5.17 (1.09-24.50)

MORTALITY AS A POST ACUTE SEQUELAE

- We undertook a study to investigate risk factors for post-acute COVID-19 mortality
  - Mainous AG 3rd, et al. COVID-19 Post-acute Sequelae Among Adults: 12 Month Mortality Risk. *Front Med* (Lausanne). 2021 Dec 1;8:778434. doi: 10.3389/fmed.2021.778434.

COHORT

- Only patients with at least 365 days of follow-up time after their baseline date were retained in the cohort. Patients with more than 365 days of follow-up were censored at 365 days. COVID-19 positive patients were also categorized as having had either a severe or mild/moderate COVID-19. Patients seen only in an outpatient setting were classified as having mild/moderate COVID-19, while those who were hospitalized during their initial COVID-19 episode were classified as severe.
- The cohort was also censored for 30 days post-baseline in the COVID-19 negative patients or until 30 days post hospital discharge for the severe COVID-19 patients to ensure that health care utilization was post-acute and not part of the initial COVID-19 episode of care (e.g., not a readmission).

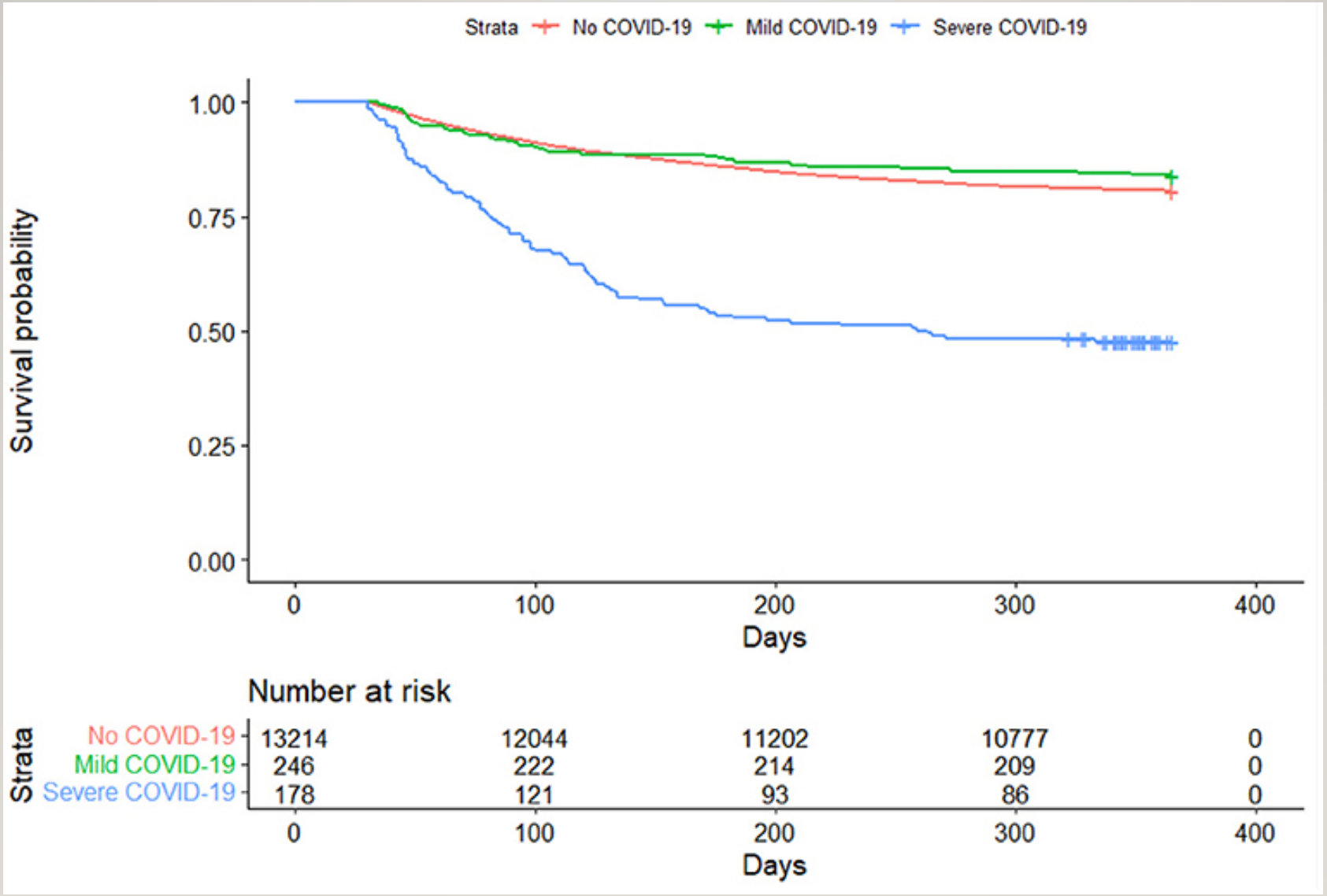
COVID-19 DEFINITIONS

- For patients with multiple COVID-19 tests, if at least 1 test gave a positive result, the patient was classified as COVID-19 positive, and the date of their earliest positive COVID-19 test result was used as their baseline date.
- For patients with multiple COVID-19 tests that were all negative, the patient was classified as COVID-19 negative, and the date of their earliest negative COVID-19 test results was used as their baseline date.
- Patients were tested in the context of seeking care for COVID-19; the tests were not part of general screening and surveillance.

PRIMARY FINDINGS

- A total of 13,638 patients were included in the final cohort.
- The characteristics of the sample split into the 3 groups of (a) mild/moderate COVID-19, (b) severe COVID-19, and (c) negative COVID-19.

	Total (n = 13,638)	Severe COVID-19 (n = 178)	Mild/Moderate COVID-19 (n = 246)	No COVID-19 (n = 13,214)
No. (%) with data				
All-cause deaths	2,686 (19.7%)	93 (52.2%)	39 (15.9%)	2,554 (19.3%)
Cardiovascular deaths	191 (1.4%)	11 (6.2%)	1 (0.04%)	179 (1.4%)
Respiratory deaths	181 (1.3%)	13 (7.3%)	2 (0.8%)	166 (1.3%)
Male	5,674 (41.6%)	75 (42.1%)	87 (35.4%)	5,512 (41.7%)
Non-Hispanic White	8,706 (63.8%)	86 (48.3%)	113 (45.9%)	8,507 (64.4%)
Non-Hispanic Black	3,379 (24.7%)	76 (42.7%)	80 (32.5%)	3,223 (24.3%)
Hispanic	764 (5.6%)	5 (2.8%)	32 (13.0%)	727 (5.5%)
Age				
Under 65	8,801 (64.5%)	81 (45.5%)	196 (79.7%)	8,524 (64.5%)
65+	4,837 (35.5%)	97 (54.5%)	50 (20.3%)	4,690 (35.5%)
Charlson Comorbidity Index score	6,753 (49.5%)	46 (25.8%)	181 (73.6%)	6,526 (49.4%)
0–1				
2–3	2,856 (20.9%)	48 (27.0%)	23 (9.3%)	2,980 (22.6%)
4+	3,834 (28.1%)	84 (47.2%)	42 (17.1%)	3,708 (28.1%)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Mild COVID-19
Severe COVID-19
Survival probability
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0.75
0.50
0.25
0.00
0
100
200
300
400
Days
Number at risk
Strata
No COVID-19 13214 12044 11202 10777 0
Mild COVID-19 246 222 214 209 0
Severe COVID-19 178 121 93 86 0
0
100
200
300
400
Days

	Hazard ratios (95% CI)					
	Unadjusted			Adjusted[a]		
	Mild/moderate vs. no COVID-19	Severe vs. no COVID-19	Severe vs. mild/moderate COVID-19	Mild/moderate vs. no COVID-19	Severe vs. no COVID-19	Severe vs. mild/moderate COVID-19
Full cohort	0.81 (0.59, 1.12)	3.61 (2.93, 4.44)	4.43 (3.05, 6.44)	1.34 (0.97, 1.84)	2.50 (2.02, 3.09)	1.87 (1.28, 2.74)
Under 65	0.80 (0.50, 1.28)	4.54 (3.22, 6.39)	5.66 (3.20, 10.0)	1.17 (0.74, 1.88)	3.33 (2.35, 4.73)	2.83 (1.59, 5.04)
65 and Older	1.36 (0.88, 2.09)	2.49 (1.92, 3.23)	1.84 (1.12, 3.02)	1.54 (0.99, 2.40)	2.17 (1.66, 2.84)	1.41 (0.84, 2.34)

[a]*Models were adjusted for age, race/ethnicity, sex, and the Charlson Comorbidity Index. Models which were stratified by age above/below 65 were further adjusted for age as a continuous variable to adjust for the presence of residual confounding.*

OTHER RESEARCHERS HAVE REPORTED SIMILAR RESULTS FOR HOSPITALIZATION AND MORTALITY AS POST ACUTE SEQUELAE

- Ziyad Al-Aly and colleagues used claims and EHR VA data and have shown an increased risk of death and hospitalization
  - They also showed that Post Acute sequelae were consistently higher in people with poorer baseline health and in those with more severe acute infection
    - Al-Aly Z, et al. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021 Jun;594(7862):259-264. doi: 10.1038/s41586-021-03553-9.
- Daniel Ayoubkhani and colleagues used EHR data in England's National Health Service and showed hospitalization risk after initial COVID-19 hospitalization
  - "The diagnosis, treatment, and prevention of post-covid syndrome requires integrated rather than organ or disease specific approaches."
    - Ayoubkhani D, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. *BMJ*. 2021 Mar 31;372:n693. doi: 10.1136/bmj.n693.

CURRENTLY THERE IS NO PREVENTION OF POST ACUTE COVID-19 SEQUELAE EXCEPT FOR VACCINATION (DECREASE LIKELIHOOD OF SEVERE EPISODE)

CDC, updated May 5, 2022

https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html

SEVERE POST ACUTE COVID-19 SEQUELAE EXIST: UNDERSTANDING WHY COULD LEAD TO PREVENTION

SEVERAL THEORIES EXIST

- **Immune Function**
  - Phetsouphanh C, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. *Nat Immunol.* 2022 Feb;23(2):210-216. doi: 10.1038/s41590-021-01113-x.
- **Inflammation**
  - PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022 Apr 22:S2213-2600(22)00127-8. doi: 10.1016/S2213-2600(22)00127-8.

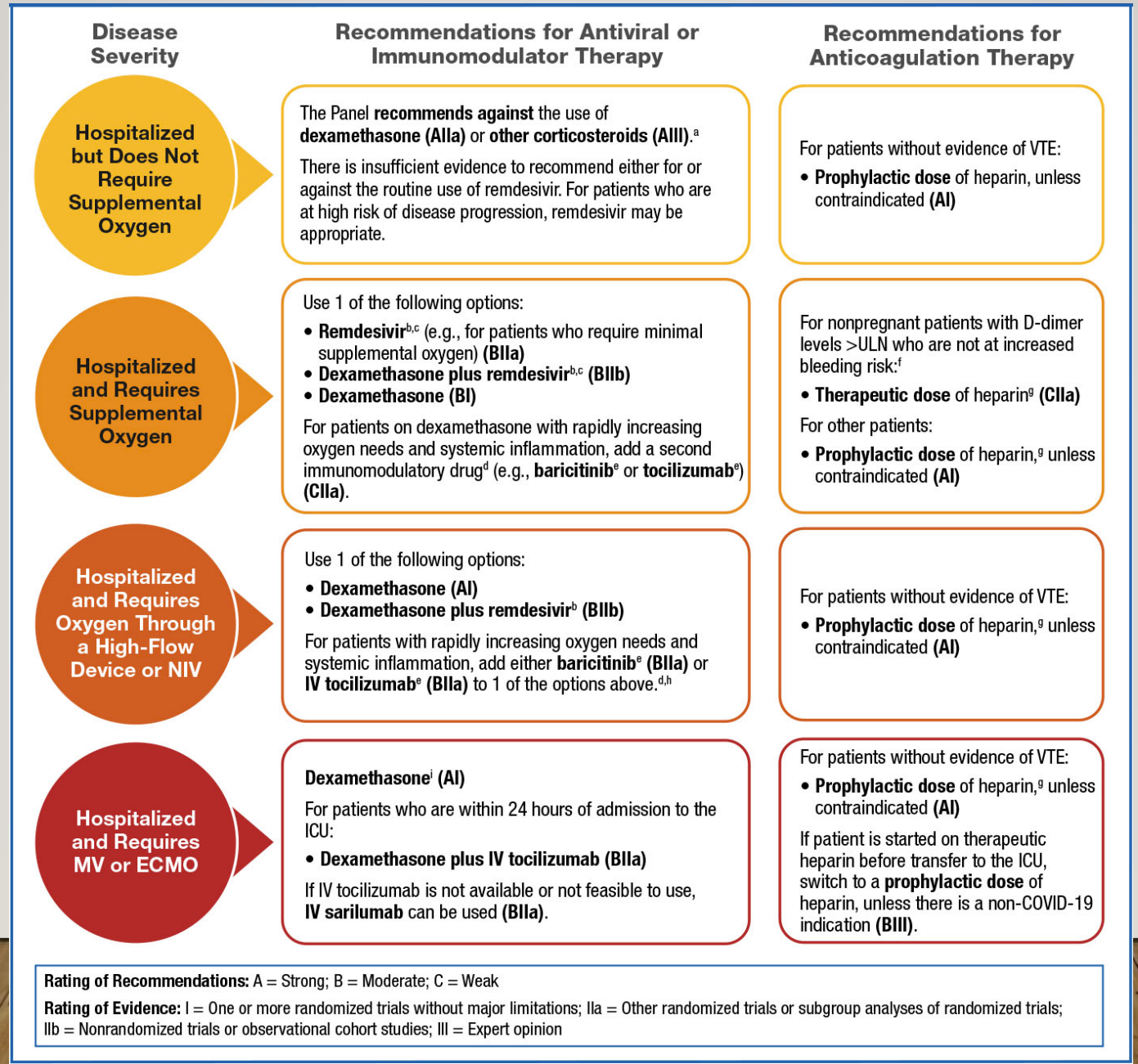
INFLAMMATION

- During a COVID-19 episode there is substantial systemic inflammation.
- Pulmonary, cardiovascular, neuroinflammation and renal inflammation have all been documented in the initial episode
  - Tissue damage has been documented
- Inflammation has been shown 40-60 days after the initial episode
  - A recent analysis in Australia showed sustained inflammation and immunological dysfunction 8 months after COVID-19

POTENTIAL FOR ANTI-INFLAMMATORIES

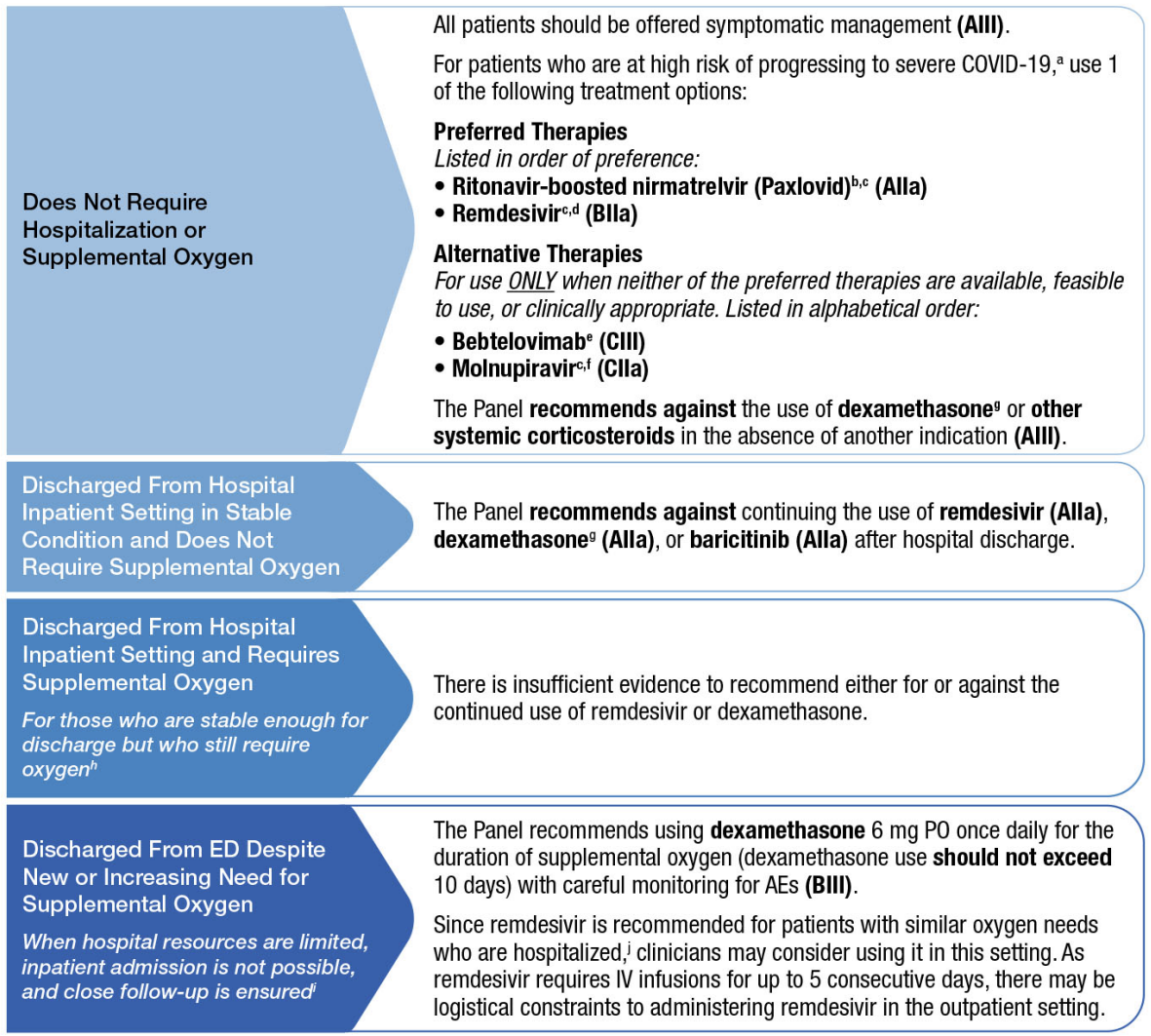
- Lung function abnormalities appear to be more common among patients whose acute COVID-19 was severe with high levels of inflammatory markers.
- In a small study of patients with radiological inflammatory lung disease, 30 received steroid treatment, resulting in improved forced vital capacity, with significant symptomatic and radiological improvement.
  - Myall KJ, et al. Persistent Post-COVID-19 Interstitial Lung Disease. An Observational Study of Corticosteroid Treatment. *Ann Am Thorac Soc*. 2021 May;18(5):799-806. doi: 10.1513/AnnalsATS.202008-1002OC.
- One study with 1164 patients did not find an effect of dexamethasone at discharge for 14 day readmission or mortality
  - Huang CW, et al. Association Between Dexamethasone Treatment After Hospital Discharge for Patients With COVID-19 Infection and Rates of Hospital Readmission and Mortality. *JAMA Netw Open*. 2022 Mar 1;5(3):e221455. doi: 10.1001/jamanetworkopen.2022.1455.
- A current trial identified at clinicaltrials.gov is investigating corticosteroids for post COVID diffuse lung disease.
  - Remember inflammation affects multiple systems not just respiratory system

Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity



Therapeutic Management of Nonhospitalized Adults with COVID-19

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19



Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

IMPACT OF INITIAL COVID-19 INFLAMMATION ON MORTALITY WITHIN 12 MONTHS POST-HOSPITAL DISCHARGE

Mainous AG 3rd, et al. The Impact of Initial COVID-19 Episode Inflammation Among Adults on Mortality Within 12 Months Post-hospital Discharge. *Front Med* (Lausanne). 2022 May 12. doi: 10.3389/fmed.2022.891375.

COHORT

- We studied a longitudinal cohort of patients who tested either positive for COVID-19 as determined by polymerase chain reaction (PCR) testing within a large health care system.
- Adult patients aged 18 years and older who were hospitalized for COVID-19.
- The cohort was censored for 30 days to ensure that mortality was post acute. Only patients with at least 365 days of follow-up time after their baseline date were retained in the cohort. Mortality data were obtained from both patient electronic health records and the Social Security Death Index.

VARIABLES

- **Inflammation**—C-reactive Protein. For patients with multiple measurements of CRP the maximum value was used.
- **Steroids**—Intravenous dexamethasone during the initial COVID-19 hospitalization. Oral steroids prescribed at/post discharge was assessed in the EHR.

SEVERITY OF COVID-19 HOSPITALIZATION

- 1207 patients were in the study
- Mean CRP in the lowest severity (no supplemental oxygen) was 59.4 mg/L while the mean in the intermediate severity (supplemental oxygen) was 126.9 mg/L and the mean in the highest severity group (ventilator or ECMO) is 201.2 ($p<.001$).
- Dexamethasone inpatient is only recommended for the most severe patients. Mean CRP for those on dexamethasone was 158.8 mg/L and 102.8 for those not on dexamethasone ($p<.001$).

All-cause mortality comparing CRP median or higher with below median level

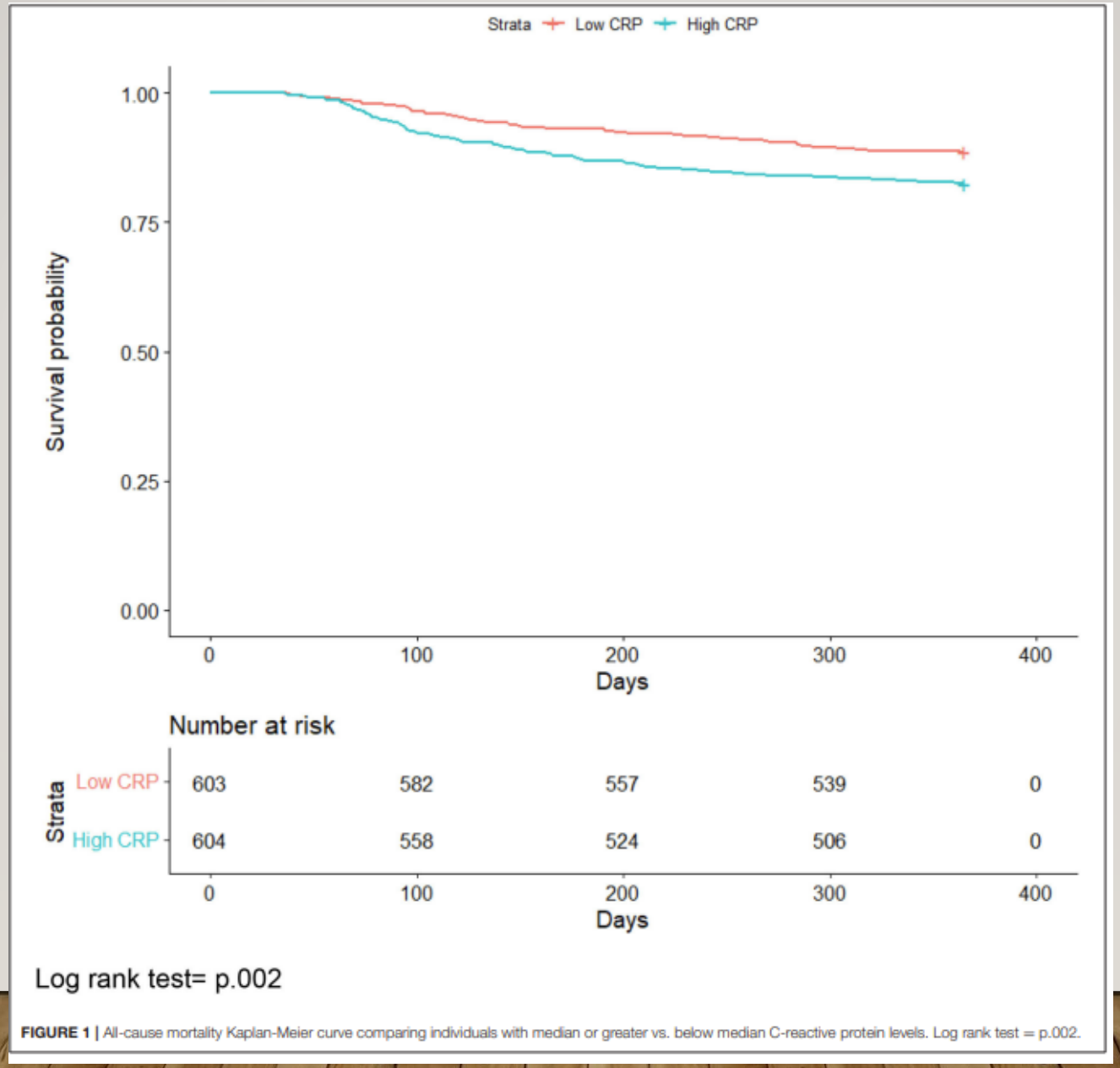


FIGURE 1 | All-cause mortality Kaplan-Meier curve comparing individuals with median or greater vs. below median C-reactive protein levels. Log rank test = p.002.

All-cause mortality hazard ratios by inflammation and steroid use

	Hazard ratios (95% CI)	
	Unadjusted	**Adjusted[a]**
Inflammation		
Top 50% vs. bottom 50% for CRP	1.60 (1.18, 2.17)	1.61 (1.19, 2.20)
Top tertile vs. bottom tertile for CRP	1.50 (1.05, 2.15)	1.61 (1.12, 2.32)
Steroid use		
Steroid prescriptions at discharge	0.43 (0.29, 0.63)	0.49 (0.33, 0.74)

[a]*Models were adjusted for age, race/ethnicity, sex, and the Charlson Comorbidity Index.*

NEEDS FOR FUTURE RESEARCH

- There is limited research on severe sequelae and so more research is needed to understand the differences in long COVID and severe sequelae
- Clinical trial is needed to examine the utility of anti-inflammatories post acute COVID-19 as prevention of long COVID and severe sequelae

CONCLUSIONS

- COVID-19 has significant post-acute sequelae.
- These results reinforce the importance of preventing hospitalizations for COVID-19.
- Benefits of preventing severe COVID-19 goes beyond flattening the curve to saving lives after a patient has "recovered" from COVID-19.
- Inflammation during the initial COVID-19 episode seems to be a key and may be a potential treatment focus for prevention of post acute sequelae

QUESTIONS??