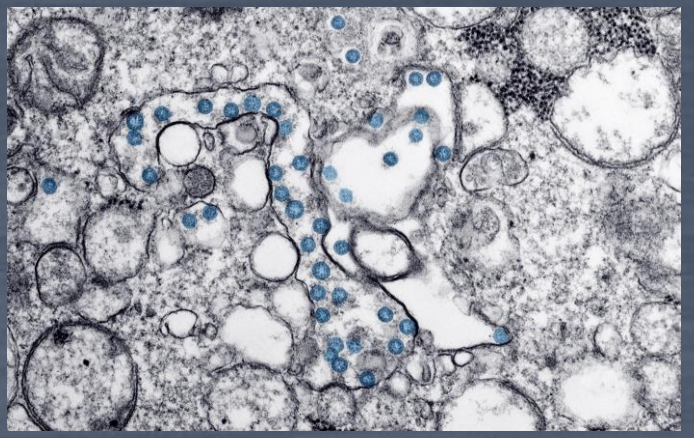
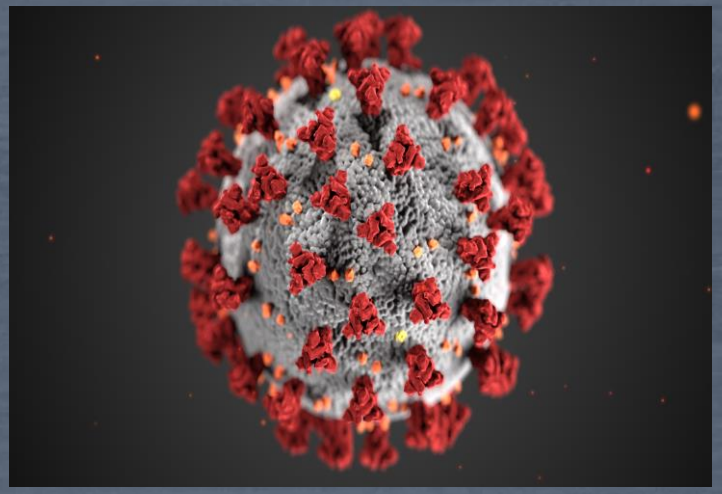


COVID19 TREATMENTS: REALITY VS: HOPE



Fadi Haddad, MD, FIDSA Sharp Grossmont Hospital
George Sakoulas, MD Sharp Memorial Hospital
Anuja Vyas, MD Sharp Memorial Hospital

DISCLAIMER

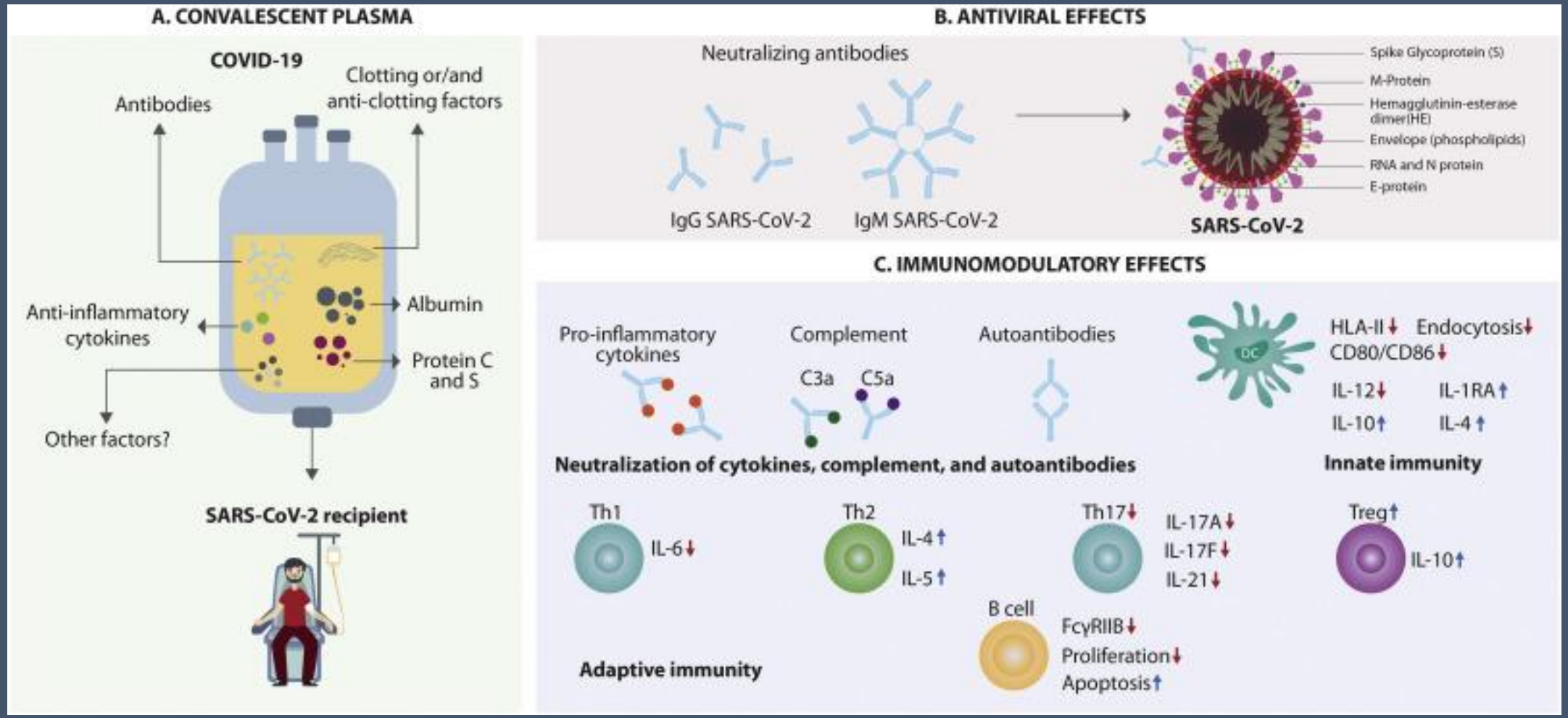
- Subinvestigator for the Roche-Actemra clinical trial

CONVALESCENT PLASMA (CCP)

- Plasma obtained from patients who have recovered from the disease
- First described in JAMA in 1893, used in Diphtheria in Germany
- Described in 1918 Pandemic Flu, 2012 MERS-CoV, 2003 SARS and Ebola
- Adverse reactions same as blood products

Rubin R. Testing an Old Therapy Against a New Disease: Convalescent Plasma for COVID-19. JAMA. Published online April 30, 2020. doi:10.1001/jama.2020.7456
https://www.history.com/news/blood-plasma-covid-19-measles-spanish-flu

CONVALESCENT PLASMA: MECHANISM OF ACTION



Rojas et al Autoimmunity review In Press May 2020

CONVALESCENT PLASMA IN THE US

- Obtained from Covid+ patients: symptom free for 14 days AND negative PCR, OR symptom-free for 28 days
- Apharesis donation (1 donor can provide plasma for upto 4 patients), ABO matched and screened
- 2 options:
  - Emergency use of Investigation New Drug (eIND) applied through FDA
  - Mayo Clinic Protocol (www.uscovidplasma.org)
- Adult, Hospitalized, Covid+ patients with severe or life-threatening disease

Severe	Life-threatening
•Dyspnea •RR>30/min •O2sats<93% •P/F ratio <300 •Infiltrates >50% of lung w/in 24-48 hours	•Respiratory failure •Septic Shock •MOF

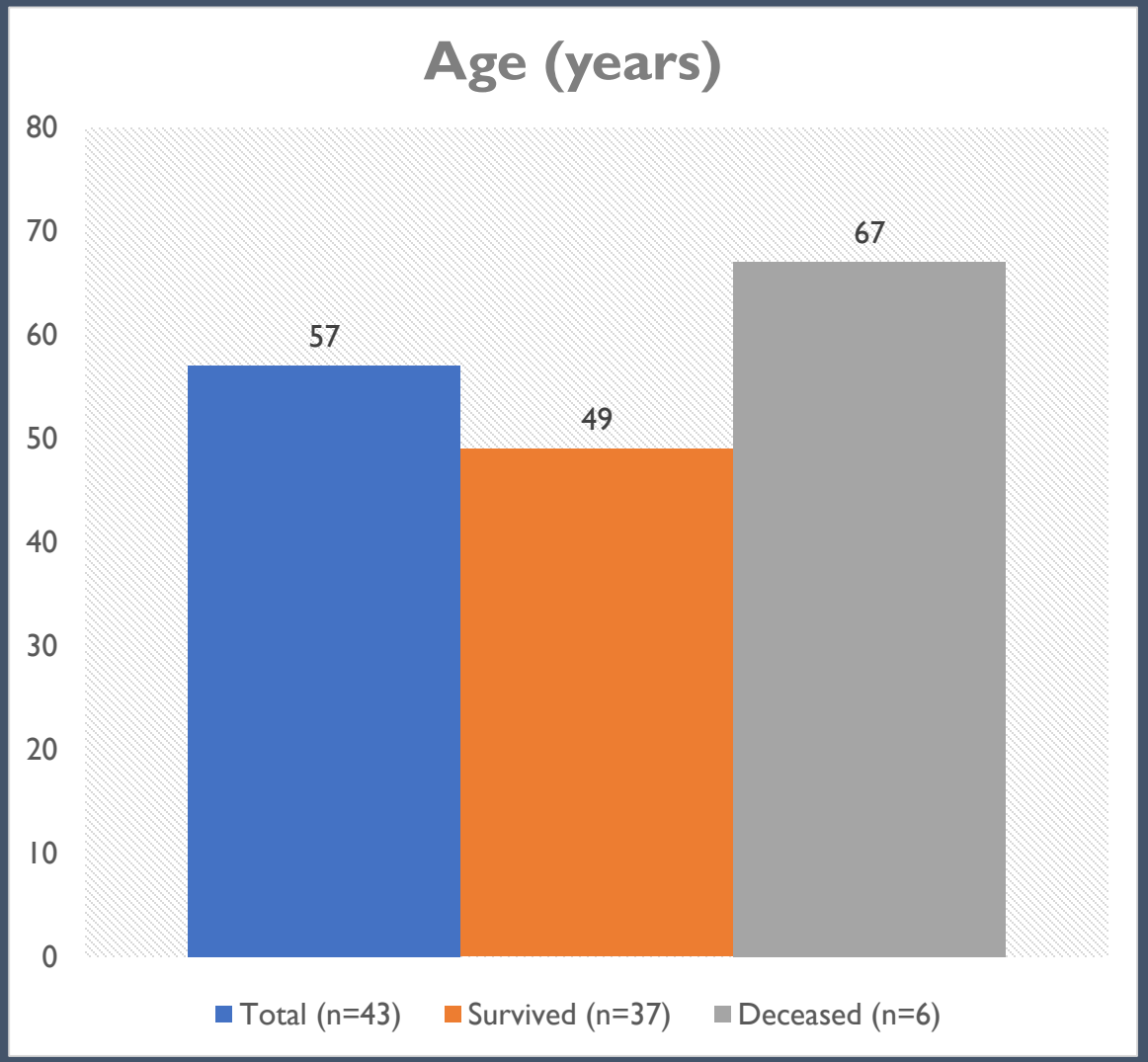
CONVALESCENT PLASMA: DATA

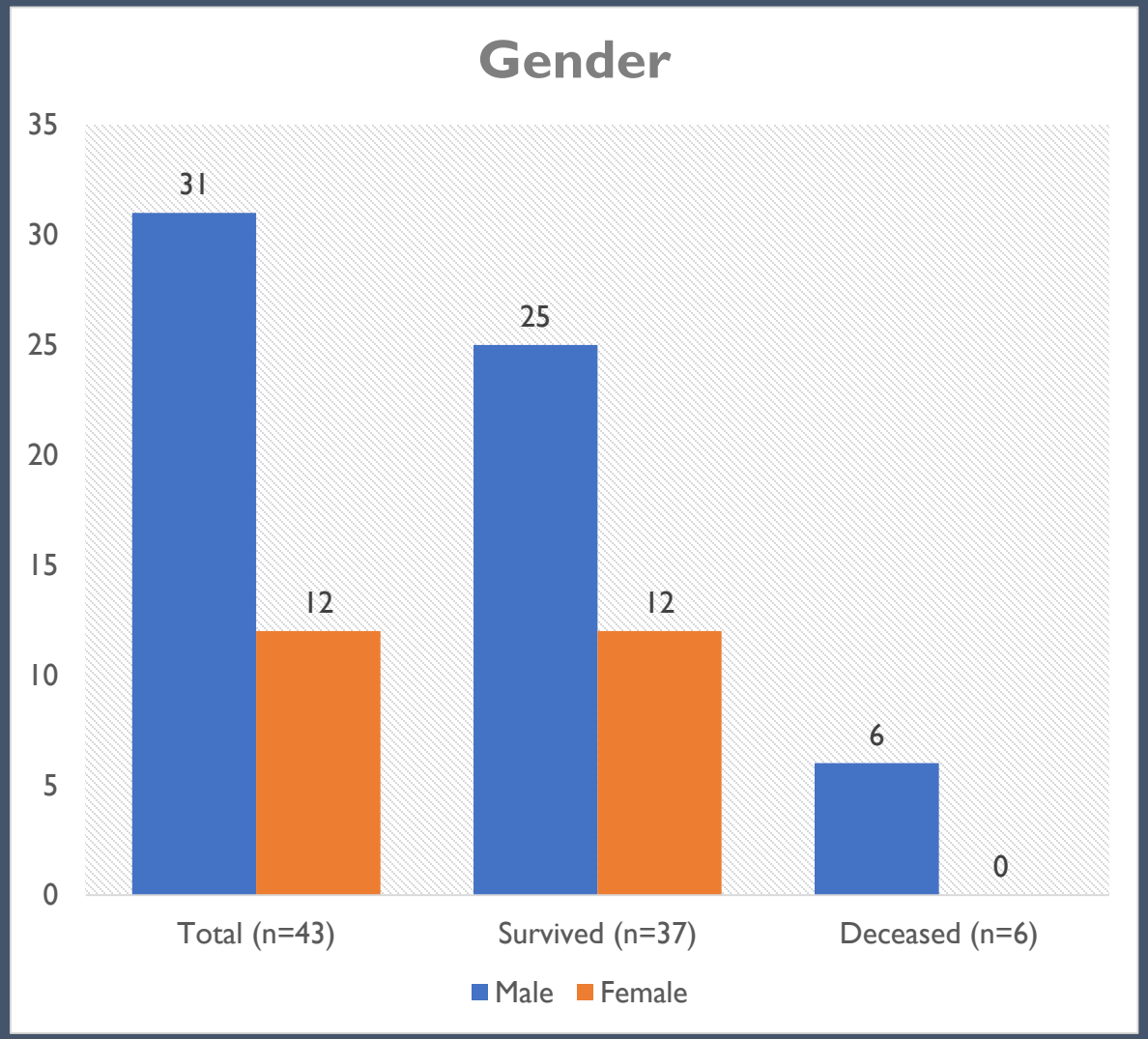
	Location	Study design	Average time to administration	Dose	Titer	Outcomes	Comments
Duan et al	Wuhan, China	Uncontrolled, case series, 10 critically ill patients	11-19 days (post symptom onset)	200ml	Neutralizing Anti-SARS-CoV2 Titer >1:640	Clinical improvement in all patients + viral loads	Steroids, antibiotics, antivirals
Shen et al	Shenzen, China	Uncontrolled, case series, 5 patients	10-22 days (post admission)	400ml	Anti-SARS-CoV2 Titer >1:1000	Improvement in all patients + viral loads	All had steroids, antivirals
Ahn et al	Seoul, South Korea	Case series, 2 patients	7-22 days	200ml	Unable to test	Improved oxygenation and viral loads	Lopinavir/Ritonavir, HCQ, steroids
Ye et al	Wuhan, China	Case series, 6 patients	8-30 days	200-600ml	Not reported	Improvement in viral loads	Not reported

CONVALESCENT PLASMA: THE SHARP EXPERIENCE

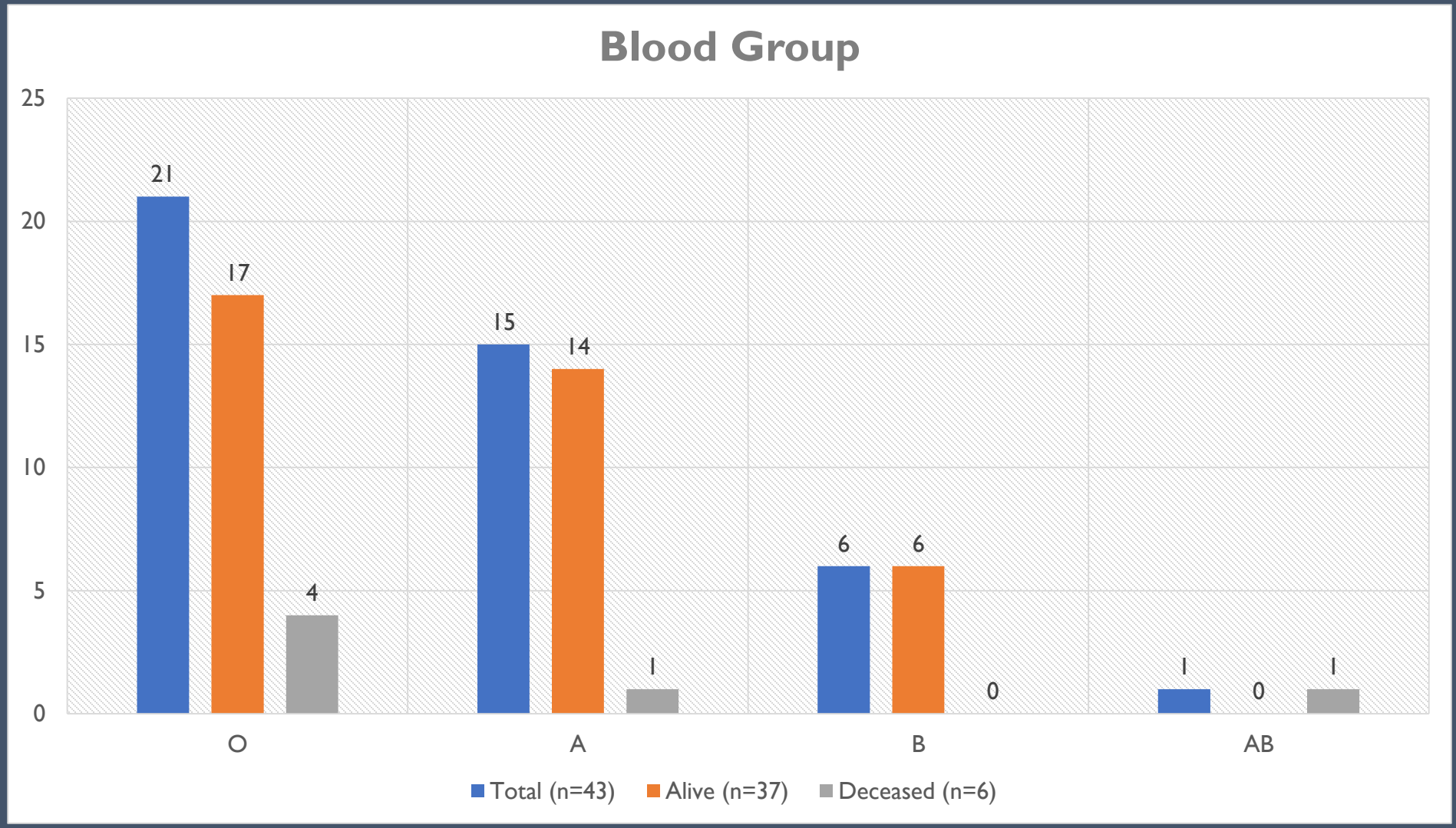
- Total 43 patients received CCP at SHC between 4/16/2020 - 5/7/2020
- 25 at SCV, 9 at SGH, 6 at SMH and 3 at SCO
- All Allogenic plasma donor source (none with directed donor)
- 6 discharged, 6 died, 31 still hospitalized

CONVALESCENT PLASMA: THE SHARP EXPERIENCE

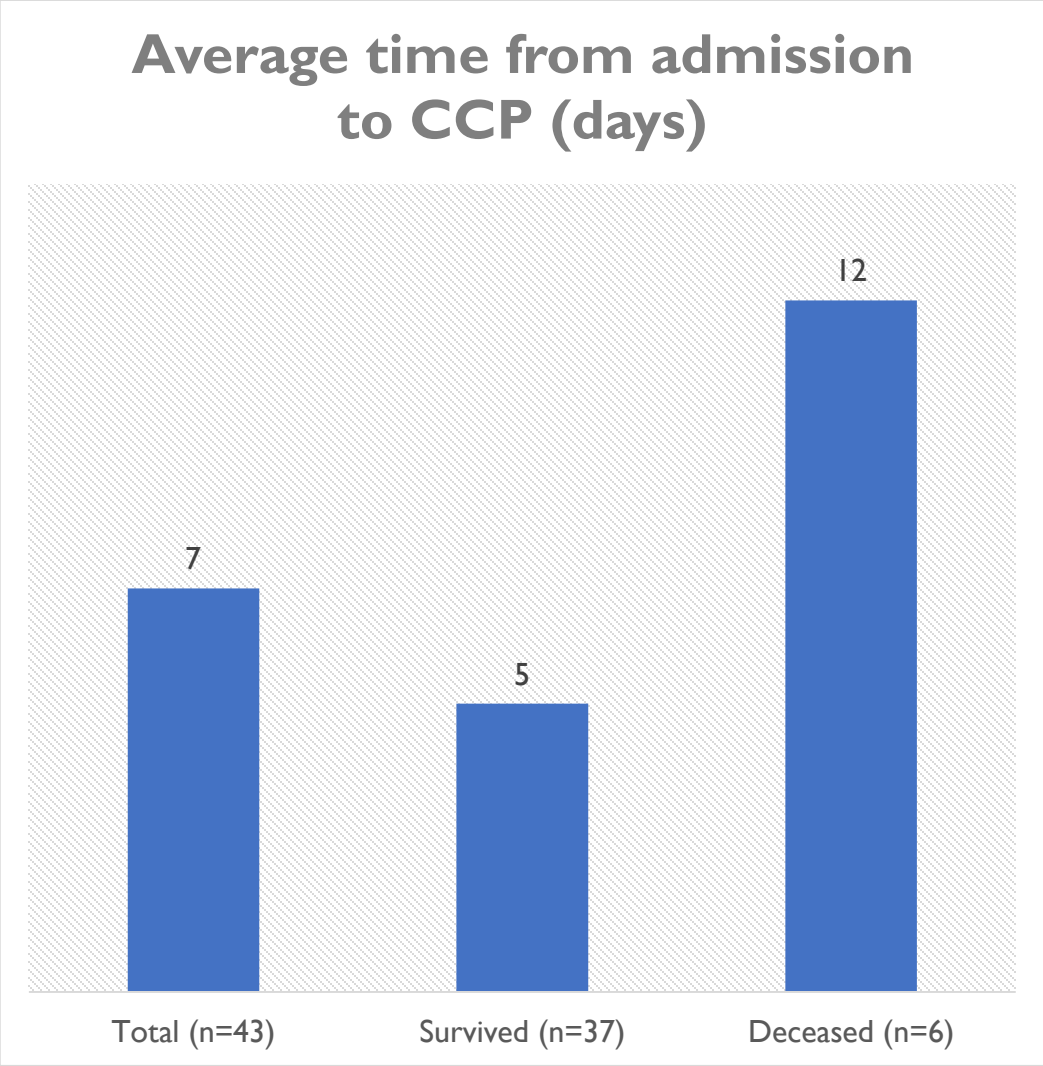


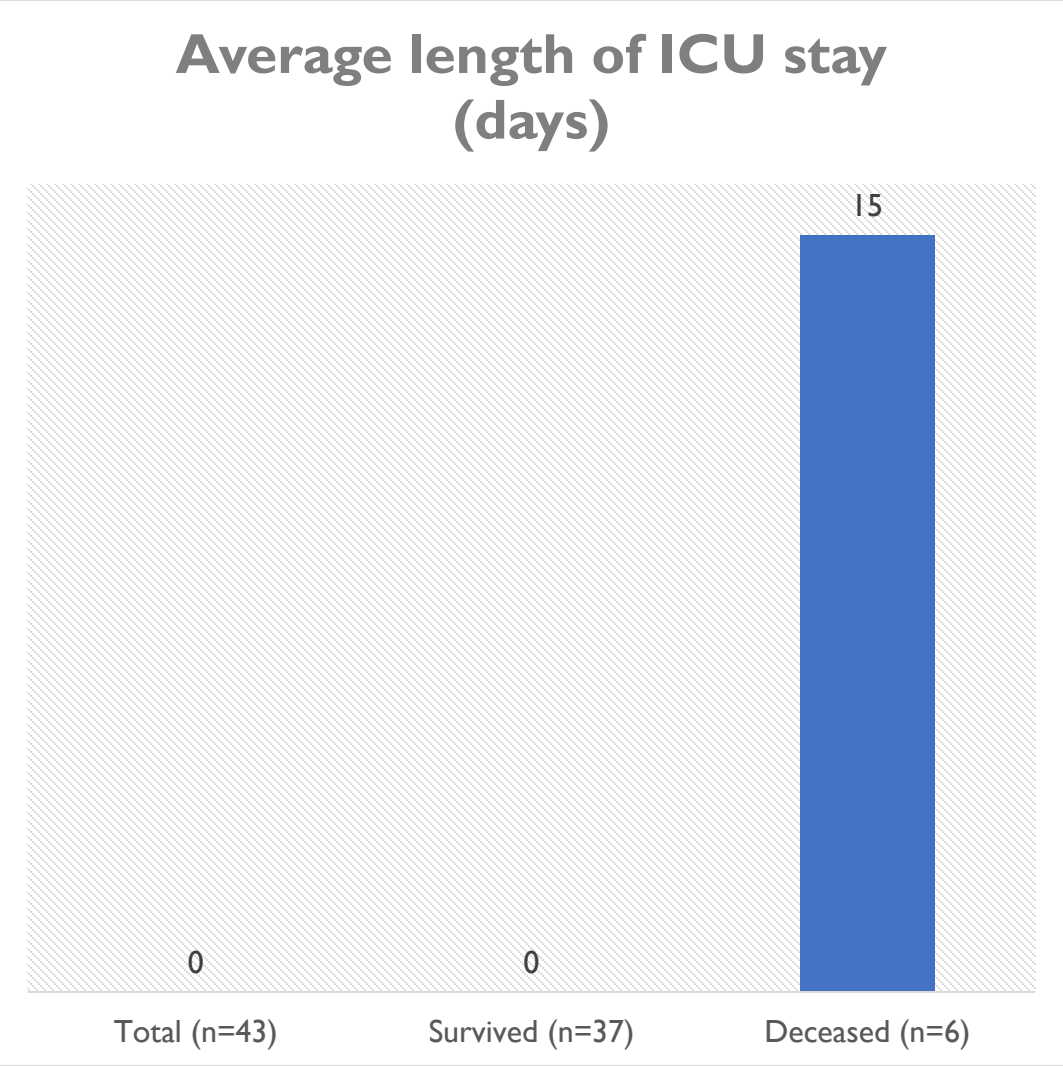


CONVALESCENT PLASMA: THE SHARP EXPERIENCE

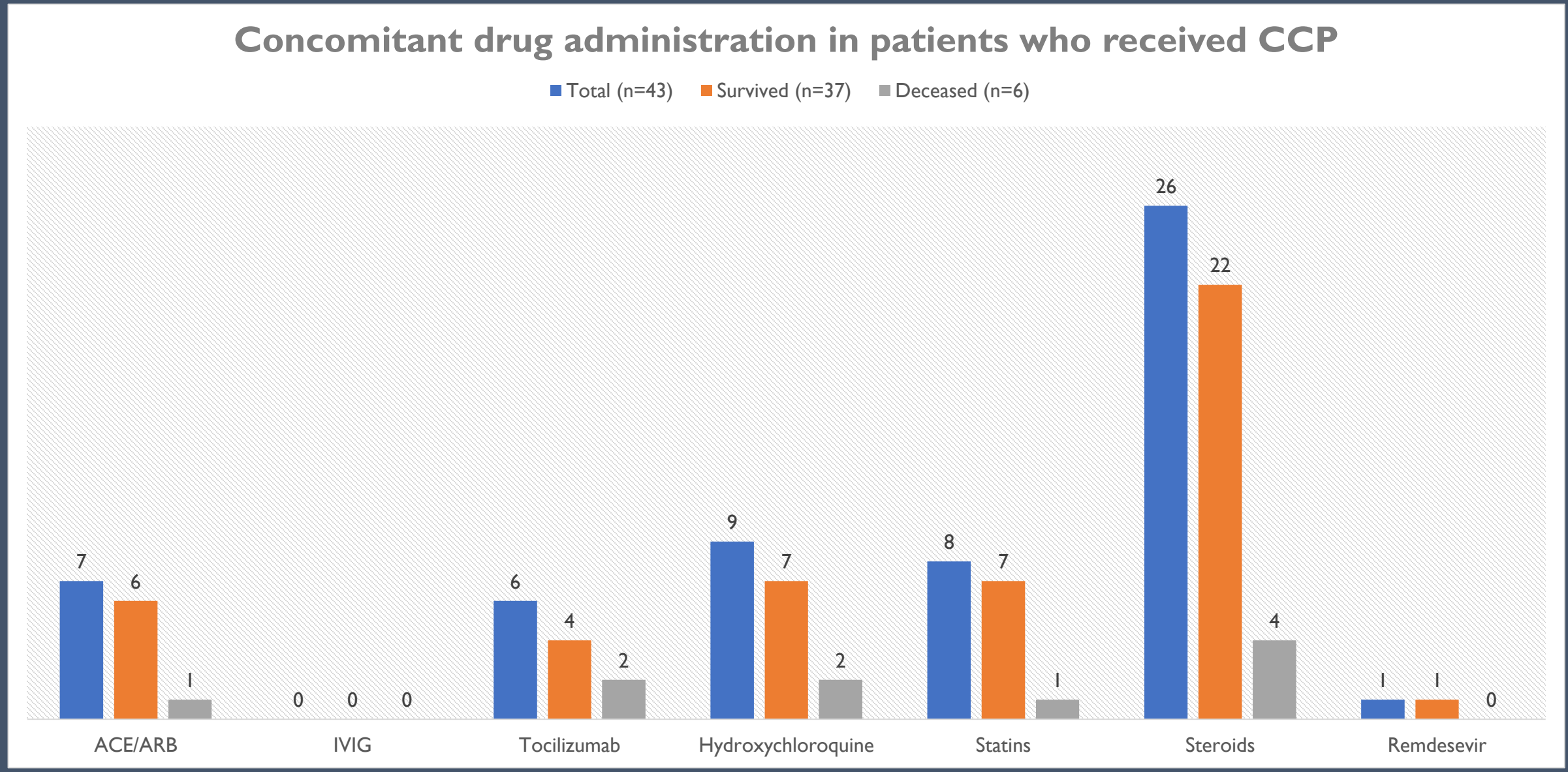


CONVALESCENT PLASMA: THE SHARP EXPERIENCE

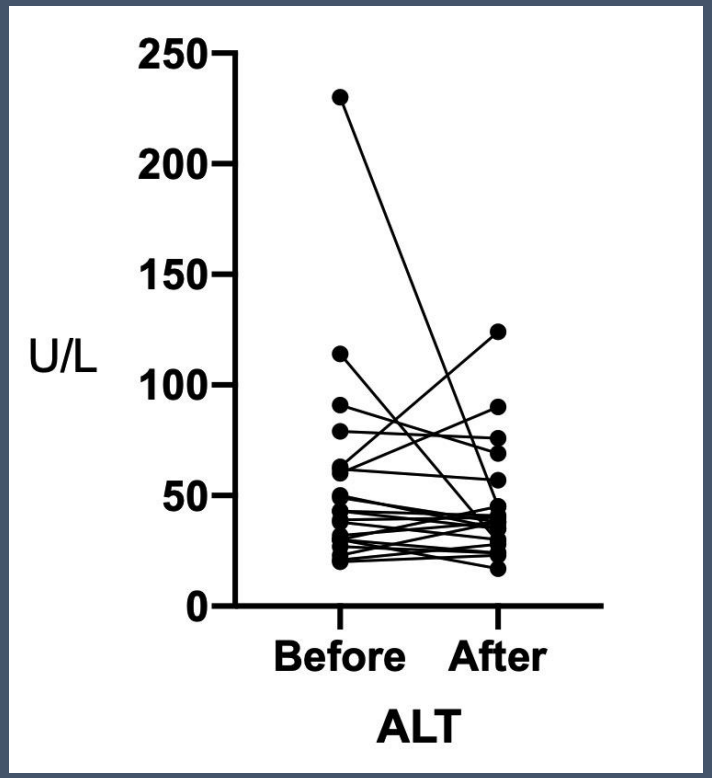


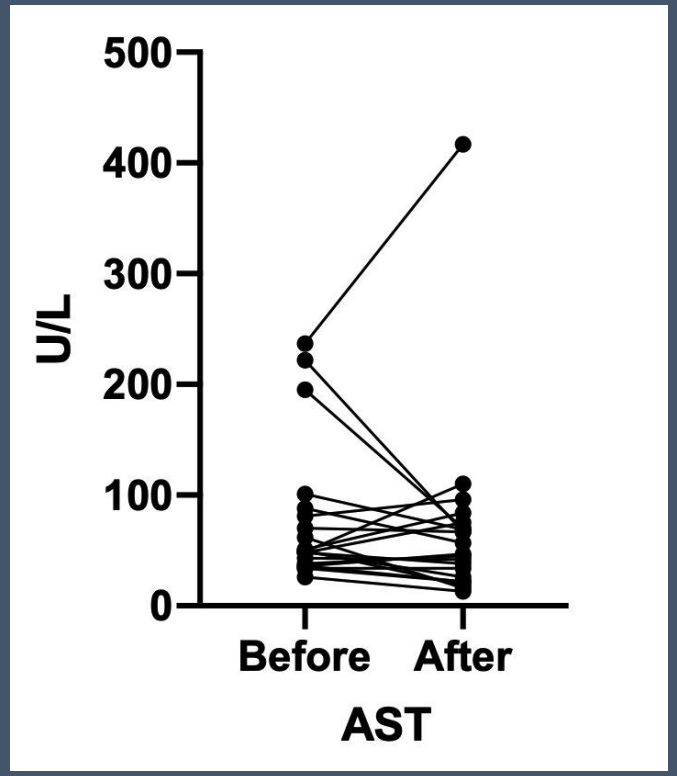


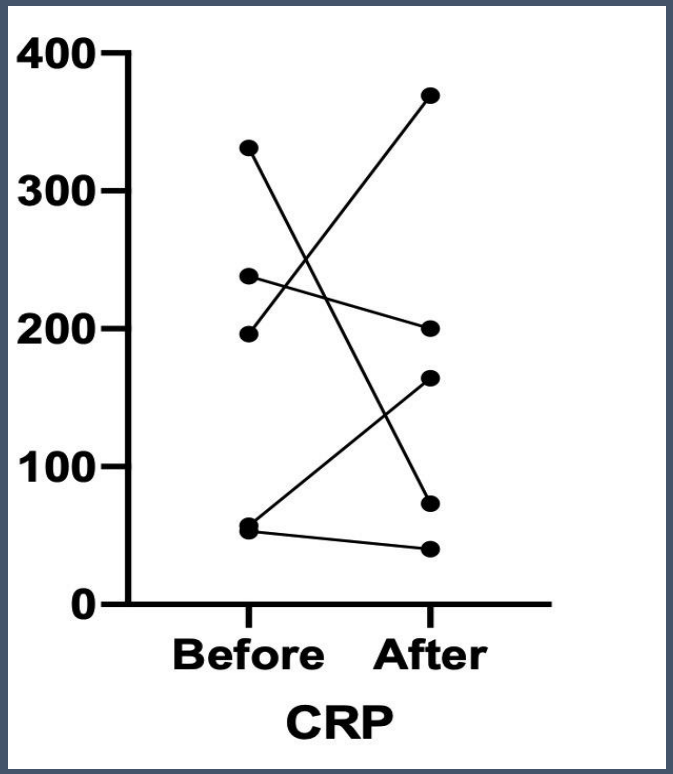
CONVALESCENT PLASMA: THE SHARP EXPERIENCE



CONVALESCENT PLASMA: THE SHARP EXPERIENCE





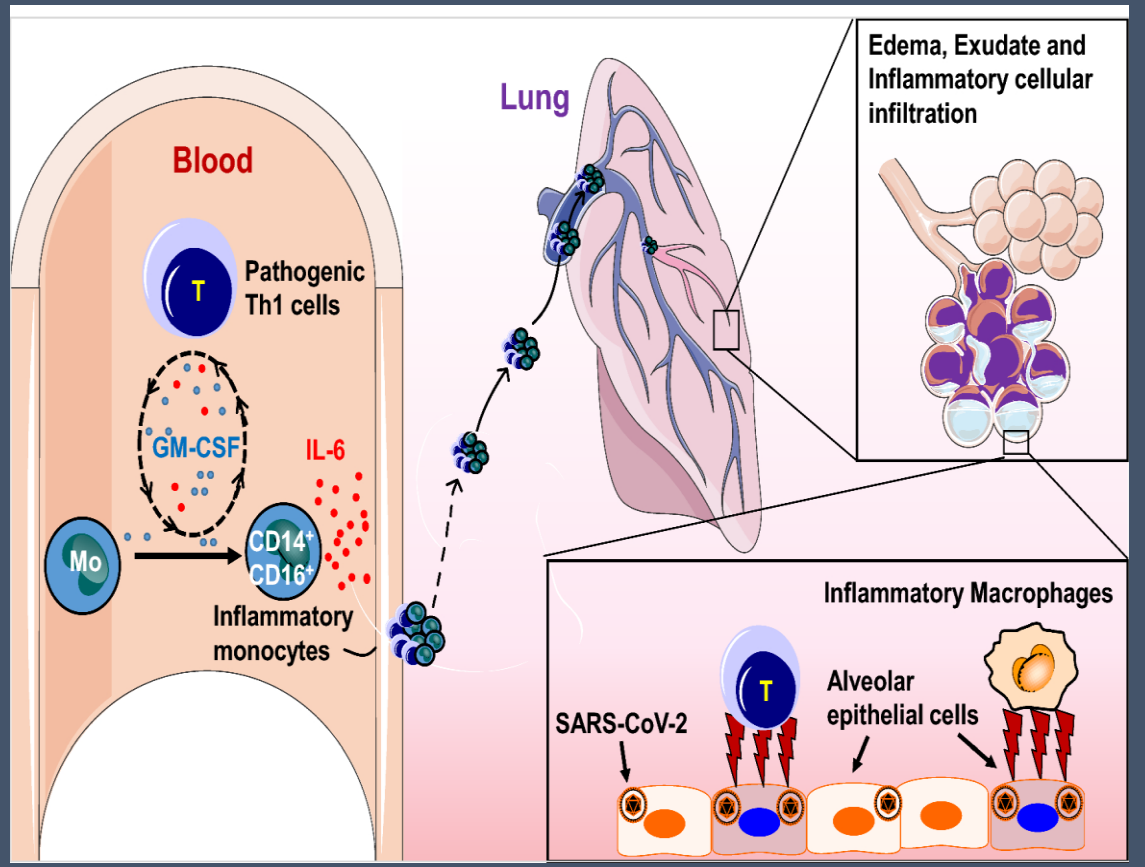


CONVALESCENT PLASMA: SUMMARY

- Should be considered for all hospitalized patients with Covid-19
- May be beneficial, difficult to form correlation due to other ongoing interventions
- Low risk (blood transfusion reactions)
- Early administration!

TOCILIZUMAB (ACTEMRA)

- Recombinant humanized monoclonal antibody which binds to Interleukin-6 (IL-6)
- Used for Rheumatoid Arthritis, Cytokine Release Syndrome (CRS) after CAR-T Cell Therapy
- Dose 4-8mg/kg (400mg), maybe repeated once 12 hours later
- Adverse reactions: Elevated AST, ALT, Infusion reaction, increased risk of opportunistic infections



Fu, B., Xu, X. & Wei, H. Why tocilizumab could be an effective treatment for severe COVID-19?. *J Transl Med* **18,** 164 (2020). https://doi.org/10.1186/s12967-020-02339-3

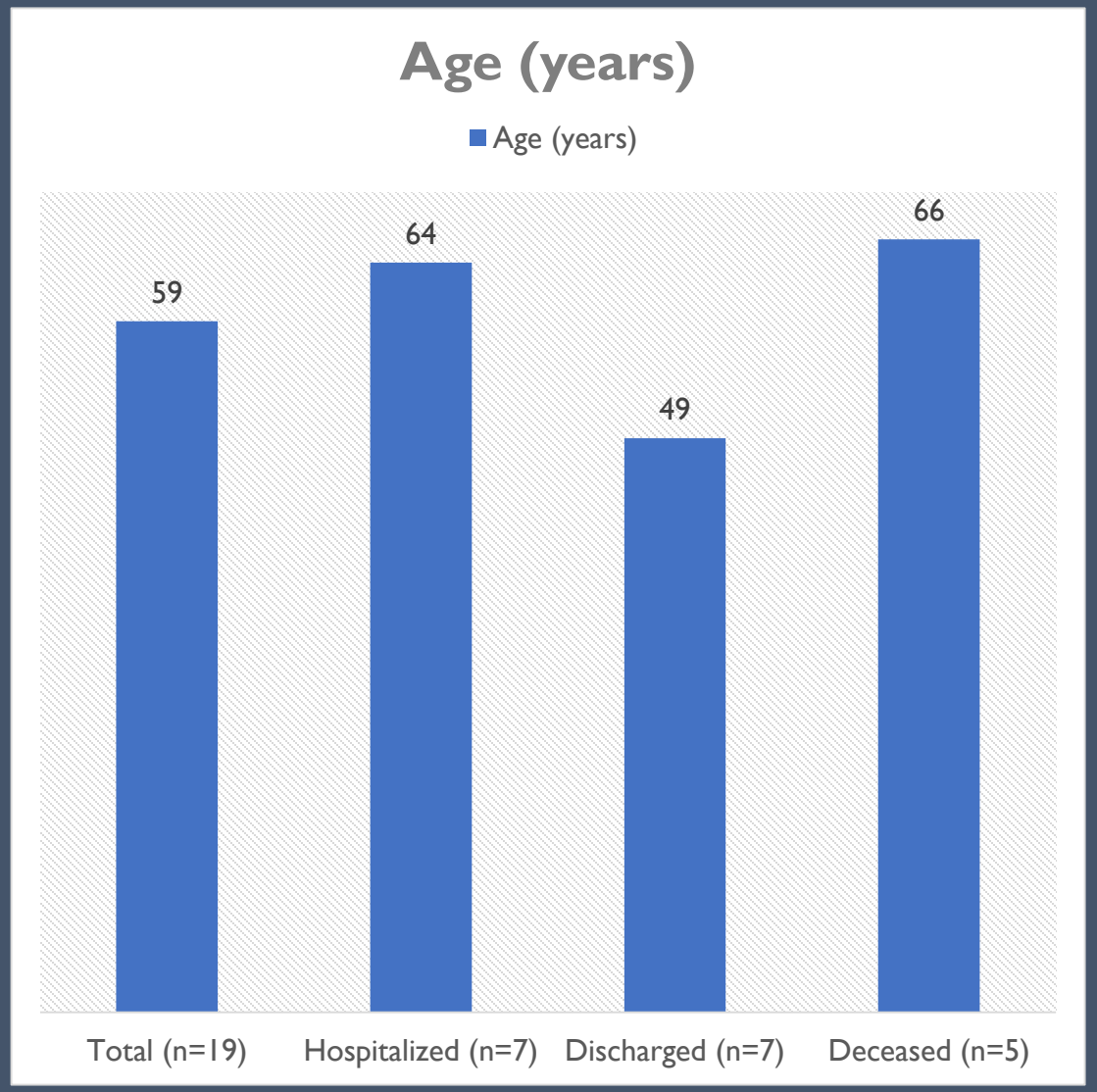
TOCILIZUMAB: DATA

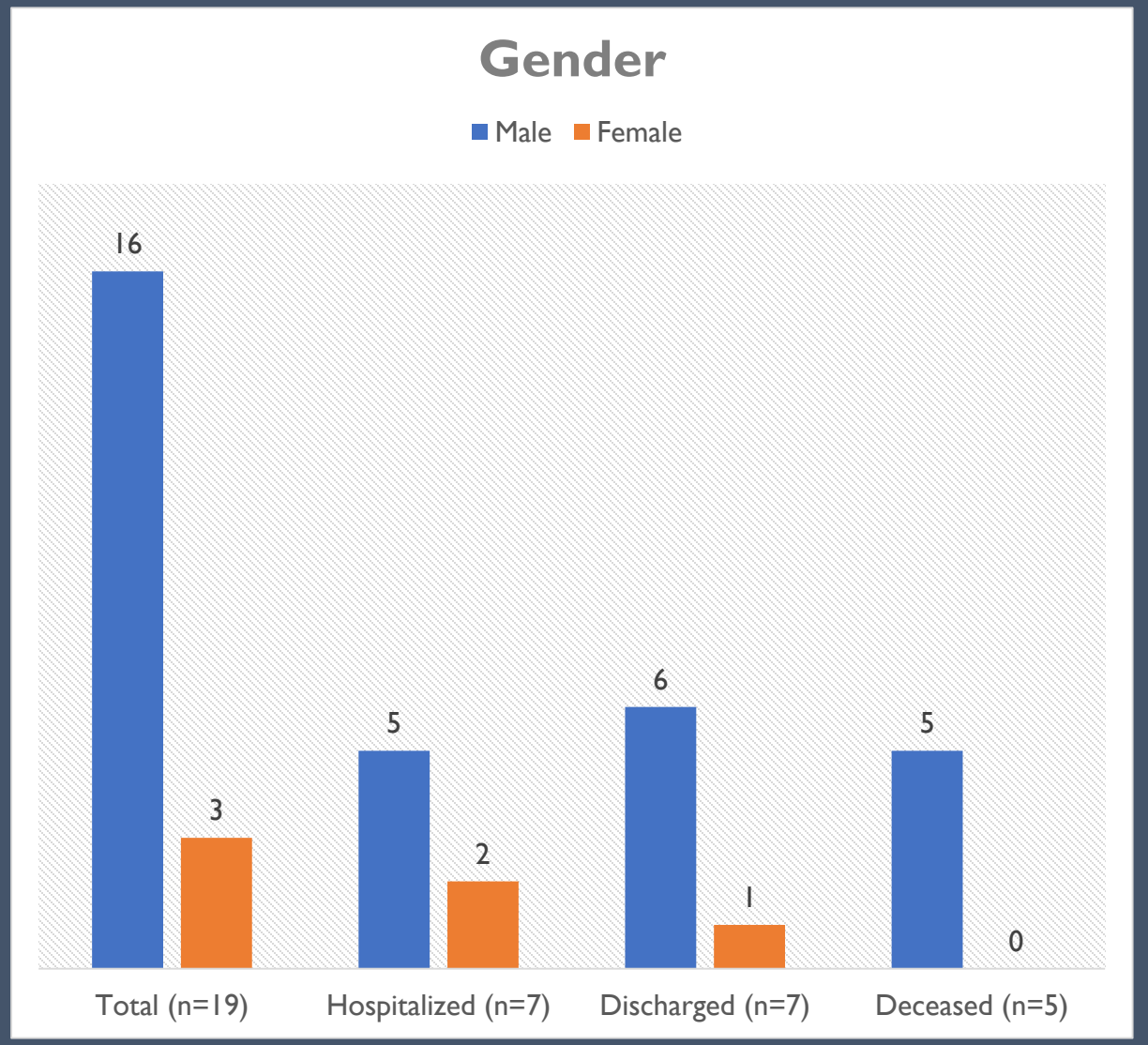
	Location	Study design	Dose	Outcomes	Comments
Xu et al	China	Case series, 21 patients	400mg	Clinical improvement, no adverse effects	
Luo et al	Wuhan, China	Case series, 15 patients	80-600mg	Decrease in IL-6, CRP	8 patients received steroids
Gritti et al (Siltuximab)	Italy	Case series, 21 mechanically ventilated patients	700-1200mg	16 patients improved or stabilized	?early administration

OFF-LABEL TOCILIZUMAB: SHARP EXPERIENCE

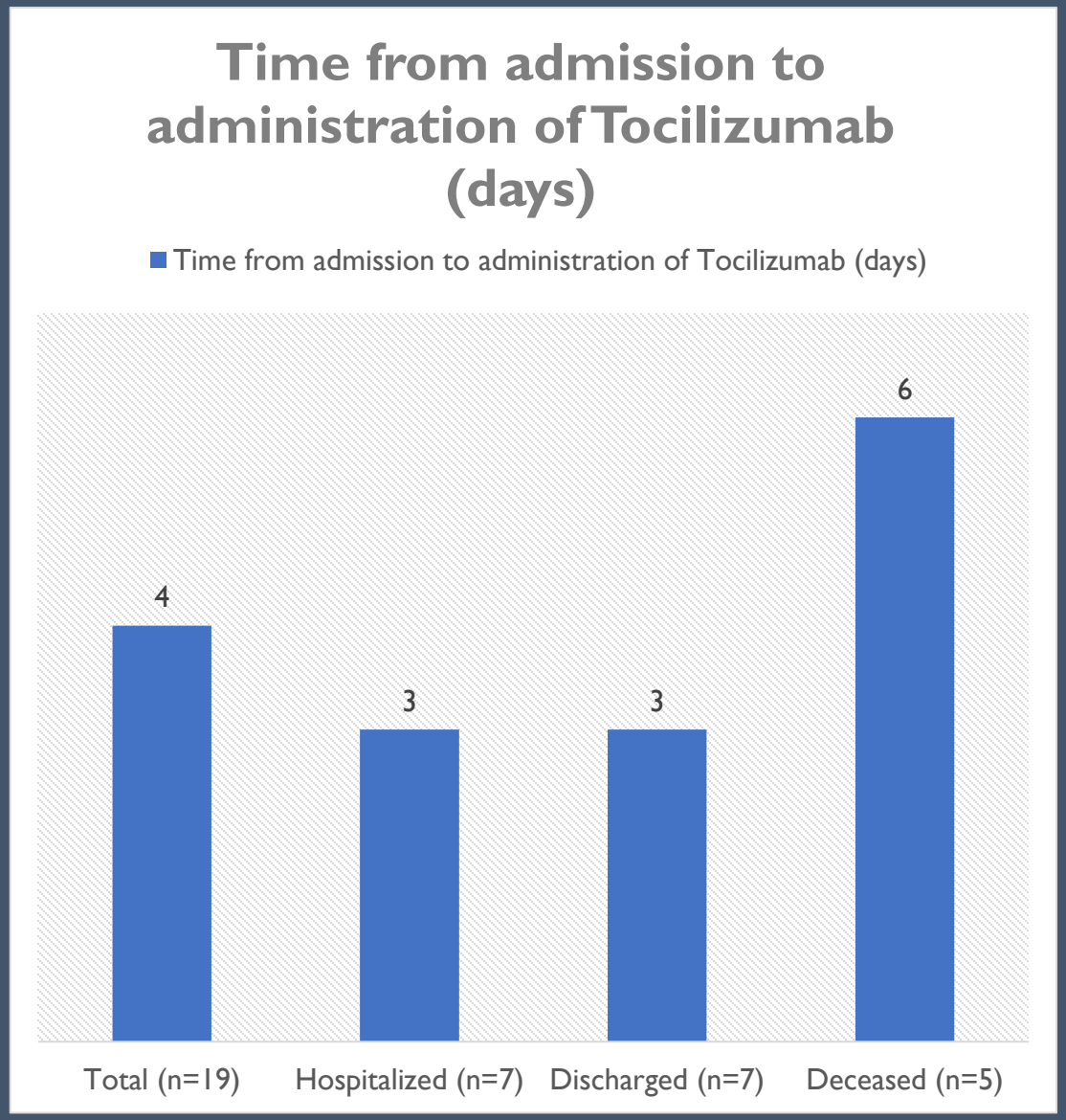
- Total 19 patients received Tocilizumab between 3/20/2020 - 4/20/2020
- 11 at SGH and 8 at SMH
- 7 have been discharged, 5 died, 7 are still hospitalized

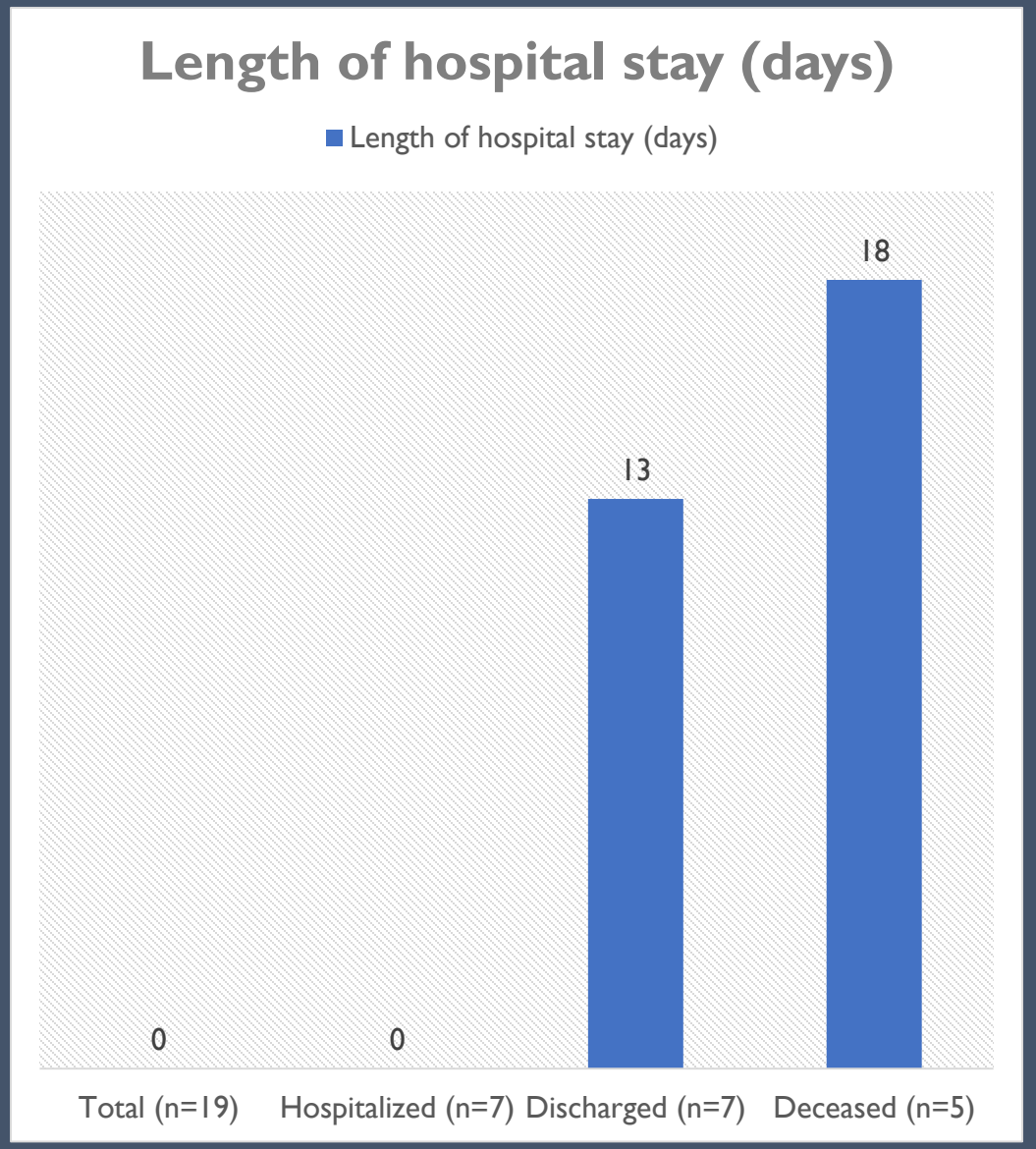
OFF-LABEL TOCILIZUMAB: SHARP EXPERIENCE



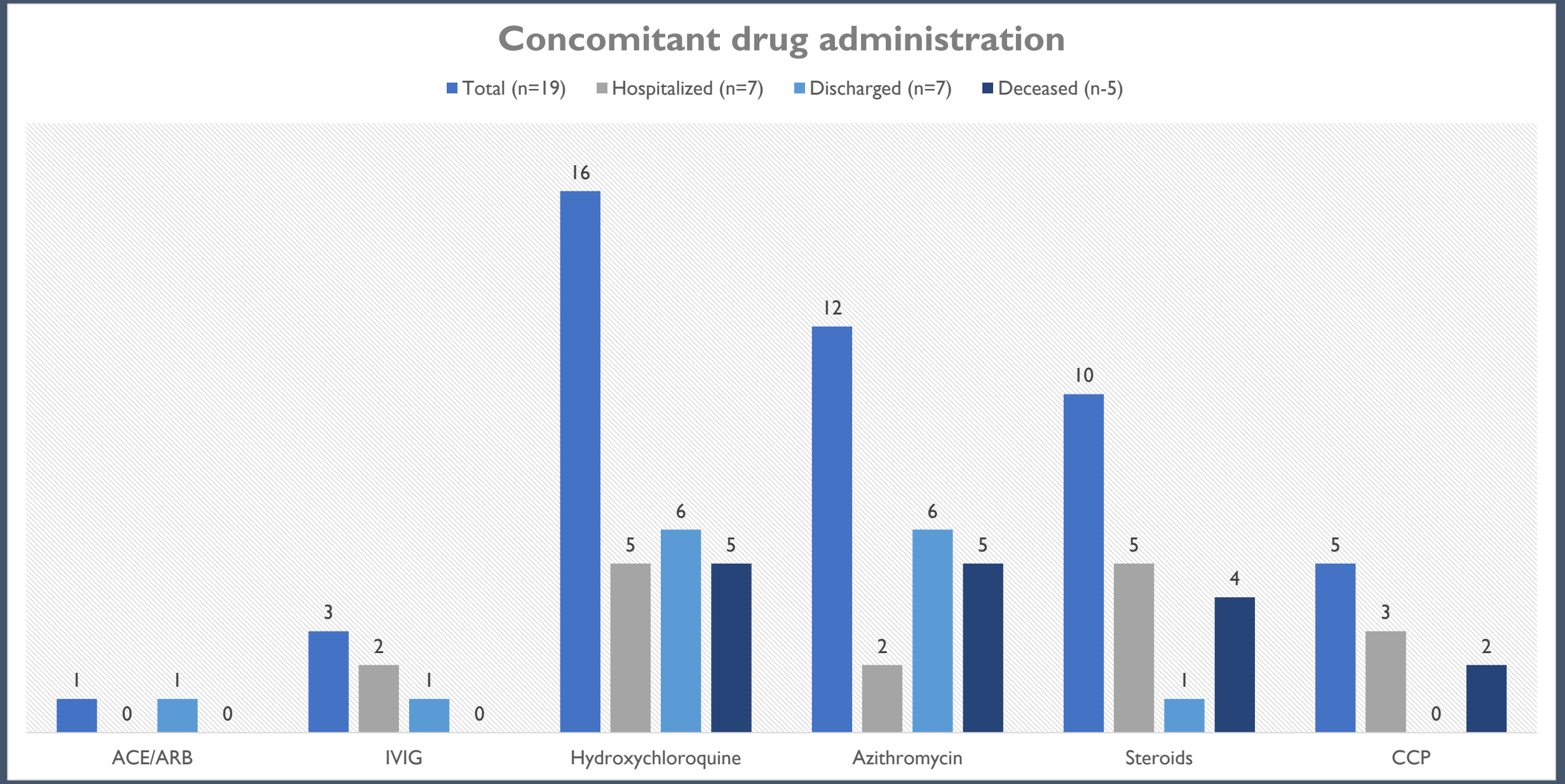


OFF-LABEL TOCILIZUMAB: SHARP EXPERIENCE

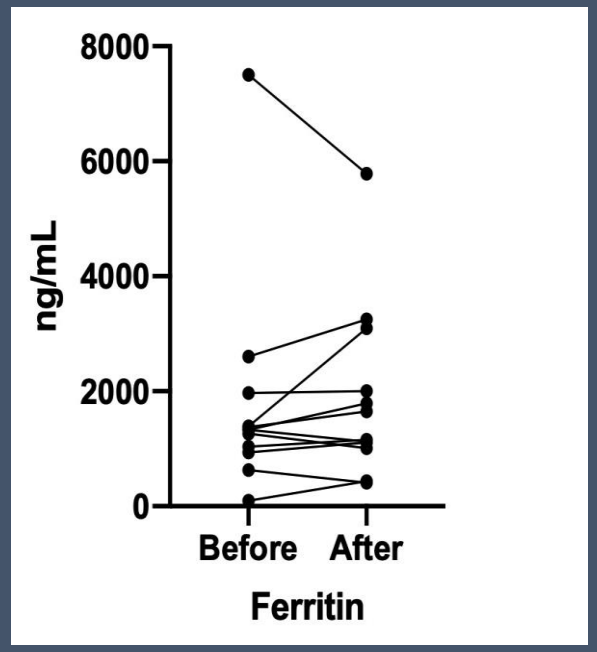


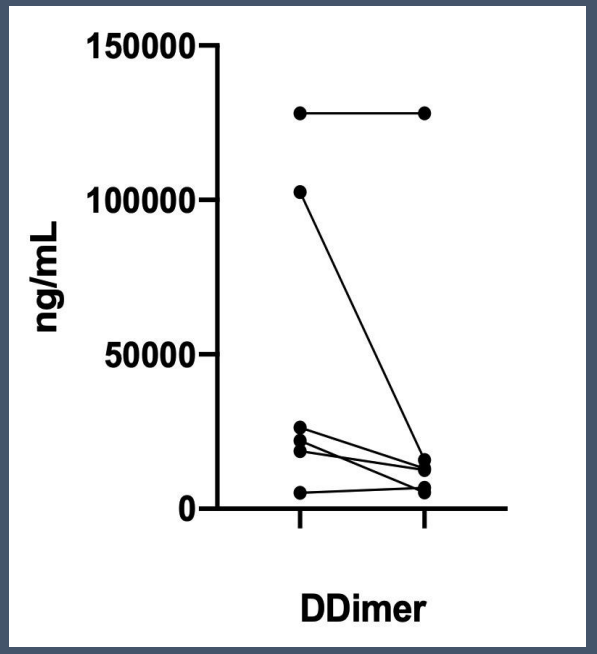


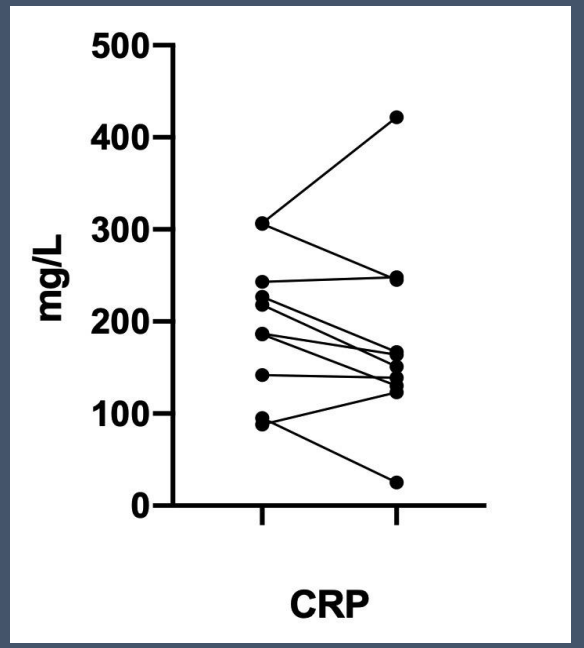
OFF-LABEL TOCILIZUMAB: SHARP EXPERIENCE

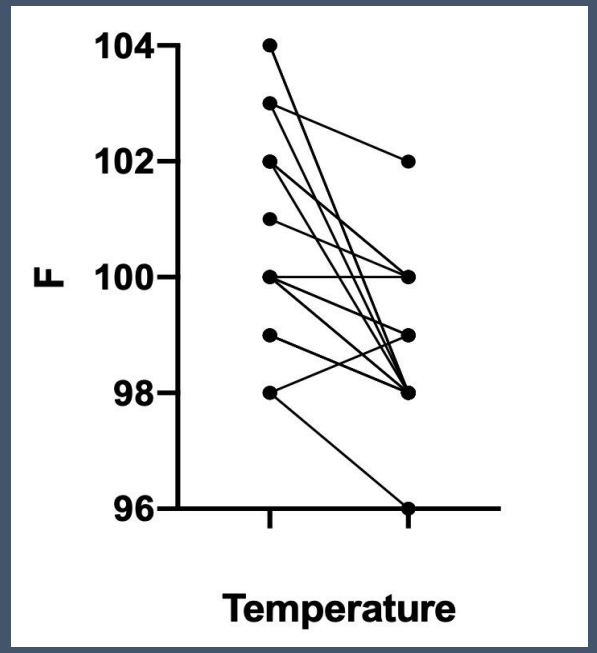


OFF-LABEL TOCILIZUMAB: SHARP EXPERIENCE









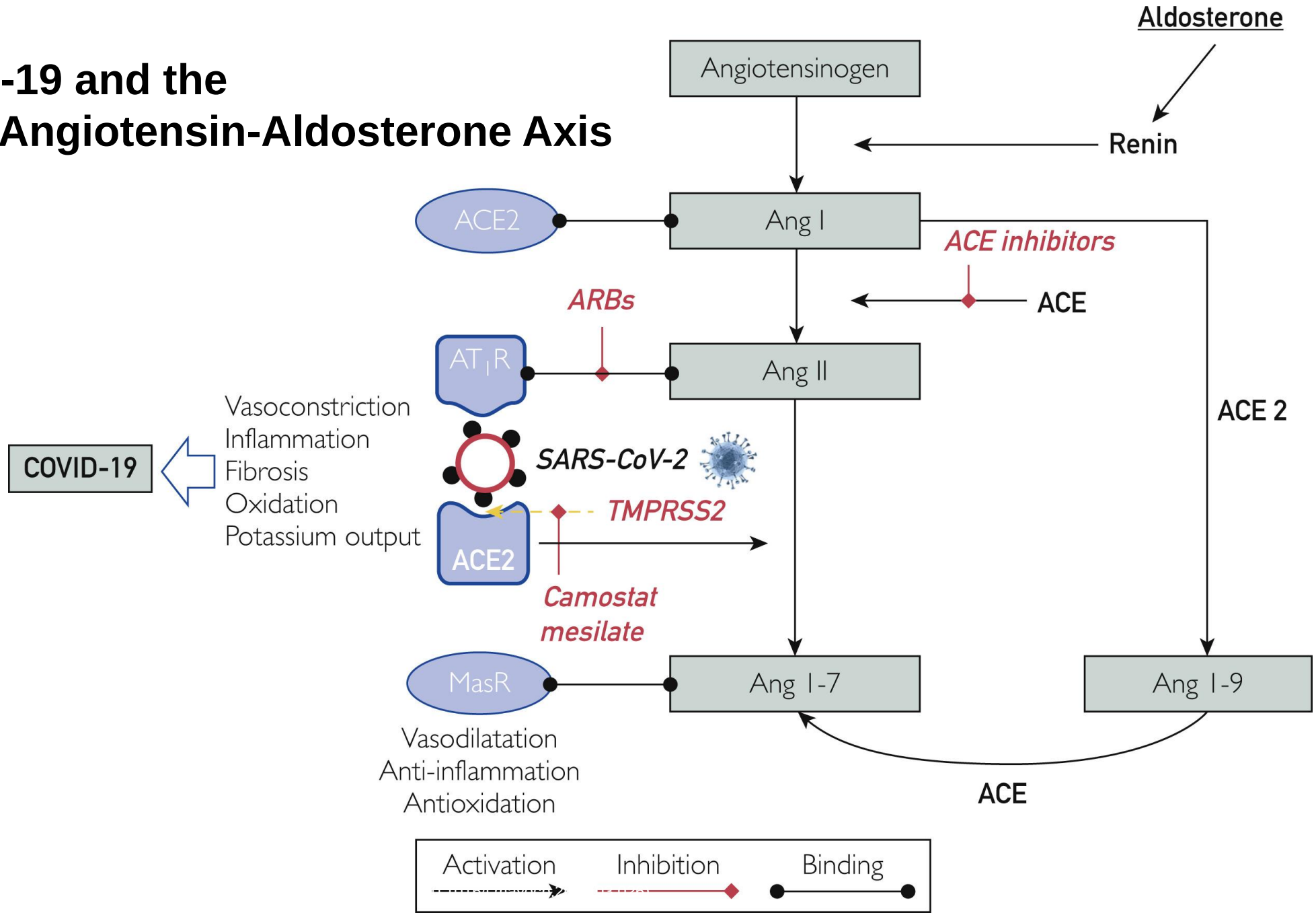
TOCILIZUMAB: SUMMARY

- Study enrollment should be considered for all hospitalized Covid-19 patients who meet eligibility criteria
- Evolving data
- Early administration!

THANKS!

- Dr Amy Adome and her team
- Dr Deann Cary, IRB Sharp
- Matthew Geriak, Sharp Research Pharmacy
- Shiva Bojak, Sharp Clinical Pharmacy

COVID-19 and the Renin-Angiotensin-Aldosterone Axis



PHYSIOLOGIC CONDITIONS

ANGIOTENSIN CONVERTING ENZYME

ANGIOTENSIN CONVERTING ENZYME II

ANGIOTENSIN 1 → + ANGIOTENSIN 2 - → ANGIOTENSIN 1-7

↓

ANGIOTENSIN 1 Receptor

↓

Capillary Leak
ARDS

Delicate Balance
Opposing Roles of ACE and ACE 2

ANGIOTENSIN CONVERTING ENZYME

ANGIOTENSIN CONVERTING ENZYME II

ANGIOTENSIN 1 → + ANGIOTENSIN 2 - → ANGIOTENSIN 1-7

COVID-19

ANGIOTENSIN 1 Receptor

Capillary Leak
ARDS

COVID-19 Tips Balance in Favor of ACE

More Angiotensin 2

More AT1R Binding

ARDS

ANGIOTENSIN CONVERTING ENZYME

ANGIOTENSIN CONVERTING ENZYME II

ANGIOTENSIN 1 → + ANGIOTENSIN 2 - → ANGIOTENSIN 1-7

COVID-19

Angiotensin Receptor Blocker

ANGIOTENSIN 1 Receptor

Capillary Leak
ARDS

ARB Blocks AT1R Mediated Capillary Leak

ARB Study-Status Update 5/12/20

- Randomized Open Label Pilot, N=200 (100/arm)
- Patients +COVID $\leq$ 3 liters O_2 for sat $\geq$ 92%
- Endpoints: Prevention of MV, Days on O_2, Hospital Days
- Difficult to enroll-patients decline, many admitted on ACE-I, ARB
- Screened 100+ patients

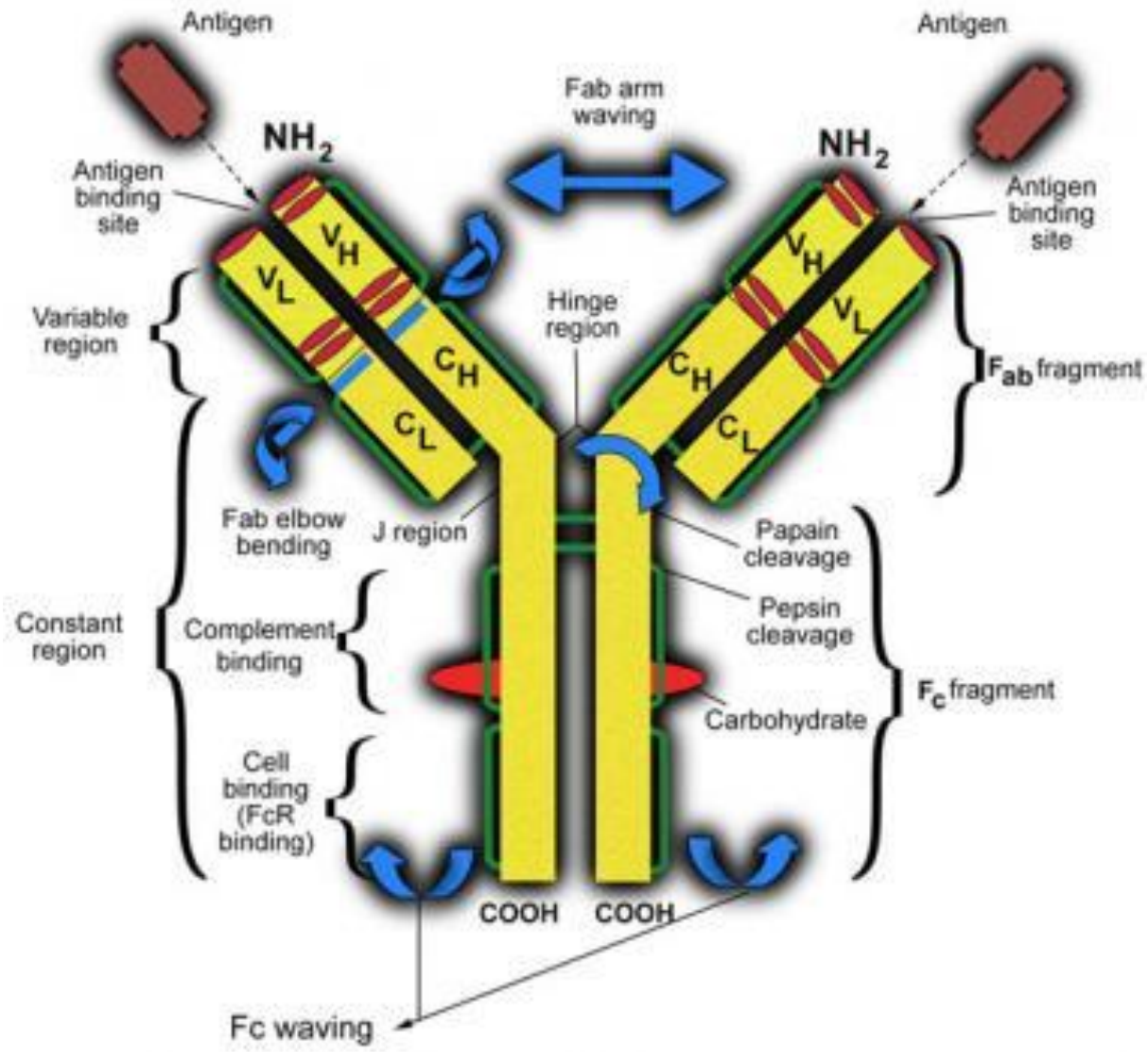
- Note University of Minnesota is doing similar blinded studies (inpatient, outpatient), results expected May 2021

Randomized Open Label Study of Standard of Care Plus an A ngiotensin II Receptor Blocker Compared to Standard of Care Alone to Minimize the Progression to Respiratory Failure in SARS-CoV-2 Infection (through 5/12/20)

Characteristic	Standard of Care Arm n = 10		ARB Intervention + Standard of Care Arm n = 9	
Age				
Age Range	23 - 80		33 - 95	
Median Age	51		69	
Intubation Status				
No Progression to Mechanical Ventilation	10	100.0%	8	88.9%
Progression to Mechanical Ventilation	0	0.0%	1	11.1%
Service Utilization				
Number of Patients Requiring ICU	0	0.0%	1	11.1%
ALOS from Enrollment to Discharge [1]	5.7		4.3	
Disposition				
Discharged on Room Air to Home/Hotel	8	80.0%	4	44.4%
Discharged on Room Air to Other Hospital	0	0.0%	1	11.1%
Disharged on Room Air to Skilled Nursing Facility	0	0.0%	1	11.1%
Discharged on Nasal Cannula to Home	1	10.0%	0	0.0%
Still Hospitalized [2]	1	10.0%	2	22.2%
Died in Hospital [3]	0	0.0%	1	11.1%

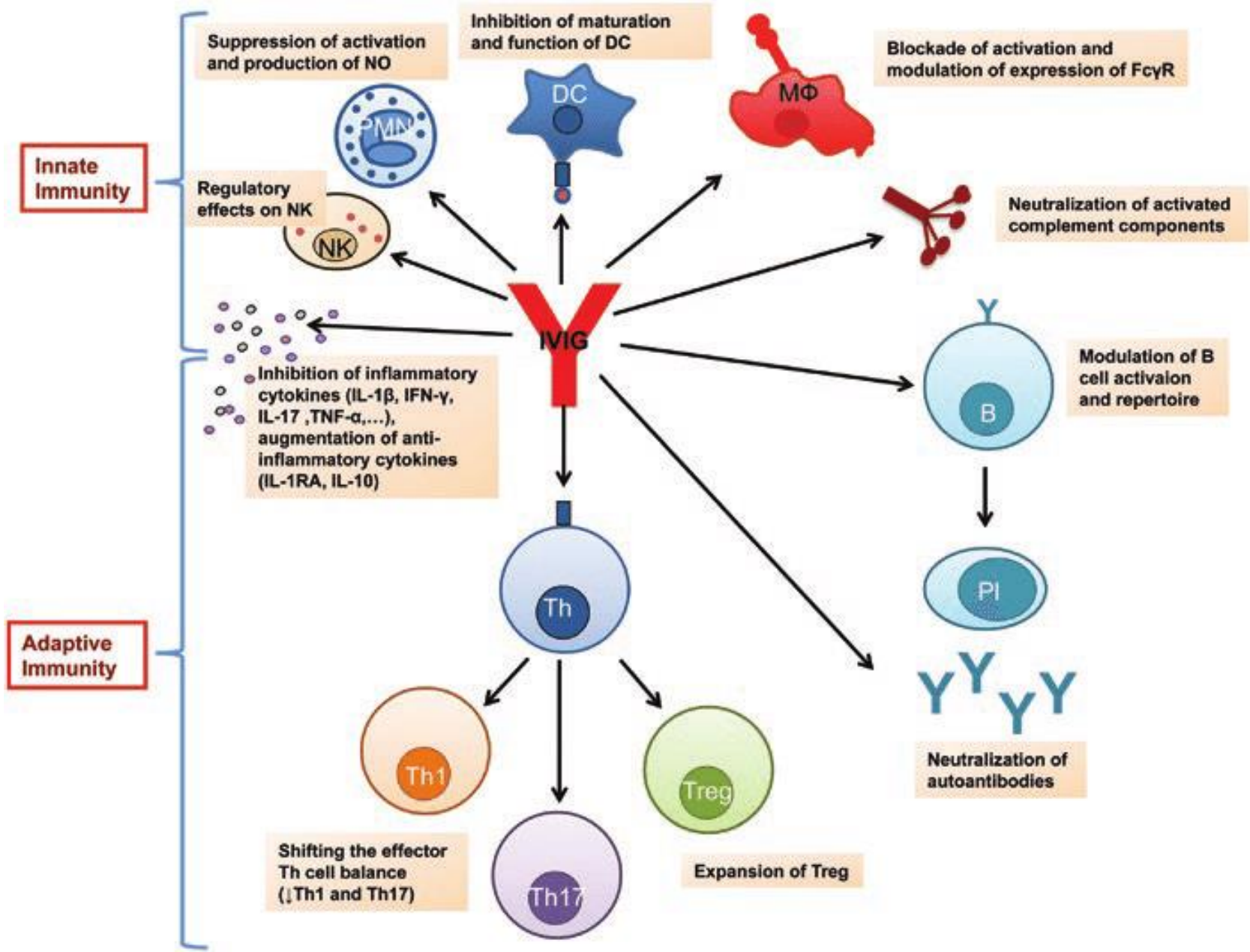
1. *ALOS calculation excluded the patient who died in the hospital.*
2. *For the three patients who are still hospitalized, one is on room air (ARB Intervention + SOC Arm) and two have a nasal cannula (one in the SOC Arm, one in the ARB Intervention + SOC Arm).*
3. *The patient who died in the hospital (ARB Intervention + SOC Arm) was 55 years old, and was the only study patient who required intubation with an ICU stay of 25 days. This was also the first patient enrolled in the study at SGH*

Immunoglobulin



The Antibody Molecule

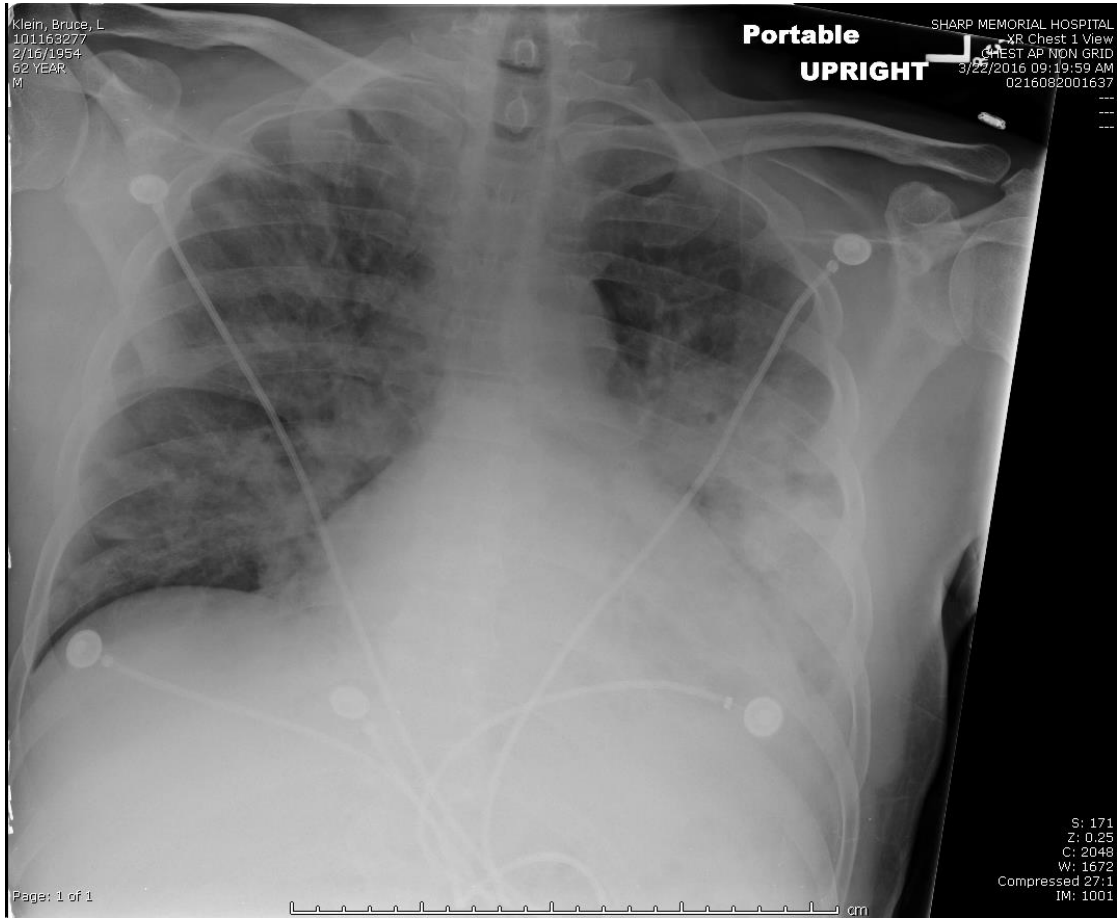
More than just an antigen neutralizer



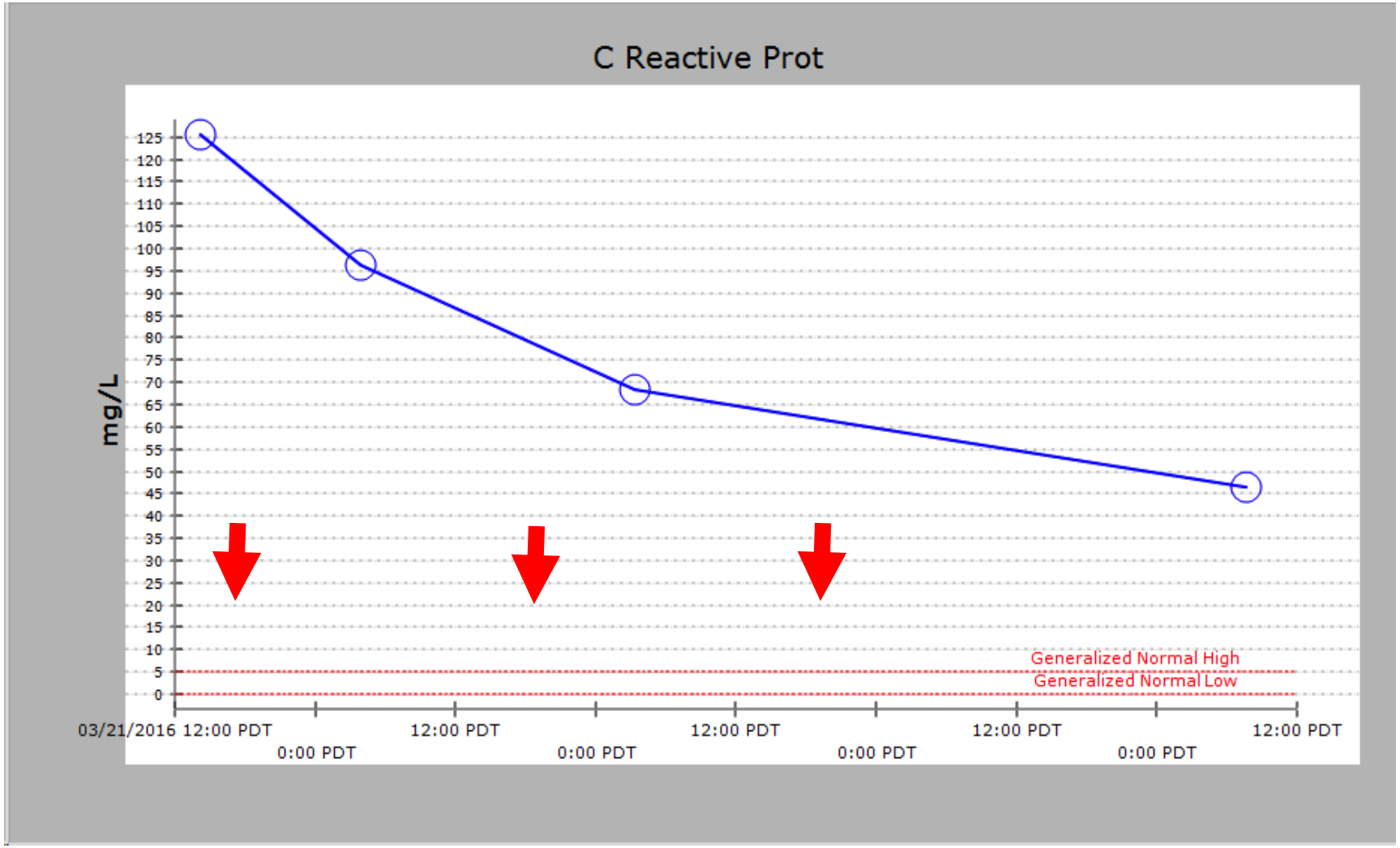
DOI: 10.1093/intimm/dxx039

Viral Pneumonias and IVIG

- IVIG employed ad hoc for severe ARDS and immunological complications of viral infection
- ICU or high risk
- Immune complications
  - (eg encephalitis)
- 62 M, chronic kidney dz
- 5 days cough, fever, malaise
- + FLU



Tm	**39.7C**	**38.5C**	**36.6**	**37.2**



	3/21/16		**3/22/16**	**3/23/16**	**3/24/16**	**3/25/16**
FIO2	**15L NRB**	**BIPAP**	**40 L/min NC**	**40L/min NC**	**40L/min**	**5L NC**

By 3/28/16 down to 2L NC, went home with supplemental O2

Authors	Study	Reference	No. of Patients	Overview/Results
Shao et al	multicenter retrospective cohort study	MedRxIV; Accepted, in press	325	early administration of high-dose IVIG improves the prognosis of critical patients with COVID-19
Xie et al	Retrospective analysis on prognosis of severe pneumonia in patients with COVID-19	Journal of Infection; Accepted, in press	58	IVIG <48 hours of admission to the ICU can: 1) reduce the use of mechanical ventilation; 2) reduce length of stay in hospital/ICU; 3) reduce 28-day mortality in patients with severe COVID-19 pneumonia.
Zhou et al	Case Series	Preprints; Posted March 8, 2020	10	reversing continued deterioration of COVID-19 patients who failed to respond to low-dose corticosteroid therapy.
Cao et al	Case Series	OFID March 21, 2020	3	Three (3) deteriorating patients with severe COVID-19 received high-dose IVIG with satisfactory recovery.

IVIG IN COVID-19

N=58

Wuhan, China

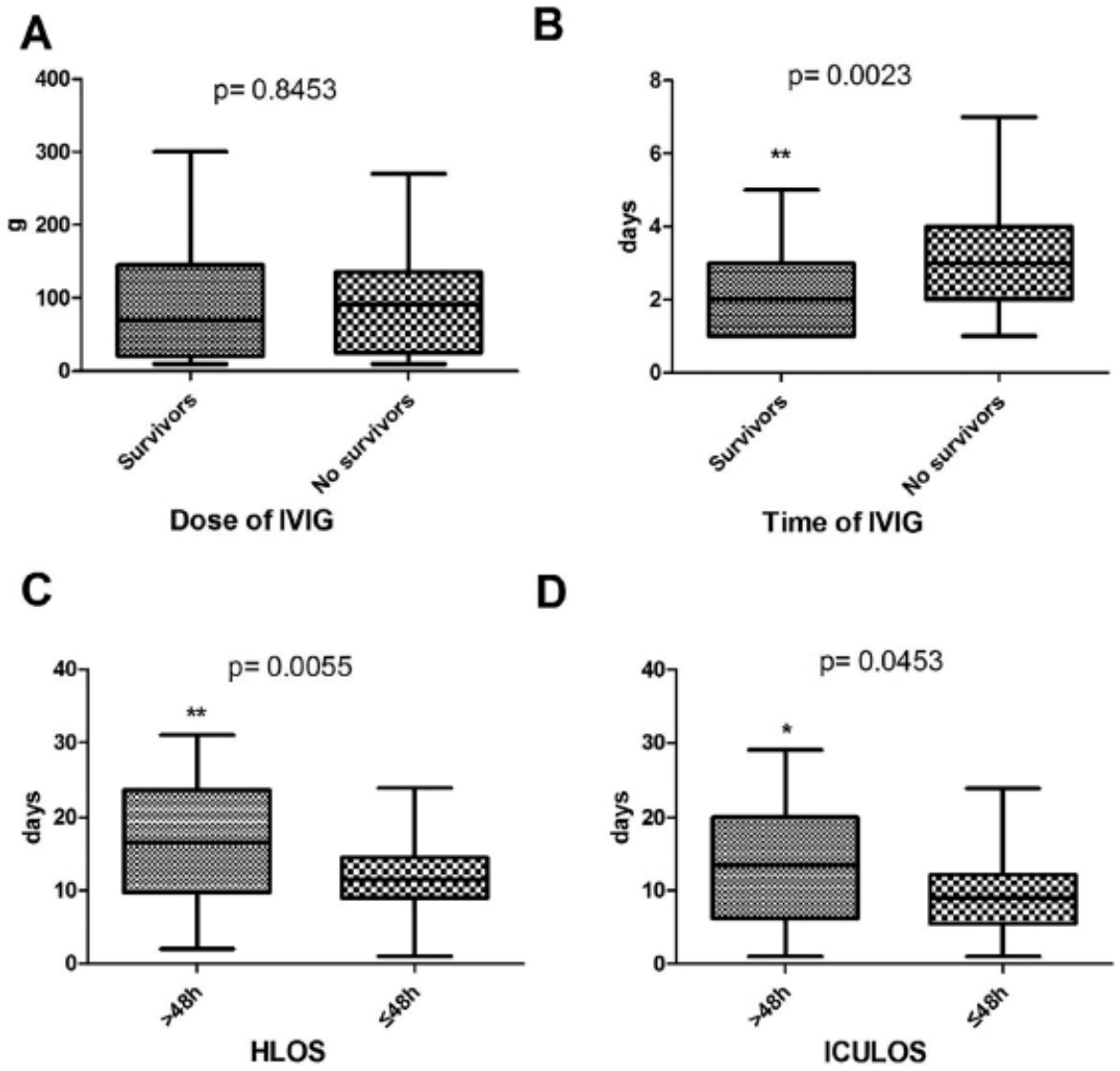
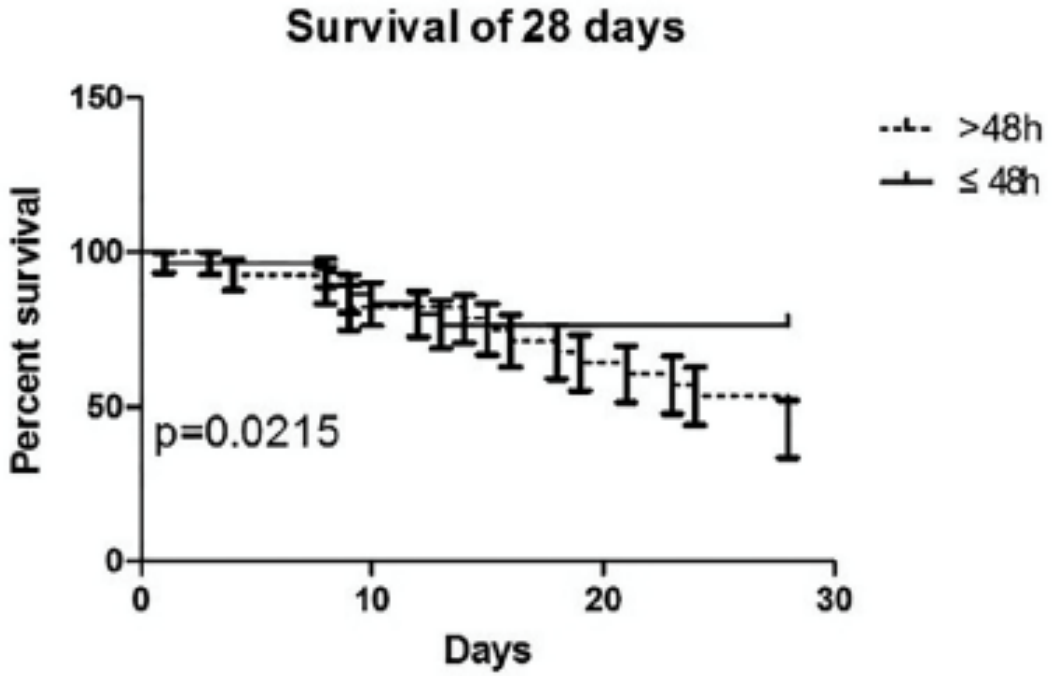


Fig. 1. A. Dose of IVIG B. Time of IVIG C. Hospital length of stay D. ICU length of stay.



https://doi.org/10.1016/j.jinf.2020.03.044

Clinical Efficacy of Intravenous Immunoglobulin Therapy in Critical Patients with COVID-19: A Multicenter Retrospective Cohort Study

	Total (N=174)	IVIG>7d (N=16)	IVIG≤7d (N=158)	P value
Primary outcomes N(%)				
28-day mortality	22(13%)	3(19%)	19(12%)	0.441
60-day mortality	33(19%)	7(44%)	26(17%)	0.008
Secondary outcome，median(IQR)				
In-hospital days	23.5(16.0-33.0)	31.0(23.0-39.8)	22.0(16.0-32.0)	0.025
Total course of disease [a]	31.0(23.0-39.0)	41.5(31.0-49.0)	30.0(23.0-38.0)	0.005

[a] Total course of disease：Time from illness onset to death or discharge, days

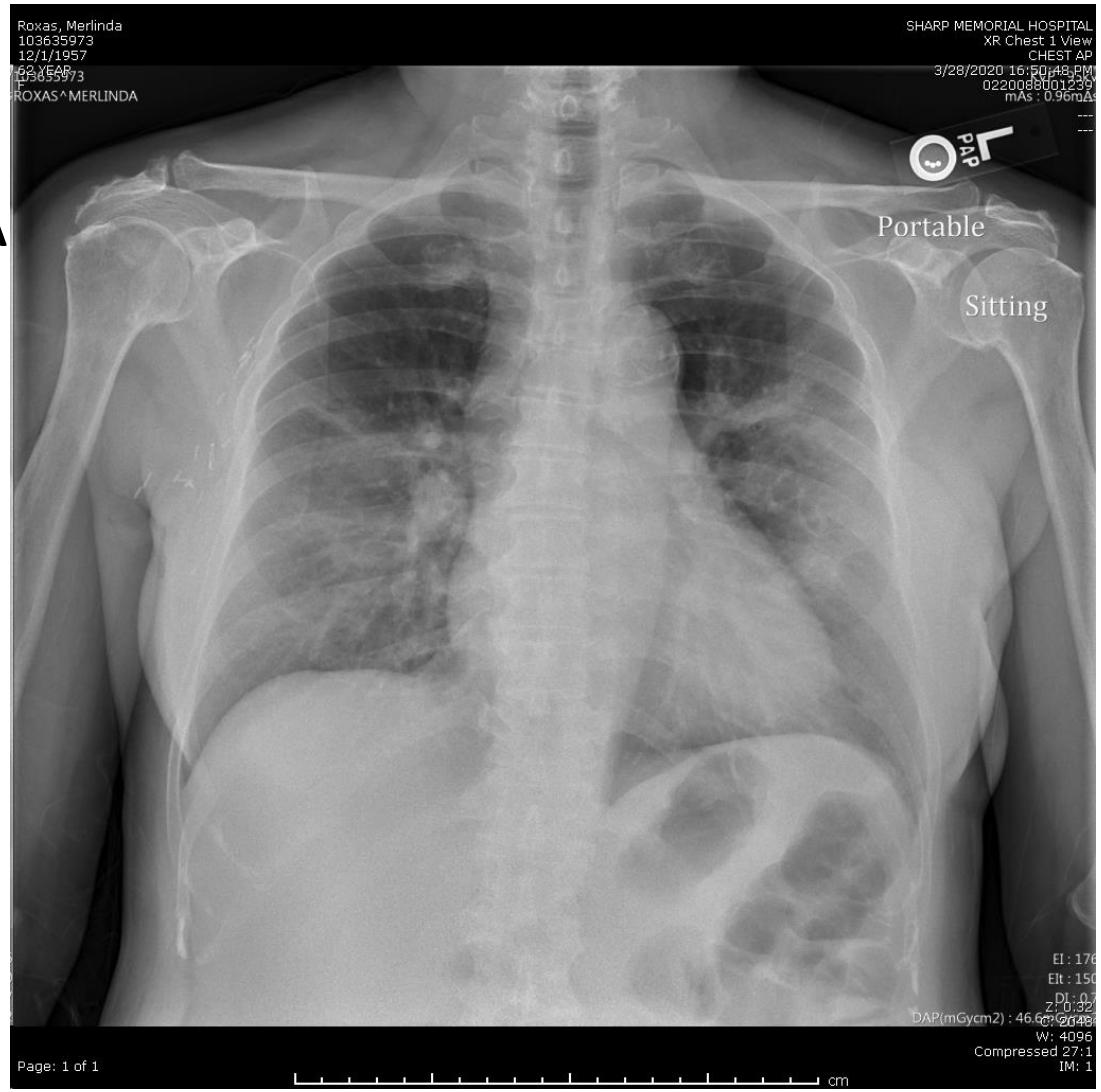
	Critical type IVIG>15g/d (N=40)	IVIG≤15g/d (N=31)	P value
Primary outcomes N(%)			
28-daymortality	5(13%)	14(45%)	0.002
60-daymortality	9(23%)	21(68%)	<0.001
Secondary outcome，median(IQR)			
In-hospital days	28.0 (18.3-36.0)	16.0 (7.0-33.0)	0.011
Total course of disease [a]	35.5 (27.342.5)	26.0 (14.0-47.0)	0.034

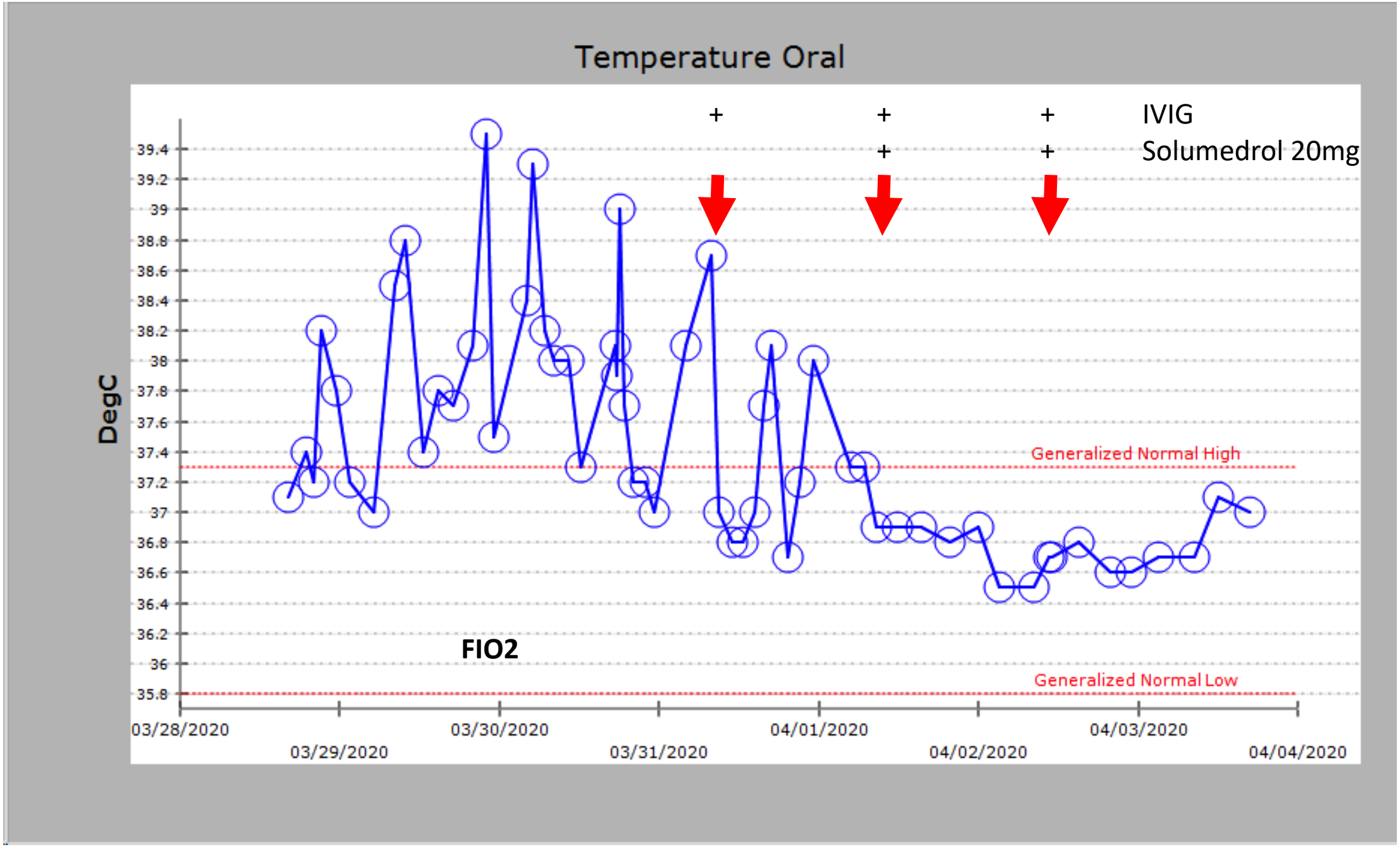
Shao et al. https://doi.org/10.1101/2020.04.11.20061739.

COVID IVIG Patient 0

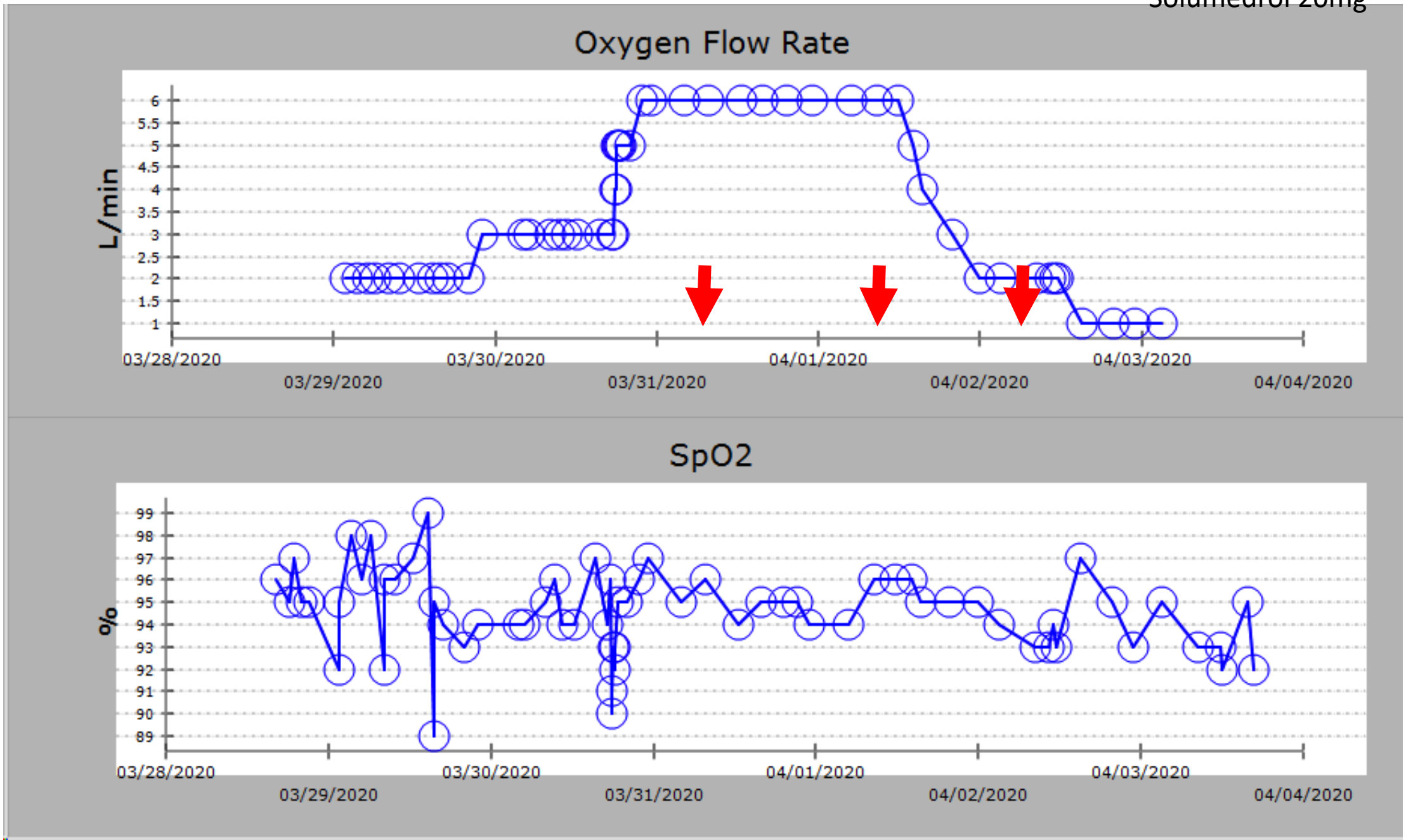
- 60s F DM, hypertension, h/o breast CA
  - Charlson Score 3
- 5 days cough, fever, increase SOB
- +COVID-19
- Admitted 3/28/20

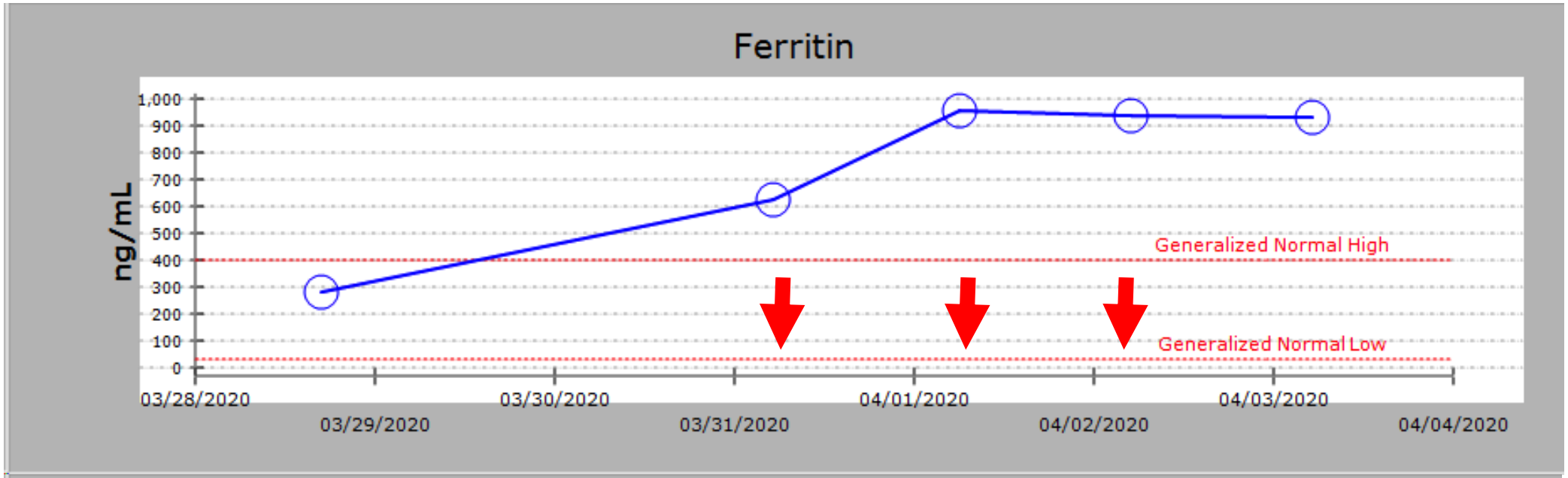
- ID consulted 3 days into floor stay

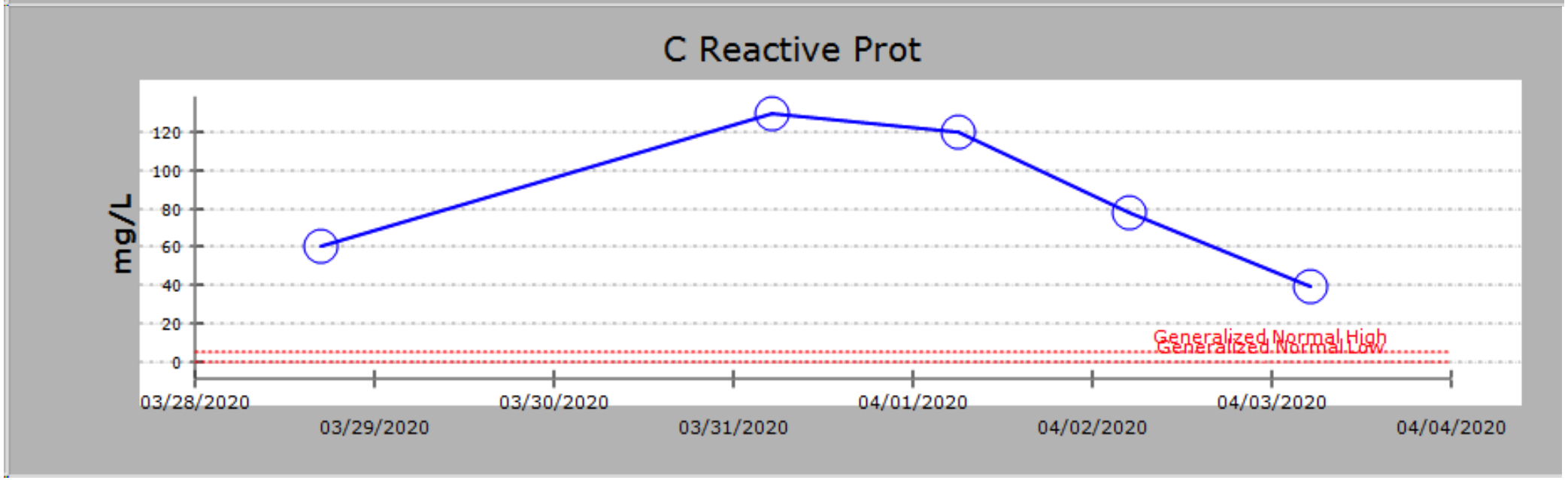



Temperature Oral
+
+
+
IVIG
+
+
Solumedrol 20mg
DegC
39.4
39.2
39
38.8
38.6
38.4
38.2
38
37.8
37.6
37.4
37.2
37
36.8
36.6
36.4
36.2
36
35.8
Generalized Normal High
FIO2
Generalized Normal Low
03/28/2020
03/29/2020
03/30/2020
03/31/2020
04/01/2020
04/02/2020
04/03/2020
04/04/2020

+	+	+	IVIG
	+	+	Solumedrol 20mg

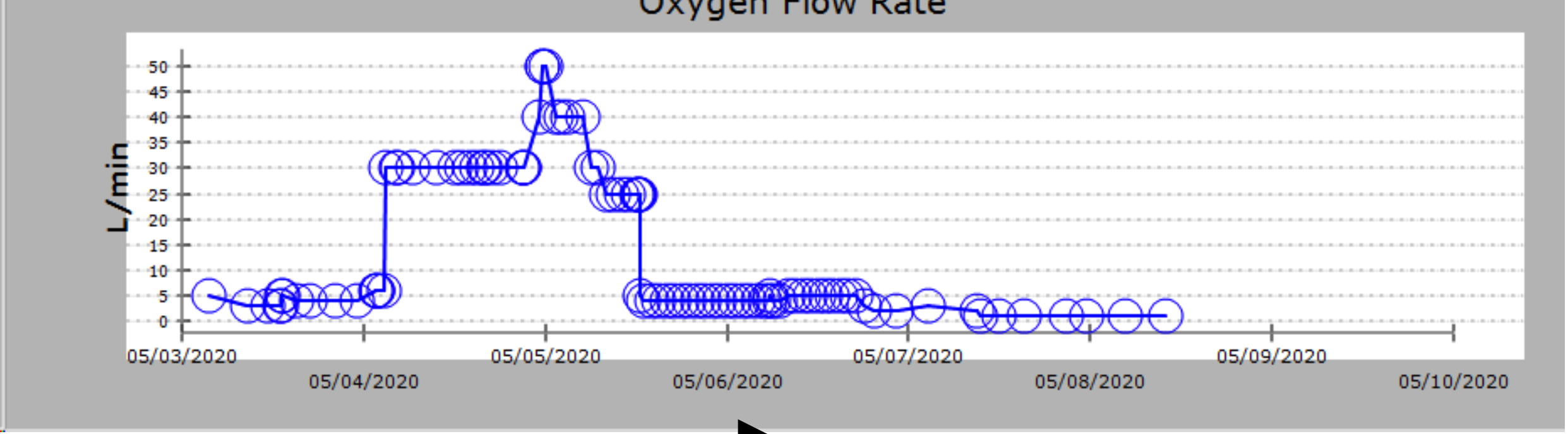


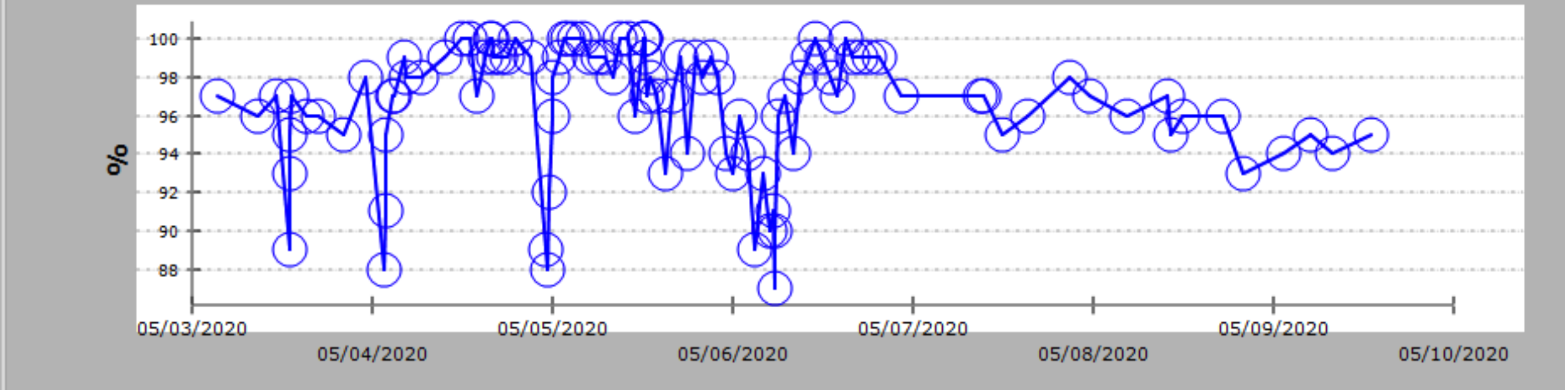

Ferritin
ng/mL
1,000
900
800
700
600
500
400
300
200
100
0
Generalized Normal High
Generalized Normal Low
03/28/2020
03/29/2020
03/30/2020
03/31/2020
04/01/2020
04/02/2020
04/03/2020
04/04/2020


C Reactive Prot
mg/L
120
100
80
60
40
20
0
Generalized Normal High
Generalized Normal Low
03/28/2020
03/29/2020
03/30/2020
03/31/2020
04/01/2020
04/02/2020
04/03/2020
04/04/2020

IVIG Sharp Study-Status Update 5/12/20

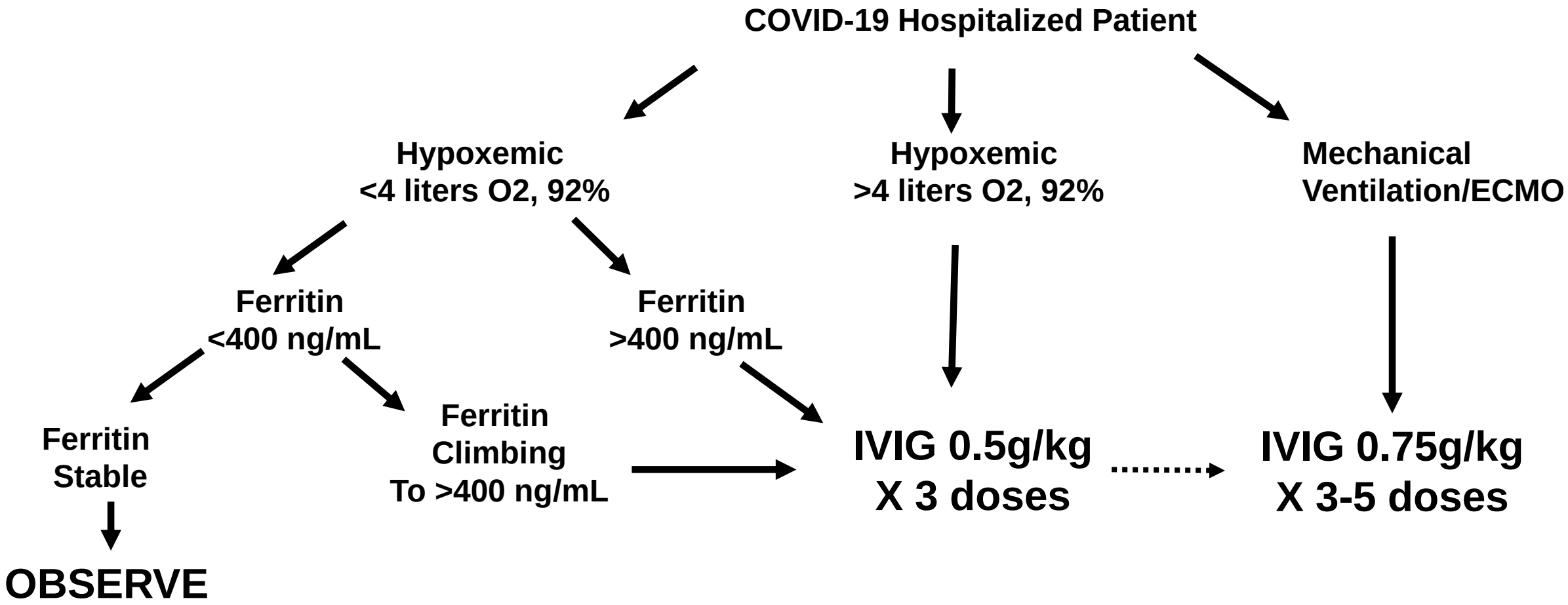
- Randomized Open Label Pilot, N=20 (10/arm)
- Patients +COVID $\geq$ 4 liters O_2 for sat $\geq$ 92%, not on ventilation
- IVIG 0.5 g/kg qd x 3 days, solumedrol 0.5 mg/kg iv x 1 30 min prior
- Endpoints: Prevention of MV, Days on O_2, Hospital Days
- Enrollment began 5/1/2020
- 12 patients from SGH, SMH; 8 completed regimen, 4 new cases last 48 hr
  - 6 IVIG (Charlson Scores 1,1,2,2,2,5)
  - 6 SOC (Charlson Scores 0,0,1,2,4,4)
- 3 pt randomized to IVIG, 1 SOC while in ICU, others were on the floor
- IVIG: 0 intubated, 1 discharged home, 1 ICU, 4 Floor
  - 4 were in ICU at some point
- SOC: 3 intubated ICU, 1 ICU non-intubated, 1 Floor, 1 discharged home


Oxygen Flow Rate
L/min
50
45
40
35
30
25
20
15
10
5
0
05/03/2020
05/04/2020
05/05/2020
05/06/2020
05/07/2020
05/08/2020
05/09/2020
05/10/2020


SpO2
%
100
98
96
94
92
90
88
05/03/2020
05/04/2020
05/05/2020
05/06/2020
05/07/2020
05/08/2020
05/09/2020
05/10/2020

Proposed IVIG Going Forward?

- **Discussions between Octapharma and FDA began last week**
- **Our proposed scheme**



CURRENT COVID STUDY OPTIONS

STAGE 1	STAGE 2	STAGE 3
Fever, Cough, Diarrhea, Pharyngitis	SOB Hypoxia Lung Infiltrates	ARDS/SIRS Shock Heart Failure
Up to 3 liters O2	*4+ liters O2, non-intubated*	*Intubated*

(Remdesivir) →

Losartan Open Label Trial*
(Angiotensin Receptor Block, Open Label)
12.5mg q12 d1, 25 mg q12 d2, 50 mg po q12 d3-10 →

IVIG 0.5 g/kg IV QD x 3
Solumedrol 20-40 mg iv 30-60 min prior

Tociluzumab (Actemra)* →
(IL-6 Blocker, Randomized Placebo)
8mg/kg x 1

Convalescent Plasma from COVID19 Patients →

Conclusions

- Clinical guidance on the optimal management of COVID will take months to years to trickle down to clinicians by the usual channels
- While anti-virals offers some promise, the real battle of severe COVID-19 disease appears to be in the realm of immunology
- Sharp Healthcare has taken a very active response to the COVID pandemic by recruiting established trials and even designing its own
- Patients may be seeing benefits of some interventions
- **DESPITE TENDENCIES FOR CLINICIANS TO WAIT BEFORE IMPLEMENTING PLAN B, *EARLY ACTION APPEARS TO BE CRITICAL* TO HARNESS POTENTIAL BENEFITS OF ADJUNCTIVE TREATMENT**
- Diminishing returns for intervention once a patient ion the ventilator

"Quick! Go buy some batteries for the smoke detector before it's too late!"

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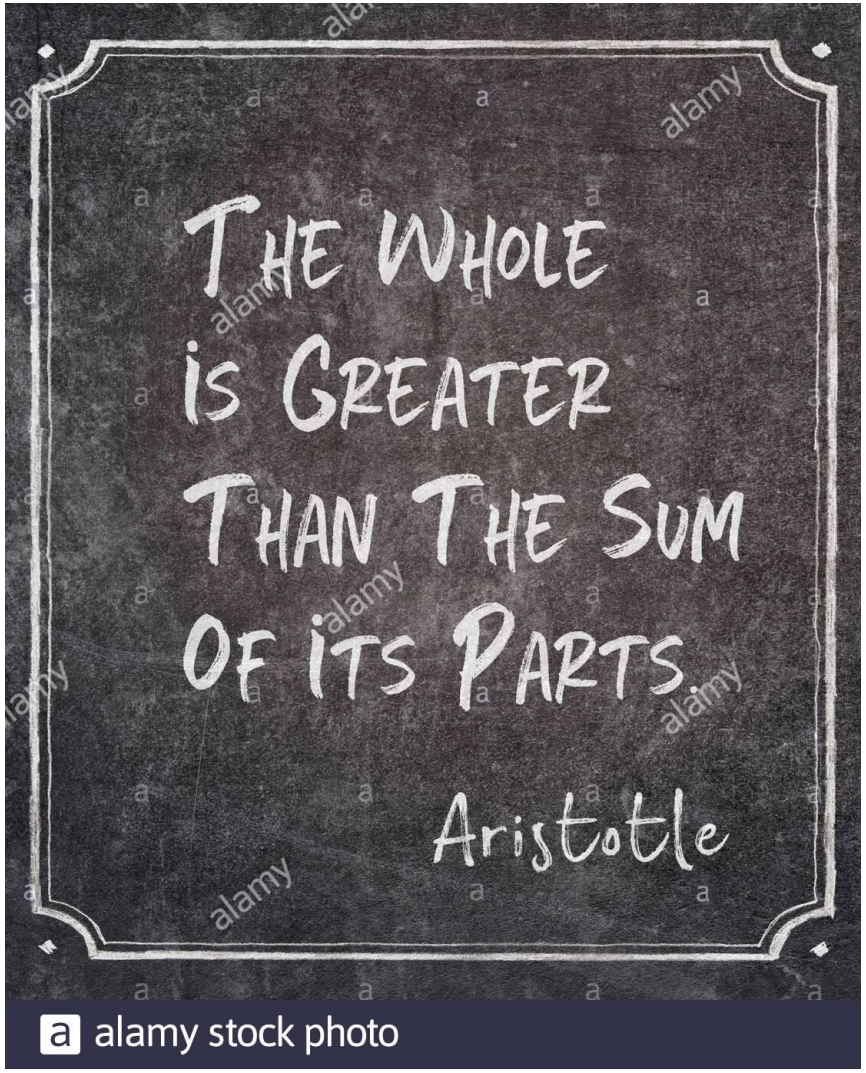
THE WHOLE
IS GREATER
THAN THE SUM
OF ITS PARTS.
Aristotle
alamy stock photo