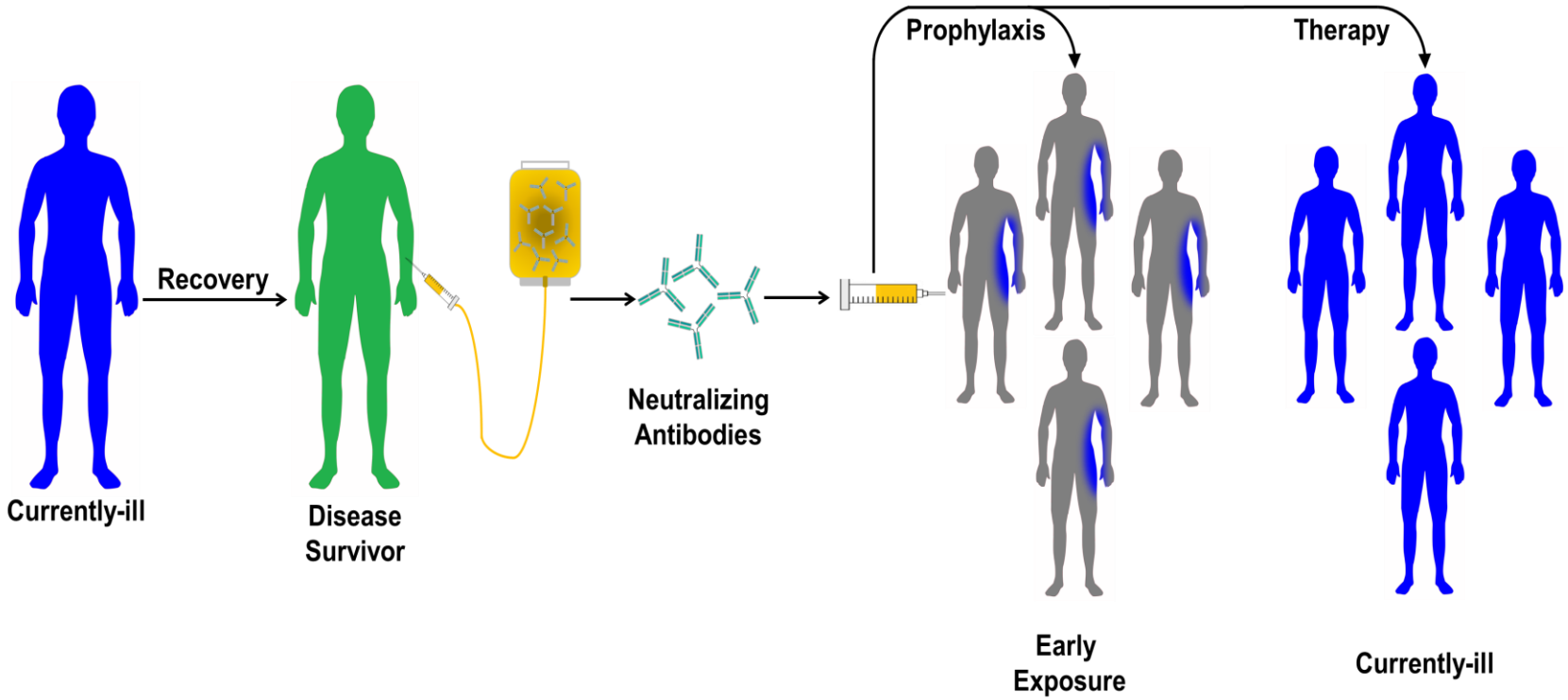
Convalescent Plasma for COVID-19

Michael J. Joyner, MD

Arturo Casadevall, MD/PHD

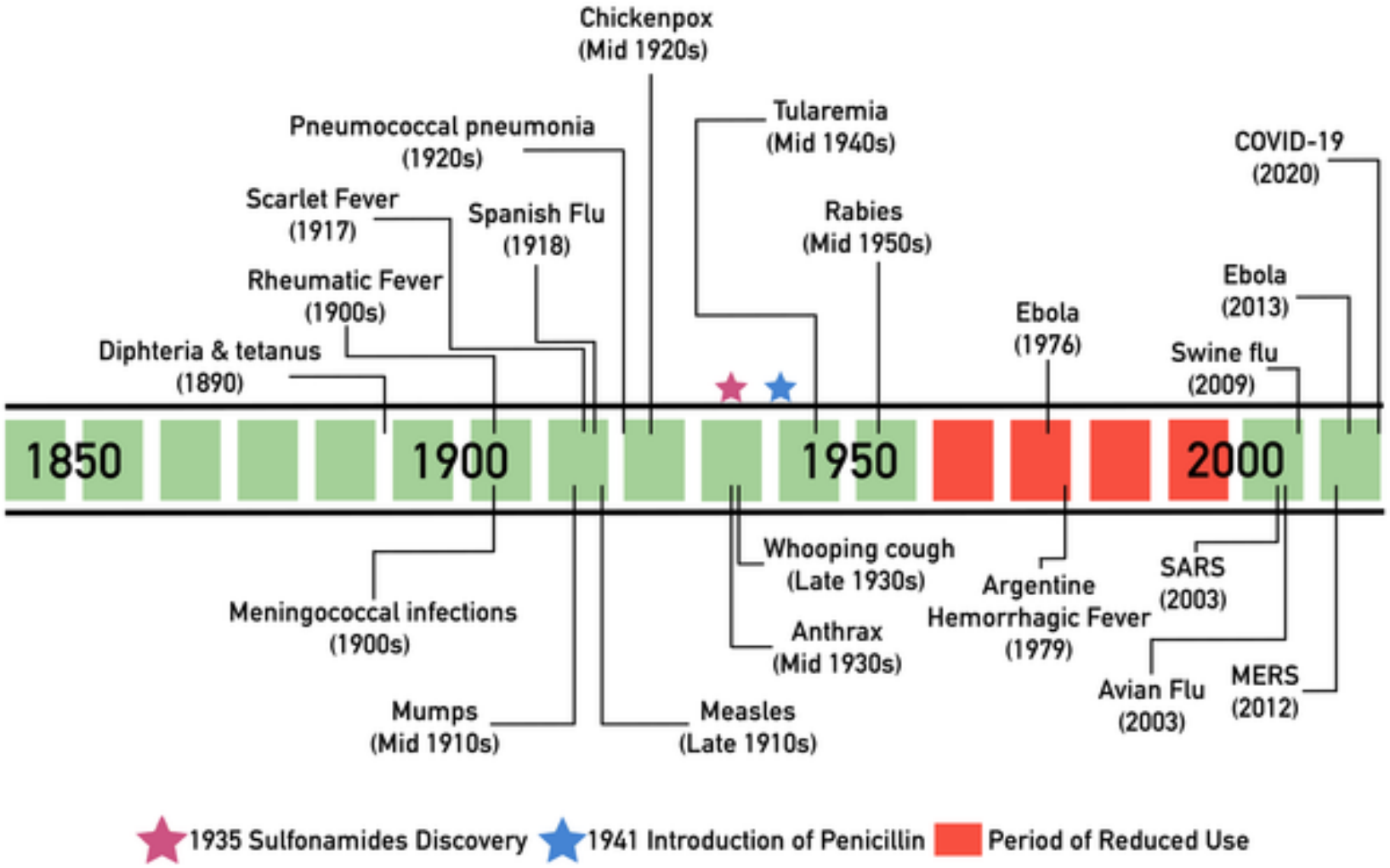
Updated 12/31/22

CP – Conceptual Model



Adapted from Casavedall & Pirofski 2020

Notable Historic Uses of Antibody TX Against Infectious Diseases



Montelongo-Jauregui et al PlOS Path 2020

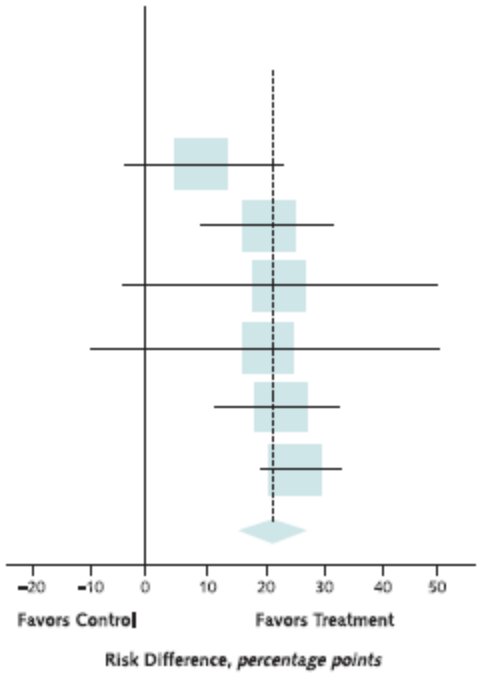
Meta Analysis 1918

Annals of Internal Medicine | Review

Meta-Analysis: Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

Figure 2. Absolute risk differences in mortality among patients treated with convalescent blood products and controls.

Study (Reference)	Mortality Rate, *n/n (%)*		Risk Difference (95% CI), *percentage points*
	Treatment Group	Control Group	
Stoll (17)	25/56 (45)	201/379 (53)	8 (–6 to 22)
O'Malley and Hartman (18)*	3/46 (7)	28/111 (25)	19 (8 to 29)
Ross and Hund (19, 20)	6/28 (21)	9/21 (43)	21 (–5 to 47)
Kahn (21)	12/25 (48)	12/18 (67)	19 (–11 to 48)
Gould (22)	2/30 (7)	82/290 (28)	22 (11 to 32)
McGuire and Redden (23, 24)*	6/151 (4)	120/400 (30)	26 (21 to 31)
Overall	54/336 (16)	452/1219 (37)	21 (15 to 27)



Luke et al Ann Int Med 2006

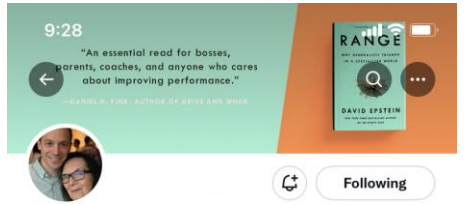
Horace Hodes on Time to Treatment: Antitoxin & Diphtheria (Nelson's Pediatrics, 1946)

INFLUENCE OF TIME OF INJECTION OF ANTITOXIN ON MORTALITY

Time of Injection after Onset	Patients	Died	Mortality, Per Cent
1st day	355	1	0.27
2d day	1,018	17	1.67
3d day	1,509	57	3.77
4th day	720	82	11.39
Later	469	119	25.37
TOTAL	4,071	276	6.77

History Shows For Antibody Therapy– *Early Use, High Titer Essential!*

Twitter Saves Lives?
WSJ February 27, 2020



OPINION | COMMENTARY

How a Boy's Blood Stopped an Outbreak

A school physician's approach to measles in 1934 has lessons for the coronavirus.

By Arturo Casadevall

Feb. 27, 2020 6:48 pm ET

It isn't every day that a school physician's work gets published in a medical journal. But it happened in 1934, and the story contains a lesson for the coronavirus epidemic.

Early Signals of Efficacy 2020-2021

- ***Experiments of Nature?***
- ***Dose Response Relationship Between Abs vs Outcomes?***
- ***Matched Control Data?***
- ***Real World Data?***

Experiment of Nature Patients

- Proof of concept
- Smoldering cases
- Replacement therapy
- Ethical to wait for trials?
- Epistemology in a Pandemic?

Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 improved with convalescent plasma

Haoli Jin, MD, PhD[a,*], James C. Reed, MD, MHS[b,*], Sean T.H. Liu, MD, PhD[c,*], Hsi-en Ho, MD[a], Joao Pedro Lopes, MD[a], Nicole B. Ramsey, MD, PhD[a], Omar Waqar, MD[a], Farah Rahman, DO[c], Judith A. Aberg, MD[c], Nicole M. Bouvier, MD[c,d], and Charlotte Cunningham-Rundles, MD, PhD[a]; The Mount Sinai Health System Convalescent Plasma Team†

Clinical Implications

- We describe 3 patients with X-linked agammaglobulinemia with coronavirus disease 2019 who failed supportive treatment but recovered after receiving convalescent plasma.

J Allergy Clin Immunol Pract 2020

Patients With Deficient Antibody Responses:
Dramatic Temporal Associations Frequently Noted

Panel: Anecdotal statements supporting the efficacy of convalescent plasma

- In the present case, the rapid clinical improvement followed by viral clearance after administration of hyperimmune plasma argue that passively transferred antibodies played a key role in COVID-19 recovery.[23]
- One day later [after convalescent plasma transfusion], the patient was afebrile for the first time in 3 weeks and had improved energy.[13]
- On day 122 (of illness), due to worsening symptoms, the patient was given convalescent plasma. He defervesced within 24 hours and was discharged nine days later.[31]
- …she was transferred to the intensive care unit for intubation. In the meantime…the patient received convalescent therapy instead and did not undergo intubation following the immediate improvement after plasma therapy infusion.[52]
- Based on the lack of clinical improvement…we transfused 1 unit of convalescent plasma…Importantly, the patient did not receive any other treatment potentially having an effect on the course of COVID-19…After transfusion of the convalescent plasma, the patient showed a dramatic clinical improvement, became asymptomatic, and was discharged home only 2 days later.[36]
- The patient was discharged after 2 weeks [convalescent plasma transfusion] with a dramatic response to therapy. Both newborns had no COVID-19 symptoms and negative PCR results.[54]
- 36 hours after [convalescent plasma] transfusion, the patient was discharged from the hospital reporting that he felt improved.[53]
- COVID-19 antibody testing showed complete lack of COVID-19 antibodies…She received 2 units of convalescent plasma…with rapid improvement in oxygen requirements. She was weaned off high-flow nasal cannula within 48 h and within a few days was discharged home in stable condition.[32]
- Intravenous convalescent plasma…was administered…Her health condition quickly improved, allowing [withdrawal of oxygen supplementation]…[23]
- Within a day of receiving her first transfusion of convalescent plasma, she reported improvement in shortness of breath and cough, had fever resolution, and decreasing oxygen requirements.[24]
- She received COVID convalescent plasma…She showed remarkable improvement [the next day]…with reduction of respiratory rate…and oxygen requirements.[21]
- …the patient received a transfusion of convalescent plasma…one day later her [arterial oxygen saturation] increased to 98%...clinical symptoms and pathological criteria improved rapidly within 3 days.[29]
- Within hours after receiving the convalescent plasma… [The patient's] fever started going down. Days later, his breathing and kidney function improved.[45]
- [The patient]…received a transfusion of convalescent plasma…He is recovering at home after spending two and a half weeks in a coma fighting for his life...[44]
- …received 217 mL of convalescent plasma…24 hours later, his heart rate had improved to 60-70 bpm with less frequent premature atrial contractions and premature ventricular contractions and he was breathing comfortably on room air…36 hours after transfusion the patient was discharged from the hospital…[53]
- Stagnancy in the patient's evolution, as represented by the lack of response to any of the treatments dispensed....we administered on day 23 COVID-19 convalescent plasma...after 24 hours of infusion, fever ceased without subsequent reappearance and with progressive improvement of asthenia.[14]

Senefeld et al Transfusion 2021

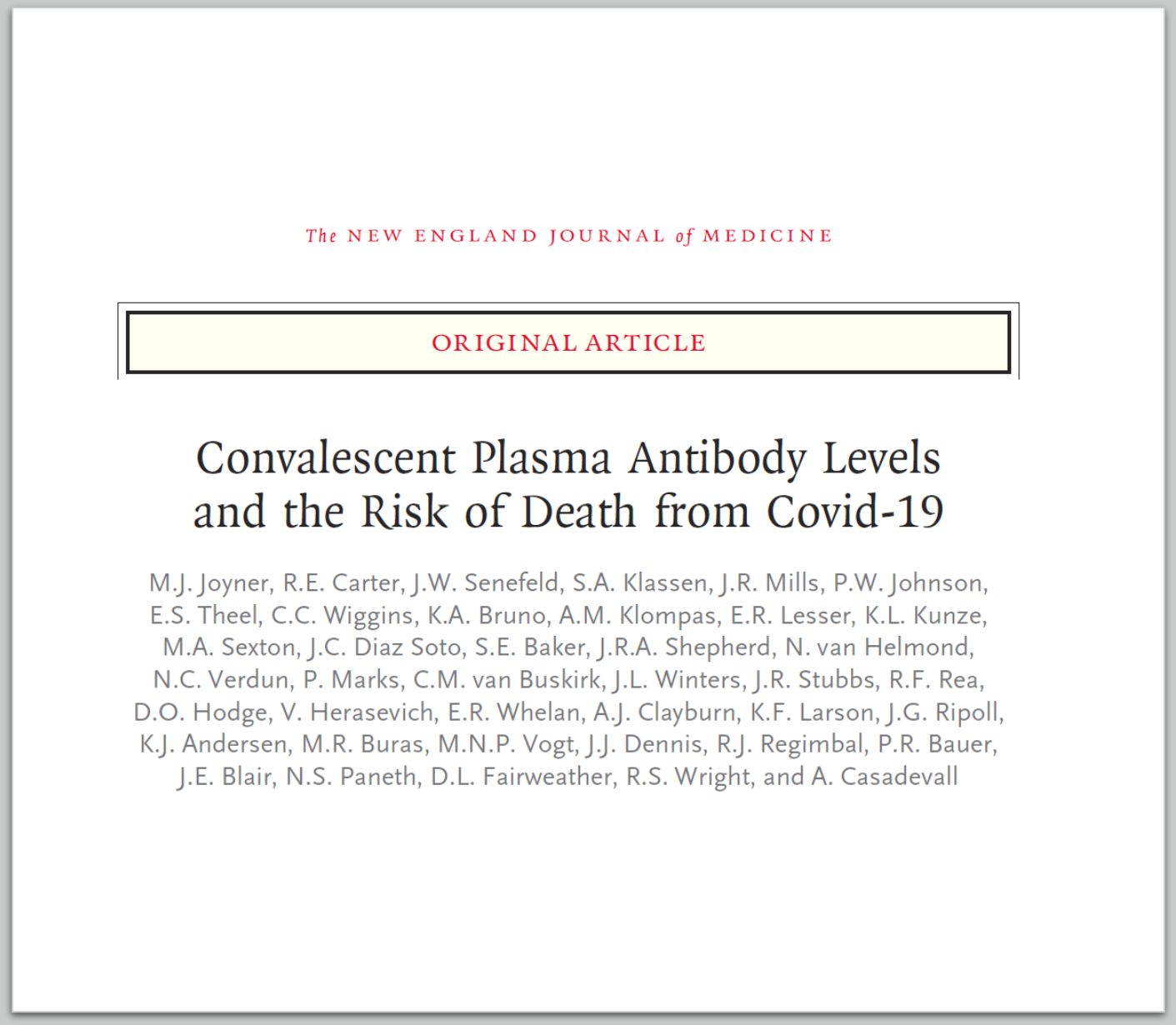
US Expanded Access Program - 2020

- **3/30** FDA contacts Joyner/Mayo about EAP
- **4/1** Mayo IRB approves EAP & is central IRB
- **4/1** ***Enrollment Cap set at 5000,↑ many times***
- **4/3** Website roll-out Including:
  - Site, MD, and patient enrollment
  - Workflow
  - Navigator and FAQ functions
  - Case report tools
  - Full-service communication center
- **4/6** **1st patient transfused**
- **8/24** **Emergency Use Authorization (EUA) issued**
- **8/31** ***Enrollment Stops – 100,000 patients treated all over the US, ~2500 mostly community hospitals, high patient diversity***

3 Goals
Safety
Access
Efficacy!

January 2021

- Dose Response Relationship
- Early use
- Confirms pre WW2 insights about antibody therapy
- Pre-print available in August of 2020
- 5 months
  - ***Access***
  - ***Safety***
  - ***Efficacy***



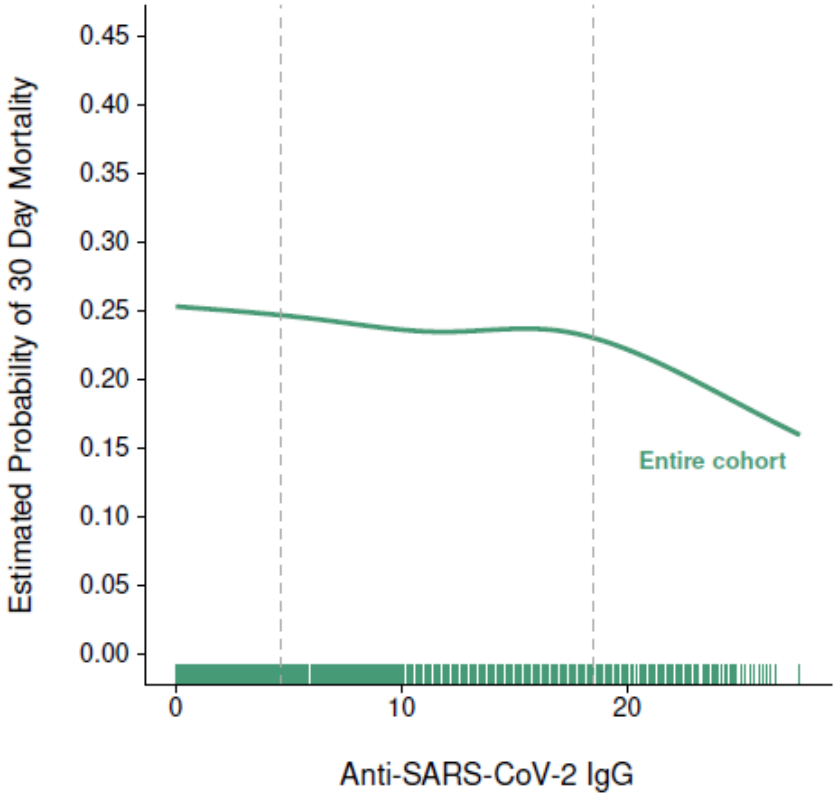
The NEW ENGLAND JOURNAL of MEDICINE

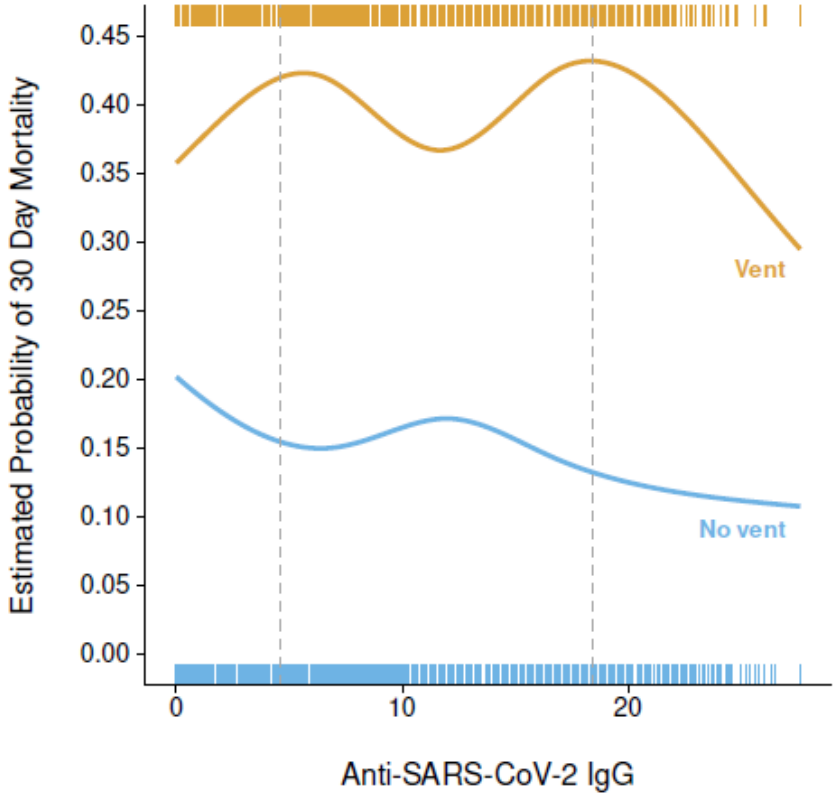
ORIGINAL ARTICLE

Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

M.J. Joyner, R.E. Carter, J.W. Senefeld, S.A. Klassen, J.R. Mills, P.W. Johnson, E.S. Theel, C.C. Wiggins, K.A. Bruno, A.M. Klompas, E.R. Lesser, K.L. Kunze, M.A. Sexton, J.C. Diaz Soto, S.E. Baker, J.R.A. Shepherd, N. van Helmond, N.C. Verdun, P. Marks, C.M. van Buskirk, J.L. Winters, J.R. Stubbs, R.F. Rea, D.O. Hodge, V. Herasevich, E.R. Whelan, A.J. Clayburn, K.F. Larson, J.G. Ripoll, K.J. Andersen, M.R. Buras, M.N.P. Vogt, J.J. Dennis, R.J. Regimbal, P.R. Bauer, J.E. Blair, N.S. Paneth, D.L. Fairweather, R.S. Wright, and A. Casadevall

Antibody Dose Response Seen in EAP Ortho Vitros Qualitative Assay

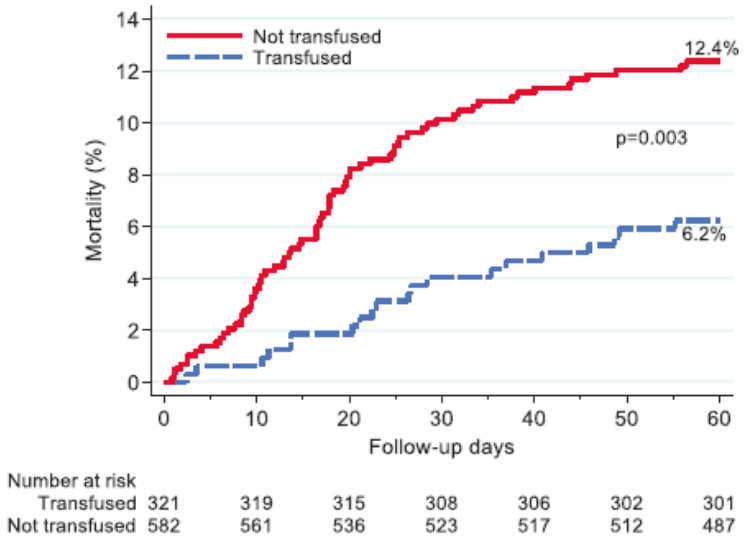




Joyner et al NEJM 2021

Houston Matched Control Data Oct 2020

Value of Preprints!

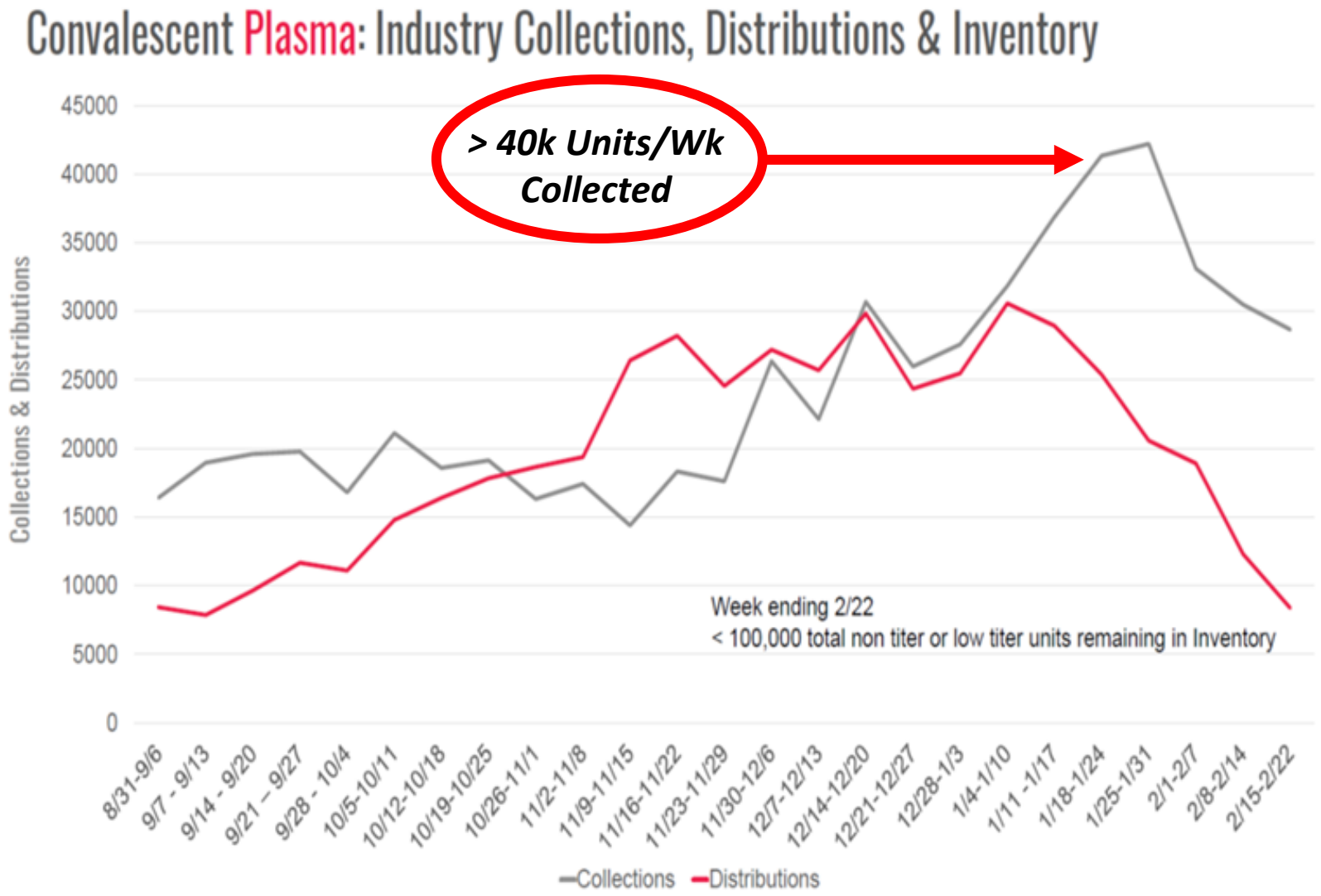


Early transfusion of a large cohort of COVID-19 patients with high titer anti-SARS-CoV-2 spike protein IgG convalescent plasma confirms a signal of significantly decreased mortality

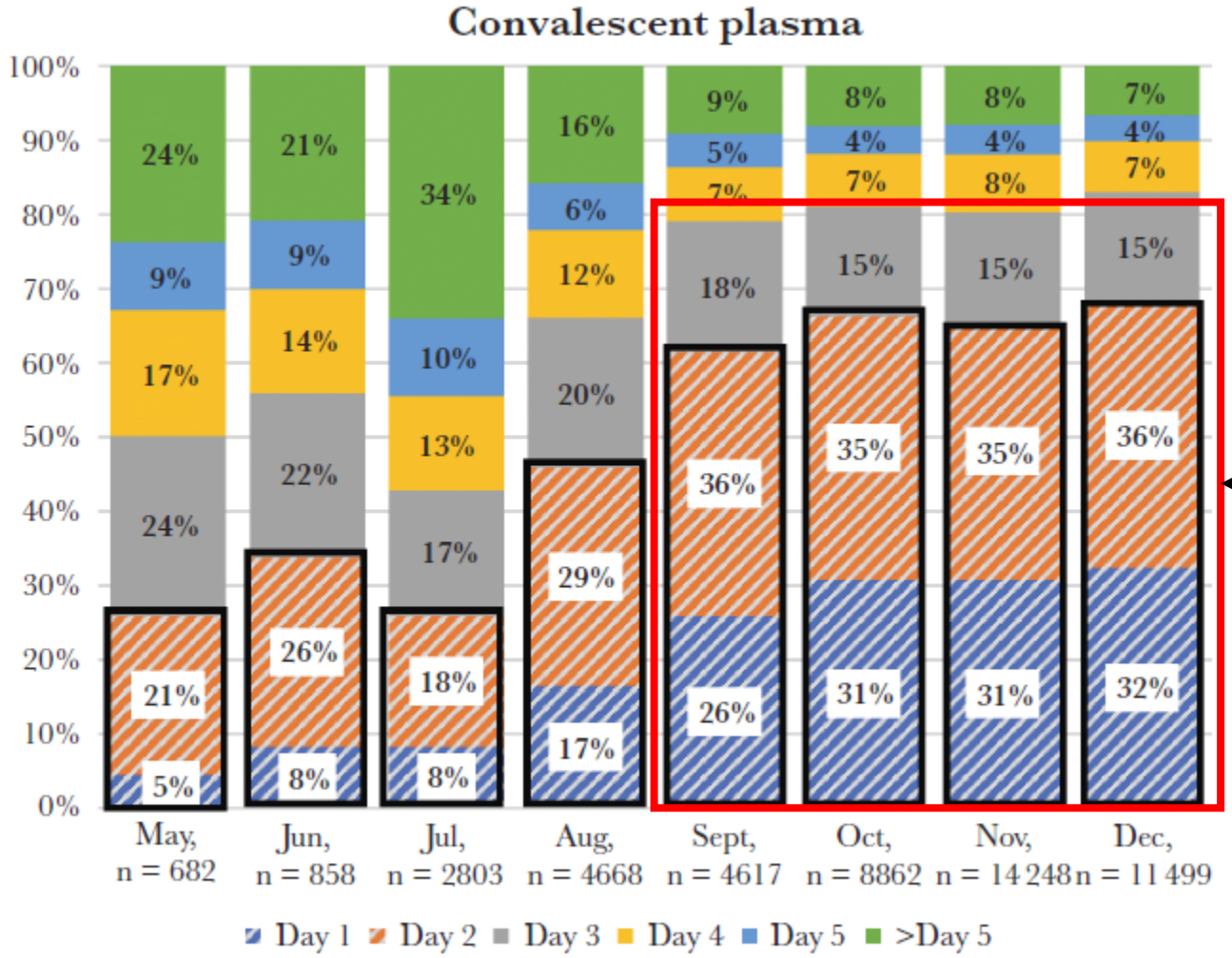
Eric Salazar[a,b], Paul A. Christensen[a], Edward A. Graviss[a,c], Duc T. Nguyen[c], Brian Castillo[a], Jian Chen[a], Bevin Valdez Lopez[d], Todd N. Eagar[a,b], Xin Yi[a,b], Picheng Zhao[a], John Rogers[a], Ahmed Shehabeldin[a], David Joseph[a], Faisal Masud[e], Christopher Leveque[a], Randall J. Olsen[a,b,c], David W. Bernard[a,b], Jimmy Gollihar[f], and James M. Musser[a,b,c,#]

CP Used at Scale in the US

Sept 2020 – Feb 2021 CP Collections & Distributions



Fall 2020 Real World Clinicians Get It!
Early Use – High Titer

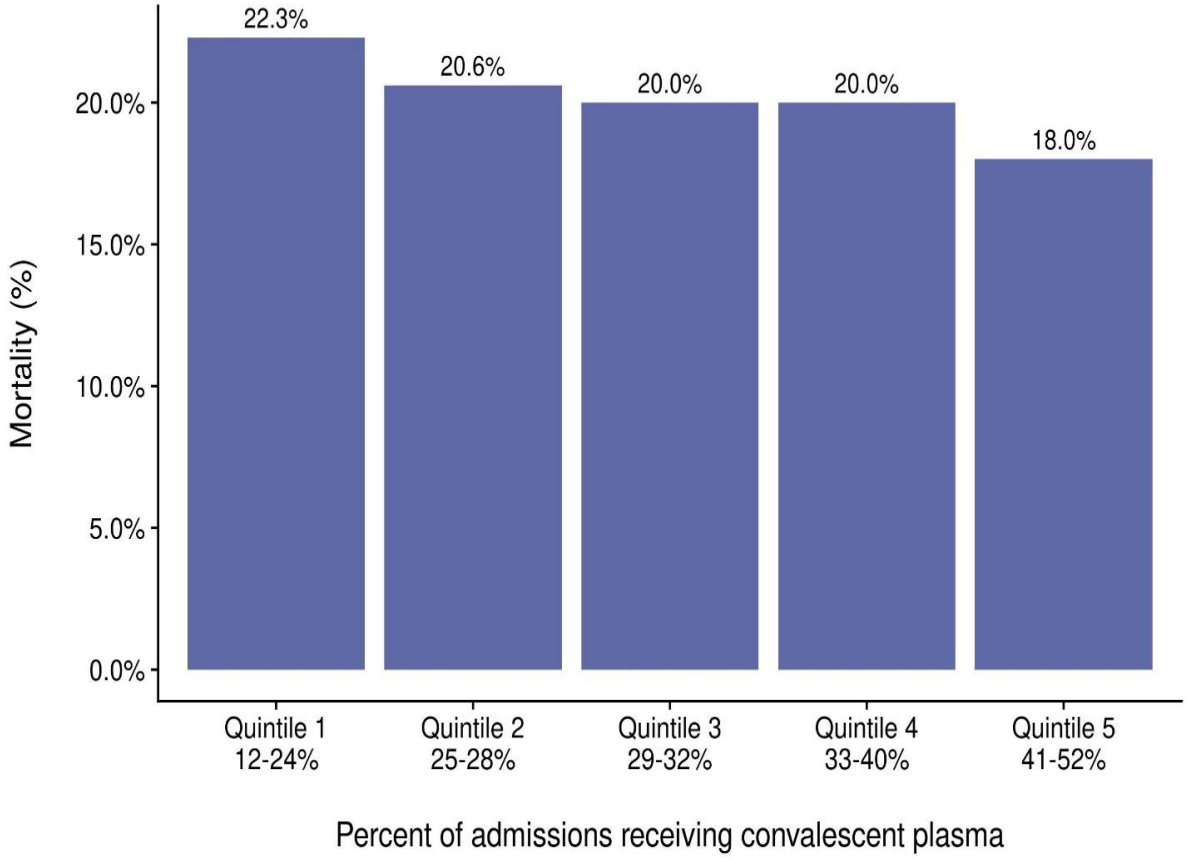


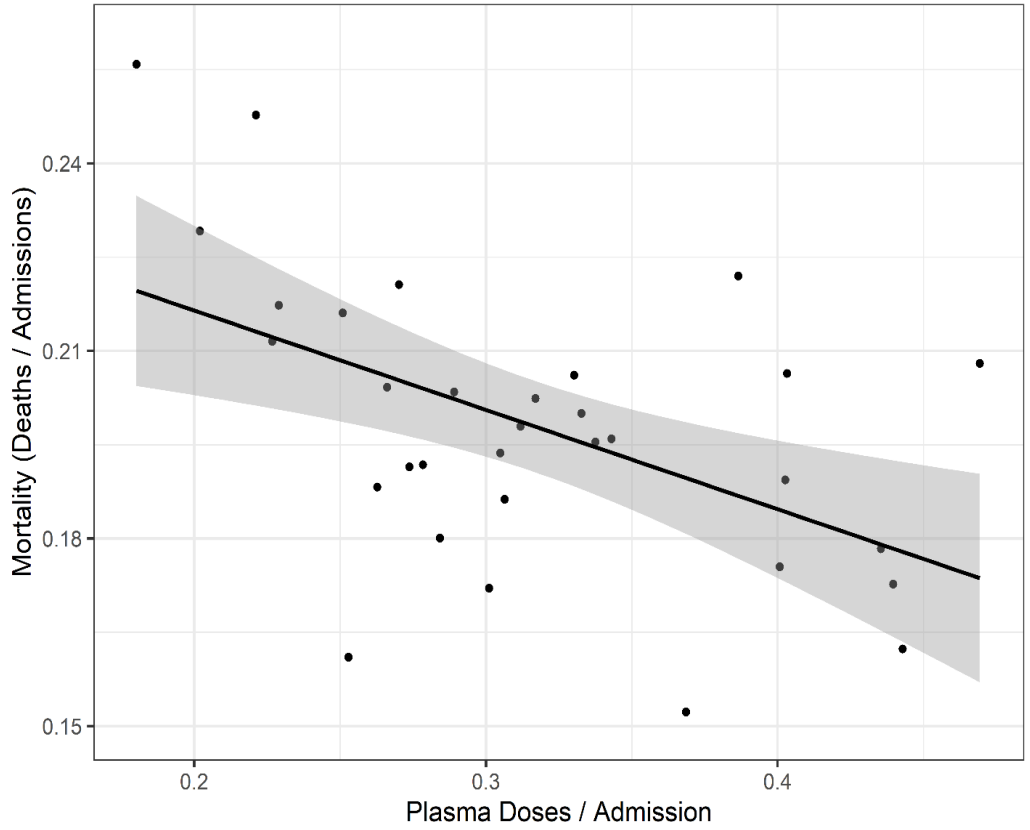
Early use of high titer plasma was happening!

Mozaffari et al 2021

RWD - Hospital Corp America: JCI 2021

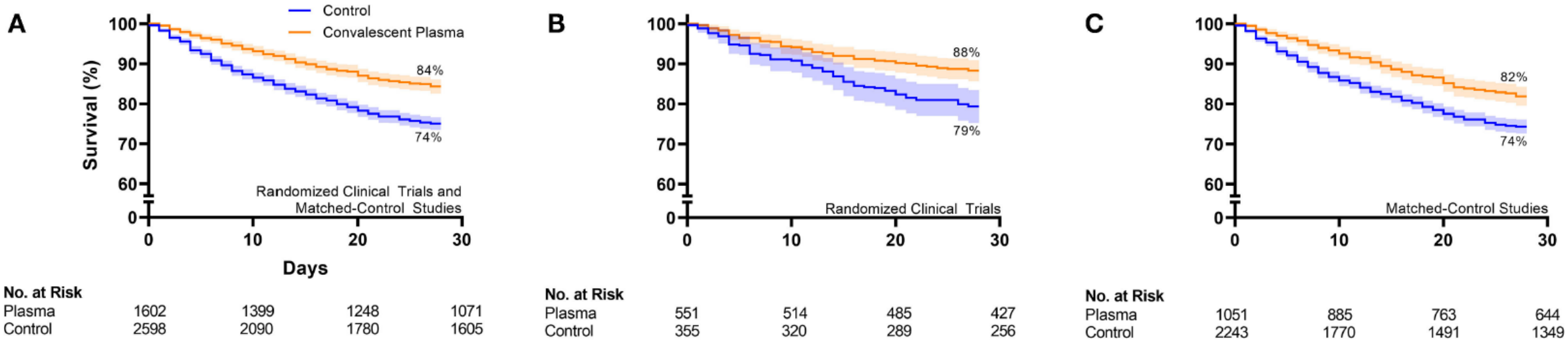
The Population Data Shows An Inverse Relationship Between Plasma Use & Mortality





Casadevall et al eLife 2021

2021: What Happens When You Aggregate Early K-M Curves?



Klassen et al Front Med 2021

By Fall/Winter of 2020-21 We Know:

1. CP was safe
2. High titer likely worked if given early
3. Clinicians using high titer in the real world
4. Especially promising in the immunocompromised

- ***No concerns about variants "yet"…***

2021 RECOVERY & The Valley of Death

- Large UK platform trial
- Late use
- No benefit of plasma
- Preprint over-interpreted
- Signals of efficacy in key use cases
- Methodological issues

Why did they continue to test late use when all other sources of data indicated early use a key?

Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial

*RECOVERY Collaborative Group**

Summary

Background Many patients with COVID-19 have been treated with plasma containing anti-SARS-CoV-2 antibodies. We aimed to evaluate the safety and efficacy of convalescent plasma therapy in patients admitted to hospital with COVID-19.

Methods This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. The trial is underway at 177 NHS hospitals from across the UK. Eligible and consenting patients were randomly assigned (1:1) to receive either usual care alone (usual care group) or usual care plus high-titre convalescent plasma (convalescent plasma group). The primary outcome was 28-day mortality, analysed on an intention-to-treat basis. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Findings Between May 28, 2020, and Jan 15, 2021, 11558 (71%) of 16287 patients enrolled in RECOVERY were eligible to receive convalescent plasma and were assigned to either the convalescent plasma group or the usual care group. There was no significant difference in 28-day mortality between the two groups: 1399 (24%) of 5795 patients in the convalescent plasma group and 1408 (24%) of 5763 patients in the usual care group died within 28 days (rate ratio 1·00, 95% CI 0·93–1·07; p=0·95). The 28-day mortality rate ratio was similar in all prespecified subgroups of patients, including in those patients without detectable SARS-CoV-2 antibodies at randomisation. Allocation to convalescent plasma had no significant effect on the proportion of patients discharged from hospital within 28 days (3832 [66%] patients in the convalescent plasma group *vs* 3822 [66%] patients in the usual care group; rate ratio 0·99, 95% CI 0·94–1·03; p=0·57). Among those not on invasive mechanical ventilation at randomisation, there was no significant difference in the proportion of patients meeting the composite endpoint of progression to invasive mechanical ventilation or death (1568 [29%] of 5493 patients in the convalescent plasma group *vs* 1568 [29%] of 5448 patients in the usual care group; rate ratio 0·99, 95% CI 0·93–1·05; p=0·79).

Interpretation In patients hospitalised with COVID-19, high-titre convalescent plasma did not improve survival or other prespecified clinical outcomes.

Published Online
May 14, 2021
https://doi.org/10.1016/
S0140-6736(21)00897-7

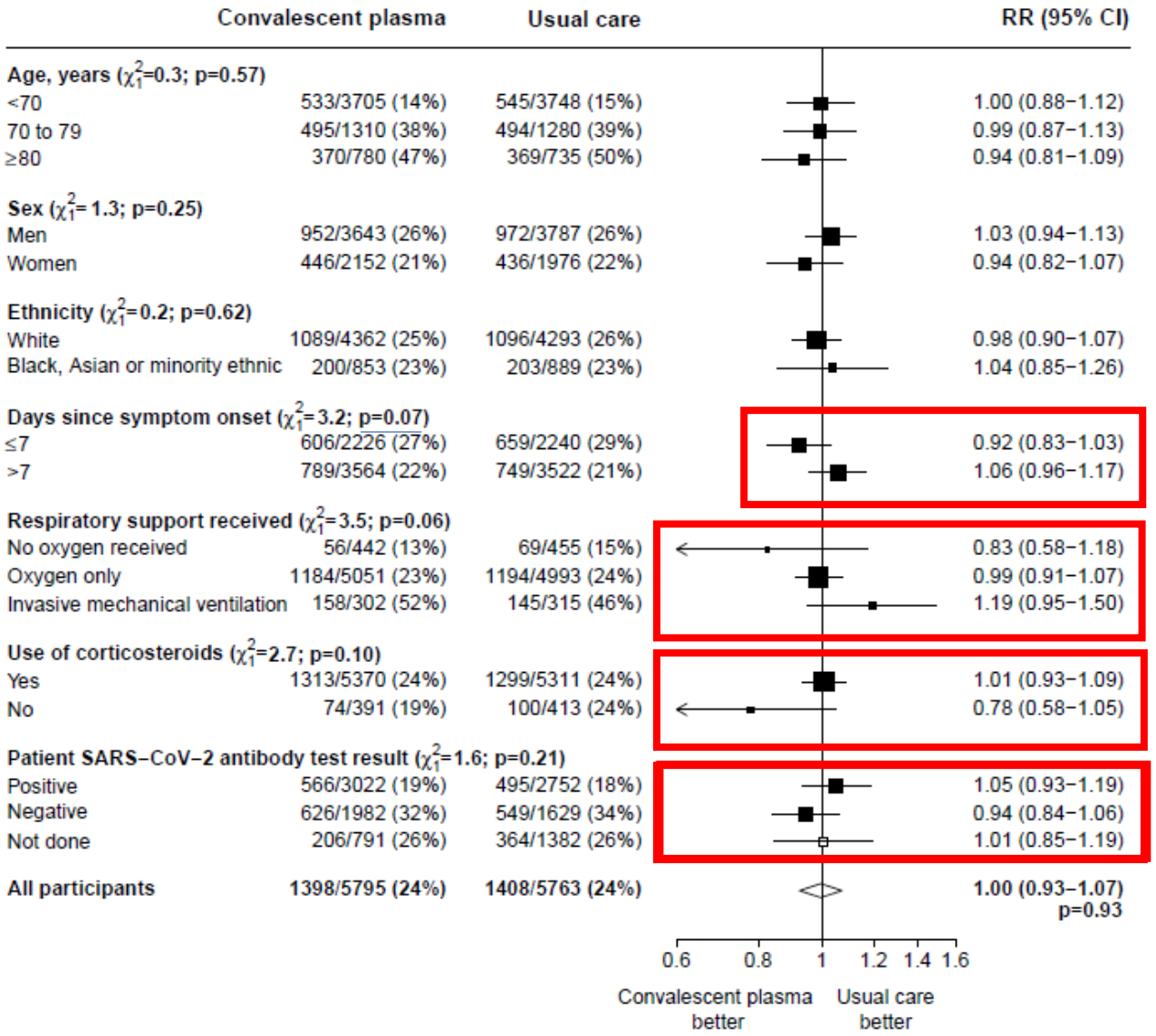
See Online/Comment
https://doi.org/10.1016/
S0140-6736(21)01064-3

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the RECOVERY trial is provided in the appendix (pp 2–28)

Correspondence to:
Prof Peter W Horby and
Prof Martin J Landray, RECOVERY
Central Coordinating Office,
Oxford OX3 7LF, UK
recoverytrial@ndph.ox.ac.uk

See Online for appendix

Recovery: Signals of Efficacy In Key Use Cases



Signals of efficacy

1. *Early tx p=0.07*
2. *No O2 p=0.06*
3. *No Steroids p=0.10*
4. *No Abs p=0.21*

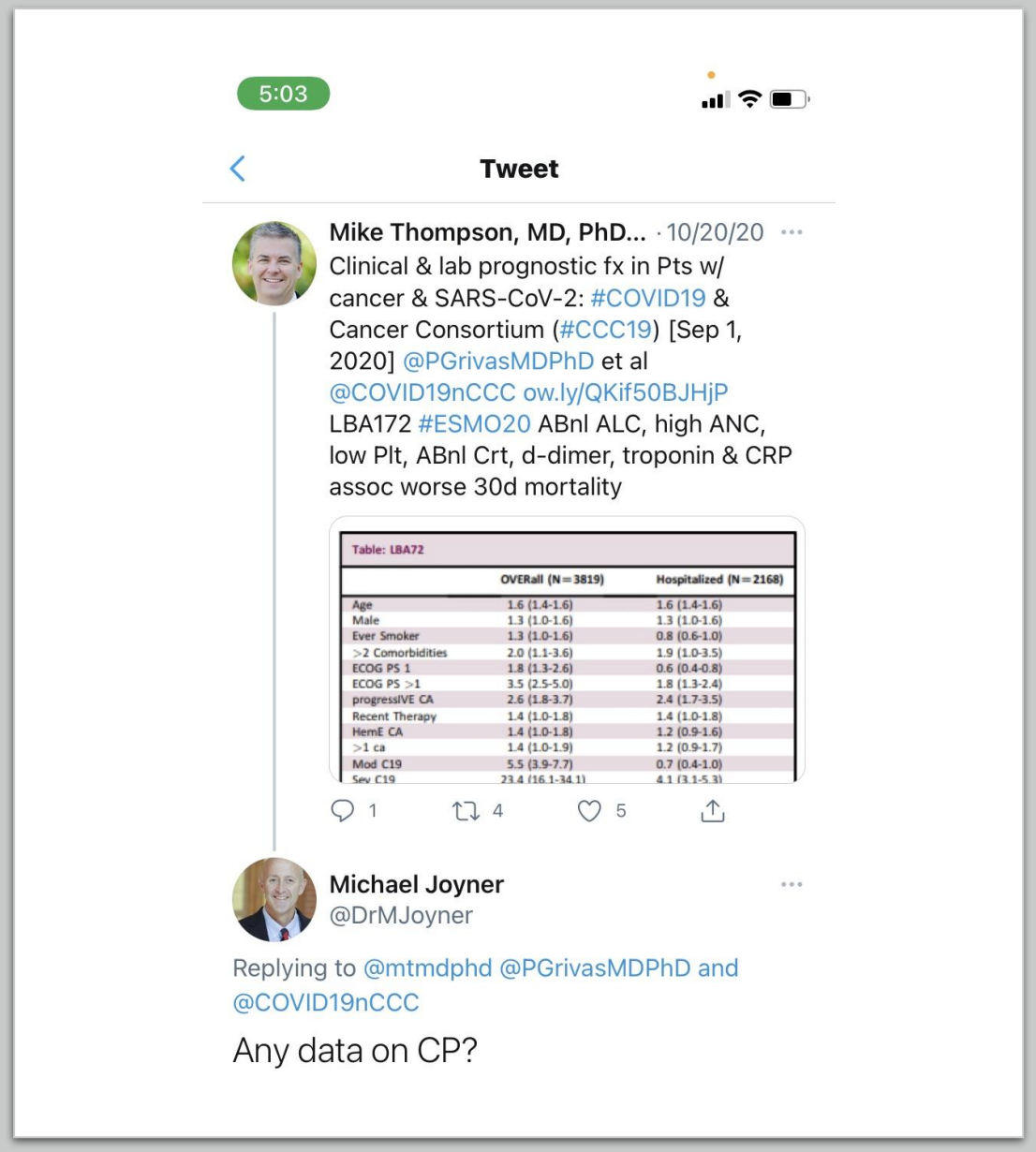
All consistent with the early use & less severe disease use case.

We (& Others) Persisted

Twitter Saves Lives Again
CP & Heme Malignancies

- CCC19 generates a cancer focused registry
- Mike Thompson Tweets
- Oct of 2020 - MJJ asks a question
- Collaboration born
- Matched Control study shows CP saves live

(The M Thompson back story is wild)



CP Improves Survival in Heme Malignancy Patients

- Heme Malignancy
- Patients who don't make endogenous antibodies
- Prolonged disease course
- Rapid improvement seen post CCP administration in many
- Low mortality reported in these high-risk patients

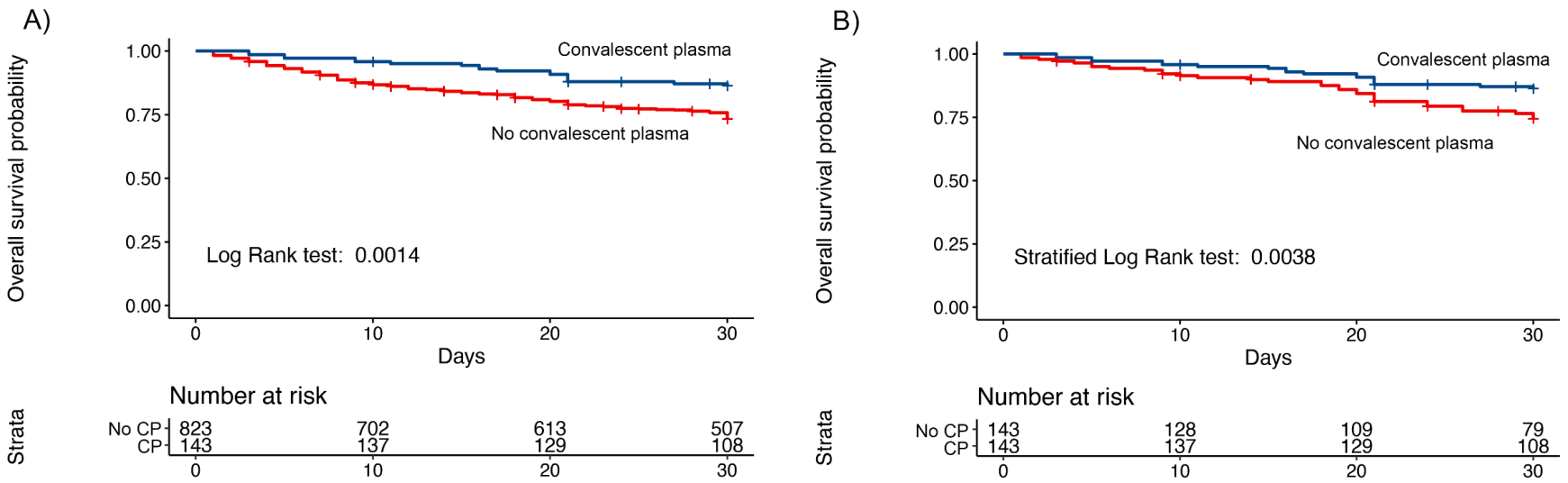


Figure 1: Primary Outcome in the A) Overall Population and B) Propensity-Score Matched Population

Thompson et al. 2021, *JAMA Onc*

Early Use of CCP in the Outpatient Setting Reduces More Than 50% of COVID-19 Related Hospitalizations

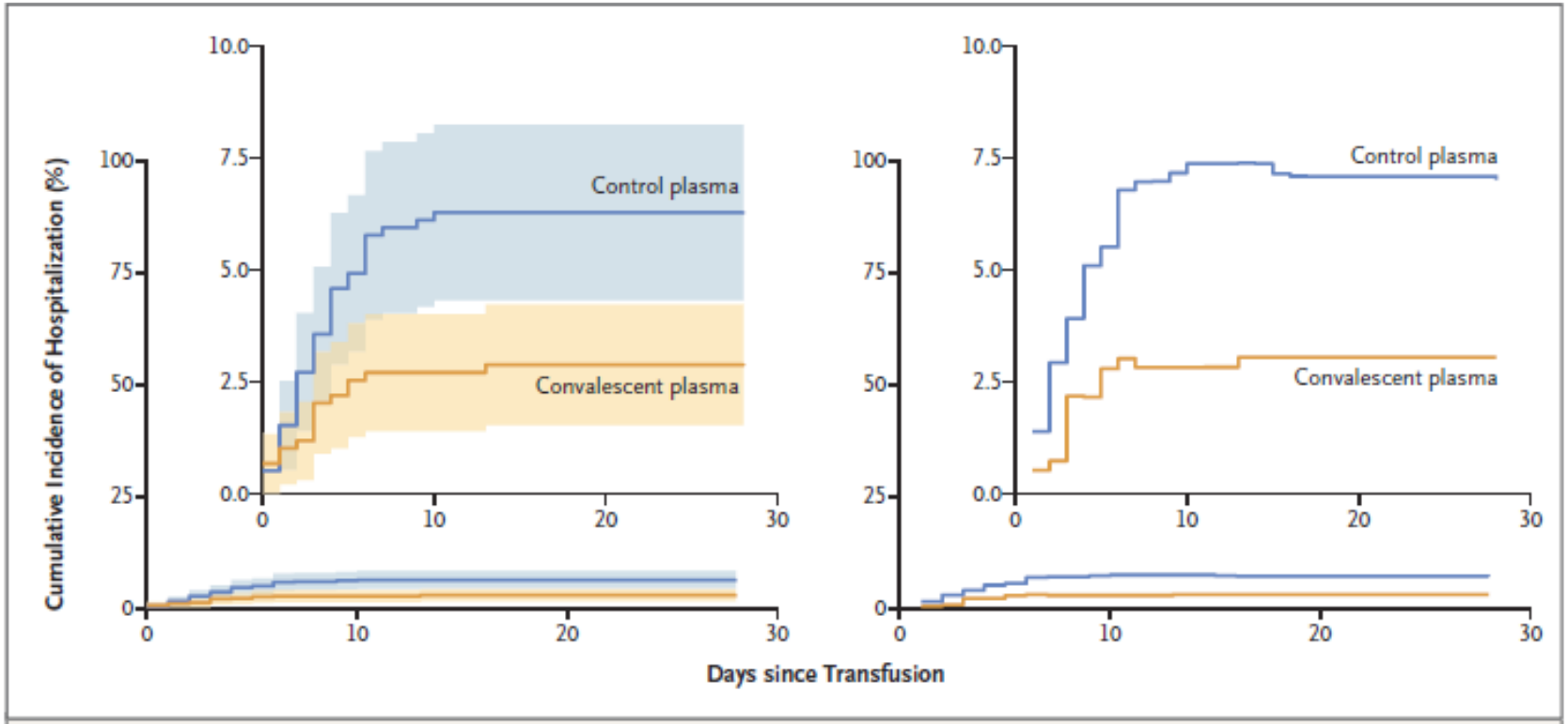
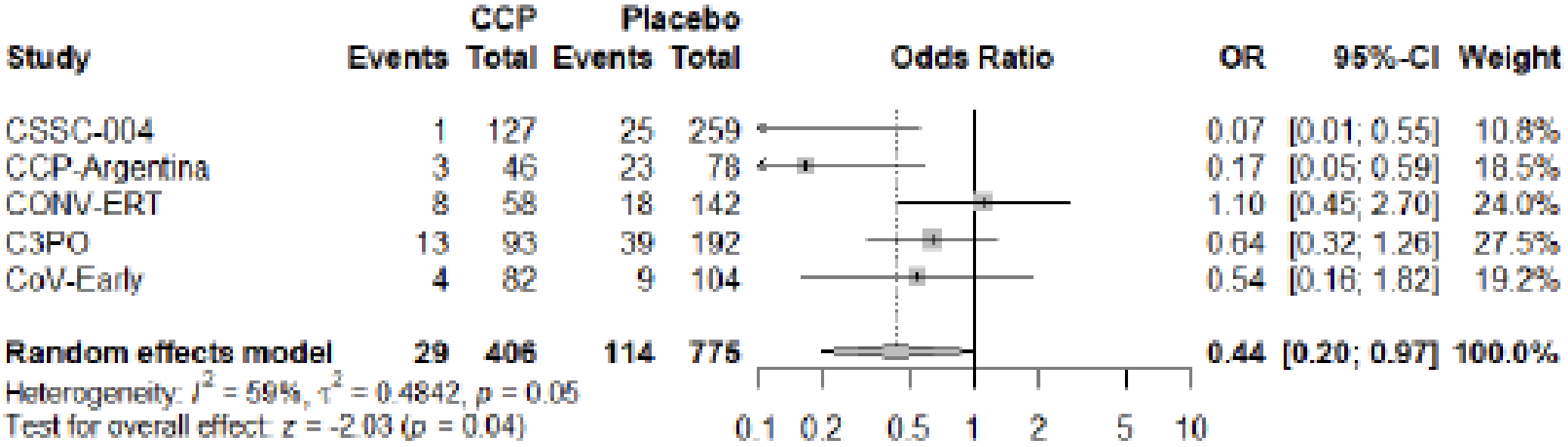


Figure 2. Cumulative Incidence of Coronavirus Disease 2019–Related Hospitalization.

On the left, the results of the unadjusted analysis are shown. Shading indicates the 95% confidence interval. On the right, estimates according to the adjusted targeted minimum loss–based estimation model are shown. The insets show the same data on an expanded y axis.

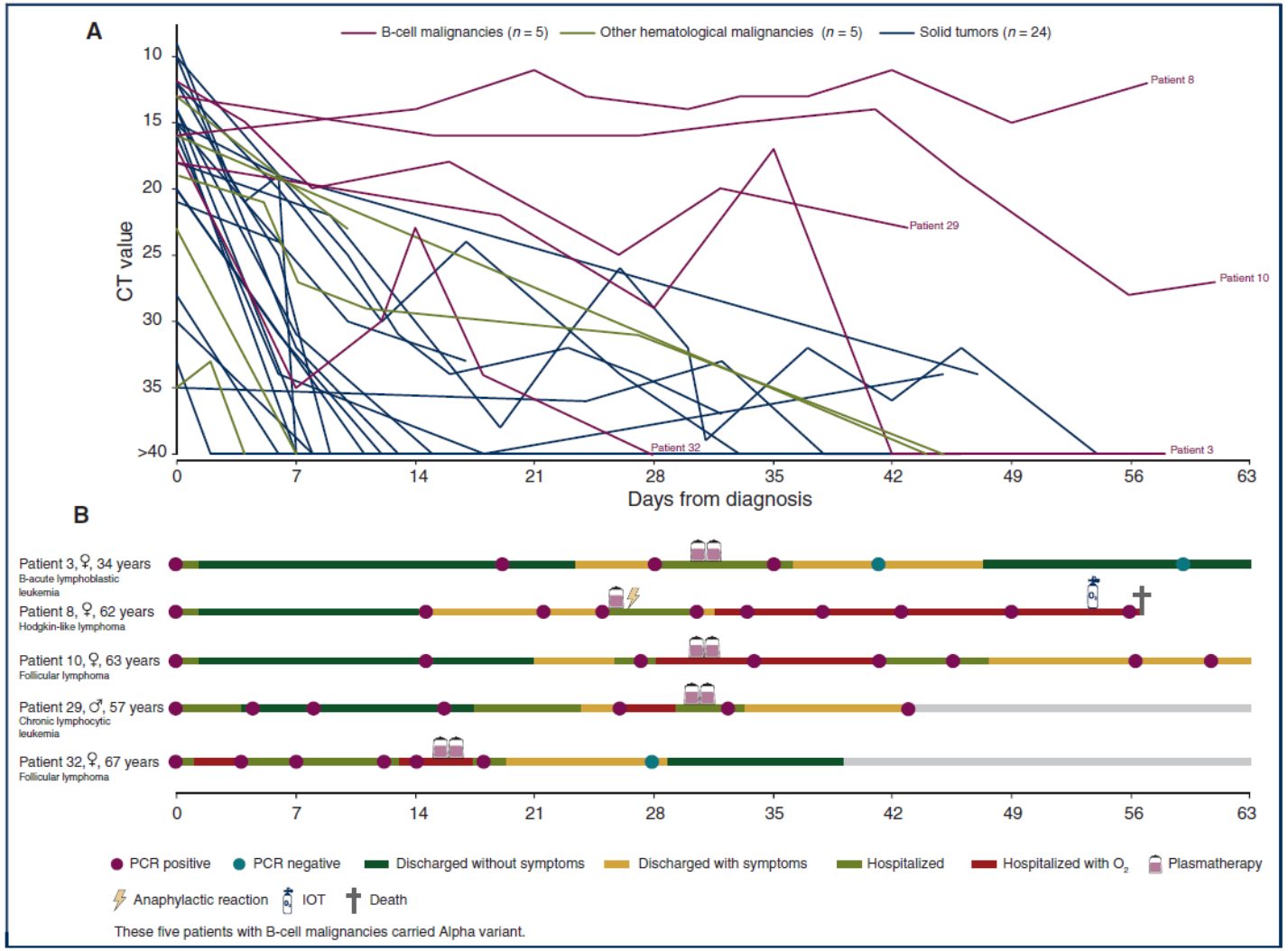
Sullivan et al, *NEJM* 2022

Meta-analysis - Outpatient Trials: <5 Days & High Titer



Levine... & Sullivan et al Preprint 2022

CP “Rescues” B-Cell Depleted Patients With mAb Escape Variants



Pommeret et al *Annals of Onc* 2021

2021- “VaxPlasma” Becomes Available

- Plasma harvested from vaccinated donors post breakthrough infection
- Extremely high titer
- Polyclonal/broad spectrum
- Adapts to variants
- Potentially widely available
- Low cost

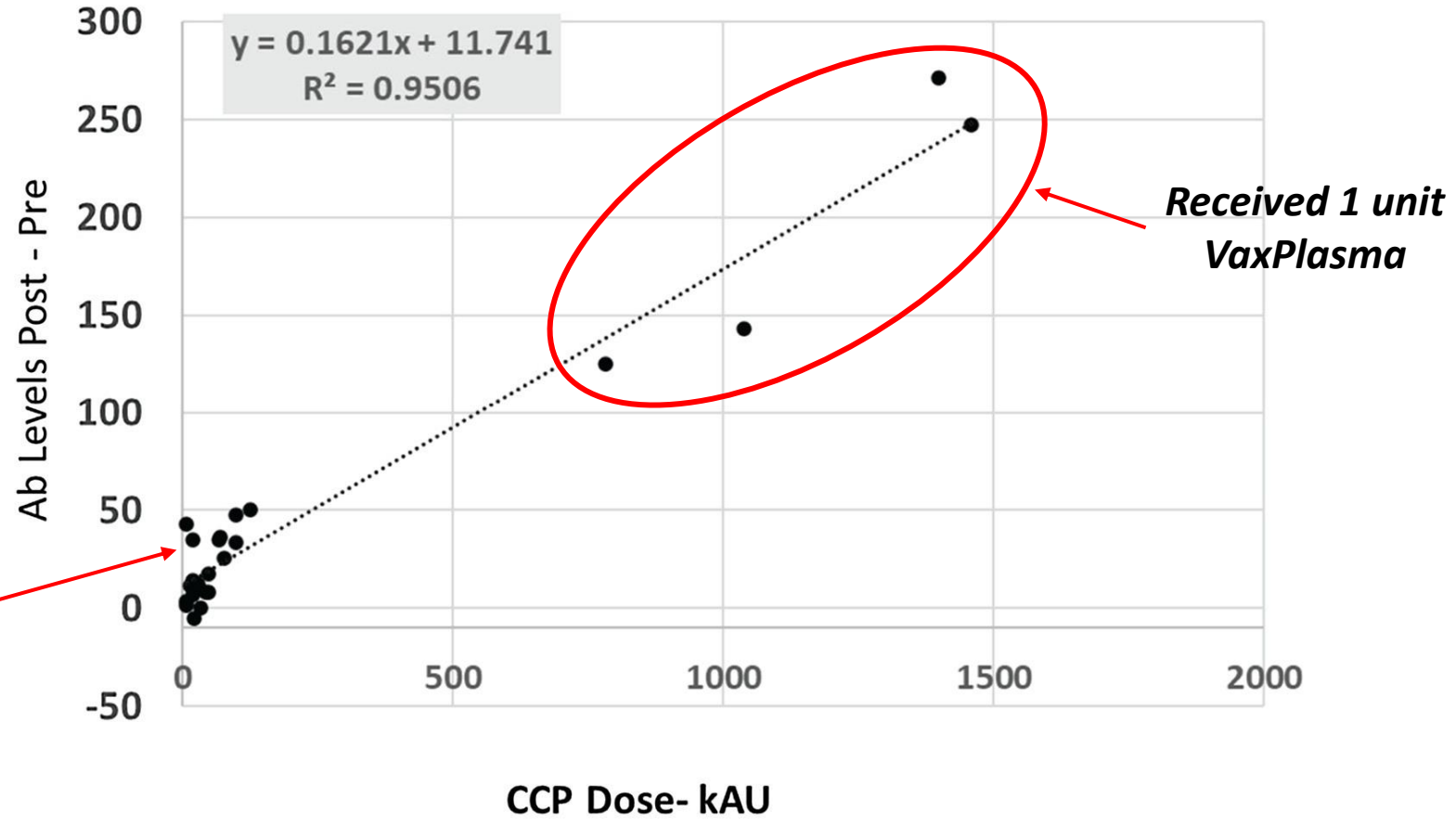
Breakthrough (Hybrid) VaxPlasma & Commercial Assays (Roche)

- Triple vaxed donor
- Omicron breakthrough May 2022
- Assay maxes out at 250
- Serial dilutions ~ 25,000
- 100x compared to summer 2020
- Seems to cover/keep up with variants

The results (U/mL) were as follows:
Neat = >250
On board X10 = >2500
X10 = 10*>250= >2500
X100 = 231*100= 23,100
X500 = 56.8*500 = 28,400
X1000 = 29.4*1000 = 29,400

The following comment with the result will be as follows:
"A x10 dilution was performed and the result was >2500 U/mL. The laboratory is unable to perform additional dilutions to achieve an absolute concentration. No minimum antibody level or threshold has been established to indicate long-term protective immunity against re-infection."

VaxPlasma: High Post Infusion Ab Levels



Received 1 unit VaxPlasma

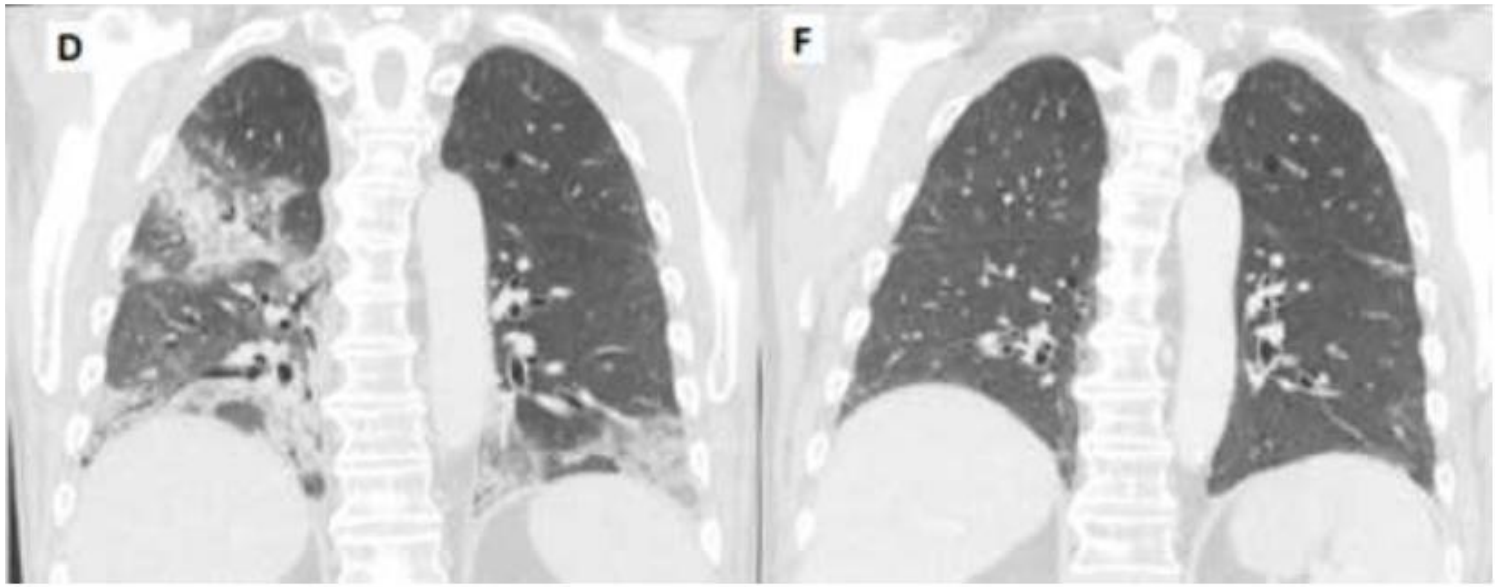
Received 2 units "standard" high titer CCP

Leon et al Trans Aph Sci 2021

VaxPlasma in a B-cell Depleted Patient COVID+ 270 Days!

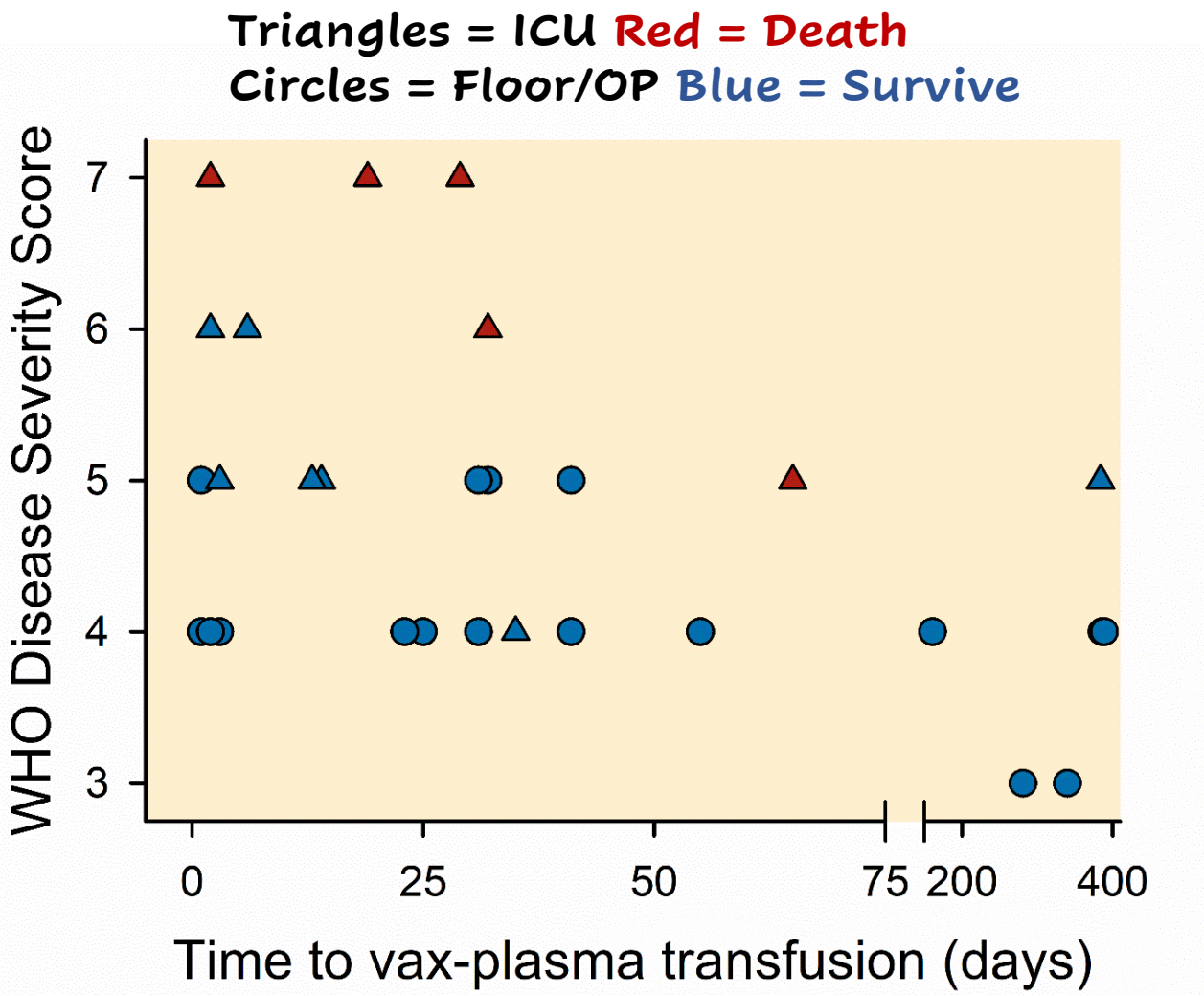
Pre-VaxPlasma

3 days post VaxPlasma



Espinosa et al MCP 2021

Tx of Last Resort: VaxPlasma in Immune Suppressed COVID Patients - Mayo Experience



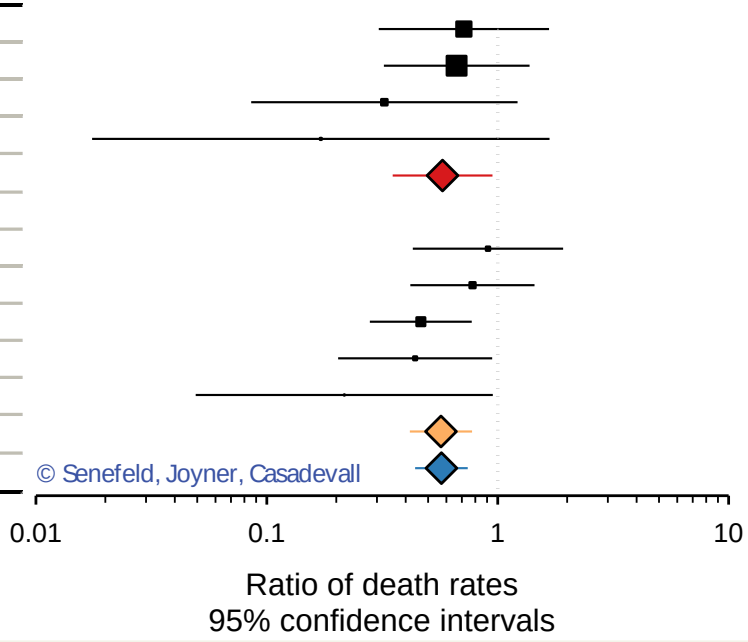
- 31 Pts, 2/3 heme malignancy
- *Treatment of Last Resort*
- 16 anti CD20, 5 BK inhibitors, 3 CAR T
- 7/12 ICU survived
- 19/19 non-ICU survived/"cured"
- 5 PCR+ >150d survived/"cured"
- Many had rapid improvement/"cure"
- Currently 1-2 per wk
- 2 Units VaxPlasma (or more)

~ 50 pts per week in France

Outpatient non-last resort use started on 11/30/22

CCP & Hospitalized Immunocompromised Patients

Source	Deaths/patients (%) CCP Group	Usual care group	OR (95% CI)
Müller-Tidow et al, 2022	12/68 (18%)	15/65 (23%)	0.71(0.31-1.67)
REMAP-CAP, 2021	31/66 (47%)	37/60 (62%)	0.66 (0.32-1.37)
Lacombe et al, 2022	4/22 (18%)	11/27 (41%)	0.32 (0.09-1.22)
Bar et al, 2021	1/15 (7%)	5/17 (29%)	0.17 (0.02-1.68)
RCT Total	48/171(28%)	68/169 (40%)	0.58 (0.35-0.95)
Cristelli et al, 2021	13/58 (22%)	9/22 (41%)	0.91(0.43-1.92)
Lanza et al, 2022	19/79 (24%)	46/159 (29%)	0.78 (0.42-1.45)
Thompson et al, 2021	19/143 (13%)	204/823 (25%)	0.47 (0.28-0.77)
Hueso et al, 2022	13/61(21%)	29/76 (38%)	0.44 (0.20-0.95)
Biernat et al, 2021	3/23 (13%)	9/22 (41%)	0.22 (0.05-0.95)
MCT Total	67/364 (18%)	297/1,102 (27%)	0.57 (0.42-0.78)
Overall	115/535 (21%)	365/1,271(29%)	0.57 (0.44-0.74)

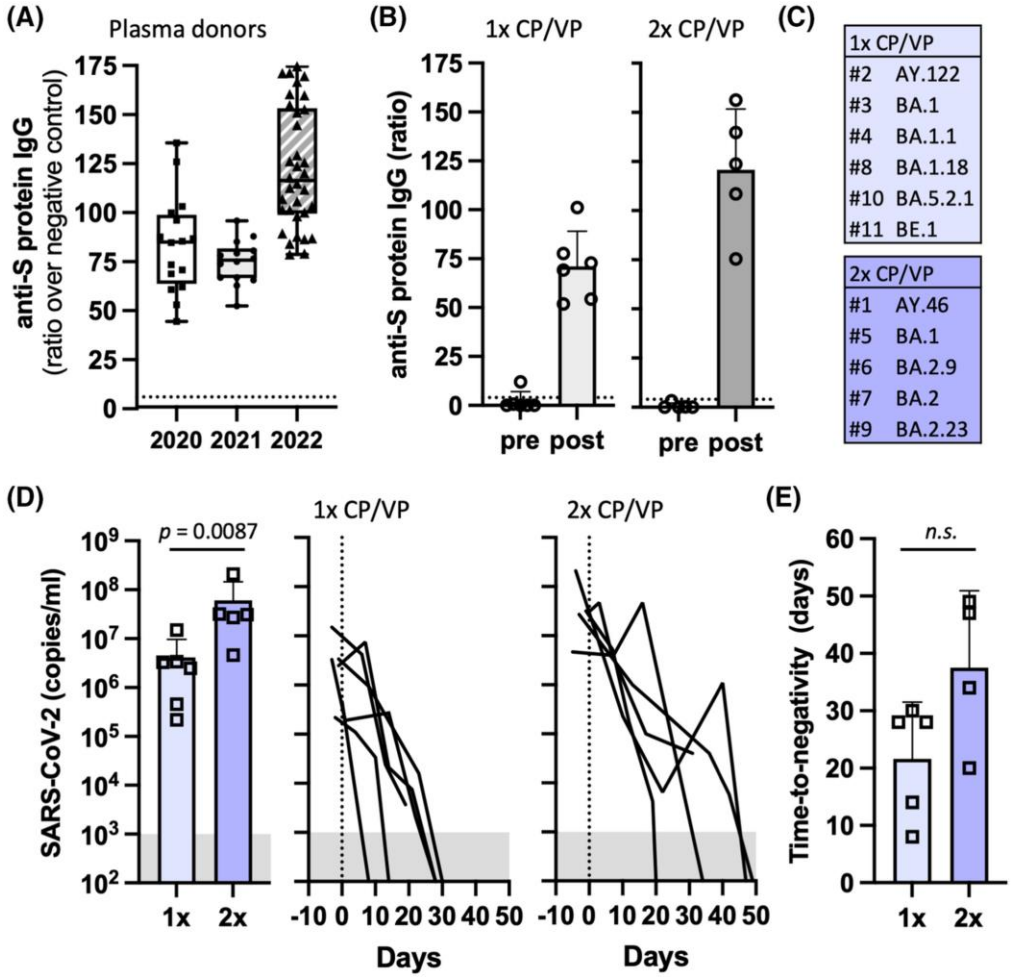


Mortality benefit associated with COVID-19 convalescent plasma

Odds Ratio: 0.57 (0.44-0.74)
- CCP group (n = 535)
- Control group (n = 1,271)
- 9 trials

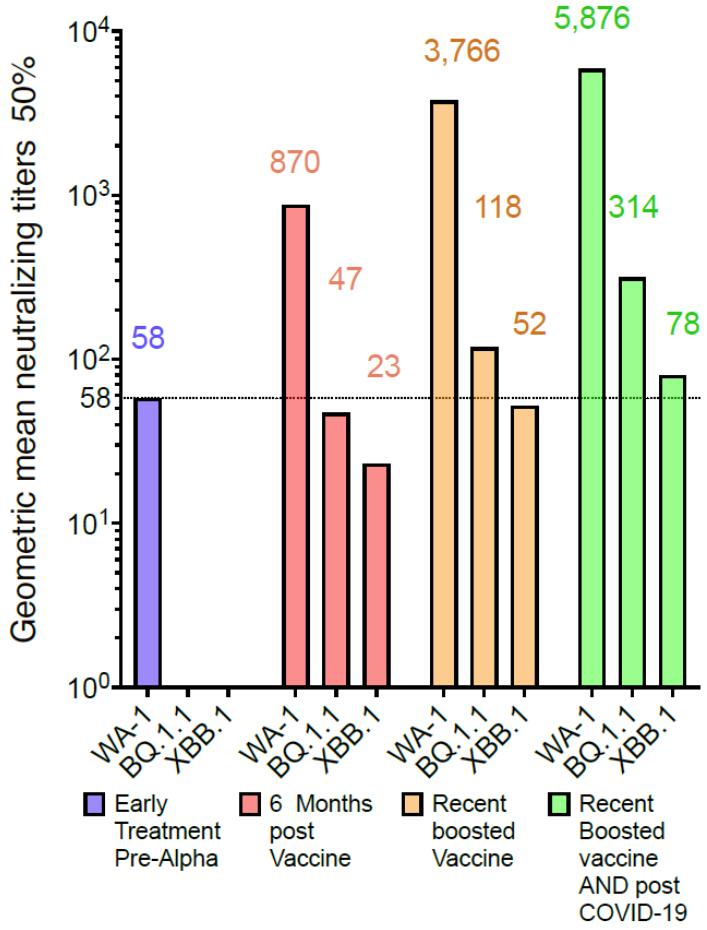
Senefeld, Casadevall & Joyner unpublished

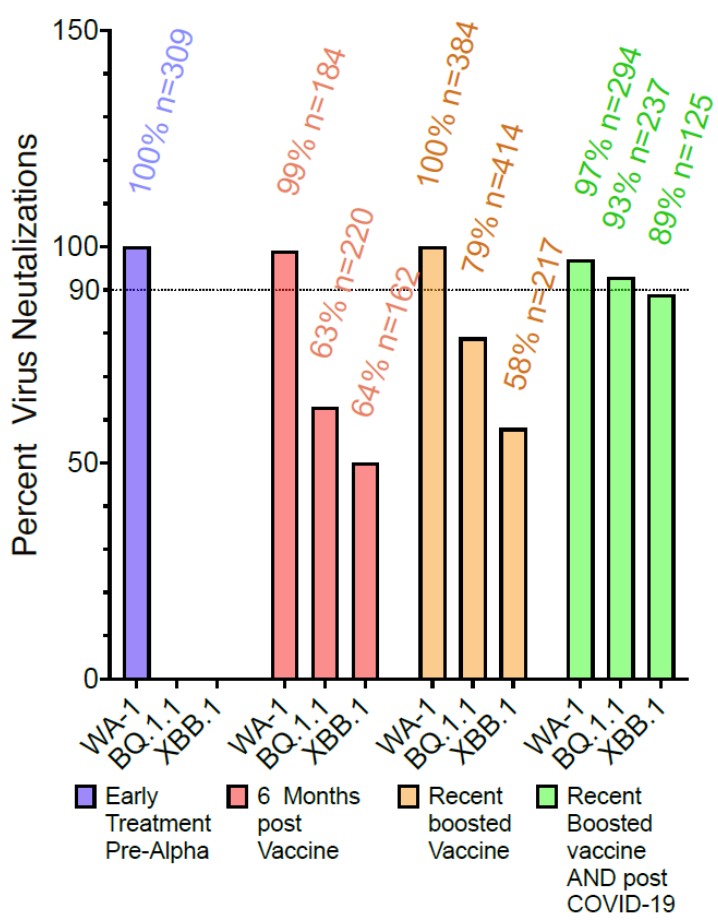
VaxPlasma – Give 2 Units



Gachoud et al Br J Haematol 2022

VaxPlasma Covers Newest Variants

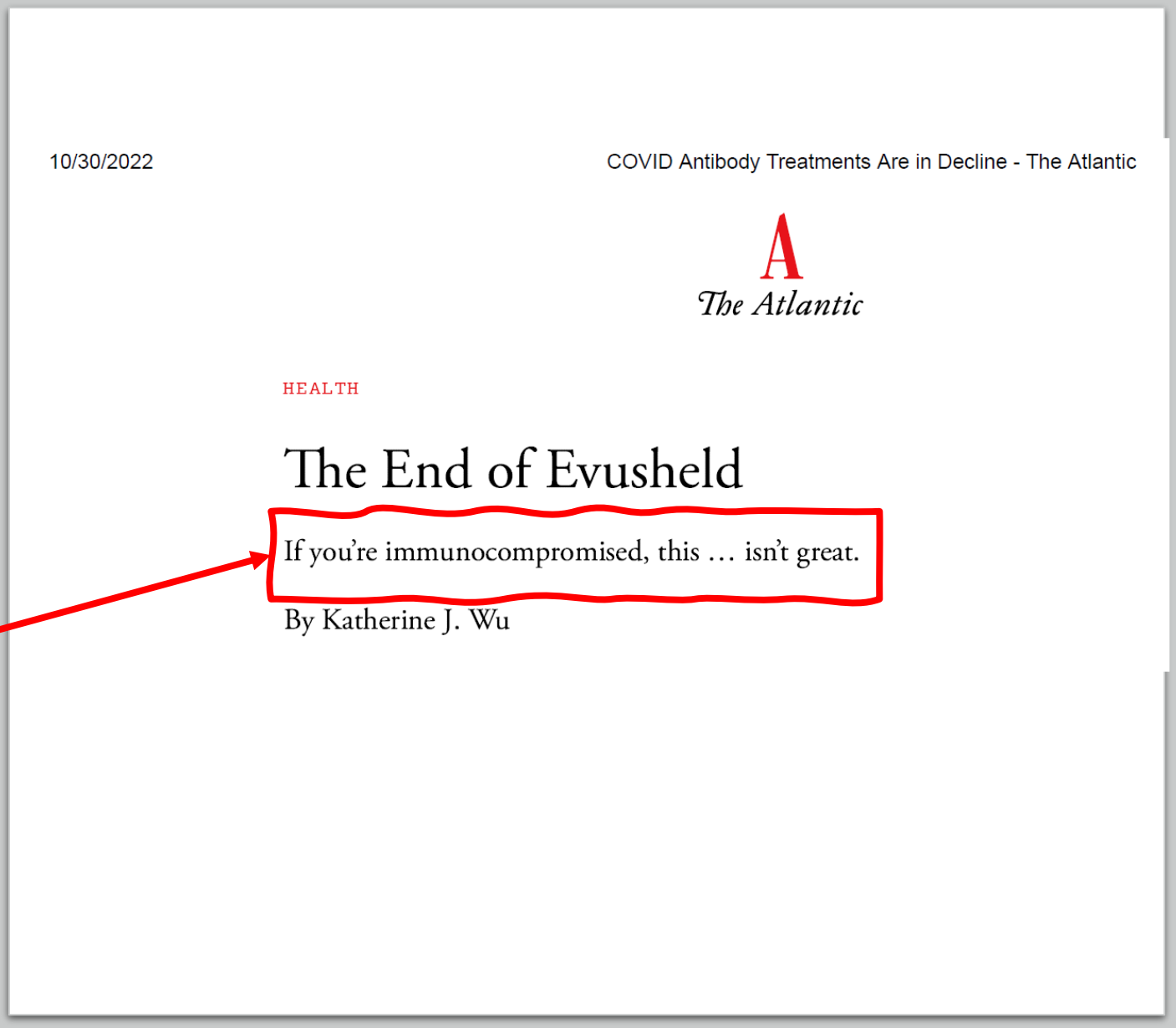




Sullivan et al submitted

Why Do We Need VaxPlasma In Late 2022?

- New COVID-19 variants have “escaped” previously effective monoclonal antibodies.
- VaxPlasma has very high anti-COVID antibody activity that can neutralize the new variants. https://pubmed.ncbi.nlm.nih.gov/36309490/
- Unless VaxPlasma is available, IC patients will be out of options and vulnerable when the emerging COVID-19 variants become dominant.

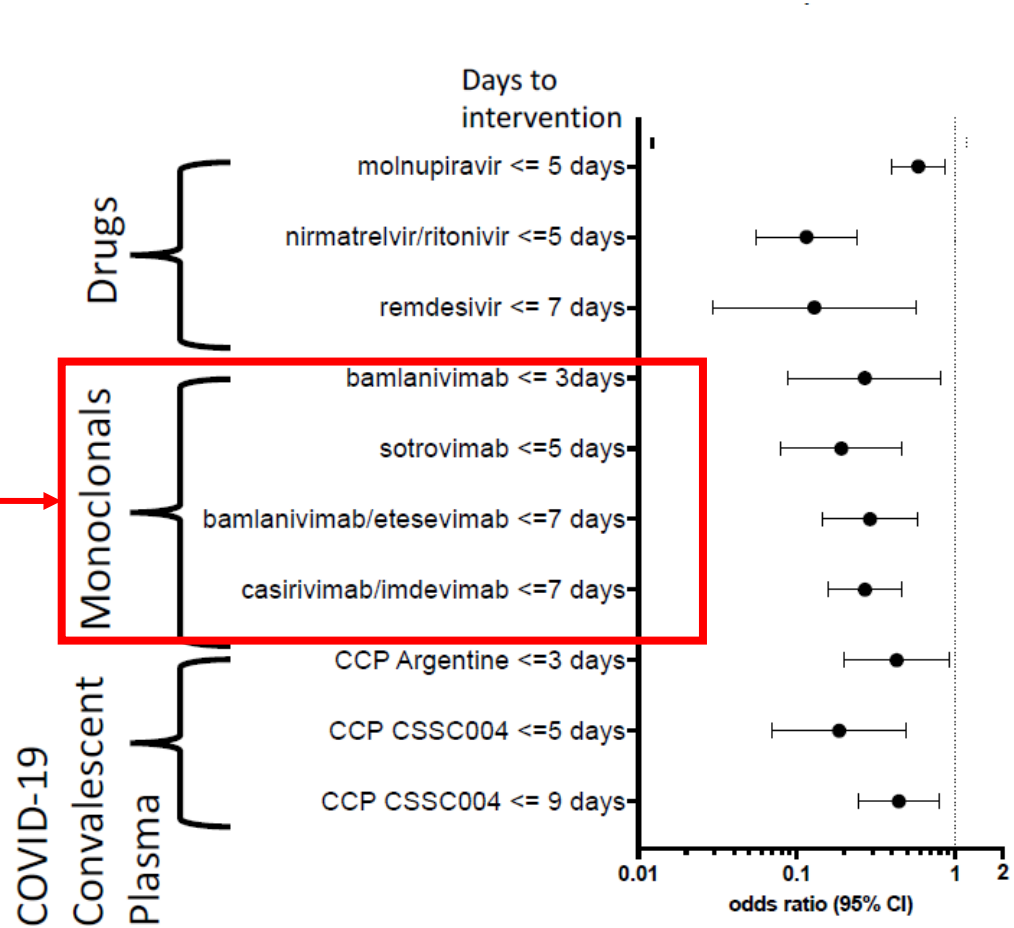


Antibody Therapy for COVID-19 After Three Years: *Take Home Messages*

- Convalescent Plasma (CP) is safe.
- High titer CP is effective if used early and in patients who don't make endogenous antibodies.
- mAbs are safe and effective in preventing hospitalization and in patients who don't make endogenous antibodies – *however, mAbs are subject to escape by novel variants.*
- Very high titer VaxPlasma from donors who have been both vaccinated and infected *adapts to and retains efficacy against variants.*
- High titer CP including VaxPlasma is available worldwide at relatively low cost.

Outpatient Antivirals, mAbs & CP Comparison

No longer in use due to escape



Control hospital	Control No hospital	Intervention hospital	Intervention No hospital	odds ratio	(95% CI)	Control h	Rel Rate
68	699	48	709	0.5853	(0.3986 to 0.8595)	9.7%	29%
66	1046	8	1039	0.1152	(0.0550 to 0.2412)	6.3%	88%
15	283	2	279	0.1290	(0.0292 to 0.5695)	5.3%	87%
9	156	5	309	0.2686	(0.0885 to 0.8158)	5.7%	44%
30	529	6	528	0.1912	(0.0789 to 0.4633)	5.6%	80%
36	517	11	518	0.2899	(0.1459 to 0.5760)	6.9%	69%
62	1341	18	1355	0.2697	(0.1587 to 0.4583)	4.6%	71%
25	80	13	80	0.4269	(0.1998 to 0.9120)	31%	48%
Argentine only-hypoxemia or tachypnea = hospital.							
25	259	5	258	0.1850	(0.0697 to 0.4912)	9.6%	80%
37	589	17	592	0.4411	(0.2455 to 0.7926)	6.3%	54%

Courtesy D Sullivan