Convalescent Plasma Therapy in Covid-19

49th Myanmar Health Research Congress

Prof Rai Mra

Chair

Ad-hoc Advisory Committee for Use of Convalescent Plasma in Patients with COVID-19

18th January 2021

Time-line

❖ December 2019	cluster of cases of unknown pneumonia reported in Wuhan, China
❖ 12 January 2020	China shared genetic sequence of new coronavirus on internet
❖ 30 January 2020	WHO declared the new coronavirus outbreak Public Health Emergency of International concern
❖ 11 February 2020	the name SARS-CoV-2 given to new virus
❖ 23 March 2020	first case of covid-19 in Myanmar

23 March 2020 – 1st case of covid-19 in Myanmar

16 April – Formation of *Ad hoc Committee for Use of Convalescent Plasma in Patients with Covid-19* by MoHS

- To explore possibility of using convalescent plasma in patients with covid-19 as there is no specific treatment,
- To try to save lives
- Based on available scientific evidence
- To be scientific, according to international standards
- To carry out according to ethical principles
- To obtain IRB approval
- To record and analyse.

Previous experience with convalescent plasma therapy

- Convalescent plasma has been used in many diseases in the last century including measles, polio, Spanish flu of 1918

Disease outbreaks	Use of convalescent plasma as treatment vs no treatment
Spanish ‘flu 1918	21% reduction in the case-fatality rate (Langhi Jr. 2020).
SARS	lower mortality rate, compared to non-transfused patients (12.5% vs 17%) (Cheng 2005)
H1N1	Mortality (20% vs 54.8%) (Hung 2015).
Ebola	some degree of effectiveness has been claimed - not conclusive/ equivocal, antibody titre not determined (Griensven 2016).

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

Kai Duan PNAS April 28, 2020 117 (17) first published April 6, 2020 https://doi.org/10.1073/pnas.2004168117

- 10 severe patients confirmed by real-time viral RNA test.
- One dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above **1:640** was transfused to patients
- maximal supportive care and antiviral agents (remdesivir, ribavirin, piramivir,etc.)
- Severe cases, 7 not on respirator (3 on respirator ; 1 remained on respirator after CP)
- median time from onset of illness to CP transfusion was 16.5 d (11.0 d to 19.3 d)
- Clinical symptoms were significantly improved with increase of PaO2 within 3 d.
- Imagings showed varying degrees of absorption of lung lesions within 7 d.
- The viral load was undetectable after transfusion in seven patients who had previous viremia.
- No severe adverse effects were observed
- 3 cases discharged ; 7 cases in much improved status and ready for discharge
- Historic control group - 3 deaths, 6 remained stable and one improved.

Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients

Qing-Lei Zeng, et al *The Journal of Infectious Diseases*, jiaa228, https://doi.org/10.1093/infdis/jiaa228 **29 April 2020**

- 6 COVID-19 patients with respiratory failure
- Convalescent plasma 200 – 600 ml given median 21.5 days
- **5 out of 6 patients died**
- All tested negative 4 days after CP transfusion
- Mortality not reduced in critically end-stage patients

- Commonly, viraemia peaks in first week in most acute viral diseases
- usually a primary immune response occurs by day 10 to 14, followed by virus clearance .
- In third week, clinical deterioration is result of inflammatory or hyperimmune attacks rather than direct viral-induced tissue damage
- convalescent plasma should theoretically be more effective when given in the early course of disease (i.e., **before day 14**, or during the viremic stage)
- failure to reduce mortality may be attributed to late transfusion of convalescent plasma, which were given on median day 21.5 during viral shedding.
- On the contrary, one critical patient in treatment group infused on day 11 during viral shedding finally recovered

Miles stones

▪ 16th April	Ad hoc committee for CP formed by MoHS
▪ 8th May	IRB approval obtained
▪ 14th May	CP donations accepted at Waibargi
▪ 26th May	1st case of CP treatment
▪ 17th July	Roche Elecsys IgG antibody first measured
▪ 15th Sept	CP collection moved to DMR compound. Apheresis programme started
▪ 17th Nov	Ability to measure Roche anti-Spike antibody

Covid-19 Severity Classification
China- (WHO)

Mild	Common	Severe	Critically severe
Mild clinical manifestation, None Imaging Performance	Fever, respiratory symptoms, pneumonia performance on X-ray or CT	Meet any of the followings: 1. Respiratory distress, RR ≥ 30/min; 2. Oxygen saturation ≤ 93% at rest state; 3. Arterial partial pressure of oxygen (PaO_2) / Fraction of inspiration O_2 (FiO_2) ≤ 300mnHg, 1mmHg=0.133kPa	Meet any of the followings: 1. Respiratory failure needs mechanical ventilation; 2. Shock; 3. Combined with other organ failure, patients need ICU monitoring and treatment

Indication for convalescent plasma therapy in many international studies and trials

Criteria for patient selection adopted by Ad-hoc Committee

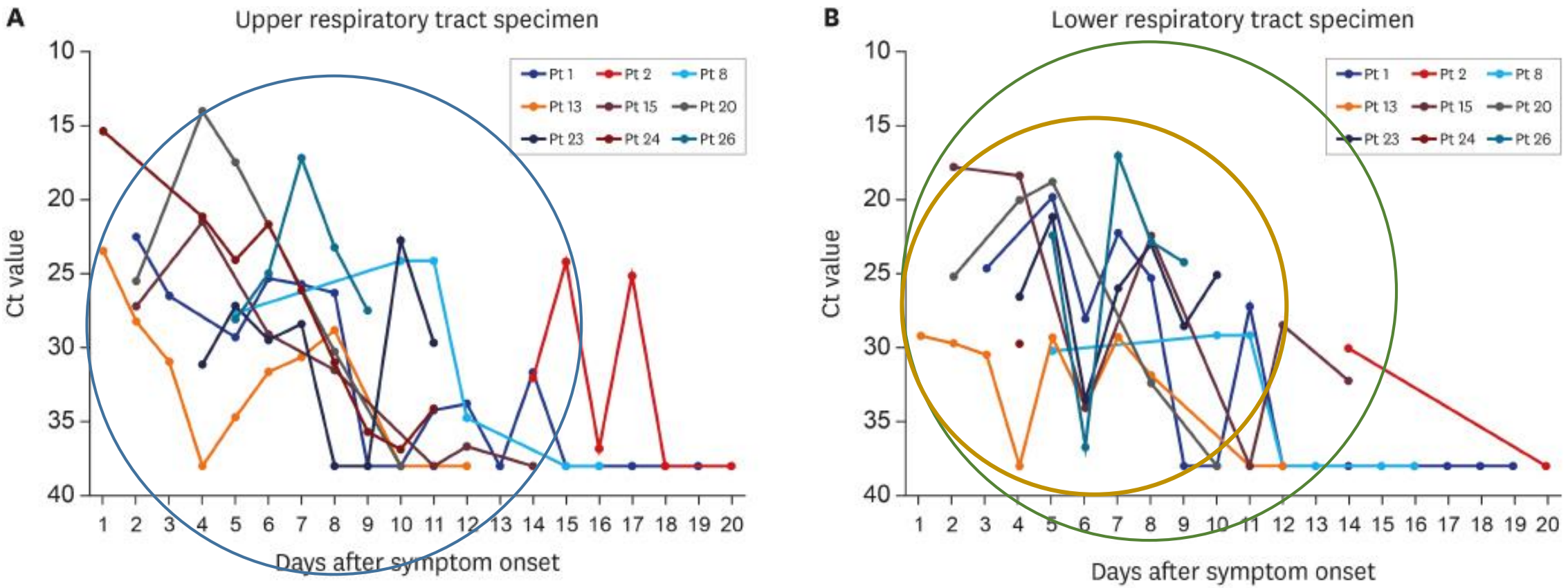
- At least 18 years of age
- Patient with diagnosed as COVID-19 by molecular test and who has severe or rapidly progressive or life-threatening COVID-19
- Must have informed consent

Severe disease (one or more of the following)	Life-threatening disease (one or more of the following)
• Dyspnoea + Respiratory rate ≥ 30/min • Oxygen saturation < 93% • PaO2/FiO2 ratio < 300 and/or • Lung infiltrates > 50% or within 24 to 48 hours	• Respiratory failure • Septic shock and/or • Multiorgan dysfunction or failure • Early or as soon as it happens

- **N.B** –Due consideration for - immunosuppressed patients, elderly patients (arbitrarily 65 yr) esp with co-morbidities diabetes, heart disease, hypertension, cancer patients, once nucleic test is positive, depending on condition, may be considered since the risk of rapid deterioration is very high.

Amount of convalescent to be transfused –

✓ 200 ml in 2 hr may be repeated in 24-48 hr.



Viral load represented by Cycle Threshold (CT) values is highest end of 1st week and little or absent after 2nd week

ES Kim, https://doi.org/10.3346/jkms.2020.35.e142

80% - mild
15% - severe
5% - ICU

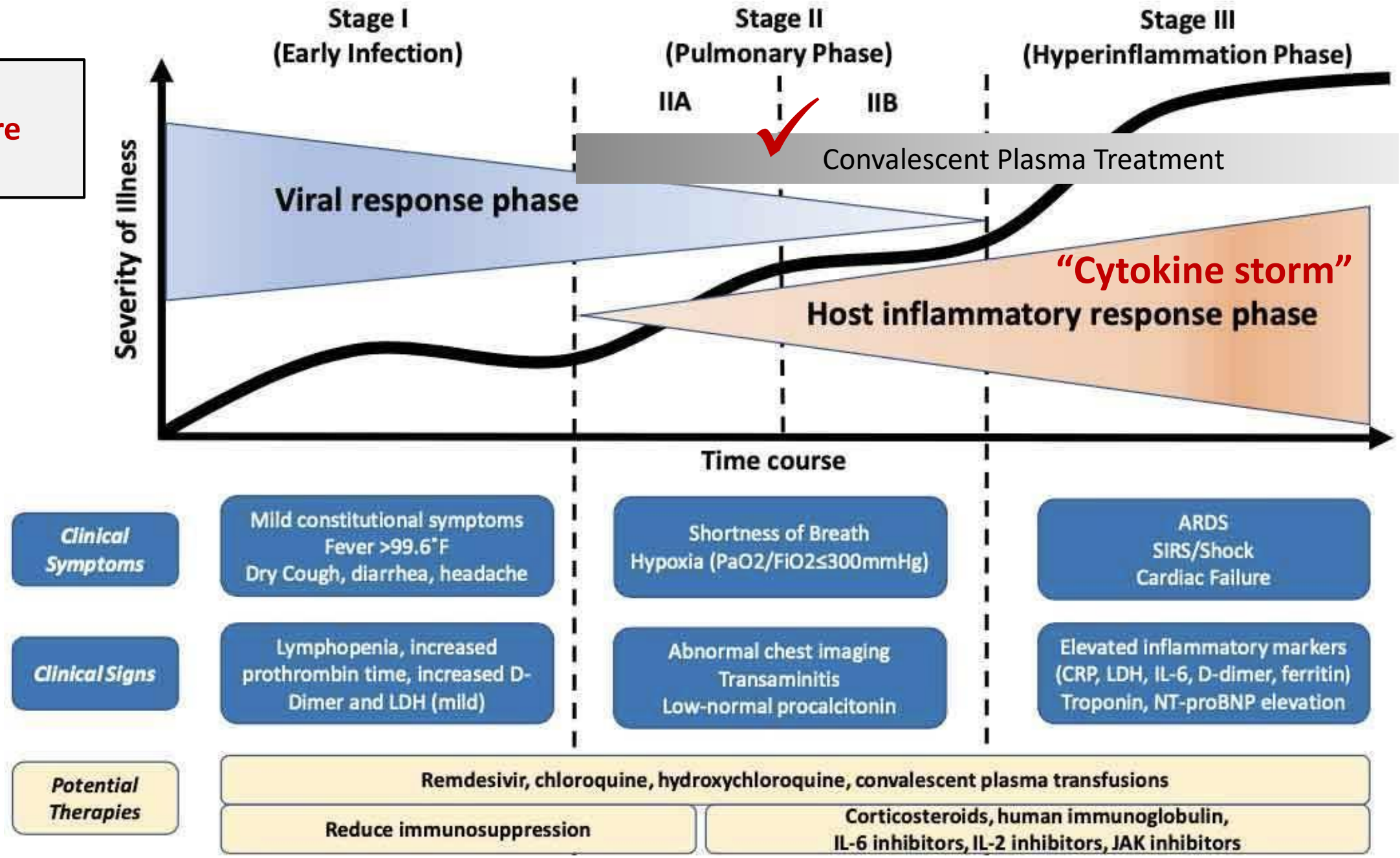


Image source: https://els-jbs-prod-cdn.literatumonline.com/pb/assets/raw/Health%20Advance/journals/healun/Article_2-1584647583070.pdf

The effectiveness of convalescent plasma therapy will depend on -

- the virulence and infecting dose of pathogen
- the timing, volume, dose of administration
- neutralizing titre of the plasma that is administered.
- Host factors – genetic, age, co-morbidities

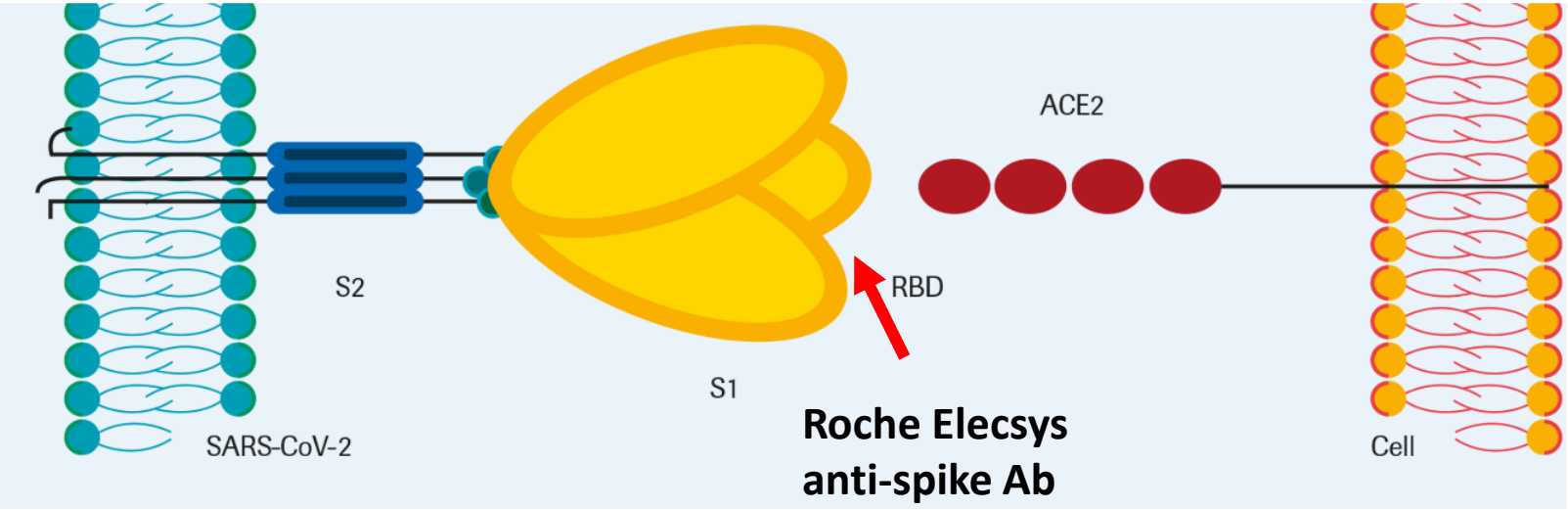
Convalescent Plasma Donations

- **Donor recruitment-**
  - Personal recruitment- at discharge, follow up at first; by phone
  - Media – Newspapers, TV, radio, newspapers, Facebook, interviews
- **CP donations –**
  - Waibargi Hospital from May 14, 2020 – Manual -29
    - Apheresis- 6
    - Total – 35
  - DMR – NBC Branch from Sept 22 to Jan 8
    - Manual- 68
    - Apheresis – 596
    - Total- 664
- Total donations – 699
- **1446 units up to 8.1.21 issued to 720 patients**

Preparation

Convalescent Plasma potency – Antibody titres

- Initial collection of convalescent plasma at Waibargi Hosp -
  - Donors who have had symptomatic covid disease especially with severe symptoms selected since they are reported to have high antibody titres from various studies
- 17 July Roche ELECSYS SARS-CoV2 IgG (against Nucleocapsid Ag) with COI-20 corresponding to **IgG titre 1:160** and higher used to select donors
- 17 November Roche ELECSYS SARS-CoV2 IgG anti-Spike antibody test used selecting donors with **Ab titres at least 1: 320.**



Roche Elecsys® Anti-SARS-CoV-2 S is an immunoassay for the in vitro quantitative determination of antibodies (including IgG) to the SARS-CoV-2 spike (S) protein receptor binding domain (RBD) in human serum and plasma.
Positive ≥0.8 U/mL to maximum ≥ 250 U/mL

Covid Convalescent Plasma Observational Study MOHS

- Predonation screening for plasmapheresis-
  - Full Blood Count
  - Serum albumin
  - Serum calcium
  - CRP
  - IgG (Roche Elecsys) COI >20
  - Donor deferral
  - Consent

30.23% - COI < 20

Number of patients treated with convalescent plasma

	Hospital	Date	No. of patients treated
1	Waibargi	June 2020 to 30 Dec 2020	205
2	South Okkala	4 Sept to 31 Dec 2020	122
3	AYA Centre	30 Oct to 8 Jan 2021	123
4	YGH	23 Oct to 4 Jan 2021	123
5	NOGH	25 Nov to 8 Jan 2021	123
	Total		**696**

Age range of convalescent plasma patients

Age range	Waibargi	SOSH	AYA	YGH	NOGH	Total	%
21-30	7	0	1	2	6	16	2.3%
31-40	14	7	10	2	4	37	5.31%
41-50	30	12	9	8	8	67	9.62%
51-60	42	22	30	31	22	147	21.12%
61-70	68	43	43	30	44	228	32.7%
71-80	25	25	20	37	27	134	19.25%
81-90	17	11	11	13	11	63	9.05%
91-100	1	2	0	1	1	5	0.72%
						696	

> 60 yr - 61.78%

Sex ratio of convalescent plasma patients

Sex ratio	Waibargi	SOSH	AYA	YGH	NOGH	Total
Male	105	62	74	84	53	378 (54.3%)
Female	100	60	49	39	70	318 (45.7%)
Totql	205	122	123	123	123	696

Male : Female – 1: 0.84

Blood group distribution among convalescent plasma patients

Blood group	Waiba rgi	SOSH	AYA	YGH		Total	Normal population
A	50	29	32	27		138 (23%)	23.8%
B	79	33	39	47		198 (34.55%)	32.7%
O	59	46	35	34		174 (30.36%)	35.7%
AB	17	14	17	15		63 (10.99%)	6.95%
Total	205	122	123	123		573	

Comorbidities in convalescent plasma patients

Comorbidities	Waibargi	SOSH	AYA	YGH	NOGH	Total
Hypertension	104	78	68	70	68	**388 (55.74%)**
Diabetes	70	54	37	64	40	**265(36.78%)**
Heart disease	16	5	10	13	27	**71(10.20%)**
Chronic Kidney ds	18	4	3	21	12	58
Cancer	7	4	0	7	1	19
Autoimmune ds	4	1	0	5	4	14
HIV	18	1	1	2	4	26
All patients	205	122	123	123	123	696

Number of comorbidities present in convalescent plasma patients

No. of comorbidities	Waibargi	SOSH	AYA	YGH	NOGH	Total
1 comorbidity	64	75	54	37	26	256 **(36.78%)**
2 comorbidities	63	27	25	42	42	199 **(28.59%)**
3 comorbidities	20	12	5	15	18	70
> 3 comorbid	1	8	1	-	5	15
No of total patients	205	122	123	123	123	696

Waibargi Specialist Hospital
Convalescent plasma early ≤ 7 days vs > 7 days

No. of days from onset of symptoms to con plasma transfusion	Total	Alive	Died	Mortality percent
Up to 7 days	83	70	13	15.66%
After 7 days	122	99	23	18.8%
	205	169	36	17.5%

P > 0.05

Number of convalescent plasma units transfused per patient

No. units	WB	SOSH	AYA	YGH	NOGH	Total	%
1 unit	82	49	12	4	59	206	29.6 %
2 units	**113**	**65**	**111**	**119**	**62**	**470**	**67.53%**
3 units	10	8	0	0	2	20	2.87%
4 units	0	0	0	0	0	0	0
Total	205	123	123	123	123	696	100%

AYA COVID TEST & TREAT CENTRE

Convalescent plasma early ≤ 3 days vs > 3 days

No. of days from admission to con plasma transfusion	Total	Alive	Died	Mortality percent
Up to 3 days	103	84	19	18.4 %
After 3 days	20	5	15	75 %
	123	89	34	27.64 %

$P < 0.05$

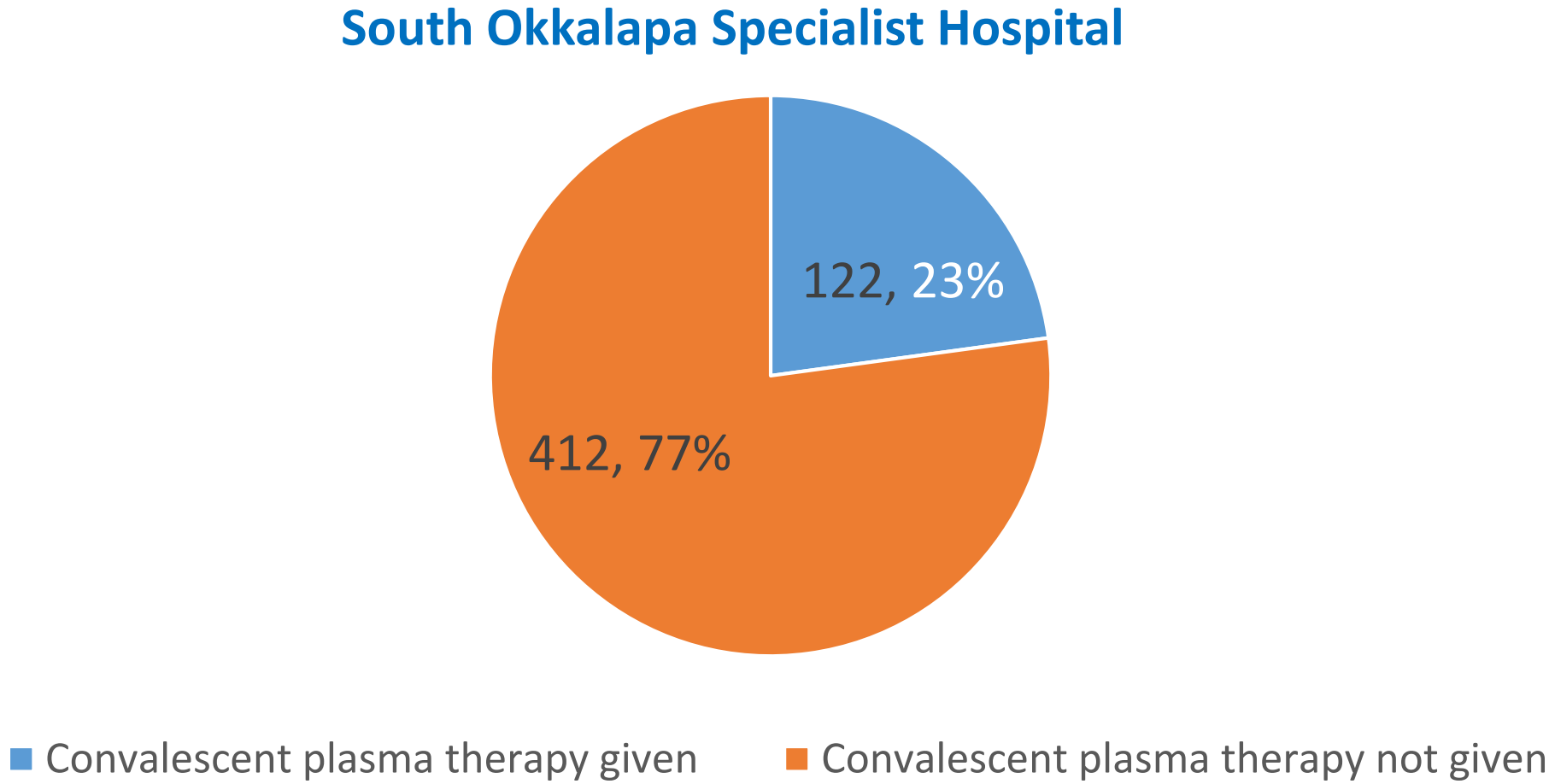
AYA COVID TEST & TREAT CENTRE

Convalescent plasma early ≤ 7 days vs > 7 days

No. of days from onset of symptoms to con plasma transfusion	Total	Alive	Died	Mortality percent
Up to 7 days	38	32	6	15.78 %
After 7 days	85	57	28	32.94 %
	123	89	34	27.64 %

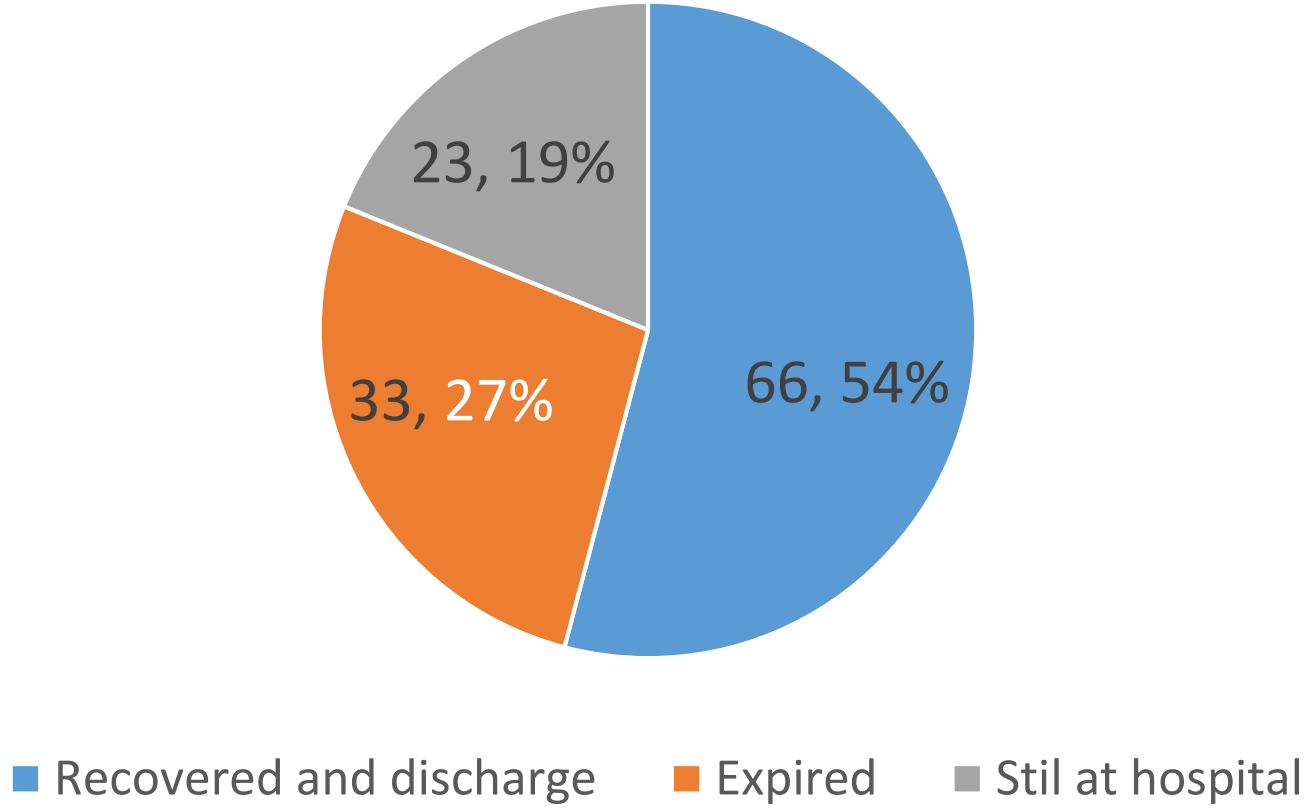
P < 0.05

Convalescent plasma therapy in COVID 19 patients (n=534) (4th Sept-31st Dec,2020)

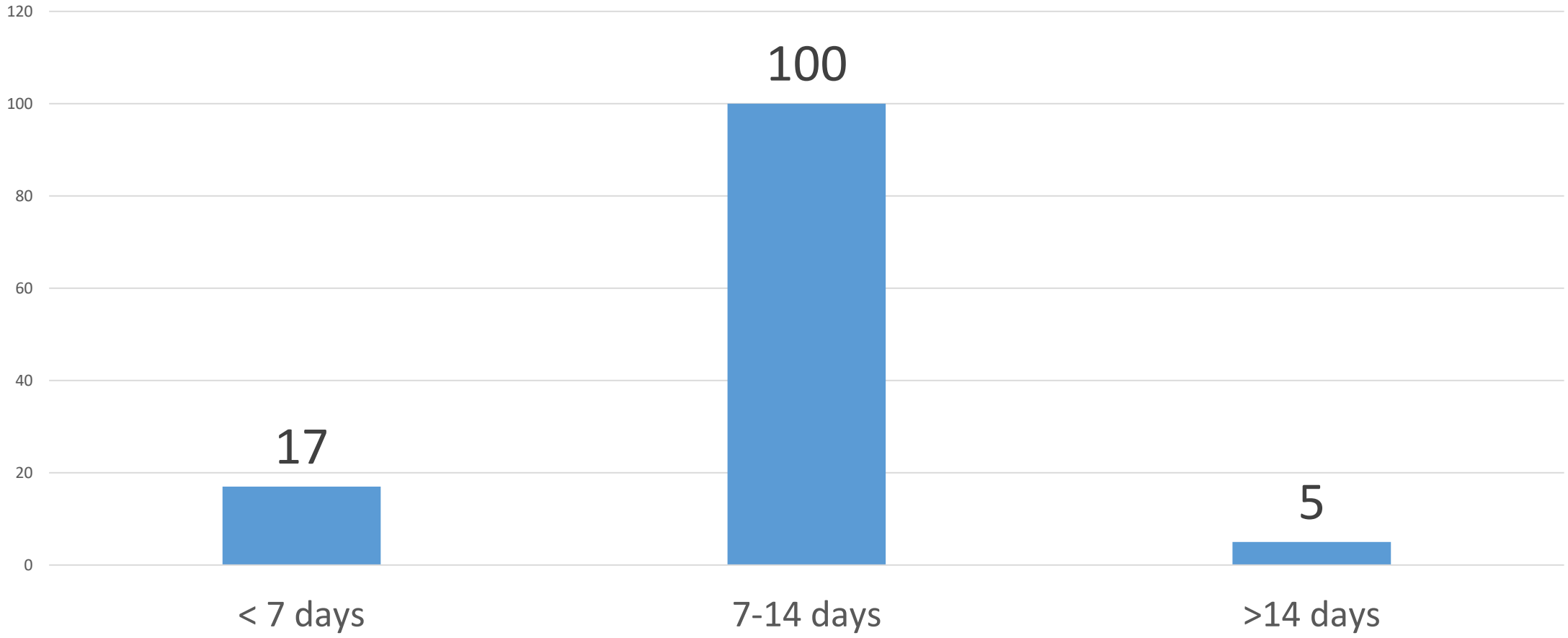


Outcome of Convalescent plasma therapy recipients (n=122) *South Okkalapa Specialist Hospital*

Expired
33/122
27%



Distribution of day of illness among convalescent plasma treated COVID-19 patients (n=122) SOSH



Effect of Convalescent plasma on Prognostic parameters of COVID 19 patients (n=122) SOSH

	Before con plasma	7 days after con plasma
Mean ALC ($x10^3$ /µL)	1.16	↑ 2
Mean CRP (mg/L)	122	↓ 74
Mean LDH (U/L)	506	↓ 435
Mean D Dimer (ng/L)	2006	↓ 1889

South Okkalapa Specialist Hospital

Hospitals, Number of patients given convalescent plasma and mortality rate

	Hospital	No of patients transfused	No of expired cases	Mortality rate	Remarks
1	Waibargi	205	36	17.5 %	
2	SOSH	122	33	27 %	
3	AYA	123	34	27.64 %	
4	YGH	123	42	34.1 %	
5	NOGH	123	37	30 %	
6	TSGH	3	0	0	
7	Haematology NOGH	37	6	16.21%	*Haem malig, AA-CP given early
8	Phaunggyi	-			
9	Mandalay	51	10	19.6%	Started 30 Nov
10	Nay Pyi Taw	1	0	0	
11	Pa-an	1	0	0	
12	Kalay	3			
13					
14		*649*			

Safety of Convalescent Plasma

Complications of Convalescent Plasma Transfusions –

Incidence of allergic reaction 1.14 %- easily treated(8/696)

		WBSH	SOSH	AYA	YGH	NOGH	Total
1	**Allergic rash mild**	**1**	**0**	**3**	**2**	**0**	6
2	**Allergic rash severe**	**2**	**0**	**0**	**0**	**0**	2
3	**Transfusion reaction with hypotension**	**0**	**0**	**0**	**0**	**0**	
4	**Circulatory overload**	**0**	**0**	**0**	**0**	**0**	
5	**TRALI**	**0**	**0**	**0**	**0**	**0**	
	Total cases	**3**		**3**	**2**		**8(1.14%)**
	Total CP transfused	**205**	**122**	**123**	**123**	**123**	**696**

Waibargi – Total cases 205			
	Complicatons	Before con pl	After con pl
1	ARDS	27 (+ 28 very severe pneumonia)	
2	AMI	3	
3	Myocarditis	4	
4	Hypotension	6	
5	Acute heart failure	5	
6	Bradycardia	3	
7	Tachycardia/atrial fib	3 AF	
8	Venous thrombosis	4	
9	Pulm embolism	1	
10	Arterial thrombosis, limb	2	
11	Stroke	6	2

South Okkalapa Specialist Hospital – Total cases - 122			
	Complicatons	**Before con pl**	**After con pl**
1	ARDS		33 (expired cases)
2	AMI		1
3	Myocarditis		
4	Hypotension		
5	Acute heart failure		
6	Bradycardia		28
7	Tachycardia/atrial fib		
8	Venous thrombosis		
9	Pulm embolism		
10	Arterial thrombosis,limb		
11	Stroke		1

AYA COVID Centre – Total cases - 123			
	Complicatons	Before con pl	After con pl
1	ARDS		
2	AMI	3	
3	Myocarditis	15	5
4	Hypotension		
5	Acute heart failure		
6	Bradycardia	15	5
7	Tachycardia/atrial fib		
8	Venous thrombosis		
9	Pulm embolism		
10	Arterial thrombosis,limb		
11	Stroke	1	

Yangon General Hospital – Total cases - 123			
	Complicatons	**Before con pl**	**After con pl**
1	ARDS		
2	AMI		
3	Myocarditis		
4	Hypotension		
5	Acute heart failure		
6	Bradycardia		
7	Tachycardia/atrial fib		
8	Venous thrombosis		
9	Pulm embolism	1	
10	Arterial thrombosis,limb		
11	Stroke		1

Mortality of Patients With Severe COVID-19 in the Intensive Care Unit: An Observational Study From a Major COVID-19 Receiving Hospital Peshawar, Pakistan

Fawad Rahim

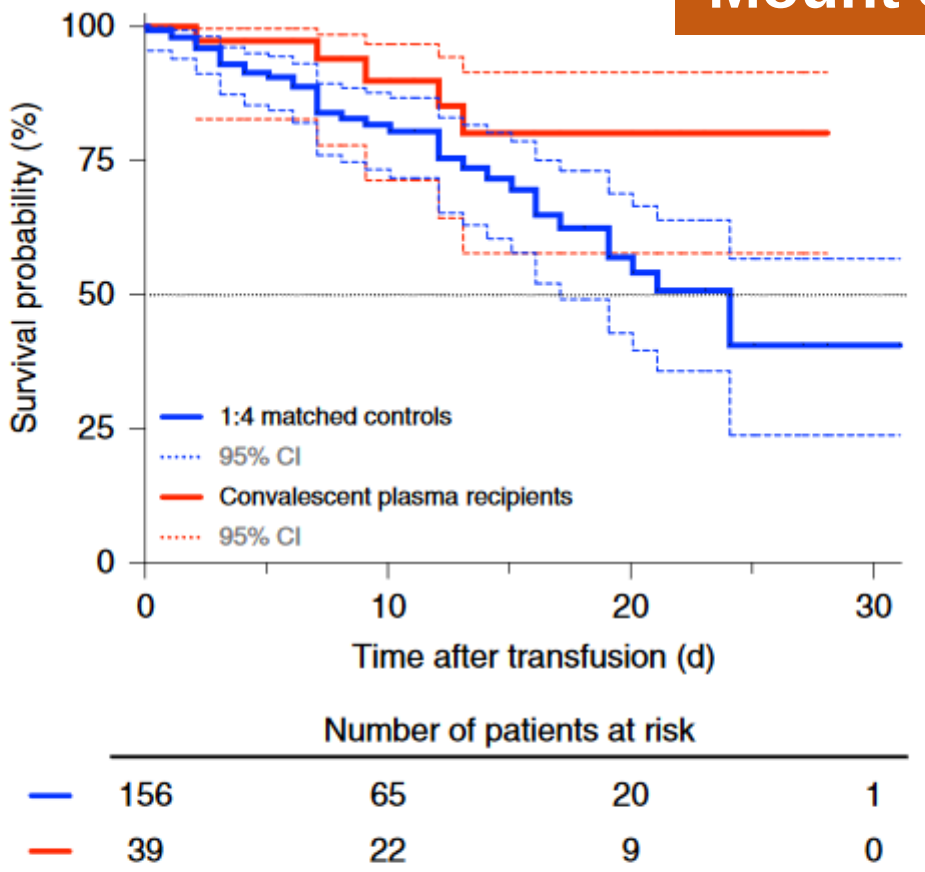
DOI: 10.7759/cureus.10906

Overall mortality was 77%.

Mortality 93.6% - mechanical ventilation

Non-invasive ventilation – 66.7 %

Mount Sinai, New York Study



✓ **Improved survival**

Mortality 12.8% vs 24.4%

Fig. 1 | Survival probability. As of 1 May 2020, 5 (12.8%) of 39 convalescent plasma recipients and 38 (24.4%) of 156 1:4 matched control patients had died. The median follow-up time was 11 d (range 1–28 d) for the plasma group and 9 d (0–31 d) for the control group. Overall, improved survival was observed for the plasma versus the control group.

NATURE MEDICINE | VOL 26 | NOVEMBER 2020 | 1708–1713 | www.nature.com/naturemedicine

Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)

BMJ 2020 (Published 22 October 2020)

Results:

- 235 were assigned to convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm).
- Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (**19%**) participants in the intervention arm and 41 (**18%**) in the control arm (risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54).
- **Conclusion:**

  Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality.
- Critique – Low neutralizing antibody titre in convalescent plasma (1:40)

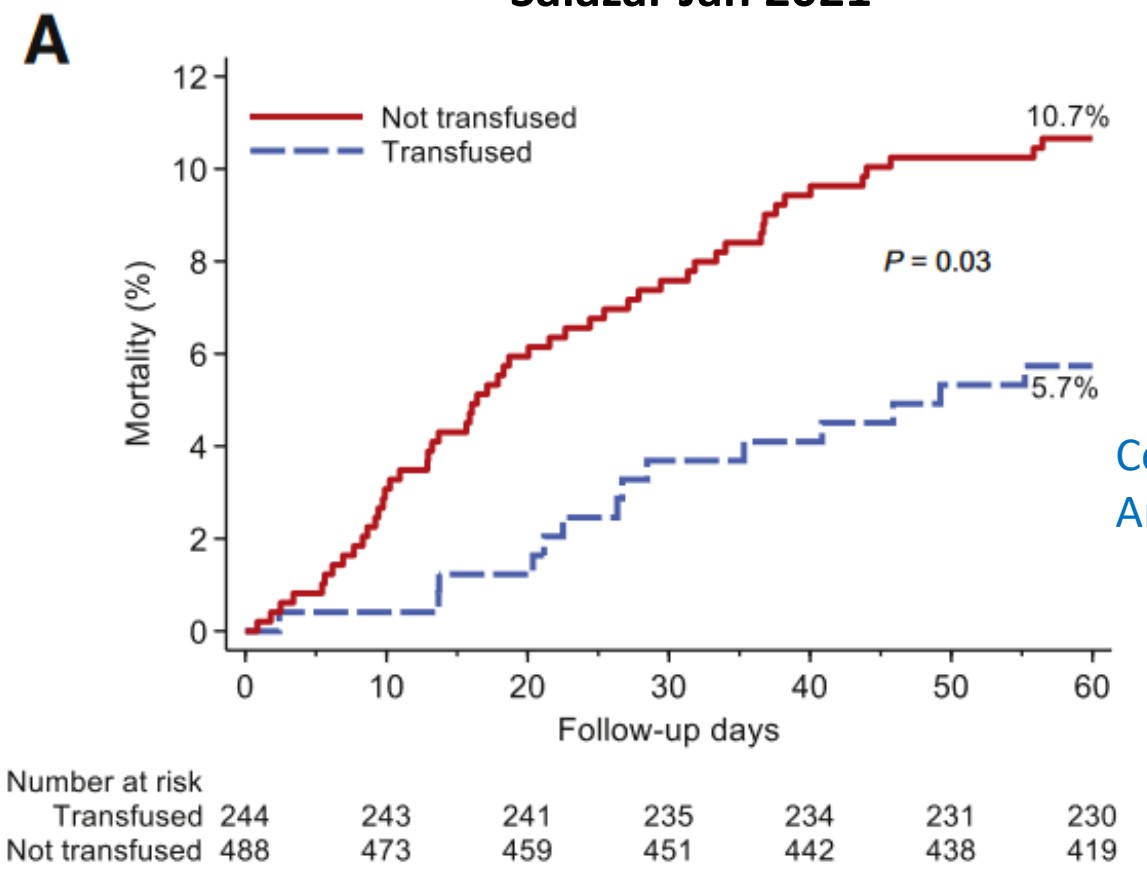
MAYO CLINIC – INITIAL THREE MONTH STUDY -*Joyner, medRxiv August 12, 2020*

Results: Convalescent plasma reduced mortality in hospitalized covid-19 patients

- ✓ **35,322** transfused patients
- ✓ critically-ill patients-52.3% 73 in the intensive care unit (ICU) and 27.5% on mechanical ventilation.
- ✓ Seven-day mortality rate was **8.7%** [95% CI 8.3%-9.2%] in 75 patients transfused within 3 days of COVID-19 diagnosis
- ✓ But **11.9%** [11.4%-12.2%] in 76 patients transfused 4 or more days after diagnosis (p<0.001).
- ✓ **Response also depended on antibody titre of convalescent plasma** (p=0.048)

	Signal/cut off ratio (Ortho)	Mortality at 7 days	Range
High IgG plasma	>18.45	8.9%	6.8%, 11.7%
Medium IgG plasma	4.62 to 18.45	11.6%	10.3%, 13.1%
Low IgG plasma	<4.62	13.7%	11.1%, 16.8%

Salazar Jan 2021



10.7%

5.7%

Convalescent plasma
Anti-spike antibody ≥ 1350

Figure A. Kaplan-Meier curves for mortality within 60 days after day 0 for different cohorts of propensity score-matched patients and controls. Patients transfused with plasma with an anti-receptor binding domain (RBD) IgG titer>1:1350 and transfused **within 72 hours of admission** (blue) propensity score matched to control patients (red) Salazar et al (The American Journal of Pathology,Vol 191:1, Jan 2021, Pages 90-107)

Timing of convalescent plasma therapy

- The optimal period is within 7 days from the onset of symptoms but the therapy seems to be effective also within 2 weeks. CP does not seem to be effective after 3 weeks from the onset of disease (Italian position paper 2020).

Discussion

- Late arrival of patients and late referral have effect on mortality
- Difficulty or delay to get laboratory investigations in time
- Difficulty in retrieving data back
- Doctors too busy having to rotate and look after both covid and non-covid patients
- Many of patients who received convalescent plasma were also receiving other drugs – Remdesivir, dexamethasone, tocilizumab, so the beneficial effects of treatment cannot be attributed to convalescent plasma alone
- This is an observational study; very difficult to do RCTs even in wealthy countries with large number of covid patients
- The main objective is to save lives as much as possible

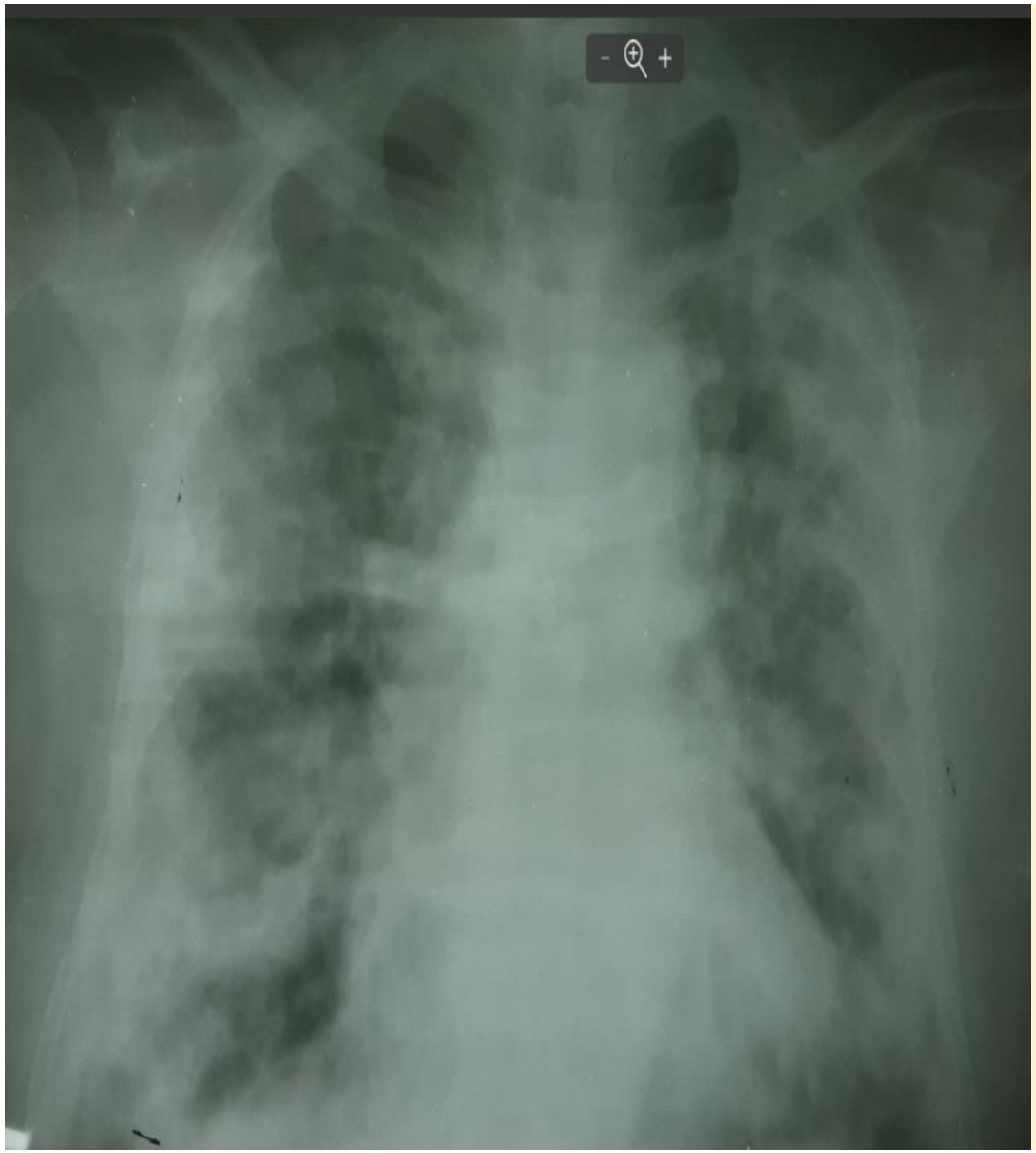
Conclusion – 1

- It is possible to successfully start a convalescent plasma programme for covid-19 patients
- It is possible to recruit and maintain enough convalescent plasma donors to supply the needs of all patients for whom treatment is indicated.
- It is possible to provide convalescent plasma with high antibody titres
- Convalescent plasma has beenfound to be safe when given to patients with severe covid disease

Conclusion – 2

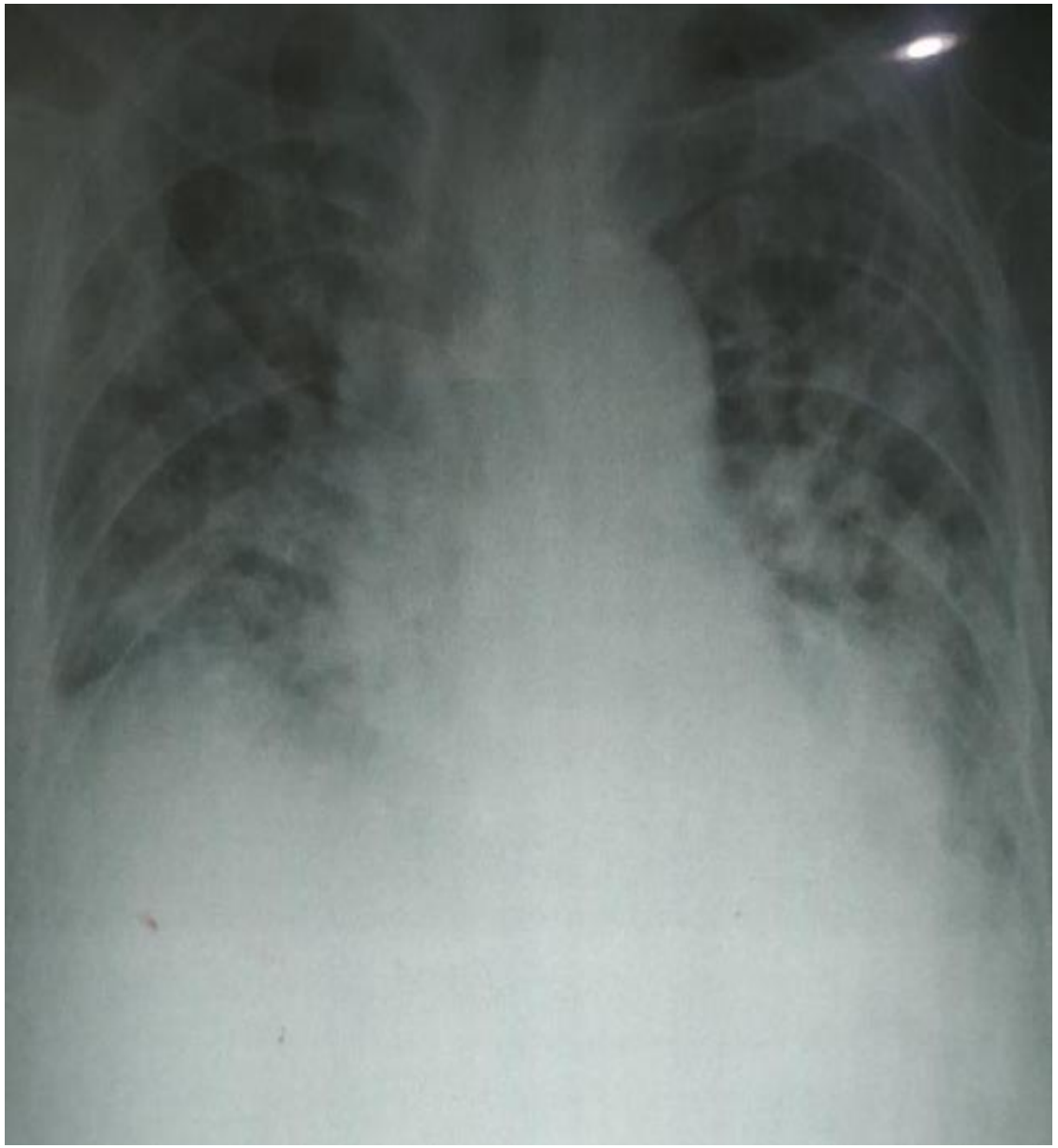
- The earlier convalescent plasma can be given if criteria of severity are present the better the results.
- If convalescent plasma can be given within 7 days of onset of symptoms, the mortality of severe covid is 15.66% whereas if there is a delay beyond 7 days the mortality can rise to over 30%.
- Dedicated departments for treating severe covid-19 have better results than very busy general hospitals where staff have to rotate very often and have to care for both covid and non-covid patients.
- The most important thing is to give convalescent plasma in time. Time is of utmost importance.

Case example



- 72M Senior doctor retd govt
- Admitted for anosmia, diarrhea, DOE x 3 days
- RDT Positive for SARS-CoV-2
- **Co-morbidities** – hypertension, diabetes m, IHD with 3 stents
- **Renal transplant** 2018, on immunosuppresive drugs ; SpO2 96% on O2 10L/min
- CRP – 115, D-dimer 2818
- Treated with Dexamethasone, LMWH but not Remdesivir because of kidney condition
- Drugs for co-morbidities
- 2 units of convalescent plasma
- High Flow Nasal Oxygen
- Hospital stay > 1 month including ICU 16 days
- Recovered and discharged

Case example



- 76 M, father of doctor working in a covid ward
- Fever,cough,DOE x 7 days. Diabetes M present
- Gene X-pert + SARS-2
- SpO2 88% on admission dropped to 78%
- BP dropped – noradrenalin infusion
- CRP 59.7, D-dimer 4971, Lymphopenia 0.89
- **Given convalescent plasma 2 units**
- Treated with HFNC, Dexamethasone, LMWH, Remdesivir, Tocilizumab, antibiotics
- Recovered after 4 weeks in hospital

Acknowledgements

- All voluntary convalescent plasma donors for their altruism which has saved hundreds of very ill patients suffering from severe covid disease
- The staff of National Blood Centre who have been working tirelessly to organize convalescent plasma donations so that convalescent plasma could be given to treat all patients who need them.
- All doctors looking after patients with covid-19 for their courage and perseverance having to work in such difficult, sometimes risky circumstances
- All staff of NHL, DMR, nurses and laboratory and administrative personnel of many departments who are heroes in the background
- To all volunteer workers, medical and non-medical for their selfness devotion and invaluable assistance during the whole crisis.
- Members of Ad-hoc Advisory Committee on Use of Convalescent Plasma for Covid-19
- WHO Myanmar for funding a plasmapheresis machine.
- Lastly the Union Minister MOHS who initiated this programme and has given his full support and encouragement all this time.

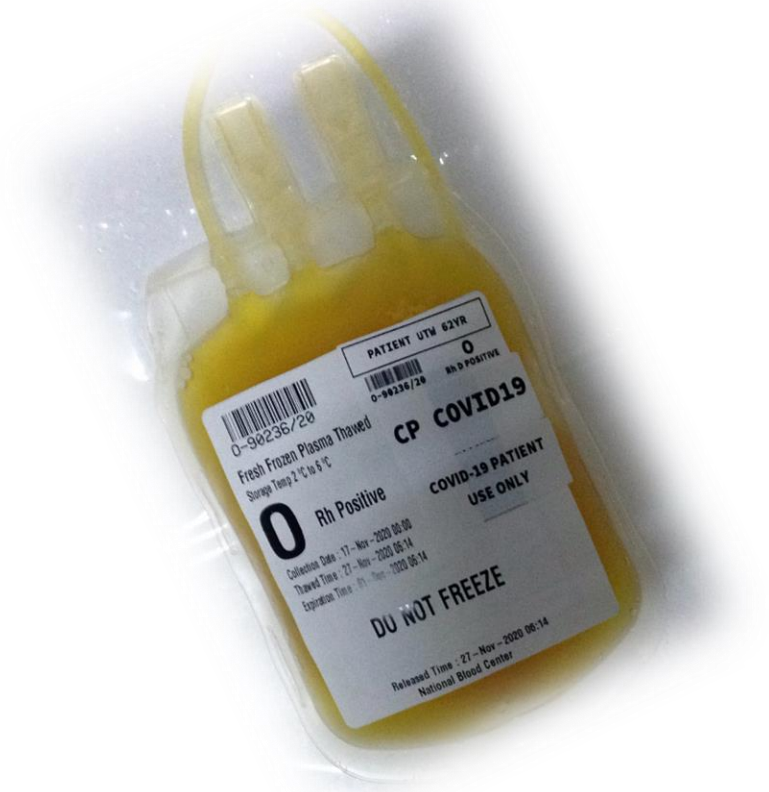
Thank you

Wear masks – save lives

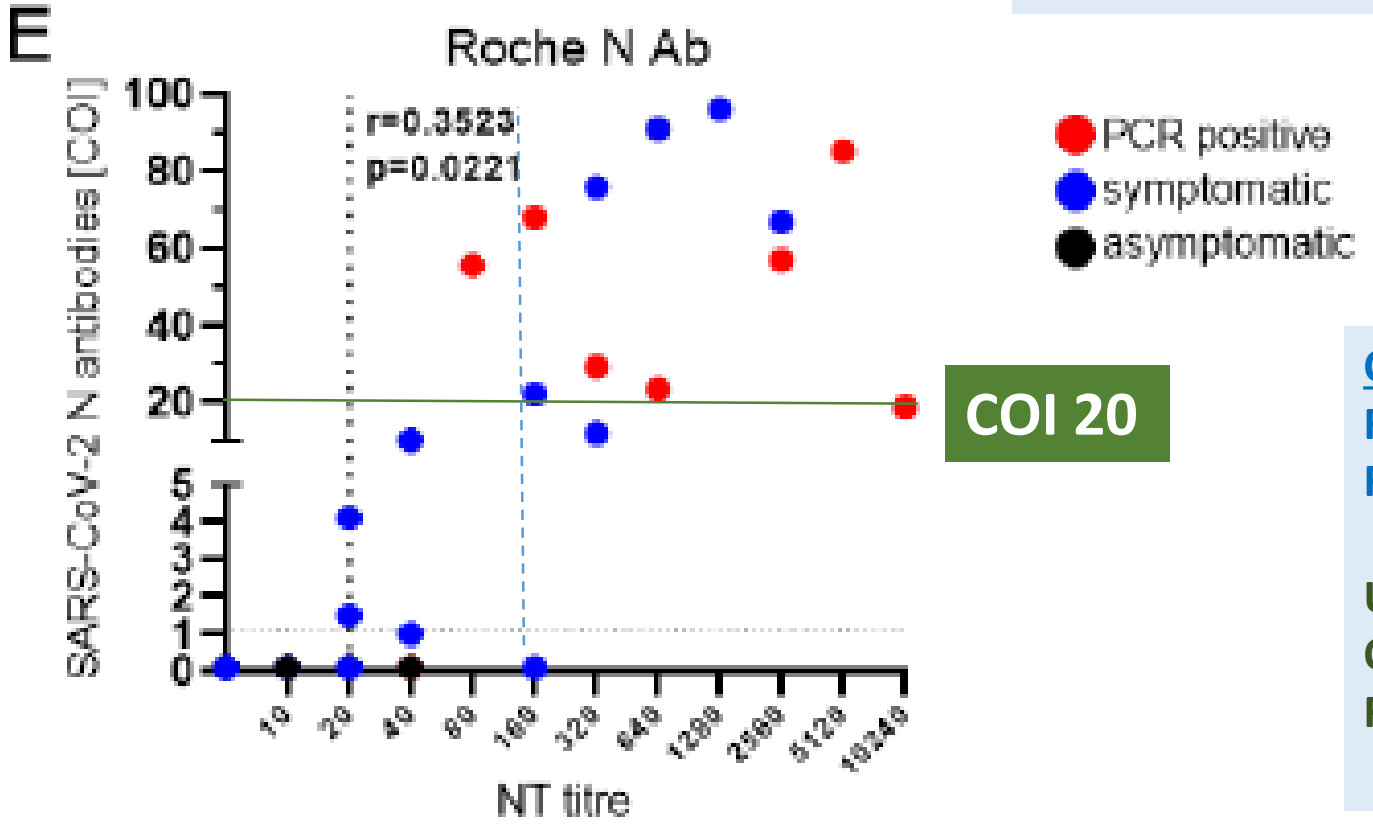
Wash hands – save lives

Do social distancing – save lives

Donate convalescent plasma – save lives



Recommended NAb titre in convalescent plasma 1:160

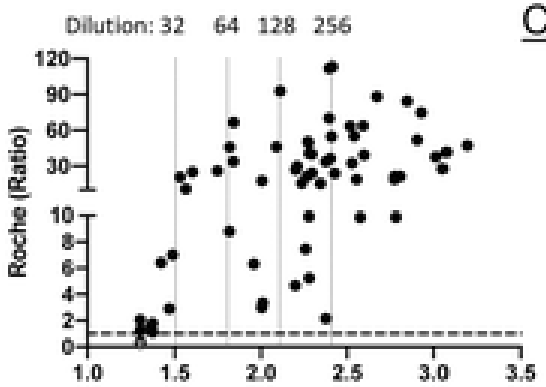
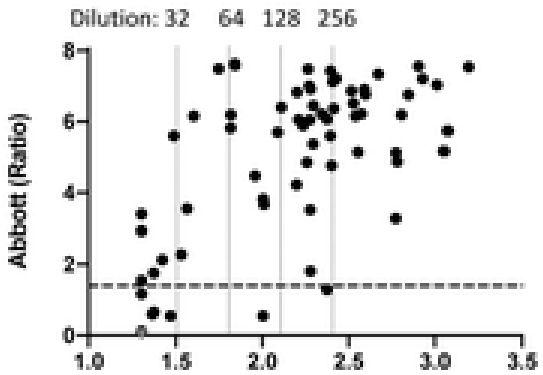
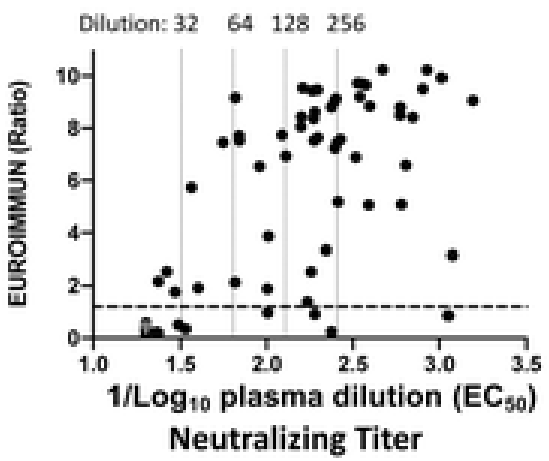


COI = Cut Off Index
Roche – Our COI is 20
For convalescent plasma

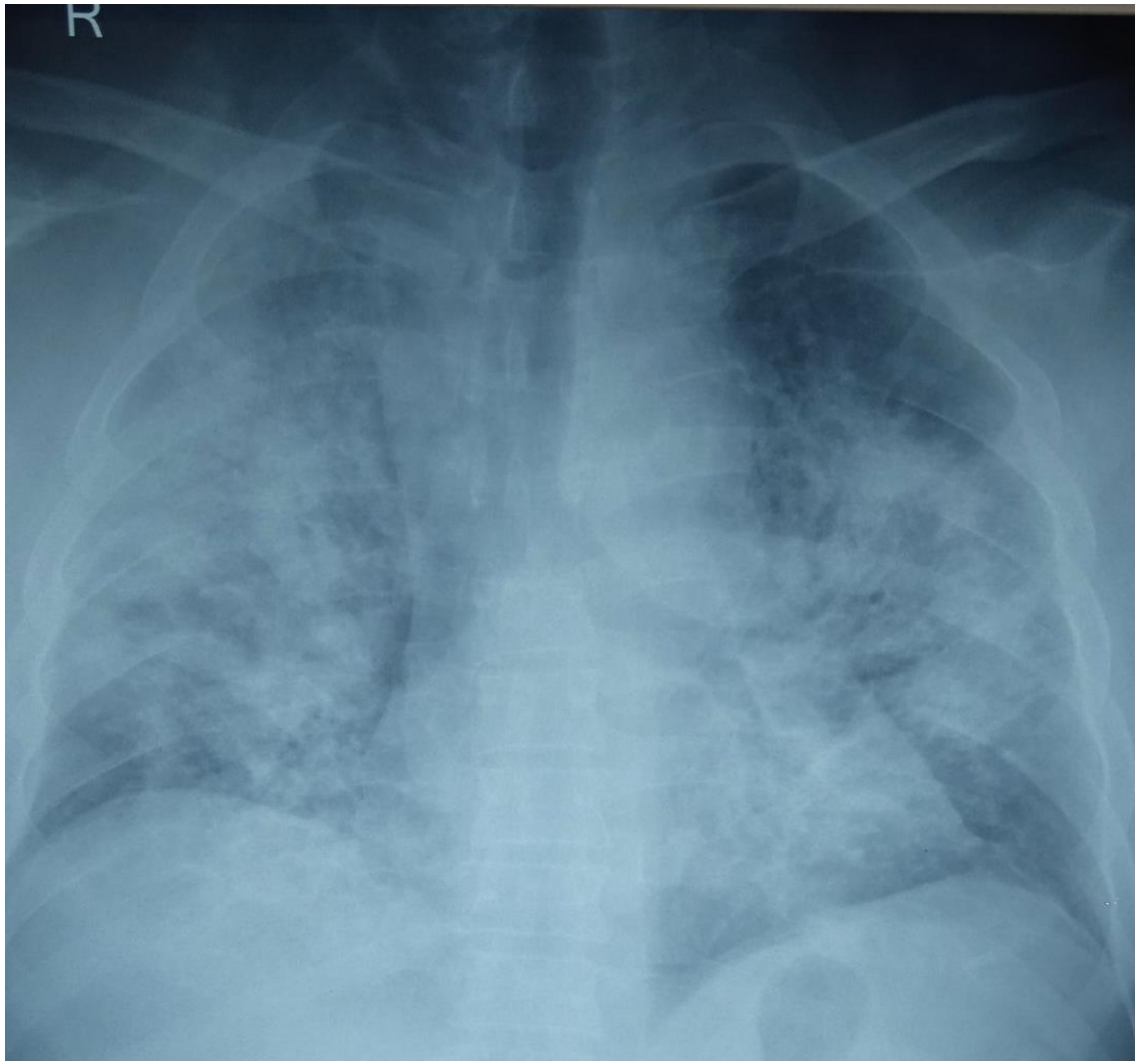
US FDA-
Ortho Vitros COI – 12
For convalescent plasma

Roche SARS CoV-2 IgG Antibody vs Neutralizing antibody

Lisa Müller: medRxiv preprint doi: https://doi.org/10.1101/2020.06.11.20128686

		Correlation	Titer	Concordance Kappa
A.		$r^2 = 0.29$	1:32	0.61 (0.35-0.86)
			1:64	0.49 (0.23-0.75)
			1:128	0.31 (0.06-0.56)
			1:256	0.11 (0.0-0.29)
B.		$r^2 = 0.47$	1:32	0.65 (0.42-0.88)
			1:64	0.52 (0.28-0.77)
			1:128	0.39 (0.16-0.62)
			1:256	0.16 (0.0-0.35)
C.		$r^2 = 0.46$	1:32	0.69 (0.49-0.89)
			1:64	0.61 (0.4-0.82)
			1:128	0.50 (0.30-0.72)
			1:256	0.27 (0.07-0.47)

Association between SARS-CoV-2 neutralizing antibodies and commercial serological assays. Mei San Tang, *Clinical Chemistry* doi: 10.1093/clinchem/hvaa211



Admission Chest X-ray. CRP 170, D-dimer 1550. Delay 4 days

history

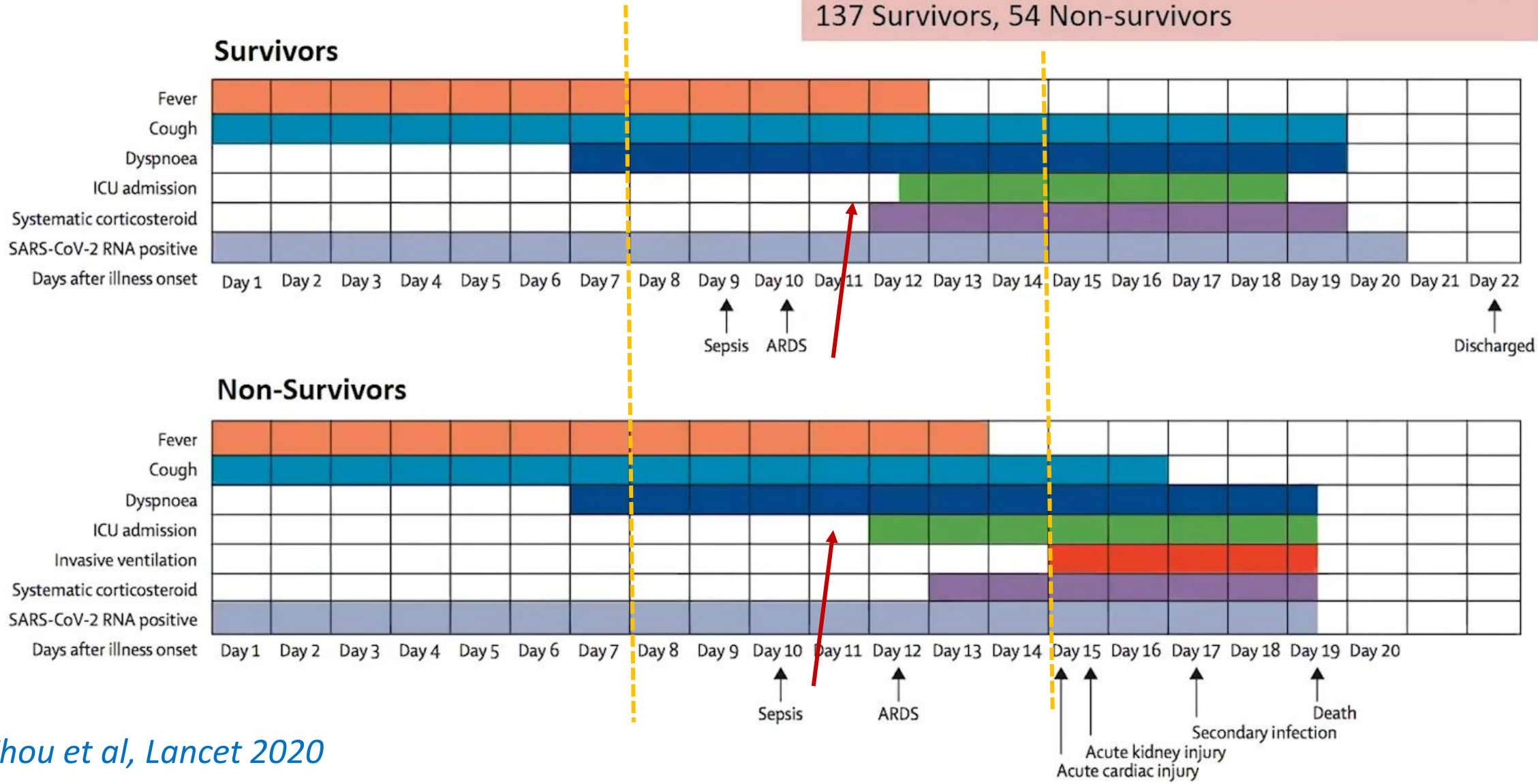
- Emil von Behring – used diphtheria antitoxin at the time known as humoral bodies to treat diphtheria successfully in 1891
- Convalescent plasma has been used in many diseases in the last century including measles, polio, Spanish flu of 1918
- Over the past two decades it has been used in the treatment of SARS, MERS and H1N1 with varying degrees of success but with no untoward side effects (Cheng 2005, Zhou 2007, Hung 2011, Ho 2018).
- It has also been used for Ebola virus disease - some degree of effectiveness has been claimed - not conclusive/ equivocal (Griensven 2016).
- No clinical trials because in all these – emergency use when no treatment was available

Previous experience with convalescent plasma therapy

- Cheng et al investigated 1775 SARS patients and found that 80 patients transfused with **SARS** convalescent plasma had a lower mortality rate, compared to non-transfused patients (12.5% vs 17%).
- Hung and colleagues in a study of **H1N1** convalescent plasma (antibody titre >1: 160) given to patients found that mortality was significantly reduced compared to a control group of patients who declined the plasma treatment (20% vs 54.8%)) (Hung 2015).
- In a meta-analysis that evaluated 8 studies including 1703 patients with Spanish influenza it was found that there was an absolute 21% reduction in the case-fatality rate among patients transfused with blood products derived from influenza convalescent individuals (Langhi Jr. 2020).
- **Ebola virus disease** - CP therapy was unable to significantly improve the survival in the Ebola virus disease, probably due to the absence of data of neutralizing antibody titration (Duan 2020).

Clinical Course

191 hospitalized patients (Wuhan) w/known outcome
137 Survivors, 54 Non-survivors



Zhou et al, Lancet 2020

Convalescent plasma therapy for the treatment of patients with COVID-19: Assessment of methods available for antibody detection and their correlation with neutralising antibody levels

Harvala et al, NHS Blood and Transplant

https://doi.org/10.1101/2020.05.20.20091694 MedRxiv May 26, 2020.

- 52 hospitalized patients with a previous laboratory confirmed SARS-CoV-2 infection at least 28 days after symptom resolution.(No data on severity).
- Assayed for SARS-CoV-2 **neutralising antibodies** by **native virus and lentiviral pseudotype** assays, and for antibodies by four different ELISAs
- All samples contained SARS-CoV-2 antibodies, whereas neutralising antibody titres of greater than 1:20 were detected in 43 out of 52 tested samples (83%) using a cut-off titre 1:20; the highest detectable titre was 1:4096
- **Robust associations between virus neutralising antibody titres and reactivity in several ELISA-based antibody tests**
- **Neutralising antibody level 1:100 was selected as a pragmatic cut-off that enables an estimated 40 % of collected plasma to be used.**
- **2 units from different donors preferable**

UK strategy

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia, Argentina- NEJM November 24, 2020

- 228 patients were assigned to receive convalescent plasma and 105 to receive placebo.
- Median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5 to 10),
- hypoxemia was the most frequent severity criterion for enrollment.
- The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1:32No00].
- Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group
- **No difference**