

Convalescent Plasma in Mechanically Ventilated COVID-19-induced Acute Respiratory Distress Syndrome (ARDS)



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Introduction

1. COVID-19 induced ARDS + Invasive Mechanical Ventilation (IMV) :
 - Mortality = 45 % at day 28 (ICNARC 2020; Lim AJRCCM 2021)
 - > 50 % shed the virus > 20 days (Saud, CID 2022)
2. No effective antiviral drug
3. Convalescent plasma proposed in March 2020 (Axfors, JAMA 2021)

Introduction

1. US ICU trials on CP stopped when FDA approved compassionate use (Bennett-Guerrero, CCM 2021)
2. CP is safe (Joyner, Mayo Clin Proc 2020)
3. Few trials with neutralization test (*versus* total Ab assessment)
4. Few trials with IMV patients (subgroups in Recovery and REMAP-CAP)

Hypothesis

- Passive immunization with CP and a high neutralizing activity may reduce mortality of patients
 - With COVID-19 associated ARDS
 - Administered early after IMV initiation

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Normal lung



ARDS / extensive pneumonia

Design

- Donor recruitment campaign by Belgian Red-Cross
 - Neutralization tests (Liège and Leuven Universities)
 - Plasma selected if $\geq 1/320$ ($>1/160$ accepted in case of shortage)
- Inclusion :
 - 18 years, Frailty score < 6 , Chest TDM < 10 days, PCR < 15 days, MV < 5 days, consent by a proxy
- Exclusion :
 - Pregnancy, side effect of a transfusion, decision to limit vital support, other trial

Design

- Stratification
 - MV $\leq$ 48h
 - MV > 48h
- Randomization
 - 2 x 250 mL plasma from convalescents after first wave
 - Standard of care
- Endpoint
 - Principal : mortality at day 28
 - Secondary :
 - Organ dysfunction (SOFA)
 - Inflammation (CRP)
 - Adverse events
 - Mortality at day 90

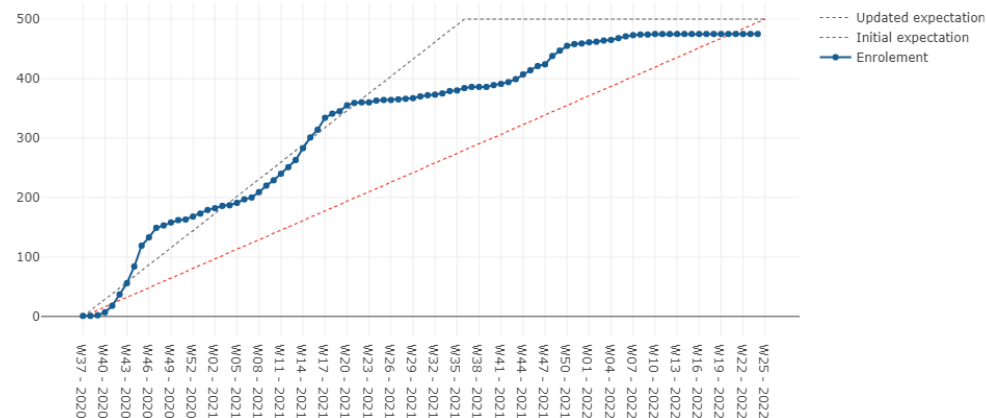
Design

- Number of patients to include
 - Expected mortality
 - Control: 40 %
 - CP: 30 %
 - alpha 5%, beta 20%
 - $n = 250 \times 2$
 - -> 500 patients in total

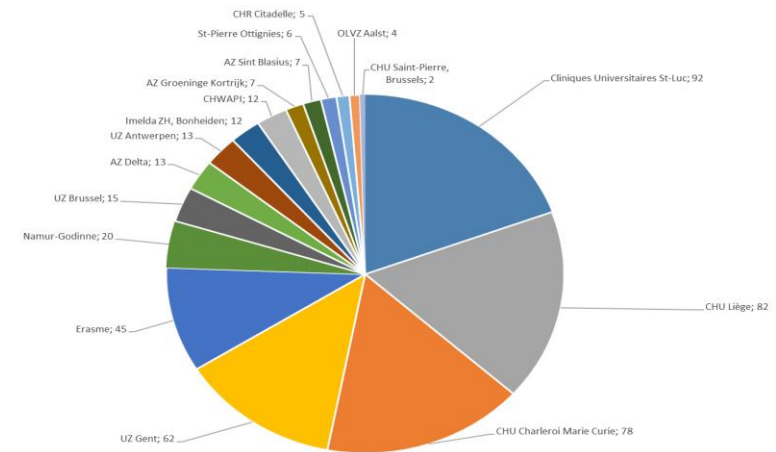
Results

- 17 centers in Belgium
- 475 patients included from October 2020 to March 2022
- 4 interim analyses, blind to the investigators : “you can continue”
- Stop in March 2022 due to no recruitment in one month (Omicron BA.2 ?)

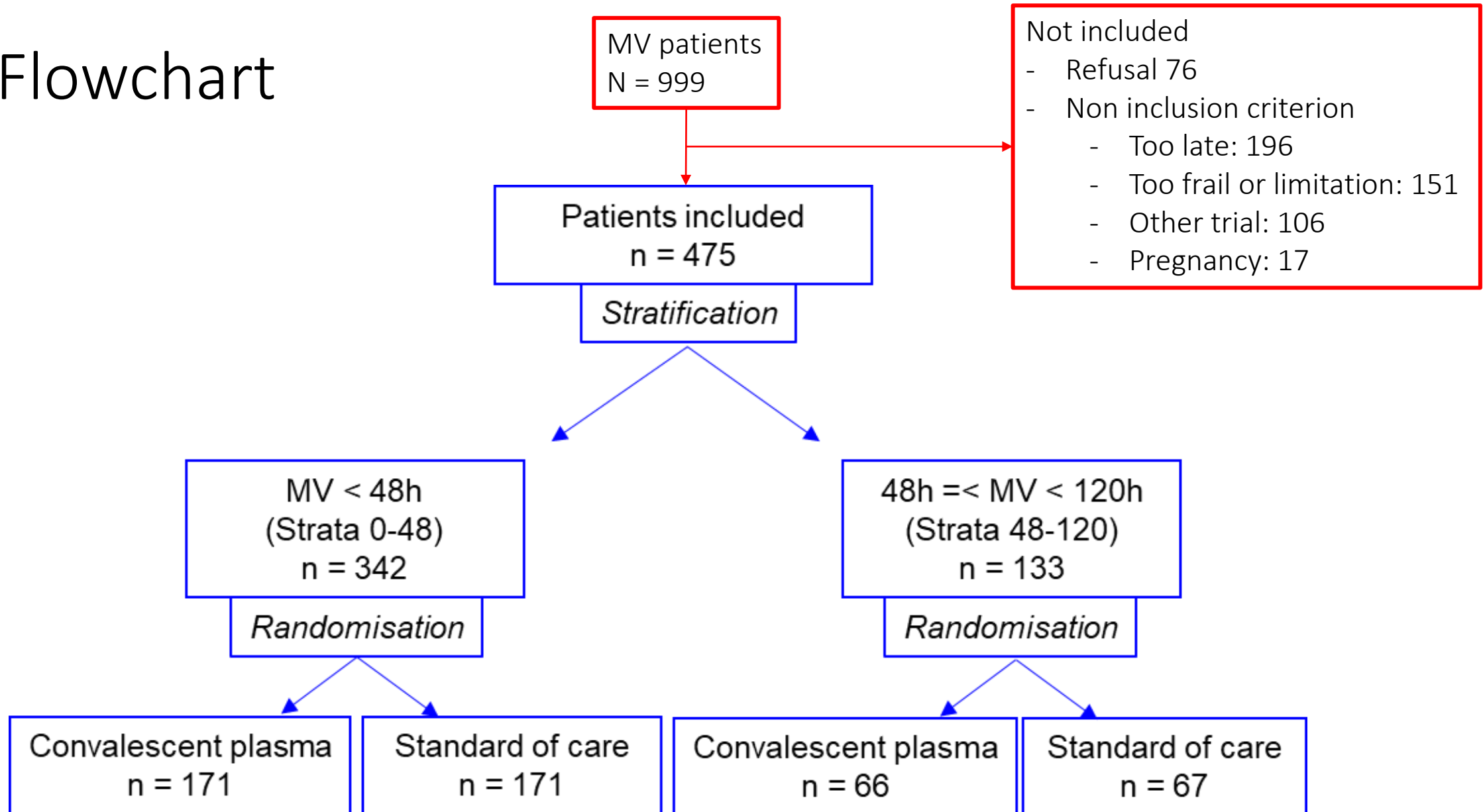
Inclusions over time



Inclusions by center



Flowchart



Patients at inclusion

	Missing CP/SOC	Convalescent Plasma	Standard of care
		N = 237	N = 238
Age, years	0/0	64 [55-71]	64 [56-70]
BMI, kg/m ²	26/20	30.5 [26.5-34.9]	29.7 [26.5-34.3]
PaO ₂ /FiO ₂ , mmHg	0/1	117 [90-162]	128 [93-160]
APACHE 2 score, points	0/3	13.0 [9.0-18.0]	13.0 [9.0-17.0]
SOFA, points	0/3	6.0 [4.0-8.0]	6.0 [4.0-8.0]
CRP, mg/L	0/1	126 [67-191]	110 [55-188]
Diabetes, yes	0/1	34.2 %	38.7 %
COPD, yes	0/1	11.4 %	10.1 %
Chronic renal failure	0/1	13.5 %	12.6 %
Time from hospital admission, days	3/7	4.6 [2.6-6.7]	5.4 [2.8-7.7]

Principal endpoint : day 28 mortality

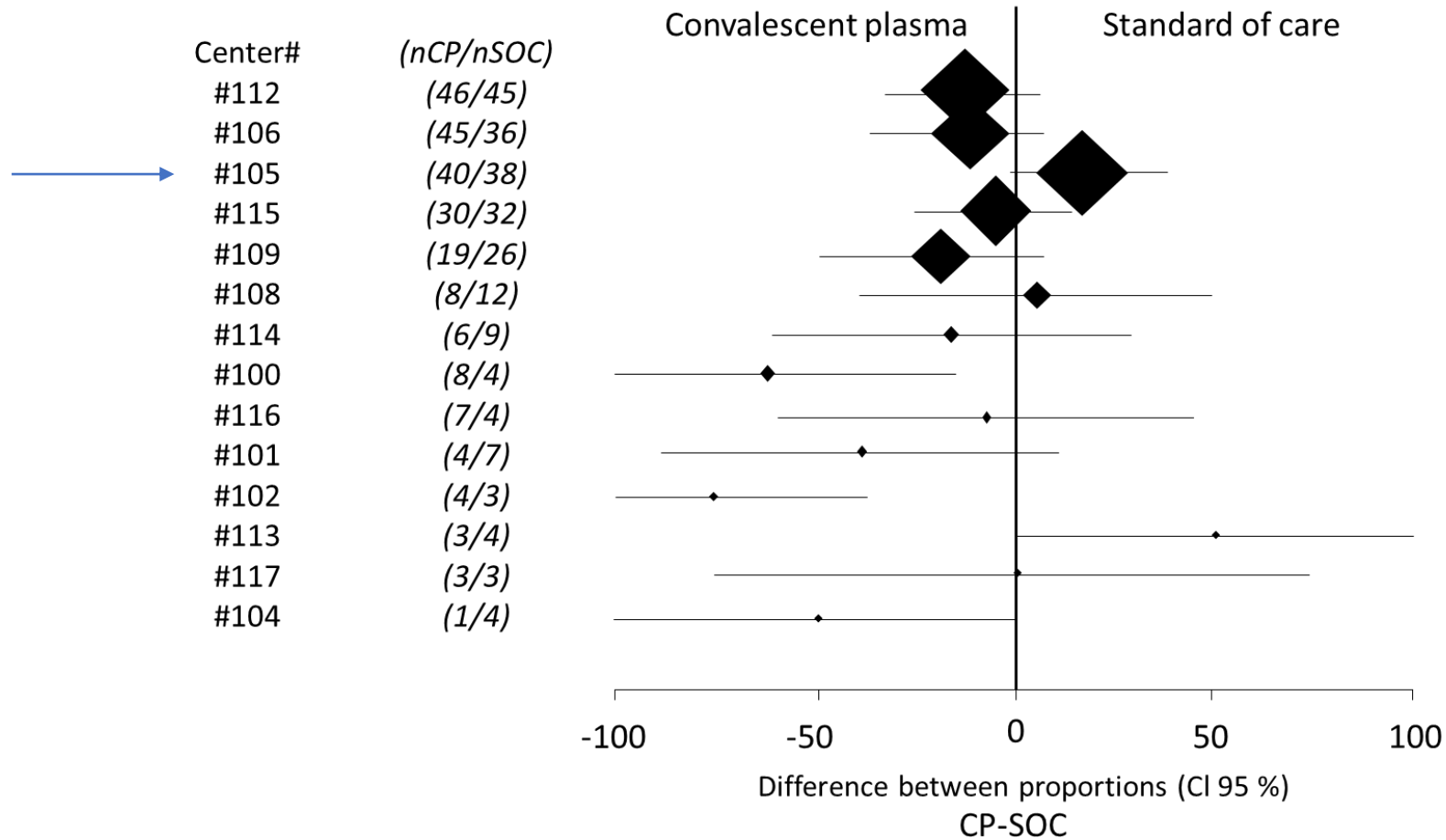
Population	Missing	Convalescent Plasma	Standard of care	<i>p</i>
Total	0/0	84/237 (35.4)	107/238 (44.9)	0.03*
Stratum MV ≤ 48 h	0/0	56/171 (32.7)	80/171 (46.8)	0.008
Stratum MV > 48 h	0/0	28/66 (42.4)	27/66 (40.3)	0.80

* before and after adjustment for stratification factor

Secondary endpoints

	Missing values	Convalescent plasma	Standard of care	CP – SOC Difference (95%CI)
Outcomes	n CP/n SOC	n = 237	n = 238	
Patients with at least one adverse event, n	0/0	158 (66.7)	173 (72.7)	-6.0 (-14.7 – 1.7)
Decision to limit therapy before day-28		21 (8.9)	32 (13.4)	-4.6 (-10.2 – 1.1)
Bacteremia (≥ 1 episode), n	5/6	62 (26.2)	69 (29.0)	-2.8 (-10.9 – 5.2)
VAP (≥ 1 episode), n	5/6	182 (76.8)	188 (79.0)	-2.2 (-9.54 – 5.05)
At day-7 in survivors (n = 421)				
CRP, mg/L	0/0	85 [37 - 182]	120 [59 - 203]	-17.3 (-35.5 - -0.50)
SOFA score, points	0/0	4 [3 – 7]	5 [4 – 8]	-1.0 (-1.0 – 0)
Time alive and free of support at day-28, days				
IMV	1/3	0 [0 - 14]	0 [0 - 10]	0 (0 – 0)
Vasopressors	4/3	19 [4 – 27]	14 [2 – 26]	1.00 (0 – 2.54)
RRT	4/5	28 [12 – 28]	28 [10 – 28]	0 (0 – 0)
Mortality at day-365, n	4/4	107 (45.9)	123 (52.6)	-6.6 (-15.7 - 2.4)

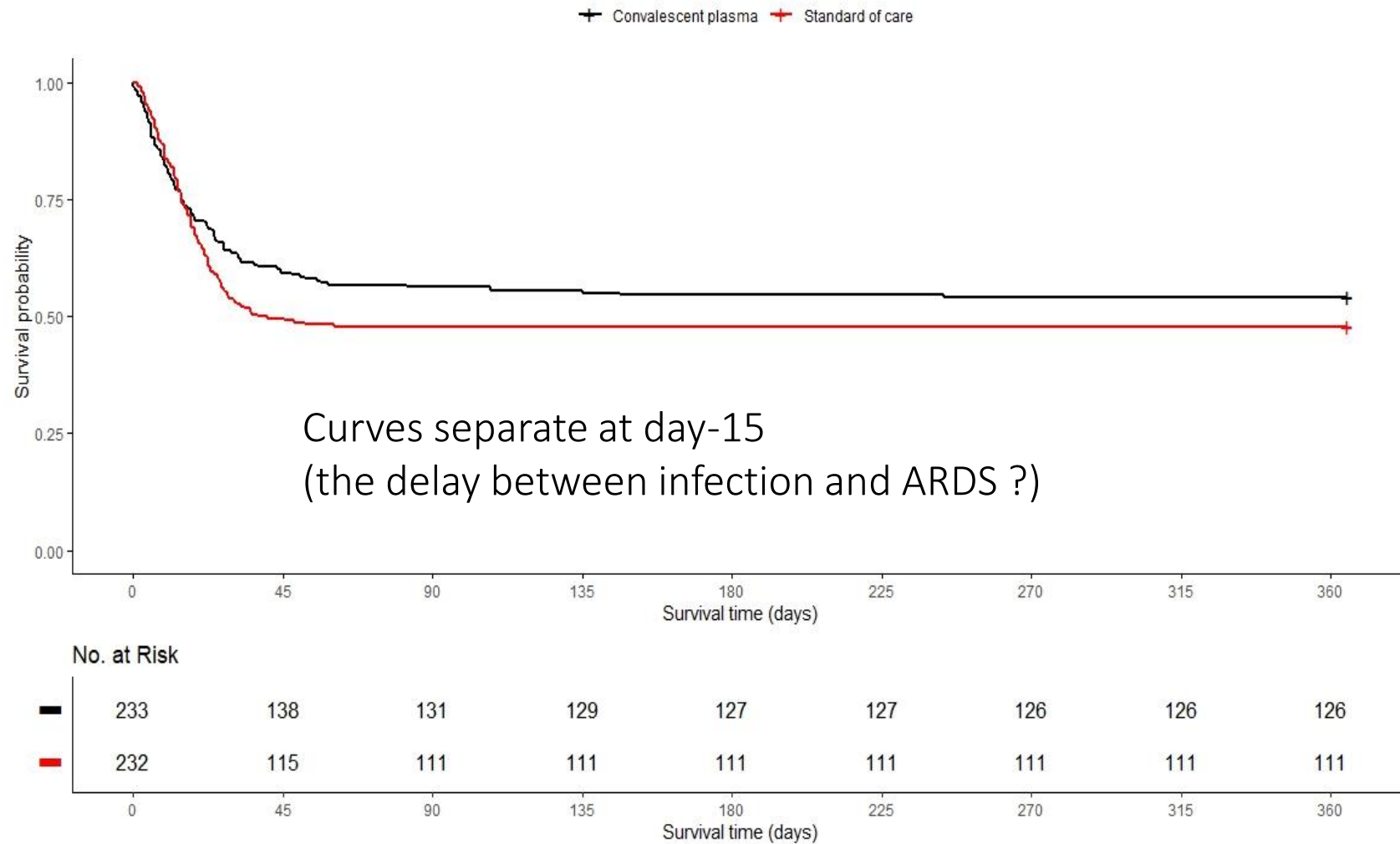
Principal endpoint by center



The positive result was not driven by a center.

In center #105, SOC group had a shorter time from hospital admission to inclusion (no stratification by center, chance?)

Survival curves at 1 year



Why do we think it worked ?

- Homogeneous population (IMV = severity // mortality)
- Homogeneous delay from infection
- When virus is still present

- Chance
- Bias

Limitations

- Not blinded
- Plasma collected during ancestral and alpha variants waves
- Premature end

Conclusion

The administration of plasma collected from convalescent donors and documented with $\geq 1/160$ titers of NAb to patients with COVID-19-induced ARDS within 5 days of IMV significantly reduced mortality at day 28.

In the pre-specified analysis, this was driven by the patient group included within 48 hours of IMV.

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Thank you for making it possible !

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