La terapia nel paziente COVID-19 “medico” e l’uso del plasma convalescente

Ordinario di Malattie Infettive, UNIPI
Direttore UOC Malattie Infettive AOUP
Presidente Gruppo Italiano per la Stewardship Antimicrobica (GISA)
Principal Investigator, TSUNAMI ITALIA

Dalla diffusione delle malattie infettive in Toscana all'epidemia di COVID- nei paesi europei: evidenze e riflessioni

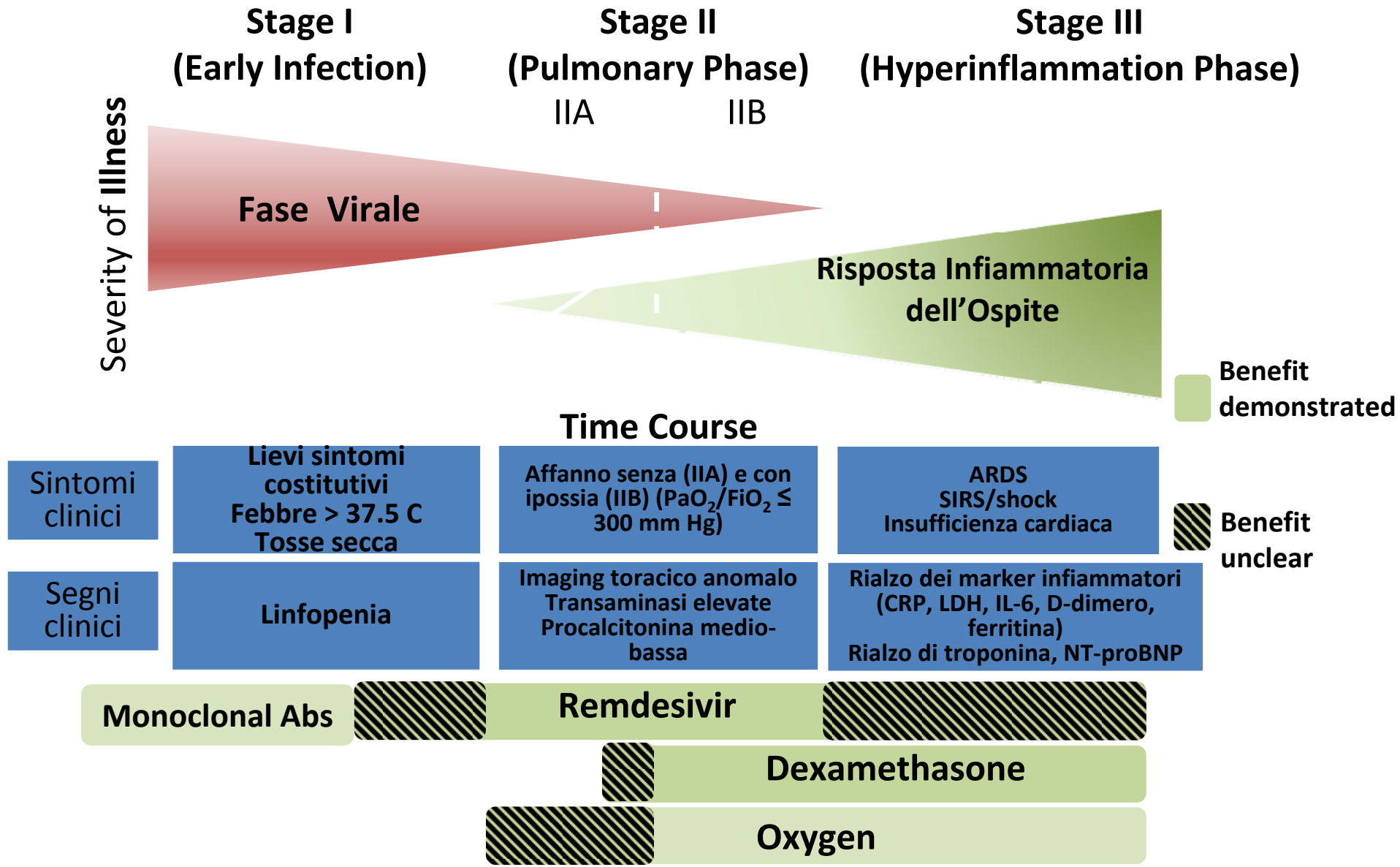
MERCOLEDÌ 3 FEBBRAIO 2021
ORE 09:30 - 13:00

ARS TOSCANA
agenzia regionale di sanità

Regione Toscana

SST Servizio Sanitario della Toscana

Terapie per COVID-19 nelle diverse fasi di malattia



Siddiqi. J Heart Lung Transplant. 2020;39:405.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.[a] These EUAs do not authorize use in hospitalized patients. **Dexamethasone** should not be used **(AIII)**.
Hospitalized[a] But Does Not Require Supplemental Oxygen	**Dexamethasone** should not be used **(AIIa)**. There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized[a] and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[e,f] • **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized[a] and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d,f] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f]
Hospitalized[a] and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d] **(AI)**[g]

The dynamic treatment of SARS-CoV-2 disease

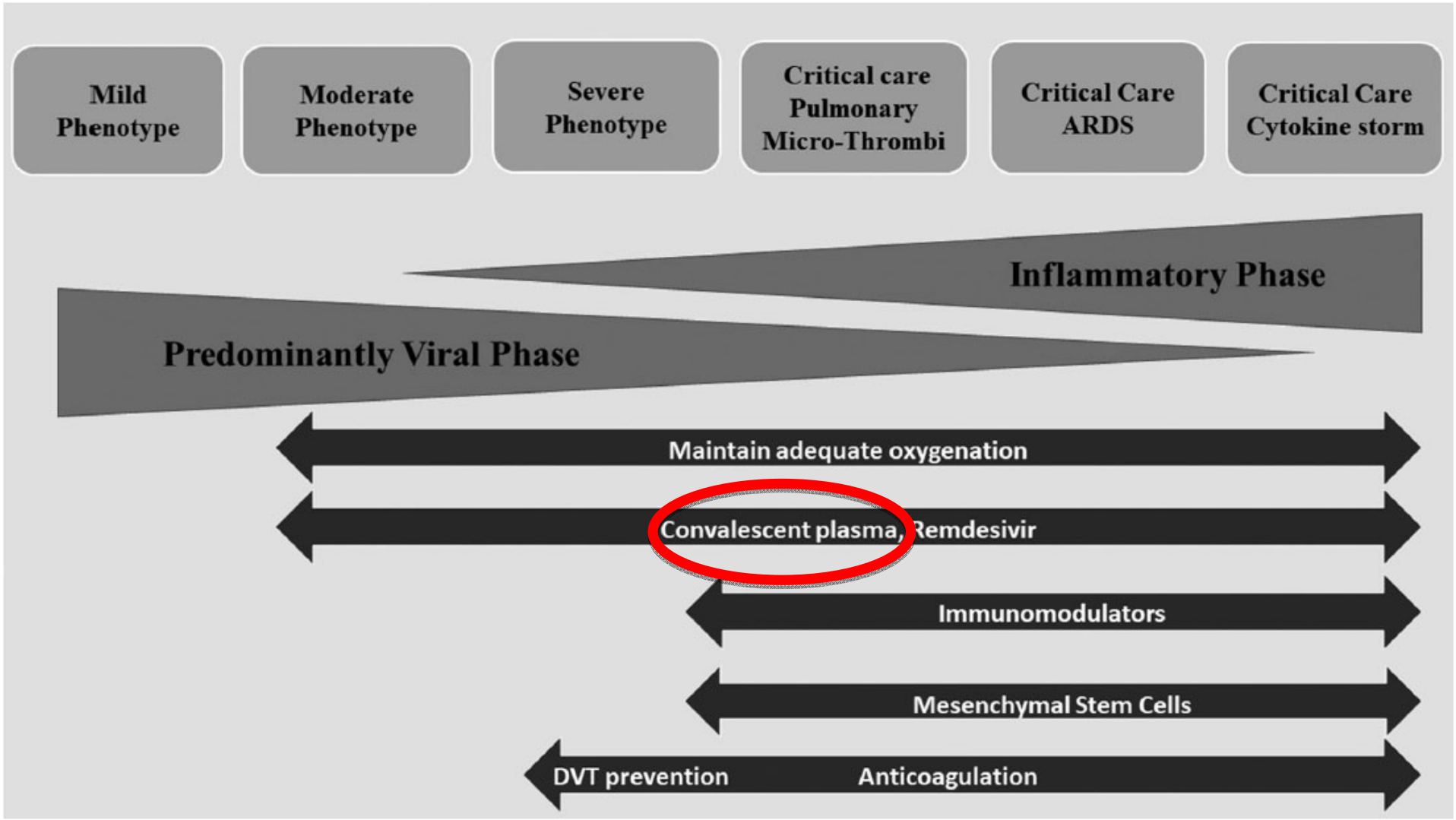


Figure 1. Phenotypes and possible therapeutic approaches for SARS-CoV-2 disease. Adapted from Siddiqi (2020).[60]

PROC (BAYL UNIV MED CENT)
2020;33(4):572–579

Table 1. Clinical phenotypes, laboratory markers, clinical characteristics, and interventions for SARS-CoV-2 disease

Clinical phenotype	Clinical/laboratory markers	Radiologic findings	Possible interventions
Mild disease	• No oxygen requirement • Mild lymphopenia	• None	• Observation
Moderate disease	• Fever • Elevated CRP • Lymphopenia • Oxygen saturation ≥95%	• Focal infiltrates on CXR • Bilateral reticular infiltrates	• Oxygen • Supportive therapy • Remdesivir • Other antivirals? • Convalescent plasma
Severe disease	• Fever, malaise, cough • Oxygen saturation ≤94% • Elevated CRP	• Bilateral CXR infiltrates	• Oxygen • Remdesivir or convalescent plasma ± immunomodulating agents
Overlapping severe phenotype	• Severe disease • Elevated ferritin and D-dimer	• Bilateral CXR infiltrates	• Oxygen supplementation • Remdesivir or convalescent plasma and immunomodulatory agents
ARDS	• $PaO_2/FiO_2 < 200$ • Inflammatory markers	• Bilateral fluffy infiltrates	• Low tidal volume • Prone positioning • ECMO (selected cases) • Remdesivir or convalescent plasma • Mesenchymal cells?
Cytokine storm	• High ferritin • High CRP • High LDH • Cytopenias	• Bilateral infiltrates	• IL-6R (?), IL-1R? • Anti-GM-CSF • Corticosteroids (?) • Convalescent plasma
Microthrombosis	• Elevated D-dimer (>3) • Increased V_D/V_T	• CXR may be clear	• Anticoagulation • Antivirals or immunomodulating agents?

PROC (BAYL UNIV MED CENT)
2020;33(4):572–579

The convalescent sera option for containing COVID-19

Arturo Casadevall[1] and Liise-anne Pirofski[2]

[1]Department of Molecular Microbiology and Immunology, Johns Hopkins School of Public Health, Baltimore, Maryland, USA. [2]Division of Infectious Diseases, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York, USA.

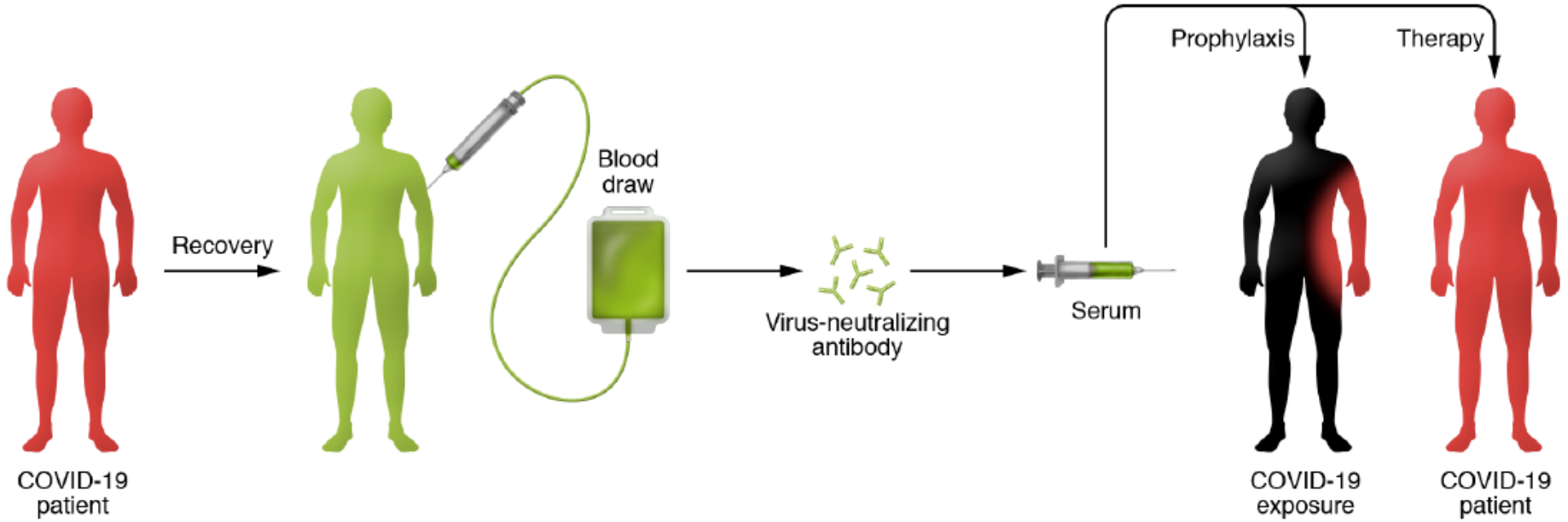


Figure 1. Schematic of the use of convalescent sera for COVID-19. An individual who is sick with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in the treatment of established disease.

Plasmaterapia iperimmune: meccanismo d'azione degli anticorpi neutralizzanti

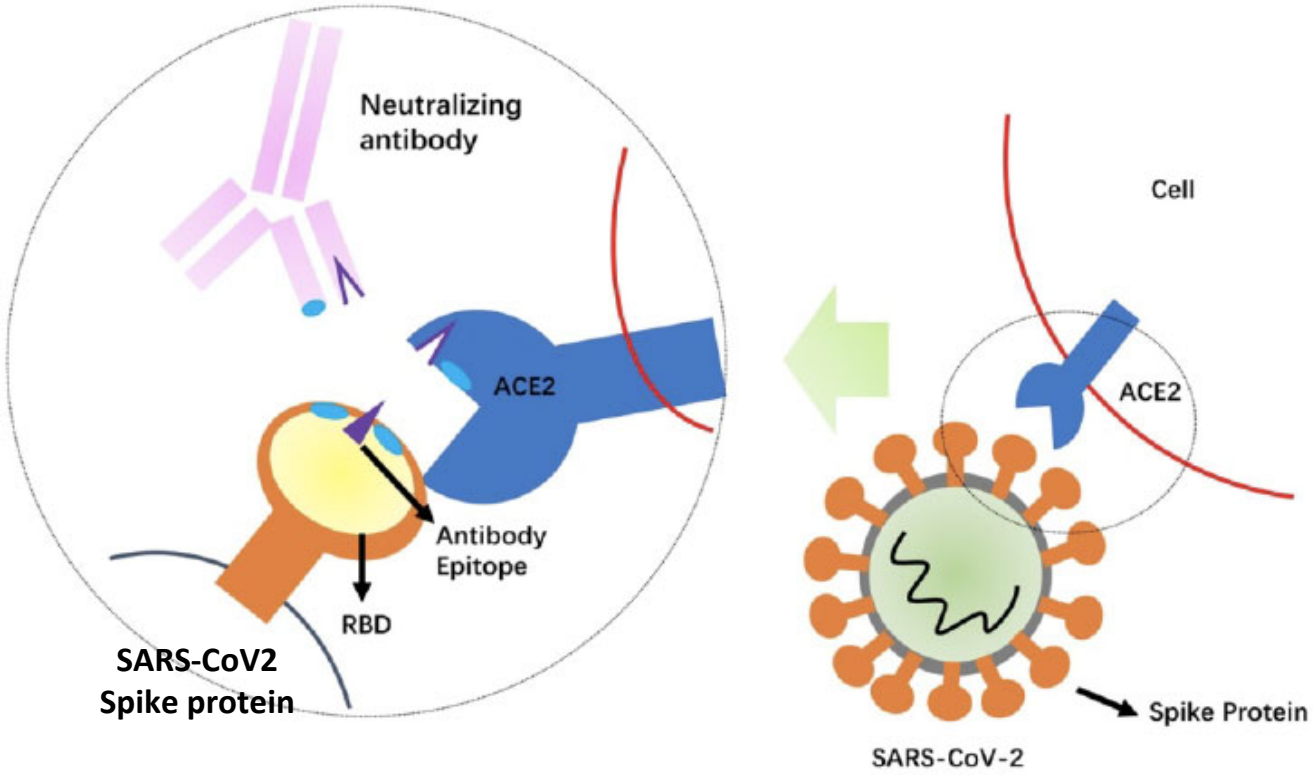


Figure 2. Schematic mechanism of the neutralizing antibodies. Competition of the neutralizing antibody with the receptor (ACE2) for binding to the receptor-binding domain (RBD) of the SARS-CoV-2 Spike protein is shown. The protruding portion (violet) of RBD is both the ACE2 receptor-binding site and the antibody epitope.

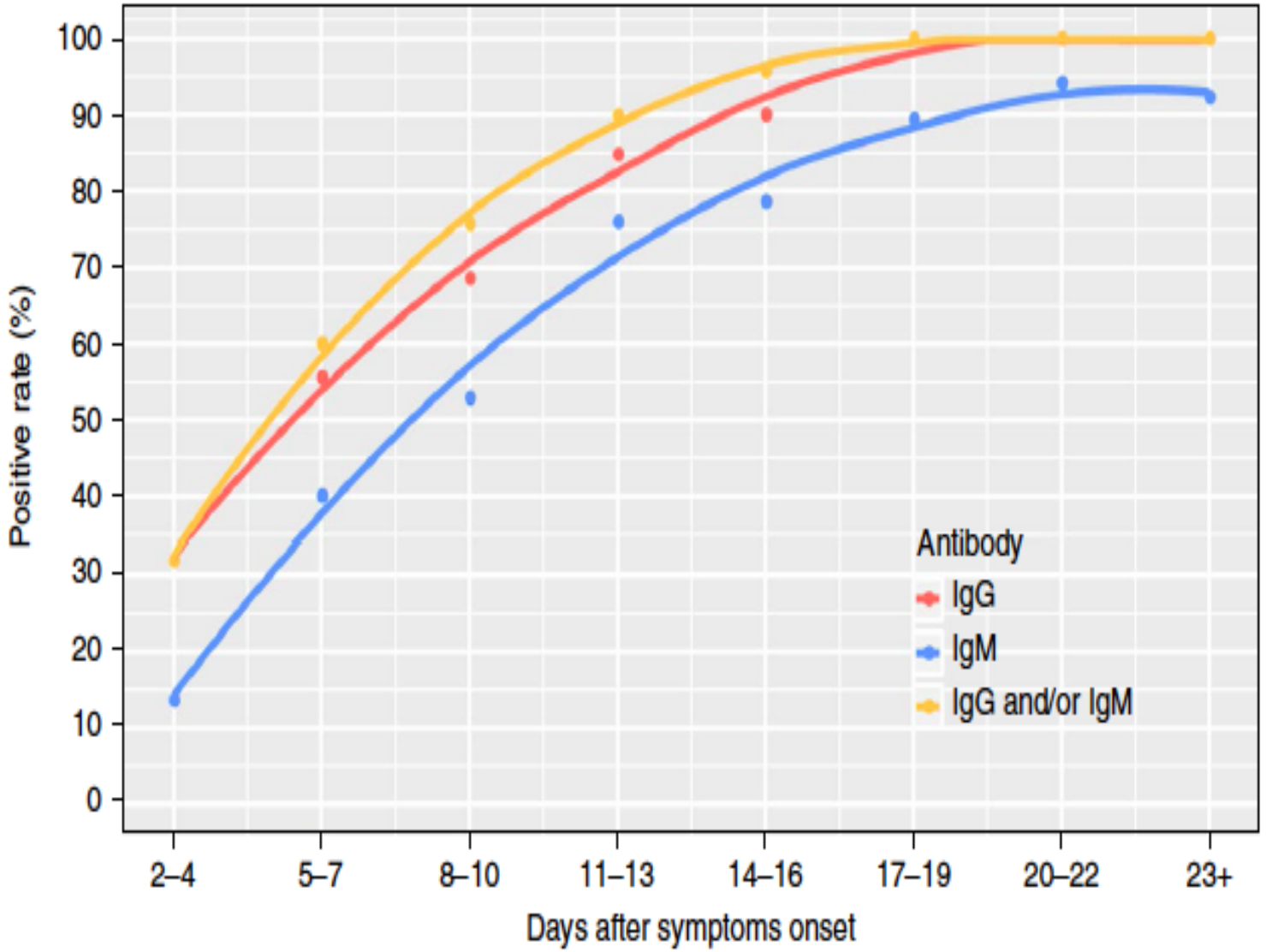
Antibody neutralization
ADCC: antibody-dependent cellular citotoxicity
ADCP: antibody-dependent cellular phagocytosis
CDC: complement-dependent citotoxicity

Int. J. Biol. Sci. 2020, Vol. 16

Convalescent Plasma: mechanism of action

- Nabs responses more robust in pts with severe disease.
- **Immunomodulation: neutralization of autoantibodies such as anti-cardiolipin IgA antibodies and anti-β2-glycoprotein antibody, which reduces the likelihood of thrombotic events**
- **CP may inhibit complement cascade and cytokines and reduce the inflammation in the lungs.**
- **SARS-CoV-2 spike protein might be a superantigen playng an important part in the hyperinflammatory response often seen in COVID-19**
- **An immunomodulatory effects of CP for COVID-19, may also reduce or prevent any superantigen effects of SARS-CoV-2.**

Antibody responses to SARS-CoV-2 in patients with COVID-19



NATURE MEDICINE | www.nature.com/naturemedicine

Longitudinal Dynamics of the Neutralizing Antibody Response to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Kai Wang,[a] Quan-Xin Long,[a] Hai-Jun Deng,[a] Jie Hu,[a] Qing-Zhu Gao, Gui-Ji Zhang, Chang-Long He, Lu-Yi Huang, Jie-Li Hu, Juan Chen,[a] Ni Tang,[a] and Ai-Long Huang[a,]

- SARS-CoV2 specific Nabs titers were measured in 30 pts over a 3-month period after symptom onset
- **NAbs titers were low for the first 7–10 days after symptom onset and increased after 2–3 weeks.**
- **The median peak time for NAbs was 33 days (range, 24–59 days) after symptom onset.**
- NAbs titers in **93.3% of the pts declined gradually over the 3-month period**, with a median decrease of 34.8%
- **CP collection window: waiting 4 weeks after the resolution of symptoms to ensure viral clearance and a rise in convalescent antibody titer and close by 12 weeks.**

CID 2020 August 3

Plasma convalescente: qualificazione

- Valutazione clinica dell'aspirante donatore convalescente (età, sesso, gruppo sanguigno, fattori di rischio, sierologia, titolazione diretta Nabs)
- Donne con pregresse gravidanza: anticorpi anti-HLA, TRALI ?
- Test di neutralizzazione della riduzione di placca (PRNT)
- Correlazione sierologico-PRNT: test Liaison IgG DiaSorin
- Titolo qualificante ≥ 1:160,
- Plasmaferesi 600 ml, foto-inattivazione con sistema Intercept, (amotosalene) oppure Mirasol (riboflavina)
- Frazionamento in tre sacche da 200 ml
- Congelamento e stoccaggio

Plasmaterapia: eventi avversi

1. **Reazioni allergiche (febbre, rash o anafilassi)**
2. **Reazioni trasfusionali da incompatibilità AB0**
3. **Rischio di infezioni trasmesse (lue, HIV, epatiti)**
4. **TRACO: sovraccarico circolatorio trasfusionale**
5. **TRALI: danno polmonare trasfusionale**
6. **Blocco risposta immunitaria da anticorpi preformati**
7. **ADE: Antibody-dependent enhancement**
8. **Aumento del rischio trombotico ?**

Plasmaterapia iperimmune

Dai presupposti teorici
alle evidenze scientifiche

Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter interventional trial

Cesare Perotti , Fausto Baldanti, Raffaele Bruno; Claudia Del Fante, Elena Seminari, Salvatore Casari; Elena Percivalle, Claudia Glingani; Valeria Musella, Mirko Belliato; Martina Garuti; Federica Meloni; Marilena Frigato, Antonio Di Sabatino; Catherine Klers; Giuseppe De Donno; Massimo Franchini

The study observed 46 patients from March, 25 to April, 21 2020. Patients were aged 63, 61% male, 30 on CPAP and 7 intubated. PaO2/FiO2 was 128 (SD 47). Symptoms and ARDS duration were 14 (SD 7) and 6 days (SD 3). Three patients (6.5%) died within 7 days. The upper one-sided 90%CI was 13.9%, allowing to reject the null hypothesis of a 15% mortality. PaO2/FiO2 increased by 112 units (95%CI 82 to142) in survivors, the chest radiogram severity decreased in 23% (95%CI 5% to 42%); CRP, Ferritin and LDH decreased by 60, 36 and 20% respectively. Weaning from CPAP was obtained in 26/30 patients and 3/7 were extubated. Five serious adverse events occurred in 4 patients (2 likely, 2 possible treatment related).

Hyperimmune plasma in Covid-19 shows promising benefits, to be confirmed in a randomized controlled trial.

This *proof of concept* study could open to future developments including hyperimmune plasma banking, development of standardized pharmaceutical products and monoclonal antibodies.

Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

- From April 3 to June 2, 2020, a sample of 20,000 hospitalized pts with COVID-19 transfused with CP were evaluated.
- **The incidence of all SAE was low: transfusion reactions (n.78; <1%), thromboembolic or thrombotic events (n.113; <1%), and cardiac events (n.677, ~3%).**
- **The vast majority of the thromboembolic or thrombotic events (n.75) and cardiac events (n.597) were judged to be unrelated to the CP transfusion**
- These data provide **robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19**

Mayo Clin Proc. 2020;95(9):1888-1897

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

- 101 pazienti randomizzati (età media, 70 anni)
- **Negativizzazione virologica a 72 ore nell' 87.2% dei trasfusi vs 37.5% dei controlli (P < .001).**
- **Miglioramento clinico entro 28 giorni nei pz. con COVID-19 severo: 91.3% (21/23) nei trasfusi vs 68.2% (15/22) nei controlli non trasfusi (P = .03);**
- **Nessuna differenza nella mortalità a 28 giorni (15.7% vs 24.0%) o nel tempo dalla randomizzazione alla dimissione** (51.0% vs 36.0% dimessi entro il giorno 28).
- Eventi avversi in due pazienti trasfusi

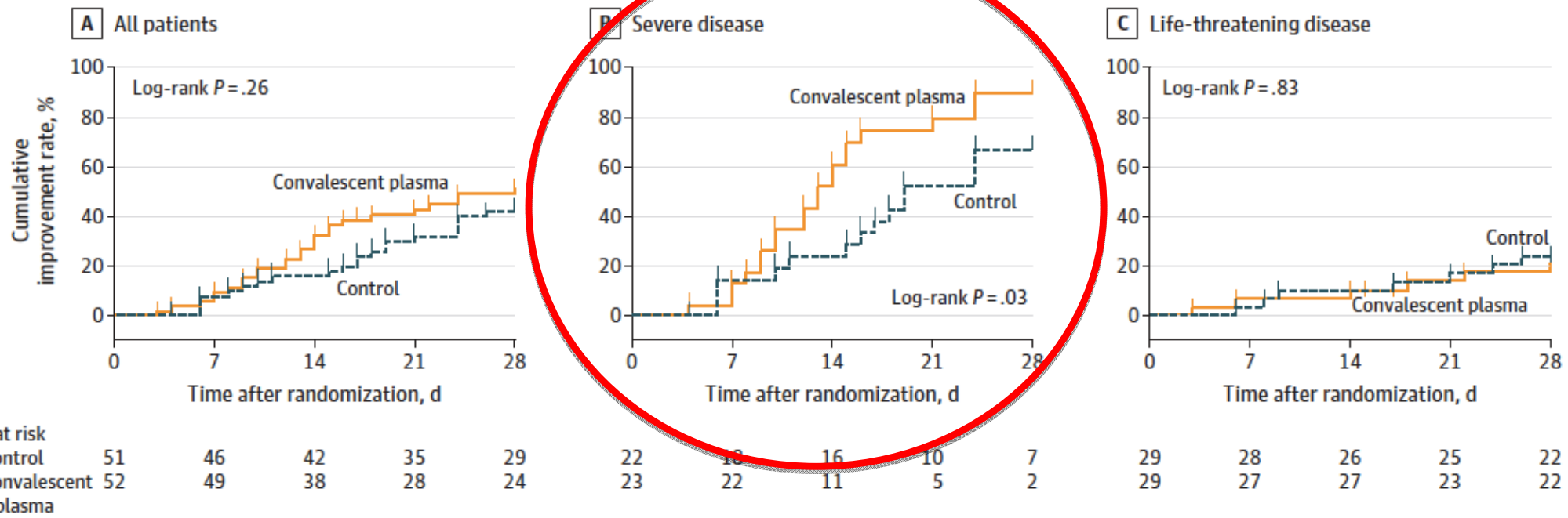
JAMA. doi:10.1001/jama.2020.10044 Published online June 3, 2020.

JAMA | Original Investigation

Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19

A Randomized Clinical Trial

Figure 2. Time to Clinical Improvement in Patients With COVID-19



CONCLUSIONI: **Tra I pazienti con COVID-19 severo o grave la plasmaterapia iperimmune In aggiunta al trattamento standard comparata al solo trattament standard, non ha ridotto in maniera statisticamente significativa il tempo necessario per il miglioramento clinico entro I 28 giorni. L'interpretazione dei risultati è limitata dalla precoce conclusione dello studio che potrebbe averlo reso sottodimensionato per cogliere una differenza clinicalmente significativa**

JAMA. doi:10.1001/jama.2020.10044 Published online June 3, 2020.

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

Anup Agarwal,[1] Aparna Mukherjee,[1] Gunjan Kumar,[1] Pranab Chatterjee,[1] Tarun Bhatnagar,[2] Pankaj Malhotra,[3] on behalf of the PLACID Trial Collaborators

- **Setting**: 39 hospitals across India.
- Hospitalized, moderately ill confirmed COVID-19 pts (PaO2/FiO2: 200-300 or RR > 24/min and SpO2 ≤ 93%) randomized to either best standard of care or intervention arm.
- Two doses of 200 mL CP was transfused 24 hours apart in the intervention arm.
- **Main Outcome Measure**: Composite **of progression to severe disease (PaO2/FiO2<100) or all-cause mortality at 28 days post-enrolment.**

Agarwal A. et al. BMJ 2020;371:m3939 http://dx.doi.org/10.1136/bmj.m3939

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

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- **Results**: 464 pts were enrolled; 235 in intervention and 229 in control arm.
- **Composite primary outcome was achieved in 44 (18.7%) participants in the intervention arm and 41 (17.9%) in the control arm [OR: 1.09; 95% CI: 0.67, 1.77].**
- Mortality was documented in 34 (14.5%) participants in intervention and 31 (13.5%) in control arm, [OR) 1.06 95% CI: 0.61 to 1.83].
- **Interpretation**: **CP was not associated with reduction in mortality or progression to severe COVID-19.**
- ***A priori measurement of neutralizing antibody titres in donors and participants may further clarify the role of CP in management of COVID-19.***

Agarwal A. et al. BMJ 2020;371:m3939 http://dx.doi.org/10.1136/bmj.m3939

BMJ Rapid Response

- Moderately severe pts with a median pre-transfusion neutralizing antibody (nAb) titre of 1:60 were transfused with CP units with a median titre of 1:40.
- **The only sustainable conclusion to date is that CP at a titre lower or equal to the titre in the recipients doesn't lead to any clinical benefits with respect to controls.**
- Therefore, it is still to be assessed whether an early treatment with CP units with titers higher than the ones in recipients may be of benefit, which is likely the most reasonable hypothesis
- in the TSUNAMI trial (NCT04393727), we are currently investigating the efficacy and safety of CP units with a titre ≥1:160 for the treatment of moderately severe patients (with a pre-transfusion titre likely < 1:160).

M. Tuccori, D. Focosi, F. Menichetti

BMJ Rapid Response

- Pathak tries to explain the clinical failure of CP with its prothrombotic nature in the setting of acquired thrombophilic disorders, such as COVID-19.
- This has not been formally demonstrated in vivo.
- Convalescent donors have no history of thrombosis, and the small reinfused CP volume only alters 15% of the recipient's plasma total volume.
- Most trials published to date suffered from short follow-up for thrombotic events, much controversy exists on the prothrombotic activity of CP
- **Several authors have currently speculated that antithrombin III replacement achieved with CP units could favour efficacy of heparin therapy.**

M. Tuccori, D. Focosi, F. Menichetti

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

V.A. Simonovich, L.D. Burgos Pratx, P. Scibona, M.V. Beruto, M.G. Vallone, C. Vázquez, N. Savoy, D.H. Giunta, L.G. Pérez, M..L. Sánchez, A.V. Gamarnik, D.S. Ojeda, D.M. Santoro, P.J. Camino, S. Antelo, K. Rainero, G.P. Vidiella, E.A. Miyazaki, W. Cornistein, O.A. Trabadelo, F.M. Ross, M. Spotti, G. Funtowicz, W.E. Scordo, M.H. Losso, I. Ferniot, P.E. Pardo, E. Rodriguez, P. Rucci, J. Pasquali, N.A. Fuentes, M. Esperatti, G.A. Speroni, E.C. Nannini, A. Matteaccio, H.G. Michelangelo, D. Follmann, H.C. Lane, and W.H. Belloso, for the PlasmAr Study Group*

NEJM, November 24, 2020

Table 2. Clinical Outcomes in Patients Who Received Convalescent Plasma as Compared with Placebo.*

Outcomes	Convalescent Plasma (N=228)	Placebo (N=105)	Odds Ratio or Hazard Ratio (95% CI)	P value
Primary outcome, clinical status at 30 days — no. of patients (%)			Odds ratio, 0.81 (0.50–1.31)	0.396
Death	25 (11)	12 (11.4)		
Invasive ventilatory support	19 (8.3)	10 (9.5)		
Hospitalized with supplemental oxygen requirement	5 (2.2)	2 (1.9)		
Hospitalized without supplemental oxygen requirement	8 (3.5)	1 (1)		
Discharged without full return to baseline physical function	30 (13.2)	8 (7.6)		
Discharged with full return to baseline physical function	141 (61.8)	72 (68.6)		
Secondary Outcomes				
Median time from intervention (IQR) — days				
To hospital discharge	13 (8–30)	12 (7–ND)	Subhazard ratio, 1 (0.76–1.32)	—
To discharge from the ICU	ND (8–ND)	ND (6–ND)	Subhazard ratio, 0.94 (0.48–1.82)	—
To complete restoration of physical functions†	15 (9–ND)	15 (7–ND)	Subhazard ratio, 0.89 (0.66–1.18)	—
To start of invasive ventilation	ND (9–ND)	ND	Subhazard ratio, 1.14 (0.72–1.81)	—
To death	ND	ND	Hazard ratio, 0.93 (0.47–1.86)	—
To improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days	12 (7–29)	12 (6–ND)	Hazard ratio, 1 (0.76–1.32)	—
Adverse events — no (%)				
Any event	153 (67.1)	66 (62.9)	Odds ratio, 1.21 (0.74–1.95)	—
Serious event	54 (23.7)	19 (18.1)	Odds ratio, 1.40 (0.78–2.51)	—
Infusion-related event	13 (5.7)	2 (1.9)	Odds ratio, 3.13 (0.69–14.11)	—

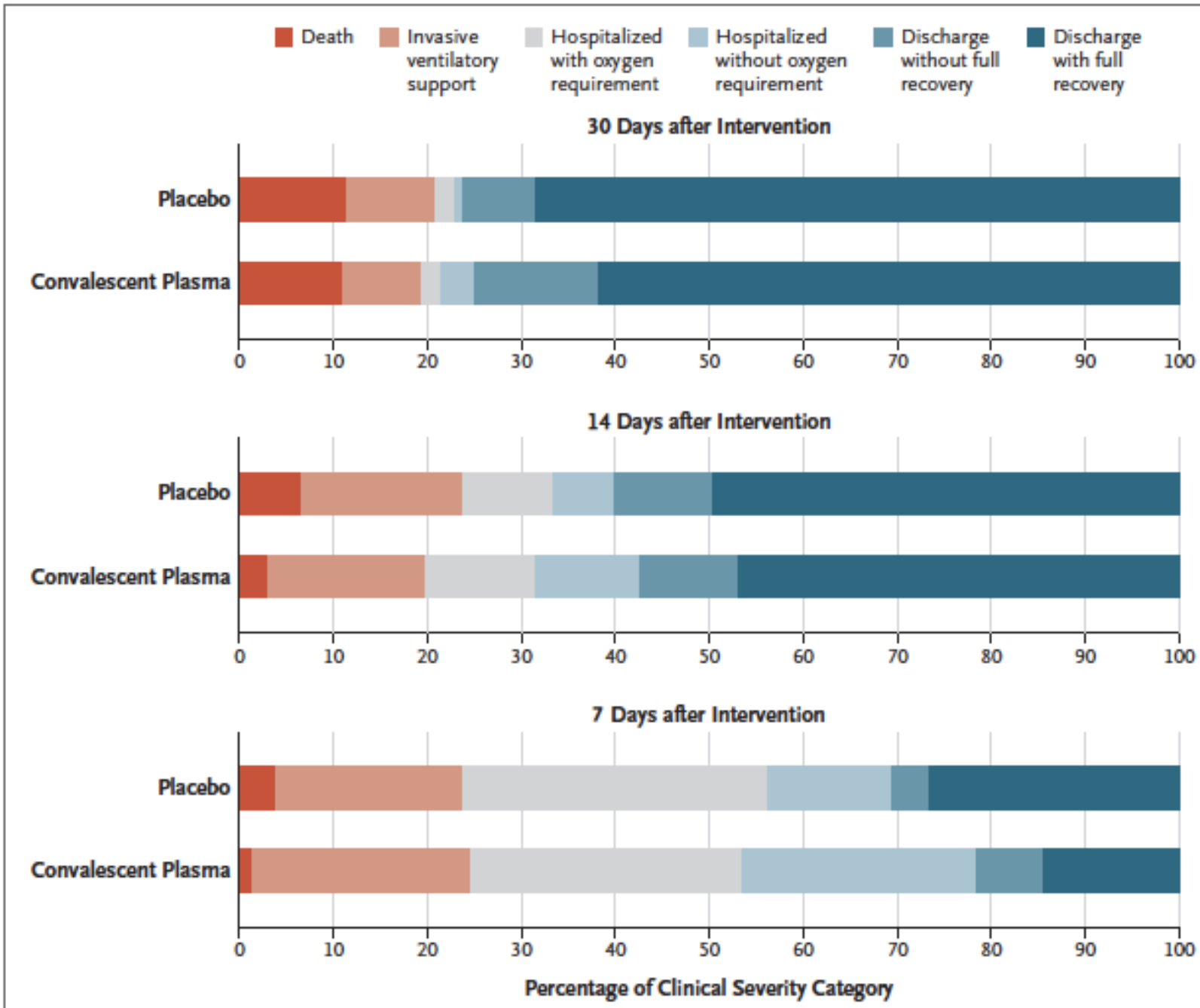


Figure 2. Clinical Outcomes among Patients Treated with Convalescent Plasma as Compared with Placebo.

The distribution of the clinical status according to the ordinal scale is shown at 30 days, 14 days, and 7 days after the intervention.

Key critical points

- **Neutralizing activity was measured with a method that may overestimate NAbs titers**
- **Analysis of Nab titers were available for 125 of the infused CP doses (56%) only**
- The median time from the onset of symptoms to progression to respiratory failure is around 7 days, similar to the median time from the beginning of symptoms to enrollment in our trial.
- Different antibody-response phenotypes and immune signatures could have different effects on disease progression.
- **Some autoantibodies that have developed in pts with life-threatening Covid-19 may be harmful by decreasing interferon-mediated immune responses.**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

R. Libster, G. Pérez Marc, D. Wappner, S. Coviello, A. Bianchi, V. Braem, I. Esteban, M.T. Caballero, C. Wood, M. Berrueta, A. Rondan, G. Lescano, P. Cruz, Y. Ritou, V. Fernández Viña, D. Álvarez Paggi, S. Esperante, A. Ferreti, G. Ofman, Á. Ciganda, R. Rodriguez, J. Lantos, R. Valentini, N. Itcovici, A. Hintze, M.L. Oyarvide, C. Etchegaray, A. Neira, I. Name, J. Alfonso, R. López Castelo, G. Caruso, S. Rapelius, F. Alvez, F. Etchenique, F. Dimase, D. Alvarez, S.S. Aranda, C. Sánchez Yanotti, J. De Luca, S. Jares Baglivo, S. Laudanno, F. Nowogrodzki, R. Larrea, M. Silveyra, G. Leberzstein, A. Debonis, J. Molinos, M. González, E. Perez, N. Kreplak, S. Pastor Argüello, L. Gibbons, F. Althabe, E. Bergel, and F.P. Polack, for the Fundación INFANT–COVID-19 Group*

NEJM January 6, 2021

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adult patients within 72 hours after the onset of mild Covid-19 symptoms. The primary end point was severe respiratory disease, defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. The trial was stopped early at 76% of its projected sample size because cases of Covid-19 in the trial region decreased considerably and steady enrollment of trial patients became virtually impossible.

RESULTS

A total of 160 patients underwent randomization. In the intention-to-treat population, severe respiratory disease developed in 13 of 80 patients (16%) who received convalescent plasma and 25 of 80 patients (31%) who received placebo (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P=0.03), with a relative risk reduction of 48%. A modified intention-to-treat analysis that excluded 6 patients who had a primary end-point event before infusion of convalescent plasma or placebo showed a larger effect size (relative risk, 0.40; 95% CI, 0.20 to 0.81). No solicited adverse events were observed.

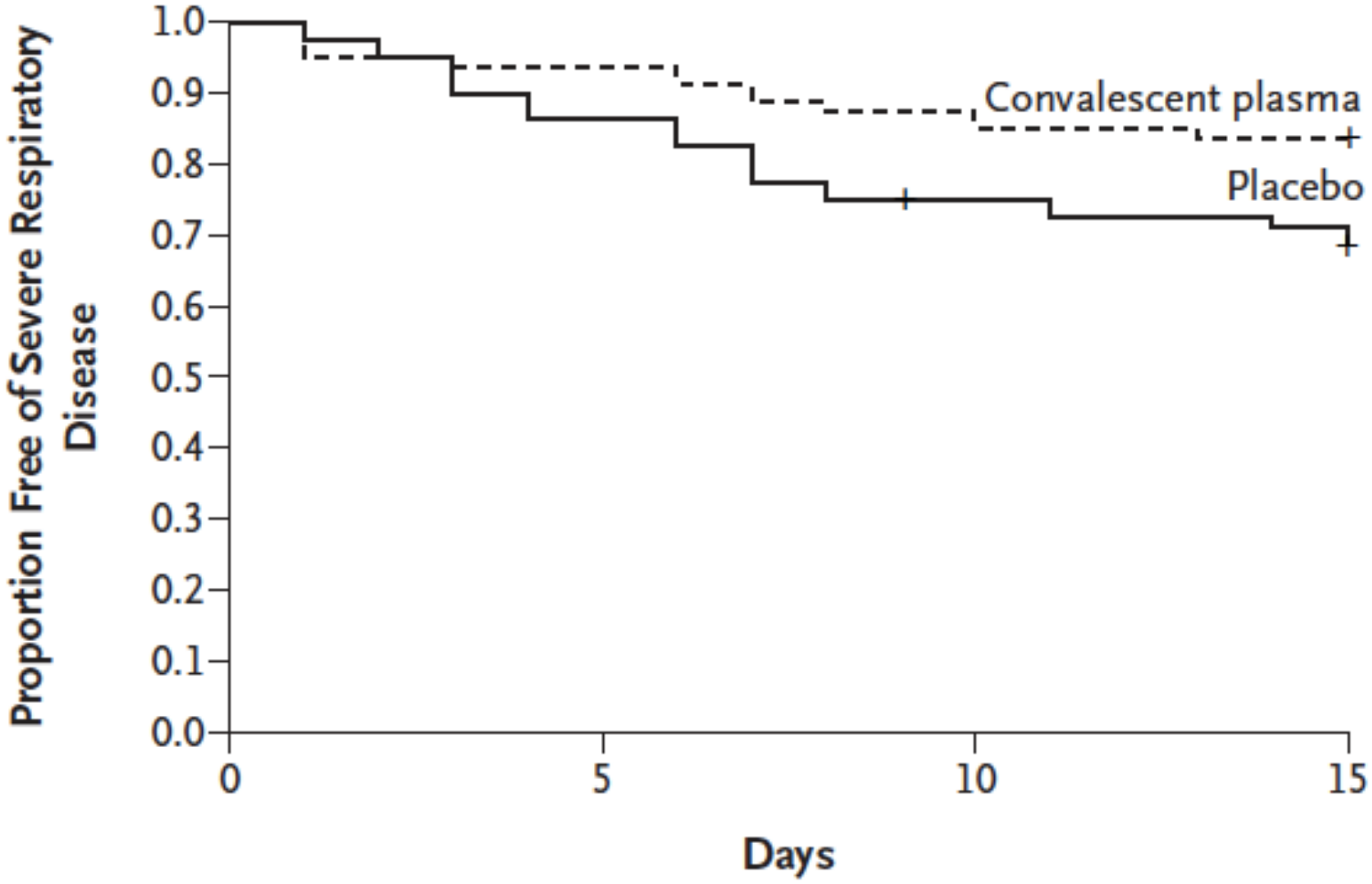
CONCLUSIONS

Early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly ill infected older adults reduced the progression of Covid-19. (Funded by the Bill and

Table 2. Trial End Points in the Intention-to-Treat Population.*

End Point	Convalescent Plasma (N=80)	Placebo (N=80)	Relative Risk (95% CI)
	no./total no. (%)		
Primary end point: severe respiratory disease	13/80 (16)	25/80 (31)	0.52 (0.29–0.94)
Secondary end points			
Life-threatening respiratory disease	4/80 (5)	10/80 (12)	0.40 (0.13–1.22)
Oxygen supplementation at an FIO_2 of 100%	4/80 (5)	6/80 (8)	0.67 (0.20–2.27)
Noninvasive ventilation	1/80 (1)	6/80 (8)	0.17 (0.02–1.35)
Admission to intensive care unit	2/80 (2)	6/80 (8)	0.33 (0.07–1.60)
Mechanical ventilation	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Critical systemic illness	5/80 (6)	6/80 (8)	0.83 (0.27–2.62)
Acute respiratory failure	2/80 (2)	5/80 (6)	0.40 (0.08–2.00)
Shock	2/80 (2)	1/80 (1)	2.00 (0.19–21.6)
Multiple organ dysfunction syndrome	3/80 (4)	5/80 (6)	0.60 (0.15–2.43)
Death from Covid-19	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination	7/80 (9)	12/80 (15)	0.58 (0.24–1.41)

NEJM January 6, 2021



No. at Risk				
Convalescent plasma	80	75	70	67
Placebo	80	69	59	56

Figure 1. Time to the Development of Severe Respiratory Disease Due to Coronavirus Disease 2019, According to Trial Group in the Intention-to-Treat Analysis.

Table 3. Primary End Point, According to Donor SARS-CoV-2 S IgG Titer.

Patient Group	Patients with Severe Respiratory Disease	Relative Risk (95% CI)	Relative Risk Reduction
	no./total no. (%)		*percent*
Placebo group	25/80 (31)	1.00	
Recipient of SARS-CoV-2 S IgG in donor plasma*			
At a titer at or above median concentration	3/36 (8)	0.27 (0.08–0.68)	73.3
At a titer below median concentration	9/42 (21)	0.69 (0.34–1.31)	31.4

* The median concentration is a SARS-CoV-2 S IgG titer of 1:3200.

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ORIGINAL ARTICLE

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

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METHODS

In a retrospective study based on a U.S. national registry, we determined the anti–SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. The primary outcome was death within 30 days after plasma transfusion. Patients who were enrolled through July 4, 2020, and for whom data on anti–SARS-CoV-2 antibody levels in plasma transfusions and on 30-day mortality were available were included in the analysis.

RESULTS

Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti–SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32).

CONCLUSIONS

Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. (Funded by the Department of Health and Human Services and others; ClinicalTrials.gov number, NCT04338360.)

B **High vs. Low Antibody Levels**

Subgroup	No. of Patients	Mortality at 30 Days
Before May 15, no mechanical ventilation, 18–59 yr	109	0.47 (0.14–1.57)
May 15 or later, no mechanical ventilation, 18–59 yr	196	0.74 (0.26–2.13)
Before May 15, no mechanical ventilation, 60–69 yr	93	0.62 (0.26–1.47)
May 15 or later, no mechanical ventilation, 60–69 yr	117	0.66 (0.31–1.38)
Before May 15, no mechanical ventilation, ≥70 yr	74	0.57 (0.26–1.22)
May 15 or later, no mechanical ventilation, ≥70 yr	128	0.73 (0.45–1.20)
Before May 15, mechanical ventilation, 18–59 yr	81	1.35 (0.72–2.54)
May 15 or later, mechanical ventilation, 18–59 yr	47	0.31 (0.10–0.97)
Before May 15, mechanical ventilation, 60–69 yr	75	1.14 (0.70–1.88)
May 15 or later, mechanical ventilation, 60–69 yr	44	0.60 (0.30–1.19)
Before May 15, mechanical ventilation, ≥70 yr	48	1.29 (0.76–2.21)
May 15 or later, mechanical ventilation, ≥70 yr	46	0.91 (0.50–1.66)
All subgroups	1058	0.80 (0.65–0.97)

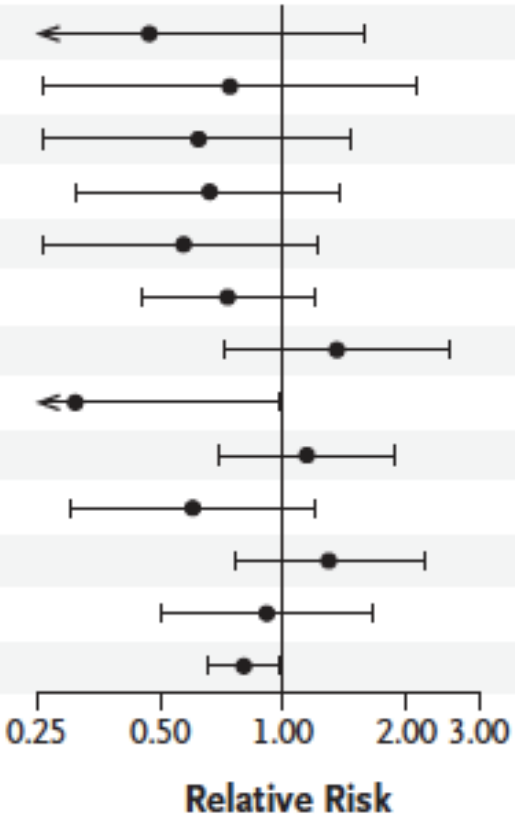


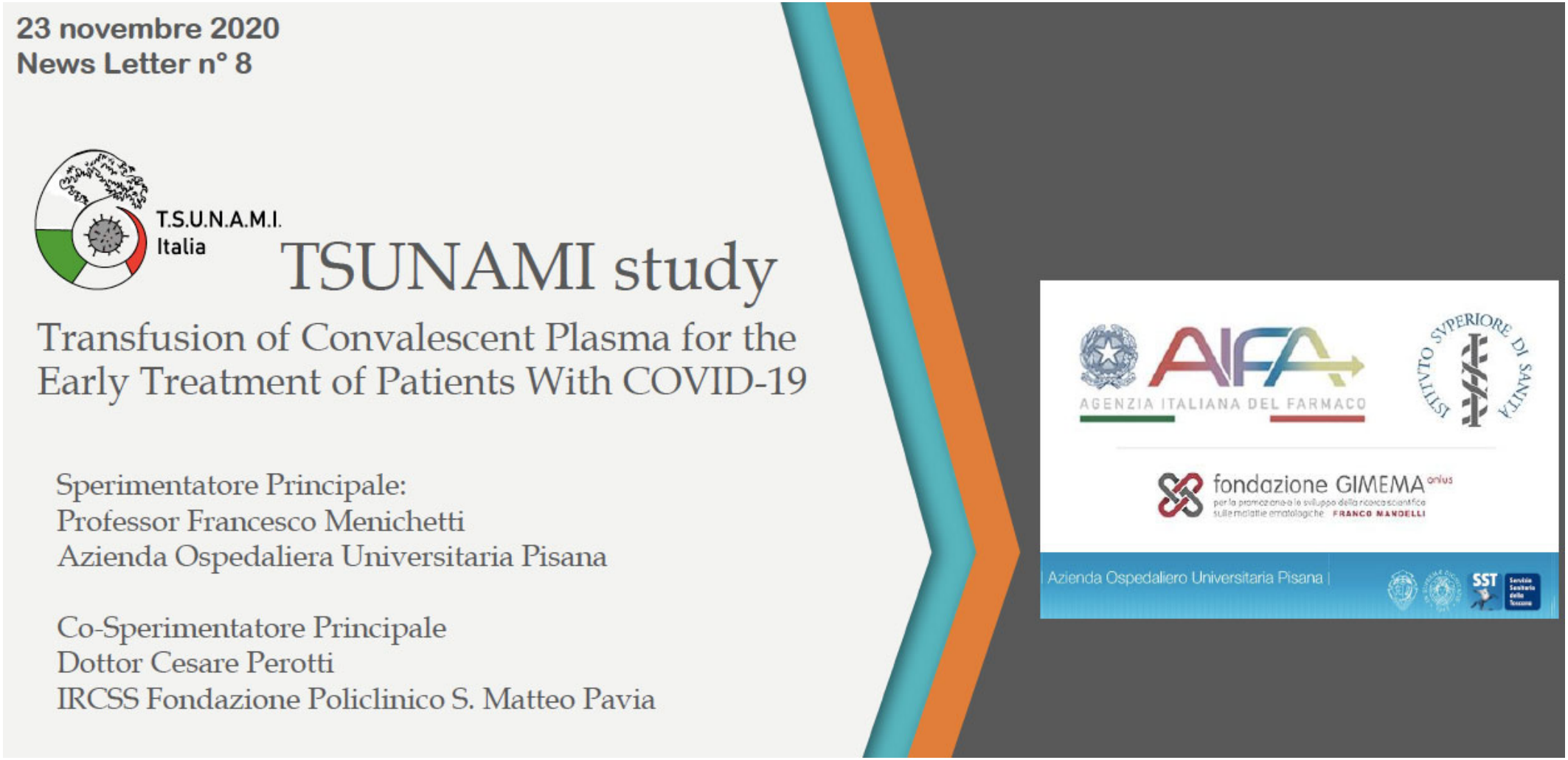
Figure 2. Relative Risk of Death within 30 Days after Convalescent Plasma Transfusion.

Timeline:
da TSUNAMI Pisa a TSUNAMI Planet
a TSUNAMI ITALIA

1. Tsunami: RCT ideato a Pisa (Menichetti, Falcone, Tiseo, Mazzoni) come plasmaterapia per pazienti critici COVID-19
2. Approvazione del CEAVNO: 6 aprile 2020
3. Richiesta del CRS Toscana di partecipazione di Toscana, Lazio, Campania, Marche, Sanità Militare ed Umbria
4. Approvazione CEAVNO emendamento unico centri partecipanti ed "early plasmatherapy" 22 aprile 2020
5. Prima randomizzazione a Pisa in data 2 maggio 2020
6. Richiesta di AIFA-ISS di utilizzare il protocollo TSUNAMI per una sperimentazione nazionale: 6 maggio 2020
7. Web conference che definisce PI (Pisa e Pavia) e comitato scientifico: 8 maggio 2020
8. Approvazione CE Spallanzani: 15 maggio 2020

TSUNAMI
Italia

Unico studio nazionale ISS-AIFA sul COVID-19



Tsunami Italia

- Studio multicentrico randomizzato controllato in aperto
- Plasmaterapia + Terapia Standard vs Terapia Standard (schede AIFA)
- Esclusione: uso di inibitori IL-1, del recettore di IL-6, JAK e TNF
- Pazienti con p/f tra 350 e 200, plasma con titolo ≥ 1:160, due sacche da 200 ml a distanza di 24 ore
- **End-point composito: p/f < 150 o mortalità a 30 giorni**
- **Stima end-point composito: 30% TS vs 18% PC+TS, delta 0,12, riduzione del 40%; arruolamento 474 soggetti**

– Nel caso in cui P0 nel gruppo di controllo sia maggiore o uguale del 26,0%, verrà condotta, come da protocollo, la prima analisi ad interim, le successive analisi rimangono invariate e non si procederà al ridimensionamento dello studio.

TSUNAMI
Italia

Plasma convalescente (PC)

- PC nel COVID-19: evidenze contrastanti
- Studi osservazionali, RCT sottodimensionati, PC a diversa concentrazione anticorpale, non stratificazione riceventi per titolo anticorpale, fasi di malattia diverse, precoci vs. più avanzate
- Buona tollerabilità (TRACO, TRALI, allergia, etc.)
- Studi osservazionali più favorevoli di RCT
- **Beneficio tangibile su pazienti trattati precocemente e con plasma ad alto titolo anticorpale**

COVID-19: dalle cure sperimentali alle evidenze scientifiche

- La pandemia ha messo in crisi l'identità del medico-ricercatore
- Il **medico** combatte la quotidiana battaglia per salvare la vita dei suoi pazienti e **ricorre spesso a cure sperimentali**
- Il **ricercatore** è **impegnato a produrre evidenze scientifiche** con metodi rigorosi (studi randomizzati con gruppo di controllo)
- L'antinomia è solo apparente, ma il punto d'equilibrio è variabile e di difficile identificazione

Considerazioni conclusive

- TSUNAMI: un occasione per la ricerca italiana
- TSUNAMI delinea un network nazionale ampio e multidisciplinare (clinici, trasfusionisti, virologi, donatori)
- Necessità di una cabina di regia: ISS-AIFA
- Possibilità di dare un contributo serio alla conoscenza ed ai comportamenti assistenziali
- **L'emergenza pandemica non esenta la ricerca clinica dal produrre evidenze, le uniche che possono garantire terapie sicure ed efficaci**