Timing of convalescent plasma administration and 28-day mortality in COVID-19 pneumonia

Soledad E González,[1] Lorena Regairaz,[2] Martin R Salazar ,[3,4] Noelia S Ferrando,[5] Verónica V González Martínez,[6] Patricia M Carrera Ramos,[7] Santiago A Pesci,[1] Juan M Vidal,[1] Nicolás Kreplak,[8] Elisa Estenssoro[9]

For numbered affiliations see end of article.

Correspondence to
Dr Martin R Salazar, Clínica Médica, Hospital Interzonal General de Agudos General San Martin, La Plata 1900, Argentina;
salazarlandea@gmail.com

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ABSTRACT

This is a multicenter cohort study including consecutive, hospitalized patients ≥18 years, with moderate to severe COVID-19, carried out to evaluate the relationship between the timing of convalescent plasma administration and 28-day mortality. Data were prospectively collected between May 14, 2020 and October 31, 2020. Patients were grouped according to the timing of administration of convalescent plasma as <3 days, between 3 and 7 days, and >7 days. The main outcome variable was 28-day mortality. Independent predictors of mortality were identified by logistic regression. Of 4719 patients receiving convalescent plasma, 3036 (64.3%) were in the general ward, 1171 (24.8%) in the intensive care unit (ICU), and 512 (10.8%) in the ICU on mechanical ventilation. Convalescent plasma was administered to 3113 (66%) patients within the first 3 days of hospital admission, to 1380 (29.2%) between 3 and 7 days, and to 226 after 7 days; 28-day mortality was, respectively, 18.1%, 30.4% and 38.9% (p<0.001). In the regression model, convalescent plasma administration within the first 3 days of admission was associated with reduced 28-day mortality, compared with the administration after 7 days (OR 0.40, 95% CI 0.30 to 0.53). Early convalescent plasma administration was associated to a significant decreased mortality in patients in the general ward (OR 0.45, 95% CI 0.29 to 0.69) and in the ICU (OR 0.35, 95% CI 0.19 to 0.64), but not in those requiring mechanical ventilation (OR 0.52, 95% CI 0.27 to 1.01). In conclusion, this study suggests that early administration of convalescent plasma to patients with COVID-19 pneumonia is critical to obtain therapeutic benefit.

Significance of this study

What is already known about this subject?

- Convalescent plasma from patients recovering from SARS-CoV-2 was considered at the beginning of the pandemic and has been safely used over the world. However, its efficacy for treating COVID-19 has been questioned, since the results related to mortality and impact on disease progression have been controversial.

What are the new findings?

- In a multicenter cohort study of 4719 adult patients with moderate to severe COVID-19 receiving convalescent plasma, its early administration (within the 3 days of admission) was associated with decreased mortality in patients in the ward and in the subgroup of non-ventilated intensive care unit patients.

How might these results change the focus of research or clinical practice?

- Most studies on plasma utilization in COVID-19 have not focused on the timing of administration. We show that the early administration in severely compromised—but not on mechanical ventilation—patients was independently associated with a better outcome.

INTRODUCTION

Since the beginning of the pandemic by SARS-CoV-2, numerous observational studies and clinical trials have investigated possible therapies but only dexamethasone, tocilizumab and remdesivir have proven effective to date.[1] In this context, passive immunotherapy, which relies on transfer of pathogen-specific antibodies, was explored as a therapeutic option and several studies evaluated the administration of convalescent plasma donated by survivors of COVID-19, hyperimmune equine serum, and monoclonal antibodies.[2–4] However, at the very onset of the COVID-19 pandemic, when no vaccines or monoclonal antibodies were available, convalescent plasma was the immediately suitable option, and has been widely used to treat the disease caused by SARS-CoV-2. On March 24, 2020, the Food and Drug Administration approved the use of convalescent plasma to treat patients with severe COVID-19.[5] In Argentina, in response to the COVID-19 pandemic, the Ministry of Health of the Province of Buenos Aires created the Centralized Registry of Convalescent Plasma Donors (CROCPD-BA) with the aim of collecting, processing and distributing convalescent plasma, and issuing recommendations for its use in patients with COVID-19.[6]

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Despite the potential benefit of convalescent plasma administration, results of randomized controlled trials or matched control studies have been mostly negative, which might be ascribed to differences in disease severity, comorbidities, concurrent treatments, convalescent plasma antibody titers, and timing of its administration.[3 7–28]

Primary mechanism for the clinical benefit of passive immunotherapy is SARS-CoV-2 viral neutralization due to antibodies which bind to the spike protein and prevent adherence to host cellular receptors.[29] The efficacy of passive immunization could thus be highly dependent on the timing of administration. While early administration of specific antibodies could block the entry of SARS-CoV-2 into the cell and therefore prevent the progression of the disease, deferred administration could be less effective due to intracellular location of the virus and/or end-organ damage caused by cytokine storm.

Using the data of the CROCPD-BA, we previously reported that the administration of convalescent plasma in patients with COVID-19 pneumonia admitted to the hospital might be associated with improved outcomes.[21] The therapeutic benefit of the convalescent plasma is supported mainly by observational studies and some recently published systematic reviews and meta-analysis.[2 15–22 24 25] However, most clinical trials have yielded negative results.[7–15] In this study, we hypothesized that the efficacy of passive immunotherapy might be associated with its administration within an optimal therapeutic window.

MATERIALS AND METHODS

This was a multicenter cohort study of data prospectively collected in the National Vigilance System (SNVS V.2.0), the Provincial Hospital Bed Management System, and the CROCPD-BA. It includes consecutive hospitalized patients ≥18 years, diagnosed with SARS-CoV-2 with RT-PCR, incorporated into an Expanded Access Program of Convalescent Plasma Administration between the period of May 14, 2020 and October 31, 2020. Methods in this manuscript were similar to that of a previous study.[20]

Recorded variables were age, gender, comorbidities (arterial hypertension, diabetes, pre-existent cardiovascular disease, chronic obstructive pulmonary disease, immunodeficiencies), requirement of mechanical ventilation, treatments and outcomes, such as 28-day mortality or discharge. Severe adverse events related to plasma infusion, as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO), were also registered. Further data about plasma collection were previously published.[20]

The request of convalescent plasma was made by assistant physicians as part of the program, in patients with COVID-19 pneumonia. Pneumonia was defined as the presence of lung infiltrates, plus one of the following: dyspnea with respiratory rate ≥30 breaths per minute, oxygen saturation ≤93%, oxygen requirement, PaO_2FIO_2 <300 mm Hg, increase in lung infiltrates >50% during the previous 24–48 hours, alteration in consciousness, multiple organ dysfunction, age >65 years, or any of the aforementioned comorbidities. Initial severity of illness was assessed according to the hospital site of admission: general ward (GW), intensive care unit (ICU), and ICU admission with requirement of mechanical ventilation (ICU-MV).

We registered the timing of plasma administration with respect to the moment of hospital admission, as <3 days, between 3 and 7 days, and beyond 7 days. All units of transfused convalescent plasma had an IgG antibody titer ≥1:400, with a volume per unit of 200–250 mL. Patients were followed up until 28 days or death, whichever occurred first.

The main outcome variable was 28-day mortality. Deaths due to COVID-19 were confirmed on patient death certificates.

Statistical analysis

Continuous variables were expressed as mean±SD or median (0.25–0.75) percentiles. Categorical variables were expressed as percentages. Differences between survivors and non-survivors, and between categories of severity on admission and of timing of plasma administration were analyzed with χ^2 test, t-test, or Mann-Whitney U test, as appropriate.

To identify independent predictors of 28-day mortality, variables differing between survivors and non-survivors, all relevant available variables were entered into logistic regression models using a conditional forward stepwise analysis constructed in a 2-block process. In the first block, the timing of administration, considering infusion after 7 days the reference category, was included to estimate unadjusted ORs and 95% CI. In the second block, covariates were added to estimate adjusted OR in 2 different models: model 1 including age, gender and comorbidities (diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease and immunodeficiencies), and model 2 including model 1 plus initial severity of illness, assessed with reference to hospital site of admission: GW, ICU, and ICU-MV. Additionally, a regression model including the time between hospital admission and plasma infusion as a continuous variable (instead a categorical one) was constructed, and unadjusted and adjusted ORs were estimated.

A 2-tailed p value <0.05 was considered significant. Data were analyzed with SSPS.

The administration of convalescent plasma required signed consent from each patient or legal representative, according to CROCPD-BA regulations (2919/2123/2020).

RESULTS

In the present study, we analyze 4719 patients with COVID-19 pneumonia admitted to 215 hospitals and treated with convalescent plasma. Epidemiological data of the cohort and comparisons between survivors and non-survivors are shown in table 1. In univariable analysis, older age, hypertension, diabetes, history of cardiovascular disease and chronic obstructive pulmonary disease were associated with higher 28-day mortality.

Convalescent plasma was administered to 3036 (64.3%) patients in GW, 1171 (24.8%) patients in the ICU, and 512 (10.8%) patients in the ICU-MV subgroup. Twenty-eight-day mortality was 22.7% for the entire group; 14.3%, 31.2% and 50.6% for GW, ICU, and ICU-MV patients, respectively (p<0.001). Convalescent plasma was administered to 3113 (66%) patients within the first 3 days of

Table 1 Characteristics of the entire group and comparison between survivors and non-survivors

	All n=4719	Survivors n=3647	Non-survivors n=1072	P value	28-day mortality (%)	Unadjusted OR (95% CI)
Age (years)	58±14	56±14	64±12	<0.001		
Gender (male)	3024 (64.1)	2317 (63.5)	707 (66.0)	0.147	23.4	1.11 (0.96 to 1.28)
Hypertension	2017 (42.7)	1460 (40.0)	557 (52.0)	<0.001	27.6	1.62 (1.41 to 1.86)
Diabetes	1306 (27.7)	954 (26.2)	352 (32.8)	<0.001	27.0	1.38 (1.19 to 1.60)
Obesity	1900 (40.3)	1457 (40.0)	443 (41.3)	0.420	23.3	1.06 (0.92 to 1.22)
Cardiovascular disease	546 (11.6)	364 (11.0)	183 (17.0)	<0.001	33.3	1.84 (1.52 to 2.24)
Chronic obstructive pulmonary disease	437 (9.3)	300 (8.2)	137 (12.9)	<0.001	31.4	1.64 (1.32 to 2.03)
Immunodeficiency	112 (2.4)	83 (2.4)	25 (2.9)	0.417	25.9	1.19 (0.78 to 1.83)

Variables are expressed as mean±SD or n (%).

hospital admission, to 1380 (29.2%) patients between 3 and 7 days, and to 226 patients after 7 days; 28-day mortality was 18.1%, 30.4% and 38.9%, respectively (p<0.001). Characteristics of the individuals according to the site of hospital admission and timing of plasma administration are shown in table 2.

The administration of convalescent plasma within the first 3 days of admission reduced 28-day mortality by 61%, compared with the administration after 7 days, and adjusted for possible confounders (table 3). Absolute values of 28-day mortality according to the timing of plasma infusion in the different strata of severity, reflected by admission site, are shown in figure 1.

The unadjusted and adjusted ORs for 28-day mortality for the different timing groups of convalescent plasma administration, and for the different admission sites, are shown in table 4. Adjusted for possible confounders, the administration of convalescent plasma within the first 3 days of hospital admission was associated with lower mortality in GW patients, and in ICU patients not requiring mechanical ventilation. Furthermore, time between admission and plasma infusion analyzed as a continuous variable was also a significant predictor of 28-day mortality, unadjusted OR 1.23, 95% CI 1.011 to 1.035; adjusted OR (model 1) 1.024, 95% CI 1.011 to 1.037; fully adjusted OR (model 2) 1.020, 95% CI 1.007 to 1.033.

Data regarding antibody titers in the transfused plasma units were available for 2451 patients; 915 (37.3%) had titers ≥1/1600. There were no differences in 28-day mortality in patients treated with plasma units with titers ≥1/1600 vs <1/1600 (23.8% vs 22.4%, respectively; p=0.416).

No episodes of TRALI or TACO were registered.

DISCUSSION

The most important finding of this study was that the administration of convalescent plasma within 3 days of hospital admission in patients with COVID-19 admitted to the GW, or to the ICU without need of mechanical ventilation, was associated to a decrease in 28-day mortality compared with delayed administration. This effect persisted after adjusting for possible confounders as age and comorbid conditions.

Table 2 Characteristics of individuals according to the site of admission and the timing of plasma administration

	GW n=3036				ICU n=1171				ICU-MV n=512			
	<3 days n=2092	3–7 days n=814	>7 days n=130	P value	<3 days n=736	3–7 days n=383	>7 days n=52	P value	<3 days n=285	3–7 days n=183	>7 days n=44	P value
Age (years)	57±14	58±14	60±16	0.036	57±14	59±14	63±11	0.001	57±14	57±14	61±11	0.185
Gender (male)	1306 (62.4)	516 (63.4)	76 (58.5)	0.553	493 (66.9)	252 (65.8)	43 (82.7)	0.049	187 (65.6)	121 (66.1)	30 (68.2)	0.945
Hypertension	839 (40.1)	356 (43.7)	76 (51.5)	0.013	304 (41.3)	179 (46.7)	26 (50.0)	0.137	139 (48.8)	81 (44.3)	26 (59.1)	0.191
Diabetes	522 (25.9)	240 (29.1)	46 (35.4)	0.016	202 (27.4)	111 (19.0)	19 (36.5)	0.352	78 (27.4)	53 (29.0)	15 (34.1)	0.646
Obesity	852 (40.7)	305 (37.5)	38 (29.1)	0.015	285 (38.7)	156 (40.7)	19 (36.5)	0.742	145 (50.9)	80 (43.7)	20 (45.5)	0.301
CVD	223 (10.7)	104 (21.8)	20 (15.4)	0.096	80 (10.9)	51 (13.3)	11 (21.2)	0.062	27 (9.5)	20 (10.9)	10 (22.7)	0.034
COPD	165 (7.8)	79 (9.7)	15 (11.5)	0.132	64 (8.7)	43 (11.2)	8 (15.4)	0.155	27 (9.5)	29 (15.8)	7 (15.9)	0.092
Immunodeficiencies	46 (2.2)	20 (2.5)	12 (9.2)	<0.001	14 (1.9)	7 (1.8)	4 (7.7)	0.018	7 (2.5)	2 (1.1)	0 (0.0)	0.357

Variables are expressed as mean±SD or n (%).
COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GW, general ward; ICU, intensive care unit; ICU-MV, ICU admission with requirement of mechanical ventilation.

Table 3 Univariate and logistic regression analysis of the timing of convalescent plasma administration with 28-day mortality as the dependent outcome

	n (%)	28-day mortality 100/patients	Unadjusted OR (95%CI)	Adjusted (model 1) OR (95% CI)	Adjusted (model 2) OR (95% CI)
>7 days	226 (4.8)	38.9	1	1	1
3–7 days	1380 (29.2)	30.4	0.68 (0.51 to 0.92)	0.75 (0.55 to 1.02)	0.46 (0.33 to 0.62)
<3 days	3113 (66.0)	18.1	0.35 (0.263 to 0.46)	0.39 (0.29 to 0.52)	0.81 (0.59 to 1.12)

Model 1: adjusted for age, gender, obesity, diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease and immunodeficiencies.
Model 2: model 1 plus initial severity of illness assessed according to the hospital site of admission: general ward, intensive care unit (ICU), and ICU admission with requirement of mechanical ventilation.

The efficacy of convalescent plasma remains controversial. Some observational studies showed a benefit of convalescent plasma administration.[16–22] Conversely, most of clinical trials published to date did not demonstrate a favorable effect of convalescent plasma on different patient outcomes. For example, Li *et al* did not find any difference in time to clinical improvement between groups.[7] Yet in 93.9% of patients receiving the intervention, the median time elapsing between symptom onset and randomization was >14 days. Likewise, in the study of Simonovich *et al*, convalescent plasma was administered at a median time of 8 (IQR 5–10) days, from the onset of COVID-19 symptoms to enrollment.[12] More recently, the Randomised Evaluation for COVID-19 Therapy trial (RECOVERY) and the Randomised Embedded Multi-factorial Adaptative Platform-Community Adquired Pneumonia COVID trial (REMAP-CAP) clinical trials showed no overall benefit of convalescent plasma administration to hospitalized patients with COVID-19.[15 16] In the RECOVERY study, in which plasma was administered at a median of 9 days after symptom onset, an effect of convalescent plasma could not be demonstrated in any of the prespecified subgroups, which included plasma infusion ≤7 days or >7 days after the beginning of symptoms. However, a Bayesian reanalysis of the RECOVERY trial suggested a real possibility of benefit with the administration of convalescent plasma in the first week.[28] The REMAP-CAP was a multinational study, conducted in critically ill patients in whom a beneficial effect of convalescent plasma administration on organ support-free days, compared with no-plasma administration, could be demonstrated.[15] A possible exception might be a beneficial effect of convalescent plasma on immunosuppressed patients, but the small number of this subgroup precludes any meaningful conclusion.

Notwithstanding these results, 3 smaller clinical trials recently published showed improved outcomes when convalescent plasma was administered. O'Donnell *et al*, who included patients with severe and critical COVID-19, demonstrated that 28-day survival was higher in participants receiving convalescent plasma.[23] The Convalecent Plasma Compared to Best Supportive Care for Treatment of Patientes with Severe COVID-19 clinical trial (CAPSID) also showed a benefit from convalescent plasma in a predefined subgroup of patients who were treated with high titers of neutralizing antibodies, although there were no differences in the primary and secondary outcomes between the convalescent plasma group and the controls.[24] Finally, Bar *et al* reported that the early administration of convalescent plasma in hospitalized patients was associated with an improvement in clinical severity score and 28-day mortality, mainly in seronegative patients.[25] Recently, the RECOVERY trial reported that the use of casirivimab-imdevimab was associated to reduced 28-day mortality compared with usual care, in patients with severe COVID-19 who were seronegative at baseline. That is to say, casirivimab-imdevimab were effective in those who were not able to mount an adequate antibody response to SARS-CoV-2.[30]

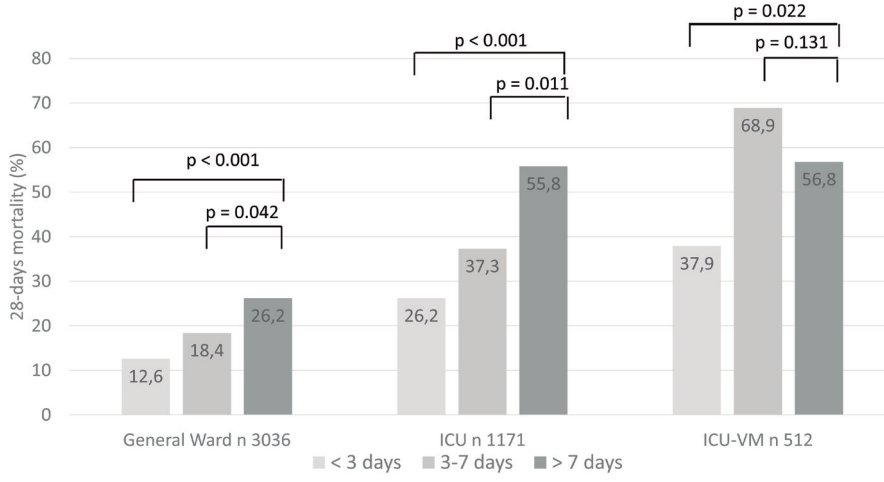

Figure 1 Absolute values of 28-day mortality according to the timing of plasma infusion in the different strata of severity, general ward (GW), intensive care unit (ICU), and ICU admission with requirement of mechanical ventilation (ICU-MV).

Table 4 Univariate analysis and logistic regression analysis of the timing of convalescent plasma administration with 28-day mortality as the dependent outcome stratified by site of admission

Site of plasma administration	Timing of admission (days)	Time (days) of admission-plasma infusion Median (IQR)	Patients receiving convalescent plasma n (%)	28-day mortality 100/patients	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
General ward (n=3036)	>7	10.8 (10)	130 (4.3)	26.2	1	1
	3–7	3.2 (2)	814 (26.8)	18.4	0.64 (0.42 to 0.98)	0.67 (0.43 to 1.05)
	<3	0.2 (1)	2092 (68.9)	12.6	0.41 (0.27 to 0.62)	0.44 (0.28 to 0.67)
Intensive care unit (n=1171)	>7	8.5 (6)	52 (4.4)	55.8	1	1
	3–7	3.3 (2)	383 (32.7)	37.3	0.47 (0.26 to 0.84)	0.56 (0.30 to 1.03)
	<3	0.3 (1)	736 (62.9)	26.2	0.28 (0.16 to 0.50)	0.35 (0.20 to 0.64)
ICU admission with requirement of mechanical ventilation (n=512)	>7	9.50 (7)	44 (8.8)	51.7	1	1
	3–7	3.5 (2)	183 (35.7)	65.5	1.68 (0.86 to 3.23)	1.98 (0.99 to 3.96)
	<3	0.1 (1)	285 (55.7)	37.9	0.47 (0.25 to 0.90)	0.52 (0.27 to 1.01)

*Adjusted for age, gender, obesity, diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease and immunodeficiencies
ICU, intensive care unit.;

Therefore, a lack of effect of convalescent plasma due to delayed administration (and/or low antibody titers) cannot fully be discarded, and some studies support this possibility. Libster *et al* conducted a clinical trial in patients with mild COVID-19, demonstrating that the administration of convalescent plasma with antibody titers higher than 1:1000 within 72 hours of symptom onset halted the progression to more severe disease.[13] The benefit of early convalescent plasma administration could also be present in more severe forms of COVID-19. Indeed, Joyner *et al*, in a retrospective analysis, show that in 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.[16] In addition, patients who received plasma within 3 days after receiving a diagnosis of COVID-19 had a lower risk of death than those who received transfusions later in the disease course. Furthermore, Salazar *et al* identified an optimal window of 44 hours after hospitalization for transfusing patients with COVID-19 with high-titer convalescent plasma.[17] Concordantly with these results, 2 recent retrospective matched cohort studies conducted in Yale New Haven Health System and in 176 HCA Healthcare-affiliated hospitals showed that early but not late convalescent plasma was associated with better survival in moderate to severe COVID-19.[19 22]

Investigations of treatments based on the development of monoclonal antibodies also support the critical importance of the appropriate timing of passive immunization.[31 32] Two monoclonal antibody therapies targeting SARS-CoV-2 (casirivimab-imdevimab and sotrovimab) are now available in the USA for the treatment of outpatients with early, mild to moderate COVID-19 and recommendations for their use are that it should be given as soon as possible after diagnosis and within 7 days of symptom onset.[33 34]

Our results are in line with these studies, underscoring the relevance of early administration of convalescent plasma to COVID-19, and expanding the favorable effect to hospitalized patients admitted to the ward and to the ICU—not requiring mechanical ventilation. Joyner *et al* and Salazar *et al* also reported decreased mortality in a similar group of patients.[16–18]

This study has limitations mostly due to its observational nature. Unmeasured confounders such as other risk factors or treatments might have influenced the results. Given that severity of illness on admission could not be evaluated with an established score, misclassification of patients might have occurred. Notwithstanding this, the use of admission site as a surrogate of acuity has already been used,[35] and recently, the rate of clinical improvement after plasma administration could be determined according to the hospital site where the patients received the infusion, among other variables.[20] A more detailed analysis of the clinical variables collected could not be done, because of the type of registry. There might be a chance that late administration of convalescent plasma might be harmful to patients on mechanical ventilation with COVID-19, the most severely affected subgroup.[14] If so, the beneficial effect observed on less severely ill patients could be indeed inexistent. While that is a certain possibility, a large body of evidence points to a beneficial effect of early plasma on non-intubated patients with COVID-19 pneumonia.[9 16–28] We did not measure antibody levels in all patients. High antibody titers might be associated to better outcomes and therefore this unknown variable could have affected our results. Finally, the date of symptom beginning might be a more adequate variable than the time to receiving plasma since hospital admission.

In conclusion, our study suggests that the early (within 3 days from hospital admission) administration of convalescent plasma to non-intubated patients with COVID-19 pneumonia might be necessary to obtain therapeutic benefits.

Author affiliations
[1]Epidemiología, Ministerio de Salud de la Provincia de Buenos Aires, La Plata, Buenos Aires, Argentina
[2]Inmunología, Hospital Interzonal Especializado en Pediatría 'Sor María Ludovica', La Plata, Buenos Aires, Argentina
[3]Clínica Médica, Hospital Interzonal General de Agudos General San Martin, La Plata, Argentina
[4]Medicina Interna, Universidad Nacional de la Plata Facultad de Ciencias Medicas, La Plata, Buenos Aires, Argentina
[5]Estadística, Instituto de Hemoterapia, La Plata, Buenos Aires, Argentina
[6]Dirección de Investigación, Ministerio de Salud de la Provincia de Buenos Aires, La Plata, Argentina

[7]Instituto de Investigaciones Pediátricas 'Prof. Fernando E. Vitieri', La Plata, Buenos Aires, Argentina
[8]Ministro de Salud Pública, Ministerio de Salud de la Provincia de Buenos Aires, La Plata, Buenos Aires, Argentina
[9]Terapia Intensiva, Hospital Interzonal General de Agudos General San Martin, La Plata, Argentina

Twitter Martin R Salazar @Salazar

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ORCID iD
Martin R Salazar http://orcid.org/0000-0002-7103-5505

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