Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Dynamics of anti-SARS-CoV-2 antibodies in repeat convalescent plasma donors

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is still a worldwide health crisis with devastating social and economic consequences. Patients with SARS-CoV-2 infection usually develop an IgM, IgA and IgG antibody response directed against the virally encoded surface spike and nucleocapsid proteins. The former, in particular, plays a key role in viral entry into cells mediating the binding of the virus to angiotensin converting enzyme 2 (ACE2) on target cells through its receptor-binding domain (RBD). The great majority of anti-spike antibodies is directed against viral RBD and has a neutralizing activity [1,2].

Although short-term seroprevalence studies have consistently demonstrated a seroconversion of IgG, IgA and IgM antibodies against viral spike and nucleocapsid proteins within 1–3 weeks after symptom onset and a rapid decline of IgM and IgA titers [3], less information is available about the long-term course of neutralizing anti-SARS-CoV-2 IgG antibodies [4]. This topic has not only speculative value but can also have important practical implications for vaccine development and administration schedule, in order to provide an adequate and long-lasting immune response against SARS-CoV-2 in vaccinated people [4]. In addition, understanding the dynamics of anti-SARS-CoV-2 antibodies is critical to collect the most appropriate plasma units from individuals recovered from COVID-19 (COVID-19 convalescent plasma, CCP). Recent studies, indeed, have highlighted that the most beneficial effect of CCP is obtained if it is transfused early in the disease course (within 3 days of hospital admission) and with a high amount ($\geq$1:160) of anti-SARS-CoV-2 neutralizing antibodies [5]. To study the dynamics of such antibodies over time and those factors possibly influencing their potency and duration, we report here our single center experience on donors recovered from COVID-19 who performed repeat CCP donations during the pandemic period in Italy.

Between April 15, 2020, and April 30, 2021, 49 consecutive individuals recovered from COVID-19 performed 103 CCP donations at the Transfusion Center of the city hospital of Mantua, Italy. Forty-two donors (85.7 %) were males and 7 (14.3 %) females (male/female ratio: 6). Their median age was 47.0 years (range 20–69 years). Forty-four (89.8 %) donors performed 2 CCP donations, 4 (8.2 %) donors 3 CCP donations and 1 (2.0 %) donor 4 CCP donations. Twenty (40.8 %) donors had suffered from moderate to severe COVID-19 requiring hospitalization, while the remaining 29 (59.2 %) donors had had an asymptomatic or pauci-symptomatic COVID-19 not requiring hospitalization. The ABO blood group was also recorded and was distributed as follows: 19 (38.8 %) group A, 21 (42.8 %) group O, 5 (10.2 %) group B and 4 (8.2 %) group AB. Donors performed the first CCP donation at a median of 28 days from the infection onset (documented through a nasopharyngeal swab positive for SARS-CoV-2 polymerase chain reaction [PCR] assay) and at least 14 days after symptom resolution or a negative PCR SARS-CoV-2 assay on nasopharyngeal swab. Depending on the number of CCP donations, each donor underwent two to four plaque reduction neutralization tests (PRNTs), as described elsewhere [6], for the titration of anti-SARS-CoV-2 neutralizing antibodies. The time of the first PRNT assay was coded as 0, whereas the following assays were coded with the time lag (days) after the first assay. The time of assays ranged from 0 to 335 days. The time variable (“timecat”) was discretized as age (days) groups with “0−29”, “30−59”, “60−89”, and “90+” as a categorical variable. Descriptive evaluation of the variable of interest, neutralization titer, was obtained stratifying by admission to hospital and time groups. The neutralization titer values by time groups were also depicted as a box plot. The time course of the neutralization titer was estimated by a linear longitudinal/mixed regression model. The model included, as explanatory variables, age, gender, hospital admission, and ABO blood group.

Descriptive statistics are reported in Table 1 and in Fig. 1, which show a progressive decrease of the anti-SARS-CoV-2 neutralization titer values at different times that reached the maximum size from two to three months after the first assay. The regression results are reported in Table 2 and the corresponding predictive margins are depicted in Fig. 2. The age stratum “30−59 days” was significantly lower than the base level “0−29 days” ($P = 0.007$). Admission to hospital exerted a significant increasing effect on anti-SARS-oV-2 neutralization activity compared to non-admission ($P = 0.014$). In addition, a non-statistically significant trend ($P = 0.069$) towards an increased neutralization titer was observed in O blood group CCP donors compared to other blood groups. Thus, in our study, the greater chance of collecting CCP units with greater neutralizing activity was reached when convalescent plasma was donated by recovered subjects who suffered from COVID-19 requiring hospitalization and within 30–60 days from the diagnosis.

The results of this study, which analyze the temporal dynamics of anti-SARS-CoV-2 antibodies in CCP donors during their repeat donations, are in line with those reported in the literature [4]. For instance, in a previous study on 494 consecutive CCP donors we have demonstrated that COVID-19 severity was associated with greater antibody responses [7]. Interestingly, Maeda and colleagues [8] observed a substantial decrease of anti-SARS-CoV-2 neutralizing activity 1–2 months after disease onset and showed that patients experiencing severe/critical symptoms and longer hospitalization had significantly greater neutralizing activity than those having mild/moderate symptoms and shorter hospitalization periods, suggesting that the longer the exposure of COVID-19 patients to higher loads of SARS-CoV-2 the greater the immune response to the virus. A similar decrease of neutralizing antibodies (half-life of 47 days) was observed by Terpos and colleagues [9] in a recent study.

In conclusion, we believe that repeat CCP donors are an interesting model for studying the temporal changes of anti-SARS-CoV-2 neutralizing antibodies. The exact knowledge of the time of decline of humoral

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Table 1
Values of the neutralization titer at the time strata, by hospital admission.

Neutralization titer	Time	N	Mean	SD	Min	p25	p50	p75	Max
Admitted	0–29	23	328.7	225.0	40	160	320	640	640
	30–59	16	282.5	258.2	40	80	160	640	640
	60–89	1	80.0	–	80	80	80	80	80
	Total	40	304.0	236.7	40	120	160	640	640
Not admitted	0–29	33	208.8	143.3	10	160	160	320	640
	30–59	20	154.5	141.2	10	80	160	160	640
	60–89	3	80.0	69.3	40	40	40	160	160
	90+	7	148.6	85.5	80	80	160	160	320
	Total	63	178.7	137.2	10	80	160	160	640

Legend. Time zero is the first assay, in all cases 28 days after the onset of symptoms of the disease. Other values are the time lag (days) after the first assay. Number of observations, mean, standard deviation (SD), minimum, maximum, 25th (p25), 50th (p50), and 75th(p75) percentiles are reported.

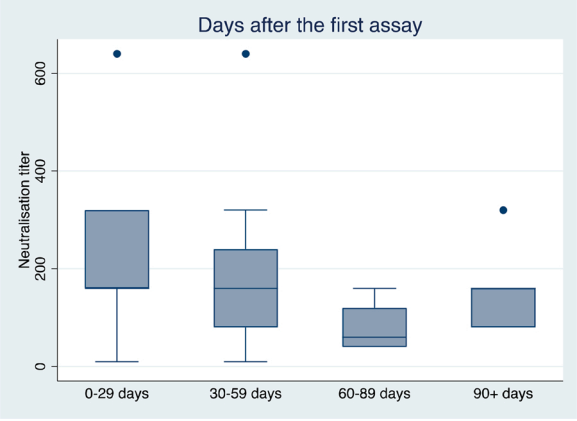

Fig. 1. Box plot depicting the median value of the neutralization titer at different delays after the first assay.
Legend. The 25th and 75th percentiles are reported (boxes) as adjacent ranges (horizontal segments) and outside values (dots).

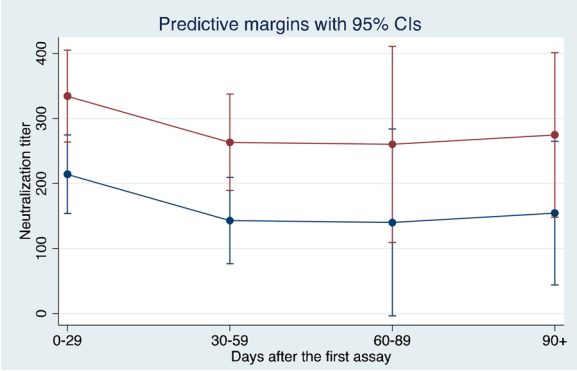

Fig. 2. Predictive levels of neutralization titer at different delays after the first assay (time = 0), and by admission to hospital, after linear longitudinal/mixed model estimation.
Legend. Blue line indicates patients not hospitalized; red line indicates patients hospitalized.

Table 2
Linear longitudinal/mixed model, table of the coefficients.

Neutralization timecat	Coefficient	Std. err.	z	P > z	[95 % conf.	interval]
30–59	−71.18	26.46	−2.69	0.007	−123.04	−19.31
60–89	−74.23	70.70	−1.05	0.294	−212.81	64.34
90+	−59.63	55.04	−1.08	0.279	−167.50	48.25
Age	−1.38	2.02	−0.68	0.494	−5.33	2.57
Female	−11.03	66.23	−0.17	0.868	−140.83	118.78
Admitted	119.79	48.78	2.46	0.014	24.18	215.39
AB-group	53.68	87.13	0.62	0.538	−117.08	224.45
B-group	19.91	76.52	0.26	0.795	−130.06	169.88
O-group	90.39	49.66	1.82	0.069	−6.95	187.73
Intercept	235.23	98.25	2.39	0.017	42.67	427.80

Legend. Timecat: time variable. The observations were 103, the number of groups (subjects) was 49, the log likelihood was -667.15, and the Wald chi2(9) was 20.16 (P = 0.0170).

responses against SARS-CoV-2 and the factors influencing antibody potency and duration are relevant issues for the optimization of CCP collection in order to obtain greater amount of highly effective, high-titer CCP units and can also have important practical implications for vaccine development and administration schedule.

Contributor ship

All the authors contributed to this work by recruiting the patients and performing the data analysis. All the authors approved the submission of this Letter.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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