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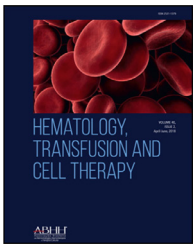

Letter to the Editor

Challenges in the production of COVID-19 convalescent plasma- analysis of donor recruitment

Dear Editor,

Currently, we are facing a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), named as 2019 novel coronavirus disease (COVID-19) by World Health Organization (WHO), emerged in Wuhan, China.[1] Since the first reported Brazilian case on February 26th to November 18th, 2020, Brazil has presented as the country with one of the highest number of cases and deaths: 8393,492 and 208,246,[2] respectively. From February 2020, in an attempt to provide passive immunization in Severe COVID-19 patients, several trials have appeared that addressed the subject, including a Brazilian study recently plublished.[3] On March 24th 2020 the Food and Drug Administration (FDA) has published the First recommendation for COVID-19 convalescent plasma (C19CP) donor eligibility,[4] updated on November 16th. [5] Based on these points, we designed a clinical trial to treat 10 Severe COVID-19 patients. It was submitted to "Comissão Nacional de Ética em Pesquisa (Conep)" on April 13rd and after review, it was approved on June 2nd, 2020. Recruitment disclosure for these specific blood donors started by social media, direct referral of patients after discharge for COVID-19 by hospital doctors and our network. The main purpose of this letter is to describe the challenges to select C19CP, that is the secondary objective of the trial.

Our inclusion criteria adopted the all of eligibility criteria by Brazilian laws for blood donors[6] and FDA recommendation:[5] age ≥ 18 years old; weight > 50 kg; previous registered COVID-19 diagnosis by Real Time polymerase chain reaction (RT-PCR); complete resolution of symptoms at least 14 days; male donors or female donors who have not been pregnant. In addition, for enhanced safety of the receiver patients participating in the study, we had included negative results for COVID-19 in RT-PCR nasopharyngeal smear samples as laboratory criterion to donate plasma.

According to the FDA recommendation concerning to the measurement of neutralizing antibody titers, we had proceeded a pilot test of neutralizing antibody assay and found that the Euroimmun test IgG antibody index < 3.4 correlate with low level of neutralizing antibody. Based on this finding we adopted this index as additional criteria to plasma donation.

Volunteer C19CP donors were recruited and attended the Clinical Research Center-Instituto de Ensino e Pesquisa São Lucas to present their previous RT-PCR exams that confirmed the diagnosis of COVID-19, and they had gone twice times to blood center. In the first step the donors had attended the selection interview and had their venous access examined. In the second step those approved in this evaluation were sent for blood sample and nasal swab collection for laboratory analysis and had released to their homes. After the exams had been performed, the selected donors were informed by telephone and a date was scheduled to donate plasma by apheresis. Eligible donors were submitted to plasmapheresis to collect 600 mL C19CP. Every plasmapheresis had been divided into two 250 mL units and 100 mL to analysis. The results of screening process are shown in Figure 1.

Some points of selection criteria to donor C19CP should be discussed correlating emergency use of investigational treatments and limitations due to new global pandemic. Thereby, we preferred to streamline and simplify criteria to be safe and more accessible. One point was to exclude female donors with previous history of pregnancy rather than Human Leukocyte Antigen (HLA) antibodies test, because, due to this criterion we kept out 4(8.16%) volunteers. At the time of study design it was no clear if COVID-19 could be transmitted by plasma and some studies introduced viral inactivation[3] procedure that could be very expensive. Thereby we decided to include this molecular diagnostic test for SARS-CoV-2 by RT-PCR in the blood and in the collected plasma bag as a security criterion to release the C19CP.

In addition, the other relevant point was IgG antibody index > 3.4, because few studies had been evaluated specificity and sensitivity about Euroimmun Anti-SARS-Cov-2 ELISA IgG[7, 8] correlated with neutralizing antibodies[8,9] at the time of this study design. Those publications demonstrated that Euroimmum anti-SARS-COV-2 ELISA IgG showed a very good correlation with a neutralization assay (91%), mainly with

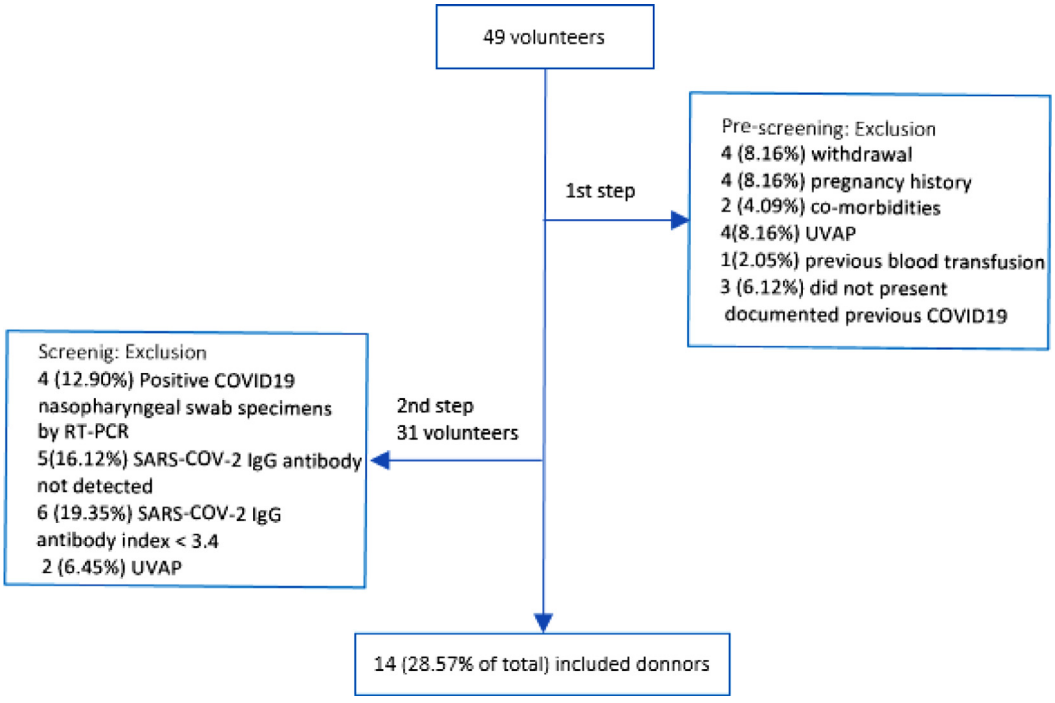

Figure 1 – Screening steps and exclusions of volunteers COVID-19 convalescent plasma (C19P) donors. RT-PCR: real time polymerase chain reaction; UVAP: unviable venous access for plasmapheresis.

high ELISA IgG titer, [8,9] but not purposed an index to evaluate the C19CP. In this sense, although the full study is not yet complete, we performed a pilot test to identify an index that could be associated to low level of neutralizing antibodies (< 1:80) and adopted 3.4 as the minimum value to accept the donation.

This experience highlights that it was necessary 3.5 volunteers to find one eligible C19P donor.

Conflicts of interest

The authors declare no conflicts of interest.

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