

Establishment of a Collection of Blood-Derived Products from COVID-19 Patients for Translational Research: Experience of the LPCE Biobank (Nice, France)

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In only a few months after its inception, the COVID-19 pandemic led to the death of hundreds of thousands of patients and to the infection of millions of people on most continents, mostly in the United States and in Europe. During this crisis, it was demonstrated that a better understanding of the pathogenicity, virulence, and contagiousness of SARS-CoV-2, all of which were initially underestimated, was urgently needed. The development of diagnostic tests to identify SARS-CoV-2 or to detect anti-SARS-CoV2 antibodies in blood, of vaccines, and of preventive and curative treatments has been relying on intense activity of scientists in academia and industry. It is noteworthy that these scientists depend on the use of high-quality biological samples taken from positive COVID-19 patients in a manner that preserves their integrity. Given this unique and emergent situation, it was necessary to urgently establish biological collections clinically annotated for immediate development of clinical and translational research projects focusing on COVID-19 biological aspects. It is in this very specific context that biobanks must rapidly adapt their infrastructure and/or operational capacity to fulfill new critical needs. We report the establishment of a biobank dedicated to the collection of blood-derived products (plasma, serum, and leukocytes) from COVID-19 patients hospitalized in the Nice Pasteur Hospital (Nice, France).

Keywords: COVID-19, SARS-CoV-2, blood, biobank, research

Introduction

THE COVID-19 PANDEMIC resulted in hundreds of thousands of deaths and several millions of infected people in only a few months, notably in the United States and in Europe.¹ During this crisis, the scientific and medical communities have designed and activated clinical and translational research programs aiming at developing vaccines, identifying curative and preventive treatments, and evaluating new diagnostic tests.^{2,3} The success of most of these research programs is based on the analysis of biological samples (cells, tissues, and biofluids) from positive COVID-19 patients and the discovery of associations between the samples' molecular features and the patients' clinical outcome or epidemiological data. During this crisis, substantial funds were immediately allocated

by the European and international organizations to support research projects to expedite discoveries in different domains of the COVID-19 pandemic.^{4,5} Many clinical trials were designed by academic teams, often in partnership with the biotech and pharmaceutical industries, to identify SARS-CoV-2 in cells or tissues or quantify anti-SARS-CoV-2 antibodies in blood samples as potential diagnostic strategies, or to develop vaccines and other therapeutic modalities.⁶ In addition, animal models were developed using samples taken from positive COVID-19 patients to better understand the patho-physiopathology associated with a SARS-CoV-2 infection.^{7,8}

The number of publications with a COVID-19 focus has increased exponentially in peer-reviewed journals, and they have been made available to the scientific community at large. This has allowed for the rapid dissemination of pivotal

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knowledge in an unprecedented manner, which sustains the rapid development of diagnostic tools and treatment options. It is important to notice that a caveat of the urgent need to discover efficient treatments, vaccines, diagnostic tests, and new biological mechanisms concerning SARS-CoV-2 pathogenicity, is the publication of erroneous data, discordant and controversial results, and the release of biological tests with a low level of sensitivity and specificity.^{9–14} Aside from the scientific competition between different research teams, this could be the result of financial and economic constraints.¹⁵

However, a more critical contributor is the use of low-quality biological resources from positive COVID-19 patients and/or poor, incomplete, or false clinical data. Biobanks play an essential role in controlling the collection, quality, and the storage conditions, in a secure manner, of biological samples from positive COVID-19 patients. They are also well-equipped to obtain accurate and reliable associated clinical data. In addition, biobankers' involvement in research projects in a collaborative manner ensures that the intricacies of biospecimen science are considered and the samples are properly used. Biobanks guarantee the quality of biological samples, which is a fundamental contributor to the robustness and reproducibility of experimental results.

We report the experience of the Louis Pasteur Hospital University Biobank (BB-0033-00025, Nice, France) in establishing a collection of blood samples from positive COVID-19 patients. For this purpose, the COVID-19 Biobank is an extension of the existing Biobank of the Pasteur Hospital, which was created in 2004. So, a new biobank was set up rapidly in a specific building for preparation and storage of blood samples from COVID-19 patients. We discuss here the key infrastructure needs for this new activity as well as the requirements of effective biosafety procedures.

The COVID-19 Biobank of the Nice Hospital University

Infrastructure and functioning

Since 2012, the Louis Pasteur Hospital Biobank has been certified according to the 96S-900 norm and the facilities of the biobank are located in one building of the Pasteur Hospital (J pavilion) (Fig. 1). Separate facilities were rapidly dedicated to the setup of a targeted activity associated with a new collection of blood samples from positive COVID-19 patients, which were established in a specific part of the hospital ("COVID-19 Biobank," I pavilion) (Fig. 1). Only the sampling and storage of blood specimens from positive COVID-19 patients were performed in these facilities, which excluded other collections. The facilities have three separate spaces, one with a desk for reception and registration of the samples, another with an airlock connected to a chamber isolated from the laboratory, and one corresponding to the laboratory itself for preparation of blood-derived products and for storage of sampling tubes (Fig. 1). The latter room has a BSL-2 environment with a BSC level 2 hood (PSM 2, MSC Advantage; Thermo Fisher Scientific, Waltham, MA), one centrifuge with a sealed rotor and safety cups for liquid specimen management (Heraeus Megafuge 16R; Thermo Fisher Scientific), a counter (pochHi-100; Sysmex France,

Paris, France) for evaluating the number of peripheral blood mononuclear cells (PBMCs), and four -80°C freezers (TSX400; Thermo Fisher Scientific) including two empty freezers serving as backups in case of one freezer failure.

Freezer temperatures were controlled using temperature sensors (Sirius probe, SPY RFU1 PT100; JRI MAXANT; Thermo Fisher Scientific) together with an alarm connected 24 hours a day to mobile phones of the personal. Moreover, an alarm system with on call duty was organized. The different procedures followed the rules established according to the S96-900 norm for biobanks.¹⁶

Staff and daily work organization

A team of six technicians (V.T., M.H., M.A., V.L., J.F., O.B.) was dedicated specifically to this activity in association with two pneumologists (C.M., S.L.), two biopathologists (V.H., P.H.), two quality technicians (Z.M., K.W.), and three clinical research associates (J.G., C.M., L.P.). Since the technicians worked exclusively to set up the collection of samples from positive COVID-19 patients as soon as the first samples arrived in the new facilities, they did not interact with the other members of the Nice Biobank located in the J pavilion. Moreover, two technicians worked at the same time in the new biobank in the I pavilion, one in the reception office and the second in the adjacent laboratory space. The other technicians teleworked. The technician working in the reception room was dressed with laboratory work clothing but wore an FFP2 mask. The technician entering into the laboratory space in the entry lock dressed with personal protective equipment (PPE) according to the international guidelines for personnel working in a BSL-2 facility, notably during the COVID-19 pandemic.^{17,18} So the technician wore an FFP2 mask, double pair of gloves, surgical cap and surgical overshoes, plastic glasses, and an adapted protective suit (Fig. 2).

After each work time in the laboratory room, the technician discarded the PPE, according to specific rules set up by the European Centre for Disease Prevention and Control (ECDC), and washed his/her hands for at least 30 seconds with an alcohol-based solution. All PPE and different plastic bags and residual tubes were discarded at the end of each day in specific plastic bags for infectious material elimination. The total surfaces of the rooms, including notably the floor, the benches, the handles (including those of the freezers), and the centrifuge, were cleaned at the end of the day by one of the technicians using a sodium hypochlorite- or alcohol-based solution.

Management of blood samples and derived blood products and associated clinical data

Management of biospecimens. For each hospitalized patient, a blood sample was taken on the first day after the admission, and after weeks 1 and 2 of hospitalization. Tubes were placed in plastic bags used in the hospital for specimen transportation according to guidelines established during the COVID-19 pandemic by the French Society for Microbiology.¹⁹ Samples were delivered by courier from the hospital. The turnaround time between venipuncture and centrifugation of the sample at the biobank was no more than 1 hour. Quality control parameters and benchmarking were established and determined following the SPRECV2 code of

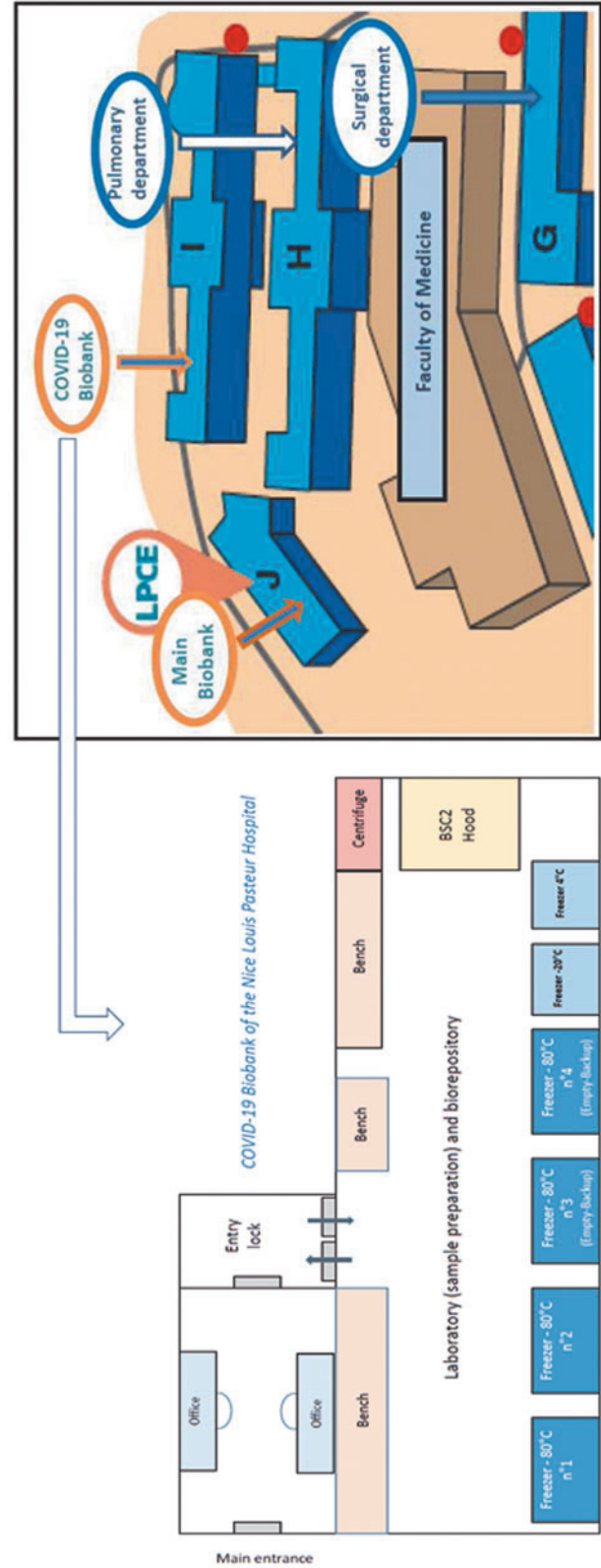


FIG. 1. Facilities of the COVID-19 Nice Louis Pasteur Hospital Biobank. LPCE, Laboratory of Clinical and Experimental Pathology.

FIG. 2. Protective personal equipment required to work in the COVID-19 Nice Hospital Biobank.



the International Society for Biological and Environmental Repositories (ISBER) guidelines.²⁰

Briefly, for each patient, blood samples were collected in one 10 mL EDTA tube (BEC366643; BD Vacutainer, Le Pont de Claix, France), for plasma and PBMC preparation, and in one 5 mL tube (BEC367814; BD Vacutainer), for serum preparation. All steps were paperless and information was transmitted on an electronic form via a secured internal hospital system. Blood was centrifuged according to protocols for plasma and serum isolation used in the Nice Hospital Biobank day-to-day operations, and according to its S96-900 certification and the BB-0033-00025 quality management system. Samples were centrifuged twice at 2000 g, 4°C for 10 minutes each, and plasma and serum were aliquoted under the BSC-2 hood using manual pipettes in vials, each containing 200 µL. PBMCs were isolated using the Lymphoprep Uni-Sep tube (Eurobio, Les Ulis, France). Briefly, 5 mL of RPMI 1640 medium (D Dutscher, Brumath, France) was added to 5 mL of whole blood. Then the mixture was placed into the Lymphoprep tube and centrifuged at 1000 g for 20 minutes at room temperature, and the PBMC layer centrifuged at 400 g for 10 minutes at room temperature. Cells were suspended in 1 mL of 4% human albumin (Vialebex, Lille, France) under the BSC-2 hood using manual pipettes.

Briefly, after counting (poch-H-100i; Sysmex France) PBMC aliquots of 5 million cells, each was frozen in a solution of 900 µL of sterile albumin at 40 mg/mL and 100 µL of DMSO (D Dutscher). Cells were progressively frozen at -80°C first in an isopropyl alcohol-jacketed closed freezing container (Nalgene, Paris, France) and kept overnight, and then transferred to liquid nitrogen tank the next day. Finally, serum and plasma aliquots were homogenized 10 seconds each using a vortex ZX3 (Humeau Laboratories, La Chapelle-sur-Erdre, France) and placed at -80°C.

The processing of the electronic data associated with the biological samples was recorded using specific software (MBioLIMS BioBanking) set up for the COVID-19 collection (Modul-Bio, Luminy, Marseille, France). This da-

tabase also allowed samples to be tracked. Different information was registered, including the date of sample registration in the biobank, patient ID, number of tubes, type of derived blood products, freezer localization, and name of the technician (Supplementary Table S1). Since only one technician could use the microbiological hood (PSM2) and the centrifuge at one time, the number of patient samples processed per day did not exceed five.

Management of clinical associated data. An electronic log book containing different files associated with the electronic biological data recorded above (Modul-Bio) was set up to record clinical parameters, including the different treatments administered and patient follow-up (Supplementary Table S2). All these data were secured with the essential health and safety requirements. The clinical data were recorded by clinical research associates.

Inclusion of samples from positive COVID-19 patients into the biobank

The first samples from patients were registered in the COVID-19 Biobank of Nice on the 15th of March 2020, and as of the 15th of May 2020, samples from 122 patients had been included. The study was approved by the Ethics Committee (CPP Sud-Méditerranée V, Nice, France) of the Nice Hospital Center (Authorization No. 2020-AO1050-39). Informed written consent was obtained from all patients. Patients younger than 18 years were excluded from this study. Among this population, there were 75/122 (61%) men (mean age, 72 years old, range 18–80 years old) and 47/122 (39%) women (mean age, 68 years old, range 28–84 years old).

The diagnosis of a SARS-CoV-2 infection was made by reverse transcriptase-polymerase chain reaction (RT-PCR) in the Laboratory of Virology (Nice Archet Hospital, France) using a nasopharyngeal sample. Briefly, primers and probes (CoV_IP2 and CoV_IP4) were designed to target the RdRp gene spanning nt 12621–12727 and 14010–14116 (positions according to SARS-CoV, NC_004718). As a confirmatory assay, the E gene assay using the Charité

protocol was performed.²¹ According to the experimental design described above, an average of 10 plasma aliquots (from 3 to 12), 2 PBMC aliquots (from 1 to 3), and 9 serum aliquots (from 2 to 11) were collected at each time point. However, 104/122 (85.2%) patients had been discharged before 7 days and 110/122 (90%) of the patients had been discharged before 14 days after the date of the first draw. The clinical data associated with these biological samples were prospectively recorded by the clinical research associates.

Discussion

We report here the rapid establishment and reorganization of an infrastructure for biobanking dedicated to blood sample collection from positive COVID-19 patients. The new facilities became part of the Nice Hospital Biobank (BB-0033-00025). Before the pandemic crisis, biobanking activity in the Nice Hospital was mainly focused on thoracic and dermato-oncology, and on a few diseases (such as interstitial pulmonary fibrosis and different thyroid pathologies). This biobanking activity was set up in a building ("J pavilion") where reception of samples (blood, urine, tissue), preparation of derivative products (DNA, RNA, plasma, sera, and PBMCs), and stocking activities were developed since the creation of the Nice Hospital Biobank in 2006. We decided, with the financial support of the Nice Hospital management, to set up a new biobank in a preexisting empty building located in the hospital center ("I pavilion"), which was dedicated to collecting samples from COVID-19 patients (Fig. 1).

Briefly, since we were aware of the COVID-19 epidemic in Italy starting early in 2020 (particularly in the Lombardy region, which is near Nice), we decided to anticipate the fact that some COVID-19 patients could be hospitalized in the Nice University Hospital. In this context, our strategy was to reorganize the biobanking activity of the different collections, with decreasing the number of collecting samples associated with thoracic oncology and thyroid diseases. Setting up the COVID-19 Biobank in the Nice Hospital was not different from setting up any kind of biobank. However, we decided to set up this new collection from COVID-19 patients in a specific separate space (Pavilion I, Fig. 1) from the actual biobank (Pavilion I, Fig. 1) since many uncertainties were associated with the SARS-CoV-2 contagiousness. Moreover, we took advantage of the fact that the clinical department of thoracic diseases where the COVID-19 patients were hospitalized was located no more than around 100 m from this new area. We set up new protocols and provided educational training for the staff members, notably concerning different biosafety procedures. The creation and development of the Nice COVID-19 Biobank raised a number of questions and considerations as discussed below.

Biological risks associated with preparation of blood derivatives from the COVID-19 patients

We adopted major and expensive precautions when handling clinical specimens, while knowing that the risk of contagion when manipulating blood samples from COVID-19 patients seemed to be very low. In fact, numerous recent publications demonstrated the absence or low virulence in

blood and PBMC samples.^{22–28} Nevertheless, the measures put in place were based on the following guidance and assumptions: (1) The international guidelines for human blood handling, recently formulated by the U.S. Centers of Disease Control and Prevention, the World Health Organization, the U.S. Food and Drug Administration, and by the University of California San Francisco, in the context of the COVID-19 pandemic.^{17,18,29,30} (2) The assumption that zero risk does not exist when handling nonfixed human biological samples, specially blood.^{23,31,32} (3) The current uncertainties related to SARS-CoV-2 pathogenesis.^{33–35} (4) The fears and concerns in the laboratory and biobank staff and in the general population regarding manipulation of samples from COVID-19-positive or suspected patients.^{36–39} (5) The fact that contagion may occur after handling plastic bags and other material coming from the clinical pulmonary department, since it was shown that SARS-CoV-2 can remain on many different surfaces for several hours or days.⁴⁰ Based on these points, it was critical to set up a new, appropriate, and secure workflow of samples that provided the personnel with reassurance and confidence.

The communication of information in an expedited manner through webinars, different courses, and training venues ensures that safety measures are understood and applied, notably for technicians who must execute safe laboratory practices.⁴¹ Notably, it was important to give information concerning the use of personal protection equipment when handling blood tubes from positive COVID-19 patients. It was highlighted that the FFP2 mask (and not surgical mask) was protective enough for the staff members and that this mask could be worn over 4 hours (but no more than 8 hours) a day according to guidelines. In addition, technicians used manual pipettes for aliquoting plasma, serum, and PBMC samples, and it was not possible to use an automated system. This latter system could be potentially used if the robot was placed in the BSC-2, but considering the relatively low number of patient samples processed each day, we decided to use a manual procedure, avoiding the possible creation of drops of aerosol from contaminated samples that could be generated during the automated pipetting system.

Staff members

We dedicated six technicians to the project even if this number could seem to be high. However, since some of these staff members could also potentially contract COVID-19 (by an external contamination, for example), we needed to sustain the ability for collection of samples in case of some technician contracting COVID-19. This team could certainly take care of samples from more than five patients per day, but we decided to limit the number of cases, notably to reduce the potential pressure on the staff. Finally, each technician spent no more than 4 hours per day processing blood, and so, we needed to have a turnover for the staff during the day.

Each day, the blood samples of three and two patients were included in the morning (before 10 am) and in the afternoon (before 3 pm), respectively. The blood samples were taken in less than 1 hour from patients being hospitalized and then immediately transmitted and processed in the biobank. In addition, we believed that it was important to include in this project some physicians, notably

pneumologists (2), and biopathologists (2), a full-time quality technician dedicated to quality assurance/quality control, and clinical research associates (3) to register associated clinical data. The staff members did not have COVID-19 testing with RT-PCR. This COVID-19 testing could be made only if one person had fever and/or other symptoms (such as cough, chest pain, ageusia, and/or anosmia). It would be certainly appropriate to test the staff by RT-PCR for COVID-19 in the case of setting up collection from fresh cytological samples (such as bronchoalveolar lavage, and nasal and/or buccal cytological samples). We thought it was not mandatory to do that when collecting blood samples only.

Choice of blood derivative based on research project need

The COVID-19 Biobank of the Nice University Hospital collected, preserved, and stored, at -80°C , aliquots of plasma, serum, and PBMC from each COVID-19-positive patient. We believe that this collection is valuable to stakeholders from academia and industry (both pharmaceutical and biotechnology companies). Researchers could request the banked PBMCs, perform nucleic acid extraction, determine germinal mutations, and investigate the genetic predisposition of patients to develop an asymptomatic infection, express mild symptoms or develop a severe form, and experience medical complications.^{42–44} The banked plasma and serum could be used to determine the cytokine profile or to perform more complex proteomic analyses.

Correlation between molecular profiling and clinical outcomes could be studied using the parameters recorded in the database.^{24,45} It is important to note that the blood sample derivatives stored in the COVID-19 Nice Biobank were collected from symptomatic and hospitalized patients. Some of these patients were included in the Discovery clinical trial. In the future, we intend to bank blood samples from healthy professionals from the Nice Pasteur Hospital that, after performing the SARS-CoV-2 RT-PCR test using nasopharyngeal swabs, are classified as positive and are asymptomatic.

We also intend to bank other types of specimens from COVID-19-positive patients such as urine, tissue, and cytological samples. A cohort of particular interest is the COVID-19-positive patients with comorbidities and pathologies such as lung cancer. We plan to collect lung cancer specimens (frozen, formalin-fixed, and paraffin-embedded) resected from COVID-19 patients. Currently, all patients undergoing thoracic surgery are tested in our institution with the SARS-CoV-2 RT-PCR assay, following new recommendations.⁴⁶ A specific collection of lung cancer in the Nice Hospital Biobank will be initiated.⁴⁷

We are aware about the uncertainty of the COVID-19 pandemic evolution and hope that a decrease in the number of infected patients will occur rapidly. If that is the case, the number of collected samples associated with positive COVID-19 patients will gradually decline. It is possible that the number of COVID-19 research projects will also decrease, leading to a lower demand for these biological samples. We intend to monitor the COVID-19 pandemic's dynamics and reorient collection platforms

quickly to support different domains of scientific research such as oncology.⁴⁸

Clauses governing the sharing and transfer of samples

It is critical to establish the models for releasing and distributing samples from positive COVID-19 patients and the regulations that apply. The informed consent form, signed by the patients before any collection is performed, must include explanations disclosing that the intended use of the biological samples is for collaborative projects with academia and/or with private companies.^{49,50} It is of strong interest to maximize the public/private partnerships to accelerate new discoveries and development.^{50,51} Although several collections have been initiated throughout the affected areas during the COVID-19 pandemic, most of the biological samples have been prospectively collected in the context of specific clinical trials. Therefore, it is not usually possible to use these samples for another project. When this is deemed plausible from a regulatory perspective, the remaining quantity of such samples is low. The establishment of a high-quality collection of COVID-19-positive samples with accurate clinical annotation is important to fulfill any research need. However, during the establishment of such a collection, the models for sharing and transfer of the samples must be determined and approved at an institutional level. This is important to ensure the capacity for fulfillment of the needs of end-users from academic, industry, and government, and to obtain visibility in different scientific communities.⁵²

Quality of samples

This represents a critical point when establishing a new bank collection.¹¹ The control and documentation of the preanalytical variables that have a direct impact on biomarker integrity become of utmost importance.^{53,54} We strongly believe that the blood collection and preservation in the Nice Hospital COVID-19 Biobank meet the criteria of optimal quality based on the issues discussed below.

Clinical and biological data accessibility

The quality of sample collection is closely related to the clinical associated data. In the present study, the clinical database in place (Supplementary Table S2) was set up for this project using specific software (MBioLIMS Biobanking COVID-19) and included only a selection of clinical and biological information. This information was registered in a prospective way by the data managers (J.G., C.M., L.P.) of the Department of Pneumology of the Nice Hospital Center. The information associated with the samples (number, volume, type, etc.) (Supplementary Table S1) was prospectively registered by two data managers (J.F., M.A.) of the biobank. The clinical and biological items were deliberately limited in number to be sure to assure that procedures were in place to exhaustively and rapidly collect them. All these data could be obtained using an automatic extraction. However, if researchers asked for other parameters not compiled in this specific database, requests for these additional clinical data and/or other different treatments could be obtained in a retrospective way via the Laboratory Information Management System (LIMS) of the Nice Hospital

Center. This latter information was available in the Nice Hospital IT system only through a manual extraction.

Accessing biological collections from certified biobanks guarantees the quality of the material used for research purposes and contributes to the robustness and the reproducibility of the research project results.⁵⁵ The impact of the COVID-19 pandemic on the biobank infrastructure and sustainability is not trivial, but this challenge has generated exciting opportunities.^{56–58} In our case, we established a biobank that prospectively collects blood from COVID-19 patients, and preserves plasma, serum, and PBMCs that are stored and clinically annotated using a comprehensive database (Supplementary Tables S1 and S2). The dissemination to the research community that this new resource has been established to provide was announced on the website of the Nice Biobank. This collection is now available to academia and private companies to develop translational research projects on SARS-CoV-2 infections.

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Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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