METHODS ARTICLE

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Multistep screening and selection of COVID-19 convalescent plasma donors at the early stage of the SARS-CoV-2 pandemic: A retrospective analysis

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Abstract

Background and Aims: The COVID-19 pandemic reached Bavaria in February 2020. Almost simultaneously, Chinese physicians published reports on the first successful treatments with plasma from COVID-19 convalescent donors. With these silver linings on the horizon, we decided to establish the manufacturing of anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody-containing plasma from COVID-19 convalescent donors at our site. Here we describe our donor selection process, built from the ground up, which enabled us to cope with the immense resonance after our social media call for donors.

Methods: As a first step, we created a specific questionnaire for telephone interviews applied by trained students to filter the wave of callers interested in plasma donation. Afterward, the medical staff evaluated the hotline questionnaires and chose eligible donors to be invited for on-site donor evaluation. Data documentation was performed with MS Excel, and statistical analyses were calculated with GraphPad Prism 8. A quantitative in-house ELISA was used to detect anti-SARS-CoV-2 antibodies and determine specific titers.

Results: Out of 1465 calls from potential plasma donors, we could register 420 persons with a completed questionnaire. Evaluation of questionnaires identified 222 of 420 persons as eligible for donation, and 55 were directly asked for on-site donor qualification. Subsequently, as anti-SARS-CoV-2 antibody titers ≥1:800 were required, we invited 89 of 222 potential donors for an antibody screening. This procedure resulted in another 28 potential donors for an on-site evaluation. Finally, 12 donors qualified with a titer of 1:400 and 24 with ≥1:800.

Andreas M. Brosig and Thomas Ossner contributed equally to this study.

Conclusion: Identifying suitable COVID-19 convalescent plasma donors was expected to be highly time-consuming. Implementing a screening procedure with our hotline questionnaire helped us streamline the donor selection process and reduce the workload for the staff. We propose combining the described selection process with the later introduced on-site antibody screening as an effective strategy.

1 | INTRODUCTION

On October 20, 2015, the Arbeitskreis Blut (working party "blood") of the German Federal Ministry of Health published a statement (S16) on the production and application of convalescent plasma (CP) in severe infectious outbreaks. This treatment option has been reported to be successful in cases of Diphtheria in the early 20th century and SARS, H1N1, and Ebola in this century.[1]

These official directives gained importance when, in March 2020, the Robert Koch Institute (RKI) reported an increasing number of COVID-19 infections (March 15, 2021: Bavaria 886, Germany 4838).[2] Bavaria became one of the hotspots of the COVID-19 pandemic in Europe due to its geographical proximity to the coeval centers of the outbreak – Austria and Italy. Simultaneously, Chinese physicians published their first experience of successful treatments with plasma containing anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies from convalescent donors.[3–5]

Under these circumstances, we decided on March 15, 2020, to establish the production of plasma from COVID-19 convalescents at the University Hospital Regensburg (UKR). In this report, we want to share our experience with donor acquisition in the early phase of the pandemic. Our new screening workflow, from scratch, was based on a student-operated telephone hotline with a specific questionnaire. Subsequently, the medical staff evaluated these questionnaires and efficiently selected suitable COVID-19 CP donors.

2 | MATERIALS AND METHODS

According to German and European laws and directives, producing CP requires special good manufacturing practice conditions. Besides the standard requirements for a typical plasma donation, interested COVID-19 convalescent donors had to provide a positive SARS-CoV-2 polymerase chain reaction (PCR) test confirming their infection and had to be free of COVID-19 symptoms for at least 14 days. We only invited persons on-site with two negative SARS-CoV-2 PCR results to minimize any risk of virus transmission for our staff. Moreover, women with a history of pregnancy were excluded as additional testing for antibodies against human platelet, neutrophile or leukocyte antigens(HPA/HNA/HLA) was not feasible.

Furthermore, the EU recommended anti-SARS-CoV-2 antibody titers higher than 1:320 in their first directive on April 8, 2020.[6] At the end of March 2020, an in-house ELISA test for anti-SARS-CoV-2 antibodies and a specific antibody titer test were developed at the Institute of Microbiology and Hygiene, UKR, and applied to all study samples.[7]

Due to the ability to quantify anti-SARS-CoV-2 antibodies in serum, we could finally select qualified donors. However, a call to the public was necessary to raise awareness for COVID-19 CP donation. As Bavaria usually reports high quotes of blood donors among its population (2017: 5.29%),[8] we anticipated an enormous response to our call to donate CP. The expected workload of donor registration and evaluation on-site seemed impracticable with the available human resources and infrastructure. Hence, we developed a specific screening questionnaire (Supporting Information: 1) based on the "Uniform Questionnaire for Blood and Plasma Donation" (version 2018) from the Paul-Ehrlich Institute (PEI).[9] Eight trained students interviewed the first wave of callers interested in plasma donation via a telephone hotline. All calls were registered, but we only completed a questionnaire if callers met our selection criteria. In a second selection step, the medical staff of our department evaluated the hotline questionnaires and chose eligible persons for the third step: on-site donor evaluation according to PEI's recommendations and requirements. To ensure donors presented sufficient titers, we implemented an intermediate screening step to obtain antibody titers ≥1:800. After completing the medical checkup, individuals meeting all inclusion criteria qualified for plasma donation.

SAP (patient administration software, SAP SE) and SWISSLAB (laboratory information system, nexus/swisslab) were used as our standard software solutions for blood product manufacturing processes. All data were recorded and processed with MS Excel. Statistical analyses were calculated with GraphPad Prism 8. Normal distribution in each group was analyzed using Kolmogorov–Smirnov tests. Afterward, Student t-tests were performed if values in both groups were equally distributed. If values in at least one group were unequally distributed, Mann–Whitney tests were performed. $p < 0.05$ were considered statistically significant. For this study and subsequent analyses, institutional ethical approval was granted by the ethics committee at the University of Regensburg (21-2295-104).
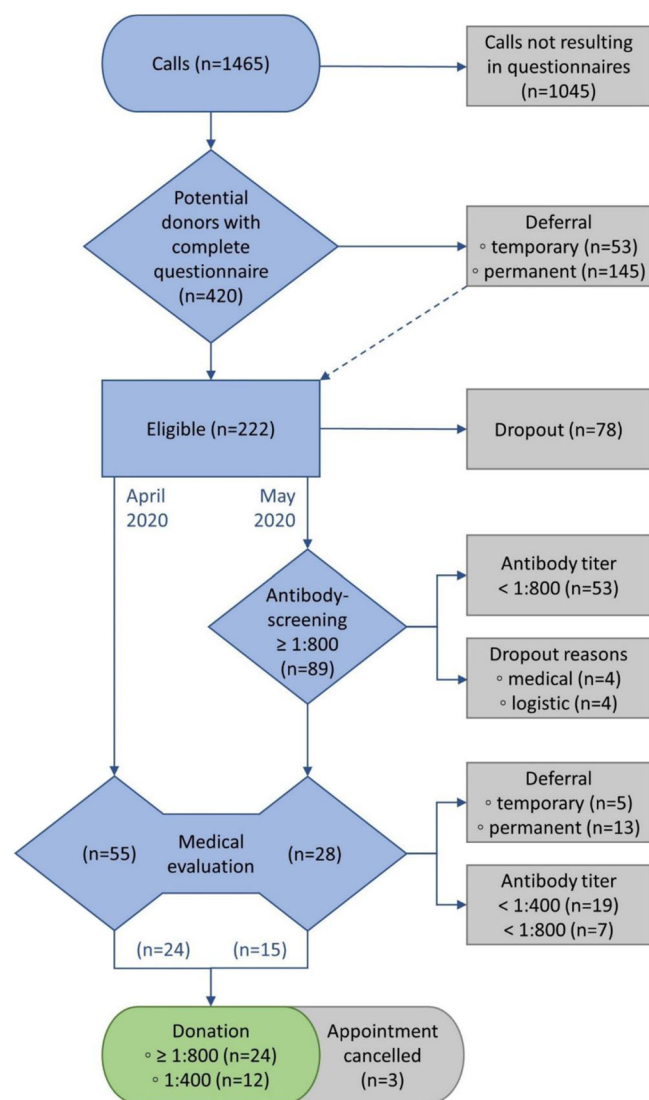
FIGURE 1 Multistep workflow of donor screening for COVID-19 convalescent plasma (CP). Donor screening was divided in four or five different hierarchic steps. Potential donors called at student hotline and completed a specific questionnaire. These questionnaires were evaluated by physicians. Eligible donors were invited to on-site medical evaluation or antibody screenings. After successfully completing the medical checkup and meeting all donation criteria individuals qualified for CP donation.

3 | RESULTS

3.1 | Donor screening and selection

After the official call for donors on social network channels and local newspapers, our students screened callers applying the specifically designed questionnaire via a telephone hotline. As shown in Figure 1, potential donors had to fulfill different criteria to pass through our multistep selection process. Taken together, we received 1465 calls from April 7, 2020, until May 10, 2020. These calls resulted in 420 potential plasma donors with a complete questionnaire. Afterward, these documents were evaluated by transfusion medicine physicians.

Subsequently, 222 of 420 (52.9%) callers were declared eligible donors. Until the end of April 2020, we considered anti-SARS-CoV-2 antibody titers of at least 1:400 sufficient for plasma donation. Thus, 55 of 222 (24.8%) persons were directly invited for medical evaluation. Out of this population, 24 individuals (43.6%) could qualify as COVID-19 CP donors.

Hoping to improve virus clearance in plasma recipients, we decided to elevate the required levels of anti-SARS-CoV-2 antibody-titers in May 2020. Therefore, we accepted only persons with antibody titers ≥1:800. These new criteria entailed a change in our selection strategy, and we implemented an antibody screening before the on-site medical evaluation of potential donors. 89 of 222 (40.1%) eligible individuals were invited to a blood draw, and antibody titers were determined. 28 of 89 (31.5%) potential donors presented with antibody titers ≥1:800 and underwent medical evaluation on-site. Finally, 15 of these 28 potential donors qualified for plasma donation (53.6%). Out of this group, three persons never donated CP at our facility. In the end, 24 donors qualified via the direct way, and another 12 donors were recruited from the cohort with prescreened antibody titers. Taking all callers registered with a questionnaire into account, 36 of 420 persons (8.6%) qualified for plasma donation.

Initially, we aimed to reduce the expected workload for on-site evaluation and minimize the infectious risks by reducing personal contacts. Therefore, the following aspect is of particular interest: only 83 of 420 (19.8%) registered callers had to be evaluated by physicians, meaning 80.2% (337 of 420) possible donors could be screened out earlier.

3.2 | Reasons for dropout

We analyzed the main reasons for dropout during our selection process. In the first step, 1045 of 1465 hotline calls did not lead to a filled-in questionnaire. Unfortunately, we have no detailed data on why callers were primarily screened out. Nevertheless, the following reasons were among the named: women with a history of pregnancy, age, permanent medication, a profession with a high risk of potential COVID-19 infection or no PCR-proven SARS-CoV-2 infection. We organized SARS-CoV-2-PCR testing for the required negative test results. Therefore, some persons inquired multiple times, and repeated calls were registered. Meaning the number of calls was not identical to the number of callers.

Most of the persons who eventually deferred or dropped out (n = 243) from the questionnaire cohort (n = 420) could be analyzed for related reasons (Table 1). A donation was mainly not possible due to deferral because of a potential SARS-CoV-2 exposure risk (18.6%), medical history (17.0%), logistical reasons, for example, travel time or distance (15.4%) or permanent medications (9.1%). Only 7.9% of persons had second thoughts and withdrew from the donation. The lack of women with a history of pregnancy is a quality feature of the hotline screening. Additionally, the effectiveness of the strict selection process is further reflected by the low number (5.7%, 83 out of 1465 callers) who qualified for on-site medical evaluation.

TABLE 1 Reasons for dropout or deferral of potential donors

Reasons for dropout or deferral	Total (%)
Professions with a high risk for infection	80 (18.6)
Medical history	73 (17.0)
Logistic reasons (e.g., time, distance)	66 (15.4)
Medications	39 (9.1)
Second thoughts	34 (7.9)
Travel history	21 (4.9)
Underweight	20 (4.7)
Complications related to blood donation	19 (4.4)
No negative SARS-CoV-2 PCR	18 (4.2)
Potential sexual risk contact	12 (2.8)
No positive SARS-CoV-2 PCR	12 (2.8)
Piercing/tattoo	8 (1.9)
No suitable venous access	7 (1.6)
No response to calls	7 (1.6)
Endoscopy	4 (0.9)
Infections	3 (0.7)
Surgery	3 (0.7)
Drug abuse	1 (0.2)

Note: Information about reasons for dropout or deferral of potential donors (n = 243) was documented. In total, 429 reasons for dropout or deferral occurred at different stages of the donor selection (n [%]).

3.3 | Epidemiological data

All potential donors registered with a questionnaire (n = 420) provided information about their date of birth, height, and weight (Table 2). Additionally, we statistically compared cohort characteristics at different stages of the donor screening to their respective control groups: eligible potential donors (n = 222), potential donors invited to on-site medical evaluation (n = 83), and qualified donors (n = 36) (Supporting Information: 2). Most parameters remained comparable after each screening step. However, the mean age between the two cohorts of medically evaluated (42.3 years) and qualified (45.0 years) male donors showed a statistically significant difference compared to their respective control groups (37.7 and 38.1 years). Due to these effects in the two male cohorts, the mean age in all medically evaluated (38.2 vs. 34.3 years) and potential donors (40.3 vs. 34.6 years) was significantly elevated. As women with a history of pregnancy were screened out at the student hotline, the mean age of the female population (28.8 years) was lower than the mean male age (38.8 years). Additionally, the mean weight of all eligible women (68.5 kg) was increased compared to registered women who were not eligible (66.4 kg). The requirement of a minimum weight of 50 kg could explain this difference.

As mentioned earlier, a positive SARS-CoV-2 PCR test was required for potential donors. Four hundred and five of 420 registered individuals (96.4%) met this criterion and reported their date of testing (Figure 2). Corresponding to the announcement of the "Katastrophenfall" (state of emergency) by the Bavarian federal government on March 16, 2020, most potential donors tested positive in the following 2 weeks. This data indicates that our call for potential donors on April 7, 2020, reached individuals infected at an early stage of the pandemic, the so-called first wave.

Fortunately, the response of the comparatively small population of COVID-19 convalescents to our announcement was enormous. Over 34 days (April 7, 2020 to May 10, 2020), 1465 calls were answered by students (Figure 3). As they worked in two shifts (9 a.m. to 1 p.m. and 1 p.m. to 5 p.m.), the workload in the early shift compared to the late shift was higher almost every day. Interestingly, potential donors called more frequently after weekends and holidays. The total number of calls per day has been decreasing for 5 weeks. As more than one-third of all calls (n = 508) occurred in the first 3 days, the hours and days after the announcement can be considered as most crucial.

Based on the information about the residency of the potential plasma donors, a geographical analysis was performed (Figure 4). Surprisingly, our call for COVID-19 CP donors generated an enormous response even in regions more than 100 km away from our site. Individuals from 40 different administrative districts in Bavaria and two in Baden-Württemberg were willing to donate plasma by calling our hotline. Out of 420 potential donors, 117 (27.8%) came from nearby areas, "Stadt" and "Landkreis" Regensburg. For instance, callers from Munich, Passau, and the back then COVID-19 hotspot Tirschenreuth were willing to take long drives to support our project. These data demonstrate the solidarity of many COVID-19 convalescents during the early stage of the pandemic. As we started the campaign for the collection of COVID-19 CP very early, the catchment area even reached regions usually expected to be covered by other university hospitals.

Blood groups were registered in questionnaires as reported by the potential donor or analyzed when on-site qualification was performed (n = 201). The distribution of blood groups differed from the expected values for the German population. With A (37.3%) and 0 (35.8%) being underrepresented and B (14.9%) and AB (11.9%) being overrepresented compared to the findings of Wagner et al.[10] in a representative South-West German population: A (41.21%), 0 (43.26%), B (10.71%), and AB (4.82%). Probably, donors have an increased awareness of a rarer blood group. The shift is even more distinct in the group of qualified donors A (33.3%), 0 (36.1%), B (13.9%), and AB (16.7%). An explanation for this observation could be a bias toward choosing donors with blood group AB, as it is ideally compatible with plasma transfusion therapy.

Since potential donors were required to be free of COVID-19 symptoms to ensure safety for our staff, we collected data about the occurrence and resolution of symptoms from potential donors. Therefore, we asked for signs of infection in the interval before and after the positive SARS-CoV-2 PCR result, which means self-

**TABLE 2** (Self-Reported) characteristics of potential donors based on questionnaires

	Male	Female	Total
Potential donors			
Persons, n (%)	264 (62.9%)	156 (37.1%)	420 (100%)
Age (years)	38.8 (18–59)	28.8 (18–58)	35.1 (18–59)
Height (cm)	181.3 (162–207)	168.2 (154–183)	176.4 (154–207)
Weight (kg)	86.4 (63–144)	67.3 (43–135)	79.3 (43–144)
Body mass index (kg/m²)	26.3 (19.8–40.7)	23.8 (17.0–44.1)	25.3 (17.0–44.1)
Potential donors (eligible)			
Persons, n (%)	152 (68.5%)	70 (31.5%)	222 (100%)
Age (years)	39.1 (18–59)	28.8 (18–58)	35.8 (18–59)
Height (cm)	181.1 (162–203)	168.7 (154–178)	177.2 (154–203)
Weight (kg)	86.6 (64–144)	68.5 (52–120)	80.9 (52–144)
Body mass index (kg/m²)	26.4 (19.8–40.7)	24.0 (18.0–41.0)	25.6 (18.0–41.0)
Potential donors (medical evaluation)			
Persons, n (%)	61 (73.5%)	22 (26.5%)	83 (100%)
Age (years)	42.3 (18–59)	27.1 (19–47)	38.2 (18–59)
Height (cm)	180.9 (170–197)	168.2 (160–176)	177.5 (160–197)
Weight (kg)	85.2 (65–144)	67.3 (55–83)	80.5 (55–144)
Body mass index (kg/m²)	26.0 (20.1–40.7)	23.8 (19.6–31.6)	25.5 (19.6–40.7)
Qualified donors			
Persons, n (%)	26 (72.2%)	10 (27.8%)	36 (100%)
Age (years)	45.0 (22–59)	28.0 (19–47)	40.3 (19–59)
Height (cm)	180.7 (170–192)	169.0 (162–176)	177.4 (162–192)
Weight (kg)	87.0 (65–144)	69.3 (60–83)	82.1 (60–144)
Body mass index (kg/m²)	26.7 (20.1–40.7)	24.3 (20.5–31.6)	26.1 (20.1–40.7)

Note: Information about personal characteristics were provided at the student hotline and documented in a specific questionnaire. Body mass index was calculated using the following formula: (body weight in kg)/(body surface area in m²). Populations at different stages (potential donors, n= 420; potential donors [eligible], n= 222; potential donors [medical evaluation], n= 83; qualified donors, n= 36) are divided in male, female and combined subcategories. Means and minimal and maximal values (mean [min–max]) of continuous variables (age, height, weight, and body mass index) are shown. The number of persons in each group is shown in absolute numbers and percentages (count [%]).

reported symptoms are most likely related to the detected COVID-19 disease. Individuals (n = 380) reported the duration of COVID-19 symptoms during the telephone interview (Figure 5). Of this population, 17 persons (4.5%) remained asymptomatic besides a PCR-confirmed SARS-CoV-2 infection. The other 363 persons reported a duration of COVID-19 symptoms between 1 and 35 days. The mean duration of symptoms was 13.0 days. Of note, 11 persons were still symptomatic when they called the hotline. The symptom duration of these individuals could not be determined. Additionally, 29 potential donors could not recall the date when symptoms occurred or were resolved. These data highlight the need for an appropriate interval between COVID-19 infection and on-site evaluation of potential donors.

4 | DISCUSSION

In the early phase of the COVID-19 pandemic, knowledge about the characteristics of the emerging virus was sparse. As treatment options were limited, any potentially helpful approach needed to be considered. Nevertheless, the safety of medical staff appeared very important, as high COVID-19 infection rates (5.9%) were detected among hospital workers until April 30, 2020 (9428 of 159.119 registered infections).[11] As we started planning the donor acquisition, we defined standards above the required criteria for plasma donation of COVID-19 convalescents. We wanted to minimize the risk for our staff, as in March 2020, the potential morbidity and mortality of COVID-19 were still largely unknown. With the possibility of
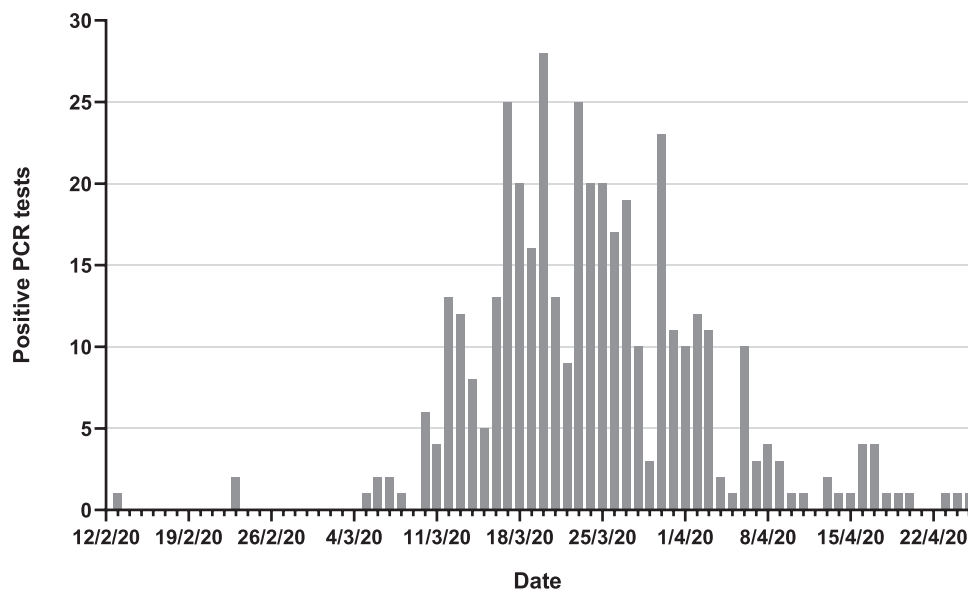
FIGURE 2 (Self-Reported) date of positive SARS-CoV-2 PCR test. Dates of positive SARS-CoV-2 PCR tests were reported by potential donors ($n = 405$) at the student hotline. PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
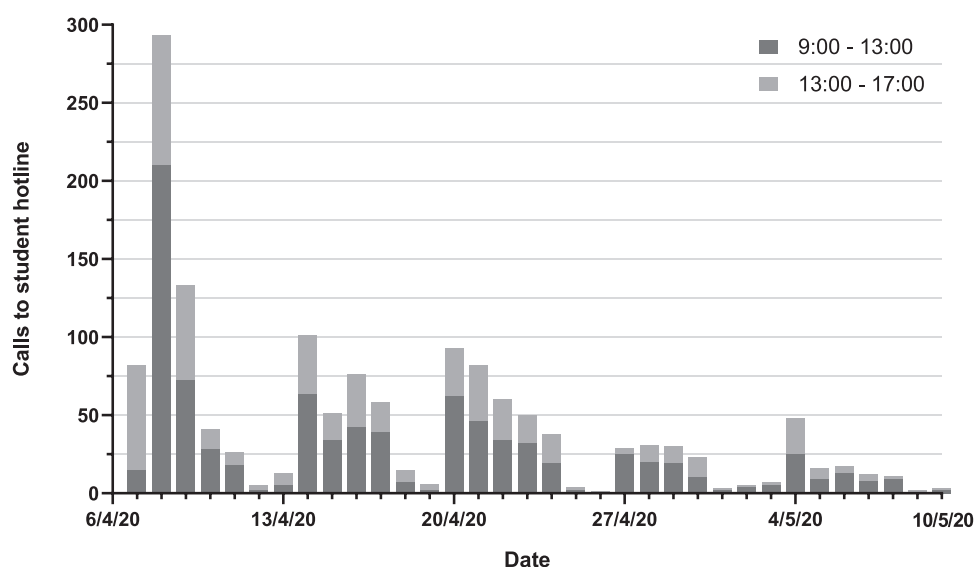

FIGURE 3 Call frequency to student hotline per day. Call frequency ($n = 1465$) at different shifts (9:00–13:00 and 13:00–17:00) of the student hotline were analyzed over 34 days (April 7, 2020 to May 10, 2020).

reinfection not being excluded, persons with potential infectious risk contacts were not allowed to qualify as plasma donors. On one hand, this restrictive policy allowed us to prevent any SARS-CoV-2 transmission on-site, on the other hand, the number of potential donors was limited, as 80 of 420 (19.0%) individuals were screened out due to our restrictions. To ensure the safety of our personnel, we demanded two negative SARS-CoV-2 PCR tests from all potential donors before the on-site invitation. Even if this requirement led to a delay in the procedure, it proved to be crucial. In several cases, potential donors were symptom-free for more than 2 weeks but remained SARS-CoV-2 PCR positive. Therefore, we recommend

negative SARS-CoV-2 PCR tests or an appropriate period after symptom resolution before inviting potential donors on-site.

Regarding the specific reasons for the deferral of donors, we could only evaluate the 420 available questionnaires since 1045 of 1465 contacts were not registered in detail, and repeated calls were counted. Therefore, a more detailed data registration in the first screening step should be considered for future projects. Nevertheless, we regard this initial screening step—applying a condensed, easy-to-use questionnaire with local regulations for admission to plasma donation—as crucial for the workflow. Implementing online forms or smartphone applications could also be an option if technical
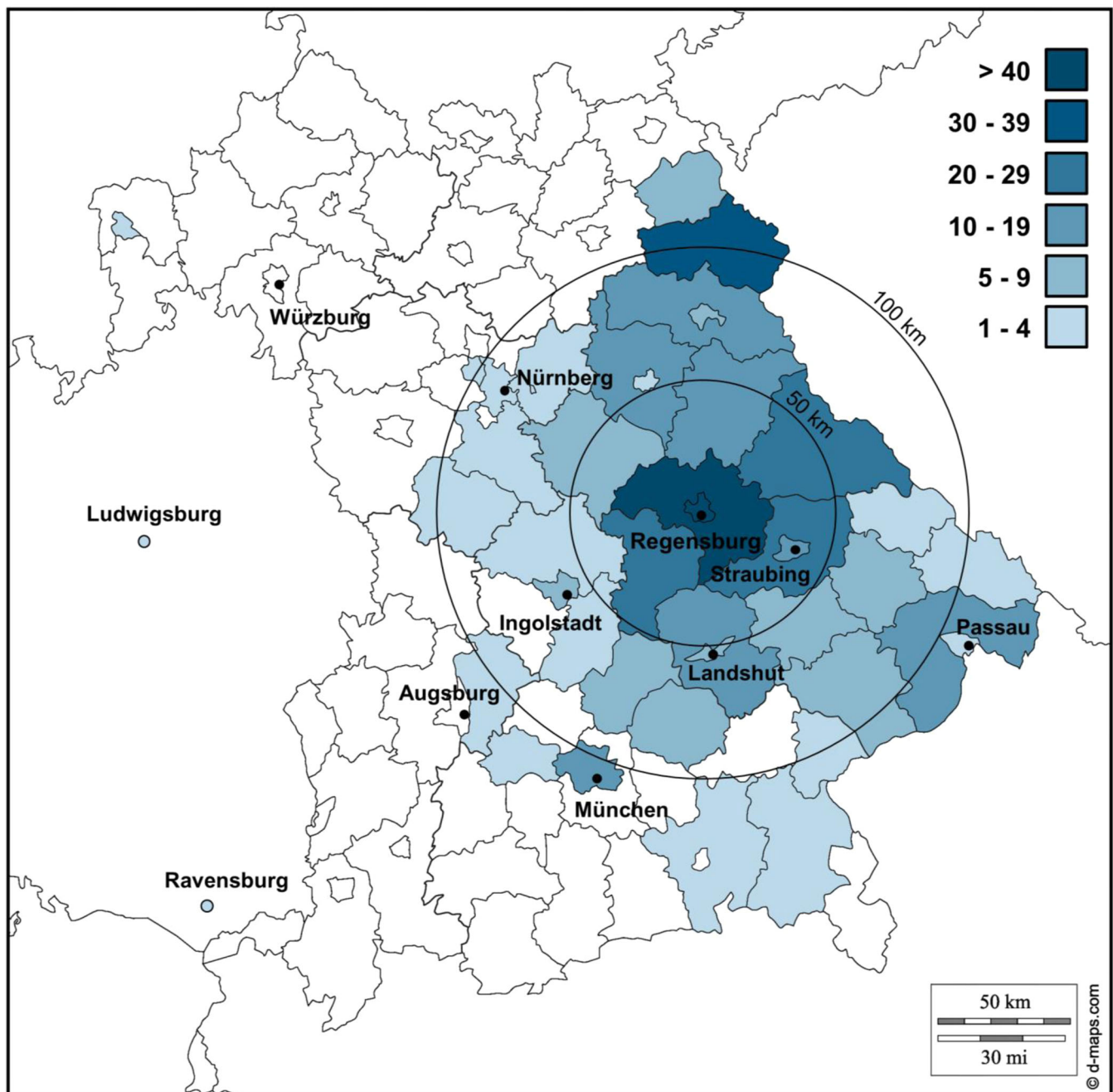
FIGURE 4   Geographical distribution of potential donors over 42 administrative districts. Potential donors (*n* = 420) were categorized in different administrative districts ("Landkreise") based on their self-reported address and postal code. Darker shades of blue indicate more potential donors contacted the student hotline. Two circles indicate 50 and 100 km distance from the University clinic of Regensburg. Original map was provided by d-maps.com (copyright: https://d-maps.com/carte.php?num_car=6121&lang=de).

availability is not an obstacle. However, it leaves the potential donor without direct personal feedback. Therefore, the telephone hotline is our first choice. We propose combining a telephone hotline screening with an on-site antibody screening is suitable to select and qualify donors in an acceptable timeframe. Our call for donors generated an overwhelming response from COVID-19 convalescents. Approximately one-third of all calls were registered in the first 3 days. Due to busy telephone lines, some calls could not be answered, resulting in a potential underestimation of the workload in the first days of the acquisition phase. Our message here is that the supply of technical equipment (e.g., phone lines, efficient IT infrastructure, and software for registration) forms a crucial basis. In addition, expanding the hotline team for the first week could be helpful managing the massive initial influx of data. For the following 2 weeks, the workload was distributed equally between morning and afternoon, but in Weeks 4 and 5, calls were registered mainly in the morning. Because of this
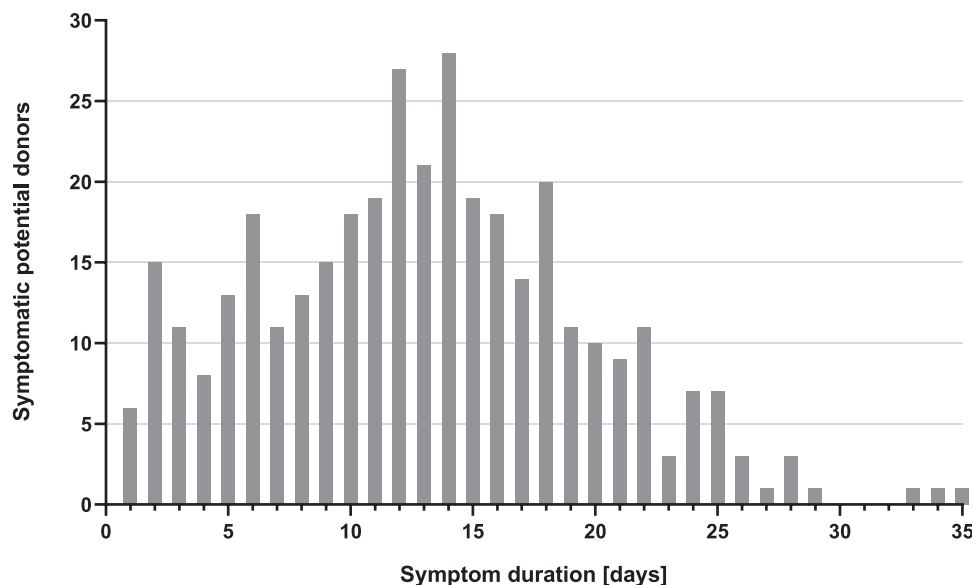
FIGURE 5 (Self-Reported) duration of COVID-19 symptoms. Potential donors (*n* = 380) reported their duration of COVID-19 symptoms at the student hotline, of which 17 were completely symptom-free. Twenty-nine potential donors could not remember either the date of symptom beginning or ending and 11 still had symptoms during the call at the student hotline. The mean duration of COVID-19 symptoms in potential donors (symptomatic, *n*= 363) was 13.0 (mean; min–max, 1–35) days.

development, a considered reallocation of the resources deployed is favorable.

Our experience with the cooperation of the staff and the well-trained and committed students was excellent, and this aspect was an essential part of the successful COVID-19 convalescent donor acquisition. Additionally, we benefitted from highly specialized departments at a university hospital, for example, transfusion medicine, virology, microbiology, and intensive care medicine. Ultimately, these institutions provided all required resources, for example, PCR testing, blood draws, antibody and PCR analyses, plasma production, and patient care. This repertoire of different expertize may not be available to smaller and mid-sized hospitals while planning a donor acquisition program. Therefore, external sources and institutions would need to be approached early on for support. In addition, a close-meshed, preferably daily consultation about the ongoing processes and distribution of resources is decisive in maintaining the workflow. Plasma from our donors was applied in individual curative trials at the UKR and surrounding hospitals in severely-ill patients. Studies revealed a positive effect of CP therapy at an early stage of COVID-19.[12–14] It seems similar to the intended use of monoclonal antibodies derived from convalescent donor plasma as an early therapy option for patients with a risk profile.[15]

AUTHOR CONTRIBUTIONS

Andreas M. Brosig: Conceptualization; Investigation; methodology; project administration; supervision; writing – original draft; writing – review & editing. **Thomas Ossner**: Conceptualization; data curation; formal analysis; methodology; software; validation; visualization; writing – original draft; writing – review & editing. **Irene Pamler**: Project administration; resources. **Susanne Friedinger**: Project administration; resources. **Adelina-Florina Bica**: Project administration; resources. **Morad Mohrez**: Project administration. **Ikram Tlili**: Project administration. **Viktoria Mueller**: Project administration; resources. **Christine Becke**: Project administration. **Viola Haehnel**: Methodology; project administration; writing – review & editing. **Veronika Baeuerlein**: Project administration. **Barbara Stemmer**: Project administration; Resources. **Ralph Burkhardt**: Supervision. **Robert Offner**: Supervision. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

Andreas M. Brosig received honoraria from Fresenius and Therakos. These financial relationships were not involved in this work. The remaining authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author (manuscript guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being

reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Due to EU general data protection regulations, we are only able to share the summary data, as original data sets contain the personal information of study participants. Andreas M. Brosig had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.