Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in Patients With Coronavirus Disease 2019

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Currently, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been reported in almost all countries globally. No effective therapy has been documented for COVID-19, and the role of convalescent plasma therapy is unknown. In the current study, 6 patients with COVID-19 and respiratory failure received convalescent plasma a median of 21.5 days after viral shedding was first detected, all tested negative for SARS-CoV-2 RNA within 3 days after infusion, and 5 eventually died. In conclusion, convalescent plasma treatment can end SARS-CoV-2 shedding but cannot reduce the mortality rate in critically ill patients with end-stage COVID-19, and treatment should be initiated earlier.

Keywords. Convalescent plasma therapy; Coronavirus disease 2019 (COVID-19); Fatality; Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Survival rate; Viral shedding.

From December 2019, coronavirus 2019 disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide from Wuhan, China [1, 2]. As of 23 April 2020, a total of 2 544 792 patients with COVID-19 have been reported globally and 175 694 have died; that is, the mortality rate is as high as 6.9% [3]. However, no specific antiviral therapy is recommended [1], which enhances the difficulty of pandemic containment and leads to empirical treatment for patients with COVID-19 [4, 5]. In addition, a recent study demonstrated that lopinavir-ritonavir provided no benefit for COVID-19, compared with supportive treatment [6].

Previous studies have shown that the use of convalescent plasma collected from individuals recovered from severe acute respiratory syndrome (SARS) can shorten the hospital stay and decrease the mortality rate for patients with SARS [7–9]. In addition, the clinical benefits of transfusing corresponding convalescent plasma were also observed in patients infected with Ebola virus, Middle East respiratory syndrome coronavirus, or influenza A H1N1 [9, 10]. However, no related data are available for COVID-19. In the current study, we retrospectively collected clinical data and analyzed treatment efficacy in contemporaneous patients who received or did not receive convalescent plasma collected from recovered COVID-19 individuals.

METHODS

Design and Study Population

This retrospective, observational study was performed mainly in The First Affiliated Hospital of Zhengzhou University and The Sixth People’s Hospital of Zhengzhou City, the highest referral hospitals for COVID-19 in Henan Province, China. Laboratory confirmed COVID-19 was diagnosed according to World Health Organization interim guidance [11]. Real-time reverse transcriptase polymerase chain reaction (PCR) tests for SARS-CoV-2 RNA were performed using nasopharyngeal swabs (Novel Coronavirus [2019-nCoV] Nucleic Acid Detection Kit [PCR Fluorescence Probing]; Shanghai BioGerm Biomedical Biotechnology).

We extracted the epidemiological, demographic, clinical, laboratory, management, and outcome data in the contemporaneous patients with COVID-19 who received or did not receive convalescent plasma. Clinical outcomes were followed up until 1 April 2020. The primary end point of current study was death or recovery (discharge), and the secondary end point was SARS-CoV-2 RNA clearance. The criteria for recovery were the same as those described by Lan et al [12]. Briefly, they are based on the recovery of symptoms and signs, consistent clearance of SARS-CoV-2, and absorption of lung inflammations (eg, ground-glass opacities and/or consolidations).

Performance of the SARS-CoV-2 RNA Detection Kit

The technical performance of the aforementioned detection kit are is detailed in the following.

Limit of Detection

The limit of detection was $1 \times 10^3$ copies/mL.
Repeatability
A reference sample with the same precision was tested in 5 days by 2 persons with 3 batches of reagents, and the coefficient of variation for intrabatch and interbatch, intraday and interday, intraoperator and interoperator, and intralaboratory and interlaboratory precision is ≤5.0% in all instances.

Positive and Negative Reference Compliance Rates Within Company
The compliance rate was 100% for 5 positive and 12 negative reference samples.

Specificity
There is no cross-reaction with the following pathogens: influenza A virus H1N1, H1N1 (2009), H3N2, H5N1 and H7N9, influenza B virus (BV and BY), human coronavirus 229E/HKU1/OC43/NL63/SARS/Middle East respiratory syndrome, parainfluenza virus (types 1, 2, and 3), rhinovirus A/B/C, bocavirus, respiratory syncytial virus, Epstein-Barr virus, measles virus, human cytomegalovirus, rotavirus, norovirus, varicella-zoster virus, mumps virus, Chlamydia pneumoniae, Legionella, pertussis, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Mycobacterium tuberculosis, Streptococcus pyogenes, Klebsiella pneumoniae, Aspergillus fumigatus, Candida albicans, Candida glabrata, Cryptococcus neoformans, and adenovirus 1, 2, 3, 4, 5, 7, and 55. In addition, the reaction is not affected by addition of the endogenous and exogenous interference substances.

Clinical Evaluation
The clinical evaluation results are compared with the confirmed or excluded results obtained using the methods recommended in “Technical Guidelines for Laboratory Testing of Pneumonia Infected with a Novel Coronavirus” and “Surveillance of Pneumonia Cases with Novel Coronavirus Infection”, which were provided and updated by the National Health Commission of China. The actual clinical usage data were collected from the Beijing Centers for Disease Control and Prevention, Guangdong Provincial Center for Disease Control and Prevention, and other 5 institutions for statistical analysis. On preliminary evaluation, it has been basically confirmed that the performance of this kit meets the clinical needs of an epidemic emergency. The specimen types for clinical evaluation include nasopharyngeal swab, oropharyngeal swab, and sputum specimens. Because only positive and negative controls were included in this kit, it was designed only for the qualitative (not quantitative) detection of SARS-CoV-2 RNA, and its results indicate the presence of SARS-CoV-2 RNA and can be used to support the diagnosis of SARS-CoV-2 infection; it was widely used during the epidemic of COVID-19 in China [12, 13].

Source of Convalescent Plasma
Convalescent plasma was obtained from individuals who had recovered from COVID-19. Young adult individuals who had recovered from COVID-19 for 1–2 weeks were eligible to be considered as blood donors. In addition, all donors were negative at SARS-CoV-2 RNA and immunoglobulin (Ig) M testing and positive at IgG testing before donation. Informed consent was obtained from all donors, who should be seronegative for hepatitis B and C, human immunodeficiency virus, and syphilis. In mid-February 2020, the first individual recovered from COVID-19 donated a blood sample. A 200–400-mL plasma sample was harvested from each donor. Blood collection and storage were performed in the Henan (Provincial) Red Cross Blood Center. Gold immunochromatography for SARS-CoV-2 IgM and IgG tests were performed using blood samples (New Coronavirus [2019-nCoV] Antibody Detection Kit, Shanghai Outdo Biotech and Tangshan Innovita Biotech).

Statistical Analysis
Continuous variables were presented as medians (with interquartile ranges), and categorical variables as numbers (percentages). Mann-Whitney U, χ², or Fisher exact tests were used to compare differences between various subgroups, where appropriate. Analyses were carried out using SPSS statistical software, version 25.0 (IBM). P values <.05 were set as the threshold for statistical significance.

Ethical Aspects
The protocol of this retrospective study was approved by the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University, and written informed consents were obtained from family members of all patients who received plasma infusions.

RESULTS
Patients Characteristics
A total of 21 contemporaneous critically ill patients with COVID-19 were enrolled in the current study (Table 1), and all of them required intensive care unit admission. Six of the patients received convalescent plasma treatment based on the limited availability of convalescent plasma and ABO compatibility. Five of 6 patients in the convalescent plasma treatment group and 11 of 15 in the non–convalescent plasma treatment (control) group were male. Their median ages were 61.5 and 73 years respectively. Demographic characteristics, clinical parameters, and management strategies were similar in the 2 groups (Table 1).

Safety and Efficacy of Convalescent Plasma Treatment
The median volume of plasma infused was 300 mL (Table 2). No immediate or noticeable adverse effects were observed with convalescent plasma infusions. Death eventually occurred in 5 of 6 patients in the treatment group and 14 of 15 in the control group (P = .18); each group had just 1 recovered patient. Viral clearance was achieved after convalescent plasma transfusion.
in all 6 patients in the treatment group. Among patients who died, all 5 (100%) in the treatment group and 3 of 14 (21.4%) in the control group had undetectable SARS-CoV-2 before death ($P = .005$). The survival period was longer in the treatment group than in the control group ($P = .03$).

### Table 1. Comparison of Demographic and Clinical Characteristics Between Treatment (Convalescent Plasma) and Control (Non–Convalescent Plasma) Groups

| Demographic and Clinical Features | Treatment Group (n = 6) | Control Group (n = 15) | PValue |
|----------------------------------|------------------------|-----------------------|--------|
| **Sex, male**                    | 5 (83.3)               | 11 (73.3)             | >.99   |
| **Age, median (IQR), y**         | 61.5 (31.5–77.8)       | 73 (60–79)            | .38    |
| **Chronic comorbid condition**   |                        |                       |        |
| Diabetes                         | 1 (16.7)               | 5 (33.3)              | .62    |
| Hypertension                     | 1 (16.7)               | 3 (20)                | >.99   |
| Chronic liver diseases           | 0 (0)                  | 2 (13.3)              | >.99   |
| Cardiovascular diseases          | 1 (16.7)               | 0 (0)                 | .29    |
| Respiratory system diseases      | 0 (0)                  | 1 (6.7)               | >.99   |
| Chronic kidney disease           | 0 (0)                  | 1 (6.7)               | >.99   |
| **Main signs and symptoms**      |                        |                       |        |
| Fever                            | 5 (83.3)               | 13 (86.7)             | >.99   |
| Cough                            | 5 (83.3)               | 14 (93.3)             | .50    |
| Fatigue                          | 4 (66.7)               | 10 (66.7)             | >.99   |
| Shortness of breath              | 4 (66.7)               | 12 (80)               | .60    |
| Dyspnea                          | 3 (50)                 | 8 (53.3)              | >.99   |
| **Chest CT findings**            |                        |                       |        |
| Bilateral pneumonia              | 6 (100)                | 14 (93.3)             | >.99   |
| Multiple mottling/ground-glass opacity | 5 (83.3) | 14 (93.3)             | .50    |
| **Laboratory parameters on ICU admission, median (IQR)** | | | |
| Leukocytes, × 10⁹/L (NR 3.5–9.5) | 6.9 (4.7–15.8)         | 6.6 (5–11.3)          | .73    |
| Neutrophils, × 10⁹/L (NR, 18–63) | 5.3 (3–14.6)           | 5.6 (4.9–10.4)        | >.99   |
| Lymphocytes, × 10⁹/L (NR, 1.1–3.2) | 1.2 (0.9–1.5)          | 0.9 (0.6–1.3)         | .34    |
| C-reactive protein, mg/L (NR, 0–5) | 46.7 (8.5–111)         | 66 (24.5–94)          | .47    |
| Procalcitonin, ng/mL (NR, 0–0.046) | 0.09 (0.07–0.12)       | 0.17 (0.08–0.47)      | .15    |
| Alanine aminotransferase, U/L (NR, 0–40) | 41.5 (18.5–675)       | 30 (21–54)            | .91    |
| Creatine kinase, µmol/L (NR, 20–115) | 192 (49–389)          | 97 (60–237)           | .73    |
| Lactate dehydrogenase, U/L (NR, 75–250) | 423 (268–510)         | 331 (254–469)         | .62    |
| D-dimer, mg/L (NR, 0–0.55)       | 1.7 (0.2–4.26)         | 2.6 (0.33–3.9)        | .68    |
| **Main complications**            |                        |                       |        |
| Respiratory failure              | 6 (100)                | 15 (100)              | >.99   |
| Acute respiratory distress syndrome | 5 (83.3)               | 13 (86.7)             | >.99   |
| Secondary infection              | 4 (66.7)               | 12 (80)               | .60    |
| Septic shock                     | 3 (50)                 | 8 (53.3)              | >.99   |
| **Management**                   |                        |                       |        |
| ICU admission                     | 6 (100)                | 15 (100)              | >.99   |
| Antibiotics                      | 6 (100)                | 15 (100)              | >.99   |
| Antiviral therapy                | 4 (66.7)               | 12 (80)               | .60    |
| Traditional Chinese medicine     | 3 (50)                 | 8 (53.3)              | >.99   |
| Intravenous immunoglobulin therapy | 5 (83.3)               | 14 (93.3)             | .50    |
| Glucocorticoid pulse therapy     | 4 (66.7)               | 12 (80)               | .60    |
| High-flow nasal cannula oxygen therapy | 6 (100) | 15 (100)            | >.99   |
| Mechanical ventilation           | 5 (83.3)               | 13 (86.6)             | >.99   |
| Extracorporeal membrane oxygenation | 4 (66.7)               | 12 (80)               | .60    |
| Continuous renal replacement therapy | 3 (50)             | 10 (66.7)              | .63    |

**Abbreviations:** CT, computed tomographic; ICU, intensive care unit; IQR, interquartile range; NR, normal range.

*Data represent no. (%) of patients unless otherwise specified.

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**First Patient to Receive Convalescent Plasma Therapy in Henan Province**

In Henan Province, the first available convalescent plasma was transfused into a 30-year-old postpartum woman on 19 February 2020 (Supplementary Figure 1). She was engaged in a beef and mutton selling business in Wuhan and came to Henan...
On the day of transfusion in 1, and on the third day after transfusion in 1. Notably, previously detectable SARS-CoV-2 was undetectable from 21 February until the patient's eventual death on 6 March 2020.

### DISCUSSION

A recent study indicated that SARS-CoV-2 was detectable until death in nonsurvivors [14], and it is unknown whether achievement of undetectable SARS-CoV-2 in critically ill patients can help avert fatalities. The current study, to the best of our knowledge, is the first to indicate that convalescent plasma treatment contributes to the discontinuation of SARS-CoV-2 shedding and longer survival in patients with COVID-19 and respiratory failure; however, it cannot reduce the mortality rate in critically ill patients with end-stage COVID-19.

As the neighbor to Hubei Province and outside province closest to Wuhan City, Henan Province was severely affected by the SARS-CoV-2 infection. It is known that Henan Province had the third largest number of patients with COVID-19 and second largest number of fatal cases in China [15]. In mid-February 2020, however, the epidemic was drawing to its end, so the enrolled patients were the most critically ill, representing the last series of COVID-19 cases in Henan Province.

Viremia commonly peaks in the first week after infection in most acute viral diseases, and patients usually develop a primary immune response by day 10–14, which is followed by virus clearance [8]. In the third week of illness, clinical deterioration is considered to be the result of inflammatory or hyperimmune attacks rather than direct virally induced tissue damage [8, 14, 16]. Hence, convalescent plasma should theoretically be more effective when given early in the course of disease (ie, before day 14, or during the viremic and seronegative stage) [8]. The failure to reduce the mortality rate may be attributed to the late transfusion of convalescent plasma, on median day 21.5 during viral shedding. In contrast, 1 critically ill patient in the treatment group, who had plasma infused on day 11 during viral shedding, did finally recover.

Based on the current findings, convalescent plasma treatment should be given to patients with COVID-19 at the right phase or severity of illness and at the right time point. It is known that most patients with mild COVID-19 can recover without treatment, and convalescent plasma may be improper therapy for those patient. And for patients with end-stage COVID-19, convalescent plasma treatment may unable to avert a poor outcome, as demonstrated by our current findings. Hence, convalescent plasma treatment should probably be used in potentially critically ill patients COVID-19 at an early stage of disease. Thus, early recognition of patients with COVID-19 who are likely to become critically ill is key to the use of convalescent plasma treatment.

### Table 2. Safety and Efficacy of Treatment (Convalescent Plasma) and Control (Non–Convalescent Plasma) Groups

| Parameter                          | Treatment Group (n = 6) | Control Group (n = 15) | P Value |
|------------------------------------|------------------------|------------------------|---------|
| Duration, median (IQR), d          | 23.5 (19.5–24.5)       | 20 (19–24)             | .38     |
| Viral shedding before treatment    | 45.5 (37.8–59)         | 31 (30–36)             | .03     |
| SARS-CoV-2 clearance before death in patients who died | 6 (100)*               | ...                    | ...     |
| Yes                                | 6 (100)                | 4 (26.7)               | .004    |
| No                                 | 0 (0)                  | 11 (73.3)              | ...     |
| SARS-CoV-2 clearance in all patients | ...                   | ...                    | ...     |
| Yes                                | 5/5 (100)              | 3/14 (21.4)            | .005    |
| No                                 | 0/5 (0)                | 11/14 (78.6)           | ...     |

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Data represent no. (%) of patients unless otherwise specified.

†Data were censored in 11 fatal patients who died and had detectable SARS-CoV-2 RNA until death.

The duration of illness was calculated from the onset of illness to the date of discharge.

‡SARS-CoV-2 clearance occurred on the second day after transfusion in 4 patients, on the day of transfusion in 1, and on the third day after transfusion in 1.
Our study has several limitations. The first is the limited number of patients. It is important to note that the COVID-19 outbreak was nearly finished outside Wuhan in China when the convalescent plasma became available, on 19 February in Henan Province. By then, the vast majority of patients had discharged, there were few new cases, and the 21 patients in the current study were almost all of the critically ill patients at that time. Conversely, patients with mild illness did not need plasma. Second, the amount of viral antibodies given to each patient was unknown and not standardized, which may lead to differences in clinical outcome. Nevertheless, viral clearance occurred after transfusion in all patients receiving plasma. Third, our study was not randomized. However, given the limited availability of plasma, the timing of when plasma became available, and ABO compatibility, there was usually only a single suitable patient for each transfusion. Finally, SARS-CoV-2 RNA levels were not determined because of the technical limitations of testing.

In conclusion, the current study is the first to suggest that convalescent plasma therapy can help stop viral shedding and extend survival in patients with COVID-19 and respiratory failure, although it cannot reduce the mortality rate in critically ill patients with end-stage disease. Based on our current findings, we suggest infusion of convalescent plasma in potentially critically ill patients with COVID-19 early in the course of disease. Future large-scale studies are needed to investigate whether early-phase infusion of convalescent plasma in appropriate recipients can prevent clinical deterioration and improve the survival rate.

Supplementary Data
Supplementary materials are available at The Journal of Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
Acknowledgments. The authors thank all participants and their families in the study.

Disclaimer. The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. Financial support. This study was supported by The National Natural Science Foundation of China (grant 81975017), Zhongyuan (Henan) Thousands Outstanding Talents Plan (grant ZYQR201912179), the Foundation for Distinguished Young Talents of Zhengzhou University Medical School (grant 2020ZQLMS), and the Key Scientific Research Project of Henan Higher Education Institutions of China (grant 20B320028).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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