No evidence of SARS-CoV-2 RNA among blood donors: A multicenter study in Hubei, China

Le Chang1,2 | Ying Yan1,2 | Lei Zhao3,4 | Guibin Hu5 | Lijuan Deng6 | Dan Su7 | Dongju Peng8 | Xinjiao Nie9 | Song Wang10 | Yuanyuan Li11 | Jundao Wang12 | Zhong Ruan13 | Shouliang Gao14 | Huasong Yang15 | Fei Guo1,2 | Lunan Wang1,2,16

1National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China
2Beijing Engineering Research Center of Laboratory Medicine, Beijing Hospital, Beijing, China
3Department of Laboratory, Wuhan Blood Center, Wuhan, China
4Confirmation Laboratory for Transfusion Transmitted Disease, Institute of Blood Transfusion of Hubei Province, Wuhan, China
5Department of Laboratory, Xiangyang Blood Bank, Xiangyang, China
6Department of Laboratory, Xianning Blood Bank, Xianning, China
7Department of Laboratory, Jingzhou Blood Bank, Jingzhou, China
8Department of Laboratory, Shiyan Blood Bank, Shiyan, China
9Department of Laboratory, Yichang Blood Bank, Yichang, China
10Department of Laboratory, Enshi Tujia and Miao Autonomous Prefecture Blood Bank, Enshi, China
11Department of Laboratory, Jingmen Red Cross Blood Bank, Jingmen, China
12Department of Laboratory, Suizhou Blood Bank, Suizhou, China
13Department of Laboratory, Xiaogan Blood Bank, Xiaogan, China
14Department of Laboratory, Huanggang Blood Bank, Huanggang, China

Background
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA could be detected in the blood of infected cases. From February 9, all blood establishments in Hubei province, China, implemented nucleic acid testing (NAT) for SARS-CoV-2 RNA among blood donors to ensure blood safety.

Study Design and Methods: Nucleic acid test screening individually (ID) or by minipool (MP) testing was performed according to the manufacturer’s instructions. Inactivated culture supernatant of SARS-CoV-2–infected Vero cells was quantified by droplet digital polymerase chain reaction (ddPCR) and series diluted with negative plasma to evaluate the assay’s performance.

Results: The limit of detection of the kit for MP testing was 62.94 and 33.14 copies/mL for N and ORF1ab region, respectively. ID testing could achieve 3.87 and 4.85 copies/mL using 1600 μL of plasma. Coefficients of variations of two different concentrations of reference samples were all less than 5% in MP testing. As of April 30, 2020, a total of 98,342 blood donations including 87,095 whole blood donations and 11,247 platelet donations were tested by ID or MP testing, and no RNAemia was found. In addition, Hubei province suffered precipitously decreased blood supply, especially in February: 86% reduction compared with the same period of 2019.

Conclusion: Nucleic acid test screening of SARS-CoV-2 on blood donations is suitable in blood establishments using the commercial real-time PCR detection kit based on available instruments. The negative result indicated that SARS-CoV-2 appears to be no direct threat to blood safety but raises some serious issues for general blood supply.

Abbreviations: Ct, cycle threshold; ddPCR, droplet digital polymerase chain reaction; ID, individual donation; LOD, limit of detection; MP, minipool; N, nucleocapsid; ORF1ab, open reading frame 1ab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
At the end of 2019, an unknown pneumonia, later named coronavirus disease 2019 (COVID-19), was found in Wuhan, China, which rapidly spread worldwide and had become a pandemic in March 2020. According to the World Health Organization (WHO), as of 25 May 2020, 216 countries have reported confirmed cases so far, bringing the total number to more than five million, and the death toll standing over 337,000 worldwide.

The origin of its etiological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was targeted quickly. The virus transmits from human to human mainly through respiratory droplets and it also has been found in feces, urine, and conjunctival secretions of infected cases or animal models, especially in the early stage of COVID-19. Moreover, viral RNA, although usually with a very low viral load, could be detected in plasma, serum, or whole blood. Viral dynamic analysis has proved that the viral load of the new coronavirus in blood ranged from 2 to 4 log copies per milliliter, which is much lower than that of the respiratory tract or stool samples and before the onset of any symptoms, viral RNA could be detected in blood. Therefore, the risk of viral transmission via blood indeed exists but it is only a kind of theoretical possibility now. Generally, prolonged or short asymptomatic blood-borne phase, the infectious agent in collected blood or components, and its ability to cause infection by the intravenous route are three key points to evaluate whether an emerging infection could transmit via transfusion. Whereas, all of the three points are still under consideration and have not be proved on SARS-COV-2 so far. Moreover, there are not yet reported transfusion-transmitted cases of SARS-COV-2, and no direct evidence has been found that the coronaviruses could transmit via blood or blood components.

However, a few studies have reported that blood donors were confirmed as COVID-19 within 14 days after donation and viral RNA was detectable in donated plasma or platelet (PLT). Therefore, although the US Food and Drug Administration (FDA) and the European Centre for Disease Prevention and Control (ECDC) have not recommended screening SARS-COV-2 RNA among blood donations, the Chinese health authorities began to concern about blood safety in China, especially in Wuhan. On January 25, Wuhan Blood Center started to real-time screen SARS-CoV-2 RNA among all blood donations and retrospectively test donation samples in December 2019 and January 2020. Subsequently, four positive donors donated in late January 2020 have been found, indicating the theoretical risk of viral transmission via blood products. Since the week of February 9, all other 11 blood banks in Hubei province, the hardest-hit area in China, began to implement nucleic acid testing (NAT) screening on blood donations for SARS-CoV-2 RNA to detect possible RNAemia in infected people eligible for blood donation.

Since no available commercial SARS-CoV-2 RNA reverse transcription–polymerase chain reaction (RT-PCR) kit specially designed for plasma viral RNA testing were approved by the Chinese National Medical Products Administration (NMPA), the FDA, the European Commission (CE), or the WHO, in this study we first evaluated the performance of a real-time PCR detection kit for the analytical properties and suitability in routine work of blood establishments and then reported the NAT data of SARS-CoV-2 RNA from all blood establishments in Hubei province from February 9 to April 30, 2020.

1 MATERIALS AND METHODS

1.1 Sample source and data collection

All blood donations donated from the week of February 9 to April 30, 2020, were tested in 12 blood establishments (one blood center and 11 blood banks, shown in Table 1) in Hubei province. Blood establishments located in the capital of a province are usually named “blood center” and in other cities are named “blood bank.” All the laboratories reported detection data once a week to the National Center for Clinical Laboratories. NAT detection data in the same period of 2018 and 2019 was collected by National Center for Clinical Laboratories through the data reported by all blood establishments every month in
the past 2 years. The total number of confirmed COVID-19 cases in cities of Hubei province was collected on the website of the Hubei Province Health Committee, and the population data were from statistics released by the Hubei Provincial Bureau of statistics in 2019.

1.2 Nucleic acid extraction and detection

At the beginning of NAT for SARS-CoV-2 RNA, the number of donations was small, and thus all donations were tested individually (ID) using 1000 to 1600 μL of plasma samples. With the increase of blood donors in March and April, part of donations was tested by minipool (MP) testing with 125- to 200-μL aliquots of eight samples. All the pooling, nucleic acid extraction, and detection procedures were performed on automated workstations and instruments listed in Table 1. Forty microliters of the total eluted volume of 100 μL was added into the RT-PCR mix. The Taqman-based real-time amplification of SARS-CoV-2 RNA was performed using a commercially available SARS-CoV-2 real-time RT-PCR assay according to the manufacturer’s instructions (Lot AY20200203, PerkinElmer, SYM-BIO LifeScience, Suzhou, China).

Nucleocapsid (N) region and open reading frame 1ab (ORF1ab) region of the viral genome were both tested. The cycle threshold (Ct) value of a positive result was not more than 42 for one region and not more than 45 for the other region. In other situations for any amplification of the two regions, such as only one region detected or Ct value of the two regions both between 42 and 45, the specimen should be retested. The specimen was determined to be positive if the same result was observed in repeated testing.

| No. | Blood establishments          | Samples within a MP | Plasma volume (μL) | Nucleic acid extraction system            | Amplification and detection instrument |
|-----|-------------------------------|---------------------|--------------------|-----------------------------------------|---------------------------------------|
| 1   | Wuhan Blood Center            | 8                   | 200 1600           | ChiTaS BSS1200 (PerkinElmer, Austin, TX) | ABI 7500                              |
| 2   | Xiangyang Blood Bank          | 8                   | 150 1200           | Microlab STAR (Hamilton, Reno, NV)/ EZBead System-32 (TGB, Richardson, TX) | ABI 7500                              |
| 3   | Xiaogan Blood Bank            | 8                   | 125 1000           | DA3000 (Daan Gene, Guangzhou, China)     | AFD 9600                              |
| 4   | Huanggang Blood Bank          | 8                   | 150 1200           | Microlab STAR (Hamilton, Reno, NV)       | ABI 7500                              |
| 5   | Huangshi Blood Bank           | 8                   | 150 1200           | Janus (PerkinElmer, Austin, TX)/ EZBead System-32 (TGB, Richardson, TX) | ABI 7500                              |
| 6   | Jingmen Red Cross Blood Bank  | 8                   | 150 1200           | BACME ABT (BACME, Suzhou, China)         | ABI 7500                              |
| 7   | Jingzhou Blood Bank           | 8                   | 150 1200           | ChiTaS BSS1200 (PerkinElmer, Austin, TX) | ABI 7500                              |
| 8   | Shiyan Blood Bank             | 8                   | 150 1200           | Microlab STAR (Hamilton, Reno, NV)/ EZBead System-32 (TGB, Richardson, TX) | ABI 7500                              |
| 9   | Yichang Blood Bank            | 8                   | 150 1200           | ChiTaS BSS1200 (PerkinElmer, Austin, TX) | ABI 7500                              |
| 10  | Xianning Blood Bank           | 8                   | 125 1000           | DA3000 (Daan Gene, Guangzhou, China)     | AFD 9600                              |
| 11  | Suizhou Blood Bank            | 8                   | 150 1200           | Microlab STAR (Hamilton, Reno, NV)       | ABI 7500                              |
| 12  | Enshi Tujia and Miao Autonomous Prefecture Blood Bank | 8 | 150 1200 | ChiTaS BSS1200 (PerkinElmer, Austin, TX) | ABI 7500                              |
1.3 | Reference samples and evaluation

Inactivated culture supernatant of SARS-CoV-2–infected Vero cells, provided by the Chinese Academy of Military Medical Sciences (Genbank MT135042.1), was first quantified by droplet digital PCR (ddPCR). Viral RNA was extracted using automated nucleic acid purification system (PreNAT II, PerkinElmer, Austin, TX). The primer and probe sequences for detecting N and ORF1ab region of the SARS-CoV-2 genome published by the Chinese Center for Disease Control and Prevention were used. Twenty microliters of reaction mixture, comprising 5 μL of RNA template, 900 nM primers, and 250 nM probe, was prepared according to the instruction of a one-step RT-ddPCR advanced kit for probes (Bio-Rad). Each reaction mix was converted to droplets using a droplet generator (QX200, Bio-Rad), transferred to a 96-well plate (Bio-Rad), heat-sealed, and amplified in a nexus thermal cycler (Mastercycler, Eppendorf). The thermal cycling conditions were as follows: 50°C for 60 minutes, 95°C for 10 minutes, 40 cycles of 94°C for 30 seconds and 58°C for 45 seconds, and 98°C for 10 minutes. The cycled plate was then transferred to the droplet reader (QX200, Bio-Rad) and analyzed using the droplet reader software (QuantaSoft, V1.7.4, Bio-Rad). Each region was tested three times simultaneously and calculated the mean concentration for the two genes, respectively.

Culture supernatant was then diluted with negative plasma for the evaluation of the real-time PCR detection kit. Serial gradient diluted reference samples were prepared to evaluate the limit of detection (LOD) for MP and ID testing. MP testing performed using 200 μL of reference samples together with 200-μL aliquots of seven negative plasma samples to simulate the routine work for MP testing. A quantity of 1600 μL of reference samples were used for ID testing. Reference samples of each dilution were repeatedly tested 20 times by MP or ID testing.

To evaluate the precision of the real-time PCR detection kit, culture supernatant diluted to a viral load of three times and 30 times of MP LOD were tested four times per day and successively tested for 5 days. SD and CV of the assay testing samples with high viral load was smaller than that with low viral load and The CV ranged from 1.33% to 2.10%. No negative sample gave a reactive result. The results of the Ct values were shown in Table 3.

1.4 | Statistical analysis

The Probit analysis of LOD was performed with computer software (SPSS v21.0, IBM SPSS, Chicago, IL). Standard deviation (SD) and the coefficient of variation (CV) of the real-time PCR kit were calculated with computer software (Microsoft Excel 2010, Microsoft Corp., Redmond, WA).

2 | RESULTS

2.1 | LOD

Inactivated virus culture supernatant was quantified by ddPCR with a concentration of 2.925 × 10⁶ copies/mL for N gene and 2.790 × 10⁶ copies/mL for ORF1ab region. The concentration of the two regions was similar. Then a series of diluted reference samples were prepared to evaluate the limit of detection (LOD) of both MP and ID testing. Each dilution was tested 20 times. The results were shown in Table 2. Probit analysis of these data yielded a detection probability of more than 95% in parallel MP tests when an average of at least 62.94 copies/mL (95% confidence interval [CI], 46.23-111.53 copies/mL) for N region and 33.14 copies/mL (95% CI, 26.13-49.42 copies/mL) for ORF1ab region. The LOD of ID testing was 3.87 copies/mL (95% CI, 2.85-9.89 copies/mL) for N region and 4.85 copies/mL (95% CI, 3.33-19.48 copies/mL) for ORF1ab region. All the negative samples were nonreactive.

2.2 | Precision

Precision is defined as the closeness of the agreement between the results of the successive analysis. Because the procedure of an MP testing is more complicated, we only evaluated the precision of an MP testing. Two levels of reference samples with viral loads of three times and 30 times of MP LOD were tested four times per day and successively tested for 5 days. SD and CV of the assay testing samples with high viral load was smaller than that with low viral load and The CV ranged from 1.33% to 2.10%. No negative sample gave a reactive result. The results of the Ct values were shown in Table 3.

2.3 | Detection of blood donations

From the week of February 9, a total of 12 blood establishments began screening SARS-CoV-2 RNA in all blood donations. By April 30, 2020, a total of 98,342 donations, including 87,095 whole blood and 11,247 PLT donations, were tested, among which 94,511 were tested by MP while 3831 were tested ID. And all the donations were nonreactive.
negative for SARS-CoV-2 RNA during the past 12 weeks. The number of donations tested by every blood establishment was shown in Figure 1C.

2.4 | Precipitously decreased blood supply in Hubei province

In China, all the blood donations are tested by serologic viral markers (HBV, HCV, HIV, and TP) and viral nucleic acid (HBV, HCV, and HIV). Therefore, we collected the number of donations tested by viral nucleic acid from January to April 2020 and the same period of 2018 and 2019 in all 12 blood establishments in Hubei province, which could directly reflect the situation of blood supply during the pandemic. Figure 1A showed the decrease of blood supply started in January and occurred a sharp decrease in February. Comparing with the same period of 2019, the number of donations reduced by 86% in both Wuhan and the whole Hubei province in February, dropping from 12,531 to 1747 in Wuhan and from 34,059 to 4778 in Hubei province. In some cities in Hubei province, the reduction could reach 90% and even 95%. With the restarting of Wuhan and Hubei province, the blood supply gradually increased and almost returned to the same period of previous years in April. Figure 1B shows the prevalence of COVID-19 confirmed cases in cities of Hubei province. In Week 7 of 2020, strict community quarantine policy was implemented in Hubei province; therefore, extremely few blood donors donated, and in Weeks 12 and 13, cities except Wuhan in Hubei province gradually started to reopen the community and recover the traffic intraprovince, the blood supply also recovered (Figure 1C).

### Table 2: LOD evaluation of the real-time PCR detection kit

| Viral load (copies/mL) | N region | Mean Ct | Detection rate | ORF1ab region | Mean Ct | Detection rate |
|------------------------|----------|---------|----------------|---------------|---------|----------------|
| MP                     |          |         |                |               |         |                |
| 146.25                 | 36.92    | 20/20   | 139.50         | 36.68         | 20/20   |
| 73.13                  | 37.83    | 19/20   | 69.75          | 37.97         | 20/20   |
| 36.56                  | 38.66    | 17/20   | 34.88          | 39.17         | 19/20   |
| 18.28                  | 39.08    | 13/20   | 17.44          | 39.35         | 13/20   |
| 9.14                   | 39.57    | 13/20   | 8.72           | 39.61         | 10/20   |
| 4.57                   | 40.83    | 6/20    | 4.36           | 39.66         | 3/20    |
| LOD (copies/mL)        | 62.94 (46.23-111.53) | 33.14 (26.13-49.42) |

### Table 3: Precision evaluation of the real-time PCR detection kit

| Viral load | N region (n = 20) | ORF1ab region (n = 20) |
|------------|-------------------|------------------------|
|            | Mean Ct | SD | CV%       | Mean Ct | SD | CV%       |
| MP LOD     | 34.33 (20/20) | 0.46 | 1.33       | 34.07 (20/20) | 0.55 | 1.61       |
| 3x MP LOD  | 37.82 (20/20) | 0.79 | 2.10       | 37.46 (20/20) | 0.67 | 1.78       |
| 0          | UD (0/20) | UD (0/20) | UD (0/20) | UD (0/20) | UD (0/20) | UD (0/20) |

Abbreviation: UD, undetected.
3 | DISCUSSION

Due to the relatively low viral load of SARS-CoV-2 RNA in blood, a sensitive assay for plasma testing was required. The results of MP and ID LOD showed that two to five copies per reaction were detectable at 95% probability, which was already the limit of an amplification reaction in the ideal state. Compared with reported studies, the LOD of the real-time PCR detection kit was better than other NAT assay or methods. The precision analysis showed that CVs of two different concentrations of reference samples were all less than 5%, indicating a stable testing performance, especially on the detection of samples with low viral load. Therefore, the real-time PCR
shortage has been managed by the allocation of blood supply chain of different areas and the urgent blood information system had been set up to optimize the blood height of the epidemic, the national blood management supply was still the main concern in hospitals. At the demand for blood supply. However, the shortage of blood have been delayed in hospitals leading to a decreased epidemic fast spread in China, many elective surgeries supply in late January and February. Although after the whole Hubei province suffered a great reduction of blood drives were affected by the outbreak of COVID-19. The blood donation centers were closed and mobile blooduals are not recommended to go out of the home. Some mention of strict community quarantine (total stay-home) of Wuhan City on January 23, 2020, and the implementa-ince were the first to bear the brunt. After the lockdown of Wuhan City on January 23, 2020, and the implementa-ition of strict community quarantine (total stay-home) policy in Hubei province on February 11, 2020, individu-als are not recommended to go out of the home. Some blood donation centers were closed and mobile blood drives were affected by the outbreak of COVID-19. The whole Hubei province suffered a great reduction of blood supply in late January and February. Although after the epidemic fast spread in China, many elective surgeries have been delayed in hospitals leading to a decreased demand for blood supply. However, the shortage of blood supply was still the main concern in hospitals. At the height of the epidemic, the national blood management information system had been set up to optimize the blood supply chain of different areas and the urgent blood shortage has been managed by the allocation of blood stocks of neighboring provinces. According to the data from the National Health Commission of the People’s Republic of China, 12 provinces supported Hubei province during the past 3 months, bringing a total of 46,000 units of red blood cell and 1856 units of PLTs to alleviate the pressure of blood supply on cities in Hubei. Social media or mobile applications also played an important role in the recruitment of blood donors. To minimize the risk of viral transmission and the convenie-nce of blood donation, donors were asked to make an appointment beforehand via telephone or mobile apps. Therefore, when the restrictions were eased, the blood supply increased and quickly returned to the level during the same period of previous years.

There are some limitations in this present study. First of all, we did not use the real SARS-CoV-2 RNA–positive plasma specimens because of the extremely low viral load of the only four samples we have identified so far and the biosafety concerns. Reference samples from different sources (virus culture, positive plasma, or virus-like particles) tested by the same assay may display different performance. Second, different nucleic acid purification systems were used in these involved 12 blood establish-ments and the nucleic acid purification step is the critical limiting factor in NAT assay. We did not evaluate these differences in putative RNA inputs that may impact the sensitivity of the whole procedure and the final testing results.

In conclusion, NAT screening of SARS-CoV-2 on blood donations is suitable in blood establishments using the commercial real-time PCR detection kit based on available equipment. During the past 12 weeks, we have not found RNAemia among blood donors in Hubei province, indicating that the novel coronavirus may be no direct threat to blood safety but raises some serious issues for general blood supply. Although blood establishments in Hubei province suffered from precipitously decreased blood supply due to the pandemic, the allocation of blood stocks effectively alleviated this problem.

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CONFLICT OF INTERESTS
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
L.C. and L.W. designed the study and wrote the paper; L. Z., G.H., L.D., D.S., D.P., X.N., S.W., Y.L., J.W., Z.R., S.G., and H.Y. performed the screening SARS-CoV-2 RNA on
blood donations and provided the detection data; L.C., Y. Y., and F.G. performed the evaluation of the performance of the RT-PCR kit and gathered and analyzed the data; and all authors reviewed and approved the final version of the manuscript.

ORCID
Le Chang https://orcid.org/0000-0002-6154-7304
Lunan Wang https://orcid.org/0000-0003-3163-7891

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