Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Blood Safety

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Keywords

Severe acute respiratory syndrome coronavirus 2 · Blood safety · Blood transfusion transmission · Asymptomatic infection

Abstract

Since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has spread rapidly around the world and caused a serious global social crisis. During the epidemic, the blood collection and supply industry have been greatly impacted, due to the sharply dropped blood donors and transfusion transmission risk of SARS-CoV-2. Many infected individuals are asymptomatic and they may donate blood without awareness of the infection or before symptoms appear. In addition, viral RNAs have been detected in the blood of some patients infected with SARS-CoV-2. Although no infectious SARS-CoV-2 virus was found in the blood nor the blood components, there is a risk of transmission through blood transfusion which may endanger blood safety, especially during the pandemic period. This review briefly introduces the biological characteristics, epidemiology of SARS-CoV-2, with a particular focus on SARS-CoV-2 infection and blood safety.

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Introduction

It has been 2 years since the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused a severe global dilemma and has impacted every aspect of life [1]. Although numerous diagnostic kits, antiviral drugs, and vaccines were used to defend against the COVID-19 outbreak caused by SARS-CoV-2, it is still active in our view by producing various mutant strains, like Alpha, Beta, Gamma, and Delta, Omicron [2]. SARS-CoV-2 belongs to *Nidovirales*, *Coronaviridae*, and *Orthocoronavirinae*, and this family can be further divided into four genera, namely, α -coronavirus, β -coronavirus, γ -coronavirus, and δ -coronavirus [3]. So far, in addition to SARS-CoV-2 belonging to β -coronavirus, a total of six coronaviruses (HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS-CoV) were found to be able to infect human beings, while HCoV-OC43, SARS-CoV, HCoV-HKU1, and MERS-CoV were all β -coronaviruses [4].

Coronaviruses usually exist in the respiratory tract, but they may also exist in the blood at some stages after

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Fig. 1. Genome structure of SARS-CoV-2 and its viral proteins. The genome of SARS-CoV-2 was about 29,903 bp, which encodes four structural proteins, S, M, E, and N, and nine auxiliary proteins (3a, 3b, 6, 7a, 7b, 8b, 9b, 9c, and ORF10). S protein exists in homotrimers bulging on the viral surface, M protein is a multitransmembrane protein and exists in the membrane in the form of the dimer. E protein is the smallest among the four structural proteins and exists in the membrane, and N protein is the only protein in the nucleocapsid with the main function to bind to viral RNA.

infection [5]. The prevalence of SARS-CoV-2 reduced blood donation and the availability of blood collection facilities, which had a negative impact on the safety and supply of blood and blood components. Despite the fact that SARS-CoV-2 nucleic acid (RNA) was detected in blood, data on the live/infectious virus in blood, body fluid and various tissues and organs are still very limited [6]. Up till now, no SARS-CoV-2 infection has been reported to transmit from the blood transfusion.

This review briefly summarizes the research progress of SARS-CoV-2, including the structure and epidemiology. In addition, we also discuss SARS-CoV-2 infection in the context of blood safety and supply, and practical measures that blood supply agencies can adopt to ensure blood safety and supply during the SARS-Cov-2 pandemic.

Genome Structure of SARS-CoV-2

The electron micrography of SARS-CoV-2 shows a spherical outline with obvious spikes (9–12 nm) [7]. The genome of SARS-CoV-2, with 29,903 bp in length, shares 80% and 50% homology with that of SARS-CoV and MERS-CoV, respectively [8, 9], and 96% homology with bat SARS-like coronavirus [10]. Therefore, it is speculated that bat may be one of the intermediate hosts of SARS-CoV-2. The SARS-CoV-2 genome consists of 15 open reading frames (ORFs) encoding 29 proteins [11]. Located at the 5' end of the genome are ORF1ab and ORF1a genes, which are the largest genes in the genome, spanning almost two-thirds of the whole genome, encoding 1ab and 1a polypeptide, respectively [12]. The 3' end of the genome encodes four structural proteins, spike (S), membrane (M), envelope (E), and nucleocapsid (N), and nine auxiliary proteins (3a, 3b,

6, 7a, 7b, 8b, 9b, 9c, and ORF10) [13]. The S glycoprotein belongs to class I viral fusion protein that is composed of 1,160–1,400 amino acids with 21–35 N-glycosylation sites. S protein exists in homotrimers bulging on the viral surface, which mediates the entry of the virus into host cells [14]. As the most abundant protein of coronavirus, which determines the shape of the viral envelope, M protein is a multi-transmembrane protein composed of 218–263 amino acids and exists in the form of the dimer. The E protein is the smallest among the four structural proteins, which is composed of 74–109 amino acids and participates in the assembly, budding, capsule formation, and other processes of the viral life cycle [15]. Composed of 349–470 amino acids, N protein is the sole protein in the nucleocapsid with the main function to bind to viral RNA [16]. Figure 1 shows the genome structure and viral proteins of SARS-CoV-2.

Epidemiology of the SARS-CoV-2

On December 8, 2019, the first case of SARS-CoV-2 patient was found, and more cases were reported on December 31, 2019 [17]. On January 30, 2020, WHO announced the outbreak of coronavirus and declared the new coronavirus outbreak as an international public health emergency [18]. Due to the rapid transmission, WHO declared SARS-CoV-2 a global pandemic on March 11, 2020. As of January 29, 2022, SARS-CoV-2 has infected more than 360 million people with a death toll of over 5.6 million globally [19].

Epidemiological data [20] showed that, when talking, coughing, or sneezing, droplets discharged from face-to-face contact are the most common transmission mode. Long-term exposure to infected persons (at least 15 min within 6 feet) and short-term exposure to symptomatic individuals (such as those with coughing) have a high risk of being infected. However, short-term exposure to asymptomatic patients is unlikely to lead to transmission. Aerosols (smaller droplets suspended in the air) may also be one of the transmission modes. Current studies have shown that the mean incubation period of SARS-CoV-2 infection is 3–7 days, which is very close to SARS-CoV (5 days) and MERS-CoV (5.7 days) [21].

SARS-CoV-2 Infection and Blood Safety

Studies published in many countries showed that SARS-CoV-2 RNA was detected in the blood, plasma, or serum [22–26]. Huang et al. [23] reported that there were

6 cases (15%) of SARS-CoV-2 RNA positive in the blood among 41 SARS-CoV-2 patients in Wuhan, China, and the median PCR cycle threshold was 35.1 (95% CI: 34.7–35.1), indicating that the RNA concentration was very low. Additional studies also reported the presence of SARS-CoV-2 RNA in blood samples from blood donors. Chang et al. [27] screened more than 7,000 blood samples of blood donors and found 4 samples with SARS-CoV-2 RNA positive. Of these 4 samples, 2 were still asymptomatic and 2 experienced fevers after blood donation. Another report from Cappi et al. [28] identified three blood donors with SARS-CoV-2 RNA positive after blood donation due to the appearance of typical symptoms of COVID-19 such as fever and headache. Yao et al. [29] found that a systemic viral distribution in COVID-19 patients and SARS-CoV-2 was detected in monocytes, macrophages, and vascular endothelium at the blood-air barrier, blood-testis barrier, and filtration barrier. Coincidentally, Shen et al. [30] found that SARS-CoV-2 may infect platelets and megakaryocytes in a way that does not rely on the ACE2 receptor.

About 20–25% of individuals infected with SARS-CoV-2 have severe symptoms, and many individuals are asymptomatic and may donate blood without awareness of infection or before symptoms appear [23, 28]. Therefore, more attention should be given to the transmission of SARS-CoV-2 through blood transfusion.

Collectively, current data supported that the transfusion-transmitted risk of SARS-CoV-2 is very low even receiving a transfusion from RNA-positive blood. Loubaki et al. [31] reported that six Canadian blood donors were diagnosed as SARS-CoV-2-confirmed cases after blood donation. The SARS-CoV-2 RNA detection was performed in the six blood donation samples, and only one was weakly positive (36.1 cycle threshold). The infectivity of SARS-CoV-2 RNA-positive samples was further evaluated by Vero E6 cells, and the results showed that there was no infection to Vero cells. Furthermore, no SARS-CoV-2 infection was observed in the recipients who received a blood transfusion from the RNA-positive blood [31]. In addition, a Korean study by Kwon et al. [32] reported that seven blood donors were identified as SARS-CoV-2-confirmed cases after blood donation, and all the blood recipients did not have SARS-CoV-2 infection symptoms from 19 to 29 days after blood transfusion. Cho et al. [33] reported that a 21-year-old severe aplastic anemia Korean male received a platelet transfusion from a SARS-CoV-2 RNA-positive blood donor, and he was also not infected. Similarly, Anurathapan et al. [34] reported that a 7-year-old girl with β -thalassemia received

ported, a series of measures can be taken: (1) isolate the unissued blood; (2) emergency recall and isolation of uninfused blood; (3) carefully documented the infused blood; and (4) notification of relevant hospitals and report to the local health department.

PRT can reduce the risk of blood transfusion transmission for emerging pathogens. However, no universal PRT is available for all blood products since PRT treatment can damage certain blood components [40]. SARS-CoV-2 is an enveloped, positive-strand RNA virus, which is relatively stable at 4°C and sensitive to acid, alkali, and heat [40]. Studies have shown that riboflavin and ultraviolet can effectively reduce the titer of SARS-CoV-2 in human plasma and platelets [41, 42].

Theoretically, screening for SARS-CoV-2 RNA in blood samples can minimize the risk of blood transfusion transmission of SARS-CoV-2 and ensure blood safety from the source. However, Chang et al. [43] tested 98,342 blood samples from volunteer donors and no RNA-positive samples were found. Monique et al. [44] found that SARS-CoV-2 RNA was detected in the blood of SARS-CoV-2 patients but without infectious virus. Since SARS-CoV-2 only has the risk of blood transfusion transmission in theory, and it will cost a lot of money to perform SARS-CoV-2 NAT for all blood samples, the cost-effectiveness is relatively low and mandatory NAT assay for SARS-CoV-2 is not recommended.

When community transmission of SARS-CoV-2 occurs, blood is temporarily isolated in the blood collection agencies for 14 days, which helps to guarantee blood safety. Although the delayed issuances of blood or blood components are beneficial to the control of the epidemic, blood collection decreased sharply during the outbreak, and the delayed issuances are very difficult.

Measures to Ensure Blood Supply during the SARS-CoV-2 Pandemic

SARS-CoV-2 pandemic has hit almost all countries worldwide, posing a serious threat to public health [7]. Many blood collection agencies were affected, and the supply of blood and blood components was decreased [45]. In February 2020, the blood donation in Wuhan and Hubei Province, China decreased by 86%. The number of blood donors in Wuhan decreased from 12,531 to 1,747, and that in Hubei decreased from 34,059 to 4,778. In some cities of Hubei Province, a 90% or even 95% decrease was observed [43]. Due to the closure of schools, commercial and religious sites, the blood volume collect-

ed at the New York Blood Center in the USA dropped by 75% from March 16 to March 22, 2020 [46]. A retrospective study in Saudi Arabia showed that the blood volume collected in the blood center decreased by 39.5% during the SARS-CoV-2 pandemic [45]. Since the outbreak of SARS-CoV-2, blood donation in Madrid has decreased by about 45% [47]. During the SARS-CoV-2 pandemic, hospitals have to postpone most elective surgeries and nonemergency medical care, to reduce the demand for blood or blood components. Unfortunately, many SARS-CoV-2 patients have severe cell loss or coagulation disorders, which increased the blood demand. To cope with the impact of SARS-CoV-2 pandemic on blood supply, blood collection agencies can take the following measures (Fig. 2) [36].

First, strengthen blood inventory management. Blood collection agencies should arrange blood collection accurately according to the demand of blood/blood components from hospitals. In the meantime, they should keep close communication with medical institutions to ensure the supply for emergency blood use. In addition, according to the information in the blood management system, repeated blood donors from low-risk areas are encouraged to recall through messages and phone calls. Furthermore, medical institutions are encouraged to adopt autologous blood transfusion wherever possible to decrease the blood demand.

Second, protect the staff of blood collection agencies appropriately. During the SARS-CoV-2 pandemic, once the staff members are infected, it may lead to the suspension of blood collection, which greatly damages the blood supply. Therefore, appropriate staff protection is very important. These measures include but are not limited to: (1) reasonable arrangement of staff working hours; (2) group scheduling based on workload; (3) reducing contact between groups; and (4) limiting employee activity areas to reduce the cross-contamination opportunities. Once the employees from blood collection agencies appeared with SARS-CoV-2-related symptoms and with contact history to confirmed or suspected SARS-CoV-2 cases, they will not allow entering the blood collection agencies temporarily.

Third, shorten delayed blood donation after vaccination. One of the most effective ways to prevent the spread of SARS-CoV-2 is to establish herd immunity through large-scale vaccination. Generally, vaccines can be divided into live-attenuated vaccines, inactivated vaccines, recombinant subunit vaccines, adenovirus-based vaccines, and nucleic (mRNA and DNA) vaccines [48]. WHO recommends that the vaccination of inactivated vaccines

does not require delayed blood donation, and the vaccination of attenuated live vaccines needs to be delayed for 4 weeks. In China, the delayed blood donation time after inactivated vaccine vaccination was shortened from 28 days to 48 h; thus, more vaccinated donors could participate in blood donation. The American Association of Blood Banks (AABB) in the USA and European Center for Disease Control and Canadian Blood Centers require no delay in blood donation after the vaccination of inactivated vaccines. 3 days delays of blood donation after inactivated vaccine vaccination in Singapore, 7 days delay in Britain and Australia, and 14 days delay in India have been proposed [48].

Conclusions

The SARS-CoV-2 infection has spread to most countries and regions of the world leading to a pandemic. Although progress has been made in the determination of viral genome, viral life cycle, and diagnosis as well as vaccine development, no specific antiviral therapy is available. Under the immune pressure from natural infection and vaccination, this virus mutates rapidly to become more adaptable to infect human beings. The transmission risk of SARS-CoV-2 through blood transfusion remains theoretical. At present, there is no history of any respiratory viruses including influenza, MERS, SARS, or SARS-CoV-2 to be transmitted through blood transfusion. Although SARS-CoV-2 RNA can be detected in some SARS-CoV-2 patients and blood donors, no infectious SARS-CoV-2 virus was found in the blood nor the blood components. SARS-CoV-2 RNA detected in blood samples does not necessarily represent the presence of infectious SARS-CoV-2 virus particles. Many studies have de-

tected SARS-CoV-2 RNA in blood and feces from COVID-19 patients or asymptomatic patients. However, up to now, no one has successfully isolated and cultured infectious SARS-CoV-2 from these RNA-positive feces or blood. Perhaps the virus cannot be isolated and cultured for technical reasons, or the viral RNA detected is nucleic acid fragments, rather than the full infectious SARS-CoV-2 virus particles. Due to the ongoing pandemic, we still need to pay attention to SARS-CoV-2 infection and blood safety.

Conflict of Interest Statement

No competing financial interests exist.

Funding Sources

This work was partially supported by Sino-German Center for Research Promotion, National Natural Science Foundation of China (C-0029); National Key Research and Development Program (2018YFE0107500); Science and Technology Partnership Program, Ministry of Science and Technology of China (KY201904011); and Health Commission of Chengdu (No. 2020179).

Author Contributions

He B.R. and Shi Y.Q. wrote the first draft of the manuscript, contributed equally and share lead authorship. He B.R., Shi Y.Q., Li B., and Duan X.Q. collected/analyzed the data; and Wang Q.H. conceptualized and designed the structure of the manuscript and performed critical editing and proofreading. All authors have read and approved the final manuscript. He B.R. and Shi Y.Q. contributed equally to this manuscript as co-first authors.

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