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The SARS-CoV-2 Disease and the Risk of Transfusion Transmission: A Narrative Review

SARS-CoV-2 Hastalığı ve Kan Transfüzyonuyla Bulaş Riski: Bir Literatür Derlemesi

Ülkü Ceren KÖKSOY[a], Gizem KAHRAMAN[b], Güle ÇINAR[c]

[a]Department of Anesthesiology and Reanimation, Ufuk University Faculty of Medicine, Ankara, TURKEY
[b]Department of Anesthesiology and Reanimation, Ankara University Faculty of Medicine, Ankara, TURKEY
[c]Department of Infectious Diseases and Clinical Microbiology, Ankara University Faculty of Medicine, Ankara, TURKEY

ABSTRACT Emerging infection outbreaks have a deteriorating effect for the blood supply by limiting resources and compromising the safety of transfusion of blood products. The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) which leads to a self-limited upper respiratory disease emerged from China and turned into a pandemic in January 2020. Symptomatic, asymptomatic and recuperative patients can be reservoirs for transmission but their viral load in plasma, serum, or lymphocytes in the incubation period is not known, thus their rate of infectivity remains uncertain. Even though transmission by blood is not detected yet, a solitary case has reported a neonate born to a mother with coronavirus disease-2019 (COVID-19) with elevated antibody levels and abnormal cytokine test results 2 hours after birth, pointing at the possibility of vertical transmission. With the pandemic spreading wider, the number of blood donations from asymptomatic patients keeps rising, resulting in blood transfusions from COVID-19 patients to SARS-CoV-2 free recipients. It is stated that if all the blood donations were tested for SARS-CoV-2 RNA up to 15% of donors in the incubation phase would have to be excluded for carrying viral RNA. Although data suggest that it is not transmissible through transfusion with no confirmed cases of transfusion transmission, presence of SARS-CoV-2 RNA in the donated plasma of asymptomatic patients is still considered to constitute a risk for blood safety for both healthcare personnel and the recipients. Therefore, blood centers and banks are advised to take measure for protection from SARS-COV-2 and to avoid the risk of transmission through transfusion.

Keywords: Severe acute respiratory syndrome-coronavirus-2; blood transfusion

ÖZET Yeni ortaya çıkan enfeksiyonlara bağlı gelişen salgınlar, kaynakları sınırlandırarak ve kan ürünlerinin transfüzyonunun güvenliğini tehlikeye atarak kan tedarikini bozan bir etkiye sahiptir. Kendini sınırlayan bir üst solunum yolu hastalığına yol açan şiddetli akut solunum yolu sendromu koronavirüs-2 [severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)], Çin'den ortaya çıktı ve Ocak 2020'de pandemiye dönüştü. Semptomatik, asemptomatik ve iyileşen hastalar bulaş için rezervuar olabilirler ancak inkübasyon periyodunda plazma, serum veya lenfositlerindeki viral yük bilinmemektedir, bu nedenle bu hastaların enfektivite oranları belirsizliğini korumaktadır. Kan yoluyla bulaşma henüz tespit edilmemiş olsa da bir vaka sunumunda, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] olan bir anneden doğan ve doğumdan 2 saat sonra yüksek antikor seviyeleri ve anormal sitokin testi sonuçları olan bir yenidoğan bildirilmiş ve dikey bulaş olasılığına işaret etmiştir. Pandeminin yayılmasıyla birlikte, asemptomatik hastalardan kan bağışı sayısı artmaya devam etmekte ve bu da COVID-19 hastalarından SARS-CoV-2 bulaşı olmayan alıcılara kan transfüzyonu yapılması ile sonuçlanmaktadır. Tüm kan bağışlarının SARS-CoV-2 RNA için test edilmesi durumunda, inkübasyon aşamasındaki donörlerin %15'inin viral RNA taşıdıkları için dışlanmaları gerekeceği belirtilmiştir. Veriler transfüzyon yoluyla bulaş olmayacağını gösterse de ve doğrulanmış bir transfüzyona bağlı bulaş vakası gösterilmemiş olsa da asemptomatik hastaların bağışlanan plazmalarındaki SARS-CoV-2 RNA varlığının, hem sağlık personeli hem de alıcılar için kan güvenliği açısından bir risk oluşturduğu düşünülmektedir. Bu nedenle, kan merkezleri ve bankalara SARS-COV-2'den korunmak için önlem almaları ve transfüzyon yoluyla bulaşma riskinden kaçınmaları önerilir.

Anahtar Kelimeler: Şiddetli akut solunum sendromu-koronavirüs-2; kan transfüzyonu

Emerging infection outbreaks have a deteriorating effect for the blood supply all around the world, both by limiting resources and by compromising the safety of transfusion of blood products. Even though the emerging infection is a respiratory disease, it still provides a risk for infection transmission for both the medical staff in the blood banks, blood donors and recipients.

Correspondence: Ülkü Ceren KÖKSOY
Department of Anesthesiology and Reanimation, Ufuk University Faculty of Medicine, Ankara, TURKEY/TÜRKİYE
E-mail: cerenkoksoy@gmail.com

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In December 2019, a pneumonia outbreak of unknown origin emerged in Wuhan, a city of China. In January 2019, the Chinese government announced the cause as a new virus named "The Novel Coronavirus" aka "coronavirus disease-2019 (COVID-19)" (2019-nCoV). A while later it has then been renamed by the World Health Organization (WHO), due to its clinic properties, as "severe acute respiratory syndrome-coronavirus-2" (SARS-CoV-2). Upon its rapid escalation, on January 30rd, 2020 this new virus outbreak was declared by WHO to have turned into a pandemic, a public health emergency for all nations and it has spread all around the world since then. By March 14th, 2021 it was seen in 223 countries, with 118,754,336 confirmed cases of COVID-19 and 2,634,370 deaths, reported to WHO.[1,2] In Turkey, the first case was announced on March 10th, 2020 and there have been 2,866,012 confirmed cases of COVID-19 and 29,421 deaths since then.[3]

Coronaviruses, from the family Coronaviridae, are enveloped, non-segmented positive-sense RNA viruses that are able to cause disease in both mammals and birds.[4] Four of which can infect humans, and lead to self-limited, common upper respiratory infections. They have a more serious progression in the young, elderly and immuno-compromised, thus posing a greater threat in these populations. In humans, SARS-CoV-2 can multiply better in primary airway epithelial cells in comparison to other tissues and causes milder clinical symptoms than its priors that instead infect intrapulmonary epithelial tissue, such as SARS-CoV-2 and Middle East respiratory syndrome-coronavirus.[5-9] Though it was first detected in the bronchoalveolar lavage samples of affected patients, is actually found more in saliva compared to other respiratory samples.[10,11] Both symptomatic as well as asymptomatic and recovering patients are able to transmit infection.[12] Viral spread happens mainly two and a half days before symptoms surface, most commonly by person-to-person transmission and close contact via small, contaminated droplets in the air caused by coughing and sneezing with a mean incubation period of 0 to 14 days.[13]

On the early phase of the pandemic, Huang et al. have stated that from the first 41 cases of SARS-CoV-2 patients, 6 (15%) of them had RNAaemia.[2] The time period when RNAaemia appears is still debated with not enough studies to come to a definite conclusion.[10] Viral RNA can be found in the blood plasma or serum of the COVID-19 patients by polymerase chain reaction (PCR) usually 2-3 days after the beginning of the symptoms during different periods. However as only the viral RNA, not the intact infectious virus itself is found in blood, transmission through blood transfusion, though theoretical still possible, seems unlikely.[2,7] This notion is also supported by a declaration of WHO in 2003 which had stated that none of the reported SARS cases were caused by the transfusion of blood products.[14] Still the infectivity rate of COVID-19 patients in the incubation period stays uncertain because data on the amount of viral material present in blood as well as plasma, serum or cells such as lymphocytes, is still scarce.[7]

Even though transmission from blood has not been shown yet, a solitary case has reported a neonate whose mother was diagnosed with COVID-19 and had elevated levels of antibody and an abnormal cytokine test 2 hours following her birth which is considered pointing at the possibility of vertical transmission. The fact that her immunoglobulin (IgM) antibodies, which can not pass through placenta, had risen is likely suggesting that she was infected in utero.[15] This finding contradicted with a retrospective review aiming to investigate the vertical transmission of COVID-19, where nine women having symptomatic SARS-CoV-2 infection who delivered livebirths were evaluated. The amniotic fluid, cord blood and breastmilk of the mother, as well as their babies' throat swab, from six of the patients were all tested negative for the virus. Despite the fact that their results suggested there is no evidence for vertical transmission causing this intrauterine infection, in consideration of more recent findings, to better understand the transmission routes becomes of upmost importance in order to minimise viral transmission and the spread of COVID-19, especially through blood transfusions.[16]

Younger adults which are more likely to volunteer for blood donations have milder symptoms than the elder population, which increases the

possibility that an asymptomatic virus carrier or a patient with no fever could become a blood donor. With the number of asymptomatic patients rising blood donations became a subject of concern as it is already established that asymptomatic patients are capable of virus transmission and thus can spread SARS-CoV-2.[14]

Although, up to now, SARS-CoV-2 infection transmission by transfusion of blood products has not been reported, a relevant study stated that if all the blood donations were examined in order to detect SARS-CoV-2 RNA, nearly 15% of all blood donors, who would actually be in the incubation phase, would have to be excluded for carrying viral RNA.[7,17] Accordingly, Chang et al. have screened 2,430 real time and 4,995 retrospective blood donations with PCR from January to March 2020 and found 4 donors with plasma samples that had SARS-CoV-2 RNA within but not specific IgG and IgM for COVID-19. These results even though indicating a possible early-stage infection and a need to follow-up, in the end do not provide enough evidence to confirm the presence of virions in blood as well as any viral transmission via blood products, as detectable RNA might not signify infectivity.[18]

While the pandemic spread wider, the number of blood donations from asymptomatic patients kept rising, resulting in blood transfusions from COVID-19 patients to SARS-CoV-2 free recipients. A study on this matter, from Cho et al., reported a 21-year-old male patient suffering from severe aplastic anaemia that had a platelet transfusion from a donor carrying SARS-CoV-2, without getting infected. The apheresis platelets were obtained 2 days prior the transfusion from a seemingly healthy donor who was later diagnosed with COVID-19 on the day after the transfusion. The recipient was evaluated for SARS-CoV-2 four times with real-time reverse transcription PCR (RT-PCR), all resulting negative, remained asymptomatic and stable showing no sign of pneumonia. The paper concluded with the statement that recuperating COVID-19 patients should not donate blood before 28 days and only after symptoms disappear and the treatment is completed.[19]

Another case on the subject was presented by Essa et al. in June 2020. A 22-month-old male patient with acute pre-B lymphoblastic leukaemia who had a matched related donor hematopoietic stem cell transplant for persistent disease, received a platelet transfusion whose donor later had a positive nasal swab for COVID-19, five days following the donation. On the first and 14th days, nucleic acid amplification test and RT-PCR assay was performed from both nasopharyngeal and blood samples which all resulted negative. Due to their findings, the authors stated that even though their case supported the opinion that the probability of transmission by transfusion of blood products is low, still objective donor-screening methods and universal deactivating techniques remain a necessity.[20] Similar to this patient, another immunocompromised patient suffering from acute myeloid leukaemia from Greece is reported to have received platelets from an asymptomatic donor. Five days after the donation, the donor was diagnosed with COVID-19 which led to the patient being monitored for several weeks. The male recipient had developed no symptoms related to COVID-19, had a normal computed chest tomography, negative PCR assay and 45 days later was negative for IgG-IgA test results as well. To avoid these situations in the future, the authors recommended serological screening of COVID-19 in order to discover infected donors beforehand with point-of-care test cassettes.[21]

Pathogen-inactivating treatment for blood products, involving photochemical treatment, is an available method to provide safer blood transfusions. SARS-CoV-2 is known to be sensitive to acid and basic-pH as well as heat. In order to reduce its' activity in blood products such as plasma or platelet concentrates a range of methods could be used. Blood banks have been using pathogen inactivation technologies that utilizes heat and solvent/detergent treatments for plasma and platelet concentrates to avoid any risk of viral transmission of SARS-CoV-2; while only 15-30 minutes is needed for reduction, to achieve inactivation in plasma products 10 hours in 60°C is considered sufficient.[22-24] Solvent and detergents which SARS-CoV-2 is known to be sensitive, ultraviolet lights (A-B) combined with

amotosalen/riboflavin, ultraviolet C light on its own and methylene blue paired with visible light also prove to be useful.[7] Nevertheless, all these methods which add additional costs don't have enough proof of their efficiency against new pathogens and have shortcomings such as the short half-lifes of platelets, agents' unavailability, biochemical reactions.[20] Furthermore, as it is known that blood components are harmed during pathogen reduction, there is no single one suitable for all blood products.[25,26] Additionally, as these are expensive treatments they can not be used as widely as necessary.[25] Therefore, all these methods should be administered with care and with consideration of the circumstances such as the severeness of the disease and the greatness of the transmission risk.

In contrast to all these recommendations, a Korean paper on COVID-19 identification in donated blood products has revealed a different opinion. In this study, seven blood donors were diagnosed with COVID-19 after having donated blood. From these seven donors, six platelet units and three erythrocyte units were given to different patients of which one deceased from causes other than COVID-19 and eight went on without developing COVID-19 symptoms. As the stored blood from the COVID-19 positive donors did not contain any SARS-CoV-2 RNA, health authorities in Korea deemed performing further investigation for recipients unnecessary. Still three recipients who asked to be examined for SARS-CoV-2 RNA resulted negative from nasopharyngeal samples. In the end, the authors of this opposing study recommended that blood banks should be immediately informed by the health authorities, of all confirmed COVID-19 cases in order to avoid the transfusion of blood products as early as possible. Cross-referencing confirmed COVID 19 donors to recipients, recalling suspected blood products and waiting for 3 months for future donations are some of the precautions taken in Korea since March 2020.[27]

It is acknowledged that most patients, especially younger adults have milder symptoms than the older adults; and as the younger population are more prone to blood donation this increases the risk of patients with no fever and asymptomatic COVID-19 carriers to donate blood. Although the data on SARS-CoV-2 suggests that it is not transmissible through transfusion, and that there are no confirmed cases of transfusion transmission, the presence of viral RNA in the donated plasma of asymptomatic patients is still considered to constitute a risk for blood safety.[18,28] Therefore, despite the lack of evidence, blood centers and banks around the world have been taking measures to protect both the blood donors and medical personnel and to avoid the risk of transmission. The general pre-emptive actions against COVID-19 transmission is usually the isolation of cases, locking-down contacts, application of facial masks and maintaining social distance and hand hygiene. Still when it comes to avoiding transmission through blood transfusion to take more precaution is deemed to be necessary. Most important of all, COVID-19 patients should be isolated while their contacts are traced and quarantined as early as possible. Health-care staff in blood centers and laboratories must be aware of the risks of transmission and use personal protective gear and improve biosafety protection.[7]

In the light of all these studies and published cases, in order to maintain the safety of blood donations, most of the Chinese blood facilities started following precautions more diligently.[7,29] As it is known that virus transmission is doubted yet possible from asymptomatic COVID-19 patients, donors are carefully evaluated before donation, with preventions such as asking if they feel healthy, taking donors' body temperature, if the donor or the donors' family show symptoms for COVID-19, have commuted to locations where COVID-19 is more prevalent within 28 days, as well as if the donors are at a high risk for the disease. In regard of the safety of the blood products, all blood donors were also called back and asked about theirs and their family's current physical condition after donation.[7] To minimise the risk of transfusing blood from individuals who were asymptomatic at the time of donation, donors are asked to inform the blood centers if they develop any symptom following their donation.[29] Moreover, as more asymptomatic COVID-19 patients donate blood, screening these carriers with highly sensitive tests for viral RNA, antibodies, or utilize pathogen-inactivation for the donated blood will be critical to

ensure blood safety.[18] It is also recommended to quarantine the donated blood products for 14-28 days, delaying its release for clinical use. Furthermore, non-transfused blood products from infected donors are recollected as well.[7] For a safe transfusion, a 14 day quarantine for red blood cells, plasma and cryoprecipitation and SARS-CoV-2 detection for platelets is also recommended which results in 77.48% of all blood donations to be SARS-CoV-2 free.[17]

Despite all these regulations in China and most Asian countries, these precautions aren't considered with the same alertness throughout the world. Still similar to the regulations in China, the European Center for Disease Prevention and Control recommended having waiting intervals; postponing blood donations from donors with possible exposure to COVID-19 patients for 21 days while avoiding getting blood donations from those diagnosed with COVID-19 for at least 28 days after the end of treatment and the cessation of all symptoms.[9,30] On the other side, the American Association of Blood Banks and Centers for Disease Control and Prevention has not suggested any specific precautions for COVID-19 considering blood donations.[28]

In our opinion, as there is no consensus between guidelines from different countries, it is best to follow national guidelines set by the health authorities and wait for a determined period of time for blood donation if it is recommended or deemed necessary while following international guidelines for updates on safety of blood donation during the COVID-19 pandemic.

As of March 2021, several vaccines have been produced against COVID-19 and countries around the world initiated different vaccination programmes in line with their national health policies.[31] In consequence, despite the health benefits these vaccines have risen some dispute over the safety of blood donations from vaccinated donors. On January 19th, 2021 "The Food and Drug Administration" has published a guideline regarding this issue which recommends waiting a short amount of time, about 2 weeks, for donors who received an alive or weakened viral vaccine or are unaware of the type of vaccine that was applied. Donors vaccinated with nonreplicating, inactive, or mRNA-based vaccines, blood donations are not restricted to any time period and can donate freely afterwards.[32]

In conclusion, although the data on SARS-CoV-2 suggest that it is not transmissible through transfusion, and that no case has been published that proves transfusion transmission, finding the RNA of SARS-CoV-2 in donated plasma deriving from asymptomatic individuals is still considered to constitute a risk for blood safety for both healthcare personnel and the recipients of these donations. Therefore, despite the lack of evidence, blood centers and banks around the world are encouraged and strongly advised to take measures for protection from COVID-19 and to avoid the risk of transmission through transfusion.

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Authorship Contributions

Idea/Concept: *Ülkü Ceren Köksoy, Gizem Kahraman;* ***Design:*** *Ülkü Ceren Köksoy, Gizem Kahraman;* ***Control/Supervision:*** *Ülkü Ceren Köksoy;* ***Data Collection and/or Processing:*** *Ülkü Ceren Köksoy, Gizem Kahraman;* ***Analysis and/or Interpretation:*** *Ülkü Ceren Köksoy, Gizem Kahraman, Gül Çınar;* ***Literature Review:*** *Ülkü Ceren Köksoy, Gizem Kahraman;* ***Writing the Article:*** *Ülkü Ceren Köksoy, Gizem Kahraman, Gül Çınar;* ***Critical Review:*** *Ülkü Ceren Köksoy, Gizem Kahraman, Gül Çınar;* ***References and Fundings:*** *Ülkü Ceren Köksoy, Gizem Kahraman;* ***Materials:****Ülkü Ceren Köksoy, Gizem Kahraman, Gül Çınar.*

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