EDORIUM Journals

Int J Blood Transfus Immunohematol 2021;11:100064Z02SB2021.
www.ijbti.com

REVIEW ARTICLE PEER REVIEWED | OPEN ACCESS

The risk of transmission of SARS-CoV-2 through blood and blood products: The current state of knowledge (international review)

Sabah Bouhou, Mohammed Benajiba, Azlarab Masrar

ABSTRACT

Introduction: Severe acute reparatory syndrome coronavirus-2 (SARS-CoV-2) is a recently emerged coronavirus, and infection with SARS-CoV-2 can remain asymptomatic or lead to coronavirus infection disease. Clinical pictures range from a pre-clinical stage to severe pneumonia. The presence of this pre-clinical infection stage could pose a problem for the management of the transfusion chain as donors or employees may become infected during their travels or activities, and this may exponentially increase the number of infected but asymptomatic individuals. So, SARS-CoV-2 may pose a threat to blood safety.

Aim: In this study, we want to provide the necessary information about the real risk of transmission of SARS-CoV-2 via blood and blood products. It constitutes one of the most controversial topics with several critical questions for which both professionals in blood centers and health services seek apparent answers.

Methods: It is a literature review where we have consulted relevant papers and articles about the real risk of transmission of SARS-CoV-2 through blood or blood products. For this purpose, scientific research sites were consulted using key terms search strategy. Thus, we compiled and presented the necessary information from (i) positions of international scientific societies and public bodies; (ii) available data to date on detecting SARS-CoV-2 RNA in the blood of COVID-19 patients and blood donors; and (iii) published cases of transfusion of blood products from donors confirmed COVID-19 positive after donation and the process in recipients of these products.

Results: All papers published to date stipulated that SARS-CoV-2 is a new infectious agent. No sufficient information is available to exclude with certainty the risk of transfusion transmission, which remains a theoretical risk. SARS-CoV-2 RNA has been detected very lowly, but virus infectivity has not been confirmed in blood donors. Reported cases of product transfusion from COVID-19 positive donors after a donation have not provided any evidence of transmission of the virus to recipients. As a precautionary measure, blood transfusion centers have set up necessary measures to reduce the risk of transmission of SARS-CoV-2 through blood products and ensure the safety of donors and recipients. Strengthening the hemovigilance system and post-donation information is an essential link for blood safety during the COVID-19 pandemic.

Conclusion: All data available to date stipulated that SARS-CoV-2 is not transfusion-transmitted and that the risk of transmission of this new coronavirus through blood and blood products is still theoretical. This novel coronavirus may be no direct threat to blood safety but raises serious issues for general blood supply. All measures taken by blood centers to secure blood donation against this new virus are preventive measures that should consider the need to ensure the availability of blood products.

Keywords: Blood safety, Blood transmission, COVID-19 pandemic, SARS-CoV-2 transmission, Transfusion transmitted

Sabah Bouhou[1,2], Mohammed Benajiba[1], Azlarab Masrar[2,3]

Affiliations: [1]National Centre for Blood Transfusion and Hematology, Rabat, Morocco; [2]Hematology Research Team, Hematology Laboratory, Faculty of Medicine and Pharmacy, Mohammed V University, Rabat, Morocco; [3]Central Hematology Laboratory, Ibn Sina University Hospital Centre, Rabat, Morocco.

Corresponding Author: Sabah Bouhou, M.D., Medical Biologist, Ph.D. Student in Life and Health Sciences, In Charge of a Scientific and Technical Mission to the Directorate of the National Center for Blood Transfusion and Hematology, Rabat, Morocco; Email: sabahbouhou@hotmail.com

Received: 15 July 2021
Accepted: 01 October 2021
Published: 28 October 2021

How to cite this article

Bouhou S, Benajiba M, Masrar A. The risk of transmission of SARS-CoV-2 through blood and blood products: The current state of knowledge (international review). Int J Blood Transfus Immunohematol 2021;11:100064Z02SB2021.

Article ID: 100064Z02SB2021

****

doi: 10.5348/100064Z02SB2021RV

INTRODUCTION

Emerging and re-emerging infectious diseases have always posed a threat to the safety of blood transfusions. Blood transfusion centers have had to carry out rigorous epidemiological and scientific surveillance to detect in good time any pathogens that might pose a risk to recipients of blood products. SARS-CoV-2 is a recently emerged coronavirus which could be a new challenge for blood establishments worldwide.

The recent outbreak of novel coronavirus SARS-CoV-2 was reported at the end of December 2019 in China in Wuhan and spread quickly around the world, resulting in its declaration as a pandemic by the World Health Organization (WHO) on March 11, 2020. The new coronavirus was isolated from human airway epithelial cells and sequenced to identify microbial sequences [1]. Since the beginning of this health crisis, the pandemic has constantly evolved, and scientific evidence is rapidly accumulating. Initially, the scientists sought to have information on the epidemic characteristics of the virus and the clinical, biological, and radiological manifestations of the infection caused by this new virus.

This infection clinical pictures range from a pre-clinical stage to severe pneumonia. The presence of this pre-clinical infection stage could pose a problem for the management of the transfusion chain as donors or employees may become infected during their travels or activities, and this may exponentially increase the number of infected but asymptomatic individuals. So, knowing whether or not the virus is transmissible through blood and blood products is essential for blood transfusion centers. This information enables blood establishments to plan the necessary safety measures to protect blood donors, recipients, and staff.

Several routes of transmission have been explored for SARS-CoV-2. The transmission of respiratory droplets and mucous membrane infections are the main routes of SARS-CoV-2 transmission but not the only one [1]. Eye and ocular infections are specific transmissions that should not be ignored and might be another route to lung infection [1, 2]. Additionally, SARS-COV-2 RNA has been detected in the urine and feces of some patients without confirmation [2–4]. However, those routes should not be neglected in standard procedures for collecting and examining patients infected with COVID-19 to protect medical staff and reduce the risk of infection [1]. Other transmission routes have been cited without clear evidence: transmission through breastfeeding, mother-to-child transmission, and zoonotic transmission [2–4].

What about the SARS-CoV-2 transmission through blood or blood products?

To answer this question, we aimed to present a synthesis of information collected from literature published to date about the real risk of transmission of SARS-CoV-2 via blood and blood products.

METHODS

During the period from 12 December 2020 to 31 April 2021, we searched the data available about the real risk of SARS-CoV-2 transfusion transmission in PubMed central, HINARI, Web of sciences, Google Scholar, Google, World Health Organization (WHO) web site, European Centre of Disease Control (ECDC) web site, Food and Drug Administration (FDA) web site, International Society of Blood Transfusion(ISBT) web site, American Association of Blood Banks (AABB) web site, the Centre for Disease Control (CDC) web site, the High Council for Public Health (HCPH) web site. We used several key search terms such us: SARS-CoV-2 transmission, transfusion transmission of SARS-CoV-2, SARS-CoV-2 blood safety, SARS-CoV-2 detection, 2019-nCoV transmission, SARS-CoV-2 RNAemia, SARS-CoV-2 in serum or plasma, SARS-CoV-2 transfusion-transmitted, routes of transmission of SARS-CoV-2, 2019-nCoV and blood safety, SARS-CoV-2 and blood safety, Viral load of SARS-CoV-2, Coronavirus and blood transmission, biological detection of SARS-CoV-2.

We identified 78 papers, of which we consulted 72 references with full-text read. We identified and excluded 06 duplicates from 78. From 72 full-text consulted, we identified 28 papers without scientific input for the article's subject. In the final, we include 44 articles eligible for collecting information about the issue of our review article. All this information on the consulted database is presented in Figure 1 (PRISMA flow diagram).

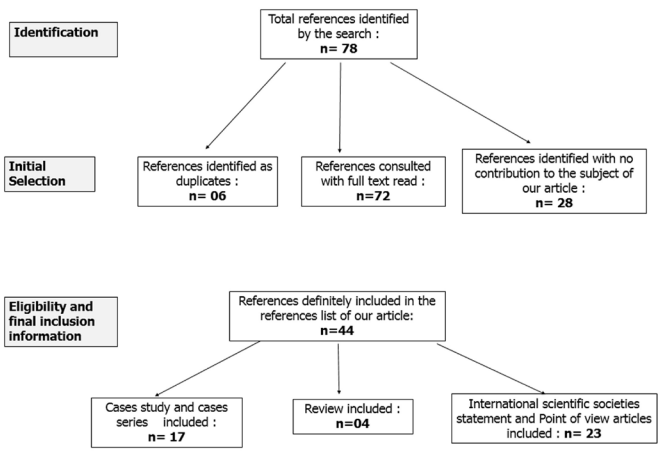


Figure 1: PRISMA flow diagram showing information about references consulted and included in the redaction of our review paper.

RESULTS

Positions of international scientific societies and public bodies

One of the essential concerns for blood establishments worldwide is known as the new coronavirus's absolute risk in blood donors and transfused patients. The blood transfusion centers have followed the publications and recommendations of international organizations regarding the management of the impact of the COVID-19 pandemic on blood donation and, in particular, on transfusion safety.

The first publications on this subject were issued from the World Health Organization (WHO), the American Association of Blood Banks (AABB), the European Centre for Disease Prevention and Control (ECDC), the Food and Drug Administration (FDA), and the High Council of Public Health (HCPH). These authorities updated their data as the COVID-19 pandemic progressed and as scientific data became available.

According to the WHO, potential viremia during the asymptomatic or subclinical phase of infection, during the disease incubation period, the symptomatic stage of the disease, or after symptom resolution, is currently unknown and, thus, remains an issue concerning the safety of blood transfusion [5]. The risk of transmission of SARS-CoV-2 by transfusion of blood and constituents of blood is currently only theoretical and the measures taken to mitigate this risk fall under precautionary measures [5–7]. The WHO recommendations to reduce this potential risk concern the strengthening of medical selection with the exclusion of donors at risk of this new virus, the strengthening of preventive measures for the staff of blood centers and donors, the strengthening of the hemovigilance system, and in particular post-donation information [5–7]. Considering the absence of reported transfusion-transmitted cases and the lack of proven infectivity of the virus in blood collected from asymptomatic donors, WHO does not recommend implementing screening techniques [5–7].

On July 9, 2020, the WHO scientific background paper about the routes of transmission of SARS-CoV-2 reported that some studies have shown the presence of SARS-CoV-2 RNA in plasma or serum and indicated that the virus could replicate in blood cells [2]. The role of transmission by blood remains uncertain, and the low titers of virus in plasma and serum suggest that the risk of transmission by this route may be low [2].

The AABB, on its first data published in January 2020, stipulated that for the CDC and FDA, the potential for transmission of SARS-CoV-2 by blood and blood components is unknown and there have been no reported cases of transfusion-transmitted coronavirus [6]. FDA and CDC are not recommending interventions since neither data nor precedents suggest a risk for transfusion transmission of 2019-nCoV [8, 9].

In its recent update on January 19, 2021, the FDA confirmed that the SARS-CoV-2 virus is not transfusion-transmitted regarding the absence of reported cases of SARS-CoV-2 transmission via transfusion. According to the FDA, no COVID-19 laboratory tests are recommended to screen blood donation [10].

For the ECDC, on April 29, 2020, the transmission of the SARS-CoV-2 virus through substances of human origin remains a theoretical risk, and screening is currently not recommended because transfusion-transmitted COVID-19 has not been reported [11]. For the ECDC, several coronaviruses are susceptible to the inactivation techniques. Blood establishments that use pathogen reduction technology may decrease the theoretical risk of COVID-19 transmission through those products [11]. The ECDC concluded that the risk of transmission of COVID-19 by substances of human origin remains theoretical but cannot be excluded entirely [11].

In updating its recommendations, the ECDC, on December 10, 2020, reported that no cases of COVID-19 transmission through Substances of Human Origin and plasma-derived medicinal products had been reported [12]. COVID-19 may affect the sufficiency and sustainability of those substance supplies by reducing donor availability, affecting the staff at these substances facilities, changing the demand for Substances of Human Origin products, and limiting the provision or distribution of critical materials, equipment, and Substances of Human Origin products [12]. The ECDC concluded that blood-borne transmission of COVID-19 seems unlikely and theoretical but cannot be excluded entirely [12].

On March 14, 2020, the French High Council of Public Health (HCPH) reported that the risk of transmission of SARS-CoV-2 by a human body product derived from an asymptomatic donor is probably low. The HCPH notice said that this information was shown by observations related to using small series and that the infectious nature of the blood is not documented for infection with SARS-CoV-2 [13]. The recommendations of the HCPH concerned: (i) the strengthening of pre-donation questioning and the exclusion of donors at risk of COVID-19 disease, (ii) the strengthening of post-donation information according to regulatory terms, (iii) the application of standard precautions for the blood drive and the need to maintain blood drive to ensure the supply of blood products [13]. Alternatively, in the May 20 report, the HCPH reported that a study of approximately 27,000 donations consisting of screening for the SARS-CoV-2 genome through Viral Genomic Screening in blood donors would begin on May 18, 2020 at the French Blood Establishment [14].

The Superior Health Council (SHC) of Belgium reported in June 2020 that blood transmission from asymptomatic donors in the incubation phase is not to be counted among the transfusion risks [15]. Regarding the results related to a very high number of asymptomatic carriers in the population in epidemic

zones, the SHC notes that many current blood donors have and will donate their blood or component blood while being positive for SARS-CoV-2 RNA [15]. At present, the hemovigilance services of the Federal Agency for Medicines and Health Products of Belgium or other countries have not reported any unexpected or adverse effects linked to the therapeutic use of blood components [15]. Therefore, the SHC concluded that this new coronavirus does not constitute a threat to the safety of blood components intended for transfusion. Consequently, there is no need to introduce preventive measures inappropriate for the epidemiological situation [15].

In November 2020, the Standing Advisory Committees on Transfusion Transmitted Infections of the United Kingdom stipulated that at the time of publication of their Position Statement, there have not been any reports of transmission of any respiratory virus via blood, tissues, or stem cells [16]. The committee noted the importance that deferral of blood donation should be balanced with any negative impact on the ability to maintain a blood supply and that the measures taken should be proportionate to this potential risk of SARS-CoV-2 transmission [16].

On November 12, 2020, Public Health Ontario published a summary document about the COVID-19 Transmission Routes [3]. In this paper, they stipulate that if SARS-CoV-2 RNA has been detected in the blood of patients with COVID-19, all studies and systematic reviews show, however, that the risk of transmission through blood or organ transplantation is inferior [3]. Compared to samples taken from the upper respiratory tract, samples of blood and blood products are rarely subjected to a viral RNA test, and a viable virus has never been detected [3]. In the same way, the National Institute of Public Health of Quebec published an epidemiological and clinical file of COVID-19 on March 3, 2021. This paper reported that urine, plasma, or serum transmission had not been documented, although virus RNA has been identified in these fluid organics [4].

Detection of SARS-CoV-2 RNA in blood, plasma, or serum: published data to date from case studies and case series studies

Chinese teams made the first publications concerning the novel coronavirus from Wuhan because Wuhan city was considered the epicenter of SARS-CoV-2 infection at the start of the epidemic in China. Thus, the first observations showed that viral RNA had been detected in the plasma or serum of patients with COVID-19. As things progress, several case studies and case series studies were published about detecting SARS-CoV-2 RNA in blood donations and reported that the risk of transmission of SARS-CoV-2 by blood products is very low.

I. SARS-CoV-2 RNA, blood, plasma, or serum detection in patients with COVID-19

In January, in a study on the clinical features of 41 patients infected with 2019 novel coronavirus in Wuhan, the results of polymerase chain reaction (PCR) testing of serum samples were evaluated and showed an RNAemia in six cases 6/41 (15%) suggesting a very low RNA concentration [17]. On February 15, 2020, a study focused on the epidemiological, clinical, laboratory, and microbiological findings of five patients in a family cluster who presented with unexplained pneumonia after returning to Shenzhen, Guangdong province after a visit to Wuhan and an additional family member who did not travel to Wuhan [18]. One of the five patients was 66-year-old. Only the serum sample of this patient was positive, and all other patients' serum, urine, and fecal samples were negative for this novel coronavirus [18]. This patient had more underlying comorbidities. His clinical features and radiological findings are more severe than the other patients included in the study [18]. According to the authors, the positivity of the serum sample of this patient for 2019-nCoV might indicate some virus spillover from the more severely infected lung into the systemic circulation, as previously reported in patients with Severe Acute Respiratory Syndrome [18].

In February 2020, a paper was published about the molecular and serological investigation of 2019-nCoV infected patients in Wuhan Pulmonary Hospital. In this investigation, 39 patients' samples were collected, 7 of which were in severe conditions [19]. These samples include oral swabs, anal swabs, and blood samples [19]. Of these patients, eight were oral swab positive, four were anal swab positive, six were blood positives, and three were serum positives. In summary, the authors reported that viral nucleotides could be found in anal swabs or blood even if they are not detected in oral swabs. The authors provide a cautionary warning that 2019-nCoV may be transmitted through multiple routes [19].

A French team evaluated 27 patients admitted to three university intensive care units (ICUs) with severe SARS-CoV-2 infection [20]. The patients required continuous renal replacement therapy, venovenous extracorporeal membrane oxygenation, or both [20]. All 27 patients were on mechanical ventilation, and 25/27 were supported by venovenous extracorporeal membrane oxygenation [20]. The patients' samples were taken, and a real-time RT-PCR targeting the E (envelope) gene of SARS-CoV-2 was performed. SARS-CoV-2 RNA has been detected in all samples from patients' lower respiratory tract and the plasma of 13/27 [20]. However, whether plasma RNA was positive or negative, SARS-CoV-2 RNA was not detected in the membrane oxygenator gas outlet condensate [3, 20].

In Italy, Morone et al. published the results of a systematic review involving 1348 recovered patients on August 2020 [3, 21]. The authors aimed to evaluate

the presence of the SARS-CoV-2 viral RNA in different biological specimens [21]. The results demonstrated that stool samples presented a positivity rate of 48.8%, urine samples showed a positivity rate of 16.4%, and blood samples showed a positivity rate of 17.5% [21]. The authors concluded that this is a detection of viral RNA and not live viral shedding. The exact correlation between RNA viral shedding and infectious viral shedding is not known [3, 21].

A German team, in June 2020, published data on molecular detection of SARS-CoV-2 in 18 patients, 2 of whom were infected in China and evacuated in Germany on February 1, 2020 [22]. The patients' clinical features varied from asymptomatic, moderate flu-like symptoms, pneumonia to one case of need of artificial respiration because of acute respiratory distress syndrome (ARDS) [22]. Three of the 18 patients included in this study had donated blood in Germany. Samples from the lower respiratory tract were RT-PCR positive in all patients. RNAemia was only detected in 1 of the 77 blood samples examined, precisely 1 out of 8 serum/plasma samples taken from the patient with ARDS [22]. Based on their data, the authors concluded that there is no measurable risk for SARS-CoV-2 transmission through blood components in asymptomatic SARS-CoV-2 infected individuals [22].

II. SARS-CoV-2 RNA, blood, plasma, or serum detection in blood donors

Although there is no evidence that this new virus can be transmitted through blood or blood products, the nucleic acid detection of SARS-CoV-2 has been added to the blood screening since the end of January 2020 in Wuhan and other cities of Hubei province to minimize the possible risks [23, 24].

In a multicenter study in Hubei, China, all blood donations donated from February 9 to April 30, 2020 were tested in 12 blood establishments in Hubei province [25]. A total of 98,342 blood donations, including 87,095 whole blood and 11,247 Platelet donations, were tested by nucleic acid test (NAT) screening: individually for 3831 and by the mini pool for 94,511 blood donations [25]. All donations were negative for SARS-CoV-2 RNA during the past 12 weeks. For the authors, these results indicate that the novel coronavirus may be no direct threat to blood safety but raises some serious issues for general blood supply [25].

By March 4, 2020, Chang et al. reported that the Wuhan Blood Center had screened retrospectively 2430 plasma donations using real-time PCR, including 1656 platelets and 774 whole blood donations. Samples from blood donors were performed by mini pools of 6 to 8 blood samples or individual screening. They founded the first positive donor who gave units of platelets on January 28 in a positive pool with a week amplification. The donor's prior donations collected on December 12, 26 and January 13 were negative for viral RNA. This team also performed retrospective testing of 4995 donations collected during December 21, 2019–January 22, 2020, using a retained nucleic template after routine pool testing. They found a positive result from donations collected on January 19, and another positive donor of whole blood was identified. Health services did not use the blood products related to the second donor. Two other donors, who donated whole blood on January 20, were recognized on telephone follow-up with donors who gave blood during January and February. In summary, this team founded four asymptomatic donors with an extremely low plasma viral load at the time of donation. They concluded that detectable RNA might not signify infectivity [26].

From January 20 to May 29, 2020, a French team investigated 311 blood donations in France. It concerned information collected from 268 post-donation information and 43 trace-back donations. They detected low amounts of viral RNA in three of the 268 post-donation information [27]. The first donor was tested positive for SARS-CoV-2 in a nasal swab on day 4 after donation. Her platelet unit was transfused on day 3 after blood donation to a recipient who remained asymptomatic. Her Red Blood Cell product was transfused to a COVID-19 patient on day 37 after blood donation, and the plasma unit was not transfused. The second donor reported post-donation information on day 4, but no blood product from her blood donation was transfused. The latest donor reported post-donation information's on the same day as blood donation, and no blood product from her blood donation was transfused. In the same study, trace-back involved four blood immunocompromised recipients from 5 to 67 years of age. They received between 2 and 25 blood products. None of the 43 traced-back repository samples were tested positive for SARS-CoV-2 RNA. The authors demonstrated that viremia was extremely rare in asymptomatic blood donors, viral RNA levels were very low when detected, and the corresponding plasma was not infectious in cell culture [27]. The French study reports that it was challenging to prove SARS-CoV-2 transfusion transmission and that hemovigilance is the essential link to ensure blood safety [27].

As of March 12, 2020, seven Korean donors were identified as COVID-19 confirmed cases after blood donation [28]. From these donations, six were whole blood donations, and one was for source plasma intended for fractionation. The Korean Red Cross Blood Services (KRCBS) was informed and put on hold blood products in the inventory and retrieved concerned blood products from the hospital. The source plasma unit was also recalled. All six platelet units were transfused to six patients. Three red blood cell units had also been transfused to three recipients. One patient died due to causes unrelated to platelet, and the eight other recipients have not developed any symptoms related to COVID-19 during 19–29 days after receiving labile blood products [28].

Cho et al. reported the case of a 21-year-old man patient with very severe aplastic anemia who received

apheresis platelet transfusion from a donor who was subsequently diagnosed with COVID-19 with a positive RT-PCR test three days after donation. For the receiver, the tests remained negative [29]. The patient did not show any symptoms of infection, and there was no evidence of pneumonia on chest computed tomography. They performed three more tests for SARS-CoV-2, and all results were negative. The patient has remained stable and was under preparation for the scheduled allogeneic hematopoietic stem [29]. The publication does not give any information on the possible presence of coronavirus in the blood collected from the donor.

A team from Saudi Arabian reported a case about a 22-month-old boy diagnosed with acute pre-B lymphoblastic leukemia (ALL) [30]. The boy underwent matched-related donor hematopoietic stem cell transplant (HSCT) [30]. On day 22+, he required platelet and red blood cell transfusion. Six different single donor apheresis platelet units were collected and transfused to this patient for 4–5 days. One platelet unit was reported as donated by a donor who was declared COVID-19-positive five days after donation. None of the other platelet donors were suspected of having COVID-19 [30]. Given the current COVID-19 pandemic and the exposure risk to the positive platelet donor, this team performed nucleic acid amplification testing (NAAT) with RT-PCR assay from both nasopharyngeal swabs and blood. Results showed no laboratory evidence of acquiring coronavirus. They confirmed the negative results with second samples from blood and nasopharyngeal swabs on day 14 following platelet transfusion [30]. The authors concluded that their report supports the currently available evidence that SARS-CoV-2 transmission through blood products is unlikely. They said that given the possibility of encountering severe disease and significant mortality and morbidity rates worldwide, objective donor screening methods, and universal deactivating techniques are warranted to decrease the risk of viral transmission, especially in pandemic situations [30].

In California, on July 17, 2020, the Stanford Blood Centre reported that in mid-April 2020, they implemented a research SARS-CoV-2 RT-PCR test on their blood donations in plasma mini-pools of 6 donors [31]. They reported the case of a volunteer blood donor, healthy on the day of blood donation, which had detectable SARS-CoV-2 RNA levels in his blood at least 40 days after resolution of coronavirus disease 2019 (COVID-19)-like symptoms. In early March, the donor had signs of upper respiratory infection, including body aches and sore throat without fever but did not seek medical attention and was not tested for SARS-CoV-2 at that time [31]. They collected index donation on April 23, 2020, after approximately 700 negative blood donations. After the donor was notified about the results and five days after the donation date, the RT-PCR assay of the donor's nasopharyngeal swab specimen showed no SARS-CoV-2 RNA. In this case, plasma viral RNA was reproducibly detected at a time point that exceeded the recommendations for deferral based on time since symptom resolution (14 days). For the authors, these results are unlikely to be false-positive given that two different regions of the SARS-CoV-2 genome were detected in separate specimens collected on the day of donation and that quality control passed on all runs, including the absence of amplification in the negative controls [31].

Del Campo et al. on August 2020, reported an allogeneic hematopoietic stem cell transplantation in a 57-year-old male from a related matched donor in the incubation period of COVID-19 where the patient did not develop the disease [32]. The donor, who was living in Brazil, traveled to Spain to start mobilization. She was asymptomatic during the medical examination before mobilization and before apheresis. The apheresis was successful, and there were no adverse effects during chemotherapy except grade 1 nausea, and no significant complications were reported during infusion [32]. On day 3+, the patient said to the medical team that the donor had a positive nasopharyngeal PCR SARS-CoV-2 test on arrival to Brazil. SARS-CoV-2 nasopharyngeal PCR tests were subsequently performed every 48 hours even though the receptor was asymptomatic. All of them resulted negative. On day 11+, the patient had febrile neutropenia. Blood and urine cultures, serology tests for bacteria, and a new nasopharyngeal swab were negative. He did not require oxygen supplementation and completed antibiotic treatment for seven days. After that, he remained afebrile, and two consecutive PCR of SARS-CoV-2 were negative. He was discharged on day 24+, and no other transplant-associated complications were reported. In the day 100+ evaluation, he remained in excellent and complete response, with a complete graft function and full chimerism. Serology tests for SARS-CoV-2 were negative both for IgM and IgG [32].

On November 13, 2020, a paper published by a team from Greece reported a case of transfusion of blood and platelets from a presymptomatic donor [33]. The donor was a 48-year-old man who donated blood on August 12, 2020, at the Hippokration Institute in Thessaloniki. The red blood cell unit from this donor was transfused on August 14 in Thessaloniki and the platelet was transfused on August 17 in Alexandroupolis, with no adverse reactions [33]. The first patient who received the red blood cell transfusion was an 86-year-old admitted to the hospital because of anemia. The second patient who received the platelet unit was a 61-year-old man diagnosed with myelodysplastic syndrome in February 2017, who achieved complete remission in October 2018 but relapsed in July 2019. In August 2020, the Hippokration Blood Institute was notified about a positive nasopharyngeal SARS-CoV-2 test in the donor. The nasopharyngeal swab testing SARS-CoV-2 in both patients was negative on August 21. Each patient was followed up for four weeks, during which they did not develop signs or symptoms of COVID-19. A second nasopharyngeal test in patient 2, seven days later, was also negative. Testing for anti-SARS-CoV-2 antibody at

week 4 was negative. The donor recovered at home with supportive care and isolation. The authors stipulate that collecting post-donation information is critical in determining whether blood and platelet transfusions from presymptomatic donors carry a risk of transmission. They suggest that blood establishments establish specific post-donation information protocols to monitor SARS-CoV-2 in donors. They concluded that transfusion with presymptomatic donors' products did not result in SARS-CoV-2 transfusion transmission even in severely immunocompromised patients [33].

In October 2020, Constantina Maria et al. published a paper about collected information on hemovigilance findings during a three-month surveillance period, from March to May 2020 [34]. The authors reported that an immunosuppressed patient had been transfused with whole blood-derived platelets from a donor subsequently diagnosed with COVID-19. The recipient exhibited no symptoms of the disease. Molecular and antibody testing results were negative. In their conclusion, hemovigilance reporting suggested the absence of transmission of COVID-19 through blood components. Asymptomatic transmission of SARS-CoV-2 remains the Achilles' heel of public health strategies COVID-19 pandemic control [34].

In Brazil, Luzzi et al. reported on October 7, 2020, the experience of their hematology and hemotherapy unit with five donors who experienced COVID-19 symptoms after donation and whose blood products have been transfused to patients [35]. The time between blood donation and COVID-19-related symptoms varied from 1 to 8 days. Two donors had the COVID-19 diagnosis confirmed by PCR, while two confirmed the infection through anti-SARS-CoV-2 immunoassays, and two had a presumptive diagnosis. Nine blood products were derived from the donations: six platelet units, one red blood cell unit, and two granulocyte concentrate. One of the nine recipients was immunosuppressed, and none presented COVID-19 related symptoms after the transfusions. One recipient with acute lymphoblastic leukemia was transfused with two granulocyte concentrates derived from two blood donors with COVID-19 in the incubation period. This patient was critically ill, but the clinical symptoms haven't worsened after transfusion, and COVID-19 RT-PCR was negative in the follow-up. The authors concluded that further evidence that SARS-CoV-2 infection is not transfusion-transmitted and that testing blood donors with immunoassays to detect anti-SARS-CoV-2 antibodies is not recommended unless the goal is to provide an epidemiological overview of the disease [35].

Statements by other authors

For Wang et al. SARS-CoV-2 is a new infectious agent, and that there are no reported cases of SARS-CoV-2 transmission by any blood product, but transfusion transmission cannot yet be excluded entirely [36].

Franchini et al. published a paper about the impact of the SARS-CoV-2 outbreak on the safety and availability of blood transfusion in Italy. The authors reported that there had been no scientifically documented evidence of the transmission of coronavirus infection through the transfusion of blood components during previous epidemics. For those authors, the current SARS-CoV-2 outbreak has stimulated further discussion on this issue, particularly on the safety of blood donation in endemic countries [37].

On April 4, 2020, Yuan et al. published the results of a predictive model to estimate the number of blood donors during the COVID-19 incubation period among 34 provincial regions in China from December 31, 2019 to March 17, 2020 [38]. They found that if all red blood cells, plasma, and cryoprecipitate were stored in isolation until the 14th day, the potential risk of SARS-CoV-2 transmission through blood transfusion was reduced by at least 65.77% after the blood donor safely passed the COVID-19 incubation period. Moreover, if the detection of SARS-CoV-2 RNA were carried out on all platelets, the potential risk would be reduced by 77.48% [38]. The authors concluded that the transmission of SARS-CoV-2 through blood transfusion is theoretically possible based on the absence of the proven virus infectivity. Considering the strong infectivity and high mortality rate of SARS-CoV-2, the occurrence of blood transfusion-mediated infectious diseases may result in interest potential for harm to recipients and society [38]. Authors proposed several strategies to decrease the risk of SARS-CoV-2 transmission through blood transfusion, such as (i) blood donors' education, (ii) strengthening of the selection criteria for COVID-19, (iii) multilevel coordination through an information-sharing system for SARS-CoV-2 infectious diseases, and (iv) the quarantine of red blood cell's plasma and cryoprecipitate until 14 days in SARS-CoV-2 severe infections regions [38]. Furthermore, they proposed detecting SARS-CoV-2 nucleic acid using RT-PCR in intense SARS-CoV-2 infection regions and the external support between severely infected and areas with minor infection [38].

According to Hashemieh's point of view, in Severe Acute Respiratory Syndrome infection (SARS), the incubation period was short, and the patients were not infectious in this period. Moreover, most infected cases with SARS-CoV had severe symptoms, and only a few asymptomatic patients have been detected [39]. The viral load of patients with SARS infection is low, and no transfusion-transmitted case has been reported [39]. Patients infected with COVID-19 might be infectious during the incubation period, and viral RNA could be isolated from plasma or serum in the first two to three days after the beginning of the symptoms [39]. The rate of infectivity during the incubation period is uncertain. Additionally, the viral load of COVID-19 in the plasma or serum of patients is not clear so far [39].

In July 2020, a literature review made by Leblanc et al. concluded that RNAemia is generally associated with a more severe disease course. Most RNAemic individuals

who are not healthy enough to donate blood further reduce the theoretical risk of transmission by transfusion [40].

Stanworth et al. published a paper about the effects of the COVID-19 pandemic on the supply and use of blood for transfusion. They stipulated that donor screening and testing strategies, the management of post-donation information for donors diagnosed with COVID-19, and changes in other transfusion practices are based on theoretical or confirmed risks of transmission. Because SARS-CoV-2 is a new virus, its potential for transfusion transmission, included by an asymptomatic viremic donor, is uncertain. For those authors, to minimize the risk of virus transmission, countries are developing guidance on the selection of donors with precautionary deferral periods following infection and symptom reporting following donation. Hemovigilance systems should be in place to monitor any potential cases of transfusion transmission [41].

Many questions remain unanswered for Basil et al. particularly how long individuals with previous SARS-CoV-2 infections should be considered ineligible for blood donation, in light of the progressive return to usual daily practice and increasing demand for blood products. For this reason, the increasing number of asymptomatic infected patients should be used as an opportunity to fill the knowledge gap regarding the transmission of the virus in the blood. The authors propose starting prospective trials by testing the recipients of blood products for SARS-CoV-2 or assessing donor blood to determine infectivity [42].

A review carried out by Kiely et al. observed that for the COVID-19 infection, an asymptomatic blood phase has not been demonstrated and that the risk of SARS-CoV-2 transfusion transmission is only a low risk because the presence of SARS-CoV-2 in the blood after the infection is brief, uncommon, and usually associated with severe forms of the disease [43]. For the authors, the most considerable risk to blood services in the COVID-19 pandemic is maintaining the sufficiency of the blood supply while minimizing the respiratory transmission of SARS-CoV-2 to donors and staff while donating blood [43].

Meyerowitz et al. published the results of a review about viral, host, and environmental factors of transmission of SARS-CoV-2 on September 17, 2020. The authors stipulated that all accumulated evidence suggests that most SARS-CoV-2 transmission route is respiratory with the virus suspended either in droplets or, less commonly, in aerosols. Sexual, fecal-oral, and blood-borne transmissions are theorized but have not been documented [44].

CONCLUSION

For years, the blood transfusion sector has been facing new epidemic outbreaks at an increasingly sustained rate. In 2020, blood centers worldwide had encountered a new challenge since the beginning of the SARS-CoV-2 pandemic because they should ensure the availability and safety of blood products.

Information issued from our literature review showed that SARS-CoV-2 is a novel infectious agent, and not sufficient data is available to exclude the virus risk of transfusion transmission with confidence. SARS-CoV-2 RNA in blood has been detected and reported with a very low viral load, and viability and infectivity of the virus were not confirmed in blood or cell donors. Reported cases of blood transfusion from donors asymptomatic on the day of donation and diagnosed as COVID-19 positive after blood donation showed no evidence of virus transmission to the recipients. At the present stage of knowledge, the novel coronavirus is no direct threat to blood safety but can impact the general blood supply. The transfusion centers' measures to minimize the theoretical risk of SARS-CoV-2 transfusion-transmission must consider the need to ensure the availability of blood products during this pandemic.

Finally, it would be appropriate to say that more powered investigations are needed to evaluate the viability and the infectivity of the SARS-CoV-2 virus in the blood or blood products in order to give even clearer answers about the transmission of this emergent virus through blood.

REFERENCES

1. Li H, Wang Y, Ji M, et al. Transmission routes analysis of SARS-CoV-2: A systematic review and case report. Front Cell Dev Biol 2020;8:618.
2. Organisation mondiale de la Santé. Transmission du SARS-CoV-2: Implications pour les précautions visant à prévenir l'infection: Document d'information Scientifique, 9 Juillet 2020. Organisation mondiale de la Santé. 2020. [Available at: https://apps.who.int/iris/handle/10665/333340]
3. Public Health Ontario. Additional Routes of COVID-19 Transmission – What We Know So Far. SYNTHESIS. 2021. [Available at: https://www.publichealthontario.ca/media/documents/ncov/covid-wwksf/2020/12/routes-transmission-covid-19.pdf]
4. Institut National de Santé Publique Du Québec INSPQ. COVID-19: Fiche épidémiologique et clinique. INSPQ. [Available at: https://www.inspq.qc.ca/publications/2901-caracteristiques-epidemiologiques-cliniques-covid19]
5. WHO Blood Regulators Network (BRN). Interim Position Paper on blood regulatory response to the evolving outbreak of the 2019 novel coronavirus SARS-CoV-2* BRN. 2020.
6. World Health Organization. Maintaining a safe and adequate blood supply during the pandemic outbreak of coronavirus disease (COVID-19): Interim guidance. 20 March 2020. World Health Organization. 2020. [Available at: https://apps.who.int/iris/handle/10665/331523]
7. World Health Organization. Guidance on Maintaining a Safe and Adequate Blood Supply during the Coronavirus Disease 2019 (COVID-19) Pandemic and on the Collection of COVID-19 Convalescent Plasma:

Interim Guidance, 10 July 2020. World Health Organization. 2020. [Available at: https://apps.who.int/iris/handle/10665/333182]
8. Update: Impact of 2019 Novel Coronavirus and Blood Safety. AABB Transfusion Tranmitted Diseases Committee. 2020.
9. Katz LM. Is SARS-CoV-2 transfusion transmitted? Transfusion 2020;60(6):1111–14.
10. Updated Information for Blood Establishments Regarding the COVID-19 Pandemic and Blood Donation. 19 January, 2021. [Available at: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/updated-information-blood-establishments-regarding-covid-19-pandemic-and-blood-donation]
11. European Centre for Disease Prevention and Control. Coronavirus Disease-2019 (COVID-19) and Supply of Substances of Human Origin in EU/EEA – First Update. Stockholm: ECDC; 2020.
12. European Centre for Disease Prevention and Control. Coronavirus Disease 2019 (COVID-19) and Supply of Substances of Human Origin in the EU/EEA – Second Update. 10 December 2020. Stockholm: ECDC; 2020.
13. Haut Conseil de la santé publique. complémentaire à l'avis des 7 et 24 février 2020 relatif aux mesures de prévention à appliquer aux donneurs de sang, produits sanguins labiles, cellules, tissus et organes ayant séjourné en zone à risque de transmission du virus SARS-CoV-2. 14 Mars 2020.
14. Haut Conseil de la santé publique. SARS-CoV-2: sécurisation des produits du corps humain. Paris: Haut Conseil de la Santé Publique; 2020. [Available at: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=839]
15. Avis 9579 - Système transfusionnel - covid19. 2020. [Available at: https://www.health.belgium.be/fr/avis-9579-systeme-transfusionnel-covid19]
16. Joint UKBTS Professional Advisory Committee (1). Position Statement: SARS-CoV-2/COVID-19 and the Safety of Blood, Tissues and Stem Cells. November 2020. [Available at: http://www.isbtweb.org/fileadmin/user_upload/JPAC_Position_Statement_SARS-_CoV-2_COVID-19_-_November_2020__3_.pdf]
17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.
18. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: A study of a family cluster. Lancet 2020;395(10223):514–23.
19. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes. Emerg Microbes Infect 2020;9(1):386–9.
20. Dres M, Burrel S, Boutolleau D, et al. SARS-CoV-2 does not Spread through extracorporeal membrane oxygenation or dialysis membranes. Am J Respir Crit Care Med 2020;202(3):458–60.
21. Morone G, Palomba A, Iosa M, et al. Incidence and persistence of viral shedding in COVID-19 post-acute patients with negativized pharyngeal swab: A systematic review. Front Med (Lausanne) 2020;7:562.
22. Corman VM, Rabenau HF, Adams O, et al. SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. Transfusion 2020;60(6):1119–22.
23. Chang L, Yan Y, Wang L. Coronaviruses disease 2019: Coronaviruses and blood safety. Transfus Med Rev 2020;34(2):75–80.
24. Cai X, Ren M, Chen F, Li L, Lei H, Wang X. Blood transfusion during the COVID-19 outbreak. Blood Transfus 2020;18(2):79–82.
25. Chang L, Yan Y, Zhao L, et al. No evidence of SARS-CoV-2 RNA among blood donors: A multicenter study in Hubei, China. Transfusion 2020;60(9):2038–46.
26. Chang L, Zhao L, Gong H, Wang L, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. Emerg Infect Dis 2020;26(7):1631–3.
27. Cappy P, Candotti D, Sauvage V, et al. No evidence of SARS-CoV-2 transfusion transmission despite RNA detection in blood donors showing symptoms after donation. Blood 2020;136(16):1888–91.
28. Kwon SY, Kim EJ, Jung YS, Jang JS, Cho NS. Post-donation COVID-19 identification in blood donors. Vox Sang 2020;115(8):601–2.
29. Cho HJ, Koo JW, Roh SK, et al. COVID-19 transmission and blood transfusion: A case report. J Infect Public Health 2020;13(11):1678–9.
30. Essa MF, Elbashir E, Batarfi K, Alharbi M. Lack of transmission of SARS-CoV-2 by platelet transfusion from a COVID-19-positive donor in a hematopoietic stem cell transplantation patient. Pediatr Blood Cancer 2021;68(2):e28658.
31. Pham TD, Huang C, Wirz OF, et al. SARS-CoV-2 RNAemia in a healthy blood donor 40 days after respiratory illness resolution. Ann Intern Med 2020;173(10):853–54.
32. Lázaro Del Campo P, de Paz Arias R, Ramírez López A, et al. No transmission of SARS-CoV-2 in a patient undergoing allogeneic hematopoietic cell transplantation from a matched-related donor with unknown COVID-19. Transfus Apher Sci 2020;59(6):102921.
33. Liapis, K, Papoutselis M, Vrachiolias G, et al. Blood and platelet transfusion from a donor with presymptomatic Covid-19. Ann Hematol 2021;100(8):2133–4.
34. Politis C, Papadaki M, Politi L, et al. Post-donation information and haemovigilance reporting for COVID-19 in Greece: Information supporting the absence of SARS-CoV-2 possible transmission through blood components. Transfus Clin Biol 2021;28(1):55–9.
35. Luzzi JR, Navarro R, Dinardo CL. COVID-19: Further evidence of no transfusion transmission. Transfus Apher Sci 2021;60(1):102961.
36. Wang Y, Han W, Pan L, et al. Impact of COVID-19 on blood centres in Zhejiang province China. Vox Sang 2020;115(6):502–6.
37. Franchini M, Farrugia A, Velati C, et al. The impact of the SARS-CoV-2 outbreak on the safety and availability of blood transfusions in Italy. Vox Sang 2020;115(8):603–5.
38. Yuan Z, Chen D, Chen X, Wei Y. Estimation of the number of blood donors during the COVID-19 incubation period across China and analysis of prevention and control measures for blood transfusion transmission. Transfusion 2020;60(8):1778–84.

39. Hashemieh M. Blood safety in SARS-CoV-2 infection. Arch Pediatr Infect Dis 2020;8(3):e104525.
40. Leblanc JF, Germain M, Delage G, O'Brien S, Drews SJ, Lewin A. Risk of transmission of severe acute respiratory syndrome coronavirus 2 by transfusion: A literature review. Transfusion 2020;60(12):3046–54.
41. Stanworth SJ, New HV, Apelseth TO, et al. Effects of the COVID-19 pandemic on supply and use of blood for transfusion. Lancet Haematol 2020;7(10):e756–64.
42. Bassil J, Rassy E, Kattan J. Is blood transfusion safe during the COVID-19 pandemic? Future Sci OA 2020;6(9):FSO626.
43. Kiely P, Hoad VC, Seed CR, Gosbell IB. Severe acute respiratory syndrome coronavirus-2: Implications for blood safety and sufficiency. Vox Sang 2020;116(2):155–66.
44. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A review of viral, host, and environmental factors. Ann Intern Med 2021;174(1):69–79.

****

Acknowledgments
The authors would like to thank all researchers, scientists, and public health professionals internationally for their efforts to share and make available their knowledge and the results of the studies they have conducted since the start of this new health crisis related to the COVID-19 pandemic. These efforts have made it possible to update all information related to SARS-CoV-2 to identify its characteristics better, including epidemiological, clinical, biological, and radiological features of the COVID-19 infection. It could make it possible to orient the implementation of appropriate measures for pandemic prevention and control.

Author Contributions
Sabah Bouhou – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mohammed Benajiba – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Azlarab Masrar – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None.

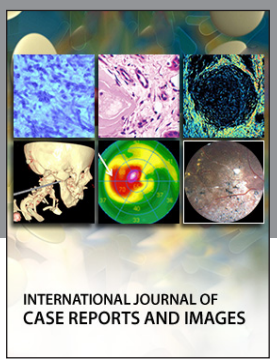
Conflict of Interest
Authors declare no conflict of interest.

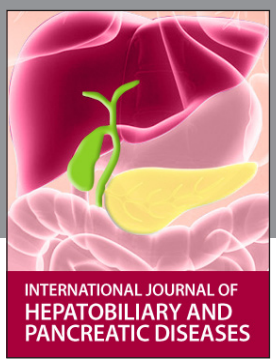
Data Availability
All relevant data are within the paper and its Supporting Information files.

Copyright
© 2021 Sabah Bouhou et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.

Access full text article on other devices

Access PDF of article on other devices





Submit your manuscripts at

www.edoriumjournals.com