



An Update on Transfusion Related Immunomodulation (TRIM) in a Time of COVID- 19 Pandemic

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Recipients' immune systems are triggered by blood and blood component therapy. Transfusion-related immunomodulation (TRIM) is a complicated immunological response to transfusion that results in immunosuppression. The mechanisms of TRIM include the presence of residual white

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blood cells and apoptotic cells, the infusion of immunosuppressive cytokines that are present in donor components or that occur during blood processing, the transfer of metabolically active growth factor-loaded particles and extracellular vesicles, and the presence of hemoglobin or extracellular vesicles binds to hemoglobin. TRIM variables include donor-specific factors and processing variables. TRIM can explain, at least partially, the controversial negative clinical results observed in patients with covid19. Many potential treatment methods have been used in clinical practice, including supportive interventions, immunomodulators, antiviral therapy, and infusion of convalescent plasma. Here, we summarize current potential treatments for COVID-19 infection-related diseases and discuss the clinical value of blood transfusion-related technologies for COVID-19 treatment in blood transfusion-related immune regulation.

Keywords: Transfusion related immunomodulation; COVID-19 pandemic; immunity; blood; recipients.

1. INTRODUCTION

Traditionally, blood or blood component therapy can elicit an immune response, which is caused by the interaction between inherited or acquired receptor antibodies and foreign antigens related to cells or body fluid components of the transfusion product of blood [1]. However, the accepted fact is that the use of blood components can have a profound negative impact on the human immune system, a situation called "transfusion-related immunomodulation" (TRIM) [2,3]. Increasing evidence indicates that TRIM represents a complex set of physiological responses, including residual white blood cells, apoptotic cells, and numerous biological response modifiers (such as cytokines, soluble mediators, and soluble HLA peptides) and extracellular-mediated / cell-derived microparticle effects. Red blood cell (RBC) blood transfusion is associated with fewer organ rejections in kidney transplant recipients, meaning that allogeneic blood transfusion has an immunosuppressive effect [4]. This phenomenon was used for treatment before effective immunosuppressive drugs were available to reduce rejection of allogeneic kidney transplantation [5]. The mechanisms of TRIM include inhibiting the activity of cytotoxic cells and monocytes, releasing immunosuppressive prostaglandins, inhibiting the production of interleukin 2 (IL2), and increasing the activity of Treg and suppressor T cells [2,6,7].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2) is a new type of zoonotic coronavirus discovered in Wuhan, China at the end of 2019. By March 2020, it had spread to more than 100 countries, and the World Health Organization declared a global pandemic. SARSCoV2 causes Coronavirus disease 2019 (COVID-19), which is characterized by a series of symptoms including

fever, cough, dyspnea/shortness of breath, sore throat, loss of smell/anorexia, nausea, diarrhea and/or mental status changes and recent confusion. Appearance [8]. Blood transfusion, which is thought to be based on the presence of neutralizing or opsonizing antibodies against the target pathogen [9]. When effective, it plays an important role by acting as a rapid source of passive transferable immunity in situations where other forms of treatment are not yet available, helping to support affected patients until they can generate their own immune response. Since PC is infused into a population of patients with a fairly high incidence at baseline, it must first be determined that its use is safe. Therefore, in this review, we will focus on the plasma treatment strategies of TRIM, COVID-19 and their effectiveness in regulating the response.

2. PATHOPHYSIOLOGY OF TRIM

Residual white blood cells and apoptotic cells White blood cells present in the blood components of may play a key role in the induction of TRIM. Of the 19 randomized controlled trials on the effects of allogeneic leukocytes in blood transfusion, 13 studied the effects of infusion of concentrated red blood cells (CRC) containing leukocytes in a surgical setting on postoperative infection and / or mortality. Compared with conflicting results from trials in other settings [9,10,11] in cardiac surgery, there is evidence that CRC containing white blood cells increases postoperative complications related to mortality [12]. There are no controlled clinical trials in tumor surgery, but several authors have suggested that whole blood and / or CRC filtered on artificial media or own plasma, or CRC with reduced leukocytes and buffy coat may reduce postoperative immunity inhibition. The use of autologous blood is also expected to minimize the risk of perioperative blood transfusion, but studies unexpectedly show that patients who

received autologous blood before surgery and those who received allogeneic blood had similar postoperative infection complications and rates of infection, cancer recurrence and / or survival. [13,14]. Two mechanisms of TRIM have been proposed: one is HLA-dependent and targets adaptive immunity; the second is mild and non-specific and targets innate immunity [15]. Leukopenia before storage of RCC units is now a routine procedure and is implemented nationwide in many countries to avoid accumulation of biologically active substances released by leukocytes participating in TRIM. The beneficial effects include reducing the risk of febrile transfusion reactions, CMV transfusion transmission, alloimmune platelet tolerance, etc., but there are still some unresolved problems because not all white blood cell populations are reduced to a similar level [16]. In addition, cardiac surgery and other types of patients may have problems related to mortality and organ dysfunction [15]. The few live leukocytes remaining after leukopenia and possible EV can still modulate the receptor's immune response [17]. In aging units of leukopenia, the concentration of cytokines remains very important [18]. Furthermore, exposure of the leukopenia storage RCC supernatant to whole blood triggers the release of IL6, IL10, and TNF [14], reduces lipopolysaccharide-induced TNF release from monocytes [19], and induces cell activation [20]. In humans, Treg cells represent approximately 1-2% of circulating CD4 + T helper cells. They jointly express a very high density of IL2 receptor alpha (CD25hi), inhibit IL2 production, and inhibit the Th1 response function of CD4 + and CD8 + T cells [20] Treg cell activation is not antigen-specific, because it can be caused by LPS and lead to immunosuppression through the Toll-like receptor 4 pathway [21]. Red blood cell storage damage (RSL) is a complex biological phenomenon that involves a decrease in quality and can lead to TRIM. Therefore, non-specific effects may be due to the infusion of apoptotic blood cells, because there is strong evidence that apoptosis changes occur during cold storage [22]. The immunosuppression caused by apoptotic cell infusion may be related to transforming growth factor β (TGF α), which is usually present in the mitochondrial space of leukocytes and platelet α particles, and is released when the cell membrane is ruptured or activated [23,24]. Perhaps more important than the injected TGF α is the injection of apoptotic cells themselves. Apoptotic cells express phosphatidylserine (PS) on their surface [25].

The expression of PS by apoptotic cells facilitates its uptake by phagocytes (such as macrophages or conventional dendritic cells), induces the secretion of anti-inflammatory cytokines (such as IL10 or TGF α), and inhibits inflammatory cytokines (such as IL12). Secretion of IL1 α , IL6 and TNF [1,26,27].

This phenomenon has been used for treatment before effective immunosuppressive drugs can be used to reduce renal transplant rejection [5]. The mechanisms of TRIM include inhibiting the activity of cytotoxic cells and monocytes, releasing immunosuppressive prostaglandins, inhibiting the production of interleukin 2 (IL2), and increasing the activity of Treg and suppressor T cells [2,7,8].

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3. INFLAMMATORY MEDIATORS

Although TGF α plays a central role as a transfusion-related inflammatory/immunosuppressive cytokine and secondary cytokines released after phagocytosis by apoptotic cells, red blood cells also contain non-polar lipids and pro-inflammatory lysophosphatidyl bile A mixture of bases (lysoPC) [22,28]. LysoPC regulates the activity of natural killer T (NKT) and T cells [28], acts as a chemoattractant for NK cells, induces

the maturation of dendritic cells, and stimulates the production of pro-inflammatory cytokines [29,30]. Eicosanoids (prostaglandins, thromboxanes, and leukotrienes) can also accumulate in CRC [31]. The general effects of these biological agents are immunosuppression and tumor promotion [32,33].

4. MICROPARTICLES

A heterogeneous population of microparticles [MP; also called extracellular vesicles, EV] produced by blood cells and tissues. They are microvesicles with a diameter of about 50 nm to 1 μ m [34]. Under normal physiological conditions, MPs are continuously shed into the circulatory system from the cell membranes of all living cells, including megakaryocytes, platelets, red blood cells, white blood cells, and endothelial cells. MP clearance can also be triggered by pathological activation of inflammatory processes and coagulation, fibrinolysis, activation of the complement system, and even shear stress in the circulation [34]. Therefore, in vitro processing of blood into its components during blood separation, centrifugation, pathogen reduction, surface contact, and storage is expected to increase the already variable amount of PM per unit of donor. Structurally, MP has a double layer of phospholipids, exhibiting highly negatively charged PS coagulation activity and expressing several membrane receptors [35,36]. From a physiological point of view, they transport biologically active molecules such as lipids, proteins or nucleic acids between cells, therefore, when infused, they can transfer genetic information (such as miRNA) to immunocompetent cells that have an immunomodulatory effect [39]. RCC has been shown to contain mixed PM groups, and not all PM comes from red blood cells. The concentration and composition of different electric vehicles (electric vehicles containing red blood cells and electric vehicles without red blood cells) and their effects on the quality of blood products vary depending on the manufacturing method used by the production unit of red blood cells. But the data is affected by methodology.

5. USE

There have been studies on the immunomodulatory potential of EVs derived from blood products in blood transfusion medicine [13,37]. EV can promote the initiation of neutrophils and activate and promote

inflammation in patients with older blood transfusions [38]. It has also been shown that platelet-derived MPs expressing CD40L can signal B cells to mimic the production of immunoglobulin G (IgG) and recruit adaptive immune responses to support CD4 + T cells [39-41]. Unstable blood components also contain PS-expressing vesicles from apoptotic cells. Alternatively, EVs expressing PS may also come from contaminated cells, such as white blood cells, or may already be present in plasma, such as platelet-derived MP (PMP). Most CCR and plasma contain residual platelets. After processing and storage, they release large amounts of biologically active TGF and RANTES, although the immunologically measured concentration is usually used as an indicator of process and product quality [38]. Therefore, they can affect early physiological defense mechanisms, such as inflammation or coagulation, and trigger the production of tissue factor (TF) [42]. In addition, electric vehicles can enhance the production of chemokines and cytokines, stimulate T cell proliferation, and induce monocytes to produce tumor necrosis factor (TNF) [43,44]. In addition, platelet-derived MP can contain a variety of growth factors, including VEGF and TGF α , and TGF β , which can interact directly or indirectly with the immune system [45,46]. Understanding the immunomodulatory effects of each type of EV on the CRC unit can help describe their potential role in poor blood transfusion outcomes [15].

6. FREE HAEMOGLOBIN BOUND TO EV AND NON-HAEME IRON

As red blood cells in RCC age under low-temperature storage conditions, metabolic components are depleted, cell membranes are destroyed, EV formation, and haemoglobin is released in the form of free hemoglobin or EV-bound hemoglobin in the surrounding environment [46,47]. In the circulation, acellular haemoglobin and EV combined with hemoglobin react with vasodilator nitric oxide (NO), increasing NO consumption, leading to vasoconstriction, hypertension, and vascular damage, and can aggravate inflammation after a blood transfusion [46,48]. In massive blood transfusions, EV-bound free hemoglobin molecules can cause multiple organ dysfunction and mortality [49-50]. EV-bound hemoglobin is more effective in reducing circulating NO than free hemoglobin because it is not removed by haptoglobin after blood transfusion [48]. Furthermore, EV in the stored RCC unit can

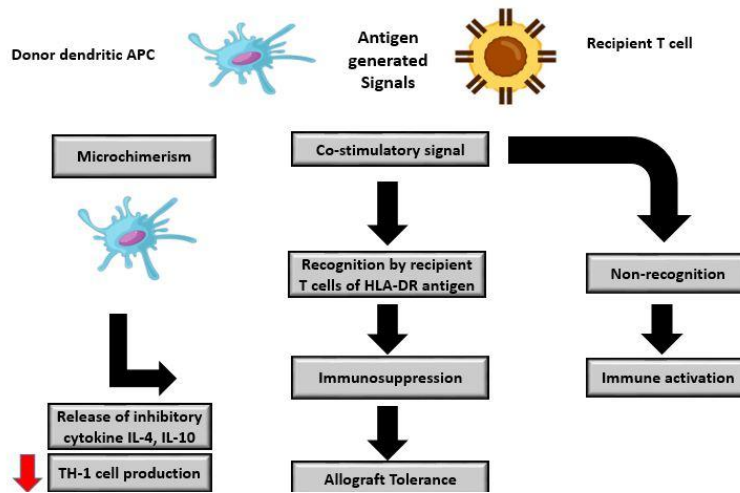


Fig.1.Cell-associated mechanisms of transfusion-related immunomodulation demonstrated, with interaction between recipient white cell and human leucocyte antigen class II-bearing donor dendritic antigen-presenting cell [54]

promote the biological activity of inflammatory chemokines when they interact with platelets in the body [45].

Hemolysis of stored red blood cells results in increased availability of unbound iron to heme, which inhibits macrophage activation. Iron compounds in stored blood and plasma inhibit the activation of THP1 monocytes [51]. This means that the potential but unproven adverse effects of old RBC units may be due to inadvertent administration of free hemoglobin and EVs combined with hemoglobin, which improves NO clearance and alters microvascular flow. Free hemoglobin has other effects, such as renal tubular toxicity and iron delocalization, that can affect redox balance, microbe killing, or intracellular signaling [52]. Finally, in addition to acting as a mediator of vascular tension, nitric oxide has other functions [53].

Therefore, many biological and environmental factors appear to affect stored RCC, including factors that may be related to donor and compound processing and storage.

7. CLIP SIGNAL

Despite our lack of understanding of the exact mechanism of TRIM, infused allogeneic leukocytes (WBCs) appear to be responsible for most of the observed or hypothetical TRIM effects. TRIM cell-related mechanisms include cells bearing dendritic antigens from HLA class II donors, representing allogeneic WBC-related

cells that are transfused. This cell-related mechanism is shown in Fig. 1. [54].

8. TRANSFUSIONRELATED TREATMENTS USED IN PATIENTS WITH COVID-19

The pathogenic mechanism of SARSCoV2 is complex and a multidisciplinary, comprehensive treatment approach should be used to account for the different pathogenic mechanisms. Infection with SARSCoV2 can induce adaptive humoral and cellular immune responses, and patients exhibit stronger immunity after recovery. As the epidemic is still ongoing, little information is available regarding the status of the immune system after 2019nCoV infection. Antibodies have been detected in the serum of some patients in the late stage of SARSCoV2 infection, and serum IL2, IL7, IL10, GCSF, MCP1, MIP1A and TNF α levels are higher in patients with severe disease than in patients with mild disease. SARSCoV2 isolated from one patient with severe COVID19 can be neutralized by serum from several other patients with COVID-19. The current transfusionrelated technologies that can be applied to COVID19 therapy include convalescent plasma therapy, plasmapheresis and mesenchymal stem cell therapy [53].

9. CONVALESCENT PLASMA THERAPY

There is currently no specific effective drug against COVID-19. Some drugs that are believed

to have virusinhibiting effects are currently being tested in clinical trials. Convalescent plasma from patients who recovered from COVID-19 contains specific antibodies that can effectively treat SARSCoV2 infection[55]. The premise of convalescent plasma treatment is that it is most effective in patients with a high viral titer, so it is suitable for patients with rapid disease progression or who are severely or critically ill[56]. Convalescent plasma may aggravate lung injury in patients with multiple organ failure, and they may experience severe adverse reactions to blood transfusion, so they should not be infused [55]. Patients should be infused with convalescent plasma early in the course of the disease when the body has not yet produced IgG antibodies[57]. After infusion, the body obtains high levels of IgG antibodies that neutralize the virus, decrease repeated stimulation of the immune system by killer T cells, improve the humoral immune response, prevent cytokine storms and shorten the course of disease[58]. COVID19 is not the first viral infection to be treated with convalescent plasma. SARSCoV, MERSCoV, Ebola virus and H1N1 infections have all been treated with convalescent plasma [59]. In 2009, a study in Hong Kong, China showed that treating patients with severe H1N1 infection with convalescent plasma containing antibody titers $\geq 1:160$ can significantly reduce respiratory viral load and mortality [60]. During the Ebola outbreak, convalescent plasma was used to treat two infected American medical personnel [61]. Ko et al. showed that convalescent plasma containing antibody titers $\geq 1:80$ is effective in treating MERSCoV infection [62]. A retrospective metaanalysis of 32 cases of SARSCoV infection showed that early use of convalescent plasma therapy after symptom onset can reduce mortality [59]. Convalescent plasma treatment of COVID19 requires attention to plasma donation standards, timing of infusion and evaluation of efficacy. Convalescent plasma donation standards are as follows: (1) The donor must have recovered completely and have no residual SARSCoV2 in the body; pharyngeal swabs, sputum, alveolar lavage fluid, blood and stools must all be negative by nucleic acid test; (2) Donors have produced high titers of protective antibodies, namely SARSCoV2-specific IgG antibodies. Convalescent plasma with an antibody titer $\geq 1:160$ or $\geq 1:320$, if possible, has the best effect. The presence of IgM antibodies indicates recent viral infection, viral replication or residual virus, so convalescent plasma that is strongly positive for or has high titers of IgM antibodies should not be used for

clinical infusion; (3) The donor's physical condition must meet basic blood donation standards and tests for hepatitis B surface antigen, hepatitis C antibodies, AIDS antibodies and Treponema pallidum antigens must be negative; (4) Donors must provide informed consent indicating that they are willing to donate plasma[55]. After being stimulated by viral antigens, the body mounts an initial immune response, with an incubation period of about 10 days, and then produces lowaffinity IgM and IgG antibodies. When the immune insult is repeated, highaffinity IgG antibodies are quickly produced. Theoretically, the best time to infuse patients with convalescent plasma is in the early stage of the disease, when IgG antibodies have not been produced, the nucleic acid test is strongly positive, and the viral load is high[63]. Given that the antigenantibody reaction time is approximately 24 h, 24–48 h after infusion of convalescent plasma is likely the best time to evaluate treatment efficacy [12]. The indicators used to evaluate efficacy include clinical symptoms, laboratory indicators, lung imaging, and nucleic acid detection.

10. PLASMAPHERESIS

Plasmapheresis involves using a blood component separator to separate the plasma from the patient's whole blood. The plasma, which contains the pathogenic substances, is discarded, and the other blood components are returned to the patient, supplemented with replacement fluids such as fresh frozen plasma or human blood albumin. SARS and MERS were treated with plasmapheresis therapy [64-66]. Using plasmapheresis to treat patients with COVID-19 removes excessive cytokines and prevents the "cytokine storm," thereby reducing damage to the body. Additionally, plasmapheresis plays an important role in blocking and reducing free radical damage. Plasmapheresis is a routine procedure conducted by blood transfusion departments; therefore, blood transfusion departments have a technical advantage in treating patients with COVID-19[67-70].

11. MESENCHYMAL STEM CELL THERAPY

Mesenchymal stem cells have immunomodulatory effects in that they prevent uncontrolled mass production of cytokines or inflammatory factors, inhibit excessive immune responses, and reduce immune damage to

tissues and organs. Mesenchymal stem cells not only play a role in suppressing immune injury through immunomodulation, but also replace and repair damaged tissue and inhibit lung fibrosis. Treating COVID-19 with mesenchymal stem cells has achieved good results [70]. Stem cell therapy can suppress excessive activation of the immune system, promote endogenous repair by improving the microenvironment, slow the progression of acute lung inflammation and relieve the symptoms of respiratory distress. Initial reports show that this is a safe and effective treatment for patients with COVID-19.

12. TRANSFUSION REACTIONS RELATED TO CONVALESCENT PLASMA THERAPY COVID-19 AGAINST SARSCOV2

Convalescent or hyperimmune plasma is extracted from patients infected with COVID-19, these patients have overcome the disease and have produced sufficient titers of antibodies against the pathogen. When injected into the recipient's body, it can promote the binding of the virus to the pathogen and promote its phagocytosis. Infusion of hyperimmune plasma allows faster immunization in infected individuals, thus shortening the disease or reducing its symptoms, so it must be administered on the first day of disease progression. 3 Like all other blood products, hyperimmune plasma can cause transfusion reactions, including allergic reactions, hemolysis, circulatory overload, and transfusion-related acute lung injury. Based on published data, the incidence of serious adverse reactions so far is very low (<1%) [71].

According to 2 cases of young male patients admitted to the intensive care unit (ICU) for COVID-19 infection, transfusion reactions occurred after transfusion of anti-COVID-19 hyperimmune plasma and blood transfusion-related immune regulation was observed.

Case 1. 48-year-old Colombian male with symptoms compatible with COVID-19 infection and positive CRP. He was admitted to the emergency room due to respiratory distress. After being admitted to the ward, his breathing deteriorated and he was transferred to the ICU. Remdesivir 200 mg was used at the beginning of treatment, then 100 mg every 24 hours and dexamethasone 20 mg every 24 hours. After administering two bags of hyperimmune plasma, he developed an urticarial reaction on his face and trunk, shortness of breath and decreased

saturation, and needed to increase oxygen concentration and flow. Treatment with dexchlorphenamine 5 mg every 8 hours was started and the skin lesions disappeared after 24 hours. The patient then performed well, stopped high-flow oxygen therapy (OAF), and was discharged back to the ward [72].

Case 2. A 45-year-old male from Cameroon. Due to the clinical deterioration in the case of SARSCoV2 infection, he went to the emergency department. He was admitted to the ward, where he showed poor evolution and needed to be admitted to the ICU. At the start of treatment, OAF and dexamethasone 20 mg, remdesivir (loading dose 200 mg, 100 mg every 24 hours) and hyperimmune plasma every 24 hours were used to produce itchy urticaria on the body and in the vein. After an injection of 10 mg dexchlorpheniramine, decreased. The course went well and he was discharged [72].

Hyperimmune plasma therapy is a promising option for the treatment of severe COVID19 pneumonia. Allergic reaction after administration is uncommon, and the possible relationship to the different antigen load of the administered plasma and the severity of the immune response is currently unclear [72].

Although our study did not find a difference in the levels of inflammatory cytokines between the positive and negative transfusion response groups, there are many other innate immune activation mechanisms in COVID-19, as evidence of activation and pyrolysis of the inflammasome, activated CD14⁺ 16⁺ monocytes, 43 as well as neutrophil activation and deployment and extracellular neutrophil traps [73-76]. COVID-19 patients may represent a group of people preparing to activate lung neutrophils, similar to the mechanism proposed for type II TRALI [77]. Studies involving patients with sickle cell anemia and autoimmune diseases have evidence that the higher incidence of initial inflammation in these patients is associated with a higher likelihood of formation of alloantibodies [78-81]. Similarly, the higher transfusion reaction rate observed in PC recipients may be due to the recipient's presensitization state, and this hypothesis deserves further study. Although it is not surprising that patients with severe illness are more likely to have a blood transfusion reaction due to their higher initial inflammatory state, our results show that it has nothing to do with cytokine levels, such as IL6, IL1 β , or TNF α . One possibility is that patients with more severe

illness are more susceptible to possible immunomodulatory effects associated with blood transfusions, a phenomenon traditionally associated with red blood cells, but there is evidence that they are also present in plasma transfusions [82]. Plasma transfusion can cause a delay in the innate immune response.

Perhaps the most unexpected association found in our study is the association between the transfusion reaction and type B blood group based on the analysis of blood transfusion events. Two studies, one of which is a preliminary study of more than 750,000 people, appear to support an association between non-O blood type and an increased risk of SARSCoV2 infection, suggesting that O blood type may play a role (protector) [83,84]. Although another study of more than 7,600 patients did not reproduce this effect, it found that the chances of being positive for the COVID19 polymerase chain reaction of blood types B and AB were increased [85]. However, the distribution of ABO types in the population we analyzed (48.6% group O, 35.0% group A, 13.1% group B, 3.3% group AB) largely reflects the general distribution from United States. In addition, 413 of 427 blood transfusions (96.7%) were the same as ABO, and the remaining 14 times were ABO-compatible in 427 blood transfusions (3.3%). Therefore, the possible role of anti-ABO hemagglutinin in response chances cannot be assessed here. One possible explanation in the existing literature may come from the study of SARSCoV1, which has determined that the SARSCoV1 spike protein contains N-linked glucans similar to ABO antigen, increasing the possibility of cross-reaction with ABO haemagglutinin [86]. Furthermore, high titer anti-A antibody levels have been shown to confer relative resistance to SARS CoV1 infection by inhibiting the SARS CoV1 spike protein and its receptors, but titer anti-A levels low do not. It is well known that the SARSCoV2 spike protein targets the same angiotensin-converting enzyme 2 receptor as SARSCoV1 [87-88]. As we all know, the anti-A titer of group B patients is usually lower than that of group O patients, and they also lack anti-A and B antibodies. We can speculate that this part of the patients (in our study accepted only plasma from group B) may represent a low-titer group that is more prone to worsening disease symptoms after blood transfusion, although these data cannot be used for testing. However, we noticed that we did not observe any association with group A receptors, and group A receptors were associated with

increased disease severity in other studies [12,89-92]. In addition, the number is small.

13. CONCLUSIONS AND FUTURE PERSPECTIVES

However, from the perspective of transfusion reactions, no serious or life-threatening reaction has demonstrated the short-term safety of PC infusion in patients with COVID-19. Although it is clear that further corroborating studies are needed, we have initially identified several previously uncharacterized risk factors for transfusion reactions, which may prompt the blood transfusion team to initially consider the potential risks of reaction in certain patients during blood transfusion of blood. Our findings raise interesting questions about the characteristics and mechanisms of CP during blood transfusion in different recipient populations and serve as the basis for future research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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