Efficiency and safety of convalescent plasma therapy in patients with COVID-19: a systematic review

Эффективность и безопасность применения плазмы реконвалесцентов у пациентов с COVID-19: систематический обзор

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Abstract

INTRODUCTION. High mortality during the pandemic of COVID-19 conducted the research for all available treatments. Convalescent plasma (CP) has become valuable empirical resource for health support, especially during the initial phase of COVID-19 pandemic. It still draws attention of many scientists, while data on the effectiveness of CP is rather controversial. **OBJECTIVES.** The purpose of this review is to analyze the results of modern studies on the efficacy and safety of the clinical use of CP. **MATERIALS AND METHODS.** The search for publications was carried out in electronic databases PubMed, MedRxiv, Cochrane Library, Cochrane COVID-19 study registry from June 7, 2021 to December 20, 2021. **RESULTS.** The article analyzes data from recent retrospective and prospective studies related to CP therapy. The use of CP is known since the 1880s in the treatment of diphtheria, Spanish flu, measles, polio. In the 21st century CP has been used in the epidemic of Ebola, H1N1pdm09, other SARS1 and MERS coronaviruses. CP therapy is based on the concept of passive immunization and includes the infusion of antibodies from convalescent donors with virus-neutralizing activity (VNA). Pathogen reduction technologies are used to minimize the risks of transfusion-transmitted infections. Historical and current data confirm the safety of CP use. The criteria for effectiveness and timing for transfusion of the CP were considered. Clinical data is presented confirming the effectiveness of CP in certain groups of patients. **CONCLUSIONS.** The use of CP is safe and reasonable in seronegative patients with COVID-19 on the early stages of the disease or in the presence of an immunodeficiency. CP with high VNA titers has the highest efficiency. CP therapy in severe patients on the late stages of the disease does not provide disease regression and increased survival.

Реферат

АКТУАЛЬНОСТЬ. Темпы развития пандемии новой коронавирусной инфекции COronaVIrus Disease 2019 (COVID-19) и высокая летальность обусловили необходимость поиска всех возможных методов лечения. Реконвалесцентная плазма (РП) стала ценным эмпирическим ресурсом для поддержки здравоохранения, особенно на начальном этапе пандемии COVID-19. Она по-прежнему остается объектом внимания многих ученых, в то время как данные относительно эффективности РП являются достаточно противоречивыми. **ЦЕЛЬ ИССЛЕДОВАНИЯ.** Целью настоящего обзора является анализ результатов современных исследований по эффективности и безопасности клинического применения РП. **МАТЕРИАЛЫ И МЕТОДЫ.** Обзор литературы был проведен в электронных базах данных PubMed, MedRxiv, Cochrane Library, Cochrane COVID-19 study registry с 7 июня 2021 г. по 20 декабря 2021 г. **РЕЗУЛЬТАТЫ.** В данной работе выполнен обзор основных сравнительных ретроспективных или проспективных исследований по применению РП. Применение РП известно с 1880-х гг. при лечении дифтерии, испанского гриппа, кори, полиомиелита, а в XXI в. РП использовали при эпидемии лихорадки Эбола, вируса гриппа H1N1, других коронавирусах. Терапия РП основана на концепции пассивной иммунизации и включает в себя введение антител от доноров-реконвалесцентов, обладающих вирус-нейтрализующей активностью (ВНА) к данному вирусу. В целях минимизации рисков гемотрансмиссивных инфекций используются технологии редукции патогенов. Исторические и текущие данные об использовании РП подтверждают безопасность ее использования. Были рассмотрены критерии эффективности применения и сроки назначения РП. Представлены клинические данные,

подтверждающие эффективность РП у определенных групп пациентов. **ВЫВОДЫ.** Применение РП является безопасным и целесообразно у серонегативных больных с COVID-19 на ранних сроках заболевания или при наличии иммунодефицитного состояния. Наибольшей эффективностью обладает РП с высокими титрами ВНА. У тяжелых больных на поздних сроках болезни терапия РП не приводит к регрессии заболевания и увеличению выживаемости.

KEYWORDS: COVID-19, SARS-CoV-2, convalescent plasma therapy, systematic review

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Introduction

A new strain of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) began to spread from Wuhan Province of China at the end of 2019. The strain gives rise to COronaVIrus Disease 2019 (COVID-2019), an infectious disease. The World Health Organization (WHO) announced a pandemic of COVID-19, a novel coronavirus infection, on March 11, 2020. By that moment, it was well-known that the virus was highly contagious, and the disease progression resulted in the development of pneumonia in some cases and even had fatal outcomes.

The pandemic development rate and the high mortality rate were responsible for the necessity to find all possible methods of treatment. All the potentially effective methods of treatment were discussed under the conditions of insufficient specificity of antiviral therapy. The administration of convalescent plasma (CP) has been known since the end of the 19th century, and it has been successfully used in previous epidemics. The rapidly developed program to manufacture and use CP became a valuable empirical resource to support health care service in the treatment of the disease, in particular at the early stage of the COVID-19 pandemic, which was evidenced in national guidelines and those for the treatment of COVID-19 including in the Russian Federation [1, 2]. Nevertheless, CP remains the object of interest for many scientists, and many articles and clinical trials devoted to using and effectiveness of CP are sufficiently controversial (Table A1). The present review aims to analyze the results of current studies on the efficacy of clinical use of CP.

Materials and Methods

Search Strategy and Selection Criteria

Clinical trials published on preprint servers or peer-reviewed journals, in which the administration of CP in treatment

of COVID-19 was studied, were identified as a result of the search in the following online databases: PubMed, MedRxiv, Cochrane Library, and Cochrane COVID-19 Study Registry — during the period from June 7, 2021 to December 20, 2021. Eligibility criteria should be full-text articles over the last 15 years; the publication status should be published; keywords used in the search were convalescent plasma, COVID-19, or SARS-CoV-2. To be considered eligible for inclusion, studies should include COVID-19 patients, use CP as a method of treatment, and report mortality. To describe the search strategy, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used.

Study Selection and Selection Criteria

Comparative retrospective or prospective studies containing control groups were selected for the analysis. Mortality was identified as an interesting outcome. Articles not published in English, not available in full text, or review articles without study results were excluded from this analysis.

Data extraction was carried out using standardized forms including general information (first author, year, and country), a sample size, a study design, as well as patients' age and gender. Additional information included disease severity, terms of CP transfusion relating to the disease onset, the volume of the CP dose, an antibody titer, and adverse events.

An initial search in the electronic databases identified 1,427 articles. In total, 1,185 potential studies were identified after removing duplicates. After screening, the number of studies was reduced to 140. After that, the articles were thoroughly evaluated in terms of the acceptance criteria. Following the evaluation, 29 full-text articles were obtained, which are included in the review (Fig. A1).

CP Administration Background

The history of passive antibody therapy traces its origin to the 1880s in the treatment of diphtheria, and in some cases, plasma was the only treatment method for some infectious diseases until antimicrobial therapy was developed in the 1940s [3–5]. German scientists used serum from recovered animals who were immunized against diphtheria to treat patients with this disease. At the beginning of the 20th century, CP was administered during the Spanish flu, measles, and poliomyelitis epidemics.

Extensive experience was accumulated by the domestic public health service on using antibacterial immune plasma, which were widely used to treat purulent-septic complications in patients in surgical and traumatological hospitals [6].

Convalescent serum was also successfully used in the Ebola epidemic in Africa in 2013 and the H1N1 influenza virus epidemic. A small non-randomized study performed by J.S. Zhang et al. revealed a significant increase in survival in those who received convalescent whole blood compared to those who received standard treatment [7].

In the 21st century, two other epidemics with coronaviruses were associated with high mortality: severe acute respiratory syndrome coronavirus (SARS-CoV-1) in 2003 and Middle East respiratory syndrome-related coronavirus (MERS-CoV) in 2012. In both outbreaks of the diseases, high mortality and lack of effective treatment methods led to using CP that contained neutralizing antibodies to the corresponding virus [8].

The largest study devoted to using CP before the current pandemic included 80 patients [4]. Patients treated before Day 14 had an improved outcome as measured by hospital discharge before Day 22 (58.3 *vs*. 15.6 %; $p < 0.01$) confirming the concept that earlier administration of this therapeutic method was more effective.

Three patients with MERS-CoV in South Korea were treated with CP; although, only two recipients were subsequently found to have neutralizing antibodies in their plasma [9]. A recent study raised the problem of using CP, as some convalescents may not have high viral neutralization activity (VNA) titers [10]. When analyzing 99 MERS-CoV convalescent serum samples, 87 had VNA with a geometric mean titer of 1 : 61. This suggests that the antibodies titer decreases over time, and only a few patients have a pronounced immune response with high VNA titer as well.

A meta-analysis to evaluate the clinical efficacy of CP or convalescent serum in the treatment of acute viral respiratory infections was carried out in 2015 [11] to help in the clinical management of MERS-CoV infection. Although the studies analyzed were considered to be of poor quality, without control groups, and with a moderate or high risk of bias, the authors concluded that plasma or serum from immunized patients could be safely administered since a reduction in the number of hospitalizations and a reduction in mortality were recorded.

Possible CP Action Mechanisms

According to WHO guidelines, the administration of CP for the treatment of diseases characterized by epidemic outbreaks and lack of specific treatment methods is based on the concept of passive immunization [12].

Using CP is also possible for the manufacture of immunoglobulin concentrates.

Passive immunization includes the administration of antibodies from convalescent donors having VNA to the virus to prevent or treat the disease caused by the virus. However, other immune defense mechanisms associated with using CP, such as antibody-dependent cellular cytotoxicity and phagocytosis, are possible.

Among the possible mechanisms of action other than VNA, plasma probably has immunomodulatory effects due to the complement system, cytokines, and other factors contained in it [13].

One possible explanation for the CP efficacy is the suppression of viremia by antibodies contained in plasma. Most commonly, the peak of the viral load is accounted for the first week of infection and the patient develops a primary immune

response between Days 10–14 followed by viral elimination. The general principle of passive antibody therapy is that it is more effective when administered at the early stage after the onset of the first symptoms of the disease. The reason for changing efficacy over time is unclear. Probably, the original virus pool is neutralized, which is probably much smaller at the early stages of the disease than at its later stages. Another explanation lies in the fact that antibodies act by altering the inflammatory response, which is also easier during the initial stage of the immune response and may be asymptomatic [14]. For example, passive antibody therapy in pneumococcal pneumonia was most effective when administered soon after the onset of the first symptoms, and no effect was if antibody administration was delayed after the third day of the disease [15].

Known Potential Risks

Historical and current data on using CP implies the safety of its transfusion. Available data suggest that serious adverse events following the administration of CP occur rarely and confirm the risks associated with transfusion of standard fresh frozen plasma for other indications. These risks include transfusion-transmitted infections, allergic reactions, anaphylactic reactions, febrile non-hemolytic reactions, transfusion-associated lung injury, transfusion-associated cardiac (circulatory) overload, and hemolytic reactions. COVID-19-related lung injury further complicates the differential diagnostics of these conditions and can increase the risk of transfusion-related reactions in these critically ill patients. Although the incidence of post-transfusion reactions among critically ill patients can be expected to be around 10%, current data demonstrate that the overall incidence of reported serious adverse events associated with CP transfusion is less than 1% [16]. To minimize the risks of transfusion-transmitted infections, pathogen reduction technologies are obtained. Donors should strictly comply with the requirements for whole plasma use donation and regular plasma donation, except for the current COVID-19 disease.

Additional risks of CP transfusion include the hypothetical risk of antibody-dependent enhancement (ADE) of SARS-CoV-2 infection and the hypothetical risk of long-term immunosuppression.

The ADE phenomenon can be observed in several viral diseases and implies an enhancement of the disease in the presence of certain antibodies in the blood or an antibody-mediated pro-inflammatory effect. In the case of coronaviruses, several ADE mechanisms were described, and hypothetically, there is a possibility that antibodies to one strain of coronavirus may enhance the infection caused by another viral strain [17]. There are reports of ADE in monkeys (macacos) who were administered anti-SARS-CoV-1 antibodies before experimental SARS-CoV-1 infection [18] and of the effects of ADE with other coronaviruses [19]. There is also fear that the administration of antibodies to individuals with significant viral load may result in the formation of antigen-antibody immune complexes that may facilitate a hyperimmune response [20, 21].

Because the intended use of CP in fighting against the COVID-19 epidemic is based on using high VNA titers against the same SARS-CoV-2 virus, the likelihood of ADE is not high.

Another hypothetical risk lies in the fact that the administration of antibodies to patients infected with SARS-CoV-2 may obstruct spreading the disease, but at the same time, it makes active immunization difficult, which will result in a risk of re-infection. In this context, it is reported that passive immunization before vaccination against the human respiratory syncytial virus weakened the humoral but not cell-mediated immune response [22].

According to the analysis performed by M.J. Joyner et al. of the first 5,000 patients with severe and critically ill COVID-19, the overall frequency of severe adverse events that developed within 4 hours after CP transfusion was less than 1% (n = 36), and the 7-day mortality was 14.9% [16].

While 70% of these adverse events were considered by attending physicians to be related to plasma transfusion, the majority of the events (56%) were considered to be possibly related indicating uncertainty regarding the role of the transfusion of it in the development of such adverse reactions. In addition, the incidence of serious adverse events definitely related to transfusion was objectively low (n = 2, < 0.1% of all transfusions).

Current Studies and Efficacy Criteria

At the onset of the pandemic, evidence of CP efficacy and safety was typically limited to case reports and small studies [23–27].

However, randomized clinical trials are necessary to prove the therapeutic efficacy of CP in patients suffering from COVID-19. Under the pandemic conditions, it is psychologically extremely difficult to maintain a control group to whom a placebo would be administered, as some studies reported [28].

Nevertheless, data from multicenter randomized trials with starkly differing views on the efficacy of using CP appeared at later stages. The final consensus on using CP in patients hospitalized with COVID-19 varies in different countries.

One of the components of efficacy associated with the treatment with CP is a VNA titer, which is repeatedly mentioned by the authors of foreign studies [9, 29]. Domestic authors also described the peculiarities of donor recruitment and the results of impact of pathogen-inactivation methods on VNA titers [30, 31]. For example, the reduction of pathogens by methylene blue or amotosalen provides a greater probability of preserving the immunological properties of CP compared to riboflavin [31]. But these peculiar properties are not indicated in all studies conducted in the world, and the effectiveness of the use directly depends on many manufacturing parameters of CP. The heterogeneity of research results in the world may be partly due to the peculiarities of plasma procurement in different countries and regions, requirements for recruiting

donors, pathogen inactivation methods, and methods for determining an antibody titer.

The WHO also emphasized the importance of standardized processes and quality control based on laboratory testing, selection of clinical indications, and the establishment of a program to recruit the relevant number of donors and maintain sufficient supplies of CP [12].

For example, most scientists exclude from the analysis the study performed by A. Agarwal et al. because most patients (~70 %) received CP with low VNA titers less than 1 : 80, and about 30 patients received plasma with an undetectable antibody titer at all [32].

The timing for transfusion is another factor related to plasma efficacy. The scientific rationale for the therapeutic effect of passive immunotherapy in other coronaviruses suggests that CP is more effective if it is administered as early as possible after the onset of the disease.

It is very important to understand and establish a target group of recipients who will have an effective use of CP.

At the beginning of the pandemic, people considered CP as rescue therapy, and several investigators used plasma in the later stages of the disease and in the most severe groups of patients.

Following the number of studies, it may be concluded that using CP in critically ill patients on mechanical ventilation and in the late stages of the disease is non-effective [23, 33–37].

From the perspective of clinical immunology, there are reasonable grounds to expect various responses to CP in patients who already have their own antibodies to SARS-CoV2 (seropositive) compared to those who do not have them (seronegative). It was shown repeatedly that the time from the disease onset to hospitalization is about 10 days. However, not all investigators performed patient screening in real time for the presence of antibodies before enrollment [38, 39].

Recent observations indicate that neutralizing antibodies were found in almost 100 % of patients three weeks after the manifestation of symptoms, which explains the lack of observed therapeutic effect in using CP at the late stages [40, 41].

Using CP at the late stages may be effective in accelerating the virus elimination, but it is insufficient for regression of inflammatory lung damage in patients suffering from COVID-19.

Summarizing the results of studies completed ahead of time may be premature. A number of these studies have limitations: the majority of CP recipients were at the late stage of the disease; patients' status was critically ill; patients were in ICUs, or they had their own anti-SARS-Cov2 antibody titer when being randomized, or they received corticosteroids that may also affect antibody production. However, when analyzing individual subgroups in these studies, some data appears in favor of CP [24, 33–36, 42-44].

A.M. Rasheed et al. showed in their randomized clinical trial a reduction in duration of infection by approximately 4 days and a reduction in mortality from 28 % to 4.8 % in the CP group ($p < 0.05$) [28]. In addition, all patients who received CP showed high levels of SARS-CoV-2 IgG and IgM 3 days after treatment ($p < 0.05$). CP therapy was effective provided that donors with high levels of SARS-Cov2 antibodies were carefully selected and provided that recipients were at the early stage of the disease.

In the study performed by E. Salazar et al. that involved patients in Houston, mortality decreased only among patients who received CP within 72 hours of hospitalization, with a VNA titer being ≥ 1 : 160 in 80 % of cases [45].

A non-randomized clinical trial performed by Abolghasemi et al. that involved moderate patients with a median of the administration of CP of 7 days from the onset of the disease also demonstrates the clinical efficacy and safety of CP. Decreased mortality, a shorter hospitalization period, and decreased intubation needs in patients suffering from COVID-19 compared to the control group were shown [46].

Most studies included inpatients. The study performed by R. Libster et al. is one in which CP was administered in outpatients [47]. CP with a high antibody titer was used in the active treatment group of elderly patients over 65 years old in the early stages of the disease up to 72 hours after the onset. As a result, a 48 % reduction in the progression of the COVID-19 disease to severe forms was revealed.

Although there is another contrasting study published by F.K. Korley et al., which also evaluated CP in outpatients for ≤ 7 days [48]. But the patients had at least 1 risk factor for severe COVID-19. The study was stopped after the interim analysis showed no benefit of CP for this patient group. At the present, the administration of CP is not approved for outpatient use in patients suffering from COVID-19 in both the Russian Federation and the United States of America (USA), for example.

Due to the large number of available serology studies, it is important to carefully carry out screening for antibodies before using CP and, in an ideal scenario, compare the result of the analysis to the VNA gold standard. It is evident that a high level of antibodies in the plasma of convalescents is necessary. Based on the guidelines of the Food and Drug Administration (FDA), the VNA titer 1 : 160 is indicated as an effective minimum. However, following the administration of CP to an adult patient, antibodies are diluted at least 10-fold. So, to achieve maximum VNA concentration in patients, it also makes sense to consider using immunoglobulins derived from CP or virus-neutralizing monoclonal antibodies [49, 50].

A large multicenter study performed by C. Avendano-Sola et al., in which 14 hospitals were participated, demonstrated the efficacy of CP. The median of CP prescription was 8 days from the onset of the disease. Patients receiving high-flow oxygen therapy, non-invasive and invasive lung ventilation were excluded from the study. As a result, a decrease in the incidence of disease progression on Days 15 and 29, as well as a decrease in mortality in the CP group compared with the standard therapy group, was recorded.

The final results of the study were published in 2021, where the significant benefit of CP in preventing disease progression on Day 28 was proven. But the effect on overall survival was not statistically significant [51].

The largest programs and an analysis of CP administration are carried out in the USA.

In an early study performed by M. J. Joyner et al., among the first 35,000 hospitalized patients, mortality at 7 days was lower among patients who received transfusion within 72 hours after establishing the diagnosis than among those who received transfusion later. Early CP administration was associated with a decrease in mortality on Days 7 and 30 of the follow-up. More significant differences were when the analysis was performed in the group of less severe patients with early administration of plasma [52].

On August 23, 2020, the FDA issued an Emergency Use Authorization for Convalescent Plasma to treat hospitalized COVID-19 patients based on retrospective indirect efficacy assessments obtained within a major expanded access program. Primarily, this program approved using CP regardless of the titer. A team of scientists reviewed the primary analysis of the results of the expanded access program and concluded that their data was not sufficient to establish the efficacy or safety of CP due to possible bias, lack of randomization, and lack of an untreated control group.

Afterward, the largest US clinical trial covering hospitalized patients (n = 3,082) revealed a lower risk of death in patients who were administered plasma transfusion at the early stages, with a higher level of IgG antibodies to SARS-CoV-2 [53]. This trial became fundamental in the development of the latest guidelines for using CP in the United States.

Among the 3,082 patients included in this analysis, 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group died within 30 days after plasma transfusion. The association of the risk of death with low anti-SARS-CoV-2 antibodies was not statistically significant in the group of patients on ventilator. Lower risk of death within 30 days was observed in patients to whom mechanical ventilation were not performed (relative risk: 0.66; 95% CI: 0.48 to 0.91) and no effect of CP on the risk of death was observed in patients to whom mechanical ventilation were performed (relative risk: 1.02; 95% CI: 0.78 to 1.32).

On 4 February 2021, the FDA revised an Emergency Use Authorization for Convalescent Plasma to limit the administration of CP only to patients with high VNA titer and only for the treatment of hospitalized patients suffering from COVID-19 at the onset of the disease or in patients with impaired humoral immunity [2].

Following the data provided by M.B. Ortigoza et al., the possible benefit of CP was observed at the beginning of the pandemic, with administering high titer CP when corticosteroids and remdesivir were not extensively used. According to the authors of the study, CP is a treatment option at the beginning of the pandemic, when other treatments are not available [54].

O'Donnell et al. found that in adults hospitalized with severe COVID-19, using CP was not associated with improvement in patients' clinical status on Day 28. However, the administration of CP was associated with a statistically significant increase in survival. A possible explanation for these findings is that survivors remained in the baseline clinical status over a period of hospitalization [42].

Administration of CP in Patients with Immunodeficiency

Clinical data supporting the efficacy of CP in patients with primary or secondary immunodeficiency are presented. CP was found to be safe and effective in patients suffering from COVID-19 with agammaglobulinemia, general variable immunodeficiency, myasthenia, and Sjogren syndrome [55].

Oncological patients receiving anticancer treatment are included in a particular group with a risk of COVID-19 due to the weakened immune system [1]. The probability of fatal outcomes from coronavirus infection in such patients is 89% higher compared to other patients. Patients with oncohematological diseases are the most vulnerable — the number of fatal outcomes from COVID-19 in this group is 48% compared to 29% in people with other types of cancer [56].

M. A. Thompson et al. published data obtained from 966 patients with leukemia, lymphoma, and multiple myeloma who were hospitalized from March 2020 to January 2021 with severe COVID-19 [57]. Among them, 143 received CP, and the other 823 received standard treatment.

There was a decrease in mortality to 13.3% when using CP compared to 24.8% when using standard therapy. For patients admitted to intensive care units, there was an even more illustrative picture: 15.8% compared to 46.9%.

The efficacy of the CP administration in patients after rituximab therapy (anti-CD20) was noted apart [58–59].

Other Interesting Clinical Trials

The economic component is equally important. Access to CP can be immediate in many low- and middle-income countries and the cost of one transfusion of $186.25 is a potentially inexpensive alternative to monoclonal antibodies [51].

Western authors proved the significance of the geography of plasma donors. It is advisable to transfuse CP from donors in the local region that contain antibodies specific for local variants of the viral infection that have a higher VNA, which reduces mortality [52, 60].

Based on the Coronavirus Disease 2019 Treatment Guidelines, the safety and efficacy of using CP during pregnancy were not evaluated. Pathogen-specific immunoglobulins are used during pregnancy to prevent infection with varicella-zoster virus and rabies virus, and they were used in clinical trials in patients with congenital cytomegalovirus infection [61]. Some ongoing clinical trials for using CP in patients suffering from COVID-19 include pregnant women [62].

Safety and efficacy of CP on a large scale were not evaluated in children, except for isolated cases where using CP in children with leukemia was described [63, 64]. The US guidelines do not recommend using CP for the treatment of COVID-19 in children to whom mechanical ventilation

is performed; however, subject to a pediatric infectious disease specialist's approval, CP with a high VNA titer may be considered to be administered on an individual basis.

Efficacy is most clearly demonstrated by meta-analyses that combine all the available studies into a single picture. The meta-analysis performed by S.A. Klassen et al. is one among them; it confirms efficacy by analyzing most studies on the administration of CP [65]. However, American scientists also emphasize that many patients received plasma in the late stages of the disease. Therefore, even the analysis performed may underestimate the reduction in COVID-19 mortality achievable by early administration of CP containing a high VNA titer. Most recently, other global meta-analyses appeared that show efficacy and mortality reduction in COVID-19 patients [66, 67].

Discussion

The administration of CP is one of the methods of COVID-19 treatment, and it can be quickly available in pandemic conditions. There are starkly differing views about the effectiveness of the administration of CP; number of studies have limitations, disadvantages, and premature termination.

The potential risks of using CP do not seem significant compared to the possibility of reducing the duration and severity of the disease, as well as avoiding complications and delivery of mechanical ventilation.

High mortality from COVID-19, especially in elderly and comorbid patients, suggests that the benefits of using CP in the treatment of high-risk patients and those with early symptoms predominate over the risks. However, for each individual case where the administration of CP is considered, especially in patients with a history of severe allergic or anaphylactic transfusion reactions, a full risk-and-benefit assessment including a multidisciplinary medical council containing a transfusiologist should be performed.

The authors of the "negative" studies equate the lack of evidence of a significant effect with the lack of benefit. But even an insignificant sign of effectiveness within the pandemic can save many patients' lives.

However, based on the analysis of foreign literature, we can conclude about the effectiveness and reasonability of using CP in the target group of patients at the appropriate time.

When using CP, the timing of its prescription (the interval from the beginning of the disease to plasma transfusion), as well as a VNA titer, correlate with an increase in the proportion of positive outcomes in the treatment of hospitalized patients suffering from COVID-19. It probably makes sense to administer passive therapy before the development of a systemic inflammatory reaction accompanied by a cytokine storm.

Using CP is worth it in patients whose specific immune responses were not developed and who do not have antibodies (an early stage of the disease or the immune deficiency state).

As for recipients of CP, severe and critically ill patients at the late stages of the disease and those who need mechanical ventilation should be excluded. It is expected and by now, it became clear that using CP in this group of patients is inappropriate and does not improve the results.

Conclusions

The administration of CP is safe and reasonable in seronegative patients suffering from COVID-19 at an early stage of the disease or in the presence of the immune deficiency state. CP with high VNA titers is the most effective. To achieve high VNA titers, it is necessary to take into consideration the manufacturing aspects of the reduction of plasma pathogens and the special aspects of recruitment of convalescent donors. In severe and critically ill patients at the late stages of the disease and those who need mechanical ventilation, CP therapy does not lead to disease regression and increased survival.

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Appendix

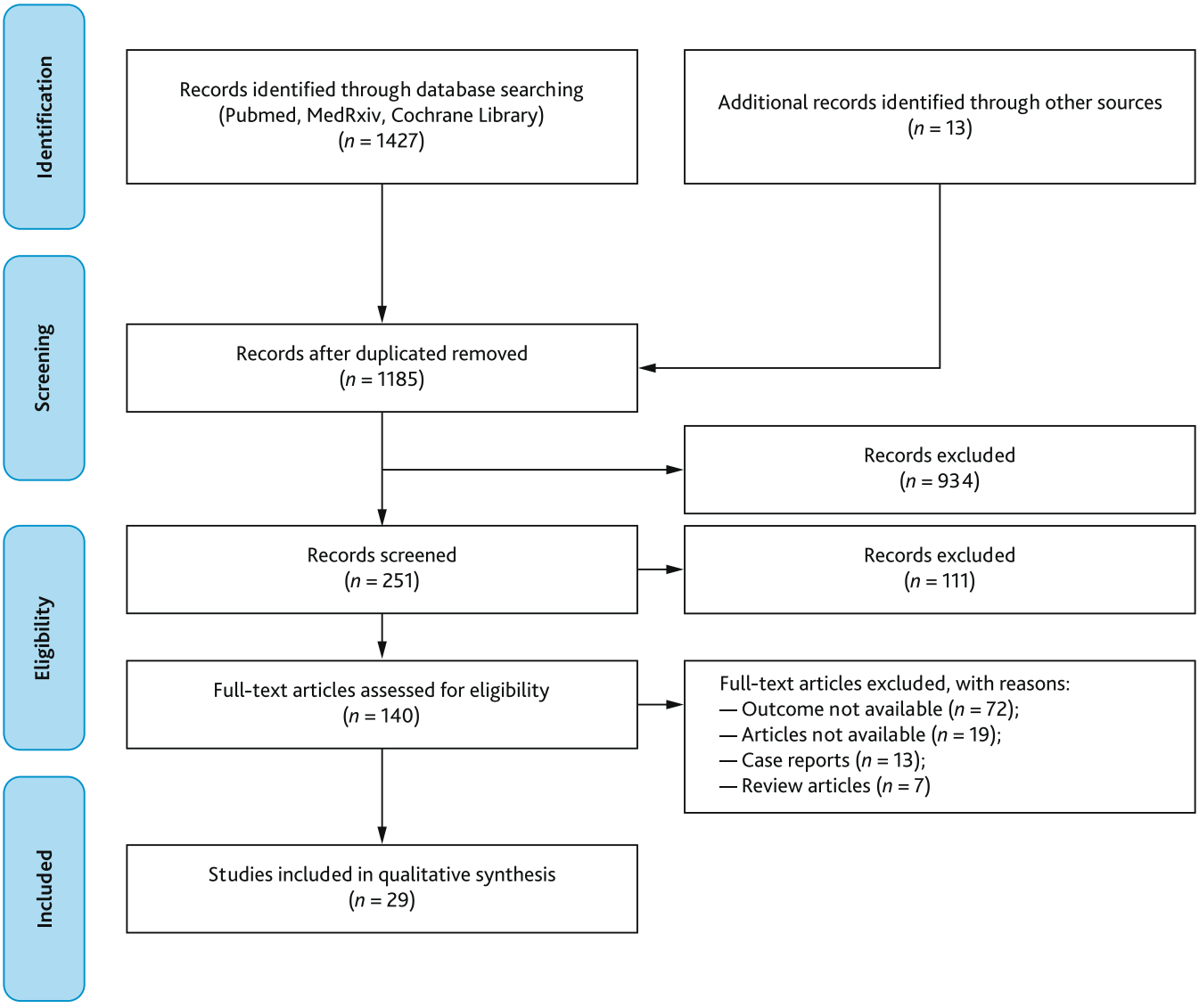

Fig. A1. PRISMA flowchart

Table A1. Summary of included studies

№	Author/study name	Year	Country	Number of patients	Result
1	L. Li et al.	2020	China	103	positive
2	A. Agarwal et al. (PLACID study)	2020	India	464	negative
3	X. Xia et al.	2020	USA	1568	positive
4	S.T.H. Liu et al.	2020	USA	195	positive
5	A. Gharbharan et al.	2020	Netherlands	86	positive
6	H. Abolghasemi et al.	2020	Iran	189	positive
7	K. Duan et al.	2020	China	20	positive
8	A.M. Rasheed et al.	2020	Iraq	49	positive
9	A. Casadevall et al.	2020	USA	103	positive
10	F. Altuntas et al.	2020	Turkey	1776	positive
11	C. Perotti et al.	2020	Italy	69	positive
12	A.S. Omrani et al.	2020	Qatar	80	positive
13	R. Rogers et al.	2020	USA	241	positive
14	E. Salazar et al.	2021	USA	903	positive
15	V.A. Simonovich et al.	2021	Argentina	333	positive
16	C. Avendano-Sola et al.	2021	Spain	350	positive
17	M.L. Donato et al.	2021	USA	1387	positive
18	E. Bennett-Guerrero et al.	2021	USA	74	positive
19	S. Körper et al.	2021	Germany	105	positive
20	M.J. Joyner et al.	2021	USA	47 047	positive
21	R. Libster et al.	2021	Argentina	160	positive
22	RECOVERY Collaborative Group	2021	UK	11 558	negative
23	The CONCOR-1 Study Group	2021	Canada, USA, Brazil	614	negative
24	REMAPCAP study	2021	UK	1084	negative
25	F.K. Korley et al. (C3PO study)	2021	USA	511	negative
26	M.R. O'Donnell et al.	2021	USA, Brazil	223	positive
27	TSUNAMI study	2021	Italy	417	negative
28	M.B. Ortigoza et al.	2021	USA	941	neutral
29	M.A. Thompson et al.	2021	USA	966	positive