Convalescent Plasma in Older Adults with COVID-19: A Systematic Review and Meta-Analysis

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Background: Among all patients infected with coronavirus disease 2019 (COVID-19), the older adult population was the most affected, with 80%–90% of fatalities occurring in this group. The effectiveness of convalescent plasma (CP) in older adults is considerably more restricted than that in adults, resulting in a demand for data on the efficacy of therapeutic CP in older adults. This meta-analysis of updated literature examined the effect of CP in older adults with COVID-19. **Methods:** Relevant literature was identified from studies indexed in the Cochrane, PubMed, and Google Scholar databases between December 2019 and April 2022. The primary outcome was all-cause mortality. Risk estimates were pooled using a random-effects model. The risk of bias was assessed by regression-based Egger test using the relative risk (RR) and upper and lower confidence intervals (CIs) of the three included studies. **Results:** Among 377 studies identified, three full-text studies that included 1,038 patients met the inclusion criteria. The results of our meta-analysis showed that CP administration lowered the mortality risk in older adults with COVID-19 (RR=0.47; 95% CI, 0.26–0.86; p=0.01; I^2=0%, p<0.81). CP therapy was more useful if delivered early in the course of the disease (within 72 hours of onset) and in less severe stages of the disease. Mortality tended to be lower in the high-titer group. **Conclusions:** CP treatment was significantly associated with a lower risk of mortality in older adults with COVID-19 than in patients not administered CP. The timing of CP administration is critical since earlier treatment after disease onset was associated with a better prognosis.

Key Words: Convalescent plasma, Immunization passive, Elderly, COVID-19, Mortality

INTRODUCTION

The epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that began in the city of Wuhan in the People's Republic of China in late 2019 has affected over 28 million people and caused nearly 900,000 deaths globally. This number has continued to increase, and it is now believed that SARS-CoV-2 has become endemic.[1] Besides comorbidities, age is a poor prognostic factor in individuals with coronavirus disease 2019 (COVID-19). In Korea and Italy, approximately 80% and 90% of

fatalities occurred in patients aged > 70 years and 60 years, respectively. Similar patterns were observed in other countries affected by COVID-19.[2] Older adults with COVID-19 also have a longer hospital stay, increased healthcare costs, and, even if they survive, an altered quality of life.

Age is a significant factor related to COVID-19 severity and clinical manifestations. Older adults with COVID-19 have a higher death rate because of the disease's high case fatality rate and symptomatic infection rate.[2] Numerous studies have indicated that advanced age is a significant risk factor for COVID-19 mortality. Age

also affects the time between hospitalization and mortality, as well as viral clearance.[3] Inflammaging is a phenomenon in which the presence of systemic basal inflammatory mediators increases with age, regardless of acute immunological assaults. This chronic, low-grade inflammation has been hypothesized to be the cause of several chronic disorders related to aging.[4] Because inflammation is a major pathogenic mechanism in COVID-19, inflammaging may lead to worse prognosis in older adults with COVID-19.[5] Additionally, inflammation plays a significant role in immunosenescence, a term that refers to general changes that occur in the immune system with age, including a decreased ability to fight new infections.[4]

Few therapies for the treatment of COVID-19 are effective; some therapies have been abandoned and others are undergoing evaluation. Several techniques have been investigated, including the administration of particular antibodies found in convalescent plasma (CP).[6] While several meta-analyses investigating the benefits of CP in adults have failed to demonstrate its efficacy in decreasing death rates, the meta-analysis by Klassen et al.[7] demonstrated a lower death rate among CP-transfused patients with COVID-19 than among non-CP-transfused patients with COVID-19. The effectiveness of CP in older adults is considerably less studied than that in adults, resulting in a high demand for the evidence of the efficacy of therapeutic COVID-19 CP in older adults. Consequently, there remains a lack of consensus regarding the use of CP in older patients with COVID-19. Thus, we conducted this systematic review and meta-analysis to assess the existing data and provide evidence of the efficacy of CP for older adults with COVID-19. We also provided an overview of the prospective advantages of CP therapy in older adults with COVID-19.

MATERIALS AND METHODS

Eligibility Criteria
We included all research articles analyzing the outcomes of CP use in older adults with COVID-19. We independently screened eligible publications based on the following inclusion criteria: older adults with COVID-19, English language, and original articles. We excluded non-research articles (e.g., case reports or series, review articles, letters to the editor, study protocols, editorials, or commentaries) and studies with insufficient data.

Search Strategy and Study Selection
We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[1] We systematically searched the PubMed, Directory of Open Access Journal, and Cochrane Central Register of Controlled Trials databases using the search terms ("Coronavirus Disease 2019" OR "COVID-19" OR "novel coronavirus pneumonia" OR "2019-nCoV" OR "SARS-CoV-2") AND ("older adults") AND ("convalescent plasma") on January 30, 2021. The full search terms are presented in Supplementary Table S1. Duplicate results were excluded. We independently screened the abstracts of the remaining articles for relevance. We then read the remaining articles to include those that fulfilled our criteria. The final inclusion of the studies was based on the agreement of all authors. Any disagreement between the authors was resolved by consensus. We assessed the full texts of the remaining articles according to the inclusion and exclusion criteria and evaluated the quality of the observational cohort studies using the Newcastle-Ottawa Quality Assessment Scale. Study quality was categorized as poor (score 0–3), fair (score 4–6), or high (score 7–9). We assessed randomized controlled trials (RCTs) using a checklist guide from the Center of Evidence-Based Medicine.

Data Extraction
All authors independently performed data extraction using standardized forms that included the author, year of study, study design, country of study, number of samples, location of study, age, method of CP administration, and outcome. Disagreement among authors was addressed using a protocol for discussion to achieve agreement. The outcome of this study was mortality.

Definitions of Older Adults, COVID-19, and CP
Older adults were defined as those aged ≥ 65 years.[2] COVID-19 positivity was defined as a nasopharyngeal swab positive for SARS-CoV-2 by polymerase chain reaction assay. Standard care was provided to each patient based on the standard protocol of the respective centers. The convalescent plasma administration protocols were performed in the respective centers. The volume varied between 250 mL and 300 mL among studies based on patient clinical responses.

Statistical Analysis
We used Review Manager 5.4.1 (https://training.cochrane.org/online-learning/core-software/revman) and Stata version 16 (StataCorp LLC, College Station, TX, USA) to perform the meta-analysis. The effects of CP administration on mortality in older adults with COVID-19 were presented as relative risks (RRs). We calculated dichotomous variables using the Mantel–Haenszel formula. The RR was reported with a 95% confidence interval (CI) for dichotomous variables. The p-value was two tailed, and statistical significance was set at $p < 0.05$.

We assessed heterogeneity using the Q-statistic and I^2 tests. The

I^2 statistic measured the percentage of total variation across the studies due to clinical or methodological heterogeneity rather than chance. We applied a random-effects model in the analysis to better represent the population. To the assess small-study effect and publication bias, we performed a regression-based Egger test.[3] We did not perform a funnel plot analysis owing to the limited number of studies.

Ethics Approval and Consent to Participate

Ethical statements and consent for publication were not applicable to this review and meta-analysis. Our study is registered in PROSPERO (ID: CRD42022312006) and complied with the ethical guidelines for publication.[8]

This study complied the ethical guidelines for authorship and publishing in the *Annals of Geriatric Medicine and Research*.[9]

RESULTS

Baseline Characteristics and Study Selection

The qualitative and quantitative syntheses (meta-analysis) included 1,038 patients from three studies (Fig. 1).[1,6,10] The characteristics of the included studies are presented in Table 1. The critical appraisals for each study are presented in Table 2. Two studies were observational, while one was a randomized, double-blind, placebo-controlled trial. Male patients comprised 46.89% of the study participants. The lowest mean age reported in the studies was 77.2 ± 8.6 years.[6]
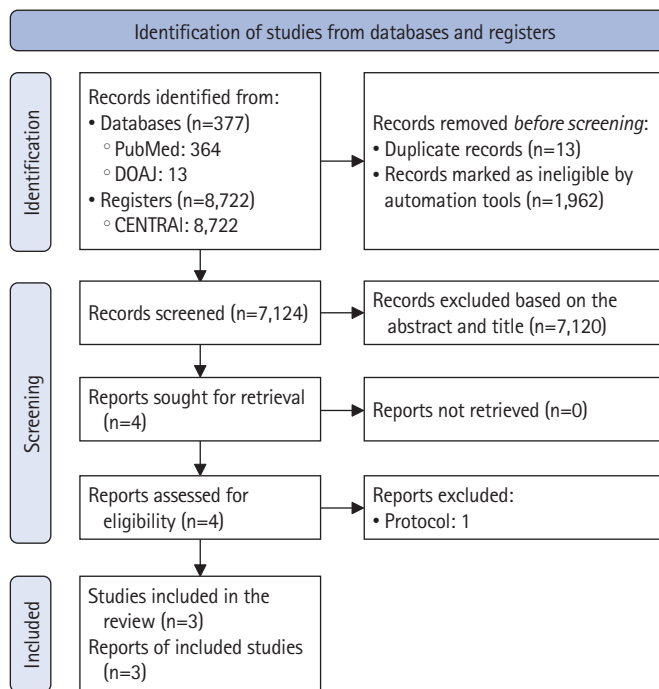

Fig. 1. Flowchart of the search strategy.

Table 1. Demographic and clinical characteristics of the included studies

| Study | Year | Design | Country | Sample | | Age (y) | | Time administration | Volume and titer CP administration | Outcome |
				Total	CP vs. control	Total	CP vs. control			
Franchini et al.[1]	2021	Observational	Italy	755	22 vs. 733	87 (82–90)	N/A	7 (4.5–8) days after symptoms	1 to 3 units of CP (300 mL per unit) ($\geq 1:160$)	Mortality rates at 28 days and at the end of follow-up: 66 (48–80) days
Libster et al.[6]	2021	Randomized, double-blind, placebo-controlled trial	Argentina	160	80 vs. 80	77.2 ± 8.6	76.4 ± 8.7 vs. 77.9 ± 8.4	< 72 hours after symptoms	250 mL of CP ($> 1:1000$)	In-hospital mortality
Romon et al.[10]	2021	Observational	Spain	123	41 vs. 82	86.7 ± 5.02	86.7 ± 5.02 vs. 85.9 ± 4.39	7 (4–10) days after symptoms	300 mL of CP (low titer, < 1: 250; high titer, > 1: 250)	In-hospital mortality

Values are presented as median (interquartile range) or mean±standard deviation.
CP, convalescent plasma.

Table 2. Critical appraisal using the Newcastle-Ottawa Quality Assessment Scale (NOS) for the included studies

Study	Design	Selection	Comparability	Outcome	Validity	Importance	Applicability
Franchini et al.[1]	Observational	***		***			
Romon et al.[10]	Observational	****	*	***			
Libster et al.[6]	RCT				(+)	(+)	(+)

RCT, randomized controlled trial.
*, one point on NOS Scale. ***, three points on NOS Scale. ****, four points on NOS Scale. (+), yes.

The inclusion criteria differed among studies. Franchini et al.[1] included older adults with COVID-19 in a long-term care facility, in which 31.8% and 48.2% had moderate and severe COVID-19, respectively. Libster et al.[6] included patients with at least one of each sign or symptom in the following two categories for <48 hours: a temperature of at least 37.5°C, unexplained sweating, or chills and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, or rhinorrhea. Romon et al.[10] included all adult patients with COVID-19 with radiologically confirmed pneumonia according to the criteria of the patient's physician and ability to receive standard treatment.

The methods of CP administration differed among studies. Franchini et al. provided the number of units of CP based on patient clinical response. Fifteen, six, and one patient received one, two, and three CP units, respectively. The median interval between the first and second CP administrations was 3 days (interquartile range [IQR], 3–12 days). The third CP unit was administered 3 days after the second CP unit.[1]

CP Administration and Patient Mortality
CP administration lowered mortality risk in older adults with COVID-19 (RR=0.47; 95% CI, 0.26–0.86; $p=0.01$; $I^2=0\%$, $p<0.81$) (Fig. 2).

We also assessed the effects of CP administration on oxygen saturation, intensive care unit (ICU) admission, and length of stay as secondary outcomes; however, we did not carry out meta-analysis analysis because of the limited number of studies and lack of data. The following sections describe the outcomes.

Patient oxygen saturation increased after CP administration from 93% (91%–95%) to 96% (95%–97%; $p<0.01$) on day 3, 97% (95–97%; $p<0.001$) on day 7, and 98% (97%–98%; $p<0.001$) on day 14.[1] Severe respiratory disease developed in 13 patients (16%) in the CP group and 25 patients (31%) in the placebo group (RR=0.52; 95% CI, 0.29–0.94; $p=0.03$).[6]

Although Libster et al.[6] observed less severe respiratory disease in the CP group, Romon et al.[10] reported that ICU admission and length of stay did not differ between the CP and control groups.

Two patients (4.9%) in the CP group and seven patients (8.5%) in the control group were admitted to the ICU ($p=0.467$). The median lengths of stay in the CP and control groups were 11 (9–16) and 11 (7.5–16) days, respectively ($p=0.073$).[10]

Publication Bias
We analyzed publication bias with a regression-based Egger test using the RR, upper CI, and lower CI of the three included studies. The regression-based Egger test showed no small-study effects ($p=0.810$).

DISCUSSION

Compared to without CP, CP treatment was significantly related to a lower risk of mortality in older adults with COVID-19 (RR=0.47; 95% CI, 0.26–0.86; $p=0.01$; $I^2=0\%$, $p<0.81$). To date, few meta-analyses have investigated the effects of CP in older adults. Kloypan et al.[11] reported that CP significantly lowered the chance of all-cause mortality by 31% compared to usual therapy (pooled RR=0.69; 95% CI, 0.56–0.86; $p=0.001$; $I^2=50.1\%$) in 47 patients; however, they included all adult populations and not specifically older adults. In contrast, in their meta-analysis, Janiaud et al.[12] reported that CP therapy had no meaningful effect on all-cause mortality or any other clinical outcomes in patients with COVID-19. Across all 10 RCTs, the summary RR was 1.02 (95% CI, 0.92–1.12). These contradictory results were most likely caused by differences in the time of administration, disease severity, and titer level. Several studies have demonstrated that the potential of CP to inhibit the course of COVID-19 is time dependent. Early (within 72 hours) delivery of high-titer CP to older adults with mild COVID-19 slowed disease progression. Early treatment resulted in reduced progression of the disease of 40%–60% compared to control.[1] In one study of patients in Houston, mortality was lower only among those who received CP within 72 hours of admission.[13] Moreover, a large multicenter study in the United States demonstrated lower 7-day mortality among hospitalized patients who received transfusions within 72 hours of diag-
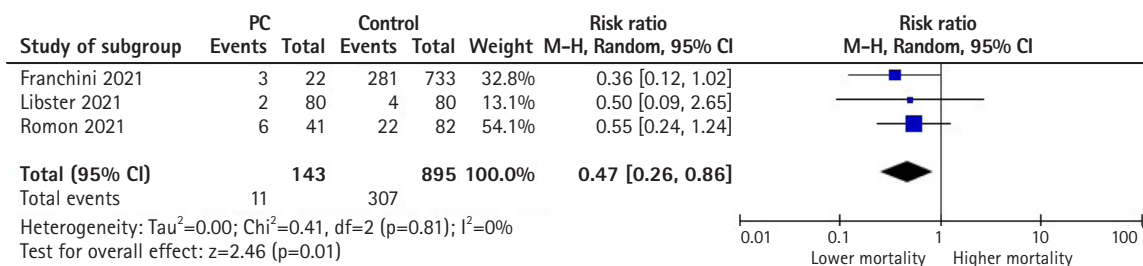

Study of subgroup	PC Events	Total	Control Events	Total	Weight	Risk ratio M–H, Random, 95% CI	Risk ratio M–H, Random, 95% CI
Franchini 2021	3	22	281	733	32.8%	0.36 [0.12, 1.02]	
Libster 2021	2	80	4	80	13.1%	0.50 [0.09, 2.65]	
Romon 2021	6	41	22	82	54.1%	0.55 [0.24, 1.24]	
Total (95% CI)		143		895	100.0%	0.47 [0.26, 0.86]	
Total events	11		307				

Heterogeneity: Tau²=0.00; Chi²=0.41, df=2 (p=0.81); I²=0%
Test for overall effect: z=2.46 (p=0.01)

Fig. 2. Forest plot and relative risk for the association of convalescent plasma administration with mortality in older adults with COVID-19.

nosis than among those who received transfusions later.[14]

While more participants in the study by Libster et al.[6] showed relative mortality risk reduction of 48%, the trial administered 250 mL of CP with an IgG titer > 1:1000 within 72 hours after the onset of mild COVID-19 symptoms. The results of this trial demonstrated a dose-dependent IgG effect in CP infusions. Plasma with IgG titers of 1:3200 or higher reduced the risk of severe respiratory disease by 73%.[6] Similarly, Romon et al.[10] reported in-hospital mortality rates of 26.8% for controls and 14.6% for patients administered CP (p = 0.131). Moreover, the ICU admission rates were 8.5% and 4.9%, respectively (p = 0.467). Mortality tended to be lower in the high-titer group (9.5%) than in the low-titer group (20%) and in patients transfused within the first 7 days of symptom onset (10%) than in patients transfused later (19.1%).[10]

Franchini et al.[1] reported that 22 patients with COVID-19 were transfused with 30 CP units (median 1; IQR 1–2): 15 patients (68.2%) with one CP unit, six (27.3%) with two CP units, and one (4.5%) with three CP units. Each unit contained 300 mL. Seven CP units (23.3%) had a neutralizing antibody titer of 1:80, 18 (60.0%) had a titer of 1:160, and five (16.7%) had a titer of 1:320. The median interval between symptom onset and the first CP transfusion was 7 days (IQR 4.5–8 days). This study reported a significantly overall mortality rate of 13.6% (3/22) compared to the control group—38.3% (281/733), p < 0.02, corresponding to a 65% reduction in mortality risk.[1] Several parameters showed varying decreases in all tests performed (white blood cell, lymphocyte, and platelet counts and aspartate aminotransferase, alanine aminotransferase, ferritin, IL-6, CRP, lactate dehydrogenase, and D-dimer levels) during follow-up. In particular, ferritin levels decreased by 24% and 44% on days 3 and 14, respectively, following CP infusion. Similarly, IL-6 concentration decreased by 29% and 56%.[1]

CP collected from patients who have recovered COVID-19 and with humoral immunity against the virus includes many antibodies that can neutralize SARS-CoV-2 and eliminate the pathogen from blood circulation and pulmonary tissues.[11,15] In older adults who are severely or critically ill, lung alveoli macrophages or epithelial cells can release large amounts of pro-inflammatory cytokines and chemokines, which attract monocytes and neutrophils to the infection site to remove the virus and infected cells, resulting in uncontrolled inflammation. This results in increased macrophage infiltration and consequently, reduced lung function. Thus, the most important aspect of CP is that antibodies can kill or stop SARS-CoV-2 and prevent viral replication.[11] In patients with COVID-19, including immunocompromised people, CP treatment enhances SARS-CoV-2 clearance, indicating an antiviral effect. Viral neutralization is hypothesized to suppress the inflamma-

tory response, thereby decreasing the risk of excessive immune response and preventing lung injury, disruption of gas exchange, and mortality.[7] Antibody-mediated interference with viral replication could lead to increased tissue repair and lower mortality. In addition, patients who received CP transfusions expressed fewer inflammatory markers, such as chemokines, IL-6, and CRP.[16]

Although our meta-analysis did not specifically analyze oxygen saturation and ICU length of stay owing to limited study findings, we aimed to describe how CP administration might also help enhance oxygen saturation and decrease the duration of ICU stay. Oxygen saturation improved following CP injection, from 93% (91–95%) to 96% (95–97%; p < 0.01) on day 3, 97% (95–97%; p < 0.001) on day 7, and 98% (97–98%; p < 0.001) on day 14.[1] Severe respiratory disease developed in 13 patients (16%) in the CP group and 25 patients (31%) in the placebo group (RR = 0.52; 95% CI, 0.29–0.94; p = 0.03).[6] This finding is also consistent with that reported by Allahyari et al.[17] who found that CP administration dramatically improved oxygen saturation and ameliorated acute respiratory distress syndrome (ARDS) when administered early in the disease course. They also reported that patients with mild ARDS administered CP (PaO_2/FiO_2 > 200 and < 250) recovered significantly more quickly than healthy control (p = 0.046). While the proportion of discharged patients with moderate ARDS (PaO_2/FiO_2 ≥ 100 and ≤ 200) was similarly higher in the plasma group (55.6 % vs. 33.3 % in the control group), the difference was not statistically significant. Both groups discharged the same number of patients with severe ARDS (PaO_2/FiO_2 < 100) (1 of 4 patients, 25%). Therefore, CP therapy may be more useful if delivered early in the course of the disease and before the patient become critically ill, thus bolstering the concept of CP efficacy in less severe stages of the disease.

The impact of timing of administration on outcomes may be due to macrophage activation. Older adults with COVID-19 may experience higher macrophage activation and innate immune cell migration to lung tissues, resulting in more severe inflammation and pulmonary injury. Inhibition of this system may help prevent cytokine storms and lung injury. This was also reinforced by a recent study that reported increased chemokines for innate immune cells in patients with COVID-19 within the first 7 days of infection.[18] Furthermore, in the absence of an acute injury, aged individuals have a higher stage of inflammation. Therefore, providing CP in the early stages of illness may minimize the degrees of systemic inflammation and cytokine storm.

Romon et al.[10] reported that ICU admission and length of stay did not differ between the CP and control groups. Two patients (4.9%) in the CP group and seven patients (8.5%) in the control group were admitted to the ICU (p = 0.467). The median lengths

of stay in the CP and control groups were 11 (9–16) and 11 (7.5–16) days, respectively (p = 0.073). This lack of difference was most likely due to the late administration of CP in their trial. The median times between symptom onset and hospitalization to CP administration were 7 days (IQR 4–10) and 1 day (IQR 0–2), respectively. A previous study suggested that the early administration of CP based on symptoms and less severe disease may have a greater effect on CP therapy. Abolghasemi et al.,[19] reported that CP transfusion within 3 days of hospitalization resulted in a greater overall proportion of patients (98.2%) who were discharged compared to Allahyari et al.,[17] in which a median time from symptoms to CP administration of 4.41 days showed a lower percentage of patients who recovered and were discharged (78.1%). Thus, CP transfusion improved patient clinical outcomes by reducing the duration of stay in the hospital, the requirement for non-invasive mechanical ventilation and intubation, and the fatality rate.

This meta-analysis had some limitations. First, some studies were observational cohorts that provided weaker strength of evidence compared to RCTs. Second, the limited number of studies may have produced false-positive results. Third, we did not consider comorbidities in predicting the mortality risk. However, older adults often have multiple comorbidities that affect mortality risk.

In conclusion, compared to patients not administered CP, CP treatment was significantly associated with a lower risk of mortality in older adults with COVID-19. The timing of CP administration is critical since earlier onset of disease are associated with better prognosis.

ACKNOWLEDGMENTS

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