Multi-center matched cohort study of convalescent plasma for hospitalized patients with COVID-19

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Abstract

Background

Although frequently used in the early pandemic, data on the effectiveness of COVID-19 convalescent plasma (CCP) remain mixed. We investigated the effectiveness and safety of CCP in hospitalized COVID-19 patients in real-world practices during the first two waves of the pandemic in a multi-hospital healthcare system in Texas.

Methods and findings

Among 11,322 hospitalized patients with confirmed COVID-19 infection from July 1, 2020 to April 15, 2021, we included patients who received CCP and matched them with those who did not receive CCP within ±2 days of the transfusion date across sites within strata of sex, age groups, days and use of dexamethasone from hospital admission to the match date, and oxygen requirements 4–12 hours prior to the match date. Cox proportional hazards model estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for effectiveness outcomes in a propensity score 1:1 matched cohort. Pre-defined safety outcomes were described. We included 1,245 patients each in the CCP treated and untreated groups. Oxygen support was required by 93% of patients at the baseline. The pre-defined primary effectiveness outcome of 28-day in-hospital all-cause mortality (HR = 0.85; 95%CI: 0.66,1.10) were similar between treatment groups. Sensitivity and stratified analyses found similar null
results. CCP-treated patients were less likely to be discharged alive (HR = 0.82; 95%CI: 0.74, 0.91), and more likely to receive mechanical ventilation (HR = 1.48; 95%CI: 1.12, 1.96). Safety outcomes were rare and similar between treatment groups.

**Conclusion**

The findings in this large, matched cohort of patients hospitalized with COVID-19 and mostly requiring oxygen support at the time of treatment, do not support a clinical benefit in 28-day in-hospital all-cause mortality for CCP. Future studies should assess the potential benefits with specifically high-titer units in perhaps certain subgroups of patients (e.g. those with early disease or immunocompromised).

**Introduction**

Transfusion of convalescent plasma (CP) is frequently proposed as passive immune therapy for emerging viral infections, including during the coronavirus disease 2019 (COVID-19) pandemic caused by SARS-CoV-2 [1]. The rationale is that antibodies can be transferred from recovered patients and theoretically treat or prevent disease [2]. While CP is one of the earliest available therapies for emerging infectious diseases, data on its effectiveness have historically been limited by non-randomized designs [3]. Based on available data, limited alternative treatment options, and historical precedents, the U.S. Food and Drug Administration (FDA) determined in March 2020, that COVID-19 convalescent plasma (CCP) was eligible for use under expanded access, as well as in controlled trials, under an active Investigational New Drug application (IND). Initially, CCP was provided under individual patient emergency IND expanded access, followed by a national expanded access protocol (EAP) sponsored by the Mayo Clinic [4], and subsequently under terms of an Emergency Use Authorization (EUA) in August 2020. In February 2021, based on updated findings of randomized controlled trials (RCTs), the EUA was restricted to the use of CCP with high titers of anti-SARS-CoV-2 antibodies early in the course of disease or in patients with impaired humoral immunity. In December 2021, with emerging evidence from RCTs and observational studies of CCP, the EUA was further restricted to the use of high titers plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment [5].

While RCTs provide more definitive evidence of treatment efficacy, analyses of the real-world use of CCP in large cohorts may offer insight into clinical effectiveness, and reasons for differences across observational studies, including assessment of concomitant therapies. Identifying factors potentially associated with the clinical benefit, or lack thereof, can inform further analyses of RCT data, assist in future trial designs, and provide valuable information for the use of CP in future emerging infectious diseases. Finally, methods used to control for confounding can inform future assessment of real-world evidence, especially in emerging pandemics. Herein, we report associations between CCP treatment and effectiveness outcomes, and describe safety outcomes following transfusion in a multi-hospital healthcare system in Texas from July 2020 to April 2021.

**Materials and methods**

This retrospective cohort study analyzed data extracted from the Epic electronic health record (EHR) system from 25 acute care Baylor Scott White & Health (BSWH) hospitals across north and central Texas from July 1, 2020 to April 15, 2021 (Fig 1). The protocol was jointly developed...
Analytic cohort

Patients who had a positive RT-PCR test for SARS-CoV-2 infection within 14 days of hospital admission were identified for risk-set sampling. Among these patients, we included patients who received CCP and those who did not receive CCP within four days (±2 days) of the transfusion date during the study period across sites. Prior to August 23, 2020, patients in the study received CCP under INDs, largely through the national EAP, while patients treated after August 23, 2020, may have received CCP under EUA or IND. Eligibility for treatment under either regulatory pathway included hospitalized patients with COVID-19, and transfused patients in this study were therefore expected to include a heterogenous mix that reflected real-world practice at the time. The heterogeneity of clinical characteristics applied to the untreated group as well. Matching on calendar date was conducted to account for the potential period effect as the standard of care changed quickly for hospitalized COVID-19 patients with the evolving pandemic. The transfusion date or the match day was defined as the index date. We matched each CCP recipient to up to four untreated patients on sex, age (±5 years), days from hospital admission to index date, oxygen requirements 4–12 hours prior to index date, and use of dexamethasone from admission to index date. Specific definitions of oxygen requirement strata (i.e., basic versus advanced oxygenation) are provided in the publicly posted study protocol and generally reflect low versus high flow oxygen requirement (Table 1 in S1 Appendix). We excluded patients who were previously admitted to hospitals due to RT-PCR-confirmed COVID-19 for potentially incomplete capture of COVID-19 treatments, who were discharged on the same day of admission due to lack of follow-up, and whose index date was <28 days from the end of the study period due to inadequate observation for the primary outcome.

Exposure

COVID-19 patients admitted to a BSWH hospital were considered for CCP transfusion according to disease severity, availability of treatments, and clinician’s judgment. CCP was
identified with ISBT-128 [6] code (Table 2 in S1 Appendix) in local Blood Bank data (i.e., SoftBank [SCC] and SafeTrace [Haemonetics]). Depending on blood donor center supplier inventory and availability of testing for titers, including labeling high titer per updated FDA requirement, CCP was sent to the individual hospital blood banks for storage, processing, and thawing per treating physician order. CCP was obtained from three blood donor center suppliers that started antibody testing between October and November 2020. Early on, however, titers were not available for testing. Our preliminary assessment found most CCP-treated patients only received one unit of transfusion. Therefore, the first exposure to CCP was of interest for patients who received multiple units.

Outcomes
The pre-defined primary effectiveness outcome was 28-day in-hospital all-cause mortality. Secondary effectiveness outcomes included discharge alive, intensive care unit (ICU) transfer, and mechanical ventilation. We identified date of death and discharge status for in-hospital mortality and discharge alive status. ICU transfer was defined as EHR transfer entries in and out of ICU departments, or ICU accommodation codes. Mechanical ventilation was identified by reviewing the oxygen therapy flowsheet for the physician-defined treatment types that met criteria.

Safety outcomes related to plasma transfusion were explored, selected from the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) Biovigilance Component Hemovigilance Module Surveillance Protocol, and identified with International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) (Table 1 in S2 Appendix).

Statistical analysis
Covariates at baseline, defined as the period prior to and including the index date, were reported as frequencies and proportions for categorical variables, and median and interquartile range (IQR) or mean and standard deviation (SD) for continuous variables, as appropriate.

To account for confounding by baseline covariates, we conducted one-to-one nearest neighbor propensity score matching without replacement using a caliper of 0.25 and exact match on age (±2.5 years), days from hospital admission to the index date, oxygen support 4–12 hours prior to the index date, and use of dexamethasone from admission to the index date between exposure groups. Absolute standardized differences were computed for each baseline covariate to check its distribution balance between exposure groups pre- and post-propensity score matching. We also visually inspected overlaps between density plots of post-propensity score matching (Fig 1 in S2 Appendix).

Crude and adjusted incidence rates for all-cause in-hospital mortality in the first 7, 14, 21, and 28 days from the index date were estimated pre- and post-propensity score matching, respectively. Cumulative incidence curves for in-hospital mortality were depicted for each exposure group and compared using the log-rank test. Cox proportional hazards regression estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using the post-propensity score matched cohort for effectiveness outcomes, with hospital site included as the random effect. Hospital site was not included in the propensity score model to preserve the degree of freedom, given the number of other covariates and the sample size. For the primary effectiveness outcome, patients were followed from the index date until the earliest of death, discharge alive, or day 28 from the index date (or the end of the study period in the sensitivity analysis below). The proportional hazards assumption was evaluated using Schoenfeld residuals test and visual inspection of log-log plots. Given the rarity of the safety outcomes, we only reported
frequencies and proportions of these among patients who received CCP in the post-propensity score matched population.

To evaluate the robustness of the effectiveness results, we conducted following sensitivity analyses for all pre-defined effectiveness outcomes: 1) restricting to a subset of patients admitted to the hospital within ±7 days of RT-PCR confirmed COVID-19 diagnosis; 2) following patients up to the end of the study period; and 3) estimating sub-distribution hazard ratios using the Fine-Gray model to account for the competing risk between in-hospital mortality and discharge alive. To further evaluate the CCP effectiveness, we conducted the following subgroup analyses for the pre-defined primary effectiveness outcome: 1) stratifying mechanical ventilation status prior to or at the index date; 2) restricting to patients receiving remdesivir prior to or at the index date; 3) stratifying the time interval from hospital admission to the index date (<72 versus ≥72 hours); and 4) stratifying oxygen support 4–12 hours prior to the index date.

Secondary outcomes (incident of ICU transfer, mechanical ventilation, and discharged alive) were also analyzed to evaluate CCP’s effectiveness on disease progression. Analysis of these outcomes was performed in the same manner as the primary outcome.

All statistical analyses were conducted with SAS 9.4 and R 3.5.1. A two-sided $P$-value of $<0.05$ was considered statistically significant. Missing values were coded as a separate category for each covariate and included in the analyses. No adjustments were made for multiple testing.

**Results**

Fig 1 presents the participating hospital sites and the identification of the analytic cohort. There were 11,322 eligible hospitalized patients testing positive for SARS-CoV-2 within 14 days of admission during the study period, of whom 2,495 received CCP. Risk-set sampling identified 1,786 patients treated with CCP and 3,552 matched patients who did not receive CCP. The propensity score matching resulted in 1,245 patients each in the CCP treated and untreated groups.

**Baseline patient clinical characteristics**

Table 1, and Table 2 in S2 Appendix, present the distribution of patient demographics, baseline comorbidities, concurrent medications, proxies for COVID-19 severity, and select laboratory results, pre- and post-propensity score matching. After risk-set sampling (or pre-propensity score matching) and propensity score matching, patient demographics and baseline comorbidities are similarly distributed between exposure groups, with the median age of 66 years, over half of the patients being male, the median length of hospital stay of one day prior to the index date and most commonly occurring comorbidities being hypertension (70%).

Risk-set sampling resulted in an even distribution of dexamethasone treatment in the pre- and post-propensity score matched cohorts with 99% of patients receiving it in the post-propensity score matched cohort. Propensity score matching improved imbalance in some comedications with absolute standardized differences $<0.1$; 90% of patients received anti-thrombotic drugs, 70% received remdesivir, and over 50% received azithromycin in each exposure group.

Proxies for COVID-19 disease severity before and after propensity score matching are also presented in Table 1. Risk-set sampling and propensity score matching resulted in the same distribution of oxygen support 4–12 hours prior to index date between exposure groups, with 67% patients requiring basic oxygen support and 25% requiring advanced oxygen support.
Table 1. Baseline demographics and clinical characteristics of convalescent plasma treated patients and matched untreated patients through risk-set sampling and propensity score matching.

| Demographics                                      | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|---------------------------------------------------|-------------|------------------------|-------------------|
| **N = 1245**                                      |             | **N = 1245**           |                   |
| **Age on the index date (years)**                 |             |                       | 0.008             |
| Mean (SD)                                         | 65 (13.5)   | 65.1 (13.4)            |                   |
| Median (IQR)                                      | 66 (56, 75) | 66 (56, 75)            |                   |
| **Days from hospital admission to the index date**|             |                       | 0                 |
| Mean (SD)                                         | 1.4 (1.1)   | 1.4 (1.1)              |                   |
| Median (IQR)                                      | 1 (1, 2)    | 1 (1, 2)               |                   |
| **Sex**                                           |             |                       | 0.049             |
| Female                                            | 529 (42.5%) | 499 (40.1%)            |                   |
| Male                                              | 716 (57.5%) | 746 (59.9%)            |                   |
| **Race/ethnicity**                                |             |                       | 0.055             |
| Non-Hispanic, White                               | 649 (52.1%) | 646 (51.9%)            |                   |
| Non-Hispanic, Black                               | 186 (14.9%) | 192 (15.4%)            |                   |
| Hispanic                                          | 347 (27.9%) | 349 (28.0%)            |                   |
| Non-Hispanic, Others                              | 45 (3.6%)   | 40 (3.2%)              |                   |
| Missing/Unknown                                   | 18 (1.4%)   | 18 (1.4%)              |                   |
| **Hospital Category**                             |             |                       | 0.719             |
| >20 ICU beds                                      | 688 (55.3%) | 877 (70.4%)            |                   |
| 16–20 ICU beds                                    | 68 (5.5%)   | 216 (17.3%)            |                   |
| 11–15 ICU beds                                    | 315 (25.3%) | 78 (6.3%)              |                   |
| ≤10 ICU beds                                      | 174 (14.0%) | 74 (5.9%)              |                   |
| **Comorbidities**                                 |             |                       |                   |
| History of cancer excluding non-melanoma skin cancer | 86 (6.9%)  | 85 (6.8%)              | 0.003             |
| **Cardiovascular conditions**                     |             |                       |                   |
| Thrombotic or thromboembolic complications        | 205 (16.5%) | 188 (15.1%)            | 0.038             |
| Stroke                                            | 112 (9.0%)  | 113 (9.1%)             | 0.003             |
| Myocardial infarction                             | 78 (6.3%)   | 70 (5.6%)              | 0.027             |
| Venous thromboembolism, Deep vein thrombosis, Pulmonary embolism | 45 (3.6%) | 43 (3.5%) | 0.009 |
| Hypertension                                      | 875 (70.3%) | 874 (70.2%)            | 0.002             |
| Heart failure                                      | 256 (20.6%) | 268 (21.5%)            | 0.024             |
| Cardiac arrhythmias                               | 225 (18.1%) | 231 (18.6%)            | 0.013             |
| **Chronic respiratory disease**                   |             |                       |                   |
| Chronic obstructive pulmonary disease             | 233 (18.7%) | 227 (18.2%)            | 0.012             |
| Asthma                                            | 137 (11.0%) | 132 (10.6%)            | 0.013             |
| Diabetes mellitus                                 | 650 (52.2%) | 652 (52.4%)            | 0.003             |
| **Chronic kidney disease**                        |             |                       |                   |
| 1 to 4                                            | 257 (20.6%) | 260 (20.9%)            | 0.044             |
| 5 or end-stage renal disease                      | 68 (5.5%)   | 81 (6.5%)              |                   |
| Chronic liver disease                             | 91 (7.3%)   | 75 (6.0%)              | 0.052             |
| **History of organ transplantation**              |             |                       |                   |
| History of organ transplantation                  | 22 (1.8%)   | 28 (2.2%)              | 0.034             |
| **HIV/AIDS**                                      |             |                       |                   |
| Obesity at hospital admission                     |             |                       | 0.031             |
| BMI 30–39.9                                       | 508 (40.8%) | 506 (40.6%)            |                   |
| BMI ≥40                                           | 172 (13.8%) | 169 (13.6%)            |                   |
| Missing                                           | 2 (0.2%)    | 1 (0.1%)               |                   |

(Continued)
Table 1. (Continued)

|                              | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|------------------------------|-------------|-----------------------|-------------------|
| **Pregnant from index date to study completion** |             |                       |                   |
| N = 1245                    | N = 1245    |                       |                   |
| 4 (0.3%)                    | 4 (0.3%)    | 0                     |                   |

**Comedications**

| Medication                  | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|-----------------------------|-------------|-----------------------|-------------------|
| Remdesivir                  | 866 (69.6%) | 858 (68.9%)           | 0.014             |
| Hydroxychloroquine/Chloroquine | 8 (0.6%)  | 8 (0.6%)              | 0                 |
| Azithromycin                | 689 (55.3%) | 708 (56.9%)           | 0.031             |

**Glucocorticoid/Steroids**

| Steroid                     | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|-----------------------------|-------------|-----------------------|-------------------|
| Dexamethasone               | 1233 (99.0%) | 1233 (99.0%)         | 0                 |
| Prednisone                  | 77 (6.2%)   | 88 (7.1%)             | 0.036             |
| Hydrocortisone              | 44 (3.5%)   | 41 (3.3%)             | 0.013             |
| Anti-platelet agents        | 479 (38.5%) | 477 (38.3%)           | 0.003             |
| Tocilizumab                 | 41 (3.3%)   | 47 (3.8%)             | 0.026             |
| ACE-Inhibitors/Angiotensin Receptor Blockers | 383 (30.8%) | 375 (30.1%)         | 0.014             |
| Anti-thrombotic drugs       | 1116 (89.6%)| 1125 (90.4%)          | 0.024             |

**Clinical Characteristics**

| Oxygenation support 4–12 hours prior to the index date | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|--------------------------------------------------------|-------------|-----------------------|-------------------|
| Room air                                                | 85 (6.8%)   | 85 (6.8%)             | 0                 |
| Basic oxygen support                                    | 839 (67.4%) | 839 (67.4%)           |                   |
| Advanced oxygen support                                 | 309 (24.8%) | 309 (24.8%)           |                   |
| Invasive ventilation                                    | 12 (1.0%)   | 12 (1.0%)             |                   |
| ECMO                                                    | 0 (0%)      | 0 (0%)                |                   |
| ICU admission prior to index date                       | 125 (10.0%) | 134 (10.8%)           | 0.024             |

**Vital signs closest to the index date**

| Respiratory rates | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|-------------------|-------------|-----------------------|-------------------|
| Mean (SD)         | 20.6 (4.6)  | 20.5 (4.6)            | 0.012             |
| Median (IQR)      | 20 (18, 22) | 20 (18, 22)           |                   |

| Heart rate | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|------------|-------------|-----------------------|-------------------|
| Mean (SD)  | 78.1 (15.0) | 78.1 (16.0)           | 0.004             |
| Median (IQR)| 76 (68, 87) | 77 (67, 87)           |                   |

| Systolic blood pressure | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|-------------------------|-------------|-----------------------|-------------------|
| Mean (SD)               | 129.8 (19.7)| 129.4 (19.2)          | 0.025             |
| Median (IQR)            | 128 (116, 143)| 128 (116, 141)       |                   |

| Temperature (F)         | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|-------------------------|-------------|-----------------------|-------------------|
| Mean (SD)               | 98.3 (0.8)  | 98.3 (0.8)            | 0.016             |
| Median (IQR)            | 98.1 (97.8, 98.6)| 98.2 (97.8, 98.6) |                   |

**Laboratory results closest to the index date**

| Creatinine Level (mg/dL) | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|--------------------------|-------------|-----------------------|-------------------|
| ≤ 1.5                    | 989 (79.4%) | 979 (78.6%)           | 0                 |
| >1.5                     | 221 (17.8%) | 227 (18.2%)           |                   |
| Missing                  | 35 (2.8%)   | 39 (3.1%)             |                   |

| D-dimer Level (ug/mL FEU) | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|---------------------------|-------------|-----------------------|-------------------|
| ≤ 1                       | 566 (45.5%) | 559 (44.9%)           | 0.059             |
| >1                        | 264 (21.2%) | 265 (21.3%)           |                   |
| Missing                   | 178 (14.3%) | 193 (15.5%)           |                   |

| Cardiac troponin Level—TnT (98%) or TnT (2%) (ng/mL) | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|-----------------------------------------------------|-------------|-----------------------|-------------------|
| ≤ 1                                                  | 864 (69.4%) | 854 (68.6%)           | 0.022             |

(Continued)
Distribution of ICU admission and vital signs closest to the index date was similar between exposure groups. After propensity score matching, approximately 11% of patients were admitted to the ICU prior to index date in each exposure group. Laboratory results closest to the index date were balanced between exposure groups after propensity score matching.

Safety outcomes

There was a single transfusion associated circulatory overload (TACO) incident in the CCP-treated group (Table 3 in S2 Appendix). Incidence of thrombotic or thromboembolic complication (11.2% CCP-treated vs. 10.5% untreated), and cardiac arrhythmias (12.9% CCP-treated vs. 13.7% untreated), were similar between exposure groups. No incidence of other prespecified, transfusion-related safety outcomes was observed.

Primary effectiveness outcomes

In-hospital mortality incidence rates (IRs) for both pre- and post-propensity score matched cohorts are given in Table 4 in S2 Appendix. After propensity score matching, there was no statistically significant difference in mortality IRs at follow-up of 7, 14, 21, or 28 days after the index date between exposure groups. Up to 28 days after the index date, the IRs were 18.1 (95%CI: 15.6, 20.9) and 15.7 (95%CI: 13.3, 18.5) for CCP-treated and untreated patients, respectively. Fig 2 demonstrates the overall cumulative incidence of in-hospital mortality was not statistically different in CCP-treated and untreated patients ($P = 0.308$).

Cox proportional hazards modeling found no statistically significant difference for 28-day in-hospital mortality (HR = 0.85; 95%CI: 0.66, 1.10) between CCP-treated and untreated patients (Fig 3). Proportional hazards assumption held with null Schoenfeld residuals test ($P = 0.190$) and the interaction term of log(time) and treatment in the Cox model ($P = 0.295$). Similar null findings were also observed in sensitivity analyses, when 1) restricting the analytic

| Table 1. (Continued) | CCP Treated | Matched CCP Untreated | Absolute Std Diff |
|----------------------|-------------|----------------------|-------------------|
|                      | N = 1245    | N = 1245             |                   |
| > 1                  | 25 (2.0%)   | 20 (1.6%)            |                   |
| Missing              | 356 (28.6%) | 371 (29.8%)          |                   |
| Absolute lymphocyte count Level (K/uL) |             |                      |                   |
| <1                   | 820 (65.9%) | 816 (65.5%)          |                   |
| ≥1                   | 69 (5.5%)   | 70 (5.6%)            |                   |
| Missing              | 356 (28.6%) | 359 (28.8%)          |                   |
| Ferritin Level (ng/mL) |            |                      | 0.057             |
| ≤400                 | 281 (22.6%) | 294 (23.6%)          |                   |
| >400                 | 634 (50.9%) | 640 (51.4%)          |                   |
| Missing              | 330 (26.5%) | 311 (25.0%)          |                   |
| C-reactive protein Level (mg/dL) |          |                      | 0.094             |
| ≤0.5                 | 18 (1.4%)   | 15 (1.2%)            |                   |
| >0.5                 | 967 (77.7%) | 988 (79.4%)          |                   |
| Missing              | 260 (20.9%) | 242 (19.4%)          |                   |

Abbreviations: ACE = angiotensin converting enzyme; BMI = body mass index; CCP = COVID-19 convalescent plasma; ECMO = extracorporeal membrane oxygenation; FEU = Forty-foot equivalent unit; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation; Std diff = Standardized difference; Tn = Cardiac troponin.

*Hospital category was not included in the propensity score model but included as a random effect in the outcome regression.

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cohort to a subset of patients admitted within ±7 days of RT-PCR confirmed COVID-19 (HR = 0.81; 95%CI: 0.63, 1.06); 2) allowing follow-up to continue until the end of the study period (HR = 0.85; 95%CI: 0.66, 1.08); and 3) considering the competing-risk of discharge alive (HR = 1.19; 95%CI: 0.91, 1.56).

Stratification by mechanical ventilation status at the index date found no statistically significant difference for 28-day in-hospital mortality between CCP-treated and untreated patients (Fig 3). Only a small proportion of patients had mechanical ventilation prior to or at the index date (16 CCP-treated, 23 untreated). Similarly, there was no significant difference between exposure groups when stratified by time from admission to index date, or by oxygen support 4–12 hours prior to the index date (Fig 3). Among patients who received remdesivir prior to or at index date, no statistically significant association was observed (HR = 0.87; 95%CI: 0.63, 1.19).

Secondary effectiveness outcomes

Compared with untreated patients, CCP-treated patients were less likely to be discharged alive up to 28 days after index date (HR = 0.82; 95%CI: 0.74, 0.91), and more likely to receive mechanical ventilation (HR = 1.48; 95%CI: 1.12, 1.96) (Fig 4). These results were similarly seen in corresponding sensitivity analyses. However, being treated with CCP was not statistically associated with ICU transfer with follow-up of up to 28 days, or in any of the corresponding sensitivity analyses. A similar discharge disposition between exposure groups was observed (Table 5 in S2 Appendix).
Discussion

Our study reports results from a large, matched cohort of hospitalized COVID-19 patients and did not find a clinical benefit in in-hospital 28-day all-cause mortality for CCP-treated compared to non-treated patients. Our study assessed the effectiveness of CCP in a population consistent with real-world clinical practices over the first two waves of the pandemic in Texas (i.e., use of CCP of unknown antibody titer across the general hospitalized COVID-19 population, including patients requiring various levels of oxygen support) (Fig 2 in S2 Appendix) and the EAP overall [7]. Crude incidence rates of in-hospital 28-day all-cause mortality in the study population (15.7% and 18.1% in control and treatment arms, respectively) fell between rates seen in RCTs in similar populations, higher than some [8], but lower than a large international RCT [9] and the EAP overall [4]. Further, our study did not find an association of CCP treatment with clinical benefit in subgroups such as those not on mechanical ventilation, those treated within 72 hours of admission, or patients across different levels of oxygen support, although these variables are likely imprecise surrogates of disease severity or immune response. While a statistically significant decreased likelihood of being discharged alive and increased probability of mechanical ventilation (both secondary outcomes) in the CCP-treated group, and a null result for the primary outcome (28-day in-hospital all-cause mortality), all
point in the direction of a lack of effectiveness of CCP, the secondary outcomes should be interpreted with caution. These secondary outcomes are based on measures taken in response to physician judgment as would be a decision to transfuse with CCP, and some of the reasons for these clinical decisions can be the potential confounders when examining the effect of CCP, and may not have been accounted for in this study.

Rates of key safety events were similar between exposure groups, and transfusion-associated adverse events were rare, with only one TACO episode reported in the transfused group. Considering the incidence of transfusion-associated adverse events (e.g., TACO and possible transfusion-related acute lung injury) was lower than typically reported for plasma transfusion in hospitalized and critically ill subjects [10–12], these events may be under-captured in EHRs using ICD-10-CM codes only [7].

Evidence of CCP’s role in the treatment of COVID-19 remains mixed. Heterogeneity of clinical practice, clinical characteristics of patient populations, and product characteristics, in addition to the evolving pandemic and concurrent clinical management, complicates the interpretation of meta-analyses [13–15]. Several RCTs of CCP for treatment of moderate-to-severe hospitalized COVID-19 patients, typically at 7 or more days post-symptom-onset, did not find clinical benefits [8, 9, 16–22], although some trials found signals of clinical benefit, sometimes in certain subgroups [21, 23–26]. Assessment of patients treated under the EAP found a modest survival benefit in patients who received high-titer CCP compared to those who received
A Bayesian reanalysis of RECOVERY argued that it remained plausible that CCP has a small but clinically significant effect on mortality in seronegative patients [29]. In the outpatient setting, some RCTs found a reduction in progression to severe disease [30, 31], while others did not [32], although patient populations, timing of treatment, and product characteristics were again variable. Observational matched cohort studies also found inconsistent results. Some studies found an association with clinical benefit [33–36], which was more likely with high titer CCP used earlier in the course of disease, or in specific subgroups, such as the immunosuppressed [37]. However, other matched cohort studies did not observe clinical benefit in hospitalized patients [38–40]. Small RCTs and observational studies are limited by insufficient statistical power to detect modest but clinically meaningful effects, particularly in subgroups, or by biases due to confounding. While one large observational study described an association between CCP transfusion and improved survival [35], an effect size much larger than expected based on subsequently reported RCT data suggests a potential for residual confounding, indicating a role for additional large observational studies such as the one described herein.

The observed lack of effect in COVID-19 patients in this study should be considered in the context of the anticipated importance of timing of passive immune therapy (such as CCP or monoclonal therapy). The high proportion of subjects already requiring oxygen support (>90%), suggests that many patients would have been more than a week into symptomatic illness [41] and that a large fraction of patients in the current study would have already been seropositive in the absence of impaired immunity [42], although this information was unlikely to be available at the time of treatment. For example, in similar study populations [9, 19, 43], approximately 50% to 70% of those with known serostatus were already seropositive. The emerging consensus signal from studies of inpatient antibody therapies, which deliver high neutralization titers, tempers expectations, as such treatments are likely ineffective if serostatus is not taken into account [44, 45]. A similar pattern was suggested in re-analyses of a large CCP RCT [29]. Clinical factors in recipients may also guide optimal patient selection for CCP therapy or future clinical studies of CCP [46].

Strengths of the current study include a large sample size selected with a priori power calculations to detect a relative risk of 0.80. As evidenced by the characteristics summarized in Table 1, our study achieved good comparability between the CCP-treated and untreated groups on measured potential confounders of baseline comorbidities, concomitant therapies, oxygen support requirements, and baseline laboratory findings, all of which may impact the risk of severe COVID-19 and progression to mortality. Finally, the diverse patient characteristics (e.g., race/ethnicity) and clinical practice in a large multi-site healthcare system contributes to the generalizability of the study results. This study contributes to the body of knowledge about the effectiveness of the CCP in COVID-19 hospitalized patients because it is an observational study that is conducted in real-world conditions of the pandemic and not in controlled conditions of an RCT, but the study design and analytic method have been able to mimic the controlled conditions of an RCT to a large extent. The null study results should not diminish its value but be interpreted in the context of a large observational study with a strong study design and analytic method and some limitations.

The current study has notable limitations. First, our study lacks anti-SARS-CoV-2 antibody titer information in the transfused CCP, either via serologic or neutralization testing, which is likely to impact potential effectiveness of the transfused CCP. Nonetheless, as availability of such tests remained limited during the study period (Fig 2 in S2 Appendix) and implementation was delayed in many blood establishments, the use of CCP of unknown titers is expected to have been common during the study period, and therefore this aspect of the study reflects real-world use in many cases. In February 2021, FDA found that low titer CCP no longer met
the evidentiary standard for EUA, and the EUA for CCP was revised to restrict use to high-titer CCP early in the course of illness. Second, patients’ baseline antibody titers or other measures of humoral immunity between the treated and untreated patients, which may affect mortality risk and likelihood of benefit for a passive immune therapy, were not assessable. Third, while the exposure groups were well balanced for measured potential confounders, the degree to which unmeasured and residual confounding impacts the findings is uncertain. Finally, the study population of hospitalized COVID-19 patients was heterogeneous with respect to disease severity and largely found to already require various levels of oxygen support and concurrent treatment with systemic steroids at the time of CCP treatment, limiting the power to examine patients earlier in the course of disease.

Conclusions
In summary, our study did not find a reduction in 28-day in-hospital all-cause mortality in a large cohort of hospitalized patients treated with CCP compared with those untreated with CCP in a multi-center hospital system in Texas. The results should be interpreted in the context of both strengths and limitations of this study, which, while reflecting real-word use of CCP, include a heterogeneous hospitalized patient population largely requiring oxygen support, a lack of data on the antibody titer in the transfused CCP and on the serostatus of patients prior to transfusion. These results can help prioritize future studies and inform the potential role of CP in future pandemics, or in the context of emerging variants, where the rapid availability of CCP, some with ability to cross-neutralize variants [47], supports the importance of continuing to evaluate data from both randomized and observational studies to guide future studies and clinical practices, and optimize patient selection and plasma qualification for CP therapy.

Supporting information
S1 Appendix. Definitions. (DOCX)
S2 Appendix. Tables and figures. (DOCX)

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References

1. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest. 2020; 130(4):1545–1548. https://doi.org/10.1172/JCI138003 PMID: 32167489
2. Casadevall A, Dadachova E, Pirofski LA. Passive antibody therapy for infectious diseases. Nat Rev Microbiol. 2004; 2(9):695–703. https://doi.org/10.1038/nrmicro974 PMID: 15372080
3. Dzik S. COVID-19 Convalescent Plasma: Now Is the Time for Better Science. Transfus Med Rev. 2020; 34(3):141–144. https://doi.org/10.1016/j.tmrv.2020.04.002 PMID: 32359789
4. Senefeld JW, Johnson PW, Kunze KL, Bloch EM, van Helmond N, Golafshar MA, et al. Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study. PLoS Med. 2021; 18(12):e1003872. https://doi.org/10.1371/journal.pmed.1003872 PMID: 34928960
5. US Food and Drug Administration. Clinical Memorandum Re: EUA 26382 2021 [cited March 25 2022]. Available from: https://www.fda.gov/media/155159/download.
6. International Council for Commonality in Blood Banking Automation. What is ISBT 128? [cited October 27 2021]. Available from: https://www.isbt128.org/istb-128-basics.
7. Chada K, Obidi J, Gruber J, Dores G, Storch E, Williams A, et al. Transfusion Trends of Whole Blood and Blood Components in Electronic Health Records and Claims Databases. Transfusion. 2018; 58:91A.
8. Menichetti F, Polpiti P, Puopolo M, Spilia Alegiani S, Tiseo G, Bartoloni A, et al. Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA network open. 2021; 4(11):e2136246–e2136246. https://doi.org/10.1001/jamanetworkopen.2021.36246 PMID: 34842924
9. Abani O, Abbas A, Abbas F, Abbas M, Abbas S, Abbass H, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. The Lancet. 2021; 397(10289):2049–2059. https://doi.org/10.1016/S0140-6736(21)00897-7 PMID: 34000257
10. Kuldanek SA, Kelher M, Skillman CC. Risk factors, management and prevention of transfusion-related acute lung injury: a comprehensive update. Expert Rev Hematol. 2019; 12(9):773–785. https://doi.org/10.1080/17474086.2019.1640599 PMID: 31282773
11. Roubinian NH, Hendrickson JE, Triulzi DJ, Gottschall JL, Chowdhury D, Kor DJ, et al. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. Vox Sang. 2017; 112(1):56–63. https://doi.org/10.1111/vox.12466 PMID: 28001313
12. Juffermans NP, Vlaar AP. Possible TRALI is a real entity. Transfusion. 2017; 57(10):2539–2541. https://doi.org/10.1111/trf.14236 PMID: 28691321
13. Piechotta V, Iannizzci C, Chai KI, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021; 7(7):CD013600. https://doi.org/10.1002/14651858.CD013600.pub4 PMID: 34013969
14. Klassen SA, Senefeld JW, Johnson PW, Carter RE, Wiggins CC, Shoham S, et al. The Effect of Convalescent Plasma Therapy on Mortality Among Patients With COVID-19: Systematic Review and Meta-analysis. Mayo Clin Proc. 2021; 96(5):1262–1275. https://doi.org/10.1016/j.mayocp.2021.02.008 PMID: 33958057
15. Janiaud P, Axfors C, Schmitt AM, Gloy V, Ebrahimri F, Hepprich M, et al. Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA. 2021; 325(12):1185–1195. https://doi.org/10.1001/jama.2021.2747 PMID: 33635310
16. Gharbharan A, Jordans CCE, GeurtstvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun. 2021; 12(1):3189. https://doi.org/10.1038/s41467-021-23469-2 PMID: 34045486
17. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020; 371:m3939. https://doi.org/10.1136/bmj.m3939 PMID: 33093056

18. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. N Engl J Med. 2021; 384(7):619–629. https://doi.org/10.1056/NEJMoa2031304 PMID: 33232588

19. Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021; 27(11):2012–2024. https://doi.org/10.1038/s41591-021-01488-2 PMID: 34504336

20. Devos T, Van Thillo Q, Compernolle V, Najdovski T, Romano M, Dauby N, et al. Early high antibody titre convalescent plasma for hospitalised COVID-19 patients: DAWN-plasma. Eur Respir J. 2022; 59(2):2101724. https://doi.org/10.1183/13993003.01724-2021 PMID: 34446469

21. Ortigoza MB, Yoon H, Goldfeld KS, Troxel AB, Daily JP, Wu Y, et al. Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial. JAMA Intern Med. 2022; 182(2):115–126. https://doi.org/10.1001/jamaipm.2021.6850 PMID: 34901997

22. Troxel AB, Petkova E, Goldfeld K, Liu M, Tarpey T, Wu Y, et al. Association of Convalescent Plasma Treatment With Clinical Status in Patients Hospitalized With COVID-19: A Meta-analysis. JAMA Netw Open. 2022; 5(1):e2147331. https://doi.org/10.1001/jamanetworkopen.2021.47331 PMID: 35076699

23. O’Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021; 131(13):e150646. https://doi.org/10.1172/JCI150646 PMID: 33974559

24. Avendaño-Solá C, Ramos-Martínez A, Muñoz-Rubio E, Ruiz-Antorán B, Malo de Molina R, Torres F, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. J Clin Invest. 2021; 131(20):e152740. https://doi.org/10.1172/JCI152740 PMID: 34473652

25. Körper S, Weiss M, Zickler D, Wiesmann T, Zacharowski K, Corman VM, et al. Results of the CAPSID randomized trial for high-dose convalescent plasma in severe COVID-19 patients. J Clin Invest. 2021; 131(20):e152264. https://doi.org/10.1172/JCI152264 PMID: 34464358

26. Bar KJ, Shaw PA, Choi GH, Aqui N, Fesnak A, Yang JB, et al. A randomized controlled study of convalescent plasma in patients hospitalized with COVID-19 pneumonia: DAWN-plasma. Eur Respir J. 2022; 59(2):2101724. https://doi.org/10.1183/13993003.01724-2021 PMID: 34446469

27. Joyner MJ, Carter RE, Senefeld JW, Klissen SA, Mills JR, Johnson PW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. N Engl J Med. 2021; 384(11):1015–1027. https://doi.org/10.1056/NEJMoa2119657 PMID: 33533377

28. Belov AH Y; Villa CH; Whitaker BI; Forshee R; Anderson S; Eder A; et al. Early Administration of COVID-19 Convalescent Plasma Containing High-Titer Antibody Content by Live Viral Neutralization Assay is Associated with Modest Clinical Efficacy. Am J Hematol. 2022; https://doi.org/10.1002/ajh.26531 PMID: 35303377

29. Hamilton FW, Lee T, Arnold DT, Lilford R, Hemming K. Is convalescent plasma futile in COVID-19? A Bayesian re-analysis of the RECOVERY randomized controlled trial. Int J Infect Dis. 2021; 109:114–117. https://doi.org/10.1016/j.ijid.2021.06.034 PMID: 34157385

30. Läbler R, Perez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021; 384(7):610–618. https://doi.org/10.1056/NEJMoa2033700 PMID: 33406353

31. Sullivan DJ, Gebo KA, Shoham S, Bloch EM, Lau B, Shenoy AG, et al. Early Outpatient Treatment for Covid-19 with Convalescent Plasma. N Engl J Med. 2022; 386(18):1700–1711. https://doi.org/10.1056/NEJMoa2119657 PMID: 33533960

32. Millat-Martinez P, Gharbharan A, Alemany A, Rokx C, GeurtsvanKessel C, Papageourgiou G, et al. Prospective individual patient data meta-analysis of two randomized trials on convalescent plasma for COVID-19 outpatients. Nat Commun. 2022; 13(1):2583. https://doi.org/10.1038/s41467-022-29911-3 PMID: 35546145

33. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG. Am J Pathol. 2021; 191(1):90–107. https://doi.org/10.1016/j.ajpath.2020.10.008 PMID: 33157066

34. Shenoy AG, Hettinger AZ, Fernandez SJ, Blumenthal J, Baez V. Early mortality benefit with COVID-19 convalescent plasma: a matched control study. Br J Haematol. 2021; 192(4):706–713. https://doi.org/10.1111/bjh.17272 PMID: 33482025
35. Arnold Egloff SA, Junglen A, Restivo JS, Wongkhaluang M, Martin C, Doshi P, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. J Clin Invest. 2021; 131(20):e151788. https://doi.org/10.1172/JCI151788 PMID: 34464352
36. Yoon HA, Bartash R, Gendlin I, Rivera J, Nakouzi A, Bortz RH, 3rd, et al. Treatment of severe COVID-19 with convalescent plasma in Bronx, NYC. JCI Insight. 2021; 6(4):e142270. https://doi.org/10.1172/jci.insight.142270 PMID: 33476300
37. Thompson MA, Henderson JP, Shah PK, Rubinstein SM, Joyner MJ, Choueiri TK, et al. Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19. JAMA Oncol. 2021; 7(8):1167–1175. https://doi.org/10.1001/jamaoncol.2021.1799 PMID: 3437799
38. Rogers R, Shehadeh F, Mylona EK, Rich J, Neill M, Touzard-Romo F, et al. Convalescent Plasma for Patients With Severe Coronavirus Disease 2019 (COVID-19): A Matched Cohort Study. Clin Infect Dis. 2020; 73(1):e208–e214.
39. Klein MN, Wang EW, Zimand P, Beauchamp H, Donis C, Ward MD, et al. Kinetics of SARS-CoV-2 antibody responses pre-COVID-19 and post-COVID-19 convalescent plasma transfusion in patients with severe respiratory failure: an observational case-control study. J Clin Pathol. 2021; https://doi.org/10.1136/jclinpath-2020-207356 PMID: 33893156
40. Cho K, Keithly SC, Kurgansky KE, Madenci AL, Gerlovin H, Wellman HM, et al. Early Convalescent Plasma Therapy and Mortality among US Veterans Hospitalized with Non-Severe COVID-19: An Observational Analysis Emulating a Target Trial. J Infect Dis. 2021; 224(6):967–975. https://doi.org/10.1093/infdis/jiab330 PMID: 34137799
41. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. New England Journal of Medicine. 2020; 383 (25):2451–2460. https://doi.org/10.1056/NEJMcp2009575 PMID: 32412710
42. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell. 2021; 184(4):861–880. https://doi.org/10.1016/j.cell.2021.01.007 PMID: 33497610
43. Writing Committee for the REMAP-CAP Investigators. Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2021; 326 (17):1690–1702. https://doi.org/10.1001/jama.2021.18178 PMID: 34606578
44. Recovery Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2022; 399 (10325):665–676. https://doi.org/10.1016/S0140-6736(22)00163-5 PMID: 35151397
45. Activ-Tico Bamlanivimab Study Group, Lundgren JD, Grund, Barkauskas CE, Holland TL, Gottlieb RL, et al. Responses to a Neutralizing Monoclonal Antibody for Hospitalized Patients With COVID-19 According to Baseline Antibody and Antigen Levels: A Randomized Controlled Trial. Ann Intern Med. 2022; 175(2):234–243. https://doi.org/10.7326/M21-3507 PMID: 34928698
46. Park H, Tarpey T, Liu M, Goldfeld K, Wu Y, Wu D, et al. Development and Validation of a Treatment Benefit Index to Identify Hospitalized Patients With COVID-19 Who May Benefit From Convalescent Plasma. JAMA Netw Open. 2022; 5(1):e2147375. https://doi.org/10.1001/jamanetworkopen.2021.47375 PMID: 35076899
47. Li M, Beck EJ, Laeyendecker O, Eby Y, Tobian AA, Caturegli P, et al. Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. Blood Adv. 2022;https://doi.org/10.1182/bloodadvances.2022007410 PMID: 35443020