

Clinical Outcomes of COVID-19 Patients Treated with Convalescent Plasma or Remdesivir Alone and in Combination at a Community Hospital in California's Central Valley

Jered Arquette¹, Regine Padilla¹, Yvonne Mai^{1,2}, Gurinder Singh³, Kristine Galang³, and Edward Liang²

¹Department of Pharmacy, San Joaquin General Hospital, French Camp, CA, USA; ²University of the Pacific, Thomas J. Long School of Pharmacy, Stockton CA, USA; ³Department of Internal Medicine, San Joaquin General Hospital, French Camp, CA, USA

Corresponding author: Dr. Jered Arquette, San Joaquin General Hospital, 500 W. Hospital Road French Camp, CA, USA 95231; TEL: (209)468-6031; email:jarquette@sjgh.org

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ABSTRACT – Purpose: The purpose of this study was to compare how treatment with convalescent plasma (CP) monotherapy, remdesivir (RDV) monotherapy, and combination therapy (CP + RDV) in patients with COVID-19 affected clinical outcomes. **Methods:** Patients with COVID-19 infection who were admitted to the hospital received CP, RDV, or combination of both. Mortality, discharge disposition, hospital length of stay (LOS), intensive care unit (ICU) LOS, and total ventilation days were compared between each treatment group and stratified by ABO blood group. An exploratory analysis identified risk factors for mortality. Adverse effects were also evaluated. **Results:** RDV monotherapy showed an increased chance of survival compared to combination therapy or CP monotherapy ($p = 0.052$). There were 15, 3, and 6 deaths in the CP, RDV, and combination therapy groups, respectively. The combination therapy group had the longest median ICU LOS (8, IQR 4.5-15.5, $p = 0.220$) and hospital LOS (11, IQR 7-15.5, $p = 0.175$). Age ($p = 0.036$), initial SOFA score ($p = 0.013$), and intubation ($p = 0.005$) were statistically significant predictors of mortality. Patients with type O blood had decreased ventilation days, ICU LOS, and total LOS. Thirteen treatment-related adverse events occurred. **Conclusion:** No significant differences in clinical outcomes were observed between patients treated with RDV, CP, or combination therapy. Elderly patients, those with a high initial SOFA score, and those who require intubation are at increased risk of mortality associated with COVID-19. Blood type did not affect clinical outcomes.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the novel coronavirus that causes the clinical syndrome coronavirus disease 2019 (COVID-19). The virus was first detected in Wuhan, China in late 2019 and has since spread globally, with the first case reported in the United States on January 19, 2020 (1). The first 2 cases of COVID-19 were reported in California on January 26, 2020, and at the time of this writing the total case count has surpassed one million with more than 19,000 deaths (2-3). San Joaquin County, located in California's central valley, reported its first known case of COVID-19 on March 9, 2020. The patient had been a passenger on the Grand Princess cruise ship (4). Since then, the case count has surged to over 36,000

with more than 500 deaths and community transmission is believed to be widespread (5-6).

As the virus continues to spread throughout the nation, the search for effective therapies has been prioritized. Currently most therapies are focused on slowing or preventing viral replication and augmenting the immune response to the virus. Viral replication is thought to be particularly active during the early stages of COVID-19, therefore antiviral therapies are currently being investigated to prevent disease progression into the hyperinflammatory state that characterizes the later stages of the disease, including critical illness (7). Several drugs have been studied for treatment of patients with COVID-19 since the start of the pandemic, including hydroxychloroquine, chloroquine, dexamethasone, azithromycin, lopinavir/ritonavir, and other HIV protease inhibitors, however none have proven to be

effective (8-10). Remdesivir, a nucleotide prodrug of an adenosine analog, is a broad-spectrum antiviral agent that has shown potent in vitro efficacy against SARS-CoV-2, and antiviral and clinical effects in animal models of SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV infections (11-13). On October 22, 2020, remdesivir was approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (age ≥ 12 years and weighing ≥ 40 kg) (8). Despite FDA approval, there is significant diversity in the recommendations for the use of remdesivir from major organizations. The National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) guidelines suggest that remdesivir may decrease time to recovery, increase clinical improvement, and decrease mortality in patients with severe COVID-19 infection (8, 14). However, the World Health Organization (WHO) currently recommends against the use of remdesivir for any hospitalized patients with COVID-19 due to lack of clear evidence that remdesivir improves survival or other significant clinical outcomes (15).

Treatment of COVID-19 with convalescent plasma (CP) from patients who have recovered from SARS-CoV-2 is also under investigation. CP has been used in the treatment of other severe infections including SARS, MERS, and Ebola (16-19). CP contains virus-specific antibodies that aim to provide passive immunity against SARS-CoV-2 until the infected patient can mount an active immune response (20). One previous study that investigated the efficacy of CP in patients infected with COVID-19 showed that it can potentially resolve ground-glass opacities and consolidation in radioactive studies, as well as increase anti-SARS-CoV-2 antibody titers (21). The IDSA Guidelines currently only recommend the use of CP in COVID-19 patients in the context of a clinical trial since there is a lack of evidence available that shows benefits of treatment (22). Investigational CP is available through the FDA under an emergency use authorization (EUA).

Several studies have evaluated risk factors for mortality among COVID-19 patients. Elderly age (≥ 60 years), male gender, chronic cardiovascular disease (including hypertension, diabetes, coronary heart disease), respiratory disorders (including lung cancer, asthma, COPD), cerebrovascular disease, Alzheimer's disease, and non-type O blood type have been associated with worse outcomes or increased risk of mortality (23-26). Regarding patients with COVID-19 admitted to intensive care units (ICUs),

studies have shown that older age (≥ 80 years), male gender, BMI > 40 , CAD, active cancer, presence of hypoxemia, liver dysfunction, and kidney dysfunction were all independently associated with higher risk of death (25). In the United States, the majority of deaths have occurred among White patients so far, however Black and Hispanic patients are disproportionately represented and the percentage of deaths among Hispanic patients has increased the most over recent months (27).

The intent of this study was to evaluate the clinical outcomes of patients treated with CP, remdesivir, or the combination of both agents. In addition, we explored risk factors associated with mortality in patients treated for COVID-19 in our hospital system.

METHODS

This was a single-center, retrospective observational study with data collection between May 1, 2020 and August 31, 2020. This study was approved by the Institutional Review Board of San Joaquin General Hospital and the requirement for informed consent was waived. We included all adult patients hospitalized with laboratory-confirmed COVID-19 infection, defined as a positive result on a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay, during the study period and received convalescent plasma (CP), remdesivir (RDV), or combination of both (CP + RDV). Available demographic characteristics, clinical history, laboratory and radiologic results at presentation were collected. Fever was reported as positive if the measured temperature was ≥ 37.8 degrees Centigrade or if the patient reported subjective fevers on the first triage encounter. Race and ethnicity data were collected from patient self-report into prespecified fixed categories. Data were collected on patients treated with CP and/or RDV and any associated adverse reactions including cardiac events, hepatic events, or renal failure. The recommended dose of RDV was 200 mg intravenously on the first day, followed by 100 mg intravenously daily for the duration of treatment (8). The recommended dose of CP was 1 or 2 units (approximately 200 mL each) infused over 30 minutes. Criteria for RDV and CP use can be found in Box 1. All laboratory and radiologic studies were performed at the discretion of the treating physician. The decision to start or stop experimental medication treatment for COVID-19 was left to the discretion of the treating physician and informed consent for use of experimental treatments

was obtained from the patient by the individual treating physician separate from this study.

Box 1. Remdesivir and convalescent plasma use criteria.

Remdesivir:

- Symptom onset \leq 10 days
- SpO₂ \leq 94% on room air/on supplemental O₂
- Age < 81 years
- Duration of mechanical ventilation < 24 hours
- GFR \geq 30 ml/min
- AST/ALT < 5 times upper limit normal

Convalescent Plasma:

- Age > 18 years plus one of the following
- Shortness of breath
- Respiratory rate > 30 BPM
- SpO₂ \leq 94% on room air
- PF ratio < 300
- Lung infiltrates > 50% within 24-48 hours
- Respiratory failure
- Septic shock
- Multi organ dysfunction

Information on coexisting medical conditions and concomitant use of select medications such as steroids was obtained from the patient's medical record. For the purpose of this study, cardiovascular disease was defined as history of documented coronary artery disease, previous myocardial infarction, congestive heart failure, or stroke. Acute kidney injury (AKI) was defined as an increase in serum creatinine of 0.3 mg/dL or more within 48 hours or an increase in serum creatinine of greater than 1.5 times the baseline value with the prior 7 days. Patients were considered to have adverse hepatic events if there was an increase in AST or ALT to more than 5 times the upper limit of normal. Cardiac adverse events were defined as unexpected cardiac arrest, development of a new cardiac arrhythmia, an increase in serum troponin to greater than 0.3 ng/mL or prolongation of the QT interval to greater than 500 msec.

All patients were followed from the date of their first positive PCR result until the end of the data collection period, at which time patient data were censored. Descriptive statistics were used to summarize the data and no imputation was made for missing data.

Baseline clinical characteristics were recorded, including APACHE II score and SOFA score. Since an APACHE II and SOFA score could not be calculated for all patients, a six-point ordinal scale was used to classify the severity of disease (Box 2) (11,13).

Box 2. Ordinal Scale

1. Discharged
2. Hospitalized, not requiring supplemental oxygen
3. Hospitalized, requiring supplemental oxygen
4. Hospitalized, requiring nasal hi-flow oxygen, non-invasive mechanical ventilation or both
5. Hospitalized, requiring mechanical ventilation, ECMO or both
6. Death

The primary objective of this study was to compare the effects of CP monotherapy, remdesivir monotherapy, and combination therapy with both remdesivir and CP on chance of survival. For analysis of secondary outcomes patients were grouped by treatment type, CP, remdesivir, and CP + remdesivir. Secondary outcomes included discharge disposition, total hospital length of stay (LOS), ICU LOS, and total ventilation days between each of the three treatment groups. A subgroup analysis was done for patients treated with CP compared with patients treated with CP + remdesivir. Results were also stratified by ABO blood group. We also conducted an exploratory analysis to identify risk factors for mortality. Adverse effects were also evaluated.

Statistical Analysis

Baseline characteristics were stratified by the pharmacotherapy treatment group. Differences in baseline characteristics were analyzed using the Pearson Chi-square and Kruskal Wallis test. Median and interquartile ranges (IQR) were calculated for numerical variables as they were nonparametric. Alpha was set at <0.05. Kaplan-Meier survival plot with log rank (Mantel-Cox) test analysis was conducted to assess significant differences in cumulative survival probability between the CP, RDV, and CP + RDV treatment groups. A multivariable analysis by binary stepwise logistic

regression was used to identify significant predictors of mortality in all patients admitted for COVID-19 who received treatment with CP, RDV, or CP + RDV. Statistics were performed using IBM SPSS Statistics for Windows, Version 26 (IBN Corp., Armonk, NY).

RESULTS

Patient Population

A total of 213 patients with COVID-19 were admitted to our hospital during the study period and 106 patients received one of the three prespecified treatments. Baseline patient characteristics can be found in Table 1. Most of the patients were male and of Hispanic ethnicity. Obesity, diabetes, and hypertension were common comorbidities in the patients included in this study. Significantly more patients in the CP and CP + remdesivir groups were admitted to the ICU compared to the remdesivir group. There were no other significant differences in the baseline characteristics.

Primary Outcome

As seen in the Kaplan-Meier survival curve in Figure 1 comparing survival in patients amongst the three treatment groups, treatment with remdesivir monotherapy showed an increased chance of survival compared to combination therapy or CP monotherapy with this difference approaching statistical significance ($p = 0.052$).

Secondary Outcomes

Secondary outcomes evaluated in this study included discharge disposition, total ventilation days, ICU LOS, and total LOS between the three treatment groups and between blood types (type O versus non-type O). Secondary outcomes are summarized in Table 2. There was a total of 30 deaths during the study period, 24 deaths occurred in patients treated with one of the 3 studied treatment regimens and 6 deaths occurred in patients who did not receive one of these specified treatments. There were 15 deaths in the CP group, 3 deaths in the remdesivir group, and 6 deaths in the CP + remdesivir group. The median (IQR) number of ventilation days was 8 (4.5-14) in the CP group and 12.5 (6-18) in the CP + remdesivir group, with this difference approaching statistical significance ($p = 0.091$). The median (IQR) ICU length of stay was 6 (5-10.5) and 8 (4.5-15.5) days in the CP and CP + remdesivir groups, respectively. This difference was not statistically significant ($p = 0.220$). The median (IQR) length of

stay was 11 (7-15.5), 8 (5-10), and 10 (8-18) days in the CP, remdesivir, and CP + remdesivir groups, respectively. This difference also was not statistically significant ($p = 0.175$) (see Table 2). The single patient admitted to the ICU and intubated in the remdesivir group had an ICU LOS of 26 days and a total of 27 ventilator days.

Based on logistic regression, age ($p = 0.036$), initial SOFA score ($p = 0.013$), and intubation ($p = 0.005$) were found to be statistically significant predictors of mortality. Other independent variables studied were not significant predictors of mortality. Similarly, treatment with either CP ($p = 0.583$) or RDV ($p = 0.999$) alone or in combination ($p = 0.299$) was not a significant predictor of mortality. The logistic regression model explained 72.7% (Nagelkerke R^2) of the variance in mortality and correctly classified 91.3% of cases. Patients with type O blood were also found to have decreased ventilation days, ICU LOS, and total LOS compared to patients with non-type O blood. However, a Mann-Whitney test showed that these differences were not statistically significant (ventilation days p -value of 0.748 with mean rank of 18.38 days for type O and 19.53 days for non-type O; ICU LOS p -value of 0.335 with mean rank 25.96 days for type O and 30.11 days for non-type O; total LOS p -value of 0.899 with mean rank of 47.64 days for type O and 48.35 days for non-type O).

A subgroup analysis was done for patients treated with CP monotherapy versus patients treated with CP and remdesivir combination therapy. In the Kaplan-Meier survival curve in Figure 2 comparing survival in patients treated with CP monotherapy versus combination therapy, combination therapy increased patients' chance of survival and this was statistically significant ($p = 0.045$). When comparing ventilation days, ICU LOS, and total LOS between these two groups, patients treated with CP monotherapy had decreased ventilation days, ICU LOS, and total LOS compared to those treated with combination therapy; however, these differences were not statistically significant (ventilation days p -value of 0.103 with mean rank of 16.48 days for CP monotherapy and 22.31 days for combination therapy; ICU LOS p -value of 0.396 with mean rank of 26.33 days for CP monotherapy and 30.00 days for combination therapy; total LOS p -value of 0.422 with mean rank of 45.98 days for CP monotherapy

Table 1. Baseline Characteristics

	CP (n = 53)	RDV (n=11)	CP + RDV (n=42)	p
Demographics				
Sex – no. (%)				
<i>Female</i>	19 (35.8)	3 (27.3)	15 (35.7)	0.854
<i>Male</i>	34 (64.2)	8 (72.7)	27 (64.3)	
Race or ethnic group – no. (%)				0.245
<i>Hispanic</i>	31 (58.5)	7 (63.6)	28 (66.7)	
<i>Asian</i>	7 (13.2)	1 (9.1)	9 (21.4)	
<i>White</i>	8 (15.1)	1 (9.1)	1 (2.4)	
<i>Black</i>	4 (7.5)	0 (0)	3 (7.1)	
Other	3 (5.7)	2 (18.2)	1 (2.4)	
Median age (IQR ^a) – yr	61 (48-67)	56 (54-68)	50.5 (40.75 – 65.25)	0.096
Clinical Characteristics				
Obesity – no. (%)	32 (60.4)	7 (63.6)	21 (50.0)	0.529
Diabetes – no. (%)	27 (50.9)	4 (36.4)	21 (40.0)	0.670
Cardiovascular Disease – no. (%)	8 (15.1)	0 (0)	2 (4.8)	0.122
Hypertension – no. (%)	25 (47.2)	5 (45.5)	15 (35.7)	0.521
Tobacco Use (current) – no. (%)	2 (3.8)	1 (9.1)	1 (2.4)	0.765
Blood Type O – no. (%)	23 (43.4)	5 (45.5)	23 (54.8)	0.536
Number of Chronic Conditions – median (IQR ^a)	3 (1-5)	2 (1-3)	2 (1-3)	0.064
Baseline Ordinal Scale Score – no. (%)				0.179
Score 2	3 (5.8)	0 (0)	1 (2.4)	
Score 3	14 (26.9)	7 (63.6)	18 (42.9)	
Score 4	19 (36.5)	4 (36.4)	12 (28.6)	
Score 5	16 (30.8)	0 (0)	11 (26.2)	
APACHE score on admission – median (IQR ^a)	10 (6-15)	8 (5.5-11.5)	8 (6 – 13)	0.324
SOFA score on admission – median (IQR ^a)	3 (2-5)	2 (2-4)	2 (2-3)	0.104
Admitted to Intensive Care Unit – no. (%)	30 (56.6)	1 (9.1)	25 (59.5)	<0.01
Intubated – no (%)	23 (45.1)	1 (9.1)	16 (39.0)	0.085
Other Medications Administered				
Azithromycin	41 (77.4)	7 (63.6)	33 (78.6)	0.568
Steroid	52 (98.1)	11 (100)	39 (92.9)	0.322
High-intensity statin	11 (20.8)	1 (9.1)	8 (19.0)	0.667

^a = interquartile range. CP = convalescent plasma. RDV = remdesivir.

and 50.55 days for combination therapy).

A total of 13 treatment-related adverse events occurred during this study. All 3 of the cardiac adverse events that occurred were QT prolongation

due to azithromycin. Transaminitis occurred in 4 patients treated with remdesivir. AKI occurred in 2 patients treated with remdesivir. Two patients experienced infusion reactions from CP.

Table 2. Clinical Outcomes

	CP (n = 53)	RDV (n=11)	CP + RDV (n=42)	p
Discharge disposition (%)				
Death	15 (28.3)	3 (27.3)	6 (14.3)	- ^g
Hospice	0	0	1 (2.4)	- ^g
LTAC ^a	5 (9.4)	1 (9.1)	2 (4.8)	- ^g
SNF ^b	4 (7.6)	0	1 (2.4)	- ^g
Home	29 (54.7)	7 (63.6)	32 (76.2)	- ^g
Ventilation Days – median (IQR ^c)	8 (4.5-14)	- ^d	12.5 (6-18)	0.091
ICU ^e LOS ^f – median (IQR ^c)	6 (5-10.5)	- ^d	8 (4.5-15.5)	0.220
LOS ^f – median (IQR ^c)	11 (7-15.5)	8 (5 – 10)	10 (8-18)	0.175

^a = long-term acute care facility. ^b = skilled nursing facility. ^c = interquartile range. ^d = Sole patient admitted and intubated in the RDV group had an ICU LOS and total ventilator days of 26 and 27 days, respectively. ^e = intensive care unit. ^f = length of stay. ^g = not applicable.

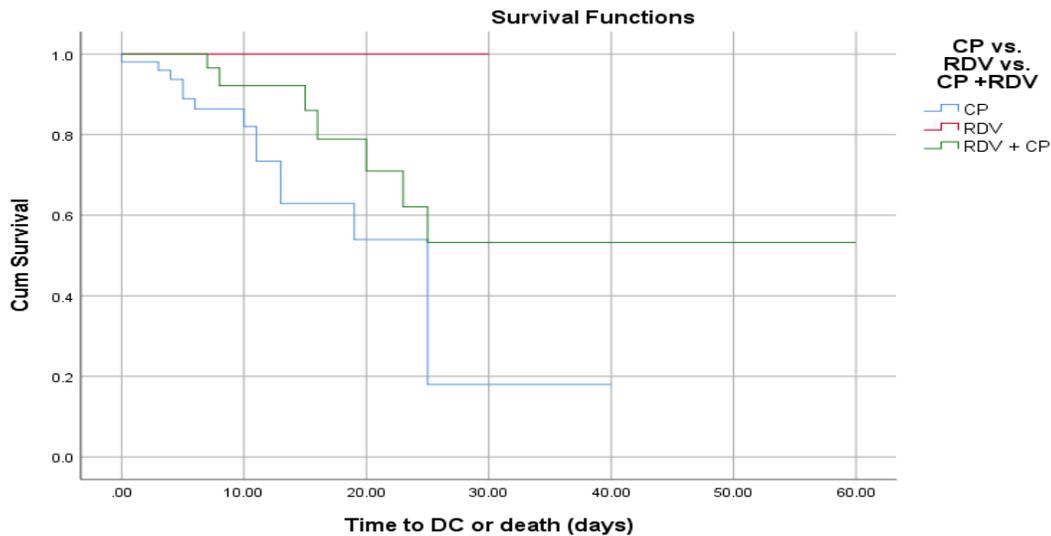


Figure 1. Kaplan Meier Survival Curve of Patients on CP, RDV, or CP + RDV. Treatment with RDV monotherapy showed an increased chance of survival compared to combination therapy or CP monotherapy with this difference approaching statistical significance (p = 0.052).

DISCUSSION

The optimal treatment regimen for COVID-19 remains to be determined. Remdesivir remains the Solidarity trial which showed no significant differences in mortality, initiation of ventilation, or hospital LOS between patients treated with remdesivir or no targeted COVID-19 treatment (25). The results from this study prompted the WHO to recommend against the use of remdesivir in hospitalized patients. Current IDSA guidelines

only medication that has been FDA-approved for the treatment of COVID-19, although the available evidence does not suggest a mortality benefit. The WHO recently published the results from their

continue to recommend the use of remdesivir in hospitalized patients with severe COVID-19 (14). IDSA’s recommendations are based largely on the results of the ACTT-1 trial which showed a significantly shorter time to recovery in remdesivir treated patients (13). In our study, treatment with CP or remdesivir alone or in combination did not result

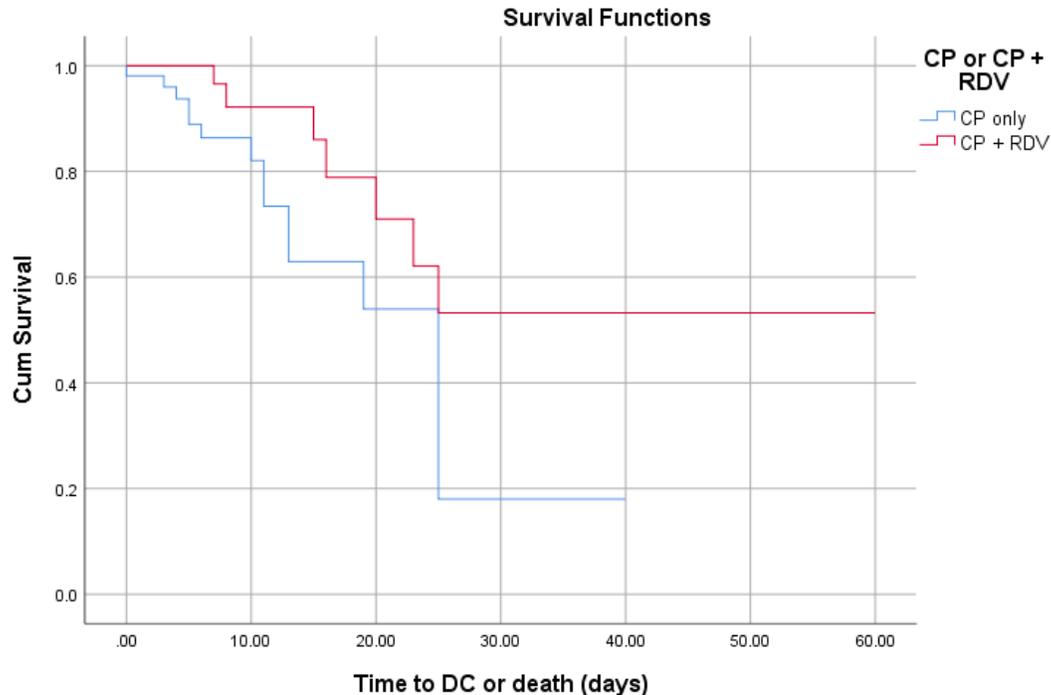


Figure 2. Kaplan Meier Survival Curve of Patients on CP or CP + RDV. Combination therapy increased patients' chance of survival compared to convalescent plasma monotherapy and this difference was statistically significant ($p = 0.045$).

in significant clinical benefit in patients with COVID-19. Neither of these treatments independently affected mortality, ventilation days, ICU LOS, or total LOS. Although remdesivir monotherapy appeared to improve the rate of survival, there were only 11 patients in this treatment group and the difference compared to treatment with CP monotherapy or combination therapy was not statistically significant. However, when comparing patients treated with CP monotherapy versus patients treated with combination therapy, those treated with combination therapy did have a statistically significant difference in improved rate of survival. One potential explanation may be that the majority of the patients in the remdesivir monotherapy group and the combination therapy group had a baseline ordinal score of 3, which would indicate that their illness was not as severe at the time they started treatment. This finding is similar to the findings in the ACTT-1 trial which showed that patients on low-flow oxygen had the greatest benefit from remdesivir therapy (13).

CP was given to a majority of patients in our study, but there were no clear benefits of this therapy. For the primary outcome of survival, the CP monotherapy group had the worst outcomes of the 3

treatment groups. The theoretical benefit of CP is to supply antibodies from recovered patients to help generate a faster immune response until the infected patient's own immune system can generate its own immune response. A trial from the Netherlands was stopped prematurely after finding that a majority of the patients in the trial already had detectable antibodies at the time of randomization. In fact, most of the patients had median antibody titers similar to those of donors (29). Under the initial FDA EUA for CP, there was no requirement for a standardized level of antibodies per unit of plasma. As a result we have no data on how many of our patients received plasma with high levels of neutralizing antibodies. While this may be perceived as a potential limitation, the recently published study by Simonovich and colleagues showed that receipt of high titer plasma had no effect on outcomes (19). In the Simonovich study all patients received transfusion of 2 units of high titer plasma, but there were no significant differences in clinical status or mortality (19). The findings of our study appear to be in line with the growing body of evidence that treatment with CP offers no benefit to patients with COVID-19.

Multiple studies have attempted to evaluate the risk factors associated with mortality in hospitalized

patients with COVID 19. A study conducted in China showed that elderly age (≥ 60 years), male gender, chronic cardiovascular disease (including hypertension, diabetes, coronary heart disease), respiratory disorders, and cerebrovascular disease were associated with risk of death in COVID-19 patients (23). A separate study evaluating patients in 93 countries showed that chronic respiratory diseases (including lung cancer, asthma, COPD), Alzheimer's disease, age >65 years, hypertension, and diabetes are associated with mortality in COVID-19 patients (24). The only risk factors found to be significant in predicting mortality in our study were age, need for intubation, and initial SOFA score. Although most patients had a history of diabetes, obesity, and hypertension, these comorbidities were not statistically significant in predicting mortality. Non-significant findings may be due to the small sample size. Recent data from the CDC shows that most COVID-19-related deaths so far have occurred in White patients, however minority groups particularly Black and Hispanic are disproportionately represented and the number of Hispanic deaths has increased the most so far (29). In our study Hispanic patients were the largest represented ethnic group, and they also had the highest death rate. Most of the patients who tested positive for COVID-19 in our hospital system were Hispanic, and therefore, this finding was not unexpected. This may be a reflection of the ethnic population of the San Joaquin Valley.

A genomewide association study evaluating patients in Europe with severe COVID-19 showed that there may be a specific gene locus associated with ABO blood type and clinical outcome. Patients with blood type A were found to have a higher risk of respiratory failure than other blood types, while type O blood appeared to have a protective effect (26). Blood type did not significantly affect clinical outcomes in our study.

Although treatment-related adverse events did not occur often during our study, they should be kept in mind when making treatment decisions. Transaminitis occurred in 4 patients treated with remdesivir. The medication was held when transaminitis was noted in 3 of these patients and never resumed afterwards. The fourth patient experienced transaminitis one day after completion of the 5-day course. Two patients experienced AKI while on remdesivir. In both patients, remdesivir was held when AKI was noted, then resumed once it resolved and both patients were able to complete a total of 5 days of therapy. Two patients treated with CP experienced infusion reactions. One patient

experienced fever after infusion while the other patient experienced itching that was resolved with diphenhydramine. Daily monitoring of both renal and hepatic function for patients receiving remdesivir is important as development of organ dysfunction may warrant cessation of therapy.

This trial had some limitations. Each treatment group had a small sample size (53 patients treated with CP monotherapy, 11 patients treated with remdesivir monotherapy, and 42 patients treated with combination therapy), therefore it is difficult to generalize these study findings for a larger population. In addition, there was only one patient in ICU that was treated with remdesivir monotherapy compared to the other treatment groups, thus we were unable to accurately determine the clinical benefits of this treatment used alone in patients requiring ICU level of care. The small overall sample size of 106 patients may explain why there is high variability and wide confidence intervals in the logistic regression for risk factors associated with mortality. Several patients did not have their blood types documented, which further decreased the sample size when analyzing this secondary outcome. Out of the patients that did have their blood types available, those with non-type O blood were not further divided into type A, B, or AB as well as RH positive or RH negative, so this may have been a missed opportunity to see if there were any associations with clinical outcomes.

CONCLUSION

No significant differences in survival or clinical outcomes were observed between patients treated with either remdesivir monotherapy, CP monotherapy, or the combination of remdesivir and CP. The possible benefit of remdesivir in patients with more mild disease and the apparent lack of benefit of CP should prompt providers to develop a more targeted approach to the use of COVID-19 treatments. Larger studies should be conducted to determine which patients may benefit the most from the available therapies. Elderly patients, those with a high initial SOFA score, and patients who require intubation are at increased risk of mortality associated with COVID-19. Blood type did not influence clinical outcomes.

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CONFLICTS OF INTEREST. None

REFERENCES

1. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al.* Covid-19 in Critically Ill Patients in the Seattle Region - Case Series: *N Engl J Med.* 2020. DOI: 10.1056/NEJMoa2004500.
2. California Department of Public Health. Two confirmed cases of coronavirus in California. <https://www.cdph.ca.gov/Programs/OPA/Pages/NR20-001.aspx> (accessed 2020 Jun 20).
3. California Department of Public Health. COVID-19 Updates. <https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/ncov2019.aspx> (accessed 2020 Dec 1).
4. San Joaquin County Public Health Services. San Joaquin County Public Health Services report first confirmed case of coronavirus disease 2019 (COVID-19). http://www.sjcphs.org/assets/20200310_PR%20PHS%20REPORTS%20FIRST%20CONFIRMED%20CASE%20OF%20CORONAVIRUS%20DISEASE%202019%20COVID-19.pdf (accessed 2020 Jun 20).
5. San Joaquin County Public Health Services. Coronavirus disease 2019 (COVID-19) outbreak in San Joaquin County understanding the data, facts and precautions. <http://www.sjcphs.org/documents/20200410%20COVID19%20Outbreak%20in%20SJC%20Understanding%20the%20Data%20Facts%20Precautions,%20,%204-10-2020.pdf> (accessed 2020 Jun 20).
6. San Joaquin County Public Health Services. SJC PHS COVID-19 Dashboard. <https://experience.arcgis.com/experience/4ec4f8e1dfd142998d1732c7f5c79e45> (accessed 2020 Dec 1).
7. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant.* 2020;39(5):405-407. doi: 10.1016/j.healun.2020.03.012.
8. National Institutes of Health COVID-19 Treatment Guidelines. <https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/> (accessed 2020 Dec 1).
9. Md Insiat Islam Rabby. (2020). Current Drugs with Potential for Treatment of COVID-19: A Literature Review: Drugs for the Treatment Process of COVID-19. *Journal of Pharmacy & Pharmaceutical Sciences*, 23(1), 58–64. <https://doi.org/10.18433/jpps31002>.
10. Gilzad-Kohan, H., & Jamali, F. (2020). Anti-Inflammatory Properties of Drugs Used to Control COVID-19 and their Effects on the Renin-Angiotensin System and Angiotensin-Converting Enzyme-2. *Journal of Pharmacy & Pharmaceutical Sciences*, 23(1), 259–277. <https://doi.org/10.18433/jpps31346>.
11. Wang W, Zhang D, Du G *et al.* Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial: *Lancet.* 2020. doi: 10.1016/s0140-6736(20)31022-9.
12. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;323(18):1824–1836. doi:10.1001/jama.2020.6019.
13. Beigel J, Tomashek K, Dodd L *et al.* Remdesivir for the treatment of Covid-19 – Final Report: *N Engl J Med.* 2020; 383:1813–1826. DOI: 10.1056/NEJMoa2007764
14. Infectious Diseases Society of America. Therapeutics and interventions: Remdesivir. <https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/remdesivir/> (accessed 2020 Dec 15).
15. World Health Organization. WHO recommends against the use of remdesivir in COVID-19 patients. <https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients> (accessed 2020 Dec 17).
16. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, *et al.* The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015;211(1):80-90. DOI: [10.1093/infdis/jiu396](https://doi.org/10.1093/infdis/jiu396)
17. Joyner MJ, Bruno KA, Klassen SA, *et al.* Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. *Mayo Clin Proc.* 2020;95(9):1888-1897. doi: 10.1016/j.mayocp.2020.06.028.
18. Li L, Zhang W, Hu Y, *et al.* Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A

- Randomized Clinical Trial. *JAMA*. 2020;324(5):460–470. doi: 10.1001/jama.2020.10044.
19. Simonovich VA, Burgos Pratz L.D., Scibona P, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *New Engl J Med*. 2020. DOI: 10.1056/NEJMoa2031304.
 20. Zhong J, Tan J, Ye C, et al. The immunology of COVID-19: is immune modulation an option for treatment?: *Lancet*. 2020. DOI: 10.1016/S2665-9913(20)30120-X.
 21. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020;92(10):1890-1901. doi:10.1002/jmv.25882. doi: 10.1002/jmv.25882
 22. Infectious Diseases Society of America. Therapeutics and interventions: Convalescent Plasma. <https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/convalescent-plasma/> (accessed 2020 Dec 15).
 23. Sun, Y., Feng, Y., Chen, J., et al. Clinical Features of Fatalities in Patients with COVID-19. *Disaster Medicine and Public Health Preparedness*. 2020: 1-3. doi: [10.1017/dmp.2020.235](https://doi.org/10.1017/dmp.2020.235)
 24. Hashim MJ, Alsuwaidi AR, Khan G. Population Risk Factors for COVID-19 Mortality in 93 Countries. *J Epidemiol Glob Health*. 2020;10(3):204-208. doi: 10.2991/jegh.k.200721.001.
 25. Gupta S, Hayek SS, Wang W, et al. Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US. *JAMA Intern Med*. 2020;180(11):1436–1446. doi: 10.1001/jamainternmed.2020.3596
 26. Ellinghaus D, Degenhardt F, Bujanda L et al, for The Severe Covid-19 GWAS Group. Genomewide association study of severe Covid-19 with respiratory failure. *N Engl J Med* 2020;383:1522-34. DOI: 10.1056/NEJMoa2020283
 27. Gold JA, Rossen LM, Ahmad FB, et al. Race, Ethnicity, and Age Trends in Persons Who Died from COVID-19 - United States, May-August 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1517-1521. DOI: <http://dx.doi.org/10.15585/mmwr.mm6942e1>
 28. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for COVID-19 - interim WHO solidarity trial results. *New Engl J Med*. 2020. DOI: 10.1056/NEJMoa2023184. DOI: 10.1056/NEJMoa2023184
 29. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19: a randomized clinical trial. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1>. <https://doi.org/10.1101/2020.07.01.20139857>