CSP #2030: Observational Study of Convalescent Plasma for Treatment of Veterans with COVID-19

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Abstract

Objectives: To determine if early treatment with convalescent plasma (CP) therapy reduces 30-day mortality among Veterans hospitalized at a Department of Veterans Affairs (VA) facility with non-severe COVID-19.

Research Design: This is a non-interventional, retrospective data collection study, designed to emulate a (hypothetical) target randomized trial using observational data from the VA electronic health record (EHR) database. Eligible patients will include Veterans admitted to a VA Medical Center with a SARS-CoV-2 positive test within 7 days of admission, had no prior plasma treatment, and non-severe disease. The intervention is CP administered within 2 days of hospitalization and SARS-CoV-2 positive test. The outcome is 30-day all-cause mortality.

Methodology: This project will access VA healthcare data in the EHR on a national basis. Data will be identified and captured using Computerized Patient Record System (CPRS), on VHA servers and the Corporate Data Warehouse (CDW) using the VA Informatics and Computing Infrastructure (VINCI) servers and non-identifiable data will be captured using the VA REDCap system. This will also include data from the VA Pathology & Laboratory Medicine Service. Additional data will be provided from the Mayo Clinic CP Registry to identify VA patients who have received CP. Death and morbidity, including intensive care unit (ICU) transition, intubation, extubation, and discharge, will be assessed using VHA data. We will fit inverse probability weighted pooled logistic models to estimate the observational analogue of the per-protocol effect of CP on 30-day mortality with cumulative incidence curves, risk differences, and hazard ratios.

Clinical Implications: This project will allow a comprehensive assessment of the impact of convalescent plasma on morbidity and mortality among Veterans with COVID-19. This study aims to produce early evidence on the effectiveness of CP therapy, a promising approach to treating COVID-19. This evidence will help clinicians deliver better clinical care to critically-ill Veterans. In addition, it will set the stage for further research that informs the use of CP in patients with COVID-19.

Acronyms and Abbreviations

CDW	Corporate Data Warehouse
COVID-19	Coronavirus disease 2019
CP	Convalescent plasma
CSP	Cooperative Studies Program
CPRS	Computerized Patient Record System
CSPCO	Cooperative Studies Program Central Office
CSPEC	Cooperative Studies Program Epidemiology Center
EHR	Electronic health record
ICU	Intensive Care Unit
III	Individually-Identifiable Information
PHI	Protected Health Information
R&D	Research and Development
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SSN	Social Security Number
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VINCI	VA Informatics and Computing Infrastructure
VistA	Veterans Health Information Systems and Technology Architecture

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1.0 Study Personnel

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2.0 Introduction

2.1 Background

The epidemic of coronavirus disease 2019 (COVID-19) in Wuhan, China disproportionately infected persons who were older, male, and infirm. [1] Mortality risk and adverse outcomes followed the same pattern.[2] Reports from United States have described a similar pattern of affected individuals.[3] Many Veterans fit the vulnerable profile. As of June 15, 2020, 13,984 Veterans have been tested or treated for known or probable COVID-19 at a Department of Veterans Affairs (VA) facility.[4]

2.2 Rationale

The convalescent plasma (CP) collected from individuals who have recovered from a viral infection contain neutralizing antibodies. Administering CP to individuals who are infected by the virus may reduce symptoms and mortality. There is some evidence of benefit of CP treatment against respiratory illnesses during previous outbreaks, such as severe acute respiratory syndrome (SARS),[5] novel influenza A subtype H1N1,[6] and avian influenza virus subtype H5N1.[7] Recent data suggest that CP may improve outcomes in patients with COVID-19.[8-12] Based on preliminary evidence of possible efficacy, this study will identify early signals of efficacy and

harm by evaluating key outcomes for Veterans with COVID-19 who have received and have not received CP treatment within the Veterans Health Administration (VHA) health care system.

2.3 Relevance to Veterans Health

Preliminary studies on the COVID-19 epidemic show that being male, of increased age, and those who are infirm are disproportionately infected with the disease.[1-3] This population is also thought to have increased risk of mortality and adverse outcomes. Many Veterans fit this profile, and the electronic health record (EHR) used to care for Veterans provides a unique opportunity to assess the morbidity and mortality for Veterans with COVID-19. CP is one of several novel therapies being used in the VHA. Veterans being treated with CP in VHA are tracked by the VA Pathology & Laboratory Medicine Service and the Mayo Clinic CP Registry. This study will provide the opportunity to observationally assess the impact of CP for all Veterans with COVID-19 using robust VHA data sources.

3.0 Aims

We will assess the effect of CP therapy on 30-day mortality in COVID-19 patients early in the hospital course. We will emulate a hypothetical randomized trial (target trial) using observational data from a large national sample of patients who received care within the VA. We will create a VA-based cohort using VA Corporate Data Warehouse (CDW) data and other VHA healthcare data sources, such as the VA Pathology & Laboratory Medicine Service, combined with Mayo Clinic CP Registry data to evaluate the impact of CP among Veterans with COVID-19 on mortality and morbidity.

4.0 Resources and Personnel

4.1 Organizational Structure

The project is a collaboration between the CSP Epidemiology Centers (CSPEC) in Boston, MA and Seattle, WA. The organizational and administrative structure of this study will include the following components: (1) CSP Central Office; and (2) the CSPECs, represented by Boston and Seattle.

The Boston and Seattle CSPECs will share in the overall administrative coordination and oversight of the study. The Study Chairs, Drs. Gaziano and Smith, will perform the scientific coordination of the study in conjunction with the Co-Investigators and CSPEC leadership.

4.2 Personnel, Location, VA Affiliation, and Role in Study

The effort is led by researchers with multidisciplinary expertise in medicine, population-based epidemiology, and biostatistics. All research activities are performed by VA employees or VA affiliates.

- Kelly Cho, PhD, MPH, Director of Data Science and Analytics, VA Boston CSPEC: Co-Investigator - Dr. Cho has experience in advanced phenotyping methods and has been leading the development of the VA Phenomics Library in partnership with the VA research community. She will coordinate all phenotyping efforts using the VA CDW for the collection and classification of clinical data from the EHR. Dr. Cho will have access to individually-identifiable information (III) and protected health information (PHI).
- Juan P Casas, MD, PhD, VA Boston CSPEC: Co-Investigator – Dr. Casas-Romero is a physician and epidemiologist with extensive experience on cohort studies using electronic medical records, genetics and other omics and innovative analytics. He has knowledge in the use of laboratory values from the EHR and the research laboratory. He

will work closely with the Co-Chairs and Co-Investigators on the data analyses for this study. Dr. Casas-Romero will have access to III and PHI.

- David Gagnon, MD, PhD, MPH, VA Boston CSPEC: Co-Investigator – Dr. Gagnon has extensive experience in clinical research, beginning with his involvement in the Framingham Heart Study. His expertise extends to categorical data analysis, statistical computing, survival analysis, longitudinal analysis, clinical trials, and research study design. He will work closely with the Co-Chairs and Co-Investigators on the data analyses for this study. Dr. Gagnon will have access to III and PHI.
- J. Michael Gaziano, MD, MPH, Director, VA Boston CSPEC: Chair – Dr. Gaziano is clinician and epidemiologist with extensive research experience working nationally and internationally on large data studies and biorepositories. He will work closely with his Co-Chair, his team in Boston, and the CSPEC program to achieve the goals of this study. Dr. Gaziano will have access to III and PHI.
- Sarah C. Keithly, MPH, Program Manager, Seattle CSPEC: Co-Investigator – Ms. Keithly is trained in epidemiology and biostatistics and has over 10 years of experience supporting a wide range of epidemiologic research projects, including large-scale surveys, program evaluations, and multi-site studies. She will work closely with the Co-Chairs and Co-Investigators to achieve the goals of this study. She will have access to III and PHI.
- Katherine Kurgansky, MPH, Senior Data Analyst, VA Boston CSPEC – Ms. Kurgansky has over 10 years of experience conducting innovative epidemiology, clinical, and laboratory research, with focus on study design, data analysis, and data interpretation. She will work closely with the Co-Chairs and Co-Investigators on the data analyses for this study. She will have access to III and PHI.
- Nicholas L. Smith, PhD, Director, VA Seattle CSPEC: Chair - Dr. Smith is an experienced and collaborative epidemiologist who has successfully coordinated national and international observational studies among VA and non-VA researchers. He will work closely with his Co-Chair, his team in Seattle, and the CSPEC program to achieve the goals of this study. Dr. Smith will have access to III and PHI.
- Jonathan D. Sugimoto, PhD, MHS, Epidemiologist, VA Seattle CSPEC: Co-Investigator - Dr. Sugimoto is a quantitative epidemiologist with expertise in the design, analysis, and implementation of vaccine trials and a wide range of infectious disease epidemiologic studies. He will work closely with the Chair on the scientific leadership of the study. Dr. Sugimoto will have access to III and PHI.

Only individuals listed as study members on the sites' approved Research and Development (R&D) Committee study staff forms will have access to identifiable data. No identifiable data will be transported or shared outside of the VA for the duration of the study. Analyses conducted on the study will receive internal quality control checks by an approved data analyst that was not involved in the data analysis.

5.0 Study Procedures

5.1 Study Design

This study is an observational study which emulates a hypothetical randomized trial (target trial)[13,14] using observational data from the VHA EHR database. VA data will be used to emulate the eligibility criteria, treatment strategies, outcome, and follow-up of the target trial.

The specifications of the hypothetical trial are as follows. Patients would include Veterans hospitalized at a VA facility with a first-ever SARS-CoV-2 positive test within 7 days of admission, oxygen saturation of ≥90% within the past day, and non-severe COVID-19. Patients previously treated with convalescent plasma or residing in long-term care in the past 90 days would not be eligible. The patient would become eligible at the first SARS-CoV-2–positive test date (if the positive test occurred during hospitalization) or at the hospital admission date (if the positive test occurred before hospitalization). Eligible patients would be randomly assigned to either receive or not receive CP within 2 days of assignment. The primary outcome is 30-day mortality.

This retrospective data collection study will be conducted at the CSPECs within the VA Boston and VA Puget Sound health care systems. This project will access VA healthcare data in the EHR at a national level. Data will be identified and captured using CPRS, on VHA servers and the CDW using VINCI servers. Approved study staff will have access to the VINCI data mart to identify Veterans with positive SARS-CoV-2 testing.

If necessary, data can be extracted from medical records. In this case, data from VINCI/CDW will be reviewed by study staff and entered into a VA REDCap database. Each subject will be assigned a unique study ID and no PHI will be captured within VA REDCap. A crosswalk will be used to link the study ID to the Patient ICN. This document will be the only document to link study data and will be kept secure within the study's VINCI workspace and will only be accessible to a limited number of study staff conducting data review.

5.2 Recruitment Methods

This is non-interventional study that does not require contact with study subjects. All subjects will be identified from the Mayo Clinic CP Registry, the VA Pathology & Laboratory Medicine Service, and from the VA CDW.

5.3 Informed Consent Procedures

There will not be any contact with subjects in the study and study subjects will not be consented into the study. We are requesting an Exemption Category 4.iii for secondary research use of identifiable private information or identifiable biospecimens.

5.4 Inclusion/Exclusion Criteria

The population to study will include all Veterans who have tested positive for SARS-CoV-2 and treated for COVID-19 within the VHA healthcare system. Data available in the VA CDW will be utilized. Data analyses will assess multiple domains at the inpatient and outpatient level and obtained through the central VA COVID-19 Shared Data Resource. Domains for Data Analysis will include, but not limited to, Initial Presentation, Prior Medical Diagnoses, Health Limitations and Habits, Current Medications, Hospital Admission and Lab, Hospital Course, and Post Discharge Course. Data review will begin from date of diagnosis, short- and long-term outcomes will be assessed up to 1-year following diagnosis. There are no exclusion criteria for this study.

5.5 Study Evaluations

This is non-interventional, retrospective data study, and therefore we will be using VA CDW data within the VA healthcare system.

5.6 Data Analysis

Data Collection/Study Measures

Data will be identified and captured using CPRS, on VHA servers and the CDW using the VINCI servers. Data captured will come from several VHA healthcare data sources and National Patient Care Databases (NPCDs), including: VA Pathology & Laboratory Medicine Service,

Veterans Health Information Systems and Technology Architecture (VistA) Medical SAS Outpatient Clinic and Patient Treatment File (PTF) datasets, Vital status crosswalk File with Real SSNs, Vital Status File with Scrambled SSNs, the Decision Support System (DSS) National Data Extract (NDE), Beneficiary Identification Records Locator (BIRLS) death file, Pharmacy files, and Pharmacy Benefit Management (PBM) system database. Data contain information on clinic visits, inpatient hospitalizations within VA, diagnosis, and procedure codes. Pharmacy data and laboratory data are available as well. All electronic databases related to the study will be stored on double password protected servers behind the VA firewall. Data accessed remotely via VINCI or in CDW will be accessible only by approved study personnel using strong IDs and passwords.

As needed, data from VINCI/CDW will be reviewed by study staff and entered into a VA REDCap database. Each Veteran identified will be assigned a unique study ID. A crosswalk document will be kept within VINCI that will link the study ID to the Patient ICN. This document will be the only document to link study data and will be kept secure within on the study's VINCI workspace and will only be accessible to a limited number of study staff conducting data review. The variables below represent a desirable list of information that will be captured using REDCap. We recognize that some of the information will not be available. Where feasible, we will make imputation for some information items.

Analyses conducted on the study will receive internal quality control checks by an approved data analyst that was not involved in the data analysis. Below we describe the primary data and variables we will use to accomplish the aims of the proposal. The list of data and variables is not exhaustive but provides a detailed summary of the types of data will be using**.**

Exposure: CP Treatment

The primary exposure of interest is the use or the non-use of CP. These data are derived from multiple sources, including the VA Pathology and Laboratory Medicine Service, CDW, and the Mayo Clinic CP Registry. Data on CP recipients from the Mayo Clinic and VA Pathology and Laboratory Medicine Service will be matched to EHR data with unique identifiers, which include name, date of birth, VA patient identifiers (e.g., Patient ICN), date of hospitalization, and VA medical center or hospital. Other identifying information to match records may also be available, such as Social Security Numbers from the VA Pathology and Laboratory Medicine Service. Mayo Clinic data will not include Social Security numbers.

Outcome variables

The primary outcome is 30-day all-cause mortality.

Other Covariates of Interest

Initial Presentation: date of encounter, date of birth, sex, race, ethnicity, zip code of residence, date symptoms started.

Prior Medical Diagnoses: chronic obstructive pulmonary disease, coronary heart disease, cardiac failure, diabetes mellitus, hypertension, cerebrovascular disease, chronic liver disease, cancer of solid organ, estimated glomerular filtration rate, immunodeficiency, autoimmune disorder [RA, IBD, lupus, etc.]

Health Limitations and Habits: smoking (never, former, current).

Current medications: diabetes oral medication, diabetes insulin used, immunosuppression therapy, blood pressure therapy, angiotensin converting enzyme angiotensin converting enzyme

(ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, human immunodeficiency virus therapy.

Outpatient Management Course: including symptoms at home, VA physician management, "progression of symptoms" and re-evaluation at the medical center, viral lab testing, and short- and long-term outcomes.

Hospital Admission and Lab: VA Facility, admission date, Initial Admission to (ward, isolation, ICU, ICU on ventilator, other), chest x-ray lung findings at admission, PaO2, admission and hospital course laboratory extremes (white blood cell count, lymphocyte count, platelet count, hemoglobin, CRP, procalcitonin, serum sodium, serum potassium, serum chloride) , and admission and hospital abnormal values (lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine aminotransaminase (ALT), bilirubin total, creatine kinase (CK), dDimer), influenza vaccine in EHR over past 12 months, assay used to diagnose SARS-CoV-2 infection, and co-infection with other respiratory viruses.

Hospital Course: ICU (start date and end date) complications (sepsis, acute kidney injury, rhabdomyolysis, ARDS, disseminated intravascular coagulation, pneumonia diagnosed by MD, hours to pneumonia from admission, hospital treatment (IV antibiotics, IV antifungal, IV antiviral (+name of antiviral), kidney dialysis, glucocorticoids, extra corporeal membrane oxygenation, IV immunoglobulin, IV hyperimmunoglobulin), other COVID-19 treatments, hospital discharge (date) and discharge facility or outcome (residence, nursing facility, death)

Post Discharge: COVID-19 antibody assay results and titer if available. Post discharge general medicine, cardiovascular care, and infectious disease follow up notes to estimate ability to perform activities of daily living. Use of VA medical care facilities and diagnoses in the recovery phase of the epidemic with focus on chronic disease complications with abstraction of information in outpatient encounters and communications with VA providers.

Statistical Analysis Plan

The target trial to emulate would include US Veterans hospitalized at a VA medical center where CP was a current practice. The patient would become eligible at the first SARS-CoV-2-positive test date (if the positive test occurred during hospitalization) or at the hospital admission date (if the positive test occurred before hospitalization).

Eligible patients would be randomly assigned to either receive or not receive CP. The exact timing of transfusion and determination of suitability for use (based on antibody levels or donor characteristics of the plasma units) would be left to the discretion of treating physicians. The primary outcome would be 30-day mortality. The causal contrasts of interest are the intention-to-treat effect and the per-protocol effect. To estimate the intention-to-treat effect (the effect of assignment to CP on outcomes), estimate the risk difference and hazard ratio comparing patients in the CP and non-CP group. The risk (cumulative incidence) of outcomes could be estimated nonparametrically using the Kaplan-Meier method or under parametric smoothing assumptions via a pooled logistic regression model including a time-varying intercept, an indicator for treatment group, and a product ("interaction") term between time and treatment group. The hazard ratio could be estimated from the pooled logistic regression model without the product term. In the case of a prespecified imbalance in baseline characteristics between intervention arms, relevant covariates could be added to the model.

To estimate the per-protocol effect (the effect of treatment with CP on outcomes if all patients had adhered to the protocol), we would restrict the above intention-to-treat analysis to patients who adhered to their assigned treatment (CP or no CP) and adjust for the a priori baseline prognostic factors, as well as trial start day relative to first eligibility. The adjustment for these covariates would be carried out via inverse probability weighting, with all continuous variables

flexibly modeled using restricted cubic splines and estimated weights truncated at the 99.9th percentile to prevent extreme weights from affecting the analyses. In a secondary analysis, the adjustment for these covariates will instead be carried out via standardization. In all analyses, we use nonparametric bootstrapping, which yields unbiased estimates of standard error, to calculate percentile-based confidence intervals (CI) for survival difference and hazard ratio estimates.

Combined analysis with other cohorts in the Mayo Clinic CP Registry: Other health systems in the registry will be performing similarly data analyses. Research groups are encouraged to share the same data analysis plan. Some will contribute summary statistics to a research collaboration.

Sample Size/Power

We present power calculations here for the mortality outcome. It is assumed that approximately 500 subjects will receive CP in the course of this study, extrapolating from the 250 known recipients to date. We would then have 500 exposed and 2,500 unexposed subjects assuming a 5:1 match. As of June 2020, nearly 4,000 COVID-19 patients have been admitted, making our sample viable. Current data shows an approximately 25% mortality rate, among those admitted who either have died or were discharged. Assuming independent observations, we would be able to detect a hazard ratio of 1.3 with 80% power and 1.35 with 90% power. Given the matched design, it is necessary to estimate a design effect due to the matching. A design effect of 2.0 would be considered extreme, assuming an intraclass correlation of 0.20 and cluster size of 6 [5:1]. This would result in an effective sample size of 1500 subjects. This would result in a detectable hazard ratio of 1.43 with 80% power and 1.50 with 90% power. These calculations assume alpha=0.05.

5.7 Withdrawal of Subjects

We will not have contact with study subjects. We do not anticipate that Veterans will contact the study if they know that they received CP. If a study subject contacts the study and requests a withdrawal, we will not collect additional data from the subject. We will, however, continue to use data previously collected.

6.0 Reporting

The Co-Chairs will be jointly responsible for ensuring that the study adheres to the reporting requirements of the VA Central IRB, local R&D Committee(s), and VA/VHA requirements (e.g., VHA Handbook 1200.12 and VHA Handbook 1058.01).

7.0 Privacy and Confidentiality

All data will be stored in compliance with applicable VA policies. This study does not involve patient recruitment. All electronic databases related to the study will be stored on double-password protected servers behind the VA firewall. Once uploaded to networked data servers, the data are maintained in a separate network system dedicated to databases containing PHI or sensitive data. There are multiple levels of security to ensure the integrity and confidentiality of all data stored on the system. The desktop computers and the data servers require authentication for access and these computers and servers are assigned to authorized staff only.

Only personnel approved to be on the study by the R&D Committees will be allowed access to these files. Personnel that are removed from the study will have their access removed. To de-identify and protect PHI, scrambled social security numbers and dates will be used in the

intermediate databases. De-identified information is provided to the PIs by the study team inclusive of the Biostatistician, and database programmer. The final analytic database will not have any PHI and will include aggregated data only. Since the data used is aggregate, this cannot be used to uniquely identify any patient. A crosswalk document linking the study ID to the Patient ICN will be kept within a VINCI workspace. No outside sources can access these data.

Where applicable, we use encryption, physical security measures, restricted access, and locked file cabinets for paper records for data protection. VA study sites will utilize technologies that meet VA standards for data transfer to protect study data during transmission. For example, VA sensitive information will be transmitted using Federal Information Processing Standards (FIPS) 140-2 compliant encryption tools or Secure File Transfer Protocol (SFTP). In accordance with VA policy, incident reporting of theft, loss of data, loss of storage media, unauthorized access to sensitive data or storage media and non-compliance with security controls will be reported promptly to the study PIs, Privacy Officer and Information Security Officer.

Upon study completion, all research data will be maintained and/or destroyed, in accordance with the VHA Records Control Schedule (RCS 10-1) and VA Directive 6500. The study team will implement approved records dispositions, while ensuring that no records are destroyed without proper authorization. Decisions regarding disposal or disposition of the data, if necessitated, will be made with the approval of the appropriate oversight committees and VA regulations.

8.0 Communication Plan

This is an analysis-only protocol involving 2 CSPEC programs, Boston and Seattle. The Chairs and Co-investigators communicate on a regular basis. For this analysis, due to the urgency, we will have weekly analyses to produce results of the associations of interest. As follow-up of Veterans continues for 1 year, we will continue to meet regularly to complete the objectives of the study.

The regulatory documents, including CIRB communications, will be maintained by Seattle and the protocol will be maintained by Boston. Seattle will also be monitoring serious adverse events related to study participation, which is limited to data security.

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