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MAJOR ARTICLE

Impact of Convalescent Plasma Therapy on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibody Profile in Coronavirus Disease 2019 (COVID-19) Patients

Juanjie Tang,[a] Gabrielle Grubbs,[a] Youri Lee,[a] Hana Golding, and Surender Khurana

Division of Viral Products, Center for Biologics Evaluation and Research (CBER), Food and Drug Administrationa (FDA), Silver Spring, Maryland, USA

Convalescent plasma (CP) have been used for treatment of coronavirus disease 2019 (COVID-19), but their effectiveness varies significantly. Moreover, the impact of CP treatment on the composition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in COVID-19 patients and antibody markers that differentiate between those who survive and those who succumb to the COVID-19 disease are not well understood. Herein, we performed longitudinal analysis of antibody profile on 115 sequential plasma samples from 16 hospitalized COVID-19 patients treated with either CP or standard of care, only half of them survived. Differential antibody kinetics was observed for antibody binding, immunoglobulin M/immunoglobulin G/immunoglobulin A (IgM/IgG/IgA) distribution, and affinity maturation in "survived" versus "fatal" COVID-19 patients. Surprisingly, CP treatment did not predict survival. Strikingly, marked decline in neutralization titers was observed in the fatal patients prior to death, and convalescent plasma treatment did not reverse this trend. Furthermore, irrespective of CP treatment, higher antibody affinity to the SARS-CoV-2 prefusion spike was associated with survival outcome. Additionally, sustained elevated IgA response was associated with fatal outcome in these COVID-19 patients. These findings propose that treatment of COVID-19 patients with convalescent plasma should be carefully targeted, and effectiveness of treatment may depend on the clinical and immunological status of COVID-19 patients, as well as the quality of the antibodies in the convalescent plasma.

Keywords. COVID-19; SARS-CoV-2; convalescent plasma; antibody therapy; treatment.

An expedited access to treatment of coronavirus disease 2019 (COVID-19) patients with convalescent plasma (CP) was issued by the Food and Drug Administration (FDA) under Emergency Use Authorization on 23 August 2020. Early studies supported the safety of CP transfusions [1], but their effectiveness remains an area of intense investigation. Li et al reported no significant difference in clinical improvement or mortality between CP treated group versus control group [2]. More recent reports suggested that convalescent plasma with predetermined high titers of neutralizing antibodies (≥1:640) may improve clinical symptoms but did not change the mortality rates [1, 3–6]. However, the impact of CP on the quality of antibody profile of treated COVID-19 patients is not known, and the antibody markers that predict COVID-19 outcome are still not fully understood. Therefore, there is need to perform longitudinal evaluation of the antibody profile in COVID-19 patients treated with/without CP following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to identify the impact of antibody therapy and hopefully to identify antibody markers associated with resolution versus fatal clinical disease outcome.

Therefore, to better understand the impact of convalescent plasma on antibody response in COVID-19 patients, we performed longitudinal analysis of antibody profile in 115 serial samples collected from 16 acute hospitalized COVID-19 patients with different clinical outcomes (fatal vs survived); 8 of these patients were treated with CP. In addition to functional neutralization titers, the evolution of antibody repertoires following SARS-CoV-2 infection was elucidated using surface plasmon resonance (SPR) technology to measure real-time antibody binding kinetics, immunoglobulin isotypes, and affinity maturation against the SARS-CoV-2 native prefusion spike protein.

METHODS

Plasma Samples

In total, 115 longitudinal plasma samples were collected from 16 hospitalized COVID-19 males (age 30–77 years) from the day of admission until patients were discharged or expired at Washington Adventist Medical HealthCare, Maryland (Table

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[a]J. T., G. G., and Y. L. contributed equally to this work.

Correspondence: S. Khurana, Division of Viral Products, CBER, FDA, 10903 New Hampshire Ave, Silver Spring, MD 20993, USA (Surender.Khurana@fda.hhs.gov).

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Table 1. Patient Characteristics, Clinical Features, and Outcomes of the COVID-19 Cohort

Patient ID	Age (years)	Sex	Date Onset of Symptoms	Clinical Outcome	CP (DPoS)	Preexisting Conditions
CP-treated COVID-19 patients						
F-00 (P)	64	Male	4/19/2020	ICU-expired	17	Diabetes, acute chronic kidney disease
F-36 (P)	59	Male	4/19/2020	ICU-expired	22	Diabetes, acute chronic kidney disease
F-46 (P)	30	Male	4/23/2020	ICU-expired	15	Morbidly obese, prediabetic
F-61 (P)	65	Male	4/9/2020	ICU-expired	27	Hypertension
S-81 (P)	52	Male	3/22/2020	ICU-discharged	23	Hypertension, diabetes, kidney disease
S-83 (P)	59	Male	4/16/2020	ICU-discharged	2	Hypertension, obese
S-85 (P)	65	Male	5/5/2020	ICU-discharged	2	Hypertension, morbidly obese
S-94 (P)	63	Male	5/4/2020	ICU-discharged	13	Morbidly obese
Untreated COVID-19 patients						
F-27	48	Male	3/27/2020	ICU-expired	None	Morbidly obese, hypertension, and diabetes mellitus
F-89	77	Female	5/4/2020	ICU-expired	None	Hypertension, morbidly obese
F-92	57	Male	4/26/2020	ICU-expired	None	Diabetes mellitus
F-94	63	Male	5/4/2020	ICU-expired	None	Morbidly obese
S-81	61	Male	7/12/2020	ICU-discharged	None	Hypertension, obese
S-84	53	Male	7/12/2020	ICU-discharged	None	Hypertension
S-93	59	Male	7/10/2020	ICU-discharged	None	Diabetes
S-95	67	Male	7/11/2020	ICU-discharged	None	Diabetes mellitus

Abbreviations: COVID-19, coronavirus disease 2019; CP, convalescent plasma; DPoS, days post-onset of symptoms; F, fatal; ICU, intensive care unit; S, survived.
[c]

1). We designed the study to collect samples for age-matched adults (age >25 years) and at least 1 matched comorbidity (hypertension, obesity, or diabetes); half of them received CP and the other half did not. In a strict clinical trial design nomenclature, this study was not a planned matched case-control study during the early phase of pandemic. All patients were hospitalized in intensive care unit (ICU) with supplementary oxygen and mechanical ventilation. No other immunoglobulin preparations were given to these patients. Even though the planned study was to recruit adults (age >25 years), with equal numbers of males and females; however, during the collection timeframe, most of the patients admitted with COVID-19 at the hospital were males. So, this study observations interpretation may not be commutable to females (Table 1). Eight patients (all males) were treated with CP administered on days 2–26 post-onset of symptoms. Four patients treated with plasma survived (S-81[P], S-83[P], S-85[P], and S-94[P]), whereas 4 succumbed to disease (F-00[P], F-36[P], F-46[P], and F-61P]). Similarly, 4 of the 8 patients (total 7/8 males) not treated with plasma died (F-27, F-89, F-92, and F-94), whereas 4 survived (S-81, S-84, S-93, and S-95). The patients in the sentinel groups of survived versus fatal cases were matched for sex (mostly males), age, and comorbidities (hypertension, diabetes, obesity). We were not unblinded for CP and did not get complete information on which convalescent plasma lot was used for treatment of each specific patient. The neutralization titers for the CP lots ranged between 160–640. This study was approved by FDA's Research Involving Human Subjects Committee (RIHSC 2020-04-02).

Samples were evaluated blindly in SARS-CoV-2 pseudovirus neutralization assay and surface plasmon resonance for antibody titers, isotype analysis, and antibody off-rate constants against SARS-CoV-2 prefusion spike (from Barney Graham, National Institutes of Health [NIH]). Methods were described in detail previously [7, 8].

SARS-CoV-2 Pseudovirus Production and Neutralization Assay

Human codon-optimized cDNA encoding SARS-CoV-2 S glycoprotein (NC_045512) was synthesized by GenScript and cloned into eukaryotic cell expression vector pcDNA 3.1 between the BamH*I* and Xho*I* sites. Pseudovirions were produced by co-transfection Lenti-X 293T cells with pMLV-gag-pol, pFBluc, and pcDNA 3.1 SARS-CoV-2 S using Lipofectamine 3000. The supernatants were harvested at 48 and 72 hours post transfection and filtered through 0.45-mm membranes.

For neutralization assay, 50 µL of SARS-CoV-2 S pseudovirions were preincubated with an equal volume of medium containing plasma at varying dilutions at room temperature for 1 hour; then virus-antibody mixtures were added to Vero E6 cells in a 96-well plate. After a 12-hour incubation, the inoculum was refreshed with fresh medium. Cells were lysed 48 hours later, and luciferase activity was measured using luciferin-containing substrate.

Antibody Binding Kinetics of Post-SARS-CoV-2 Infection Human Plasma to Recombinant Prefusion CoV-2 Spike Protein by Surface Plasmon Resonance (SPR)

SARS-CoV-2 genetically stabilized prefusion spike ectodomain (aa 1-1208), lacking the cytoplasmic and transmembrane domains (delta CT-TM), fused to His tag at C-terminus, was produced in FreeStyle293F mammalian cells. Steady-state equilibrium binding of post-SARS-CoV-2 infected human polyclonal plasma was monitored at 25°C using a ProteOn surface plasmon resonance (BioRad). The purified recombinant SARS-CoV-2 prefusion spike protein was captured via a His-tag to a Ni-NTA sensor chip with 200 resonance units (RU) in the test flow channels. The protein density on the chip was optimized such as to measure monovalent interactions independent of the antibody isotype [8]. Serial dilutions (10-, 50-, and 250-fold) of freshly prepared plasma in BSA-PBST buffer (PBS pH 7.4 buffer with Tween-20 and BSA) were injected at a flow rate of 50 µL/minute (120-second contact duration) for association, and disassociation was performed over a 600-second interval. Responses from the protein surface were corrected for the response from a mock surface and for responses from a buffer-only injection. SPR was performed with serially diluted plasma of each individual time point in this study. Antibody isotype analysis for the SARS-CoV-2 spike protein bound antibodies in the polyclonal plasma was performed using SPR to determine the relative contribution of each antibody isotype: immunoglobulin M (IgM), immunoglobulin G (IgG) (including subclasses), and immunoglobulin A (IgA) in plasma antibody bound to spike protein. Total antibody binding and antibody isotype analysis were calculated with BioRad ProteOn manager software (version 3.1). The resonance units for each antibody isotype was divided by the total resonance units for all the antibody isotypes combined to calculate the percentage of each antibody isotype. All SPR experiments were performed twice, and the researchers performing the assay were blinded to sample identity. Under these optimized SPR conditions, the variation for each sample in duplicate SPR runs was <5%. The maximum resonance units (Max RU) data shown in the figures was the calculated RU signal for the 10-fold diluted plasma sample. In addition to spike-specific binding, total IgM, IgG subtypes, and IgA in serum were measured for each individual during the peak neutralization titers (Supplementary Table 1).

Antibody off-rate constants, which describe the stability of the antigen-antibody complex, that is, the fraction of complexes that decays per second in the dissociation phase, were determined directly from the human polyclonal plasma sample interaction with recombinant purified SARS CoV-2 prefusion spike ectodomain using SPR in the dissociation phase only for the sensorgrams with Max RU in the range of 10–100 RU and calculated using the BioRad ProteOn manager software for the heterogeneous sample model as described before [7, 9]. Off-rate constants were determined from two independent SPR runs. The variation of off-rate between the 2 SPR runs was <4.8%.

Statistical Analysis

Statistical differences were performed using GraphPad prism version 8 (GraphPad Software Inc, San Diego, CA). The statistical significances between the groups were determined by non-parametric (Kruskal-Wallis) statistical test using Dunn's multiple comparisons analysis in GraphPad prism. The differences were considered statistically significant with a 95% confidence interval when the *P* value was less than .05.

Ethics Statement

The study at CBER, FDA was performed under approved study protocol number CBER-2020–04–09 on de-identified plasma donations obtained from COVID-19 patients at the Washington Adventist HealthCare Medical Center. This study complied with all relevant ethical regulations for work with human participants, and informed consent was obtained. Samples were collected from patients who provided informed consent to participate in the study. All assays performed fell within the permissible usages in the original informed consent.

RESULTS

Minimal Impact of Convalescent Plasma on Neutralizing Antibodies in Hospitalized COVID-19 Patients with Different Clinical Outcomes

To better understand the impact of CP on antibody response in COVID-19 patients, we performed comprehensive longitudinal analysis of antibody profiling in 115 serial samples collected from 16 acute hospitalized COVID-19 patients with different clinical outcomes (fatal vs survived). Eight patients were treated with CP administered on days 2–26 post-symptom onset. Four patients treated with plasma survived, whereas 4 succumbed to disease. Similarly, 4 of the 8 patients not treated with plasma died, whereas 4 survived (Table 1).

Despite the small cohort, the patients in the 2 groups (survived and fatal) were well matched for sex (mainly males) and comorbidities (Table 1). We identified a very heterogenous neutralizing antibody responses among the 16 hospitalized COVID-19 patients. Most patients (apart from F-92, F-94, and S-95) developed neutralizing antibodies that peaked around 2 weeks post-symptoms onset (Figure 1A, B). CP (PsVNA50 titers of 160–640) administration did not remarkably change neutralizing antibody titers for 7/8 patients (except S-81 [P]) that were transfused before the start of sample collection (Figure 1A). Strikingly, despite high neutralization titers prior to CP infusion, a decline in neutralization titers was observed in all 4 CP-treated fatal patients prior to their death. In the 4 CP-treated patients who survived, the neutralizing antibody titers prior to CP infusion varied between low (S-85 [P]) to high (S-94 ([P]). After CP infusions, the neutralization titers increased transiently in these survivors.

Among the 4 CP-untreated fatal patients, 3 patients had minimal neutralization titers prior to succumbing to COVID-19 (F-89, F-92, and F-94), whereas in 3/4 survivors (S-81, S-84. and S-93) the neutralization titers continue to increase until release from hospital (Figure 1B). Interestingly, except for F-36 and F-27, 6/8 of the patients who succumbed to disease demonstrated low neutralization titers at the last time-point prior to their demise, irrespective of whether they were treated with CP or no antibody therapy. However, CP transfusions did not have major impact on neutralization titers, irrespective of disease outcome.

Impact of Convalescent Plasma on Evolution of Antibody Binding and Affinity Maturation Against SARS-CoV-2 Prefusion Spike in Hospitalized COVID-19 Patients

Because neutralizing antibodies represent fraction of total antibodies targeting SARS-CoV-2, we evaluated antibody kinetics to measure antibody profile to SARS-CoV-2 prefusion spike, as previously described [7, 10]. Quantitative and qualitative analyses of IgM, IgG, and IgA antibodies were performed on longitudinal human plasma collected frequently from SARS-CoV-2 infected hospitalized patients with COVID-19 disease during acute illness, prior to disease resolution or death, during the entire duration of their hospital stay (1–38 days). In several fatal cases, the antibody binding titers (that account for total binding of all antibody isotypes) were low on the day of admittance to hospital (Figure 1C, 1D, red curves). Following treatment with CP, antibody binding to prefusion spike increased in most patients (Figure 1C). However, they declined after a few days in the fatal patients. In the survivors, the SARS-CoV-2 prefusion spike binding antibodies increased overtime, and CP infusion did not result in appreciable increase of prefusion spike binding antibodies.

In addition to total binding antibodies, it was important to determine if SARS-CoV-2 infection induced antibody affinity maturation against the native prefusion spike. Technically, because antibodies are bivalent, the proper term for their binding to multivalent antigens like viruses is avidity, but here we use the term affinity throughout, because we measured primarily monovalent interactions [7, 10]. Antibody off-rate constants, which describe the stability of the antigen-antibody complex, that is, the fraction of complexes that decays per second in the dissociation phase, were determined directly from the serial dilutions (10-, 50-, and 250-fold) of human plasma interaction with SARS CoV-2 prefusion spike using SPR [7]. The plasma antibody avidity against the prefusion spike was stronger (ie, slower dissociation rates; 0.01–0.001/sec) in survivors compared with fatal patients (~0.1/sec in untreated patient and 0.1–0.01 per sec for CP treated patients) (Figure 1C, D black curves). CP treatment did not remarkably impact the SARS-CoV-2 prefusion

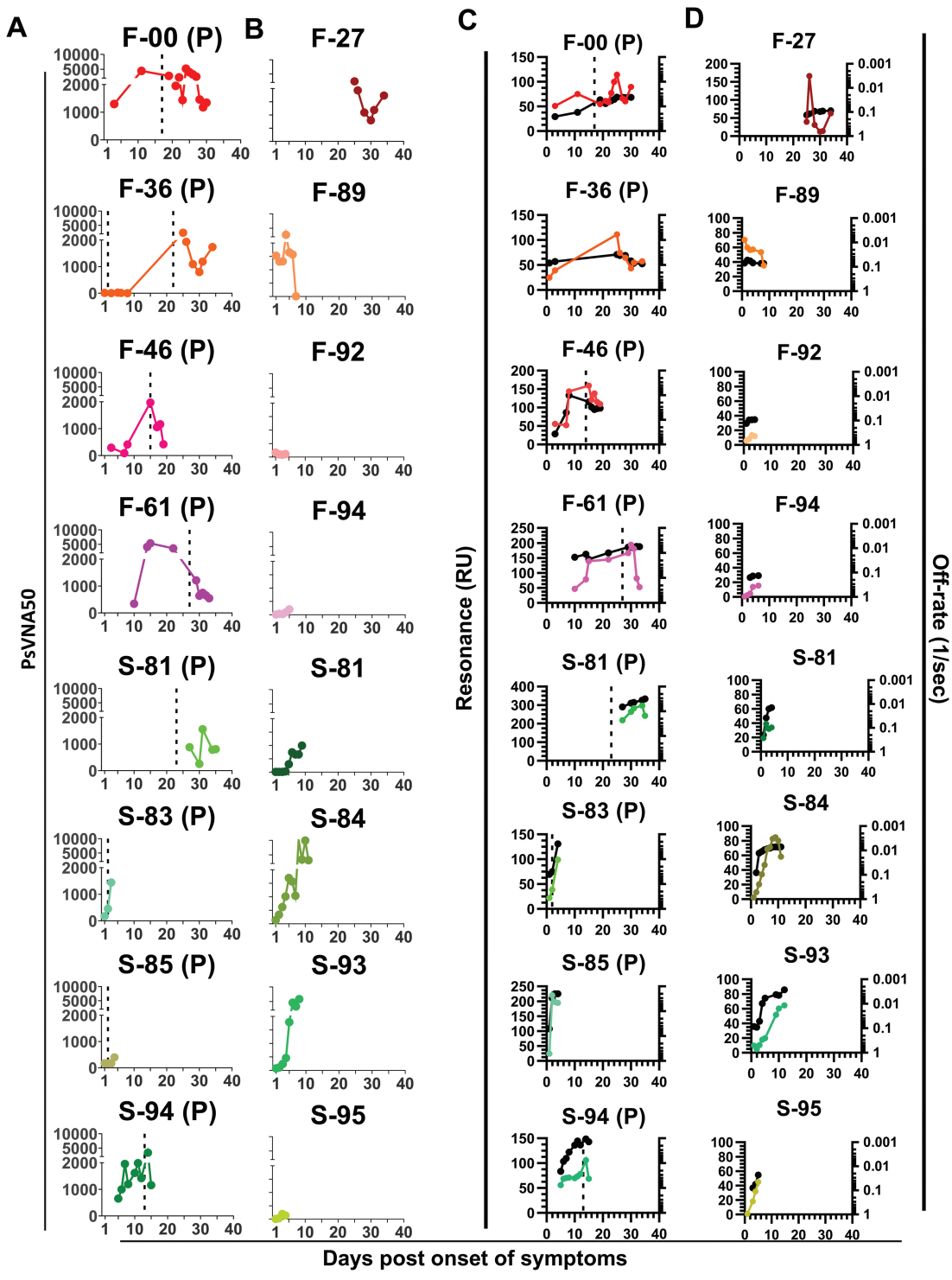

Figure 1. Longitudinal analysis of neutralizing antibody titers, antibody binding titers and antibody affinity maturation before and after CP treatment. (*A*–*B*) SARS-CoV-2 neutralizing antibody titers (PsVNA50; colored lines) in plasma of 16 COVID-19 patients at different days post-onset of symptoms. P: CP treated, F: fatal; in shades of red, and S: survived; in shades of green.*A*, Day of convalescent plasma (PsVNA50 titer ranged from 160 to 640) treatment for each of the 8 COVID-19 patients is indicated by a dotted line on *X*-axis. *B*, Evolution of PsVNA50 titers in 8 COVID-19 patients with no CP treatment. (*C*–*D*) Evolution of antibody binding and antibody avidity to SARS-CoV-2 prefusion spike in COVID-19 patients. Serial dilutions of each plasma sample were analyzed for antibody binding and antibody avidity to SARS-CoV-2 prefusion spike. Total antibody binding is represented as SPR maximum resonance units (RU) (colored lines) of 10-fold diluted plasma samples that account for binding of all antibody isotypes. Binding was determined for individual COVID-19 patients: fatal patients (F; red shades) and survivors (S; green shades) for 8 patients treated with convalescent plasma (*C*) and 8 patients not treated with any antibody therapy (*D*). Plasma antibody off-rate constants against SARS-CoV-2 prefusion spike are shown in black. All SPR experiments were blindly performed twice. Variation for each sample in duplicate SPR runs was <5%. The data shown are average values of 2 experimental runs. Abbreviations: COVID-19, coronavirus disease 2019; CP, convalescent plasma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPR, surface plasmon resonance.

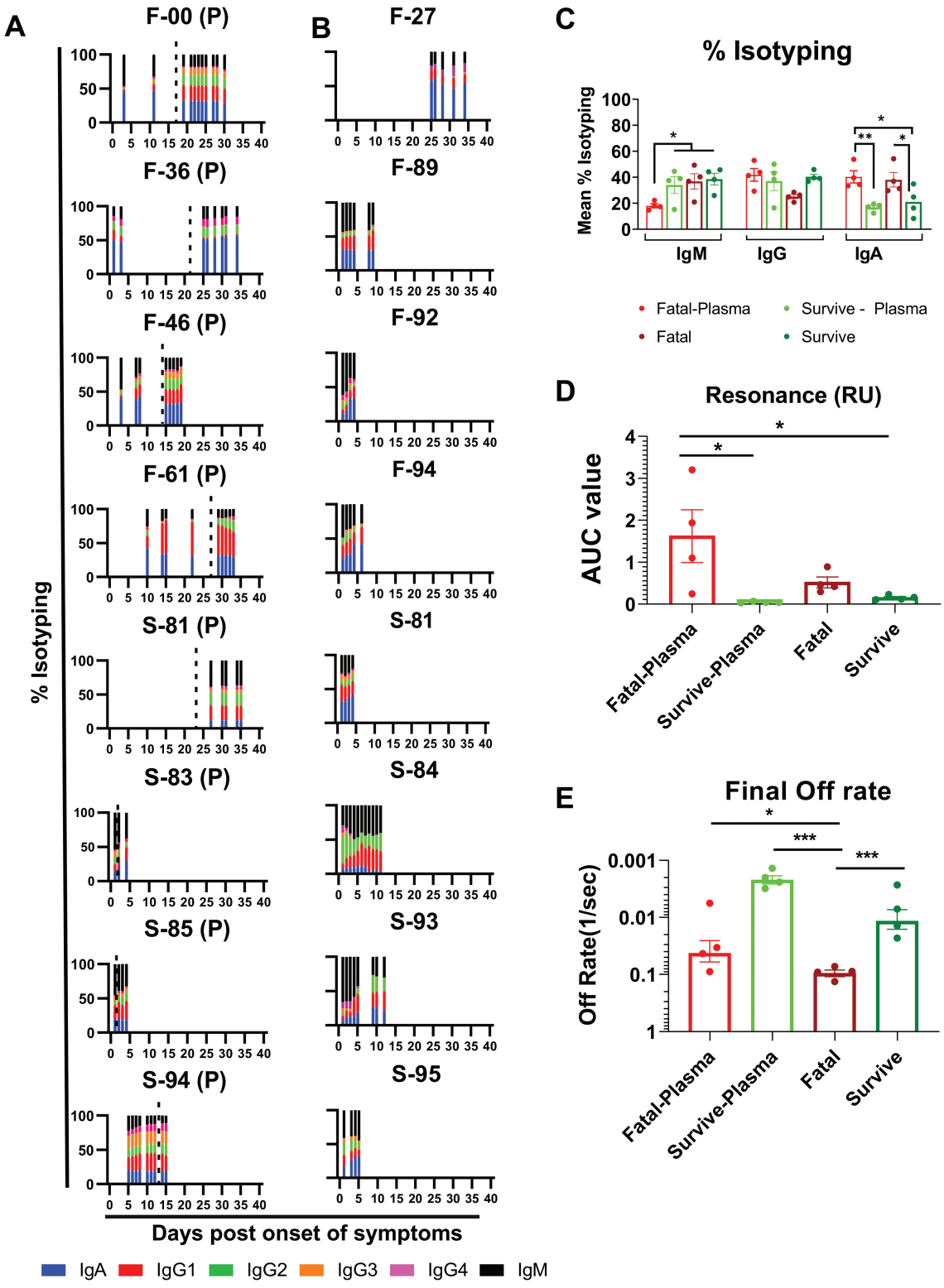

Figure 2. Impact of CP on antibody isotype composition, binding and antibody off-rates to SARS-CoV-2 prefusion spike and their association with clinical outcome. (*A–B*) Percentage of each antibody isotype (according to the color codes; IgM, black; IgA, blue; IgG1, red; IgG2 green; IgG3, orange; IgG4, fuchsia) contribution to binding to SARS-CoV-2 prefusion spike. Resonance units for each antibody isotype was divided by the total resonance units for all the antibody isotypes combined to calculate the percentage of each antibody isotype. *A*, Day of CP treatment is indicated by a dotted line on *X*-axis for each of the 8 COVID-19 patients (P: plasma; F: fatal; S: survived). *B*, Evolution of prefusion-spike bound antibody isotype in 8 COVID-19 patients who were not treated with any antibody therapy (F: fatal; S: survived). *C*, Mean % area under the curve (AUC) of antibody isotypes IgM, IgG, IgA bound to SARS-CoV-2 prefusion spike for the COVID-19 patients who expired (fatal; shades of red) vs survived (green) who were either treated with CP (plasma) or not treated with any antibody therapy. *D*, AUC of SARS-CoV-2 prefusion spike binding antibody levels (RU) for the COVID-19 patients who expired (red) vs. survived (green). Area under the curve (AUC) for the total binding antibodies (RU values in Figure 1) were calculated for the entire duration of hospitalization for these

spike antibody affinity in these of COVID-19 patients (Figure 1C).

Evolution of Isotype Class-Switching Against SARS-CoV-2 Prefusion in Hospitalized COVID-19 Patients

Isotyping analysis revealed that all immunoglobulin isotypes contributed to antibody binding to prefusion spike (Figure 2A, B). CP treatment resulted in increase of IgG subclasses of spike-binding antibodies in some COVID-19 patients (Figure 2A). Most CP-untreated COVID-19 patients contained prefusion spike antibody that consisted of 40–50% IgM isotype during the time of hospitalization (Figure 2B). Interestingly, percent contribution of IgA isotype to spike binding was significantly higher in the fatal COVID-19 patients (Figure 2C). The elevated IgA was sustained throughout the hospitalization period of fatal patients (Figure 2A, B) compared with survivors (Figure 2A–C). Following CP treatment, the percentage of anti-spike IgG isotypes was not significantly different between survivors and fatal patients (Figure 2A–C). We also measured the total IgM, IgG subtypes, and IgA concentrations during the peak neutralization titers (Supplementary Table 1). No statistically significant differences were identified between CP treated and untreated patients or between patients that died or survived (Supplementary Table 1).

The total anti-prefusion spike antibody binding (area under the curve [AUC] of RU values for total antibody binding of all antibody isotypes) was significantly higher in the CP-treated individuals who did not survive compared with the other 3 subgroups (Figure 2D). Therefore, the total antibody binding to prefusion spike negatively associated with survival in this study. Importantly, higher antibody affinity to SARS-CoV-2 prefusion spike was observed for the survivors compared with fatal cases on the final sample collected on the last day of hospitalization prior to their release or demise (Figure 1C, 1D; black lines, and Figure 2E; green bars) for these COVID-19 patients.

Together, these data underscore the limited impact of CP treatment on antibody profile and clinical outcome of severe hospitalized COVID-19 patients.

DISCUSSION

Based on historical reports on the potential use of CP in treatment of acute infectious diseases in hospitalized patients, there was hope that severe COVID-19 patients can benefit from infusion with CP from recovered individuals. At the same time some investigators expressed concerns about potential of enhanced respiratory disease after CP infusions [11, 12]. The FDA Emergency Use Authorization did not specify how the CP should be screened in terms of neutralizing antibody titers and which patient groups are most likely to benefit. Moreover, the impact of CP on the quality of antibody profile of COVID-19 patients is unknown, and antibody parameters that differentiate between those who survive and those who succumb to the COVID-19 disease are not clearly understood. Interestingly, an update to EUA on CP in January 2021 states that potential clinical benefit of transfusion of COVID-19 convalescent plasma in hospitalized patients with COVID-19 is associated with high titer units administered early in the course of disease.

Our study suggests that CP transfusion had minimal or transient impact on the composition of antibodies in hospitalized COVID-19 patients in terms of SARS-CoV-2 neutralization, prefusion spike antibody binding/isotype distribution, and antibody affinity. Positive clinical outcome correlated with high avidity antibodies but not neutralizing antibody titers or level of spike-binding antibodies in most survivors. These findings are in agreement with previous reports on discordance between serum neutralization titers and recovery from COVID-19 and evidence of prefusion spike-specific antibody affinity maturation in COVID-19 survivors [13–16].

In the current and earlier studies, we noticed a drop in virus neutralization titers in majority of ICU-admitted patients within a few days of their demise [15, 16]. The cause for this rapid drop is not fully understood. However, autopsy studies on COVID-19 patients described changes to the endothelial cells in the blood vessels lining the lungs as well as distal organs. Altered endothelial cell metabolism was associated both with thrombosis and loss of barrier intactness [17, 18]. Therefore, it is conceivable that fatal COVID-19 patients experience shift of plasma proteins including immunoglobulins from intravascular to extravascular spaces prior to death.

We identified sustained high IgA responses and minimal antibody affinity maturation against the SARS-CoV-2 prefusion spike as key feature of patients that succumb to the COVID-19 disease. A recent study suggested that IgA2 antibodies against SARS-CoV-2 correlate with NET formation and fatal outcome in severely diseased COVID-19 patients [19].

The treatment of COVID-19 patients with CP should be carefully targeted, and effectiveness may depend on the clinical and immunological status of COVID-19 patients. The most severe patients are less likely to benefit from CP infusions [5, 6, 20]. Furthermore, the selection of CP should be carefully analyzed with emphasis on antibody neutralizing titers [6, 21] and, based

individuals. Bar chart shows datapoints for each individual and presented as mean values ± SEM. *E*, Average antibody affinity against SARS-CoV-2 prefusion spike is shown for the final day sample from the COVID-19 patients who expired (red) vs survived (green) who were either treated or not-treated with CP. Bar chart shows datapoints for each individual and presented as mean values ± SEM. The statistical significances between the groups were determined by non-parametric (Kruskal-Wallis) statistical test using Dunn's multiple comparisons analysis in GraphPad prism. The differences were considered statistically significant with a 95% confidence interval when the *P* value was <.05. * $P < .05$, ** $P < .01$, *** $P < .001$. Abbreviations: COVID-19, coronavirus disease 2019; CP, convalescent plasma; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEM, standard error of the mean.

on the current study, antibody affinity against prefusion spike, to provide the optimal clinical impact of antibody therapy.

There are several limitations to our study. The overall patient size was small (only 16 patients), even though we investigated 115 sequential samples from these 16 patients. We characterized the CP used in the study; however, we were not unblinded to match the CP that were used for treatment of each specific patient. However, the 2 groups matched for age, sex and comorbidities and the percentage of survival vs. fatal outcome were the same.

This study underscores the importance of following COVID-19 patients over the entire hospitalization period and collection of sequential samples for multi-assay analyses. The interplay between exogenous and endogenous antibodies may provide important information that can help in the management of COVID-19 patients. This approach will promote identification of predictive antibody markers of disease outcome and assist in evaluating the impact of CP or other immunoglobulin preparations (ie, monoclonal antibodies and hyperimmune CoV-2 immunoglobulins).

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions: Designed research: S. K.; **Clinical specimens and clinical data:** H. G.; **Performed research:** J. T., Y. L., G. G., and S.K.; **Contributed to Writing:** S. K. and H. G.

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