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Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

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The efficacy of convalescent plasma for coronavirus disease 2019 (COVID-19) is unclear. Although most randomized controlled trials have shown negative results, uncontrolled studies have suggested that the antibody content could influence patient outcomes. We conducted an open-label, randomized controlled trial of convalescent plasma for adults with COVID-19 receiving oxygen within 12 d of respiratory symptom onset (NCT04348656). Patients were allocated 2:1 to 500 ml of convalescent plasma or standard of care. The composite primary outcome was intubation or death by 30 d. Exploratory analyses of the effect of convalescent plasma antibodies on the primary outcome was assessed by logistic regression. The trial was terminated at 78% of planned enrollment after meeting stopping criteria for futility. In total, 940 patients were randomized, and 921 patients were included in the intention-to-treat analysis. Intubation or death occurred in 199/614 (32.4%) patients in the convalescent plasma arm and 86/307 (28.0%) patients in the standard of care arm—relative risk (RR) = 1.16 (95% confidence interval (CI) 0.94–1.43, *P* = 0.18). Patients in the convalescent plasma arm had more serious adverse events (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, *P* = 0.034). The antibody content significantly modulated the therapeutic effect of convalescent plasma. In multivariate analysis, each standardized log increase in neutralization or antibody-dependent cellular cytotoxicity independently reduced the potential harmful effect of plasma (odds ratio (OR) = 0.74, 95% CI 0.57–0.95 and OR = 0.66, 95% CI 0.50–0.87, respectively), whereas IgG against the full transmembrane spike protein increased it (OR = 1.53, 95% CI 1.14–2.05). Convalescent plasma did not reduce the risk of intubation or death at 30 d in hospitalized patients with COVID-19. Transfusion of convalescent plasma with unfavorable antibody profiles could be associated with worse clinical outcomes compared to standard care.

The immune response after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection results in the formation of antibodies that can interfere with viral replication and infection of host cells in over 95% of patients[1]. Based on previous experience in other viral infections[2], the use of convalescent plasma has been proposed as a therapeutic form of passive immunization for patients with acute COVID-19 (refs. [3,4]). Early in the pandemic, several small randomized trials found no difference in clinical outcomes[5–8]. In the United States, an Extended Access Program outside of a controlled trial led to the use of convalescent plasma in over half a million patients. Data from these patients showed that the transfusion of plasma with high anti-SARS-CoV-2 antibody levels was associated with a lower risk of death in non-intubated patients compared to lower antibody levels; however, this study lacked a control group[9]. The RECOVERY trial was a large randomized trial in 11,558 hospitalized patients that found that the risk of death after the administration of high-titer plasma was not different from standard of care[10].

The Convalescent Plasma for COVID-19 Respiratory Illness (CONCOR-1) trial was a multi-center, international, open-label, randomized controlled trial designed to assess the effectiveness and safety of COVID-19 convalescent plasma in hospitalized patients. The trial used plasma collected from four blood suppliers with a range of anti-SARS-CoV-2 antibody levels. The variability in antibody titers allowed for a characterization of the effect-modifying role of functional and quantitative antibodies on the primary outcome (intubation or death at 30 d).

Results

Patients. This trial was stopped at the planned interim analysis because the conditional power estimate was 1.6% (below the stopping criterion of 20%). Between 14 May 2020 and 29 January 2021, 940 patients were randomized (2:1) to convalescent plasma or standard of care in 72 hospital sites in Canada, the United States and Brazil (Fig. 1 and Supplementary Table 1). Two patients randomized

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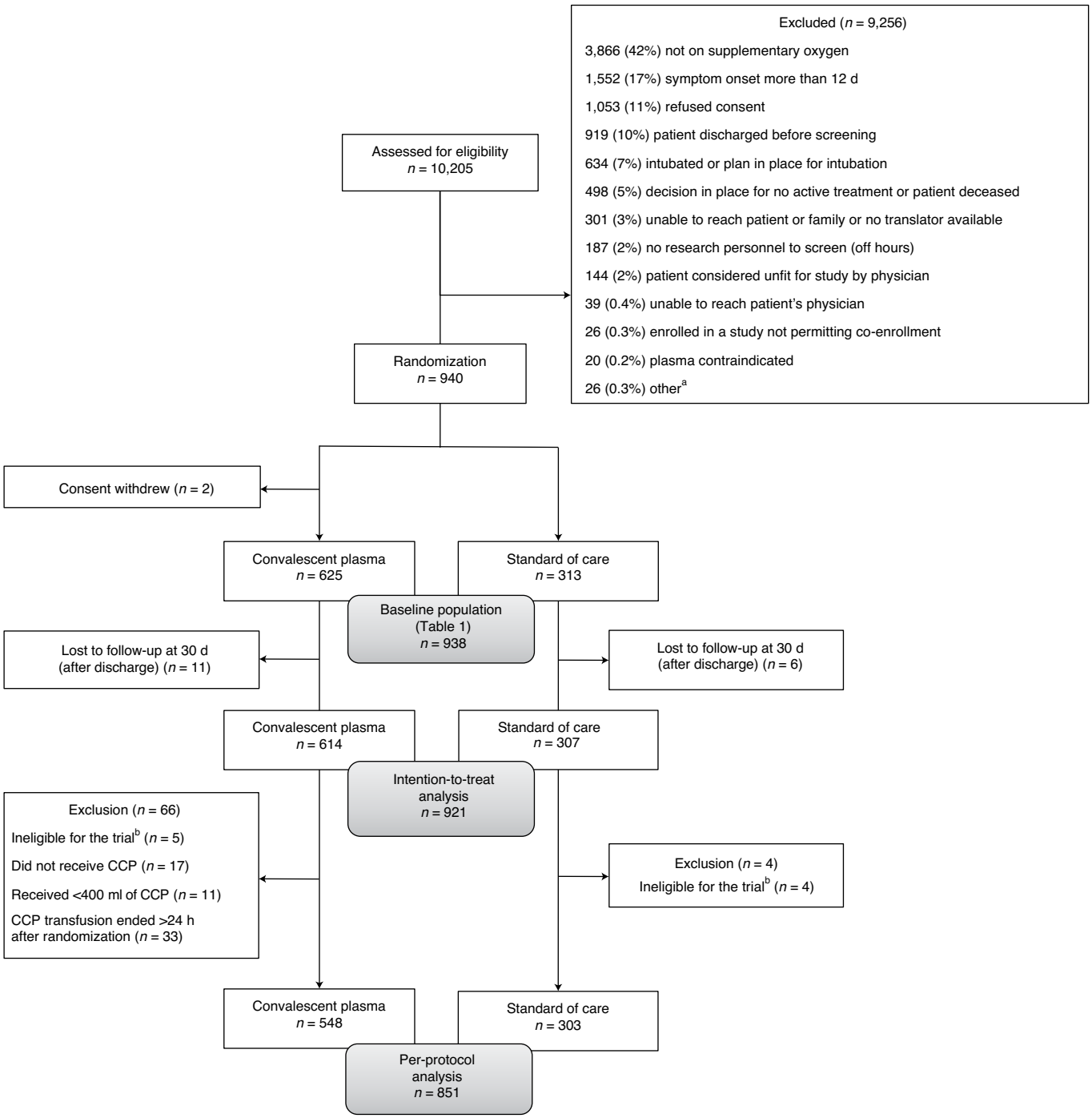

Fig. 1 | Enrollment, randomization and follow-up. Patient flow in the CONCOR-1 study detailing the intention-to-treat population, per-protocol analysis population and excluded patients. Other[a], $n=26$: <16 years of age ($n=13$), <18 years of age ($n=5$), ABO-compatible plasma unavailable ($n=5$) and other ($n=3$). [b]Includes not receiving supplemental oxygen at the time of randomization (but on oxygen at screening) and any symptom onset >12 d before randomization for protocol version 5.0 or earlier.

to plasma withdrew consent before treatment. Demographics of the baseline study population ($n=938$) were balanced between groups for all study populations (Table 1 and Supplementary Tables 2 and 3). The median age was 69 years, with 59% male and 41% female, and the median time from the onset of any COVID-19 symptom was 8 d (interquartile range (IQR), 5–10 d). Most patients ($n=766$, 81.7%) were receiving systemic corticosteroids at the time of enrolment. Seventeen patients were lost to follow-up between discharge and day 30, precluding assessment of the primary outcome.

Primary outcome. In the intention-to-treat population ($n=921$), intubation or death occurred in 199 (32.4%) of 614 patients in the convalescent plasma group and 86 (28.0%) of 307 patients in the standard of care group (RR = 1.16, 95% CI 0.94–1.43, $P=0.18$) (Fig. 2a). The time to intubation or death was not significantly different between groups (Fig. 2b). In the per-protocol analysis ($n=851$), intubation or death occurred in 167 (30.5%) of 548 patients in the convalescent plasma group and 85 (28.1%) of 303 patients in the standard of care group (RR = 1.09, 95% CI 0.87–1.35, $P=0.46$) (Supplementary Table 4).

Table 1 | Characteristics of the baseline study population (excluding two patients who withdrew consent). Categorical data are presented as number (percentage) and continuous variables as mean ± standard deviation and median (IQR)

Characteristic	Convalescent plasma, $n = 625$	Standard of care, $n = 313$	Overall, $n = 938$
Age, years	67.7 ± 16.0; 69 (58, 80)	67.1 ± 14.8; 68 (58, 78)	67.5 ± 15.6; 69 (58, 79)
≥60 years	438 (70.1)	218 (69.6)	656 (69.9)
Sex			
Male	369 (59.0)	185 (59.1)	554 (59.1)
Female	256 (41.0)	128 (40.9)	384 (40.9)
Pregnant at randomization	4 (0.6)	1 (0.3)	5 (0.5)
Ethnicity			
White	305 (48.8)	153 (48.9)	458 (48.8)
Asian	104 (16.6)	46 (14.7)	150 (16.0)
Hispanic or Latino	34 (5.4)	9 (2.9)	43 (4.6)
Black	25 (4.0)	11 (3.5)	36 (3.8)
Other	38 (6.1)	28 (8.9)	66 (7.0)
Unknown	119 (19.0)	66 (21.1)	185 (19.7)
ABO blood group			
O	270 (43.2)	113 (36.1)	383 (40.8)
A	235 (37.6)	121 (38.7)	356 (38.0)
B	89 (14.2)	57 (18.2)	146 (15.6)
AB	31 (5.0)	22 (7.0)	53 (5.7)
BMI (kg m^{-2})	30.0 ± 7.5; 29 (25, 33)	30.0 ± 7.4; 29 (25, 33)	30.0 ± 7.4; 29 (25, 33)
BMI < 30	256 (41.0)	123 (39.3)	379 (40.4)
BMI ≥ 30	198 (31.7)	102 (32.6)	300 (32.0)
Unknown	171 (27.4)	88 (28.1)	259 (27.6)
Presence of comorbidity			
Diabetes	220 (35.2)	108 (34.5)	328 (35.0)
Cardiac disease	385 (61.6)	197 (62.9)	582 (62.0)
Baseline respiratory diseases	147 (23.5)	79 (25.2)	226 (24.1)
Abnormal CT chest or chest X-ray result before randomization	563 (90.1)	266 (85.0)	829 (88.4)
Medication for other research study at baseline	53 (8.5)	41 (13.1)	94 (10.0)
Medication for COVID-19 at baseline			
Azithromycin	279 (44.6)	137 (43.8)	416 (44.3)
Other antibiotics	405 (64.8)	186 (59.4)	591 (63.0)
Systemic corticosteroids	496 (79.4)	258 (82.4)	754 (80.4)
Antiviral medications	165 (26.4)	80 (25.6)	245 (26.1)
Anticoagulants	355 (56.8)	180 (57.5)	535 (57.0)
Other COVID-19 medications	79 (12.6)	3 9(12.5)	118 (12.6)
Medication not for COVID-19 at baseline			
ACE inhibitor	85 (13.6)	63 (20.1)	148 (15.8)
ACE receptor blocker	77 (12.3)	47 (15.0)	124 (13.2)
Non-steroidal anti-inflammatory drugs	77 (12.3)	52 (16.6)	129 (13.8)
Colchicine	5 (0.8)	2 (0.6)	7 (0.7)
Systemic corticosteroids	61 (9.8)	35 (11.2)	96 (10.2)
Inhaled corticosteroids	84 (13.4)	42 (13.4)	126 (13.4)
Immunomodulatory agents	22 (3.5)	18 (5.8)	40 (4.3)
Anticoagulants	135 (21.6)	64 (20.4)	199 (21.2)
Systemic corticosteroids at baseline	504 (80.6)	262 (83.7)	766 (81.7)
Oxygen status at baseline (FiO_2)	49.5 ± 25.2; 40 (30, 65)	48.8 ± 25.1; 40 (30, 60)	49.3 ± 25.2; 40 (30, 60)
Time from any symptom onset to randomization (d)	8.0 ± 3.8; 8 (5, 10)	7.8 ± 3.4; 8 (5, 10)	7.9 ± 3.7; 8 (5, 10)
Time from COVID-19 diagnosis[a] to randomization (d)	4.9 ± 3.6; 4 (2, 7)	5.1 ± 4.4; 4 (2, 7)	5.0 ± 3.9; 4 (2, 7)
Location at randomization			
Ward	505 (80.8)	260 (83.1)	765 (81.6)
ICU	120 (19.2)	53 (16.9)	173 (18.4)
Enrolled in other clinical trials	168 (26.9)	98 (31.3)	266 (28.4)

[a]Day of positive COVID-19 test ACE, angiotensin-converting enzyme; BMI, body mass index; CT, computed tomography; FiO_2, fraction of inhaled oxygen; ICU, intensive care unit.

a

	Convalescent plasma	Standard of care	Treatment effect[a]
Intention-to-treat population with data on primary outcome available (n = 921)[b]	n = 614	n = 307	
Intubation or death at day 30 (n, %)	199 (32.4)	86 (28.0)	RR = 1.16 (0.94, 1.43), P = 0.18
Time to Intubation or in-hospital death by day 30 (d)	–	–	HR = 1.14 (0.89, 1.47), P = 0.30
Ventilation-free days by day 30 (d)	23.4 ± 10.4	24.0 ± 10.5	MD = –0.6 (–2.1, 0.7), P = 0.41
Any death by day 30 (n, %)	141 (23.0)	63 (20.5)	RR = 1.12 (0.86, 1.46), P = 0.40
Length of stay in ICU by day 30 (d)	4.3 ± 7.9	3.7 ± 7.1	MD = 0.7 (–0.3, 1.7), P = 0.22
Need for kidney replacement therapy by day 30 (n, %)[c]	10 (1.6)	6 (2.0)	RR = 0.83 (0.31, 2.27), P = 0.72
Serious adverse event by day 30 (n, %)	205 (33.4)	81 (26.4)	RR = 1.27 (1.02, 1.57), P = 0.03
Grade ≥3 events (severe)	260 (42.3)	109 (35.5)	RR = 1.19 (1.00,1.42), P = 0.05
Grade ≥4 events (life-threatening)	188 (30.6)	74 (24.1)	RR = 1.27 (1.01,1.60), P = 0.04
Grade 5 events (fatal)	141 (23.0)	63 (20.5)	RR = 1.12 (0.86,1.46), P = 0.40
Baseline study population (n = 938)[d]	n = 625	n = 313	
In-hospital death by day 90 (n, %)	156 (25.0)	69 (22.0)	RR = 1.13 (0.88, 1.45), P = 0.33
Time to in-hospital death by day 90	–	–	HR = 1.02 (0.76, 1.35), P = 0.91
Length of stay in hospital by day 90	–	–	HR = 0.91 (0.80, 1.04), P = 0.18

b

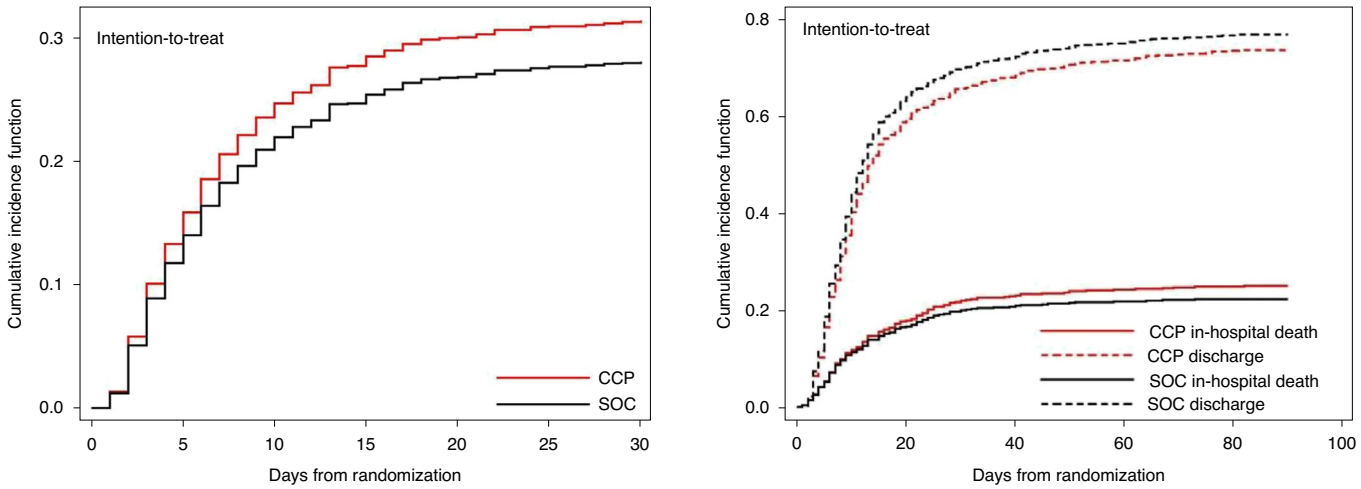

Fig. 2 | Study outcomes. a, Patient outcomes for the primary and secondary endpoints. **b**, Cumulative incidence functions of the primary outcome (intubation or death) by day 30 and of in-hospital death by day 90. [a]RR and 95% CI; hazard ratio ((HR), 95% CI); and mean difference ((MD), with 95% CI based on robust bootstrap standard errors). [b]Seventeen patients were discharged before day 30 and were lost to follow-up at 30 d, and two withdrew consent before day 30; thus, outcomes collected at day 30 (primary outcome and some other secondary outcomes for day 30) were missing. [c]Excluding 11 patients on chronic kidney replacement therapy at baseline. [d]Intention-to-treat survival analyses were based on the complete baseline population (940 randomized patients minus two patients who withdrew consent).

Secondary efficacy outcomes and subgroup analyses. Secondary outcomes for the intention-to-treat population are shown in Fig. 2a. There were no differences in mortality or intubation or other secondary efficacy outcomes. Similarly, in the per-protocol analysis, there were no differences in the secondary efficacy outcomes (Supplementary Table 4 and Extended Data Figs. 1–3). No significant differences were observed in most subgroups, including time from diagnosis to randomization <3 d for both the intention-to-treat (Fig. 3) and per-protocol (Extended Data Fig. 4) populations. The subgroup of patients served by blood supplier 3 (Fig. 3) and the post hoc subgroup of patients who were not receiving corticosteroids (Extended Data Figs. 5 and 6) had worse outcomes with convalescent plasma compared to standard of care.

Safety. Serious adverse events occurred in 205 (33.4%) of 614 patients in the convalescent plasma arm compared to 81 (26.4%) of

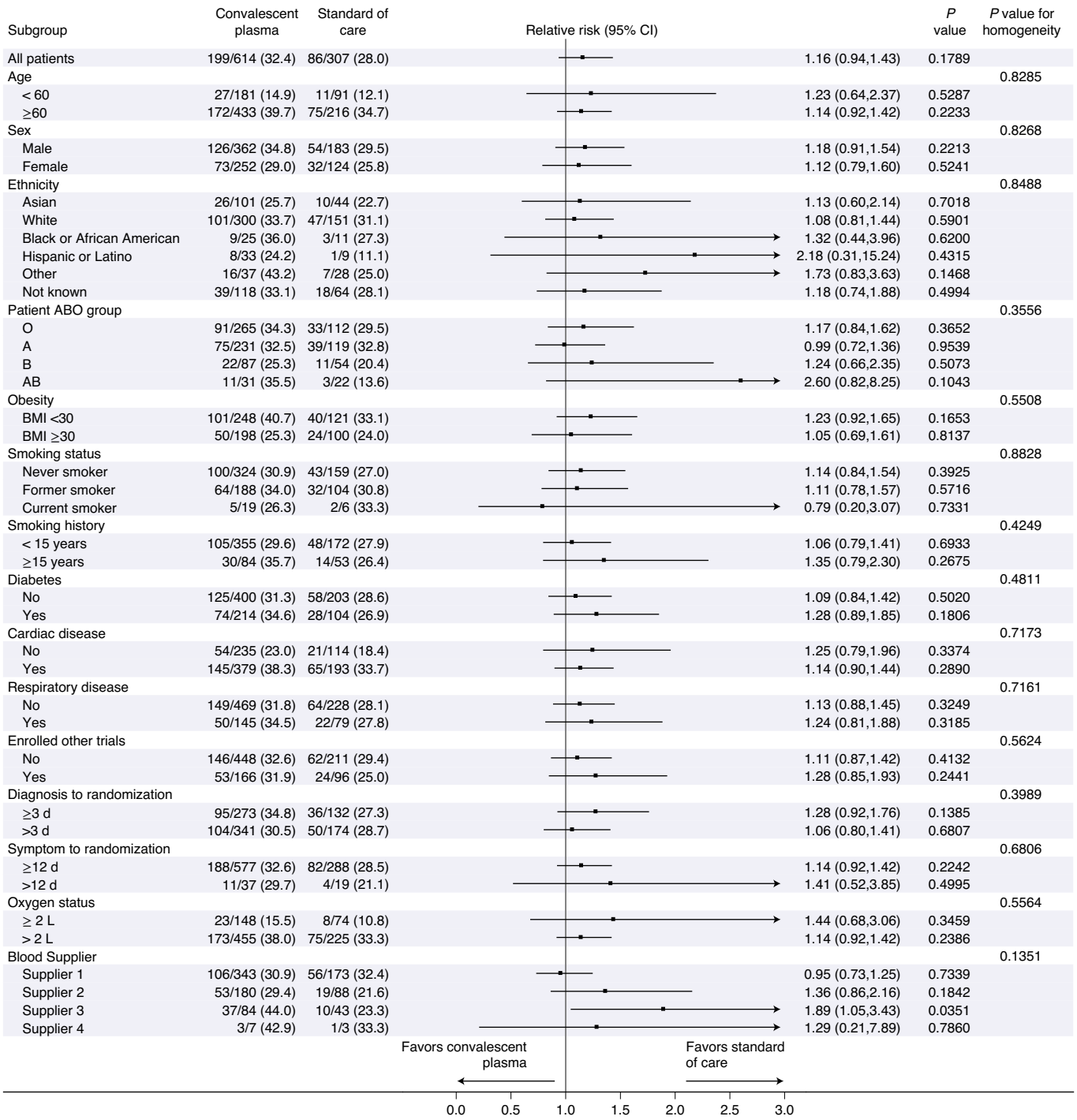

Fig. 3 | Subgroup analyses. Forest plots are presented for the subgroup analyses for the intention-to-treat population. *P* values for RR and homogeneity are two sided without adjustment for multiple comparisons. BMI, body mass index.

307 patients in the standard of care arm for the intention-to-treat population (RR = 1.27, 95% CI 1.02–1.57, $P = 0.034$; Fig. 2a and Supplementary Tables 4–6). Most of these events were worsening hypoxemia and respiratory failure. Transfusion-related complications were recorded in 35 (5.7%) of 614 patients in the convalescent plasma group (Supplementary Tables 7 and 8). Of the 35 reactions, four were life-threatening (two transfusion-associated circulatory overload, one possible transfusion-related acute lung injury and one transfusion-associated dyspnea), and none was fatal. Thirteen of the 35 reactions were classified as transfusion-associated dyspnea. Two patients underwent serological investigation for transfusion-related acute lung injury (both negative).

Effect-modifying role of antibodies in convalescent plasma. The distributions of antibodies in convalescent plasma units varied by blood supplier (Fig. 4, Supplementary Table 9 and Extended Data Fig. 7); therefore, antibody analyses controlled for supplier to address possible confounding. Transfusion of convalescent plasma with average (log-transformed) levels of antibody-dependent cellular cytotoxicity (ADCC) yielded an OR of 1.16 (95% CI 0.85–1.57)

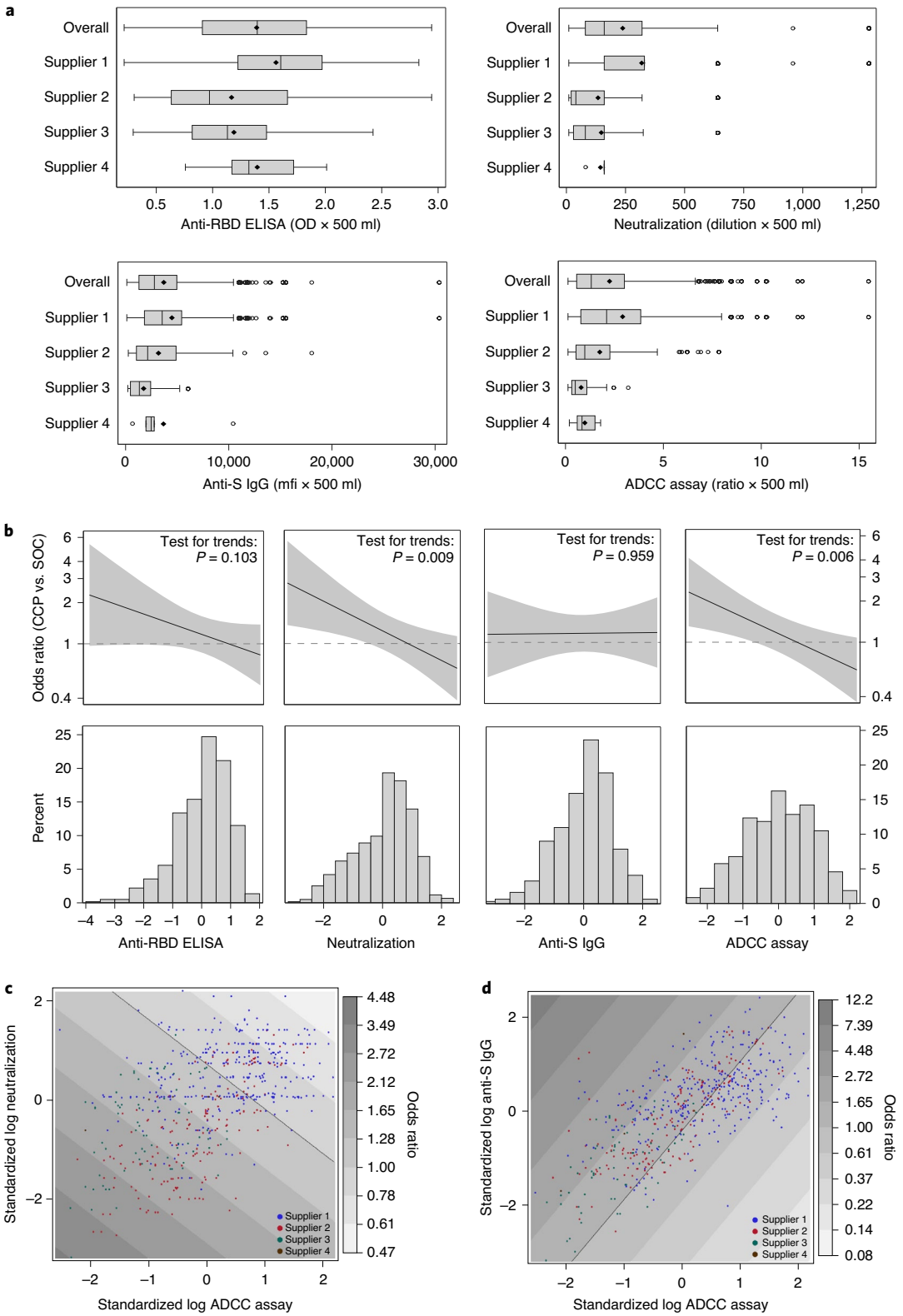

Fig. 4 | The effect-modifying role of convalescent plasma antibody content for the primary outcome. a, Absolute antibody amounts transfused per patient ($n=597$) in the CCP arm for each marker, expressed as the product of volume and concentration. Center line: median; box limits: 25th and 75th percentiles; whiskers: 1.5× IQR; points: outliers. **b**, Effect-modifying role of CCP content for the primary outcome for each marker. The top row presents the trends in CCP effect compared to SOC as a function of the marker value, along with 95% CIs. Marker values are expressed as standard deviations of log values centered around the mean (standardized log). The horizontal dotted line represents CCP with no effect (OR=1). The *P* values (two-sided test for trend without adjustment for multiple comparisons) refer to the effect modification observed with each marker (Supplementary Table 10). The histograms present the frequency distribution by marker. **c**,**d**, Contour plots of the OR for the primary outcome as a function of marker combinations. Overlaid data points indicate the value of the two markers for each CCP transfusion. Mfi, mean fluorescence intensity; OD, optical density; S, SARS-CoV-2 spike protein; SOC, standard of care.

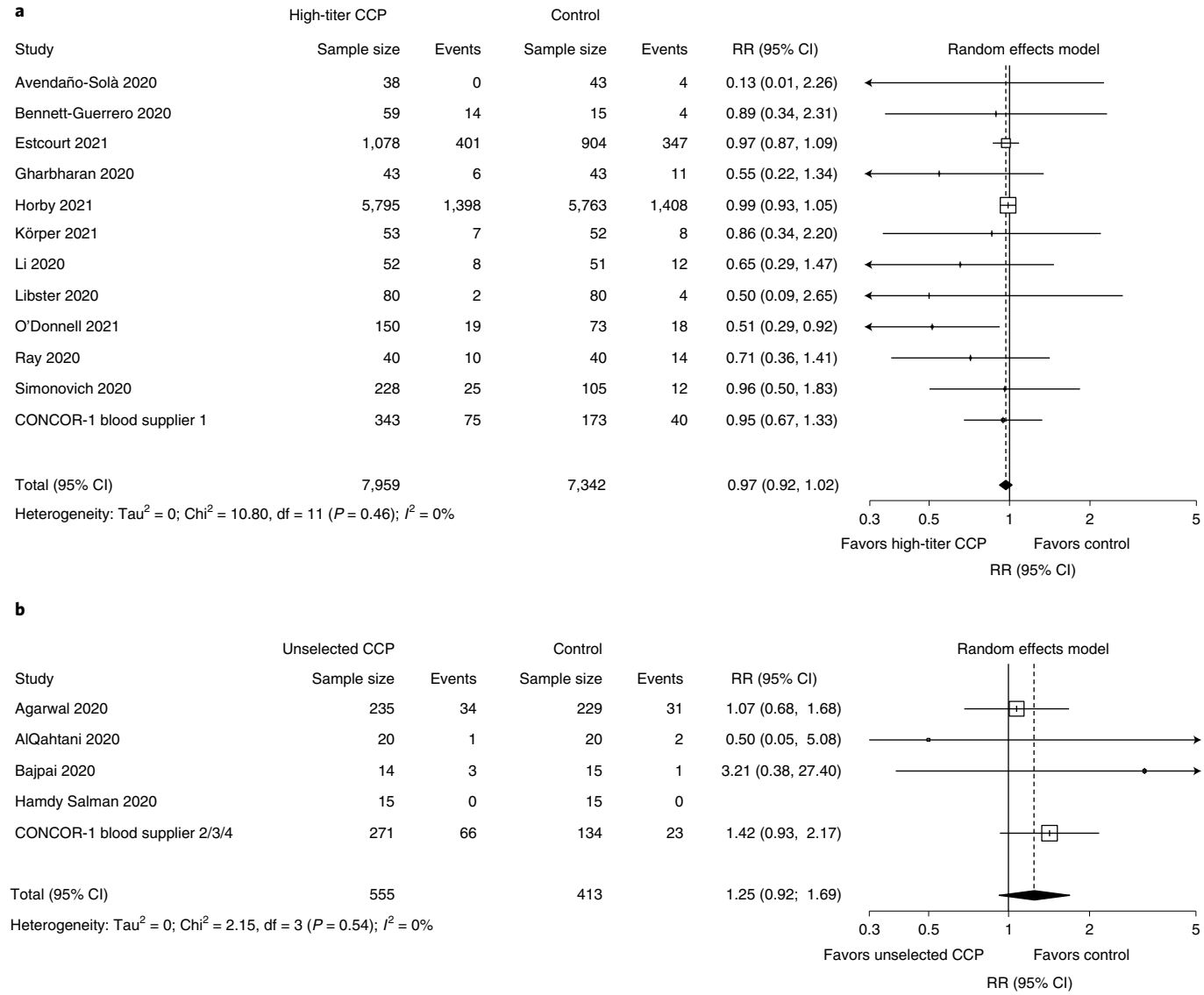

Fig. 5 | Meta-analysis of mortality at 30 d in CONCOR-1 and other trials according to convalescent plasma selection strategy. a, Meta-analysis of trials that used high-titer plasma. **b**, Meta-analysis of trials that used a mix of low-, medium- and high-titer plasma. df, degrees of freedom.

for the primary outcome relative to standard of care. Each one-unit increase in the standardized log-transformed ADCC was associated with a 24% reduction in the OR of the treatment effect (OR = 0.76, 95% CI 0.62–0.92) (Fig. 4 and Supplementary Table 10). This effect-modifying role was also significant for the neutralization test (OR = 0.77, 95% CI 0.63–0.94) but not for anti-receptor-binding domain (RBD) enzyme-linked immunosorbent assay (ELISA) (OR = 0.84, 95% CI 0.69–1.03) or IgG against the full transmembrane spike (OR = 1.01, 95% CI 0.82–1.23).

When all four serologic markers were included in the multivariate model, each one-unit increase in the standardized log-transformed anti-spike IgG marker was associated with a 53% increase in the OR for the deleterious effect of convalescent plasma on the primary outcome (OR = 1.53, 95% CI 1.14–2.05); increases in ADCC and neutralization independently improved the effect of CCP (OR = 0.66, 95% CI 0.50–0.87 and OR = 0.74, 95% CI 0.57–0.95, respectively), whereas levels of anti-RBD antibodies had no effect-modifying role (OR = 1.02, 95% CI 0.76–1.38) (Supplementary Table 10). There was no evidence of significant interaction among the four serologic measures in the general additive model (Fig. 4 and Extended Data Fig. 8).

Meta-analysis. Of the 15 other reported randomized trials, 11 used only high-titer plasma[5,7,10–18], and four applied less stringent plasma selection criteria, allowing for variable plasma titers[6,19–21]. Including the results from CONCOR-1, a total of 15,301 patients participated in trials using high-titer plasma, and 968 participated in trials applying less stringent criteria. The summary estimates for the RR of mortality in high-titer plasma trials was 0.97 (95% CI 0.92–1.02) compared to 1.25 (95% CI 0.92–1.69) in trials using unselected convalescent plasma (Fig. 5).

Discussion

The CONCOR-1 trial found that the use of convalescent plasma for the treatment of hospitalized patients with COVID-19 did not reduce the risk of intubation or death at 30 d. Patients in the convalescent plasma arm experienced more serious adverse events. Convalescent plasma was not associated with an improvement in any of the secondary efficacy outcomes or in any of the subgroup analyses. These results are consistent with the RECOVERY trial and a recent Cochrane meta-analysis[8]. A major additional contribution of our study comes from the study of immunologic markers, which

suggest that the antibody profile significantly modified the effect of convalescent plasma compared to standard of care.

The RECOVERY trial showed that transfusion of high-titer plasma was no better than standard of care in the prevention of key outcomes. The U.S. National Registry report showed that high antibody level plasma was associated with a 34% RR reduction in mortality compared to low antibody level plasma[9]. Our assessment of the role of antibody profile on the clinical effect relative to standard of care is aligned with both of these conclusions. In the RECOVERY trial, plasma with a commercial ELISA cutoff corresponding to a neutralizing antibody titer of 100 or greater was used, and the mortality rate ratio compared to standard of care was 1.00 (95% CI 0.93–1.07). In our trial, plasma from one of the blood suppliers (blood supplier 1) that used a similar antibody threshold (neutralizing antibody titer of 160 of greater) was associated with a similar effect size (OR = 0.95 (95% CI 0.73–1.25)) (Fig. 4). In contrast, the U.S. National Registry study, which lacked a control group, reported that plasma containing high antibody levels (Ortho VITROS IgG anti-spike subunit 1, which contains the RBD, signal-to-cutoff ratio >18.45) was associated with a 34% reduction in mortality compared to plasma containing low antibody levels (signal-to-cutoff ratio <4.62)[9]. In our regression model (Supplementary Table 10), plasma with anti-RBD ELISA values corresponding to this low antibody cutoff (Fig. 4 and Extended Data Figure 9) would have a predicted OR of 1.49 compared to controls (95% CI 0.98–2.29), whereas plasma with the corresponding high antibody cutoff would have a predicted OR of 0.91 (95% CI 0.60–1.40), representing a 38% RR reduction. Thus, the 34% RR reduction observed by the U.S. National Registry[9] could be explained by increased mortality with low antibody plasma rather than improved mortality with high antibody plasma.

This conclusion is corroborated by the meta-analysis of previous trials based on plasma selection strategy. Although the vast majority of patients included in convalescent plasma trials received high-titer plasma, most patients treated outside of clinical trials did not, including many of those who received plasma according to the current U.S. Food and Drug Administration (FDA) requirements (Ortho VITROS ≥9.5). Only 20% of convalescent plasma included in the U.S. National Registry was considered high-titer[9]. In our study, blood supplier 3 issued the same plasma as the one used in clinical practice as part of the emergency use authorization, and, in our subgroup analysis, convalescent plasma from this blood supplier was associated with worse clinical outcomes (OR = 1.89, 95% CI 1.05–3.43).

The antibody content is critical in determining the potency and potential harm of passive antibody therapy. Convalescent plasma demonstrating high levels of viral neutralization and high levels of Fc-mediated function were independently associated with a reduced risk for intubation or death. The importance of Fc-mediated function is in line with the known functional determinants of the anti-SARS-CoV-2 humoral response. In animal models of COVID-19, mutation of monoclonal antibodies leading to loss of Fc-mediated function, but sparing the neutralizing function, abrogated the protective effect of the antibody[22–25]. In cohort studies of severe COVID-19, low Fc-mediated function, but not neutralization, was associated with mortality[26,27].

In contrast, high levels of IgG antibodies against the full transmembrane spike protein measured by flow cytometry (which is distinct from commercial assays for IgG against spike subunit 1) were associated with an increased risk of intubation or death after controlling for other antibody markers, suggesting that the transfusion of convalescent plasma containing non-functional anti-SARS-CoV-2 antibodies might be harmful. Antibody Fc-mediated function is dependent on the ability to aggregate and crosslink Fc receptors on target cells. This process can be disrupted by competition from other antibodies with low or absent Fc function[28]. Similar observations were made during HIV vaccine trials, where the development of IgA antibodies against the virus envelope paradoxically increased the risk of infection due to competition with IgG[29,30], and in animal models of passive immunization where transfer of antibodies could be deleterious to the host[31].

One positive clinical trial in mild disease ($n = 160$) found that high-titer convalescent plasma administered within 72 h of the onset of mild COVID-19 symptoms improved clinical outcomes compared to placebo in an elderly outpatient population[13]. Furthermore, in a Bayesian re-analysis of the RECOVERY trial, the subgroup of patients who had not yet developed anti-SARS-CoV-2 antibodies appeared to benefit from convalescent plasma[32]. The C3PO trial, which also assessed early treatment with high-titer plasma in high-risk patients, was stopped prematurely for futility after enrolling 511 of 900 planned participants (NCT04355767). In our trial, the median time from the onset of symptoms was 8 d; however, we did not observe a difference in the primary outcome in the subgroup of patients who were randomized within 3 d of diagnosis.

The frequency of serious adverse events was higher in the convalescent plasma group compared to the standard of care group (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57). Most of these events were caused by worsening hypoxemia and respiratory failure occurring throughout the 30-d follow-up period. This frequency is consistent with the recent Cochrane review that reported an OR of 1.24 (95% CI 0.81–1.90) for serious adverse events[8]. The frequency of transfusion-associated dyspnea and transfusion-associated circulatory overload was 2.1% and 0.8%, respectively, which is similar to other studies of non-convalescent plasma[33]. The rates of transfusion reactions in CONCOR-1 were higher than what were reported in the RECOVERY trial, where transfusion reactions were reported in 13 of 5,795 (0.22%) patients. CONCOR-1 site investigators included many transfusion medicine specialists, and the open-label design might have encouraged reporting. However, the rate of serious transfusion-related adverse events was low (4/614 (0.65%) patients treated with convalescent plasma) and, thus, does not explain the difference in serious adverse events between groups.

CONCOR-1 was a randomized trial designed to examine the effect of convalescent plasma versus standard of care for the primary composite outcome of intubation or death, with a capacity to explore the immunological profile of convalescent plasma and its impact on the effect of convalescent plasma. The trial involved four blood suppliers that provided local convalescent plasma units based on different antibody criteria. As a result, plasma units with a wide distribution of antibody content were included, and comprehensive antibody testing using both quantitative and functional assays provided a detailed description of the plasma product. The open-label design represents a limitation of this study, as knowledge of the treatment group could influence the decision to intubate, report adverse events or administer other treatments. The antibody profile of recipients was unavailable at the time of this analysis. In future work, we will investigate the value of convalescent plasma in patients without a detectable humoral immune response. In addition, other antibody isotypes (IgM and IgA) and IgG subclasses should be evaluated in future studies to determine their effect on clinical outcomes. Additional randomized trials are warranted to assess the early use of high-titer convalescent plasma units in immunocompromised patients with COVID-19 who are unable to mount an efficient anti-SARS-CoV-2 antibody response.

In summary, the CONCOR-1 trial did not demonstrate a difference in the frequency of intubation or death at 30 d with convalescent plasma or standard of care in hospitalized patients with COVID-19 respiratory illness. The antibody content had a significant effect-modifying role for the effect of convalescent plasma on the primary outcome. The lack of benefit and the potential concern of harm caution against the unrestricted use of convalescent plasma for hospitalized patients with COVID-19.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01488-2.

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Methods

Trial design and oversight. CONCOR-1 was an investigator-initiated, multi-center, open-label, randomized controlled trial conducted at 72 hospital sites in Canada, the United States and Brazil[34]. Eligible patients were randomly assigned to receive either convalescent plasma or standard of care. The study was approved by Clinical Trials Ontario (research ethics board of record: Sunnybrook Health Sciences Centre), project no. 2159; the Quebec Ministry of Health and Social Services multicenter ethics review (research ethics board of record: Comité d'éthique de la recherche du CHU Sainte-Justine), project no. MP-21-2020-2863; the Weil Cornell Medicine General Institutional Review Board, protocol no. 20-04021981; the Comissão Nacional de Ética em Pesquisa, approval no. 4.305.792; the Héma-Québec Research Ethics Board; the Canadian Blood Services Research Ethics Board; Research Ethics BC (research ethics board of record: the University of British Columbia Clinical Research Ethics Board); the Conjoint Health Research Ethics Board; the University of Alberta Health Research Ethics Board (Biomedical Committee); the Saskatchewan Health Authority Research Ethics Board; the University of Saskatchewan Biomedical Research Ethics Board; the University of Manitoba Biomedical Research Board; the Queensway Carleton Hospital Research Ethics Board; the Scarborough Health Network Research Ethics Board; the Windsor Regional Hospital Research Ethics Board; and the Bureau de l'Éthique of Vitalité Health Network. Regulatory authorization was obtained from Health Canada (control no. 238201) and the U.S. FDA (IND 22075). The trial was registered at ClinicalTrials.gov (NCT04348656). An independent data safety monitoring committee performed trial oversight and made recommendations after review of safety reports planned at every 100 patients and at the planned interim analysis based on the first 600 patients. External monitoring was performed at all sites to assess protocol adherence, reporting of adverse events and accuracy of data entry. Full details of the study design, conduct, oversight and analyses are provided in the protocol and statistical analysis plan, which are available online.

Participants. Eligible participants were (1) ≥16 years of age in Canada or ≥18 years of age in the United States and Brazil; (2) admitted to the hospital ward with confirmed COVID-19; (3) required supplemental oxygen; and (4) a 500-ml of ABO-compatible COVID-19 convalescent plasma (CCP) was available. The availability of ABO-compatible convalescent plasma from donors who had recovered from COVID-19 infection was an eligibility requirement. Exclusion criteria were (1) more than 12 d from the onset of respiratory symptoms; (2) imminent or current intubation; (3) a contraindication to plasma transfusion; or (4) a plan for no active treatment. Consent was obtained from all donors and participants (or their legally authorized representative).

Randomization and intervention. Patients were randomized in a 2:1 ratio to receive convalescent plasma or standard of care using a secure, concealed, computer-generated, web-accessed randomization sequence (REDCap v11.0.1)[35]. Randomization was stratified by site and age (<60 and ≥60 years) with allocation made with permuted blocks of size 3 or 6. Patients randomized to convalescent plasma received one or two units of apheresis plasma amounting to approximately 500 ml from one or two donors. The plasma was stored frozen and was thawed as per standard blood bank procedures and infused within 24 h of randomization. Patients were monitored by clinical staff for transfusion-related adverse events as per local procedures. Individuals assigned to standard of care received usual medical care as per routine practices at each site. The investigational product was prepared by Canadian Blood Services and Héma-Québec (Canada), the New York Blood Center (United States)[36] and Hemorio (Brazil). Each supplier had different criteria for qualifying convalescent plasma units that were based on the presence of either viral neutralizing antibodies, measured by the plaque reduction neutralization assay and expressed as the concentration of serum that reduced the number of virus-induced plaques by 50% (PRNT50)[37,38] using a threshold titer of >1:160 or antibodies against the RBD of the SARS-CoV-2 spike protein using a threshold titer of >1:100. Female donors with previous pregnancies were excluded from donation, unless they tested negative for HLA antibodies. In addition, a retained sample from every plasma donation was tested at reference laboratories after the transfusion for (1) anti-RBD antibodies (IgM, IgA and IgG) by ELISA;[39,40] (2) viral neutralization by the PRNT50 assay using live virus;[37,38] (3) IgG antibodies binding to the full-length trimeric transmembrane SARS-CoV-2 spike protein expressed on 293T cells by flow cytometry;[41] and (4) Fc-mediated function by ADCC assay against the full spike protein expressed on CEM.NKr cells (see supplement for complete description)[42,43]. For each plasma unit, the absolute antibody content was defined as the product of the unit volume and the concentration of the antibody (or functional capacity) in the plasma. These calculations were used to estimate the total antibody content from the transfusion of two units.

Trial outcomes. The primary outcome was the composite of intubation or death by day 30. Secondary outcomes were: time to intubation or death; ventilator-free days by day 30; in-hospital death by day 90; time to in-hospital death; death by day 30; length of stay in critical care and hospital; need for extracorporeal membrane oxygenation; need for renal replacement therapy; convalescent plasma-associated adverse events; and occurrence of ≥3 grade adverse events by day 30 (classification of adverse events was performed using MedDRA (https://www.meddra.org/) and was graded by Common Terminology Criteria for Adverse Events, v4.03). All transfusion-related adverse events were classified and graded by International Society for Blood Transfusion (www.isbtweb.org) definitions. All patients were followed to day 30, including a 30-d telephone visit for patients who were discharged from hospital. Patients who were in hospital beyond day 30 were followed until discharge for the purpose of determining in-hospital mortality up to day 90.

Statistical analysis. The primary analysis was based on the intention-to-treat population, which included all individuals who were randomized and for whom primary outcome data were available. The per-protocol population was comprised of eligible patients who were treated according to the randomized allocation of the intervention and received two units (or equivalent) of convalescent plasma within 24 h of randomization.

The effect of convalescent plasma on the composite primary outcome of intubation or death by day 30 was assessed by testing the null hypothesis that the composite event rate was the same under convalescent plasma and standard of care. The RR for the primary outcome (convalescent plasma versus standard of care) was computed with a 95% CI. Secondary outcomes were analyzed as described in the statistical analysis plan (Appendix B in the (Supplementary Information). No multiplicity adjustments were implemented for the secondary analyses. Procedures planned for addressing missing data and subgroup analyses are described in the statistical analysis plan. Forest plots were used to display point estimates, and CIs across subgroups with interaction tests were used to assess effect modification.

The effect-modifying role of antibody content on the primary outcome was assessed via logistic regression controlling for the blood supplier, treatment and the antibody marker. Antibody markers were log-transformed, centered and then divided by the corresponding standard deviation before being entered into logistic regression models (see statistical analysis plan, Appendix B in the Supplementary Information). A multivariate logistic regression model was then fitted adjusting for all four markers. Generalized additive models were used to examine the joint effect of each pair of serologic markers on the primary outcome[44].

The results from CONCOR-1 were subsequently included in a meta-analysis based on the 20 May 2021 update of the Cochrane systematic review[8] and known randomized trials published since comparing convalescent plasma to placebo or standard care in patients with COVID-19. These were divided based on whether they used plasma with high antibody titer or not. For each trial, we compared the observed number of deaths at 30 d (or closest available time point before a crossover, if applicable) of patients allocated to convalescent plasma or the control group. Summary estimates for RR with 95% CI were calculated using random effects meta-analysis to account for variation in effect size among studies. Heterogeneity was quantified using inconsistency index (I^2) and P values from the chi-square test for homogeneity.

With a 2:1 randomization ratio, 1,200 patients (800 in the convalescent plasma group and 400 in the standard of care group) were needed to provide 80% power to detect an RR reduction of 25% with convalescent plasma for the primary outcome with a 30% event rate under standard of care, based on a two-sided test at the 5% significance level. An interim analysis by a biostatistician unblinded to the allocation of the intervention was planned for when the primary outcome was available for 50% of the target sample. An O'Brien–Fleming stopping rule was employed[45] to control the overall type I error rate at 5%. Conditional power was used to guide futility decisions with the nominal threshold of 20% to justify early stopping.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

De-identified individual patient data with the data dictionary that underlie the reported results will be made available upon request if the intended use is concordant with existing research ethics board approvals (requests will be reviewed by the CONCOR-1 Steering Committee within 3 months). Proposals for access should be sent to arnold@mcmaster.ca. The protocol and statistical analysis plan are available in the online supplement.

Code availability

Data were collected with RedCAP v11.0.1 (ref. [35]). Statistical analyses were conducted in SAS v9.4 and R v4.0.2 using the mgcv package v1.8–36 (refs. [46,47]).

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Author contributions

P.B., J.C., E.J., R. Cook, N.M.H., A.T., M.P.Z., G.B.B., R.B., K.C.L., R. Carl, M.C., N.D., D.V.D., D.A.F., A.M., N.R., D.C.S., L.S., N.S., A.F.T., R.Z., A.F. and D.M.A. were involved in study conceptualization, funding acquisition and methodology. P.B., J.C., R. Cook, G.B.B., R.B., H.W., A.F., N.L., Y.L. and D.M.A. developed the methodology for antibody analyses. P.B., J.C., N.M.H., A.T., M.P.Z., G.B.B., L.A., R.B., M.C., M.M.C., N.D., D.V.D., J.D., D.A.F., C.G., M.J.G., A.M., N.R., B.S.S., D.C.S., L.S., N.S., A.F.T., H.W., R.Z., A.F. and D.M.A. participated in the investigations. P.B., J.C., E.J., N.M.H., A.T., M.P.Z., L.A., R.B., M.M.C., D.V.D., C.G., M.J.G., N.R., B.S.S. and D.M.A. were responsible for project administration. P.B., J.C., E.J., R.C., G.B.B., R.B., D.V.D., N.L., Y.L., H.W. and D.M.A. were involved in data curation. P.B., J.C., R.C., N.L., Y.L. and D.M.A. were responsible for formal analyses and data visualization. P.B., J.C., Y.L. and D.M.A. verified the underlying data. P.B., J.C., R.C. and D.M.A. drafted the original manuscript. All members of the writing committee reviewed and edited the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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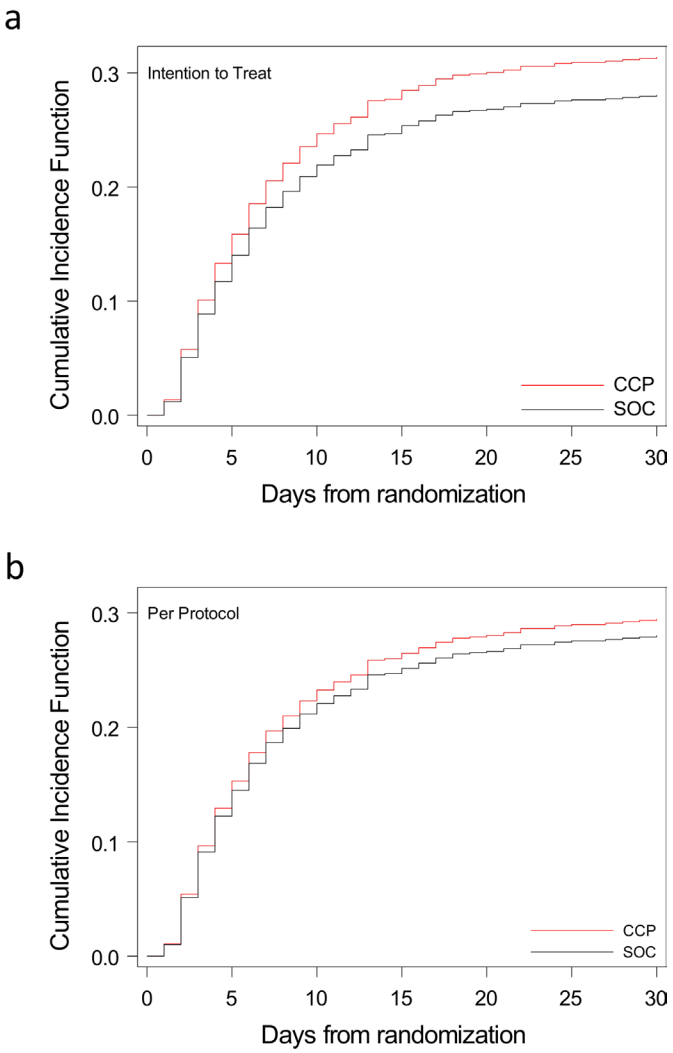
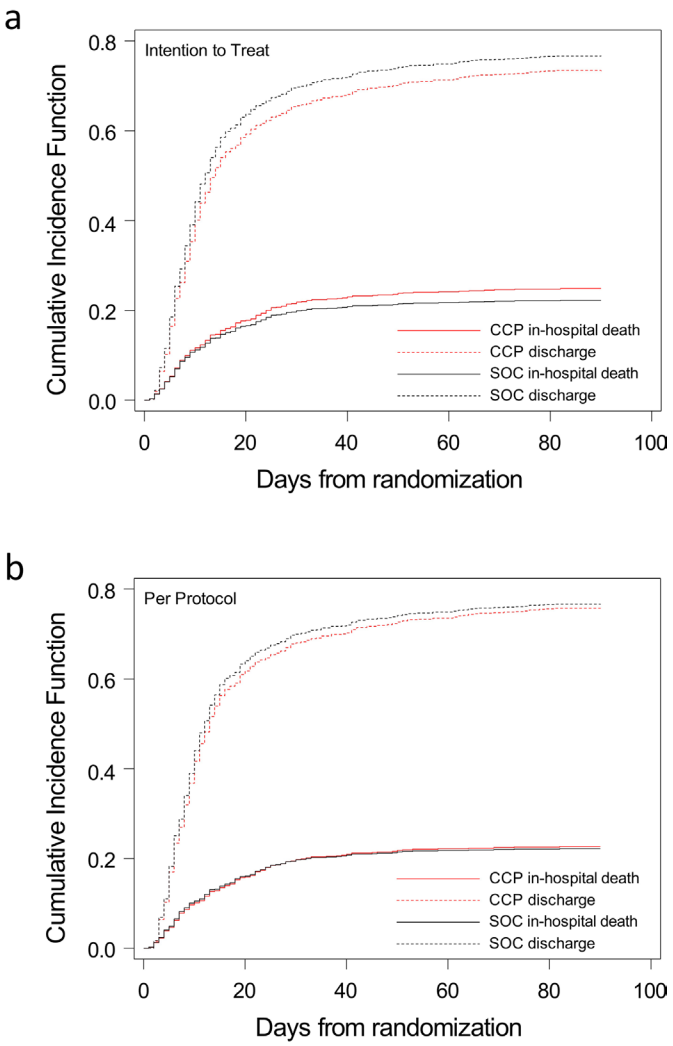


Extended Data Fig. 1 | Cumulative incidence functions of intubation or in-hospital death by day 30. Panel A presents the intention-to-treat population and panel B presents the per protocol population.



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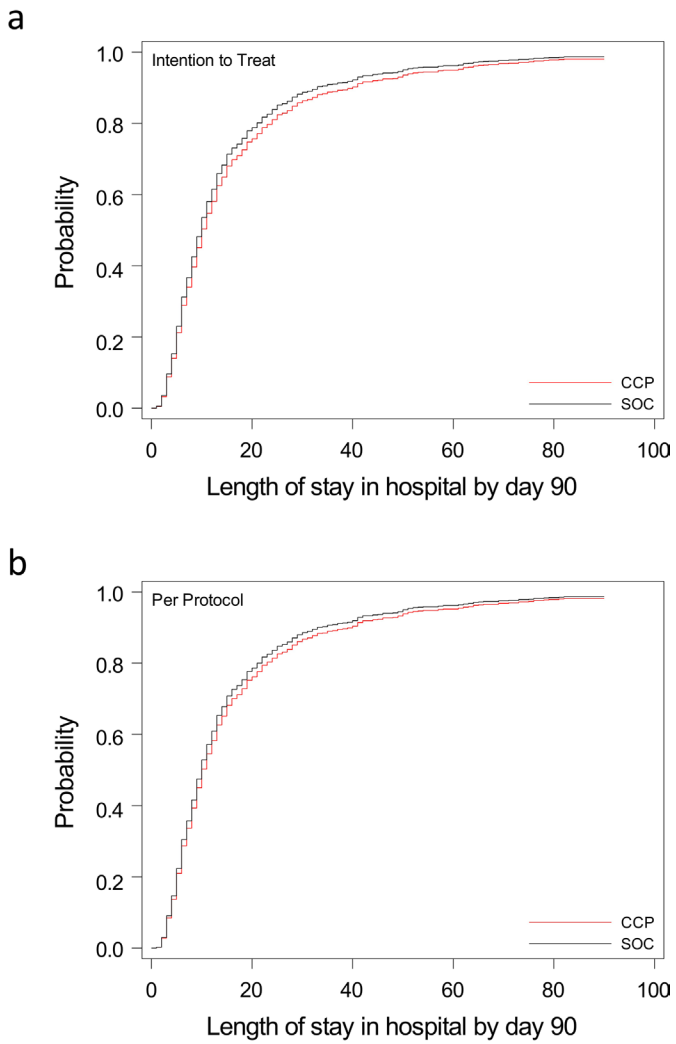
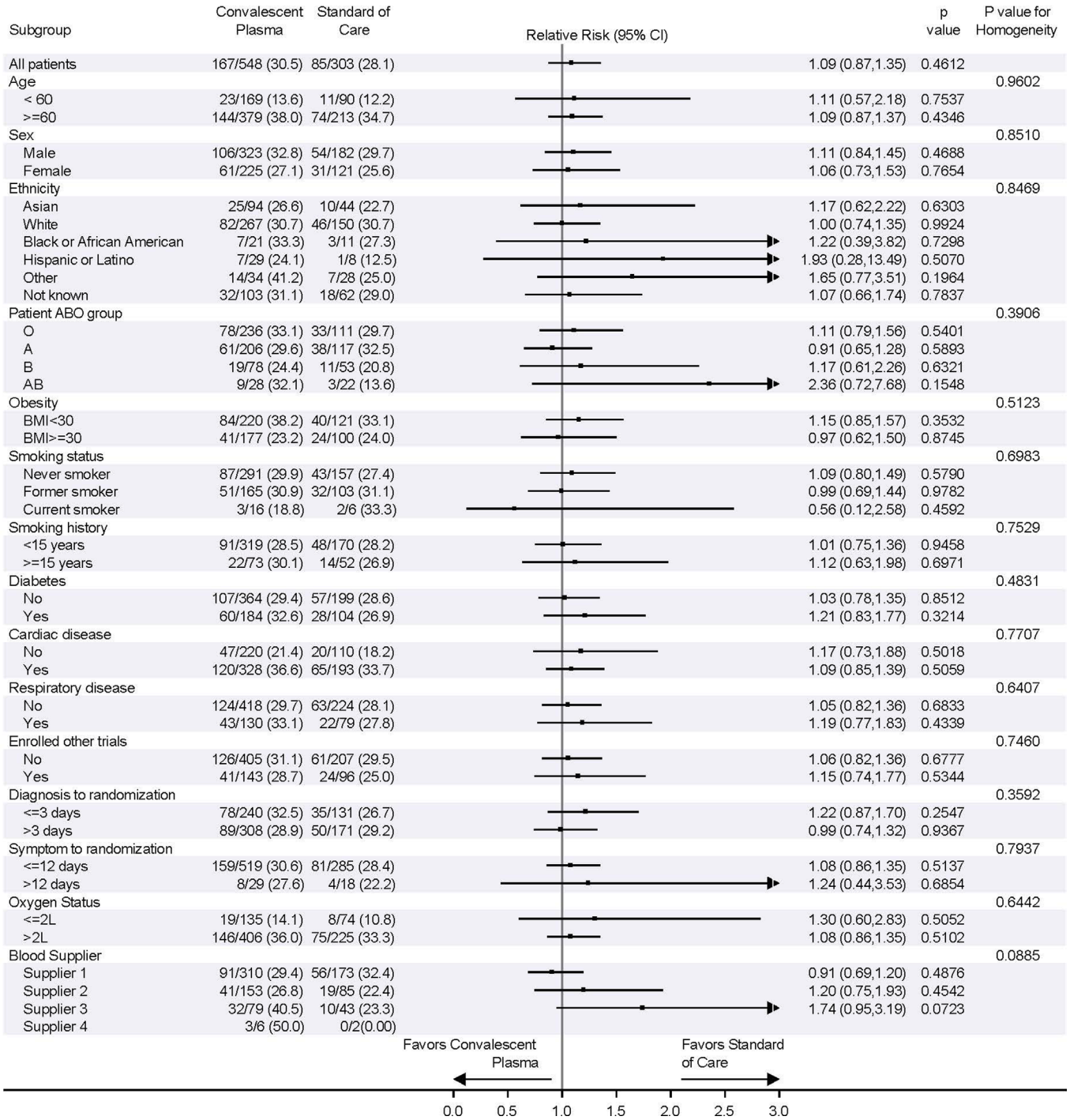
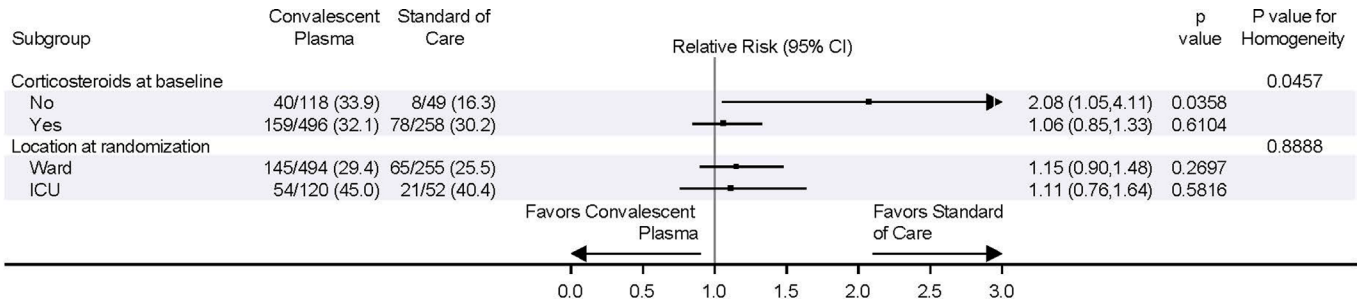


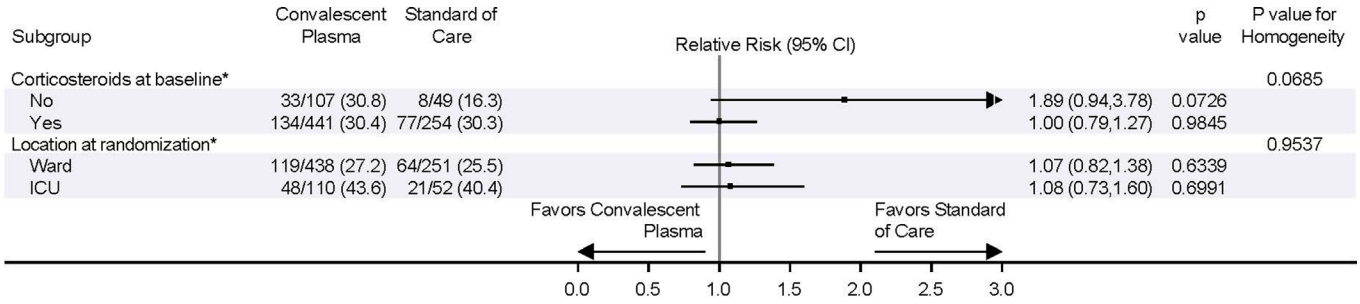
Extended Data Fig. 3 | Kaplan-Meier estimate of distribution of length of stay in hospital by day 90. Panel A presents the intention-to-treat population and panel B presents the per protocol population.



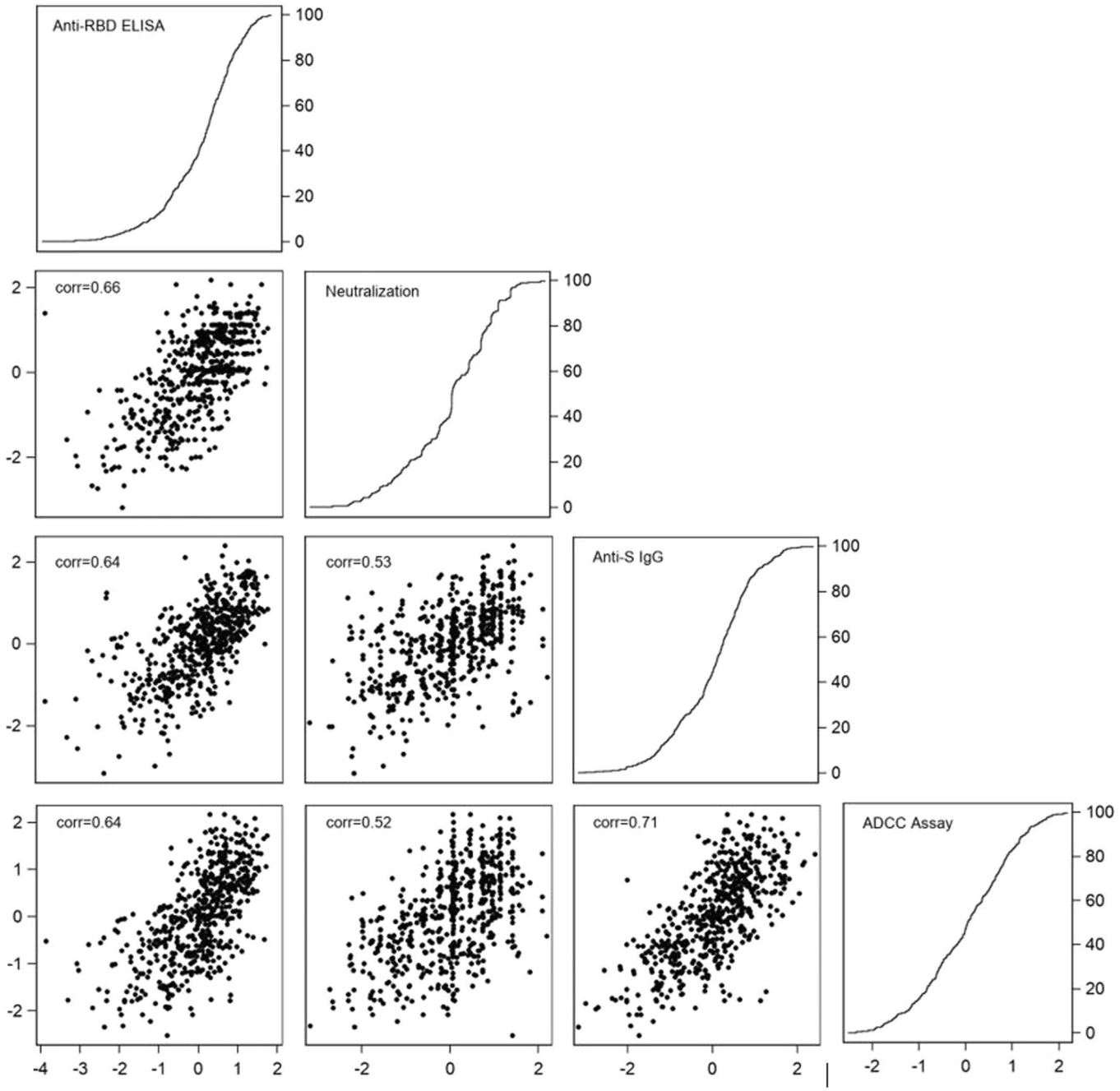
Extended Data Fig. 4 | Subgroup analysis for the per-protocol population. P-values for relative risk and homogeneity are two-sided without adjustment for multiple comparisons. BMI: Body mass index.



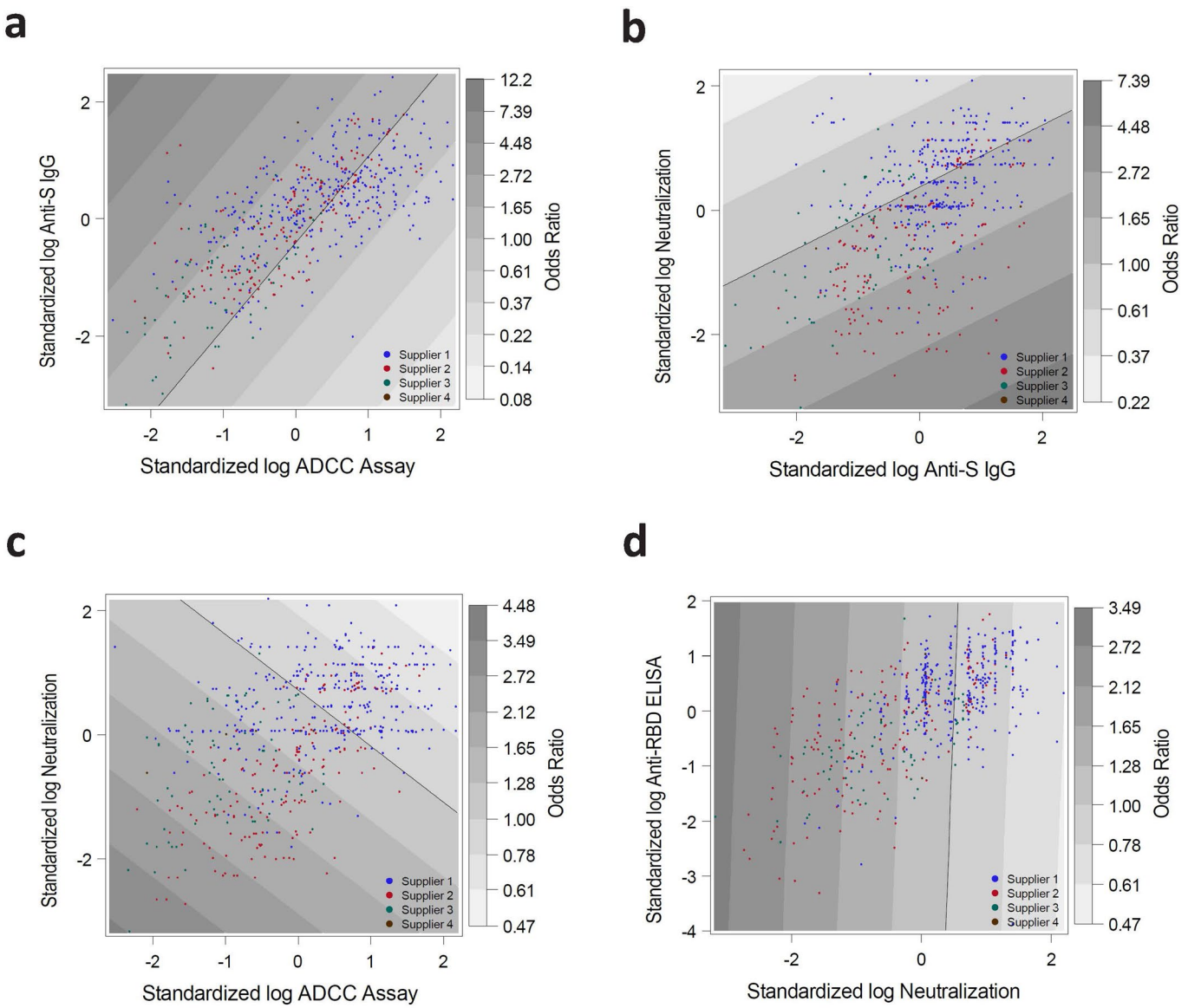
Extended Data Fig. 5 | Post-hoc subgroup analyses for the intention-to-treat population. Subgroups based on corticosteroid use and location at time of randomizations were added post-hoc at time of review. P-values for relative risk and homogeneity are two-sided without adjustment for multiple comparisons.



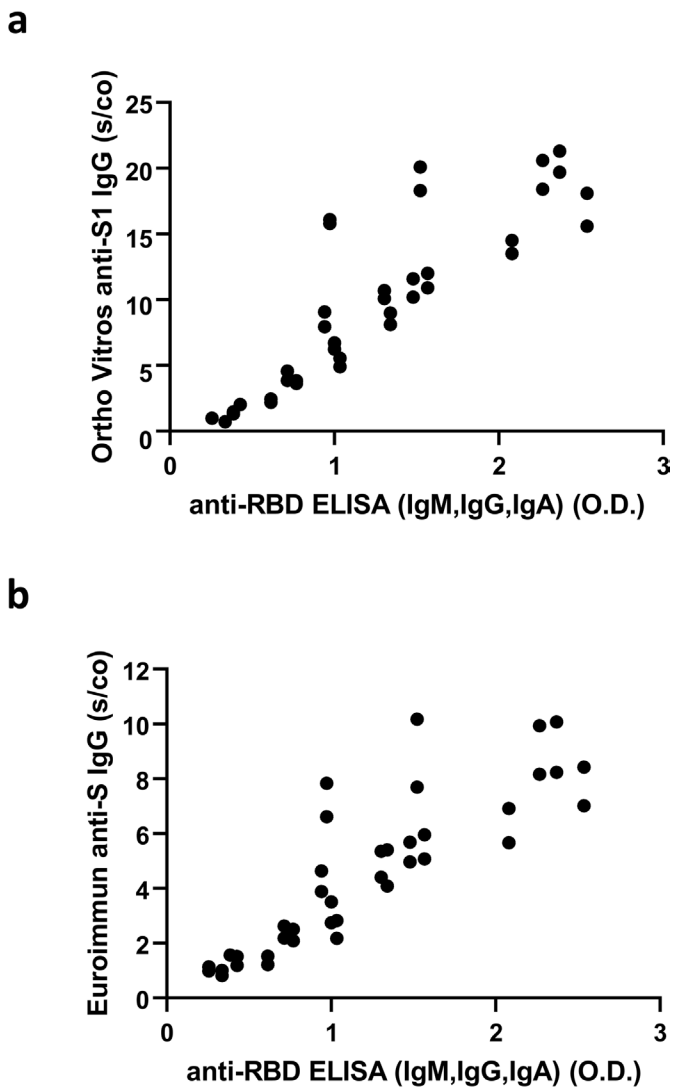
Extended Data Fig. 6 | Post-hoc subgroup analyses for the per-protocol population. Subgroups based on corticosteroid use and location at time of randomizations were added post-hoc at time of review. P-values for relative risk and homogeneity are two-sided without adjustment for multiple comparisons.



Extended Data Fig. 7 | Pairwise scatter plots of plasma antibody markers and empirical distribution functions. Markers (log transformed and standardized) include antibody (IgM,IgA,IgG) against the receptor binding domain (anti-RBD) by ELISA, plaque reduction neutralization test, IgG antibody against the full transmembrane Spike protein (anti-S IgG) by flow cytometry and the antibody-dependent cellular cytotoxicity (ADCC) assay.corr: Pearson correlation coefficients of pair of antibody markers.



Extended Data Fig. 8 | Contour plots of the joint effect-modifying role of antibody markers for convalescent plasma versus standard of care on the composite endpoint of intubation or death. The contours convey pairwise combinations of antibody markers yielding similar odds ratios for the CCP effect with the black line corresponding to an odds ratio of 1 (that is no effect of CCP). Data points for individual patients are overlaid with colours denoting the blood supply centre. Contours were obtained from fitting generalized additive logistic regression models for the primary outcome adjusting for blood supply center, treatment and the log transformed and standardized biomarkers - smoothing splines were used to relax linearity assumptions. The contour lines with positive slope suggest combinations of high (or low) values for both markers yield similar effects of CCP; the contour lines with negative slopes suggest high values of both markers yield strong CCP effects. For the combination of anti-S IgG with ADCC or anti-S IgG with anti-RBD, the general additive logistic regression models led to a complex equation that was not statistically significant nor clinical interpretable. These combinations were therefore excluded from this figure.



Extended Data Fig. 9 | Comparison of in-house ELISA to commercial assays. Values from the Héma-Québec in-house ELISA measuring antibody (IgM, IgA, IgG) binding the receptor binding domain of SARS-CoV-2 Spike protein (used in the current study) are compared to results from Euroimmun (Panel A) and Ortho Vitros (Panel B) commercial assays measuring IgG binding to subunit 1 of the SARS-CoV-2 Spike protein, which contains the receptor binding domain and which were used to qualify convalescent plasma in previous clinical trials. Each sample was tested with the commercial assays twice.

nature portfolio

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
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☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	RedCAP v11.0.1
Data analysis	SAS 9.4 (Cary, NC, USA) and R 4.0.2 (R Core Team) with the mgcv package v1.8-36

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

De-identified individual patient data with the data dictionary that underlie the reported results will be made available upon request if the intended use is concordant with the existing research ethics board approvals (requests will be reviewed by the CONCOR-1 Steering Committee within three months). Proposals for access should be sent to arnold@mcmaster.ca. The protocol and statistical analysis plan are available in the online supplement.

Field-specific reporting

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☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	With a 2:1 randomization ratio, 1200 patients (800 in the convalescent plasma group, and 400 in the standard of care group) were needed to provide 80% power to detect a relative risk reduction of 25% with convalescent plasma for the primary outcome with a 30% event rate under standard of care, based on a two-sided test at the 5% significance level. Analyses for secondary and exploratory outcomes were performed on the complete set of available data.
Data exclusions	No data was excluded from the intent-to-treat analysis. Reasons for exclusion from the per protocol analysis included inelegibility for the trial (n=9); patients that did not receive CCP (n=17); that received less than 400mL of CCP (n=11); and CCP transfusion that ended more than 24h after transfusion, as per the study protocol.
Replication	Findings were not replicated as this was a clinical trial.
Randomization	Patients were randomised in a 2:1 ratio to receive convalescent plasma or standard of care using a secure, concealed, computer-generated, web-accessed randomisation sequence (REDCap). Randomisation was stratified by site and age (<60 and ≥ 60 years) with allocation made with permuted blocks of size 3 or 6.
Blinding	This was an open label trial. The statistician performing the final analysis remained blinded throughout the trial. An open-label design was justified since the primary outcomes (intubation or death) are objective in nature. In addition, masking procedures such as plasma bag covers and additional labeling of plasma units would impose significant challenges to blood bank personnel during the pandemic, which would have made the trial infeasible in many centres. The use of standard plasma as the control was not felt to be justified because of the potential harm with no anticipated benefit.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	For PRNT: VHH72hFc from the NRC (lot # AP200512), For ADCC, CR3022 and CV3-13 WT, both produced in the Finzi lab, first described in PMID:16796401 and PMID:34237283, respectively. For ELISA, CR3022 as described above and 109-035-064 from Jackson ImmunoResearch Laboratories Inc, (lot#143450)
Validation	For VHH72hFc, see PMID: 32870820 For Jackson 109-035-064, see lot#143450 at https://www.jacksonimmuno.com/catalog/products/109-035-064 For CR3033 and CV3-13, the antibodies were separated by SDS-PAGE with and without the presence of 2-Mercaptoethanol. Furthermore, for each experiment, CR3022 and CV3-13 WT were validated by flow cytometry to make sure they recognized the Spike of SARS-CoV-2.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Vero E6 cells from ATCC laboratory; 293T and CEM.NKr-CCR5 parental cells from ATCC laboratory; CEM.NKr-SARS-CoV-2.Spike and 293T.SPike cells were produced in the Finzi Lab (PMID:33969322)
Authentication	Certificate of analysis for Vero E6 cells available at https://www.atcc.org/products/crl-1586; lot number 63290666 Certificate of analysis for 293T cells available at https://www.atcc.org/products/crl-3216; lot number 70023985 Certificate of analysis for CEM.NKr-CCR5 cells available at https://www.hivreagentprogram.org/Catalog/cellBanks/ARP-4376.aspx; lot number 150240
Mycoplasma contamination	Vero E6 and 293T cells were tested negative for mycoplasma; CEM.NKr-SARS-CoV-2.Spike cells were not tested for mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study

Human research participants

Policy information about studies involving human research participants

Population characteristics	Baseline demographics were balanced between groups for all study populations. Median age was 69 years, with 59% male and 41% female and the median time from the onset of any COVID-19 symptom was 8 days (interquartile range, 5 to 10). The majority of participants (84.0%) were receiving systemic corticosteroids at the time of enrolment.
Recruitment	Participants were partients admitted to the ward or intensive care unit of participating hospitals. Institution-specific systematic screening of newly admitted COVID-+ patients was used to identify potential patients. After permission to approach the patient was obtained from a member of the clinical circle of care, participants or their substitue decision makers were approached for consent by research personnel either in person or by phone. Screening logs were kept and reviewed on a regular basis to identify and prevent selection bias.
Ethics oversight	The study was approved by Clinical Trials Ontario (research Ethics Board of Record: Sunnybrook Health Sciences Centre); the Quebec Ministry of Health and Social Services multicer ethics review (REB of Record: Comité d'éthique de la recherche du CHU Sainte-Justine); the Brazilian Comissao Natcional de Ética em Pesquisa, the Héma-Québec Research Ethics Board, the Canadian Blood Services research ethics board; The Weil Cornell Medicine General Institutional Review Board; Research Ethics BC (REB of record: The University of British Columbia Clinical Research Ethics Board), The Conjoint Health Research Ethics Board (CHREB), University of Alberta Health Research Ethics Board (Biomedical Committee), Saskatchewan Health Authority Research Ethics Board, University of Saskatchewan-Biomedical Research Ethics Board (Bio-REB), University of Manitoba(UM) Biomedical Research Board (BREB), Queensway Carleton Hospital Research Ethics Board, Scarborough Health Network Research Ethics Board, Windsor Regional Hospital Research Ethics Board and the Bureau de l'Éthique of Vitalité Health Network.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04348656
Study protocol	The full trial protocol is included in the online supplement.
Data collection	Patients were enrolled between May 14th 2020 and January 29th 2021. Data was collected from baseline (day 1) to day 30 and in-hospital mortality data was collected up to day 90 for patients still in hospital at day 30. Data was collected by the research staff at each study site from patients or their substitute decision makers, from clinical staff and from the patient's health record and entered into a web-based electronic data collection system (REDCap). The patient's health record and study specific Case Report Forms served as source documents.
Outcomes	The primary outcome was the composite of intubation or death by day 30. Secondary outcomes were: time to intubation or death; ventilator-free days by day 30; in-hospital death by day 90; time to in-hospital death; death by day 30; lenght of stay in critical care and hospital; need for extracorporeal membrane oxygenation; need for renal replacement therapy; convalescent plasma-associated adverse events; occurence of adverse events graded 3 or higher by day 30. Primary and secondary efficacy outcomes were assessed through a review of the clinical charts and study CRFs. Classification of adverse events was performed using MedDRA (https://www.meddra.org/) and graded by the Common Terminology Criteria for Adverse Events, version 4.03. All transfusion-related adverse events were classified and graded by the international Society for Blood Transfusion definitions (www.isbtweb.org). A complete description of the outocomes and their measurements is described in the Statistical Analysis Plan.