Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among patients with COVID-19, should convalescent plasma be used as treatment?

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RECOMMENDATION

We recommend against the use of convalescent plasma in patients with COVID-19 infection. *(Moderate certainty of evidence, Strong recommendation)*

Consensus Issues
Serious adverse events and progression to respiratory distress/respiratory failure were re-rated and still considered as critical outcomes. However, the panel unanimously voted to give more value to the effect of convalescent plasma on all-cause mortality, clinical improvement, and need for invasive ventilation and ICU admission, hence, the over-all certainty of evidence was retained as moderate.

Recommendation remains strong given that convalescent plasma is no different from placebo in terms of efficacy, clinical outcomes, and harm; yet there is a lot to consider in terms of cost, value preferences, equity, and feasibility.

PREVIOUS RECOMMENDATION

We recommend against the use of convalescent plasma in patients with COVID-19 infection. *(Moderate certainty of evidence; Strong recommendation)*

Previous Consensus Issues
None were raised during panel meetings.

What's new in this version?

Eight (8) new randomized controlled trials have been added to this review.

Key Findings

There are 22 randomized controlled trials (RCTs) that compared the effect of convalescent plasma therapy against placebo and/or standard of care among confirmed COVID-19 patients. Pooled estimates of critical patient outcomes (i.e., all-cause mortality) on the use of convalescent plasma were not statistically significant. Exploratory subgroup analysis done for all-cause mortality by age, severity of disease, and timing of administration did not show any statistically significant benefit except for the subgroup of early administration (defined as within 3 days of

hospitalization) of high-level titers of convalescent plasma (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%; 4 RCTS, n = 376).

The incidence of adverse and serious adverse events (e.g., transfusion-related events) were not significantly different between the convalescent plasma group and those given standard care or placebo. The over-all certainty of evidence was retained as moderate.

Introduction

The use of convalescent plasma for passive immunity has been shown to be safe and effective in reducing viral load with consequent decreases in cytokines in a diverse range of viral diseases, such as the Spanish flu (1915), type A flu (H1N1, 2009-2010), avian flu (H5N1), Ebola virus, Zika virus, Middle East Respiratory Syndrome (MERS-CoV), and Severe Acute Respiratory Syndrome (SARS), specifically in the case of SARS-CoV-1.[1-7]

Convalescent plasma contains neutralizing antibodies that may aid in more rapid clearance of SARS-CoV-2 through accelerated viral clearance and blunting of the pro-inflammatory profile with decreases in IL-6, IL-10, and tumor necrosis factor-α as proposed mechanisms evaluated during those other epidemics.[3] The results of a study by Cheng in 2005 and a meta-analysis by Mair-Jenkins in 2015 support the usefulness of passive immunization using convalescent plasma to treat the disease and also suggests that the use of convalescent plasma is more effective if administered before day 14 following the onset of the disease.[8]

Majority of studies on convalescent plasma documented minimum risk factors or side effects with the latest efficacy studies demonstrating inconclusive results [9] and therefore immediate studies should target convalescent plasma preparations with high titer levels of anti–SARS-CoV-2 antibodies given early in the disease course with comparative research studies that involve the determination of antibody titers to demonstrate efficacy.

Review Methods

A systematic search was done on Medline, Cochrane Library, and Google Scholar until September 11, 2021 with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and convalescent plasma. The COVID-NMA Living Data was also checked and a search for ongoing studies in the NIH *clinicaltrials.gov* and various trial registries was done. Preprints using medrxiv, chinaxiv and biorxiv were also searched. Only randomized controlled trials that compared convalescent plasma against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical improvement, time to clinical improvement/resolution of symptoms, progression to respiratory distress or failure, duration of hospitalization, need for ICU admission, viral clearance, time to viral clearance, and adverse events or serious adverse events. Planned subgroup analysis was done for severity, time of administration of titer plasma, and oxygen support as needed.

Results

There are 22 (17 published and 5 preprints) RCTs [10-32] comparing the effect of convalescent plasma therapy against placebo/fresh frozen plasma and/or standard of care among confirmed COVID-19 patients (n = 17, 251). Pooled estimates from the meta-analysis of the Living COVID-NMA and other eligible studies from the search yield were adopted for the outcomes reported.

Trials were conducted in different countries and different centers including two studies in Argentina [10,11], and USA [24, 30], three studies in India [12,13,18], and one study each in

Bahrain [14], China [15], Netherlands [16], Spain [17], United Kingdom [20], Italy [22], Egypt [23], Germany [25], Chile [28], Uganda [29], Iraq [31], and Brazil [32]. There were 3 multicenter trials, one study conducted in Brazil and USA [21], one conducted in Canada, Brazil, and USA [26], and one conducted in Australia, Canada, UK and USA [27]. The summary of characteristics of included studies can be found in Appendix 3.

There were inconsistencies and imprecision in some critical outcomes and majority of the studies had serious risk of bias due to concerns with performance, detection, selection, and attrition bias. Serious adverse events and progression to respiratory distress/respiratory are considered as critical outcomes, however, the panel unanimously voted to give more value to the effect of convalescent plasma on all-cause mortality, clinical improvement and need for invasive ventilation and ICU admission. Hence, the over-all certainty of evidence was retained as moderate. The risk of bias summary is in Appendix 4. The GRADE evidence summary is in Appendix 5.

Overall, pooled estimates showed that the use of convalescent plasma in terms of all patient-centric outcomes did not reach statistical significance except for viral clearance at day 7 (RR 1.59, 95% CI 1.06, 2.37; 6 RCTs) but with substantial heterogeneity (I^2 = 61%) and the subgroup analysis by time of administration for all-cause mortality, which showed significant benefit when high level titers of convalescent plasma are given early (within 3 days of hospitalization) to patients (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%; 4 RCTs, n = 376).

Outcomes

Pooled estimates from 21 RCTs (n = 17,221) did not show significant difference in all-cause mortality between those who received the convalescent plasma versus those who received standards of care (RR 0.96, 95% CI 0.87, 1.06; I^2 = 17%). Likewise, pooled estimates for the remaining outcomes, namely duration of hospitalization (MD -1.42 days, 95% CI -4.5, 1.65; I^2 = 91%; 4 RCTs), time to clinical improvement/resolution of symptoms (MD -0.90 days, 95% CI -2.20, 0.41; I^2 = 95%; 3 RCTs), clinical improvement (RR 1.06, 95% CI 0.98, 1.15; p=0.07, I^2 = 41%; 12 RCTs), progression to respiratory distress/failure (RR 0.85, 95% CI 0.68, 1.07; I^2 = 19%; 9 RCTs), need for invasive ventilation (RR 1.00, 95% CI 0.91, 1.09; I^2 = 0%; 8 RCTs), need for ICU admission (RR 0.74, 95% CI 0.33, 1.66; I^2 = 38%; 2 RCTs), time to viral clearance (MD -0.76 days, 95% CI -6.73, 5.21 higher; I^2 = 90%; 2 RCTs) were not statistically beneficial. Most of these outcomes (duration of hospitalization, time to clinical improvement/resolution of symptoms, clinical improvement, time to viral clearance) had significant heterogeneity.

Sensitivity analysis excluding preprint studies revealed no significant difference in the all of the outcomes: all-cause mortality (RR 0.96, 95% CI 0.83, 1.12, I^2 = 17%), clinical improvement (RR 1.05, 95% CI 0.97, 1.14), progression to respiratory distress/failure (RR 0.88, 95% CI 0.68-1.07) need for invasive ventilation (RR 0.99 95% CI 0.74, 1.06), and duration of hospitalization (MD -0.73 days, 95% CI -4.4, 2.94, I^2 = 94%). Results of the sensitivity analysis are similar results with the over-all analysis, except for the outcome on viral clearance at day 7 where it initially showed benefit in the over-all analysis but not on the sensitivity analysis (RR 1.59, 95% CI 0.98, 2.57).

Subgroup Analysis

For the outcome of all-cause mortality, exploratory subgroup analysis was done according to severity of disease, age, oxygen support, and time of administration of high-level plasma titers. Subgroup analysis done for patients with mild disease severity (RR 0.86, 95% CI 0.49, 1.52; I^2 = 12%), moderate to severe disease severity (RR 1.03, 95% CI 0.84, 1.25; I^2 = 0%), moderate to critical disease severity (RR 0.95, 95% CI 0.84, 1.08; I^2 = 52%), severe/critical disease severity

(RR 0.89, 95% CI 0.63, 1.25; I^2 = 39%) did not show statistically significant benefit in the use of convalescent plasma versus standard of care or placebo.

Subgroup analysis done by age demonstrated no statistically significant benefit in the use of convalescent plasma versus standard of care and/or placebo for both aged 50 years old and above (RR 0.88, 95% CI 0.70, 1.10; I^2 = 15%) and aged 60 years old and above (RR 0.96, 95% CI 0.90, 1.03; I^2 = 0%). Sensitivity analysis excluding preprints on aged 50 years old and above (RR 0.94, 95% CI 0.80, 1.10; I^2 = 5%) yielded a similar result.

Subgroup analysis done for oxygen support showed that the use of convalescent plasma was not significantly beneficial compared to standard of care and/or placebo for both non-oxygen requiring patients (RR 0.83, 95% CI 0.60, 1.14; n = 907, I^2 = %), patients on supplemental oxygen (RR 0.89, 95% CI 0.59, 1.32; I^2 = 40%), and patients on invasive ventilation (RR 0.88, 95% CI 0.45, 1.73; I^2 = 68%).

Subgroup Analysis by Time of Administration of High Titer Convalescent Plasma

Subgroup analysis by time of administration revealed that high level titers of convalescent plasma given early (within 3 days of hospitalization) to patients showed significant benefit compared to standard of care (RR 0.42, 95% CI 0.21, 0.86; I^2 = 0%, 4 RCTs, n = 376). There was no benefit noted for those given within 7 days (RR 0.98, 95% CI 0.65, 1.48; n = 5,931), and for those given within 14 days (RR 0.81, 95% CI 0.57, 1.17; n = 6,036) from onset of symptoms or hospitalization.

Characteristics of studies included in the early (within 3 days of hospitalization) subgroup were reviewed. Of the 4 RCTs, 1 was a double-blind placebo-controlled trial and 3 are open-label. These were conducted in different countries namely Argentina, Netherlands, Spain, and Iraq. The trials in Argentina and Netherlands only included patients aged ≥ 65 years and aged ≥ 55 years respectively, while the trials in Spain and Iraq included a wider age range of patients aged 45 to 76 years and 32 to 74 years respectively. One study involved mild COVID-19 patients, 1 study involved mild to moderate patients, 1 involved moderate to critical disease and 1 enrolled critically ill patients. In all the trials, transfusion was done within 3 days from hospitalization.

Safety

The incidence of adverse events (e.g., transfusion-related events) was not significantly different between the convalescent plasma group compared to those given standard of care and/or placebo (RR 1.11, 95% CI 0.98, 1.25; I^2 = 0%, n = 1,147). The proportions of serious adverse events were also not significantly different between the two groups (RR 1.19, 95% CI 0.93, 1.51; p=-.02, I^2 = 54%). Adverse events reported include cardiovascular (sinus bradycardia, tachycardia, arrhythmia, hypertension, hypotension); respiratory (dyspnea, hypoxia, pneumonia); neurologic (headache, dizziness); hematologic (bleeding, thrombosis, thrombocytopenia, leukocytosis, anemia); gastrointestinal (elevated liver enzymes, diarrhea, abdominal pain, nausea); and metabolic (fever, chills, hyperglycemia, electrolyte disturbances e.g., hyperkalemia, hypokalemia, hypernatremia). Serious adverse events reported include cardiovascular (sinus bradycardia, arrhythmia, hypotension, ventricular tachycardia, syncope, volume overload); neurologic (cerebral bleed, cerebral infarct); respiratory (dyspnea, hypoxia, pneumonia, pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), respiratory failure); hematologic (anemia, hemolysis, site hematoma); renal (acute kidney injury (AKI)); gastrointestinal (GI hemorrhage); and multi-organ failure. In majority of the studies, frequency of adverse events and serious adverse events was similar in both the convalescent plasma and the control groups. Transfusion-related events reported include febrile reaction, allergic reaction,

transfusion associated dyspnea, transfusion associated circulatory overload (TACO), and transfusion-related acute lung injury (TRALI). Most of the transfusion-related complications were non-fatal and had complete recovery after treatment except in a trial in India wherein mortality in 3 participants (1%) was assessed as possibly related to CP transfusion.

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Surviving Sepsis Campaign Guidelines (as of March 2021)	Recommends against the use of convalescent plasma for adults with severe or critical COVID-19 outside of clinical trials (*Low certainty of evidence, Weak recommendation).*[33]
NIH COVID-19 Treatment Guidelines (as of September 15, 2021)	• Recommends against the use of low-titer COVID-19 convalescent plasma for the treatment of COVID-19. *(Strong recommendation*) • Recommends against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients who do not have impaired immunity that are mechanically ventilated. *(Strong recommendation)* • Recommends against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients without impaired immunity who do not require mechanical ventilation, except in a clinical trial. *(Strong recommendation)* • For hospitalized patients with COVID-19 who have impaired immunity, there is insufficient evidence for the panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19. • There is also insufficient evidence for the panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.[34]
Infectious Diseases Society of America (as of August 25, 2021)	Suggests against COVID-19 convalescent plasma among patients hospitalized with COVID-19 *(Conditional recommendation, Low certainty of evidence)* and recommends COVID-19 convalescent plasma among ambulatory patients with mild-to-moderate COVID-19 only in the context of a clinical trial.[35]
Australian Guidelines (as of September 6, 2021)	Recommends against the use convalescent plasma for the treatment of COVID-19.[36]

Research Gaps

As of September 11, 2021, there are 93 ongoing clinical trials on convalescent plasma therapy registered. This review will be updated as soon as full results from these trials become available.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 9)

FACTORS	JUDGEMENT (n=9)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					
Benefits	Large	Moderate (2)	Small (7)	Uncertain			• Viral clearance at D7 (non-critical outcome) was significantly beneficial
Harm	Large (1)	Small (8)	Uncertain				• The incidence of adverse and serious adverse events was not significantly different between 2 groups
Certainty of Evidence	High	Moderate (1)	Low (1)	Very low (7)			• It is rated very low due to serious risk of bias, inconsistency and imprecision in some critical outcomes
Balance of effects	Favors drug (2)	Does not favor drug (3)	Uncertain (4)				• Convalescent plasma showed net potential benefit [significantly beneficial for Viral clearance at D7and early (within 3 days) high titer plasma administration and beneficial but not statistically significant for all the remaining patient outcomes]and with no significant adverse events and serious adverse events reported.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (6)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (8)	Moderate cost (1)	Negligible cost	Moderate savings	Large savings	• One patient needs 2 aliquots. 1 aliquot is Php 28,000. • Total cost per patient is Php 56,000 (2 x 28,000/aliquot).
Certainty of evidence of required resources	No included studies (1)	Very low (2)	Low	Moderate (6)	High		• The cost is based on the UP-PGH Laboratory rate.
Cost effectiveness	No included studies (7)	Favors the comparison (1)	Does not favor either the intervention or the comparison (1)	Favors the intervention			
Equity	Uncertain (6)	Reduced	Probably no impact (1)	Increased (2)			
Acceptability	Uncertain (8)	No	Yes (1)				
Feasibility	Uncertain (4)	No (3)	Yes (2)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("Coronavirus Infections"[MeSH Terms] OR "Coronavirus"[MeSH Terms] OR ("Coronavirus"[MeSH Terms] OR "Coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR ("novel"[All Fields] AND "Coronavirus"[All Fields]) OR "novel coronavirus"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "ncov"[All Fields]) OR "COVID-19"[Supplementary Concept] OR ("COVID-19"[MeSH Terms] OR "COVID-19"[All Fields] OR "covid19"[All Fields]) OR ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR ("COVID-19"[All Fields] OR "COVID-19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("Coronavirus"[MeSH Terms] OR "Coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sars2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sars 2"[All Fields]) OR ("SARS"[All Fields] AND "COV2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields]) OR ("sarscov 2"[MeSH Terms] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields])) AND (("convalesce"[All Fields] OR "convalesced"[All Fields] OR "convalescence"[MeSH Terms] OR "convalescence"[All Fields] OR "convalescences"[All Fields] OR "convalescent"[All Fields] OR "convalescents"[All Fields] OR "convalescing"[All Fields]) AND ("plasma"[MeSH Terms] OR "plasma"[All Fields] OR "plasmas"[All Fields] OR "plasma s"[All Fields])) AND (("random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "random"[All Fields] OR "randomization"[All Fields] OR "randomized"[All Fields] OR "randomisation"[All Fields] OR "randomisations"[All Fields] OR "randomise"[All Fields] OR "randomised"[All Fields] OR "randomising"[All Fields] OR "randomizations"[All Fields] OR "randomize"[All Fields] OR "randomizes"[All Fields] OR "randomizing"[All Fields] OR "randomness"[All Fields] OR "randoms"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields]))	9/6/21 23:36:39	176	15

CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {Convalescent Plasma} AND {Randomized trial}	9/8/21	134	17
COVID-NMA Initiative	Convalescent plasma	9/9/21	22	22
Google Scholar	{Coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND {Convalescent Plasma} AND {Randomized trial}	9/10/21	7860	20
ClinicalTrials.gov	Coronavirus AND Convalescent plasma	9/9/21	45	11
Chinese Clinical Trial Registry	Coronavirus AND Convalescent plasma	9/10/21	473	0
EU Clinical Trials Register	Coronavirus AND Convalescent plasma	9/10/21	5	0
Republic of Korea - Clinical Research Information Service	Coronavirus AND Convalescent plasma	9/9/21	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Coronavirus AND Convalescent plasma	9/9/21	2	0
CenterWatch	Coronavirus AND Convalescent plasma	9/9/21	22	0
WHO database COVID-19 studies	Convalescent plasma	9/11/21	72	9
chinaxiv.org	Coronavirus AND Convalescent plasma	9/11/21	0	0
Medrxiv.org	Coronavirus AND Convalescent plasma	9/11/21	758	7
Biorxiv.org	Coronavirus AND Convalescent plasma	9/11/21	413	0

Appendix 3: Characteristics of Included Studies

Study ID	Participants	Sample Size	Comparisons		Design	Outcomes
			Treatment 1	Treatment 2		
ChiCTR2000029757 Li L, JAMA, 2020	Patients with COVID-19 (severe to critical) admitted to 7 centers in China	N = 103	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Clinical improvement D28, Incidence of viral negative conversion at D7, Adverse events, Serious adverse events, Time to clinical improvement, Time to death
NCT04342182 Gharbharan A, medRxiv, 2020	Patients with COVID-19 (moderate-critical) admitted to 14 centers in the Netherlands	N = 86	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Clinical improvement D28, Serious adverse events
NCT04345523 Avendano-Sola C, medRxiv, 2020	Patients with confirmed COVID-19 (moderate) admitted to 14 centers in Spain	N = 81	Convalescent plasma	Standard care	RCT	All-cause mortality D28, WHO Progression score level 7 or above at D28, Serious adverse events, Time to clinical improvement
CTRI/2020/04/024775 PLACID Agarwal A, BMJ, 2020	Patients with confirmed COVID-19 (mild to severe) admitted to 39 centers in India.	N = 464	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Incidence of viral negative conversion at D7
NCT04346446 Bajpai M, medRxiv, 2020	Patients with confirmed COVID-19 (severe) admitted to a single center in India	N = 31	Convalescent plasma	Fresh frozen plasma	RCT	All-cause mortality D28, Improvement in O2 saturation at D7, Need for MV within 7 days, Duration of Hospital stay, ICU stay, Adverse events, Serious adverse events
NCT04356534 AlQahtani M, medRxiv, 2020	Patients with confirmed COVID-19 (severe) admitted to 2 centers in Bahrain	N = 40	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Clinical improvement D28, Need for ventilation, Length of stay
NCT04479163 Libster R, N Engl J Med, 2021	Patients with confirmed COVID-19 (mild) admitted to multiple centers in Argentina	N = 160	Convalescent plasma (high titer)	Placebo	RCT	All-cause mortality, Adverse events, Serious adverse events
NCT04383535 PlasmAr Simonovich VA, N Engl J Med, 2020	Patients with confirmed COVID-19 (severe) admitted to 12 centers in Argentina	N = 334	Convalescent plasma	Placebo	RCT	All-cause mortality D28, Clinical improvement D28, WHO Progression score level 7 or above at D28, Adverse events, Serious adverse events, Time to clinical improvement, Time to WHO progression score level 7 or above, Time to death
CTRI/2020/05/025209 Ray Y, medRxiv, 2020	Patients with confirmed COVID-19 (severe) admitted to a single center in India	N = 80	Convalescent plasma	Standard care	RCT	All-cause mortality D28, Time to death, duration of hospital stay
NCT04530370 Salman OH, Egypt J Anaesth, 2020	Patients with confirmed COVID-19 (severe) admitted to a single center in Egypt	N = 30	Convalescent plasma	Standard care	RCT	Incidence of viral negative conversion at D7

NCT04381936; EudraCT 2020-001113-21; ISRCTN5018967 Horby P, (RECOVERY) medRxiv, 2021	Patients with suspected or confirmed COVID-19 (mild-moderate-severe-critical) admitted to 177 centers in the UK.	N = 11,558	Convalescent plasma (high titer)	Standard care	RCT	All-cause mortality D28, Clinical improvement D28
NCT04359810 O Donnell M, medRxiv, 2021	Patients with confirmed COVID-19 (mild-critical) admitted to 5 centers in Brazil and USA	N = 223	Convalescent plasma	Control plasma	RCT	All-cause mortality D28, WHO Progression score level 7 or above at D28, Adverse events, Serious adverse events, Time to clinical improvement
Pouladzadeh 2021	Patients with specified COVID-19 symptoms (less than 7 days since the onset of the symptoms) and severe disease.	N = 60	Convalescent plasma	Standard care	RCT	2month mortality after admission; length of in-hospital stay (LOS), 2-month mortality after admission, the improvement in the 8-point WHO severity score, and the frequency of CP therapy-related side effects
Bennett-Guerrero 2021	Patients hospitalized with a confirmed diagnosis of COVID-19 infection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription polymerase chain reaction (PCR) testing.	N = 74	Convalescent plasma	Standard care	RCT	Total number of ventilator-free days from randomization to day 28; All-cause mortality through 9- days post randomization; WHO ordinal scale; Immune response
Koerper 2021	Patients with (1) SARSCoV-2 infection confirmed by PCR (bronchoalveolar lavage, sputum, nasal and/or pharyngeal swap); (2) age ≥ 18 years and ≤ 75 years and (3) severe disease	N = 105	Convalescent plasma	Standard care	RCT	Treatment success (dichotomous composite outcome of survival and no longer requiring ventilation support or ICU treatment and no tachypnea (i.e., respiratory rate <30 breaths/minute) on day 21; time to clinical improvement and the frequency and severity of adverse events (AE); all-cause mortality
NCT04348656 Begin, P (CONCOR-1) July 2021	Patients aged >16 in Canada or >18 years of age in the United States and Brazil who were admitted to the hospital ward with confirmed COVID-19 and who required supplemental oxygen.	N = 921	Convalescent plasma (high titer and low titer)	Standard care	RCT	Composite of intubation or death by day 30; 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; occurrence of ≥3 grade adverse events by day 30
Estcourt June 2021 Preprint	Patients aged 18 years or older with confirmed SARS-CoV-2 infection admitted to hospital and classified as moderately or severely ill, equivalent to severely or critically ill respectively, as per the World Health Organization (WHO) case definitions in Australia, Canada, UK and USA.	N = 2,011	Convalescent plasma (high titer)	Standard care	RCT	Respiratory and cardiovascular organ support-free days up to day 21; 28-day survival; 90-day survival; progression to invasive mechanical ventilation, extra corporeal mechanical oxygenation (ECMO) or death; intensive care and hospital length-of-stay; and World Health Organization ordinal scale at day 14; All-cause mortality at 28 days; Serious treatment-related adverse events; Serious Adverse Events (SAE)
Balcells March 2021	Patients over 18 years old who were hospitalized in an academic medical center in Santiago Chile with COVID-19 symptoms present at enrollment and confirmed with a positive SARS-CoV-2 real-time PCR	N = 58	Convalescent plasma	Standard of care and deferred plasma	RCT	Composite of mechanical ventilation, hospitalization for >14 days, or death; time to respiratory failure; days of mechanical ventilation; hospital length of stay; mortality at 30 days; and SARS-CoV-2 real-time PCR clearance rate

Kirenga Aug 2021	Patients with documented SARS-CoV-2-positive RT-PCR irrespective of severity performed at the trial laboratory of Makerere University Department of Immunology and Molecular Biology in Uganda	N = 136	Convalescent plasma + SOC	Standard of care	RCT	Time to viral clearance; time to symptom resolution, clinical status on the modified WHO Ordinal Clinical Scale for clinical improvement (≥1-point increase) and progression to severe/critical condition (defined as oxygen saturation (SPO2 < 93% or needing oxygen)
Korley Aug 2021	Multicenter trial (21 States in the US) of patients 50 years of age or older or had one or more risk factors for disease progression, with SARS-CoV-2 infection as confirmed by nucleic acid assay, with an onset of symptoms within 7 days before enrollment and patient's condition was stable for outpatient treatment without new supplemental oxygen	N = 511	Convalescent plasma (high titer)	placebo	RCT randomized, multicenter, single-blind trial)	Disease progression within 15 days after randomization; worst severity of illness on an 8-category ordinal scale, hospital-free days within 30 days after randomization, and death from any cause
Rasheed 2020	Critically-ill COVID-19 patients affected by pneumonia and residing in Respiratory Care Units (RCU) in Baghdad, Iraq	N = 49	Convalescent plasma + SOC	Standard of care	RCT	Recovery or death, length of stay in hospital, and improvement in the clinical course of the disease
Sekine 2021	Patients admitted to the hospital in Porto Alegre, Brazil (severe or critically ill) 18 yo or older, with confirmed COVID 19 infection, less than 15 days of initial symptoms onset and severe respiratory disease (defined by the presence of at least one of the following: respiratory rate >30 breaths per minute in room air; oxygen saturation (O2) ≤93% in room air; arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤ 300; need for supplemental O2 to maintain O2 saturation >95%; need for supplemental O2 by high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation)	N=160	Convalescent plasma + SOC	Standard of care	RCT	Clinical improvement 28 days after enrolment; RT PCR for SARS-CoV-2 from nasal and oropharyngeal swab at day 7 from enrolment or hospital discharge (if earlier than 7 days); clinical status assessed using the 6-level ordinal scale and all-cause mortality at days 14 and 28 after enrolment; time to hospital discharge and days alive and free of supplemental oxygen support (non-survivors and patients requiring oxygen support at day 28 were assigned as 0 supplemental oxygen support free-days) within 28 days from enrolment; Sequential Organ Failure Assessment (SOFA) score and National Early Warning Score 2 (NEWS) 2 on day 7 after enrolment; and length of invasive ventilatory support (for those who received mechanical ventilation)

Appendix 4: Methodological Assessment of Included Studies

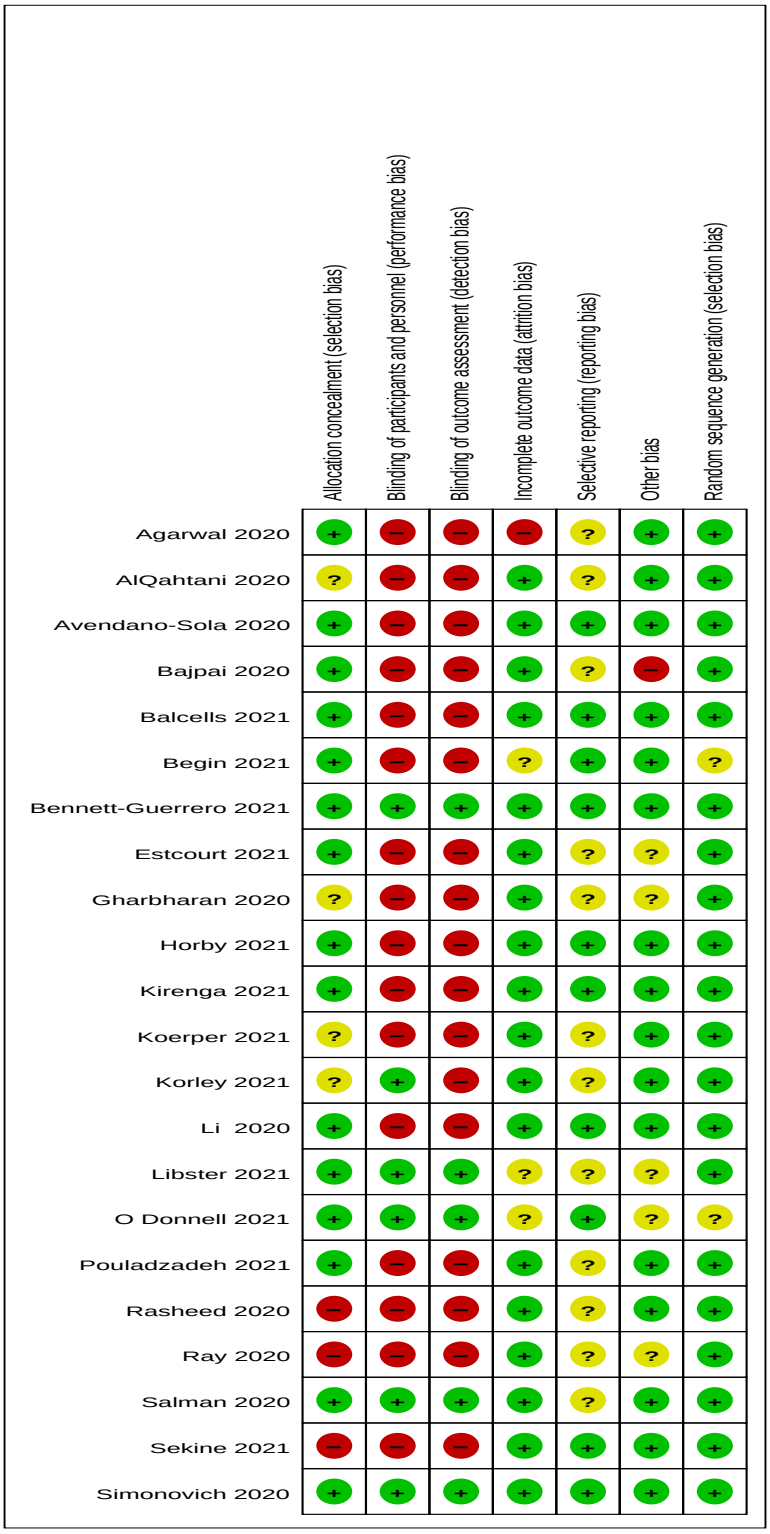

Figure 1. Risk of bias summary table

Appendix 5: GRADE Evidence Summary

Author(s): Liza Marie Bejemino, MD
Question: Convalescent plasma compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19
Setting: Worldwide
Bibliography: Convalescent Plasma versus Standard of Care for COVID 19 Infection. Cochrane Database of Systematic Reviews.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Convalescent Plasma	Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
21	randomized trials	serious [a]	not serious	not serious	not serious	none	2113/8985 (23.5%)	1982/8236 (24.1%)	**RR 0.96** (0.87 to 1.06)	**10 fewer per 1,000** (from 31 fewer to 14 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of hospitalization												
4	randomized trials	serious [b]	serious [c]	not serious	serious [d]	none	108	109	-	MD **1.42 lower** (4.50 lower to 1.65 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Time to Clinical Improvement or Resolution of Symptoms												
3	randomized trials	serious [e]	serious [c]	not serious	serious [d]	none	128	130	-	MD **0.90 lower** (2.20 lower to 0.41 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Clinical Improvement												
12	randomized trials	serious [a]	not serious	not serious	not serious	none	4446/6721 (66.2%)	4240/6482 (65.4%)	**RR 1.06** (0.98 to 1.15)	**39 more per 1,000** (from 13 fewer to 98 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for Invasive Ventilation												
8	randomized trials	serious [a]	not serious	not serious	not serious	none	792/6611 (12.0%)	754/6377 (11.8%)	**RR 1.00** (0.91 to 1.09)	**0 fewer per 1,000** (from 11 fewer to 11 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Progression to Respiratory Distress/Respiratory Failure												
9	randomized trials	serious [a]	not serious	not serious	serious [d]	none	173/1030 (16.8%)	189/904 (20.9%)	**RR 0.85** (0.68 to 1.07)	**31 fewer per 1,000** (from 67 fewer to 15 more)	⊕⊕◯◯ LOW	CRITICAL
Need for ICU admission												
2	randomized trials	not serious	not serious	not serious	serious [d]	none	125/308 (40.6%)	69/186 (37.1%)	**RR 0.74** (0.33 to 1.66)	**96 fewer per 1,000** (from 249 fewer to 245 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse Events												
7	randomized trials	serious [e]	not serious	not serious	serious [d]	none	319/673 (47.4%)	170/474 (35.9%)	**RR 1.11** (0.98 to 1.25)	**39 more per 1,000** (from 7 fewer to 90 more)	⊕⊕◯◯ LOW	IMPORTANT

Serious Adverse Events

13	randomized trials	serious [e]	serious [c]	not serious	serious [d]	none	441/8284 (5.3%)	220/7539 (2.9%)	**RR 1.19** (0.93 to 1.51)	**6 more per 1,000** (from 2 fewer to 15 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Risk of bias downgraded by 1 level: some concerns regarding selection, attrition, performance and detection bias.
b. Risk of bias downgraded by 1 level: high risk of bias in performance and detection bias in all studies, other bias in 1 study
c. Inconsistency was downgraded by 1 level due to substantial heterogeneity
d. Imprecision was downgraded by 1 level due to the wide confidence interval
e. Risk of bias downgraded by 1 level: some concerns regarding selection, performance, and detection bias.

Appendix 6: Forest Plots

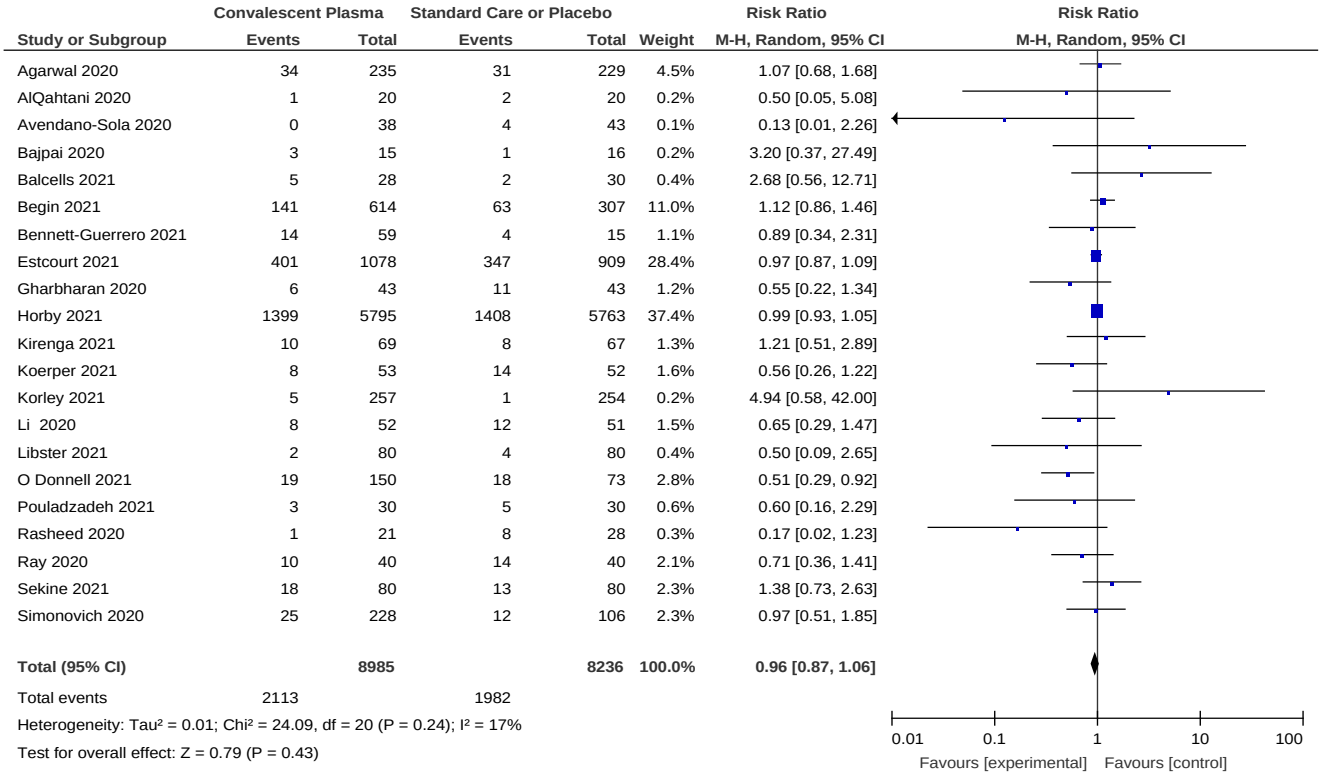

Figure 1. Forest plot of comparison: 1 Convalescent Plasma Versus Control, Outcome: 1.1 All-cause mortality

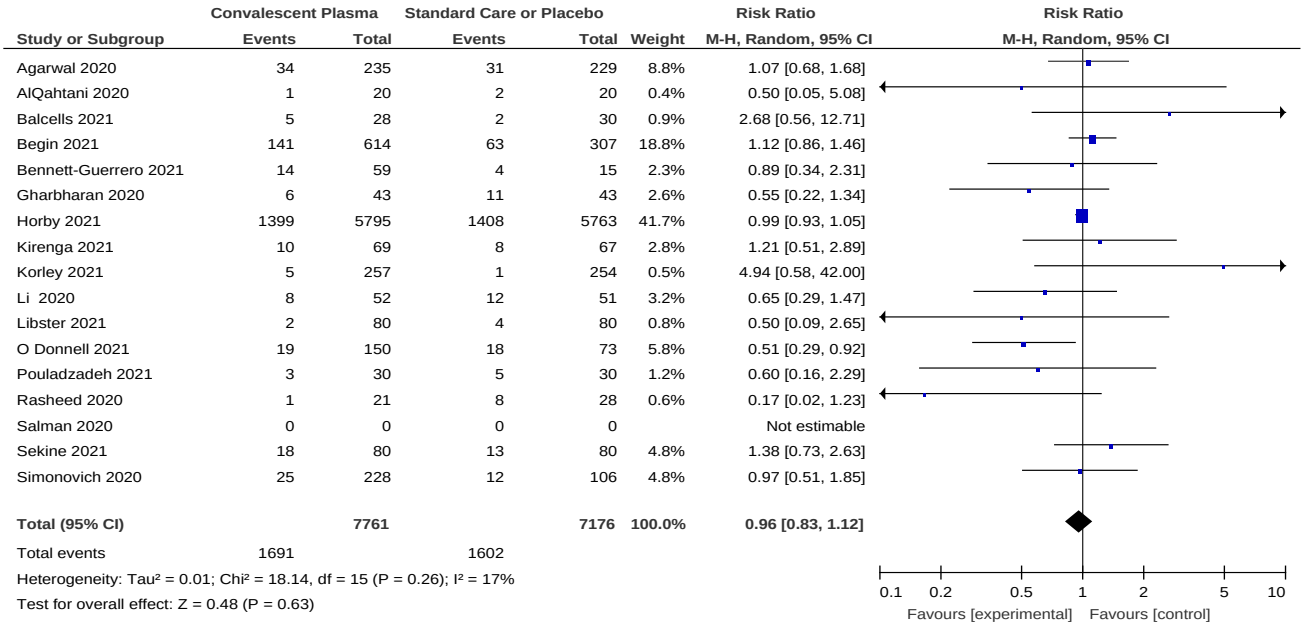

Figure 1a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.18 All-cause Mortality (Sensitivity Analysis)

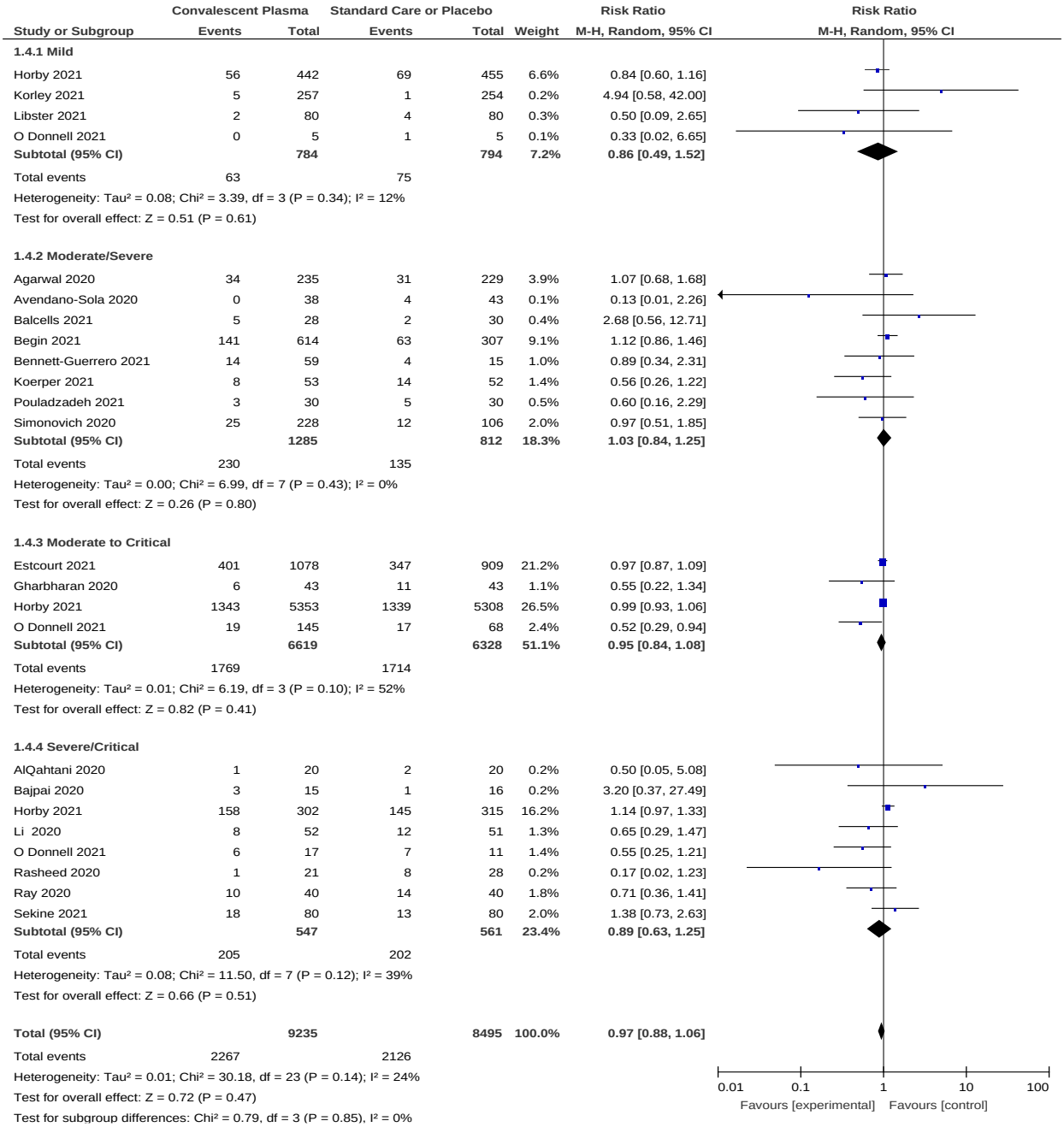

Figure 2. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.4 All-cause Mortality (by severity)

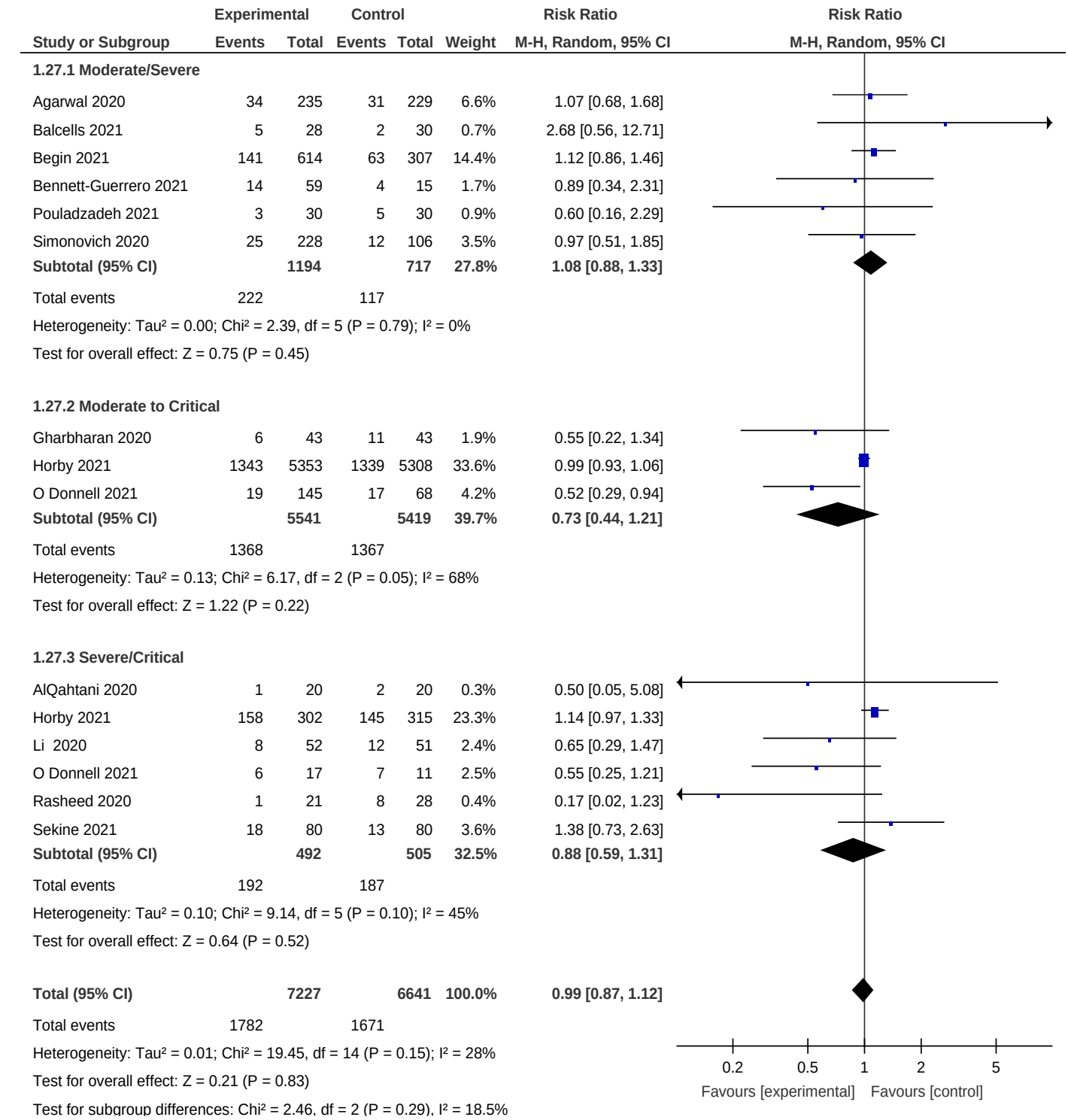

Figure 2a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.27 Mortality (Sensitivity Analysis on Severity)

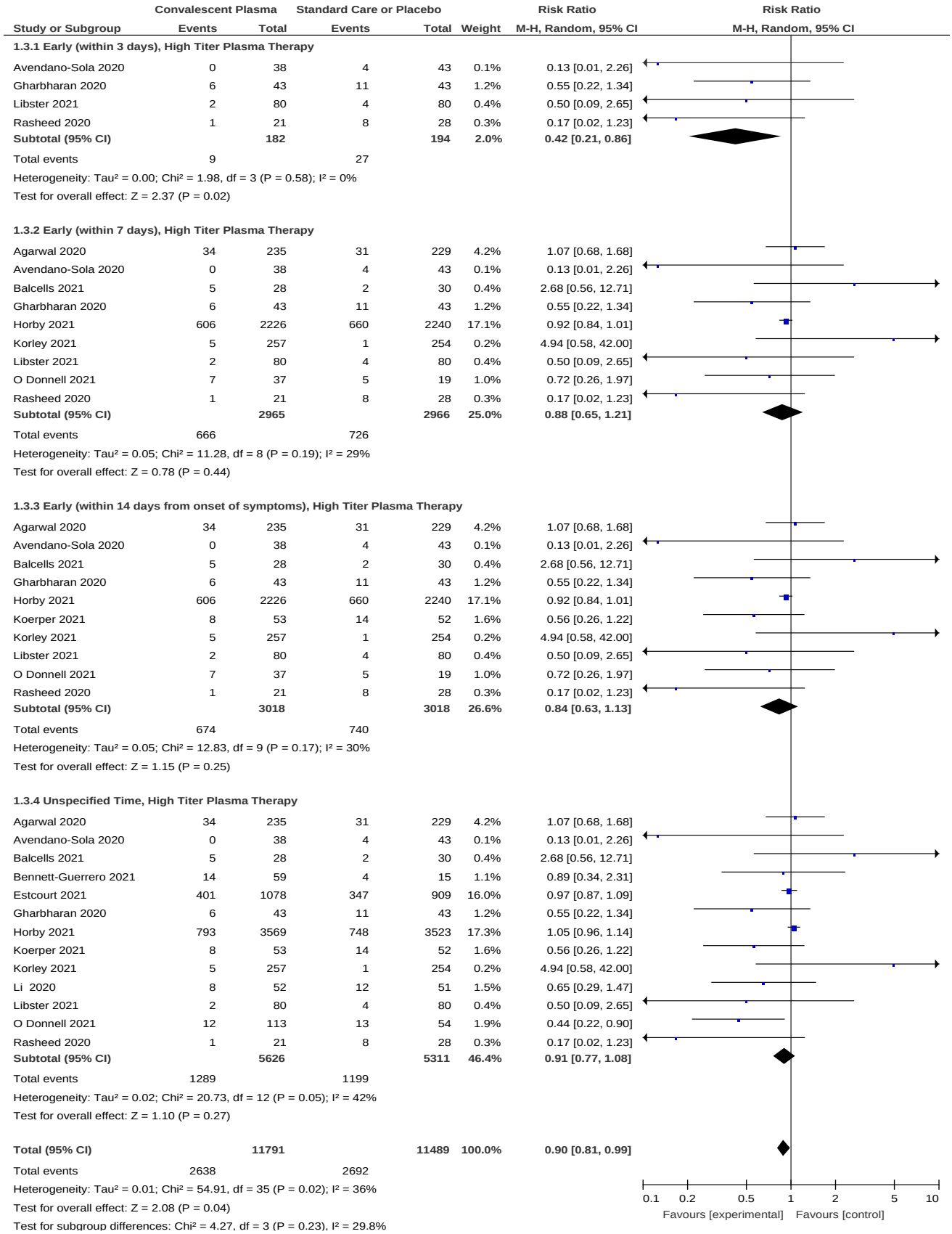

Figure 3. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.2 All-Cause Mortality (Time of administration of High Titer Plasma)

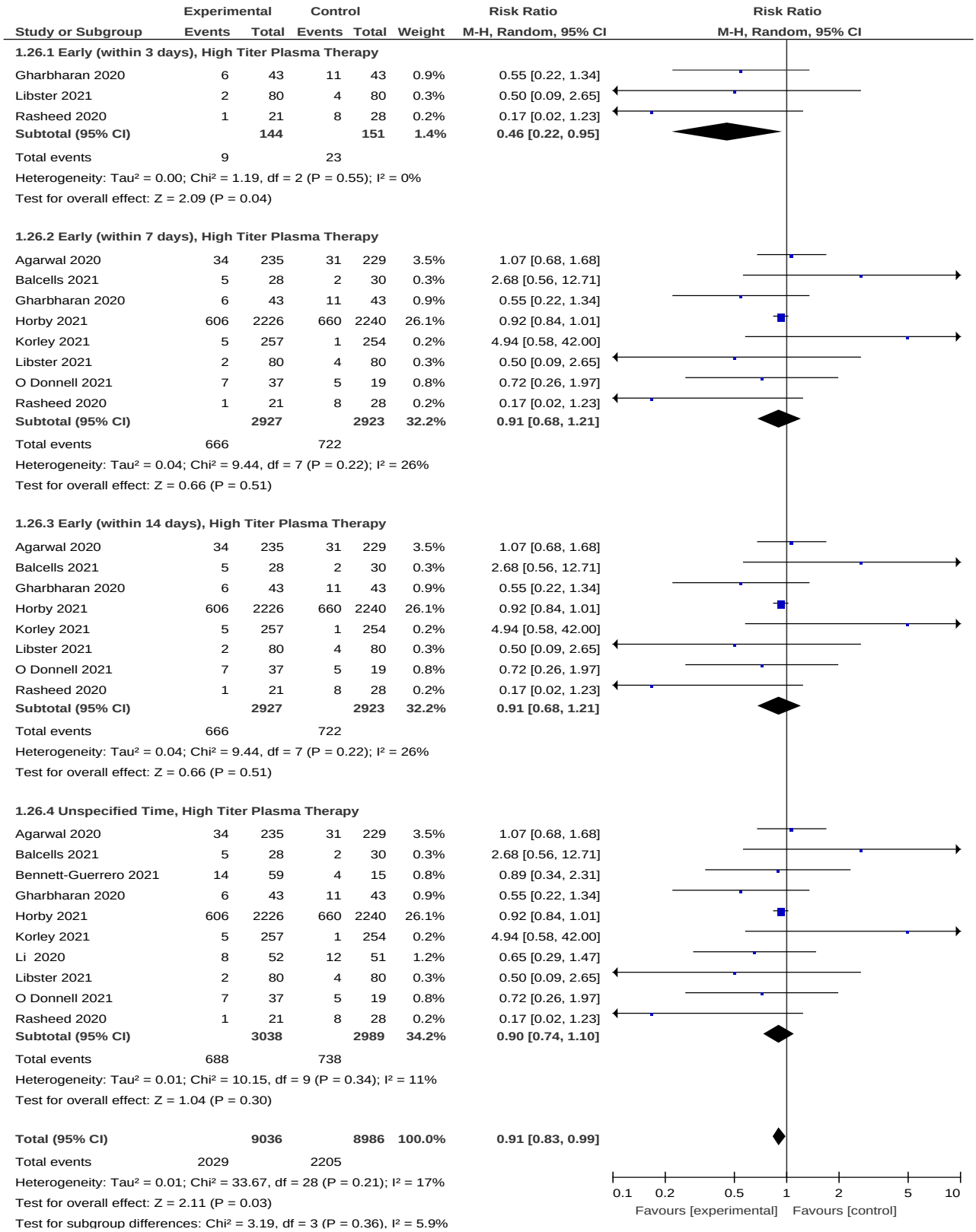

Figure 3a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.26 Mortality (Sensitivity Analysis on Time of Administration of High Titer Plasma)

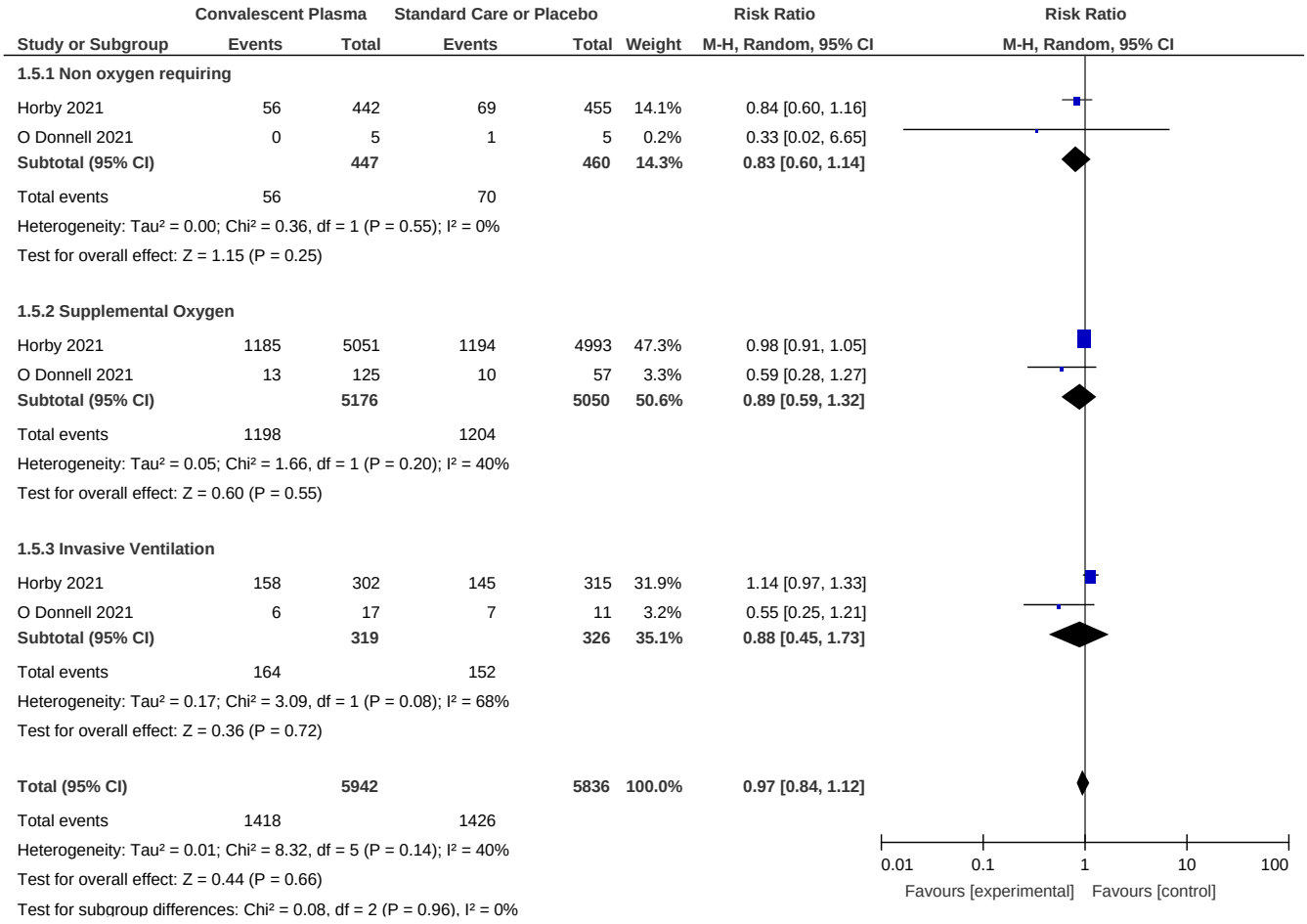

Figure 4. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.5 All-cause Mortality (by oxygen support)

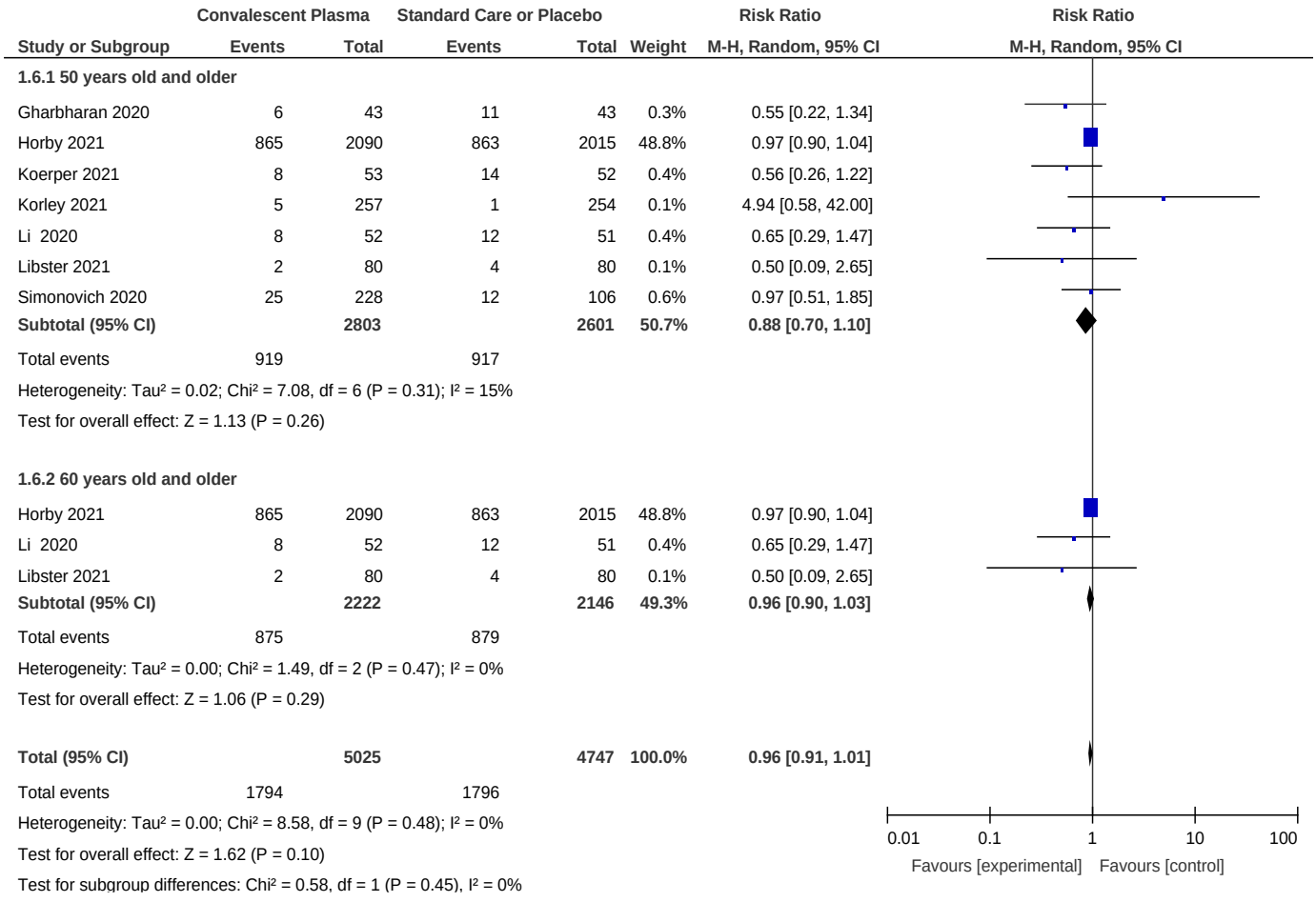

Figure 5. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.6 All-cause Mortality (by Age)

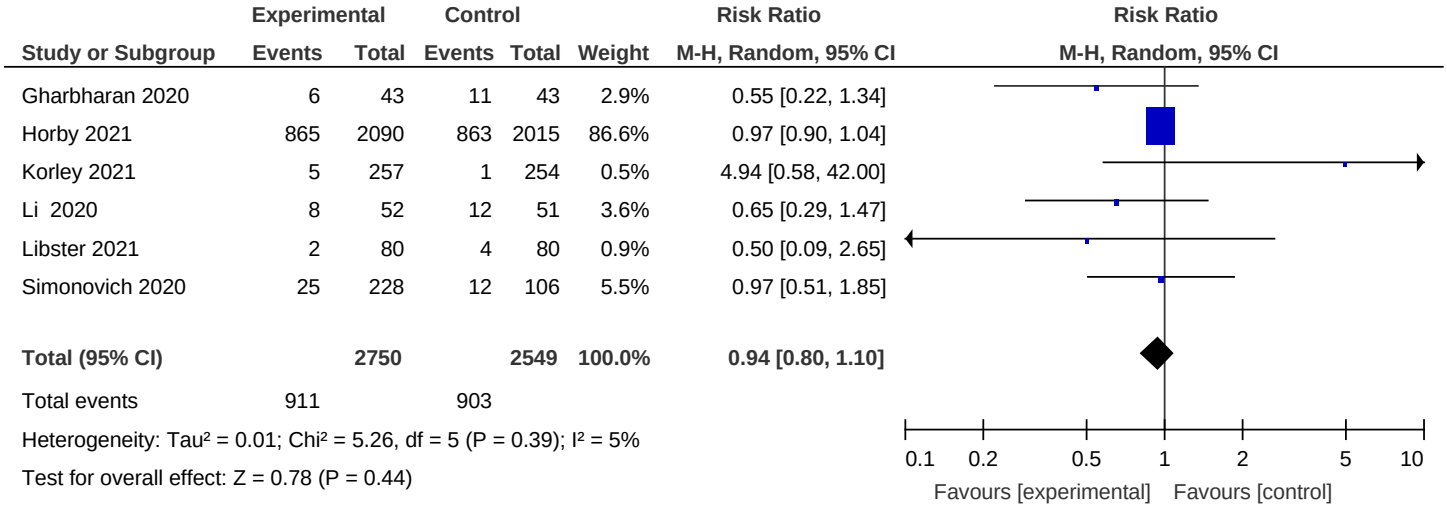

Figure 5a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.28 Mortality (Sensitivity of Aged 50 years old and above)

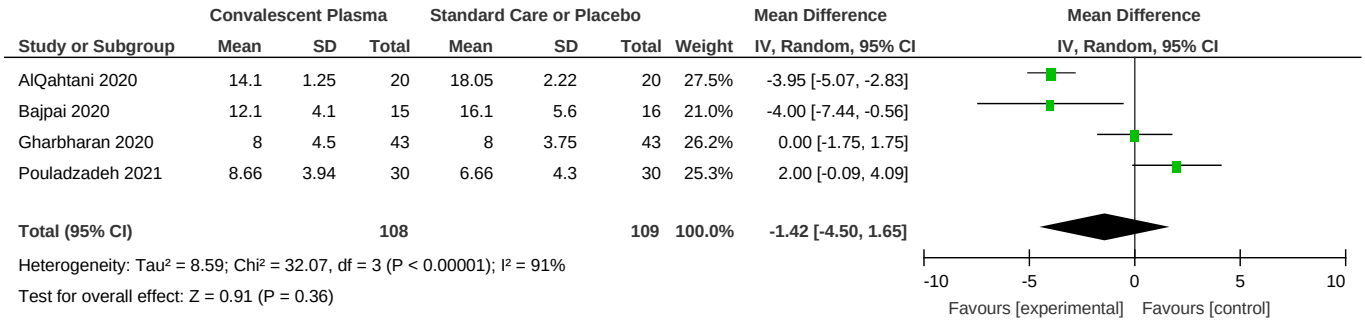

Figure 6. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.7 Duration of hospitalization

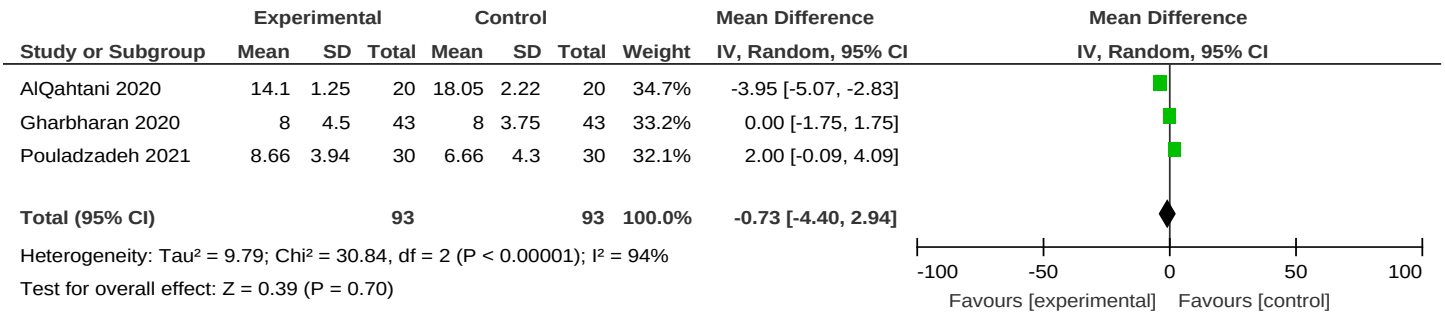

Figure 6a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.20 Duration of Hospitalization (Sensitivity Analysis)

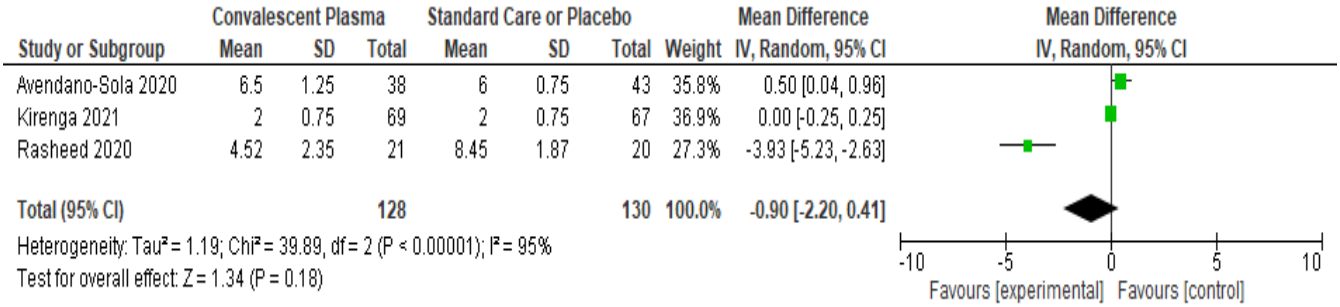

Figure 7. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.8 Time to Clinical Improvement or Resolution of Symptoms

Study or Subgroup	Convalescent Plasma Events	Total	Standard Care or Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Agarwal 2020	140	235	119	229	13.0%	1.15 [0.97, 1.35]
AlQahtani 2020	19	20	18	20	11.8%	1.06 [0.88, 1.26]
Bennett-Guerrero 2021	12	20	3	20	0.5%	4.00 [1.33, 12.05]
Gharbharan 2020	25	43	25	43	4.2%	1.00 [0.70, 1.43]
Horby 2021	3850	5795	3846	5763	28.5%	1.00 [0.97, 1.02]
Koerper 2021	23	53	17	52	2.3%	1.33 [0.81, 2.18]
Li 2020	27	52	22	51	3.3%	1.20 [0.80, 1.81]
O Donnell 2021	108	150	48	73	10.6%	1.09 [0.90, 1.33]
Pouladzadeh 2021	16	30	8	30	1.3%	2.00 [1.01, 3.95]
Salman 2020	6	15	2	15	0.3%	3.00 [0.72, 12.55]
Sekine 2021	49	80	52	80	8.0%	0.94 [0.74, 1.19]
Simonovich 2020	171	228	80	106	16.1%	0.99 [0.87, 1.13]
Total (95% CI)		**6721**		**6482**	**100.0%**	**1.06 [0.98, 1.15]**
Total events	4446		4240			

Heterogeneity: Tau² = 0.01; Chi² = 18.63, df = 11 (P = 0.07); I² = 41%

Test for overall effect: Z = 1.46 (P = 0.15)

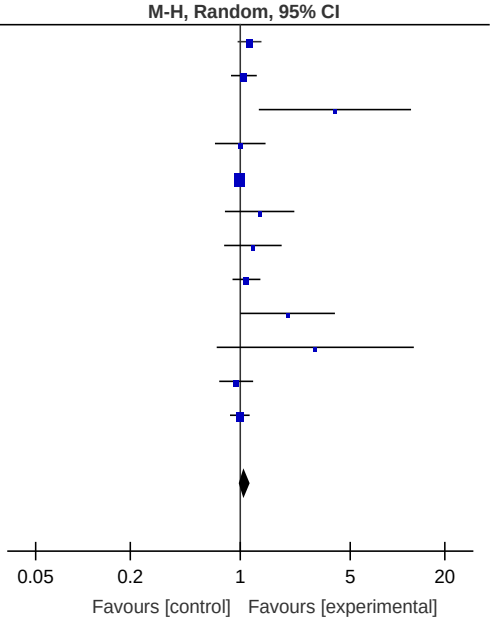

Figure 8. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.9 Clinical Improvement.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Agarwal 2020	140	235	119	229	13.3%	1.15 [0.97, 1.35]
AlQahtani 2020	19	20	18	20	12.1%	1.06 [0.88, 1.26]
Bennett-Guerrero 2021	12	20	3	20	0.5%	4.00 [1.33, 12.05]
Gharbharan 2020	25	43	25	43	4.2%	1.00 [0.70, 1.43]
Horby 2021	3850	5795	3846	5763	29.3%	1.00 [0.97, 1.02]
Li 2020	27	52	22	51	3.4%	1.20 [0.80, 1.81]
O Donnell 2021	108	150	48	73	10.9%	1.09 [0.90, 1.33]
Pouladzadeh 2021	16	30	8	30	1.3%	2.00 [1.01, 3.95]
Salman 2020	6	15	2	15	0.3%	3.00 [0.72, 12.55]
Sekine 2021	49	80	52	80	8.2%	0.94 [0.74, 1.19]
Simonovich 2020	171	228	80	106	16.5%	0.99 [0.87, 1.13]
Total (95% CI)		**6668**		**6430**	**100.0%**	**1.05 [0.97, 1.14]**
Total events	4423		4223			

Heterogeneity: Tau² = 0.01; Chi² = 17.38, df = 10 (P = 0.07); I² = 42%

Test for overall effect: Z = 1.31 (P = 0.19)

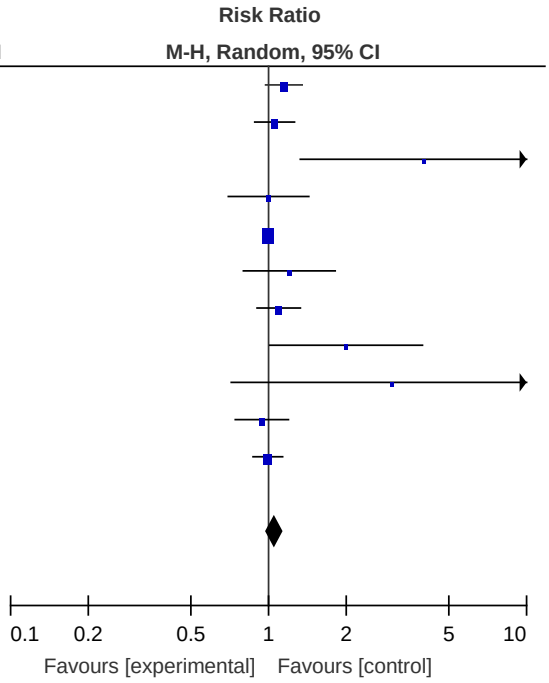

Figure 8a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.22 Clinical Improvement (Sensitivity Analysis)

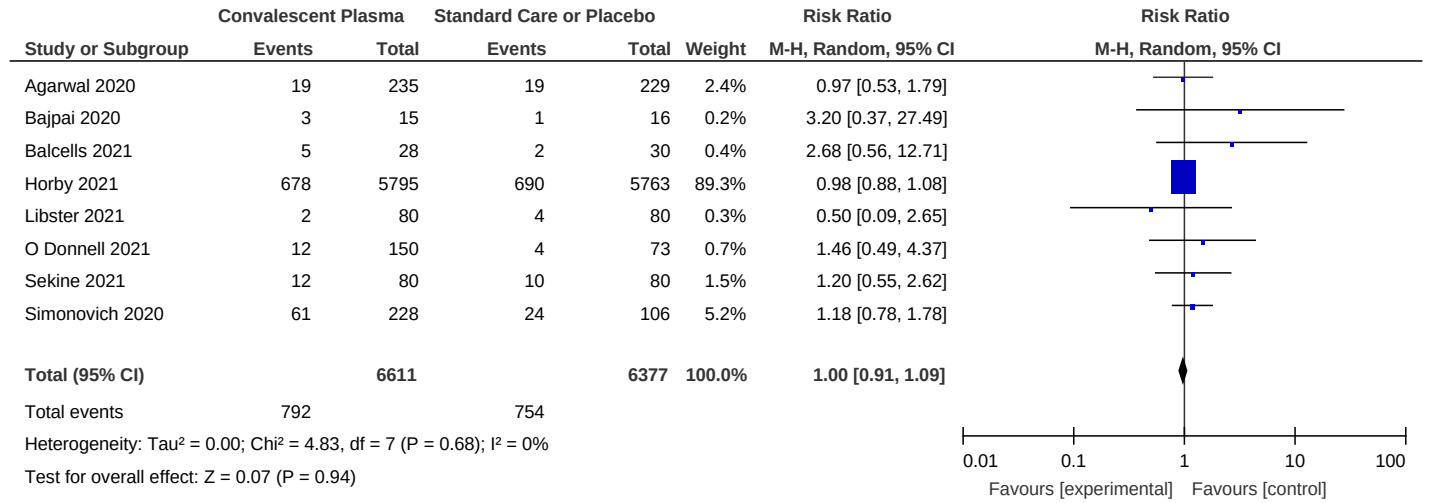

Figure 9. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.10 Need for Invasive Ventilation.

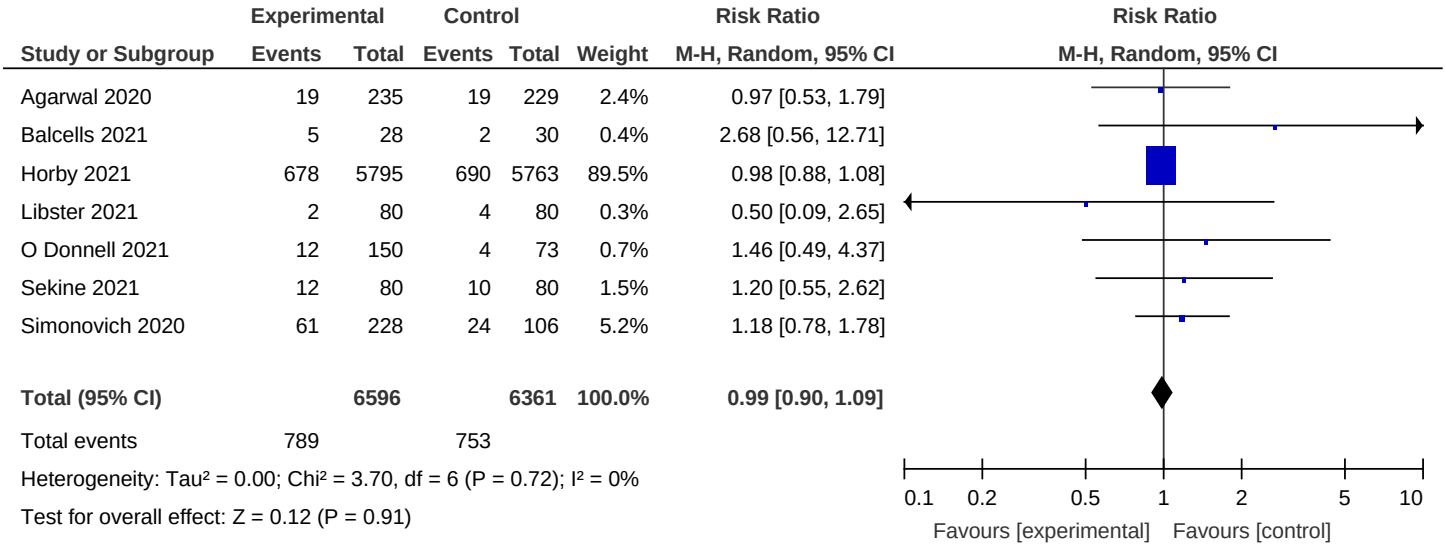

Figure 9a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.23 Need for Invasive Ventilation (Sensitivity Analysis)

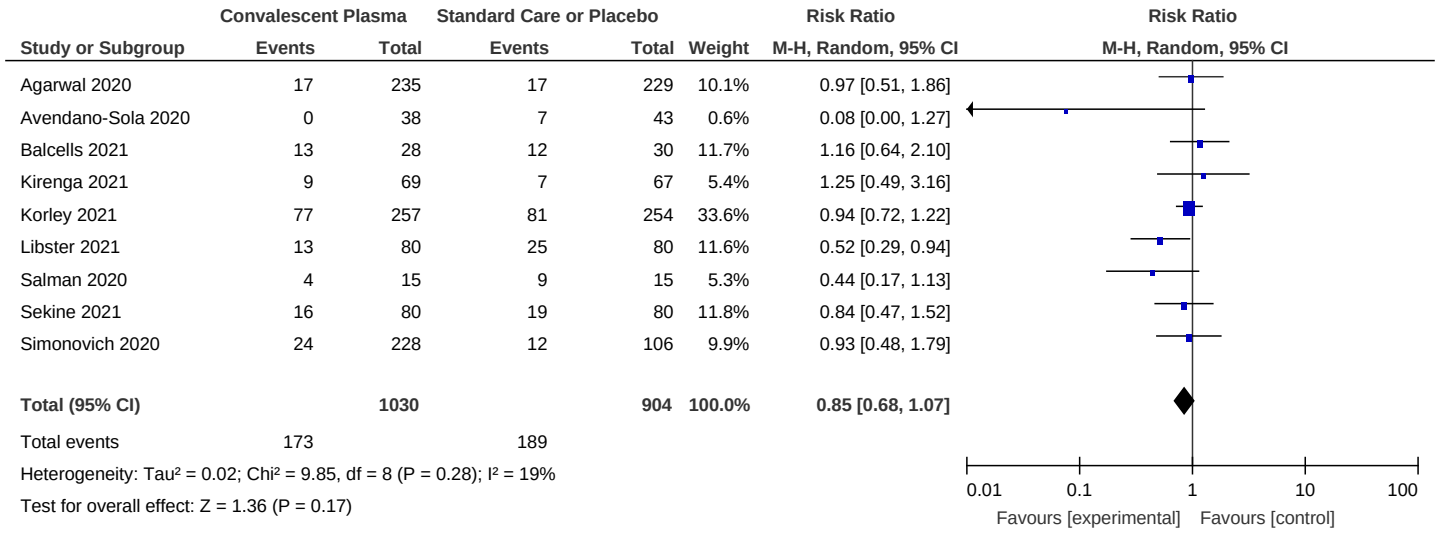

Figure 10. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.11 Progression to Respiratory Distress/Respiratory Failure

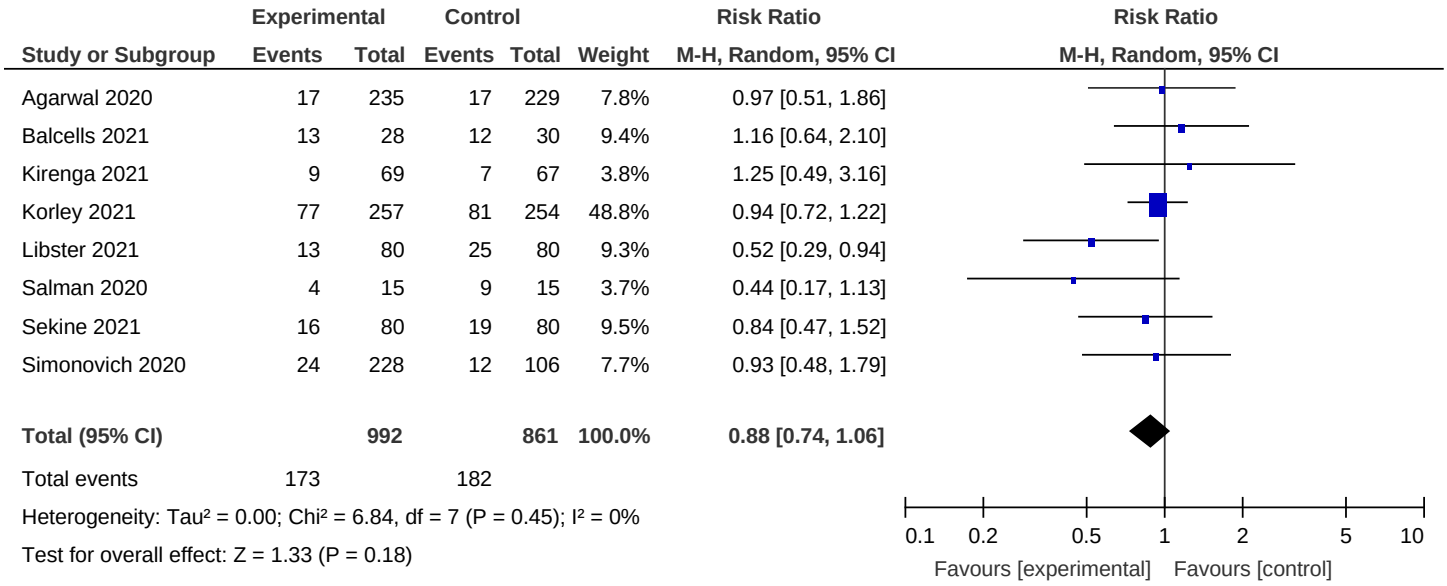

Figure 10a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.24 Progression to Respiratory Distress/Respiratory Failure (Sensitivity Analysis)

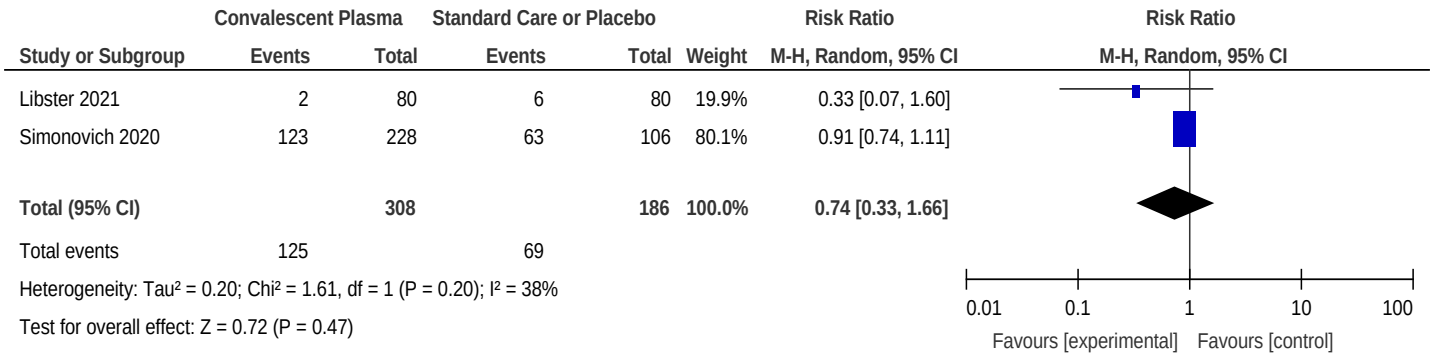

Figure 11. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.12 Need for ICU admission

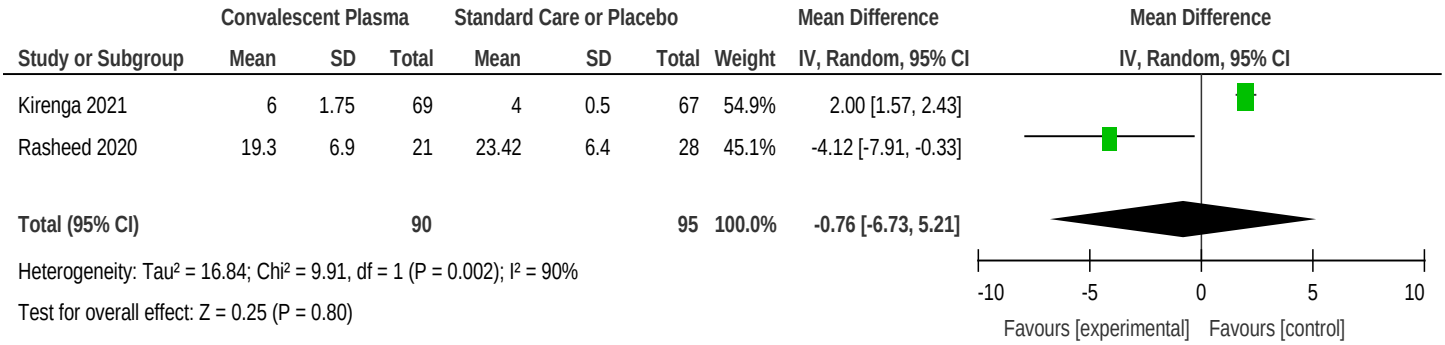

Figure 12. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.13 Time to Viral Clearance

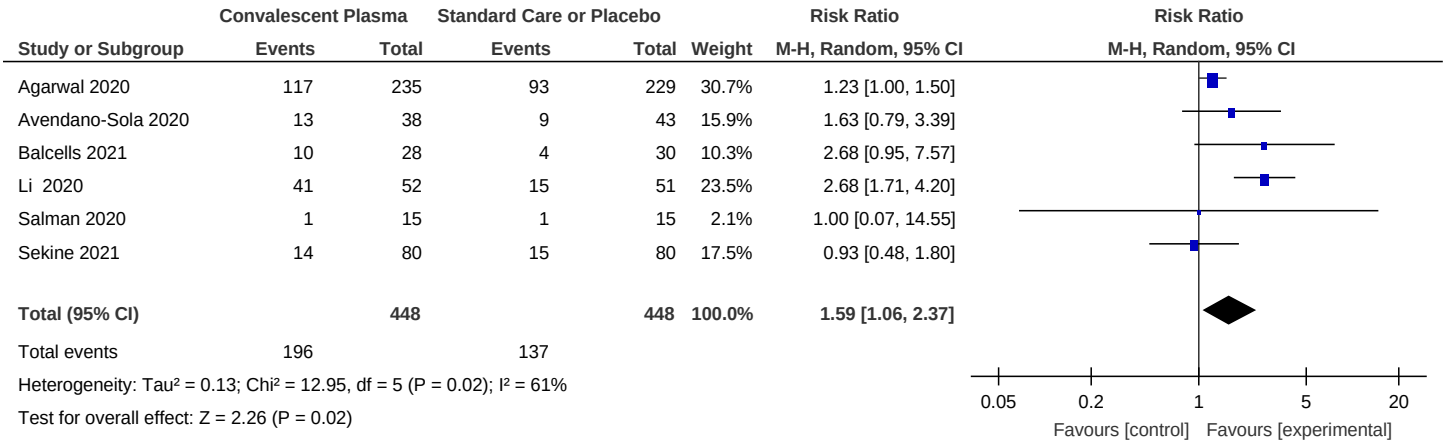

Figure 13. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.14 Viral Clearance D7

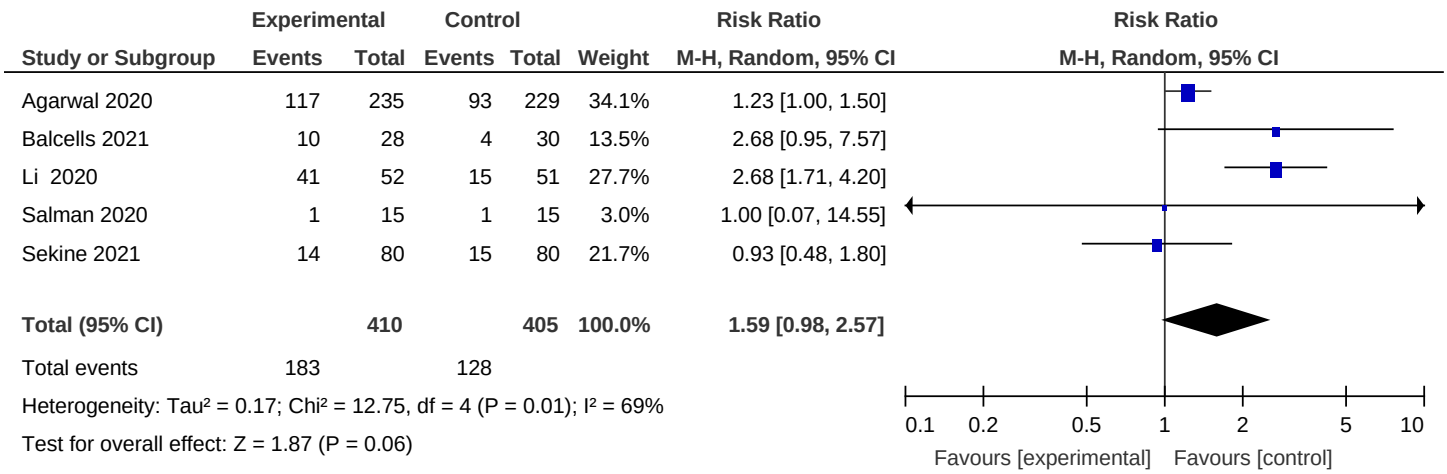

Figure 13a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.25 Viral Clearance D7

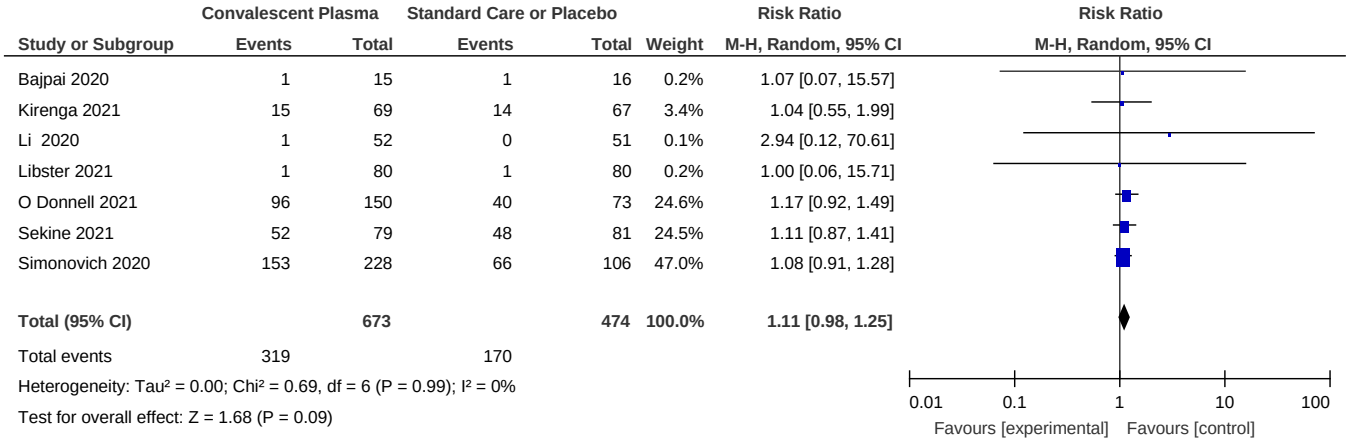

Figure 45. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.15 Adverse Events

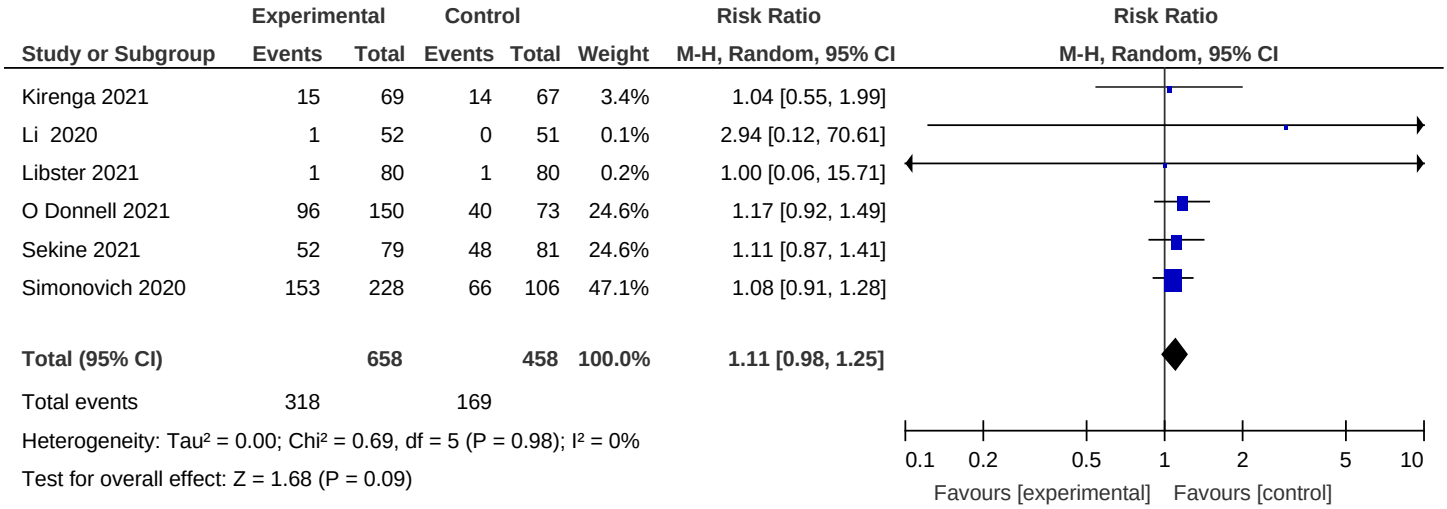

Figure 14a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.29 Adverse Events (Sensitivity Analysis)

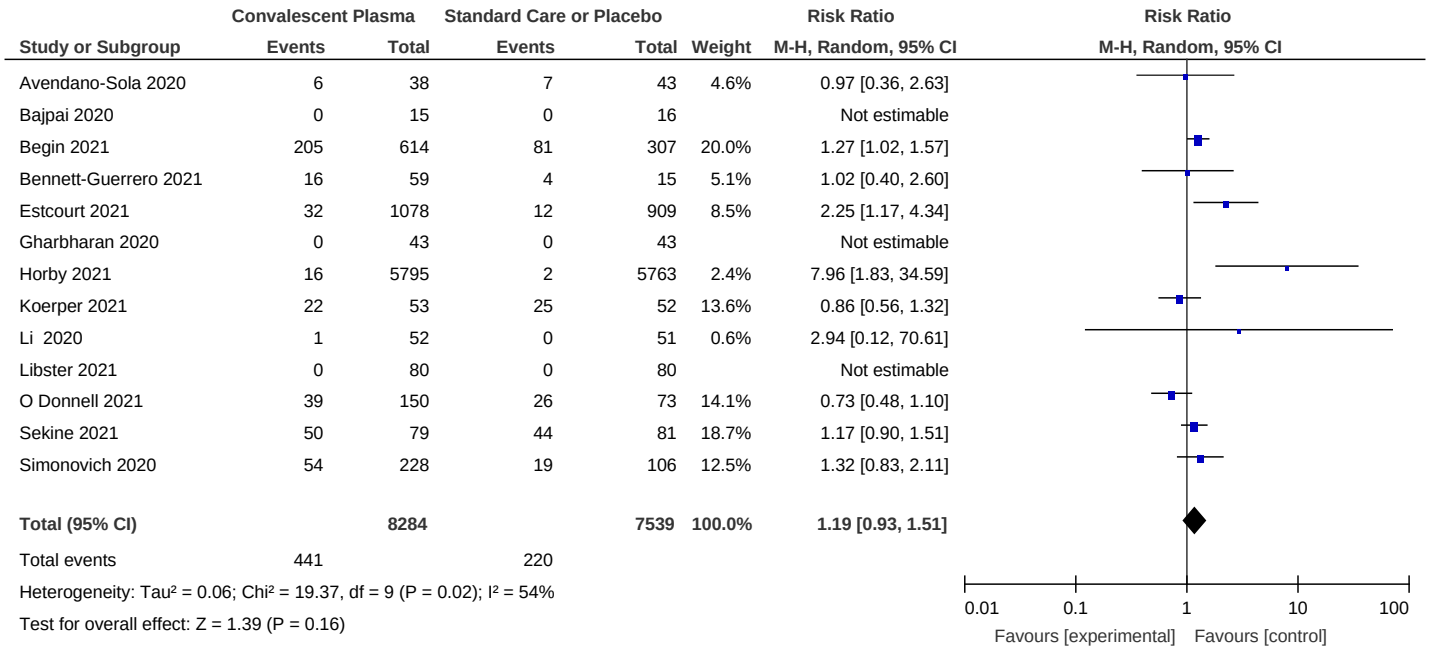

Figure 15. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.11 Serious Adverse Event

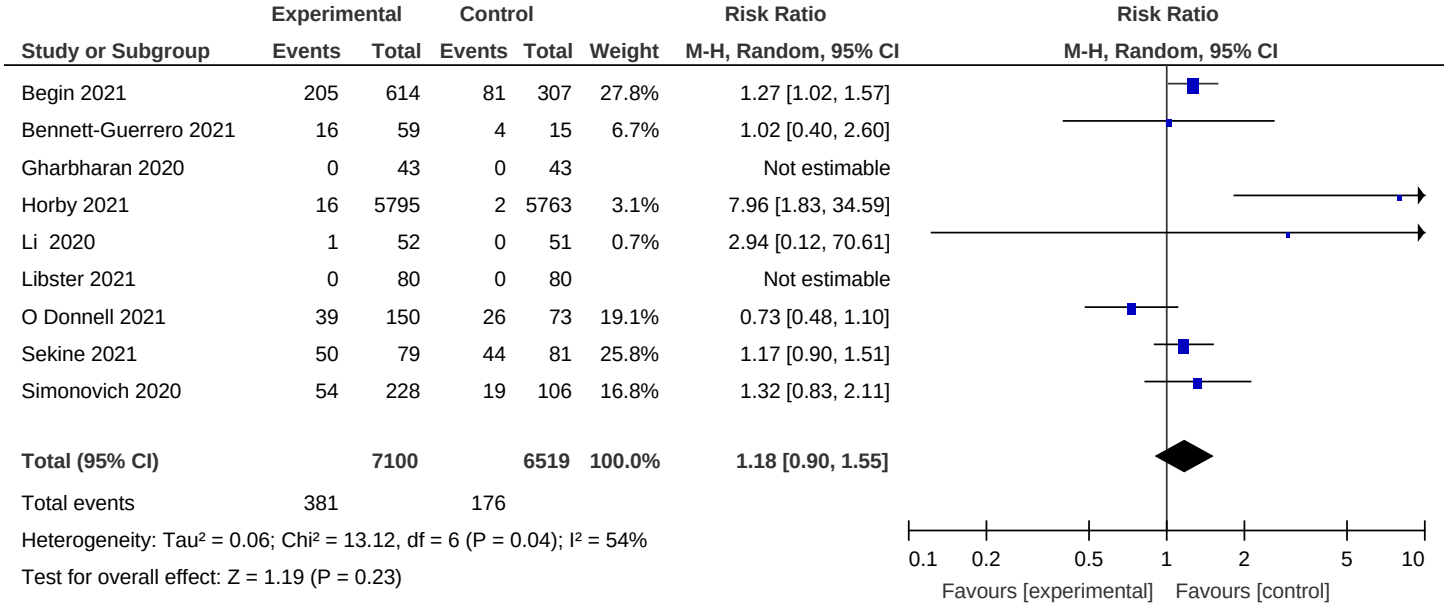

Figure 15a. Forest plot of comparison: 1 Convalescent Plasma vs Standard of Care, Outcome: 1.30 Serious Adverse Events (Sensitivity Analysis)

Appendix 7: Characteristics of Ongoing Studies

	Title	Population	Interventions	Characteristics	Outcome Measures
1	COVID-19 Convalescent Plasma (CCP) Transfusion	18 Years and older (Adult, Older Adult)	Biological: COVID Convalescent Plasma Study	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change in PaO2/FiO2 after CCP transfusion Change in pulse oximetry status after CCP transfusion Change in aO2 after CCP transfusion Change in respiratory rate after CCP transfusion Change in intubation status after CCP transfusion Change in Sequential Organ Failure Assessment (SOFA) Change in 8-point ordinal clinical deterioration scale Length of ICU/hospital stay Development of plasma transfusion reactions Development of immune complex disorders Change in anti CoV-2 IgM and IgG levels.
2	Convalescent Plasma for Treating Patients With COVID-19 Pneumonia Without Indication of Ventilatory Support	Child, Adult, Older Adult	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Area under the curve of SARS-COV-2 viral load obtained from nasopharyngeal and /or oropharyngeal swabs Assessment of clinical improvement using an Ordinal Severity Scale Evaluate oxygen saturation Evaluate oxygen supplementation Assess respiratory rate Evaluate the PaO2 / FiO2 ratio (for patients on mechanical mechanisms) Length of hospital stay Length of stay in intensive care Assess the rate of orotracheal intubation Change in the profile of cytokines/chemokines in both groups
3	PERUCONPLASMA: Evaluating the Use of Convalescent Plasma as Management of COVID-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Transfusion-related Serious Adverse Events All-cause in-hospital mortality Length of hospital stay Length of ICU stay Need of invasive mechanical ventilation Duration of mechanical ventilation Clinical Improvement at 14 days
4	Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study	18 Years and older (Adult, Older Adult)	•Biological: SARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Number and proportion of patients with progression to ventilation or sustained requirement of supplementary oxygen therapy Adverse events Dose of plasma needed to clear viremia Clearance of viremia Fever and symptoms Inflammatory parameters Antibody response to SARS-CoV-2
5	Efficacy of Convalescent Plasma Therapy in the Early Care of COVID-19 Patients.	18 Years to 90 Years (Adult, Older Adult)	Drug: Transfusion of SARS-CoV-2 Convalescent Plasma Drug: Transfusion of standard Plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Survival time without needs of a ventilator Morbidity Mortality Length of stay Effect on viral pharyngeal specimen clearance Effect on viral blood specimen clearance Effect on hemostasis disorders Kinetics of appearance of neutralizing antibodies Transfusion endotheliopathy effect Transfusion biological Inflammation effect Transfusion hemovigilance Decrease in the consumption of antibiotics
6	Convalescent Plasma as Adjunct Therapy for COVID-19	18 Years to 60 Years (Adult)	Biological: Convalescent plasma treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	The mortality in COVID-19 patients treated with convalescent plasma Change in clinical status category in CP receiving patients Duration of hospitalization Duration of mechanical ventilation Duration of ICU stay Change in lung image radiography in CP receiving patients Change in inflammatory parameters in CP receiving patients Change in coagulation parameters in CP receiving patients Change in viral load in CP receiving patients Changes in anti-SARS-CoV-2 antibody levels in CP receiving patients
7	Treatment of Patients With COVID-19 With Convalescent Plasma	18 Years and older (Adult, Older Adult)	Biological: convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time elapsed until clinical improvement or hospital discharge Acute adverse events Clinical Status Duration of clinical events SARS-CoV-2 in nasopharyngeal swab IgG, IgM and IgA titers for SARS-CoV-2 Neutralizing antibodies
8	Treatment With Investigational Convalescent Plasma and Measure Antibody Levels in Patients Hospitalized With COVID-19	18 Years and older (Adult, Older Adult)	Drug: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Prevention	Correlation between the NAb dose titer in the convalescent plasma and change or lack of change when comparing pre-treatment and day one NAb titers to inpatients with documented COIVD-19 infection Rapid deterioration as evidenced by increase in ordinal or news score within 4 hours of transfusion Number of participants with clearance of viral shedding of SARSCoV-2 in nasopharyngeal or nasal samples
9	Convalescent Plasma as Treatment for Acute Coronavirus Disease (COVID-19)	18 Years to 80 Years (Adult, Older Adult)	Biological: SARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Disease progression Adverse events (AE) Time to resolution of fever and symptoms Clearance of viraemia Inflammatory parameters Antibody response to SARS-CoV-2
10	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	For patients hospitalized for COVID-19 but not intubated Primary objective for patients with COVID-19 already intubated Duration of hospitalization Duration of mechanical ventilation Time to symptoms resolution Overall survival Rate of virologic clearance by nasopharyngeal swab at day 10 Impact of donor titers level on efficacy

					Impact of donor titers level on safety Recipient Anti-SARS-CoV2 titer assessment on days 0 (pre-infusion),3,10,30, 60
11	Evaluating the Efficacy of Convalescent Plasma in Symptomatic Outpatients Infected With COVID-19	18 Years and older (Adult, Older Adult)	Biological: CCP	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time to Resolution of Symptoms SAEs within 24 hours of plasma infusion Decrease in Inflammatory Markers Hospitalization within 28 days
12	Convalescent Plasma for the Treatment of Patients with Severe COVID-19 Infection	18 Years and older (Adult, Older Adult)	Procedure: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival Clinical improvement (i.e., percentage of patients not fulfilling the criteria for severe disease)
13	Convalescent Plasma as Treatment for Subjects with Early COVID-19 Infection	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Other: Best Supportive Care	Allocation: Randomized Intervention Model: Crossover Assignment Masking: None (Open Label) Primary Purpose: Treatment	Hospitalization Rate Time to symptoms resolution Overall survival Rate of virologic clearance by nasopharyngeal swab at 2 and 4 weeks Rate of nasopharyngeal swab positivity in donors •Rate of donor titers level Impact of donor titers level on efficacy Patients' anti-SARS-CoV2 titer assessment preinfusion for the Treatment group, at 2 weeks, 4 weeks, and 2 months.
14	Convalescent Plasma as a Possible Treatment for COVID-19	40 Years and older (Adult, Older Adult)	Biological: Convalescent plasma Biological: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Oxygen supplementation 28-day and in-hospital mortality rate Number of participants transferred to the Intensive Care Unit (ICU) Number of participants intubated Length of hospital stay in days Type of respiratory support C-reactive Protein (CRP) Lymphocyte count •Length or respiratory support required, in days Lactate dehydrogenase (LDH)
15	Convalescent Plasma as Adjunctive Therapy for Hospitalized Patients With COVID-19	19 Years and older (Adult, Older Adult)	Drug: Anti-SARS-CoV-2 convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Incidence of serious adverse events Quick SOFA (qSOFA) score Cardiopulmonary arrest ICU mortality ICU length of stay Hospital mortality Hospital length of stay Dialysis-free days Vasopressor-free days ICU-free days
16	Safety and Efficacy of Convalescent Plasma Transfusion for Patients With COVID-19	18 Years and older (Adult, Older Adult)	Biological: convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Severity and death Adverse events that require study treatment interruption Time to clinical improvement Antibodies against SARS-CoV-2 Disease progression 1 Disease progression 2 Time on mechanical ventilation Number of days with fever Adverse events attributed to the study intervention
17	Convalescent Plasma Transfusion in Severe COVID-19 Patients in Jamaica	18 Years to 65 Years (Adult, Older Adult)	Biological: Convalescent Plasma Infusion	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Mortality Viral load Antibody titre for Immunoglobulin (IgG) antiSARS-CoV-2 antibody Antibody titre for Immunoglobulin A (IgA) antiSARS-CoV-2 antibody Procalcitonin titres Interleukin 6 (IL-6) D-dimer C-reactive protein Ferritin Length of ICU admission Days to recovery
18	Statistical and Epidemiological Study Based on the Use of Convalescent Plasma for the Management of Patients With COVID-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Care Provider) Primary Purpose: Treatment	All-cause mortality Side effects Length of stay in Intensive Care Unit (ICU) Length of stay in hospitalization Days of mechanical ventilation •Inflammatory biomarkers (d-dimer) Inflammatory biomarkers (c-reactive protein) Inflammatory biomarkers (lactate dehydrogenase) Inflammatory biomarkers (ferritin)
19	Anti-COVID-19 Convalescent Plasma Therapy	18 Years and older (Adult, Older Adult)	Biological: anti-SARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Changing of viral load of SARS-CoV2 Changes in immunoglobulin G COVID-19 antibody titer Changes at the cytokine pattern Intensive Care Unit Admission Length of hospital stay Duration of mechanical ventilation Clinical Status Mortality
20	Convalescent Plasma for Treatment of COVID-19: An Open Randomized Controlled Trial	18 Years and older (Adult, Older Adult)	Biological: SARS-CoV-2 convalescent plasma •Other: Standard of care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	COVID-19 related mortality within 28 days COVID-19 related mortality within 60 days Requirement of invasive ventilation or Pao2/ FiO2 # 70 for # 12 hours in the case of patients not eligible for intensive care Adverse events Dose of plasma needed to clear viremia Time to clearance of viremia
21	Application of Convalescent Plasma in the Treatment of SARS CoV-2 Disease (COVID-19) With Evaluation of Therapy Effectiveness	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma treatment	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Death, for any reason For patients with respiratory support, the time to take one's own breath (extubation) Stay in the intensive care unit (ICU) Time to disconnect CPAP respiratory support Time to elimination of SARS-Cov-2 (RT-PCR) Time to serological response (anti-SARS-COv-2 antibodies)
22	Efficacy of Convalescent Plasma to Treat COVID-19	18 Years and older (Adult, Older Adult)	Drug: Transfusion of COVID-19 convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment	Survival without needs of ventilator utilization or use of immunomodulatory drugs WHO progression scale #6

	Patients, a Nested Trial in the CORIMUNO-19 Cohort			Masking: None (Open Label) Primary Purpose: Treatment	Severe adverse events WHO progression scale Overall survival Time from randomization to discharge Time to oxygen supply independency Survival without needs of ventilator utilization Survival without use of immunomodulatory drugs
23	Convalescent Plasma in the Early Treatment of High-risk Patients With SARS-CoV-2 (COVID-19) Infection	18 Years to 99 Years (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Determine the therapeutic efficacy (response rate) of convalescent plasma infusion in patients at high risk for mortality when infected by SARS-CoV-2 (COVID-19). Determine the immunologic effects of convalescent plasma infusion Absolute lymphocyte count (10*3/uL) Creatinine kinase (mg/dL) C-reactive protein (mg/dl) D-Dimer (ng/ml FEU) Interleukin-6 (pg/ml) Ferritin (ng/mL)
24	Therapeutic Plasmapheresis in Critically Ill Adult Patients With COVID-19 Confirmed Diagnosis	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	In-hospital mortality Incidence of renal replacement therapy Incidence of adverse events
25	Assessment of Efficacy and Safety of Therapy With COVID-19 Convalescent Plasma in Subjects with Severe COVID-19 (IPCO)	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change in SOFA score from Baseline Visit Assessment of impact of immune therapy with COVID-19 convalescent plasma on markers for ARDS due to severe COVID-19 infection Assessment of impact of immune therapy with COVID-19 convalescent plasma on short-term all-cause mortality Assessment of impact of immune therapy with COVID-19 convalescent plasma on oxygen supply in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on oxygen demand in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on Duration of Oxygen supply in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on PEEP in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on FiO2 in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on driving pressure in patients with ARDS due to severe COVID-19 Assessment of impact of immune therapy with COVID-19 convalescent plasma on Duration of invasive mechanical Ventilation in patients with ARDS due to severe COVID-19
26	Convalescent Plasma for Early Treatment of COVID-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma (anti-SARS-CoV-2 plasma) Biological: Control (albumin 5%)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Outcomes Assessor) Primary Purpose: Treatment	Rate of Severe Disease Rate of measurable anti-SARS-CoV-2 titers Rate of SARS-CoV-2 PCR Positivity Duration of SARS-CoV-2 PCR Positivity Levels of SARS-CoV-2 RNA
27	Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first Impact of 300ml convP therapy on hospital days •Impact of 300ml convP on weaning from oxygen therapy Impact of 300ml convP on overall mortality in patients admitted to the ICU within 24 hours after admission Difference in the effect of convP on mortality in patients with a duration of symptoms less or more the median duration of symptoms in the study population Impact of 300ml convP therapy on ICU days in patients admitted to the ICU within 24 hours after admission Impact of plasma therapy on the decrease in SARS-CoV2 shedding from airways Impact of CTL and NK cell immunity on the likelihood of being protected from immune serum transfer Safety of convP therapy Change of the 8-point WHO COVID19 disease severity scale on day 15
28	Convalescent Plasma in ICU Patients With COVID-19- induced Respiratory Failure	18 Years and older (Adult, Older Adult)	Biological: Multiple Doses of AntiSARS-CoV-2 convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Proportion of subjects who consent to the study and receive at least one dose of convalescent plasma Overall survival of patients in the ICU receiving at least once dose of convalescent plasma for Covid-19-induced respiratory failure
29	Standard or Convalescent Plasma in Patients with Recent Onset of COVID-19 Respiratory Failure	18 Years and older (Adult, Older Adult)	Drug: Standard Therapy Protocol (STP) Other: STP + Standard Plasma (SP) •Other: STP + COVID-19 Convalescent Plasma (CP)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor) Primary Purpose: Treatment	30-days survival Ventilator free survival 6-months survival •Incidence of complications Days in intensive care units (ICU) Positivity for Immunoglobulin G to SARS-Cov-2 Clearance of viral load •Sequential Organ Failure Assessment (SOFA) score Any variation from Standard Therapy Protocol
30	Convalescent Plasma for COVID-19 Patients (CPCP)	18 Years to 75 Years (Adult, Older Adult)	Biological: Convalescent Plasma as Therapy for Covid-19 patients	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change in mortality Change in requirement for mechanical ventilation Change in the duration of mechanical ventilation Incidence of Treatment-Emergent Adverse Events
31	Open-label Treatment of Severe Coronavirus Disease 2019 (COVID-19) With Convalescent Plasma	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma transfusion	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Change is clinical status Transfusion related events SOFA score at days 0, 7, 14, 21, 28 Length of Hospital Stay Supplemental oxygen Mechanical Ventilation Change in mechanical ventilation status Mortality Change in inflammatory markers

32	Experimental Use of Convalescent Plasma for Passive Immunization in Current COVID-19 Pandemic in Pakistan in 2020	18 Years to 55 Years (Adult)	Other: convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label)	Change in COVID-19 severity status
33	Convalescent Plasma in the Treatment of Covid-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma from COVID-19 donors Biological: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Safety (SAE) Rate of intubation Number of participants initiating systemic corticosteroids Hospital stay Mortality ICU stay Ventilator days Severity of respiratory failure Viral load Antibody measurements
34	Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19	18 Years to 85 Years (Adult, Older Adult)	Other: convalescent plasma from recovered COVID-19 donors	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	ICU length of stay Safety of convalescent plasma & Serious adverse reactions. Number of days on mechanical ventilation 30 days of mortality Days to clinical recovery
35	Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications	18 Years to 85 Years (Adult, Older Adult)	Drug: Convalescent Plasma Other: Standard Care Therapy	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Composite measure of the avoidance of – 1 Progression to severe ARDS (P/F ratio 100) and 2 All-cause Mortality at 28 days Time to symptom resolution-Fever, Shortness of Breath, Fatigue Hospital length of stay Change in SOFA pre and post transfusion Duration of respiratory support required a. Duration of Invasive Mechanical Ventilation b.Duration of Non-Invasive Radiological improvement Adverse events (AE) associated with transfusion To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR [Time Frame: Days 0, 1, 3, and 7 after transfusion] Levels of bio-markers pre and post transfusion Need of Vasopressor use
36	Convalescent Plasma as Potential Therapy for Severe COVID-19 Pneumonia	18 Years and older (Adult, Older Adult)	Biological: COVID19 convalescent plasma infusion	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	28 days survival Efficacy of plasma infusion according to antibodies levels in the infuse bags Clinical efficacy of plasma infusion according to frame time from symptoms onset and hospitalization Change in clinical WHO ordinal scale from 1 to 10 points
37	Effectiveness and Safety of Convalescent Plasma in Patients With High-risk COVID-19 Age: 18 Years and older (Adult, Older Adult) Study Completion: February 2021		Biological: SARS-CoV-2 convalescent plasma treatment Other: Standard care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Outcomes Assessor) Primary Purpose: Treatment	Mortality Adverse events ICU admission Mechanical ventilation ICU length Reduction of D Dimer LDH reduction Reduction of Troponin level Decrease in ferritin level Decrease in procalcitonin level
38	Early Convalescent Plasma Therapy for High-risk Patients With COVID-19 in Primary Care (the CoV-Early Study)	50 Years and older (Adult, Older Adult)	Biological: ConvP Biological: FFP	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Highest disease status Percentage of deaths Percentage of hospital admissions Percentage of ICU admissions Disease duration in days of symptoms Age and clinical frailty score
39	Convalescent Plasma (PC) and Human Intravenous Anti-COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma Biological: Anti-COVID-19 human immunoglobulin Drug: Standard (specific) therapy for COVID-19	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Admission to ICU and/or mechanical ventilation Length of hospital stay Neutralizing antibody (IgG) titers against COVID-19 Safety - Adverse events Death
40	Convalescent Plasma in the Treatment of Covid-19	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Number of days in need of oxygen Number of days before discharge from hospital Mortality within 3 months Number of days before need of assisted ventilation
41	Convalescent Plasma for the Treatment of COVID-19 (Coronavirus Disease 2019)	18 Years and older (Adult, Older Adult)	Biological: COVID 19 Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Cumulative incidence of serious adverse events related to the treatment intervention Mortality at Day 28 post-hospital admission Length of hospital stay Length of supplemental oxygen requirement Length of mechanical ventilation requirement Length of ICU stay
42	COVID19-Convalescent Plasma for Treating Patients With Active Symptomatic COVID 19 Infection (FALPCOVID)	15 Years and older (Child, Adult, Older Adult)	Biological: Convalescent Plasma from COVID-19 donors	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	In-hospital mortality secondary to COVID-19 among patients treated with convalescent plasma Safety of the use of convalescent plasma from COVID 19 donors Mortality at 30 days, 90 days, 6 months and 1 year In-hospital Mortality COVID-19 related compared with non-treated population according to Chilean official reports Number of days of hospitalization in high complexity facilities after convalescent plasma use Number of days of hospitalization in intensive care unit after convalescent plasma use Number of days of mechanical ventilatory support in patients after convalescent plasma use Total number of days of mechanical ventilatory support Total number of hospitalization days in patients treated with convalescent plasma Number of hospitalization days in patients after treatment with convalescent plasma

43	Convalescent Plasma Therapy in Severe COVID-19 Infection	16 Years and older (Child, Adult, Older Adult)	Biological: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Proportion of In-hospital mortality Time to death Fever Respiratory distress Saturation of oxygen Blood pressure Oxygen requirement C-reactive Protein Ferritin SGPT
44	Assessment of the Effect of Convalescent Plasma Therapy in Patients With Life-threatening COVID19 Infection	21 Years to 70 Years (Adult, Older Adult)	Biological: Convalescent Plasma Drug: Standard of Care	Allocation: Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Duration of hospitalization/Recovery status
45	Use of Convalescent Plasma for COVID-19 Study	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Arms 1 & 2: number of critical and severe COVID-19 infected patients who are transfused with convalescent plasma result in lower death rates than the reported fatality rate Arms 1 & 2: number of critical and severe COVID-19 infected patients who survive the infection Arm 3: number of high risk COVID-19 infected patients who are transfused with convalescent plasma result in lower incidence of progression to severe or critical disease than the reported case rate Arm 4: number of health care providers who are at risk to exposure to COVID-19 who are transfused with convalescent plasma result in lower incidence of developing COVID-19 infection than the reported case rate
46	Convalescent Plasma for COVID-19 Patients	18 Years to 75 Years (Adult, Older Adult)	Biological: Convalescent COVID 19 Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Evaluate the safety Change in requirement for mechanical ventilatory support
47	COVID-19 Convalescent Plasma Treatment in SARSCoV-2 Infected Patients	15 Years to 85 Years (Child, Adult, Older Adult)	Drug: COVID-19 Convalescent Plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time to clinical improvement All-cause mortality
48	Convalescent Plasma for the Treatment of Severe SARS-CoV-2 (COVID-19)	18 Years and older (Adult, Older Adult)	Drug: Convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Intrahospital mortality from any cause Length of hospital stay Free time for ventilatory support on day 60 Overall survival at day 60 since hospitalization Cumulative incidence of adverse events: transfusion reactions (fever, flare), TRALI (transfusion-associated lung injury), TACO (transfusion-related circulatory overload), transfusion- related infections
49	COVID-19 (VA CURES-1)	18 Years and older (Adult, Older Adult)	Drug: Convalescent Plasma Other: Masked Saline Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Proportion of participants developing acute hypoxemic respiratory failure or all-cause death Time (in days) to recovery Time (in days) to death or respiratory failure Proportion of patients who died from any cause, had respiratory failure, or required humidified heated high-flow nasal cannula (HHHFNC) at 15 Lpm Time (in days) to death or respiratory failure or HHHFNC at 15 Lpm Subject 28-day all-cause mortality Time to an improvement of one category using an ordinal scale Time to an improvement of two categories using an ordinal scale Participant's clinical status by ordinal scale Mean change in the ordinal scale
50	Therapeutic Use of Convalescent Plasma in the Treatment of Patients with Moderate to Severe COVID-19	18 Years and older (Adult, Older Adult)	Biological: COVID-19 convalescent plasma (CCP) plus standard of care (SOC) Biological: Standard of care (SOC) plus placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Clinical Improvement Adverse Events of special interest Serious Adverse Events Survival Invasive mechanical ventilation Disease severity Time to outcomes of interest Length of stay measures SARS-CoV PCR Inflammatory markers
51	CONTAIN COVID-19: Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Other: Saline solution	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	Score on the WHO 11-point ordinal scale for clinical improvement at 14 days Score on the WHO 11-point ordinal scale for clinical improvement at 28 days
52	CONVALESCENT PLASMA FOR ILL PATIENTS BY COVID-19	16 Years and older (Child, Adult, Older Adult)	Biological: convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical improvement Improvement in tomographic image Test positivity for COVID-19 Early and late complications associated to convalescent plasma Days at ICU
53	Convalescent Plasma for COVID-19	18 Years to 75 Years (Adult, Older Adult)	Biological: Blood plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Titers of anti-SARS-CoV-2 antibodies in the plasma derived from convalescent donors Change in titers of anti-SARS-CoV-2 antibodies in patients' plasma Change in inflammatory cytokines concentration (e.g., IL-6, HMGB1) Viral load decay in the recipient after plasma transfusion with semiquantitative assessment of nasopharyngeal swabs Number of patients with improvement in the 7- points Ordinal Scale Proportion of patients with adverse events, severity of adverse events
54	Human Convalescent Plasma for High-Risk Children Exposed or Infected With SARS-CoV-2 (COVID-19)	1 Month to 18 Years (Child, Adult)	Biological: Anti-SARS-CoV-2 Human Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Safety of treatment with high-titer anti-SARSCoV-2 plasma as assessed by adverse events Proportion of subjects with disease worsening event Pharmacokinetics of anti-SARS-CoV-2 antibodies as defined by changes in antibody titers Proportion of subjects with a natural antibody response to SARS-CoV-2 infection

55	Effectiveness and Safety of Convalescent Plasma Therapy on COVID-19 Patients with Acute Respiratory Distress Syndrome	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma Drug: Standard of care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Length of stay in intensive care unit Duration of mechanical ventilation Body temperature (degree in Celsius) The Sequential Organ Failure Assessment (SOFA) Score PAO2/FIO2 ratio C-Reactive Protein (CRP) in mg/L D-Dimer in ng/mL Procalcitonin in ng/mL Interleukin 6 (IL-6) in pg/mL
56	A Study of COVID 19 Convalescent Plasma in High-Risk Patients with COVID 19 Infection	16 Years and older (Child, Adult, Older Adult)	Drug: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival Rate
57	Preemptive Use of Convalescent Plasma for High-risk Patients With COVID-19	18 Years and older (Adult, Older Adult)	Drug: SARS-CoV-2 convalescent plasma	Allocation: Non-Randomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Prevention	Proportion of patient that progress to WHO 8 ordinal scale # 4 (oxygen requirement) Proportion of death Proportion of patients with cleared nasopharyngeal viral load
58	Clinical Study for Efficacy of Anti-Corona VS2 Immunoglobulins Prepared from COVID19 Convalescent Plasma Prepared by VIPS Mini-Pool IVIG Medical Devices in Prevention of SARS-CoV-2 Infection in High-Risk Groups as Well as Treatment of Early Cases of COVID19 Patients	21 Years to 50 Years (Adult)	Other: hyper immunoglobulins containing anti-Corona VS2 immunoglobulin	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Efficacy of COVID19 hyper immunoglobulins for patients Efficacy of COVID19 hyper immunoglobulins for high-risk groups Safety of anti-SARS-CoV-2 hyper immunoglobulins assessed by percentage of adverse events
59	Efficacy of Reinforcing Standard Therapy in COVID-19 Patients with Repeated Transfusion of Convalescent Plasma	18 Years and older (Adult, Older Adult)	Other: Convalescent Plasma with antibody against SARS-CoV-2. Other: Standard treatment for COVID-19	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	WHO clinical progression scale Lung X-ray Concomitant medication assessment Hematimetry Activated partial thromboplastin time Fibrinogen level Fragment D-dimer assessment Glomerular Filtration Rate assessment Ferritin blood assessment C-reactive protein assessment
60	A Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19 Infection	18 Years and older (Adult, Older Adult)	Biological: anti-SARS-CoV-2 convalescent plasma	Allocation: Non-Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Overall Mortality within 60 days Length of ICU stay during current admission for COVID
61	COPLA Study: Treatment of Severe Forms of COronavirus Infection with Convalescent PLAsma plasma	18 Years and older (Adult, Older Adult)	Biological: Convalescent	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Lung injury Overall survival Adverse reactions to plasma
62	Efficacy of Convalescent Plasma in Patients with COVID-19 Treated with Mechanical Ventilation	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Other: Standard of Care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Vital status Day 90 mortality Number of ventilator-free days at day 28 Number of renal replacement therapy free days at day 28 Number of vasopressors free-days at day 28 Use of ECMO before day 28 Value of the SOFA score at days 7, 14 and 28 Changes in SOFA scores (delta SOFA) over 7, 14 and 28 days Assessment of the SARS-CoV-2 viral load Blood C-reactive protein (CRP) concentration
63	Convalescent Plasma to Limit SARS-CoV-2 Associated Complications	18 Years and older (Adult, Older Adult)	Biological: SARS-CoV-2 convalescent plasma Biological: Plasma from a volunteer donor	Allocation: Randomized Intervention Model: Parallel Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Cumulative incidence of hospitalization or death prior to hospitalization Cumulative incidence of treatment-related serious adverse events Cumulative incidence of treatment-related grade 3 or higher adverse events Change in serum SARS-CoV-2 antibody titers Time to SARS-CoV-2 Polymerase Chain Reaction (PCR) negativity
64	Convalescent Plasma Therapy for COVID-19 Patients	15 Years to 80 Years (Child, Adult, Older Adult)	Biological: convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical outcome after plasma therapy Clinical response to treatment
65	Passive Immunity Trial for Our Nation to Treat COVID-19 in Hospitalized Adults	18 Years and older (Adult, Older Adult)	Biological: pathogen reduced SARSCoV-2 convalescent plasma Biological: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Outcomes Assessor) Primary Purpose: Treatment	COVID-19 7-point Ordinal Clinical Progression Outcomes Scale All-location, all-cause 14-day mortality All-location, all-cause 28-day mortality Survival through 28 days Time to hospital discharge through 28 days COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 3 COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 8 COVID-19 7-point Ordinal Clinical Progression Outcomes Scale on Study Day 29 Oxygen-free days through Day 28 •Ventilator-free days through Day 28
66	Convalescent Plasma for Treatment of COVID-19 Patients with Pneumonia	18 Years and older (Adult, Older Adult)	Drug: High-Titer Anti-SARS-CoV-2 (COVID 19) Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Transfer to ICU 28-day mortality Cumulative incidence of serious adverse events Rates and duration of SARS-CoV-2 Serum of plasma antibody titer to SARS-CoV-2 Cellular and humoral immune response Supplemental oxygen free days

					Ventilator free days ICU free days Sequential organ failure assessment score
67	Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia	18 Years and older (Adult, Older Adult)	Biological: Convalescent anti-SARSCoV-2 plasma Other: Infusion placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	All-cause mortality or need of invasive mechanical ventilation Frequency of adverse events Frequency of severe adverse events Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status Ventilator-free days Organ failure-free daysDuration of ICU stay Mortality rate Length of hospital stay Duration of supplemental oxygen
68	Donated Antibodies Working Against nCoV	18 Years and older (Adult, Older Adult)	Biological: Convalescent Plasma Drug: Standard of care	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Patients requiring mechanical ventilation or death Clinical status of subject at day 15 and day 30 (on a 10-point "WHO progression" ordinal scale)
69	Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial	30 Years to 70 Years (Adult, Older Adult)	Biological: Convalescent Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Mortality changes in day 10 Mortality changes in day 30 Changes of C-reactive protein Changes of Interleukin 6 Changes of tumor necrosis factor-# Changes of PaO2/FiO2 Ratio Changes of CD3 Changes of CD4 Changes of CD8 Changes of CD4/CD8 ratio
70	Plasma Exchange (PLEX) and Convalescent Plasma (CCP) in COVID-19 Patients with Multiorgan Failure	18 Years and older (Adult, Older Adult)	Procedure: Plasma exchange and convalescent plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Alive at Day 90 Day 8 serious adverse events Day 28 all-cause mortality Days alive without life support at day 90
71	Hyperimmune Plasma in Patients With COVID-19 Severe Infection	18 Years to 60 Years (Adult)	Other: plasma hyperimmune Drug: standard therapy	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Decrease in mortality Lymphocytes PCR levels vs control PCR levels vs before treatment AB levels and clinical improvement Inflammatory cytokines vs controls Inflammatory cytokines vs before treatment
72	Inactivated Convalescent Plasma as a Therapeutic Alternative in Patients COVID-19	18 Years and older (Adult, Older Adult)	Drug: Inactivated convalescent plasma Drug: Support treatment	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Investigator) Primary Purpose: Treatment	Mortality reduction in CoViD-19 patients treated with inactivated convalescent plasma + support treatment Clinical evolution Clinical evolution by seven-parameter ordinal scale Multi-organ failure progression Change in hemoglobin concentration Change in blood cell count Change in serum creatinine level Change in aspartate aminotransferase level Change in alanin aminotransferase level Change in bilirubin level
73	Reconvalescent Plasma/Camostat Mesylate Early in SARS-CoV-2 Q-PCR (COVID-19) Positive High-risk Individuals	18 Years and older (Adult, Older Adult)	Biological: Convalescent plasma Drug: CamostatMesilate Drug: Placebo for CamostatMesilate Other: Standard of Care (SoC)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	WHO ordinal COVID-19 scale up to day 28 Cumulative number WHO categories 4b-8 Cumulative number WHO categories 3-4a Not hospitalized All-cause mortality Reinfection Secondary sclerosing cholangitis (SSC) Chronic pulmonary disease as sequelae from COVID-19 patients with remdesivir treatment COVID-19 WHO status of patients at start of remdesivir treatment
74	COVID-19 Convalescent Plasma as Prevention and Treatment for Children with Underlying Medical Conditions	1 Month to 17 Years (Child)	Biological: anti-SARS-CoV-2 human convalescent plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Cumulative incidence of Grade 3 and Grade 4 adverse events Cumulative incidence of serious adverse events Proportion of participants with disease worsening event Serum concentration at baseline, Day 7, Day 14, and Day 28 for anti-SARS-CoV-2 antibodies Percentage of participants with a natural antibody response to SARS-CoV-2 infection
75	Convalescent Plasma to Stem Coronavirus (CSSC-001)	18 Years and older (Adult, Older Adult)	Biological: Anti- SARS-CoV-2 Plasma Biological: SARS-CoV-2 non-immune Plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment	Efficacy of treatment at Day 28 Safety of treatment with high-titer Anti- SARSCoV-2 plasma versus control - 1 Safety of treatment with high-titer Anti- SARSCoV-2 plasma versus control - 2 Cumulative incidence of disease severity
76	Convalescent Plasma Collection and Treatment in Pediatrics and Adults	31 Days and older (Child, Adult, Older Adult)	Biological: Convalescent Plasma 1 Unit Biological: Convalescent Plasma 2 Units Other: Standard of Care	Allocation: Non-Randomized Intervention Model: Sequential Assignment Masking: None (Open Label) Primary Purpose: Treatment	Survival Incident of treatment-Emergent Adverse Events [Safety and Tolerability] Morbidity reduction Reduced Length of Stay in hospital Reduced Length of Stay on Advance Respiratory Support
77	COVID-19 Plasma in Treatment of COVID-19 Patients	18 Years to 80 Years (Adult, Older Adult)	Biological: Convalescent COVID 19 Plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Reduce mortality Reduce requirement for mechanical ventilation Reduce the duration of mechanical ventilation Review of treatment related adverse events.
78	Hyperimmune Plasma for Patients With COVID-19	18 Years and older (Adult, Older Adult)	Other: treated with hyperimmune plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Death Time to extubation Length of intensive care unit stay Length of hospitalization Immune response Viral load

79	Randomized Evaluation of COVID-19 Therapy	Child, Adult, Older Adult	Drug: Lopinavir-Ritonavir Drug: Corticosteroid Drug: Hydroxychloroquine Drug: Azithromycin Biological: Convalescent plasma Drug: Tocilizumab Biological: Immunoglobulin Drug: Synthetic neutralising antibodies Drug: Aspirin Drug: Colchicine and 5 more	Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Duration of hospital stay Composite endpoint of death or need for mechanical ventilation or ECMO
80	Anti-COVID-19 Hyperimmune Intravenous Immunoglobulin (C-IVIG) Therapy for Severe COVID-19 Patients	18 Years and older (Adult, Older Adult)	Biological: Anti COVID-19 Intravenous Immunoglobulin (C-IVIG)	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Single (Participant) Primary Purpose: Treatment	28-day Mortality Immediate and serious adverse event during hospital stay Clinical Status of follow-up days according to 7- Category Ordinal Scale Change in C-Reactive Protein (CRP) levels Change in interleukin 6 (IL-6) Change in anti-SARS-CoV-2 antibody levels Change in Horowitz index Change in radiological findings
81	Plasma Rich Antibodies from Recovered Patients from COVID19	18 Years to 80 Years (Adult, Older Adult)	Other: Antibody-Rich Plasma from COVID-19 recovered patient	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Viral COVID-19 clearance Decrease of radiological abnormalities Clinical improvement
82	Study Testing Convalescent Plasma vs Best Supportive Care	18 Years and older (Adult, Older Adult)	Biological: high-titer anti-Sars-CoV-2 plasma Other: oxygen therapy	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Reduction in oxygen and ventilation support
83	Efficacy and Safety of Recovered Covid 19 Plasma Transfusion to Covid 19 Severly Ill Patients Age: 18 Years and older (Adult, Older Adult) Study Completion: September 1, 2020		Biological: recovered COVID-19 patients' plasma	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	Patients' response to recovered COVID-19 plasma (RCP) during 5 days after transfusion Satisfactory outcome (two or more of the following 4 conditions/ or otherwise unsatisfactory): 1. respiratory frequency < 30/min, 2. Sustain blood oxygen saturation ≥93% on room air, 3. partial pressure of arterial oxygen to fraction of inspired oxygen ratio > 300 mmHg, 4. Regression of pulmonary infiltrates occupying less than 50% of both lungs.
84	plasmApuane CoV-2: Efficacy and Safety of Immune Covid-19 Plasma in Covid-19 Pneumonia in Non-ICU Patients	18 Years and older (Adult, Older Adult)	Biological: immune plasma	Allocation: N/A Intervention Model: Sequential Assignment Masking: None (Open Label) Primary Purpose: Prevention	ICU admission Administration of O2 Hospital mortality Immune plasma infusion adverse reaction
85	Convalescent Antibodies Infusion in Critically Ill COVID-19 Patients	18 Years and older (Adult, Older Adult)		Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Number of mechanical ventilation days Survival Shift to Continuous Positive Airway Pressure (CPAP) ventilation Referral to a sub-intensive care unit or discharge Viral titer Anti-COVID-19 IgG antibodies Anti-COVID-19 IgM antibodies C5a concentration C3a concentration Serum C5b-9 concentration
86	Convalescent Antibodies Infusion in COVID-19 Patients	Years and older (Adult, Older Adult)	Biological: Anti-coronavirus antibodies (immunoglobulins) obtained with DFPP form convalescent patients	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Time to weaning of oxygen support Chest XR or CT scan evaluation Survival, Viral titer Anti-COVID-19 IgG antibodies Anti-COVID-19 IgM antibodies C5a concentration C3a concentration Serum C5b-9 concentration Marker of complement activation Serum IL-6 levels
87	Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia	18 Years and older (Adult, Older Adult)	Drug: Fixed-duration Hydrocortisone Drug: Shock-dependent hydrocortisone Drug: Ceftriaxone Drug: Moxifloxacin or Levofloxacin Drug: Piperacillin-tazobactam Drug: Ceftaroline Drug: Amoxicillin-clavulanate Drug: Macrolide administered for 3-5 days Drug: Macrolide administered for up to 14 days Drug: Five-days oseltamivir and 20 more	Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	All-cause mortality Days alive and not receiving organ support in ICU ICU Mortality ICU length of stay Hospital length of stay Ventilator free days Organ failure free days Health-related Quality of life assessment Proportion of intubated patients who receive a tracheostomy Destination at time of hospital discharge Readmission to the index ICU during the index hospitalization World Health Organization 8-point ordinal scale outcome
88	Study to Evaluate the Safety and Efficacy of XAV-19 in Patients With COVID-	18 Years and older (Adult, Older Adult)	Drug: XAV-19 Drug: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment	Phase 2a: XAV-19 antibody titers Phase 2a: Adverse events of XAV-19 Phase 2b: To evaluate the efficacy of XAV-19 + standard-of-care (Soc) therapy compared with placebo + Soc therapy for treatment of COVID-19

	19 Induced Moderate Pneumonia			Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment	assessed by the proportion of patients who die or develop respiratory failure between baseline and Day 15. Phase 2a: Pharmacokinetic analysis Phase 2a: Antibody titer between the two groups Phase 2a: Supplemental oxygen Phase 2a: Evaluation of Transfer to intensive care Phase 2a: Normalization of Fever Phase 2a: Biomarkers Phase 2a: Hospital length of stay
89	Selenium as a Potential Treatment for Moderately-ill, Severely-ill, and Critically-ill COVID-19 Patients.	18 Years and older (Adult, Older Adult)	Drug: Selenium (as Selenious Acid) Other: Placebo	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator) Primary Purpose: Treatment	Mean change in the ordinal scale Rate of hospital discharges or deaths Clinical status using ordinal scale Time to an improvement of one category using an ordinal scale Change in National Early Warning Score (NEWS) from baseline Cumulative incidence of serious adverse events (SAEs) Duration of hospitalization Incidence of new oxygen use Duration of new oxygen use Incidence of new non-invasive ventilation or high flow oxygen use
90	Australasian COVID-19 Trial (ASCOT) ADAptive Platform Trial	Years and older (Adult, Older Adult)	Drug: NafamostatMesilate Biological: Hyperimmune Globulin Drug: Enoxaparin Drug: Dalteparin Drug: Tinzaparin	Allocation: Randomized Intervention Model: Factorial Assignment Masking: None (Open Label) Primary Purpose: Treatment	Death from any cause or requirement of new intensive respiratory support (invasive or noninvasive ventilation) or vasopressor/inotropic support Time to clinical recovery WHO 8-point ordinal outcome scale All-cause mortality Days alive and free of hospital Days alive and free of invasive or non-invasive ventilation Shortness of breath Quality of life Antiviral domain-specific outcome: Viral clearance Antiviral domain-specific outcome: Viral load
91	Exchange Transfusion Versus Plasma from Convalescent Patients with Methylene Blue in Patients With COVID-19	18 Years to 65 Years (Adult, Older Adult)	Biological: exchange blood transfusion from normal donor Biological: plasma from convalescent patients with COVID-19 Drug: Methylene Blue 5 MG/ML	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Improvement of condition Change in organs function with PFS and OS
92	Clinical Trial to Evaluate the Efficacy of Treatment with Hyperimmune Plasma Obtained from Convalescent Antibodies of COVID-19 Infection	18 Years to 80 Years (Adult, Older Adult)	Biological: Hyperimmune plasma Drug: Standard of care for SARSCoV-2 infection	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment	Safety: Incidence of Adverse Events and Serious Adverse Events grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE). Efficacy: Death from any cause Efficacy: Need for mechanical ventilation Efficacy: Any of the following analytical data after 72h of randomization. Efficacy: SOFA scale # 3 after 72 hours of randomization or an increase of 2 points or more from the basal level Efficacy: Mortality on days 14 and 28 Efficacy: Proportion of patients who required mechanical ventilation Efficacy: Proportion of patients who develop analytical alterations Efficacy: Cure / clinical improvement (disappearance or improvement of signs and symptoms of COVID-19) in the cure test. Efficacy: PCR negative for SARS-CoV-2
93	Early Use of Hyperimmune Plasma in COVID-19	18 Years and older (Adult, Older Adult)	Other: hyperimmune plasma	Allocation: N/A Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Treatment	Clinical improvement (efficacy) Ventilation WHO (World Health Organization) scale SOFA (Sequential Organ Failure Assessment) score Naso-pharyngeal swab SARS-CoV2 P/F Thrombosis Curarization Complication kidney

Appendix 8: Characteristics of Studies in the Early (within 3 days of hospitalization), High Titer Plasma

Study ID	Participants	Settings & Sample Size	Comparisons		Design	Outcomes	Patient and Study Characteristics								
			Treatment	Control			Age (mean±SD — yr)	Sex	Time from hospitalization to randomization/ transfusion	Time from Symptom Onset to Randomization/ Transfusion	Comorbidity	Severity	Oxygen support/ Respiratory support	Standard of care treatment given	Adverse Events/ Serious Adverse events
NCT04479163 Libster R, N Engl J Med, 2021	Patients with confirmed COVID-19 (mild; had at least one of each sign and symptom in the following two categories for less than 48 hours: a temperature of at least 37.5 C, unexplained sweating or chills; and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, rhinorrhea) admitted to multiple centers in Argentina	Argentina (N = 160)	Convalescent plasma (1:1000 titer) (N=80)	Placebo (0.9% Normal Saline) (N=80)	RCT (double blind, placebo controlled)	All-cause mortality, Adverse events, Serious adverse events	CP: 76.4±8.7 ; Placebo: 77.9±8.4	CP: Male: 26/80 (32%), Female: 54/80 (68%); Placebo: Male: 34/80 (42%), Female: 46/80 (58%)	Within 24 hours	Within 72 hours (CP: 39.6±13.9 (in hrs), Placebo: 38.3±14.3 (in hrs))	Hypertension for which treatment was being received: CP: 62/80 (78%), Placebo: 52/80 (65%); Diabetes for which treatment was being received: CP: 23/80 (29%), Placebo: 13/79 (16%); Obesity: CP: 4/80 (5%), Placebo: 8/79 (10%); COPD for which treatment was being received: CP: 2/80 (2%), Placebo: 5/79 (6%); Cardiovascular disease: CP: 14/80 (18%), Placebo: 7/79 (9%); Chronic renal failure: CP: 1/80 (1%), Placebo: 3/79 (4%); At least one primary coexisting condition: CP: 69/80 (86%), Placebo: 62/80 (78%)	Mild	not requiring supplemental oxygen; baseline oxygen saturation at room air: CP: 96.1±1.6, Placebo: 96.1±1.7	None mentioned	No solicited adverse events were observed.
NCT04342182 Gharbharan A, medRxiv, 2020	Patients with COVID-19 (moderate-critical) admitted to 14 centers in the Netherlands	Netherlands (N=86)	Convalescent plasma (median PRNT50 (640, IQR 320–1280)) + SOC (N=43)	Standard care (N=43)	RCT (open-label)	All-cause mortality D28, Clinical improvement D28, Serious adverse events	CP: median 61, IQR (56–70); SOC: median 63, IQR (55–77)	CP: Male: 29 (67%), Female: 14 (33%); SOC: Male: 33 (77%), Female: 10 (23%)	median: 2 days (IQR 1–3)	median: 10 days (IQR 6–15)	Diabetes mellitus: CP: 13 (30%), SOC: 8 (19%); Hypertension: CP: 11 (26), SOC: 11 (26%); Cardiac: CP: 9 (21%), SOC: 11 (26%); Pulmonary: CP: 12 (28%), SOC: 11 (26%); Cancer: CP: 5 (12%), SOC: 3 (7%); Immunodeficiency: CP: 5 (12%), SOC: 6 (14%); chronic kidney disease: CP: 1 (2%), SOC: 6 (14%); Liver cirrhosis: CP: 1 (2%), SOC: 0	Moderate -critical	hospitalized with no oxygen: CP: 7 (16%), SOC: 1 (2%); Hospitalized with Oxygen support or NIV: CP: 31 (72%), SOC: 34 (79%); Hospitalized with invasive ventilation (MV): CP: 5 (12%), SOC: 8 (19%)	None mentioned	No plasma-related serious adverse events were observed

NCT04345523 Avendano-Sola C, medRxiv, 2020	Patients with confirmed COVID-19 [moderate (Pneumonia (CXR) or O2sat ≤94%] admitted to 14 centers in Spain	Spain (N=81)	Convalescent plasma (VMNT-ID50: median titer 1:292, IQR 238-451) (N=38)	Standard of care (43)	RCT (open-label)	All-cause mortality D28, WHO Progression score level 7 or above at D28, Serious adverse events, Time to clinical improvement	60.8 ±15.5	Male: 44 (54.3%); Female: 37 (45.7%)	within 3 days	(8.0 (6.0-9.0) (Median time (IQR) from symptom onset to randomization — days)	Diabetes mellitus: CP: 12 (31.6%), SOC: 5 (11.6%); Hypertension: CP: 20 (52.6%), SOC: 12 (27.9%); Cardiovascular disorder: CP: 6 (15.8%), SOC: 9 (20.9%); Chronic lung disease: CP: 2 (5.35), SOC: 8 (18.6%); chronic kidney disease: CP: 2 (5.35), SOC: 2 (4.7%); Immunodeficiency: CP: 2 (5.3%), SOC: 5 (11.6%)	Mild to Moderate	Not requiring supplemental oxygen: CP: 10 (26.32%), SOC: 13 (30.23%), Total: 23 (28.40%); Requiring supplemental oxygen by mask or nasal prongs: CP: 28 (73.68%), SOC: 30 (69.77%), Total: 58 (71.60%)	Hydroxychloroquine: CP: 34 (89.47%), SOC: 36 (83.72%), Total: 70 (86.42%); Lopinavir-ritonavir: CP: 15 (39.47%), SOC: 19 (44.19%), Total: 34 (41.98%); Azithromycin: CP: 24 (63.16%), SOC: 26 (60.47%), Total: 50 (61.73%); Remdesivir: CP: 1 (2.63%), SOC: 3 (6.98%), Total: 4 (4.94%); Glucocorticoid therapy: CP: 21 (55.26%), SOC: 25 (58.14%), Toatal: 46 (56.79%); Tocilizumab: CP: 10 (26.32%), SOC: 13 (30.23%), Total: 23 (28.40%); Low Molecular Weight Heparin: CP: 27 (71.05%), SOC: 33 (76.74%), Total: 60 (74.07%)	Sixteen serious or grade 3-4 AE were reported in 13 patients, 6 in the CP group and 7 in the SOC group. Two CP infusion-related AE and suspected TRALI were reported. In both cases, TRALI was ruled out after full assessment. Both patients recovered without sequelae. None of the remaining events (n=14) were considered to be related to the CP. Five of the patients with reported severe AE died due to their underlying disease (4 deaths within the study, 1 death after the end of the study, all in the SOC group). The remaining patients recovered without sequelae.
Rasheed 2020	Critically-ill COVID-19 patients aged ≥18-year-old affected by pneumonia with SpO2 <90% in resting state at their first 3 days in RCU receiving O2 or on ventilators at their early stages of admission to RCU before developing full-blown Acute Respiratory Distress Syndrome (ARDS) or respiratory and/or multiple organ failure and residing in Respiratory Care Units (RCU) in Baghdad, Iraq	Iraq (N=49)	Convalescent plasma (IgG index ≥1.25 as measured by ELISA; to ensure getting CP with the highest titers of antibodies) + SOC (N=21)	Standard of care (N=28)	RCT (open-label)	Recovery or death, length of stay in hospital, and improvement in the clinical course of the disease	CP: 55.66 ± 17.83, SOC: 47.82 ± 15.36	Not mentioned	within 3 days	CP: 14.80 ± 7.46, SOC: 16.57 ± 5.99	Diabetes mellitus: CP: 8 (38%), SOC: 9 (32%); Hypertension: CP: 7 (33%), SOC: 10 (36%); heart disease: CP: 5 (24%), SOC: 5 (18%); Obesity: CP: 10 (48%), SOC: 11 (39%); Cancer: CP: 3 (14%), SOC: 5 (18%)	early-stage (no more than 3 days in ICU) critically ill COVID-19 patients before developing full-blown ARDS or respiratory and/or multiple organ failure	With oxygen support or on ventilators	Hydroxychloquine 200 mg twice per day for at least 10 days + azithromycin once 500 mg/day loading dose, followed by 250 mg once per day for 5 days + oxygen therapy + methylprednisolone 40 mg per day after admission to RCU]	No adverse events except that 1 patient developed mild skin redness and itching that lasted for 1 hour after CP; resolved by antihistamine injection