Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Philippines: Asian Hospital and Medical Center (MIL Fernandez), Baguio General Hospital (MLF de Leon, RG Dagwasi), Batangas Medical Center (ML Almero, M Mercado), Cardinal Santos Medical Center (A Vergara), Cebu Doctors' University Hospital (F Repunte), Chinese General Hospital (SO Tan, MK Ong-Tantuco, RC Reyes, PLG Co, ALG Gabriel-Chan, AO Reyes-Addatu, JT Li-Yu, SA Ang), Diliman Doctors Hospital (KI Del Ayre), Fe Del Mundo Medical Center (SMA Santos, A Torrico), Lung Center of the Philippines (H Basobas, Z Del rosario), Makati Medical Center (KM Taladua, HF Ricaforte-Docuyanan), Manila Doctors Hospital (JS Ramos-Precilla, SA Limson), Medical Center Manila (TAE Nunez), The Medical City (A Santiago), Perpetual Succor Hospital, Cebu (TR Cuevas), Philippine Council for Health Research and Development (JC Montoya), Philippine General Hospital (JP Benedicto, M Llanes, G Astudillo, P Nala, R Abaya), Research Institute for Tropical Medicine (A Yabut), San Juan de Dios Educational Foundation Hospital (JD Cruz), San Lazaro Hospital (SM Ligutan), St. Lukes Medical Center Quezon City (AR Cumpas), Vicente Sotto Memorial Medical Center (M Bagano, MP Pablo-Villamor, GM Aquino Jr, JD Bancat), Southern Philippines Medical Center (MYC Barez, LL Torno, P Ferrer, EA Sibal),St. Lukes Medical Center Global (G Dy-Arga, R Enecilla, CE Villavicencio, DD Ona, S Unson, JD Gargar, BM Samonte), University of the East Ramon Magsaysay Memorial Medical Center (MTF Sumagaysay), University of the Philippines (FM Climacosa, ME Mercado, CDA Rozul, P Tagle, M Recana), World Citi Medical Center (DJD Reotita), Philippine Clinical Research Professionals (G Mendoza, J Arellano, AR Baniqued), Department of Health Philippines (FT Duque III, MR Vergeire), Food and Drug Administration Philippines (RE Domingo), and WHO WPRO (JP Tonolete);
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Table S1. Treatment allocation vs initiation of ventilation in those not already being ventilated at the time of randomization

Ventilation includes invasive or non-invasive mechanical ventilation or extra-corporeal membrane oxygenation.

	Remdesivir vs its control		Hydroxychloroquine vs its control		Lopinavir vs its control		Interferon vs its control*	
	Active	Control	Active	Control	Active	Control	Active	Control
Not ventilated at entry	**2489**	**2475**	**862**	**824**	**1287**	**1258**	**1911**	**1920**
Ventilated later; died	117	108	29	19	52	44	108	91
Ventilated later; discharged	139	146	42	44	67	70	81	98
Ventilated later; pending*	39	30	4	3	7	7	20	21
Total ventilated later	**295**	**284**	**75**	**66**	**126**	**121**	**209**	**210**
(number† and crude %)	11.9	11.5	8.7	8.0	9.8	9.6	10.9	10.9

* Ventilation can be reported in patients who have not yet died or been discharged.

† More complete follow-up will increase the numbers known to have been ventilated or died, but not the Kaplan-Meier (K-M) estimate of the 28-day percentage risk of death (in hospital) or ventilation initiation.

Table S2. Use of corticosteroids and other non-study drugs

Numbers and percentages are tabulated

.

	Remdesivir vs its control		Hydroxychloroquine vs its control		Lopinavir vs its control		Interferon vs its control*	
Corticosteroids	1310	1288	140	140	316	328	981	1053
Number & percentage	47.8	47.6	14.8	15.5	22.6	23.9	47.9	51.4
Convalescent plasma	52	58	7	3	24	15	43	33
	1.9	2.1	0.7	0.3	1.7	1.1	2.1	1.6
Anti-IL-6 drug	133	143	21	18	42	42	52	68
	4.9	5.3	2.2	2.0	3.0	3.1	2.5	3.3
Non-trial interferon	3	25	2	1	4	0	1	26
	0.1	0.9	0.2	0.1	0.3	0.0	0.1	1.3
Non-trial antiviral	65	152	62	54	86	90	102	144
	2.4	5.6	6.6	6.0	6.2	6.6	5.0	7.0
Number entered	2743	2708	947	906	1399	1372	2050	2050
	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table S3. Multivariate analysis simultaneously estimating all 4 effects

The pre-planned primary analyses in the main text involved 4 pairwise comparisons, one between each treatment group and its controls, as indicated in the flowchart (Figure 1). These 4 primary analyses were stratified by age and by whether the patient was already ventilated at the time of randomization, and found no definitely favorable or definitely unfavorable effect of any of the 4 study drugs on all-cause in-hospital mortality (Figure 3). The RRs in these 4 pre-planned pairwise comparisons were:

Remdesivir vs its control (pre-planned analysis) RR=0.95 (95% CI 0.81-1.11),

Hydroxychloroquine vs its control (pre-planned analysis) RR=1.19 (0.89-1.59),

Lopinavir vs its control (pre-planned analysis) RR=1.00 (0.79-1.25), and

Interferon vs its control (pre-planned analysis) RR=1.16 (0.96-1.39).

As there was some overlap between the 4 control groups, an exploratory sensitivity analysis used multivariate Cox regression to fit all 4 treatment effects simultaneously, assuming the independence of any effects of lopinavir and of interferon. This multivariate analysis was stratified by the set of study drugs that was locally available at randomization (13 occupied strata). Hence, no reduction of the dataset was needed to ensure that comparisons were only between concurrently randomized treatments, and that they were not subject to any selective biases. It was adjusted for several of the prognostic factors listed in Table 1: age (<40, 40-49, 50-59, 60-69, 70-79, 80+ years), sex, diabetes, bilateral lung lesions at entry (no, yes, not imaged at entry), and respiratory support at entry (no oxygen, oxygen but no ventilation, ventilation). This multivariate sensitivity analysis had not been pre-planned as a primary or a secondary analysis. For each of the 4 study drugs it yielded mortality rate ratios (RRs) for active treatment vs local standard of care (SoC) that were similar to those in the pre-planned primary pairwise comparisons, again finding no definitely favorable or unfavorable effect of any of the 4 study drugs:

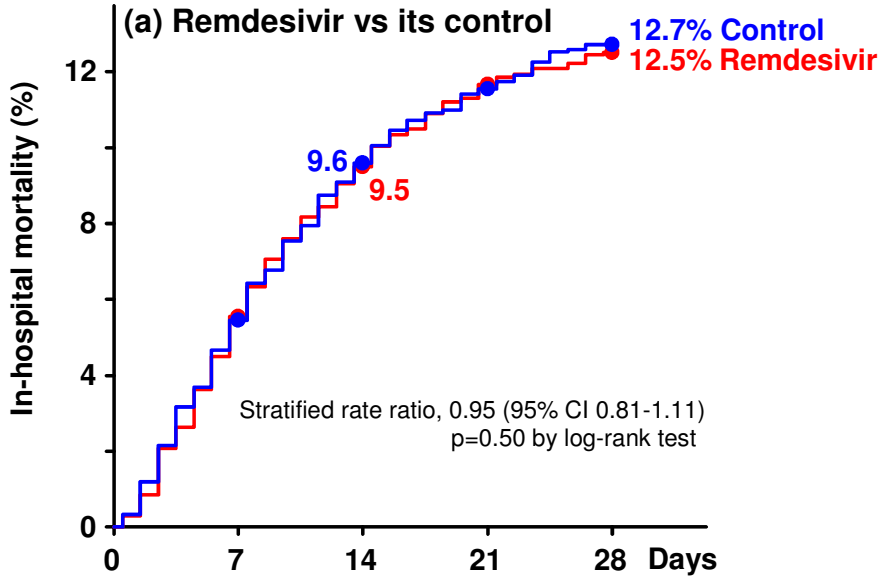
Remdesivir vs local SoC (in multivariate analysis) RR=0.95 (95% CI 0.81-1.11),

Hydroxychloroquine vs local SoC (in multivariate analysis) RR=1.14 (0.89-1.46),

Lopinavir vs local SoC (in multivariate analysis) RR=0.94 (0.76-1.16), and

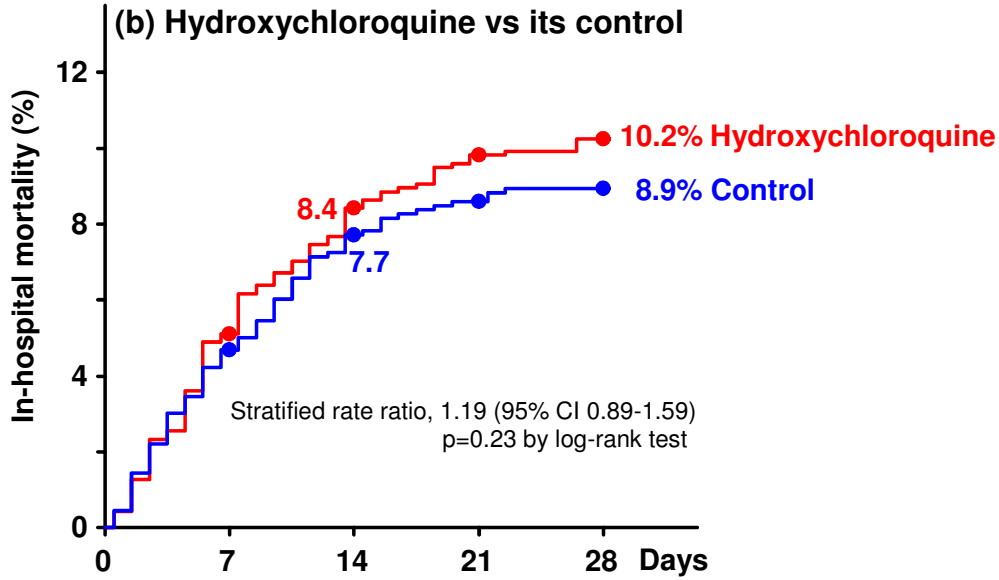
Interferon vs local SoC (in multivariate analysis) RR=1.14 (0.96-1.35).

Figure S1. Effects on in-hospital mortality of (a) remdesivir, (b) hydroxychloroquine, (c) lopinavir, and (d) interferon



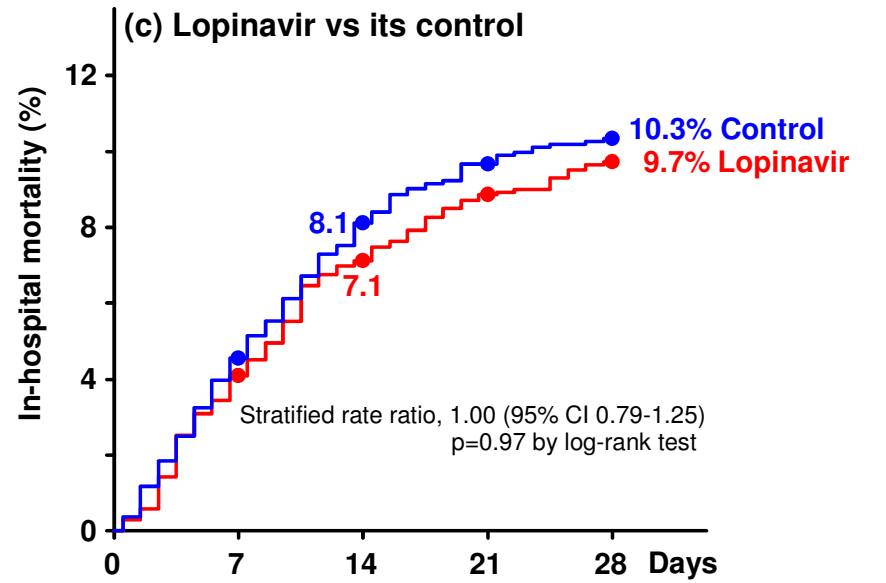
No. randomized, nos. dying, and denominators

Remdesivir	2743	129	2159	90	2029	48	1918	18	1838	16
Control	2708	126	2138	93	2004	43	1908	27	1833	14



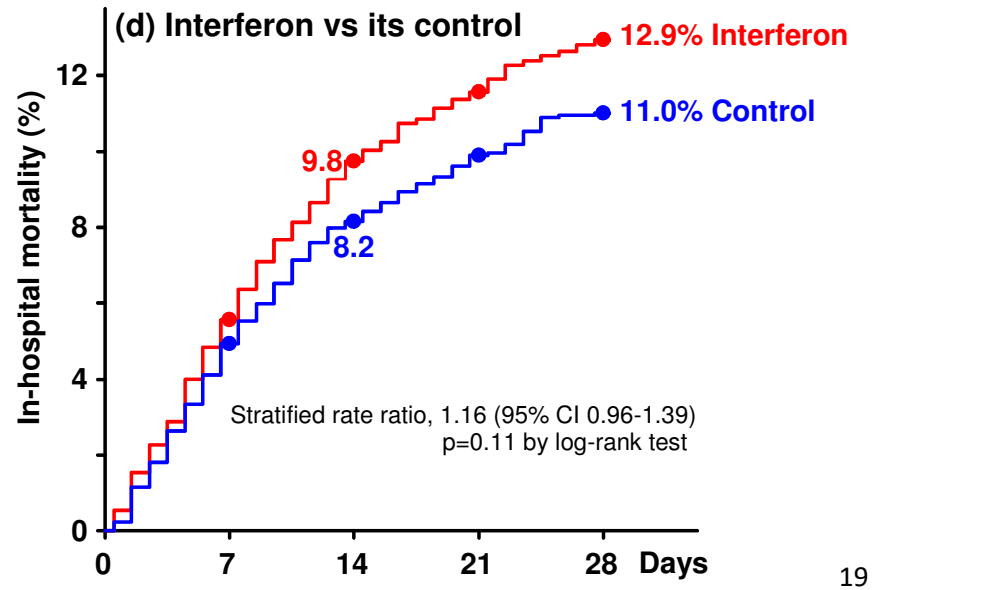
No. randomized, nos. dying, and denominators

Hydroxychlor.	947	48	889	31	854	13	838	6	833	6
Control	906	42	853	27	823	8	814	4	809	3



No. randomized, nos. dying, and denominators

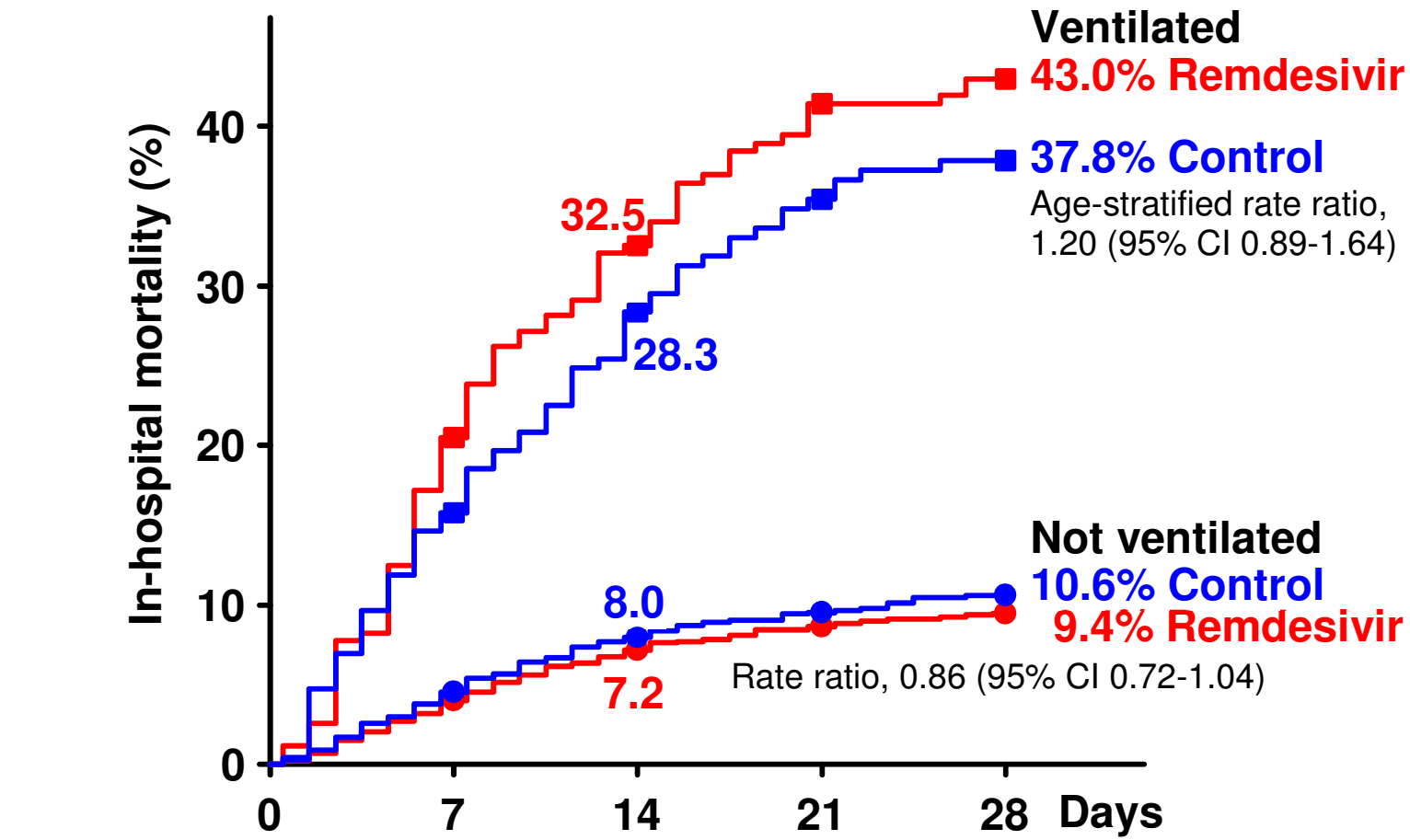
Lopinavir	1399	57	1333	42	1282	24	1257	15	1243	10
Control	1372	62	1293	48	1239	21	1216	10	1203	5



No. randomized, nos. dying, and denominators

Interferon	2050	101	1669	73	1554	31	1483	24	1410	14
Control	2050	91	1725	58	1636	31	1563	21	1498	15

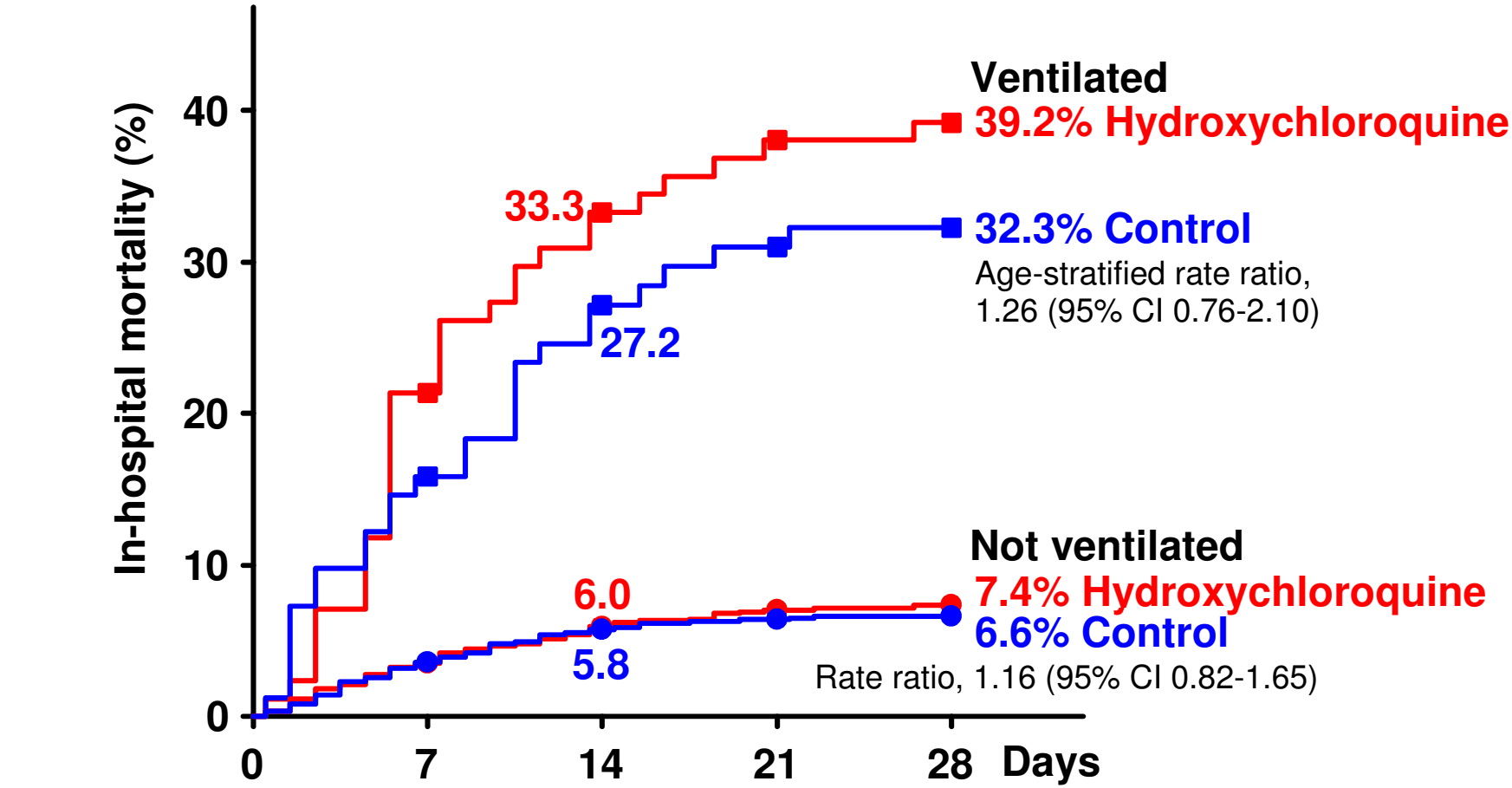
Figure S2. Subdivision by ventilation at randomization of the apparent effects of remdesivir on the probability of death in hospital from any cause



Nos. randomized, nos. dying, and denominators

Remdesivir	254	44	167	25	138	18	118	3	112	8	Ventilated
Control	233	29	151	22	123	12	108	5	102	3	
Remdesivir	2489	85	1992	65	1891	30	1800	15	1726	8	Not ventilated
Control	2475	97	1987	71	1881	31	1800	22	1731	11	

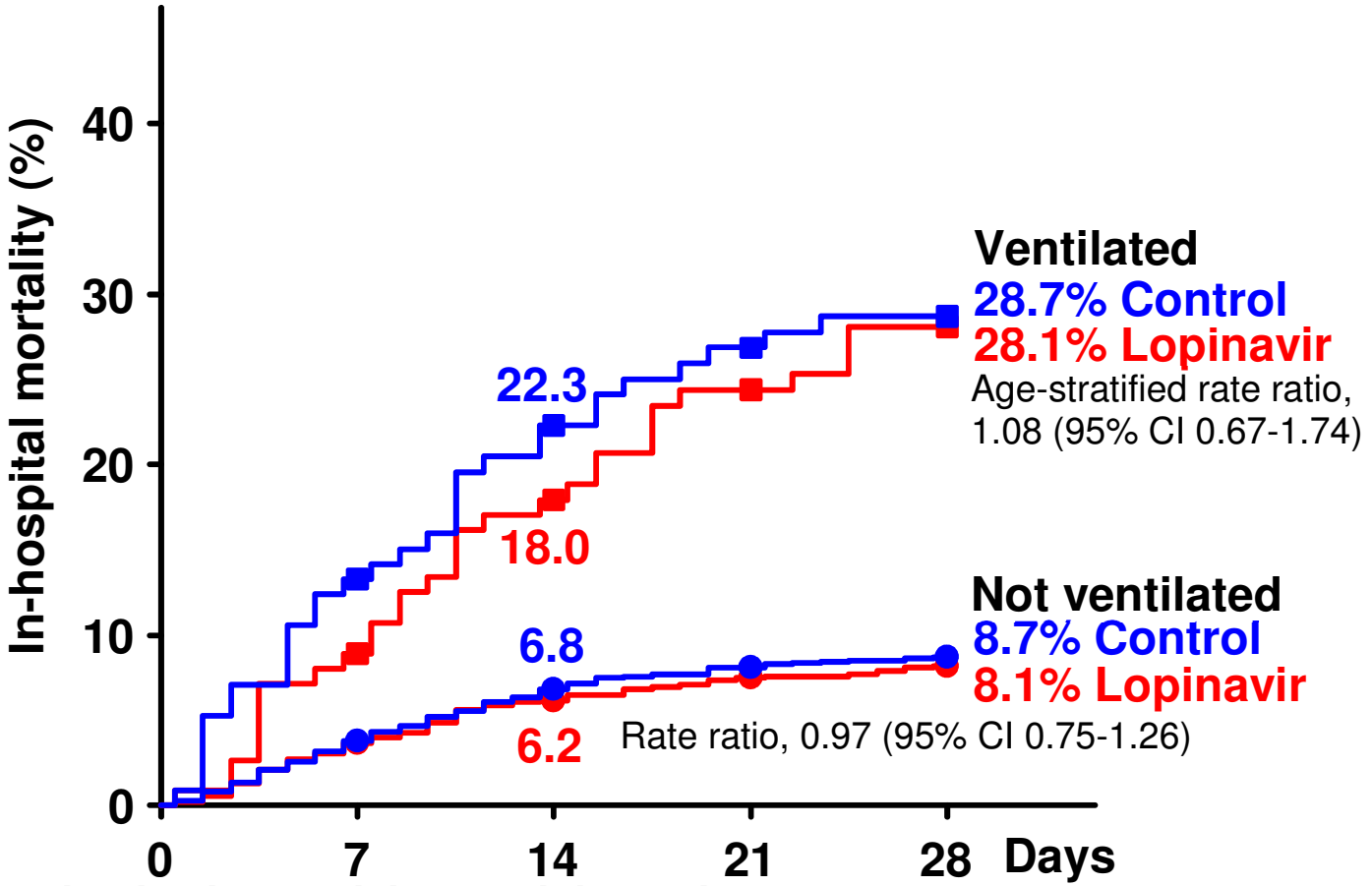
Figure S3. Subdivision by ventilation at randomization of the apparent effects of hydroxychloroquine on the probability of death in hospital from any cause



Nos. randomized, nos. dying, and denominators

Hydroxychlor.	85	18	66	10	56	4	52	2	50	1	Ventilated
Control	82	13	69	9	57	3	54	2	53	0	
Hydroxychlor.	862	30	823	21	798	9	786	4	783	5	Not ventilated
Control	824	29	784	18	766	5	760	2	756	3	

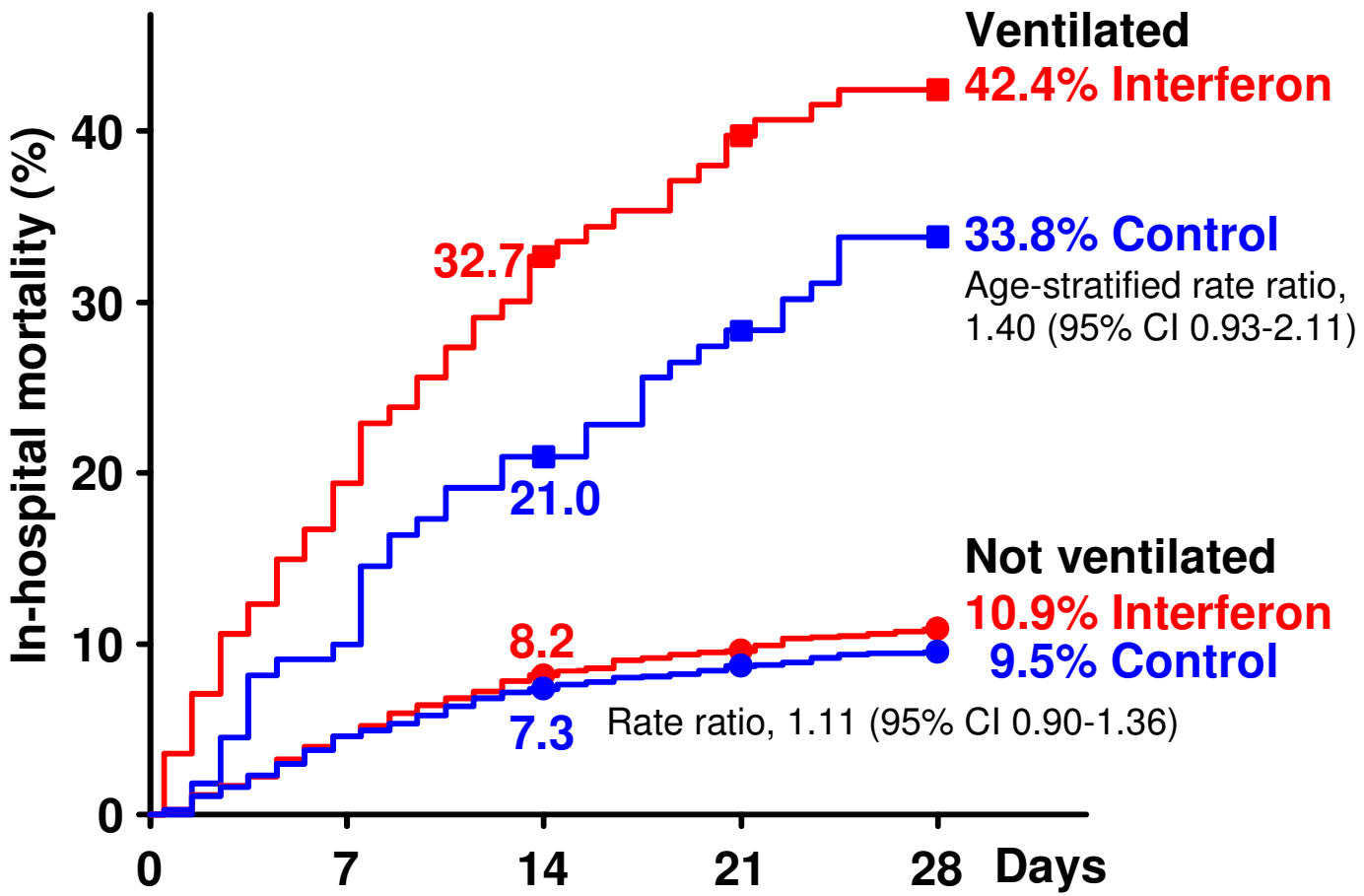
Figure S4. Subdivision by ventilation at randomization of the apparent effects of lopinavir on the probability of death in hospital from any cause



Nos. randomized, nos. dying, and denominators

Lopinavir	112	10	101	10	90	7	82	5	78	3	Ventilated
Control	114	15	98	10	85	5	80	3	78	2	
Lopinavir	1287	47	1232	32	1192	17	1175	10	1165	7	Not ventilated
Control	1258	47	1195	38	1154	16	1136	7	1125	3	

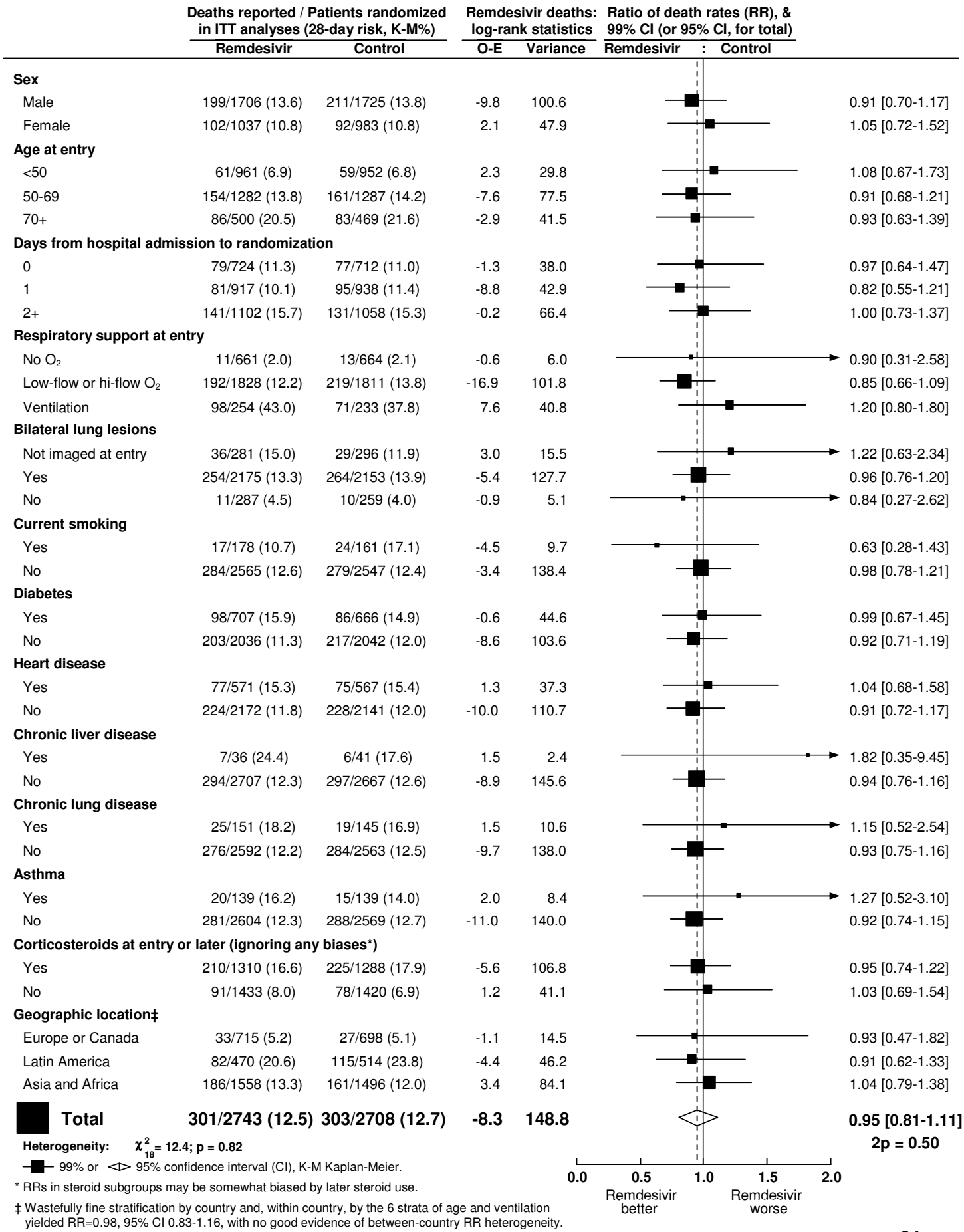
Figure S5. Subdivision by ventilation at randomization of the apparent effects of interferon on the probability of death in hospital from any cause



Nos. randomized, nos. dying, and denominators

Interferon	139	23	91	15	76	8	68	4	65	5	Ventilated
Control	130	11	99	12	86	8	78	6	72	3	
Interferon	1911	78	1578	58	1478	23	1415	20	1345	9	Not ventilated
Control	1920	80	1626	46	1550	23	1485	15	1426	12	

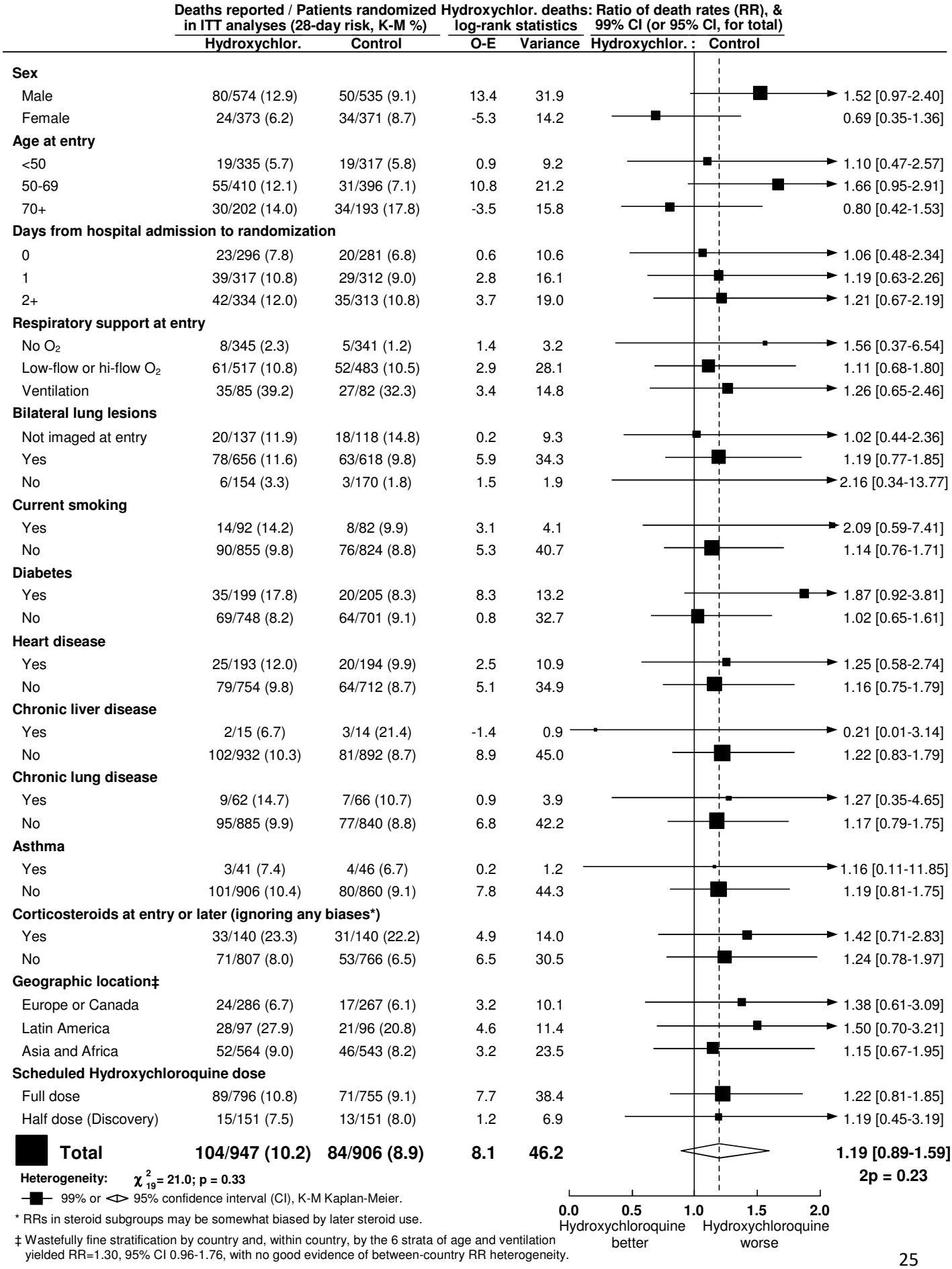
Figure S6. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 6 strata of age and ventilation yielded RR=0.98, 95% CI 0.83-1.16, with no good evidence of between-country RR heterogeneity.

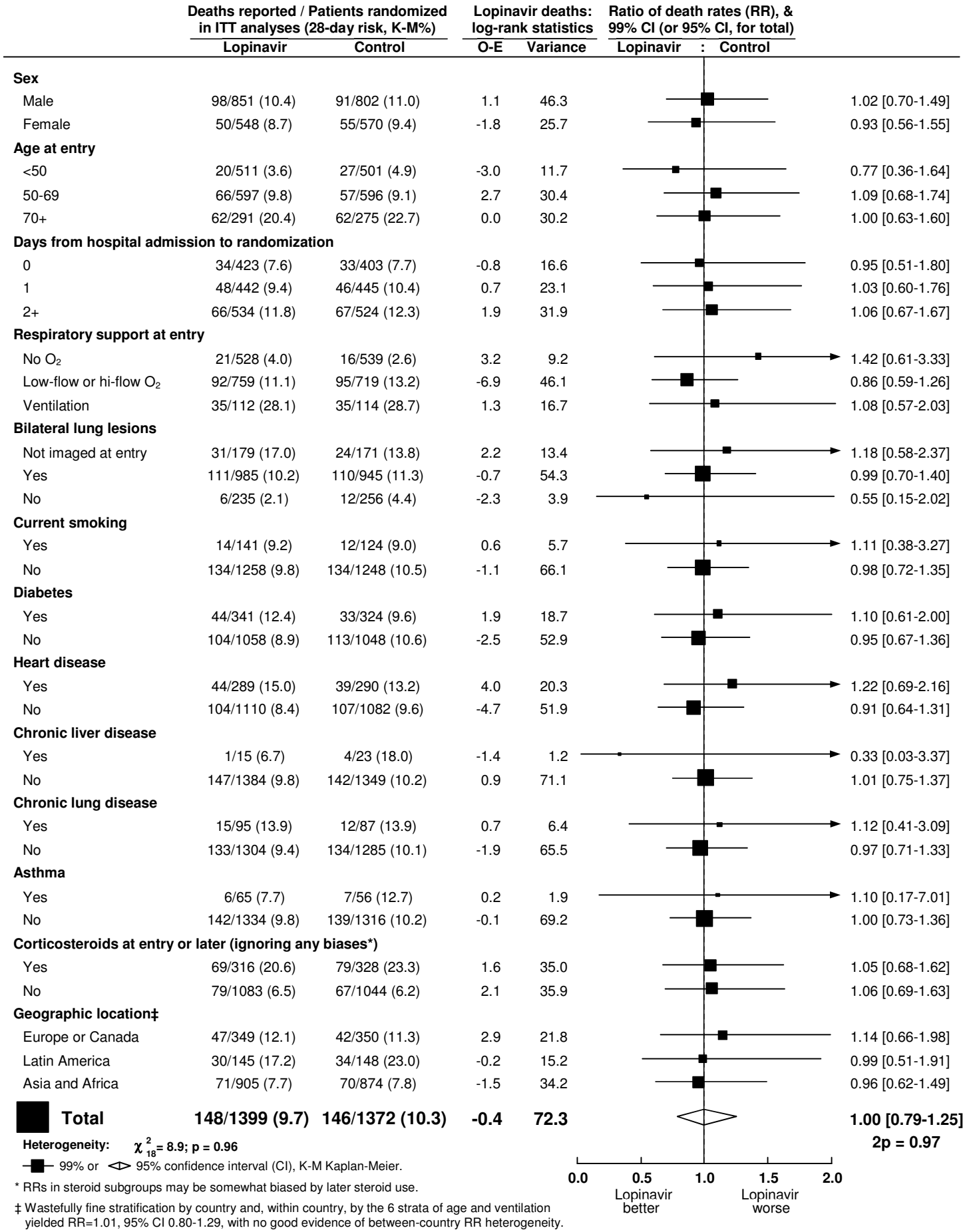
Figure S7. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, hydroxychloroquine vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 6 strata of age and ventilation yielded RR=1.30, 95% CI 0.96-1.76, with no good evidence of between-country RR heterogeneity.

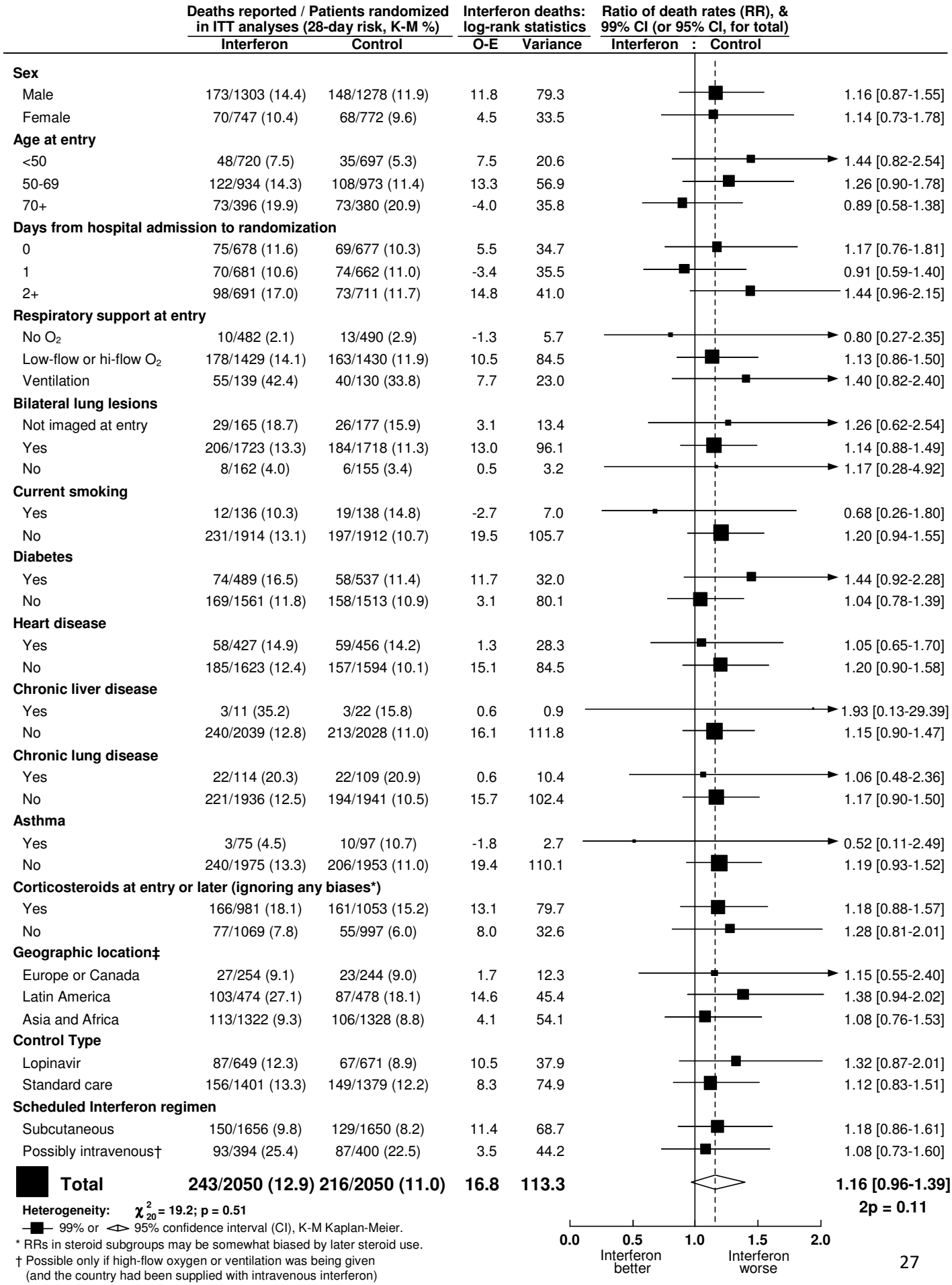
Figure S8. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, lopinavir vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

‡ Wastefully fine stratification by country and, within country, by the 6 strata of age and ventilation yielded RR=1.01, 95% CI 0.80-1.29, with no good evidence of between-country RR heterogeneity.

Figure S9. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, interferon vs its control, by entry characteristics and by steroid use at any time*



* RRs in steroid subgroups may be somewhat biased by later steroid use.

† Possible only if high-flow oxygen or ventilation was being given (and the country had been supplied with intravenous interferon)

‡ Wastefully fine stratification by country and, within country, by the 6 strata of age and ventilation yielded RR=1.23, 95% CI 1.02-1.49, with no good evidence of between-country RR heterogeneity.

Figure S10. RRs for the composite of death in hospital or initiation of ventilation: effects of (a) remdesivir, (b) hydroxychloroquine, (c) lopinavir, (d) interferon, each vs its control

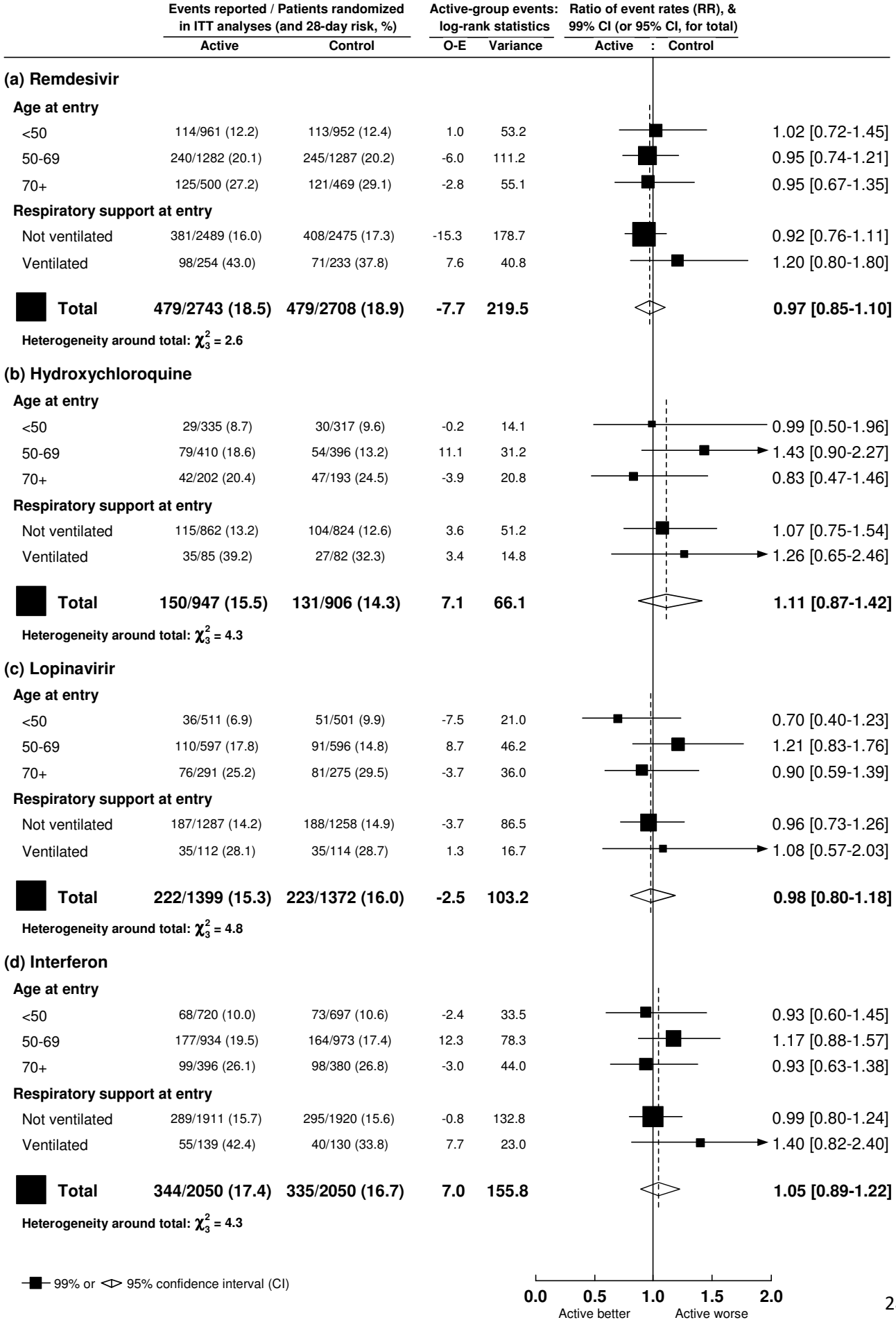
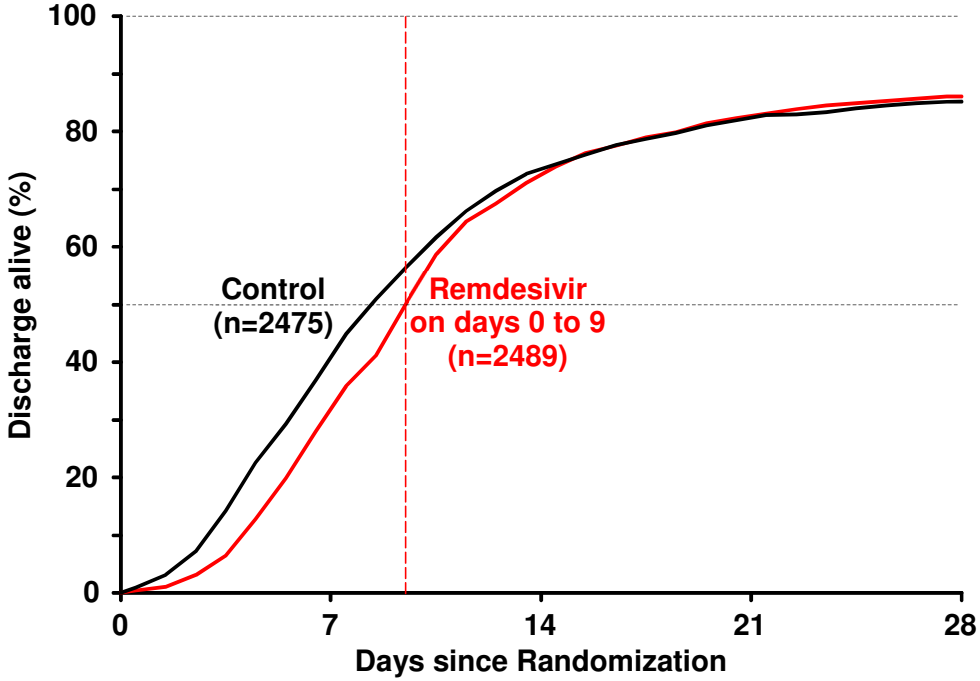
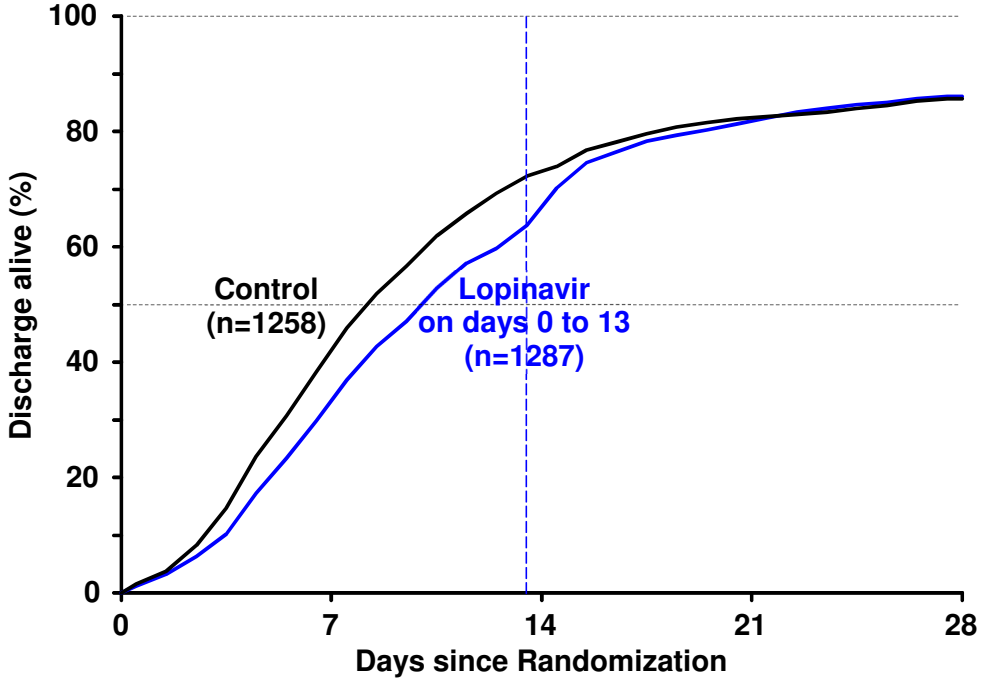
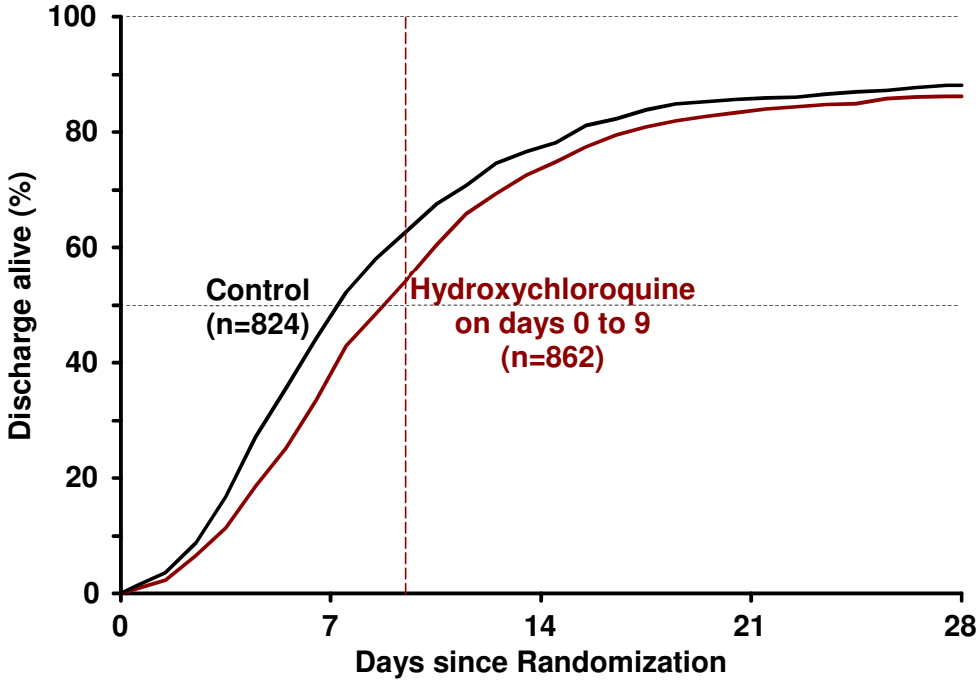


Figure S11. Remdesivir, Hydroxychloroquine, Lopinavir & Interferon, each vs its own control - effects on time to discharge alive in patients NOT being ventilated (no O2, or getting low-flow / high-flow O2) at entry Those who die in hospital remain in the analyses until after day 28.







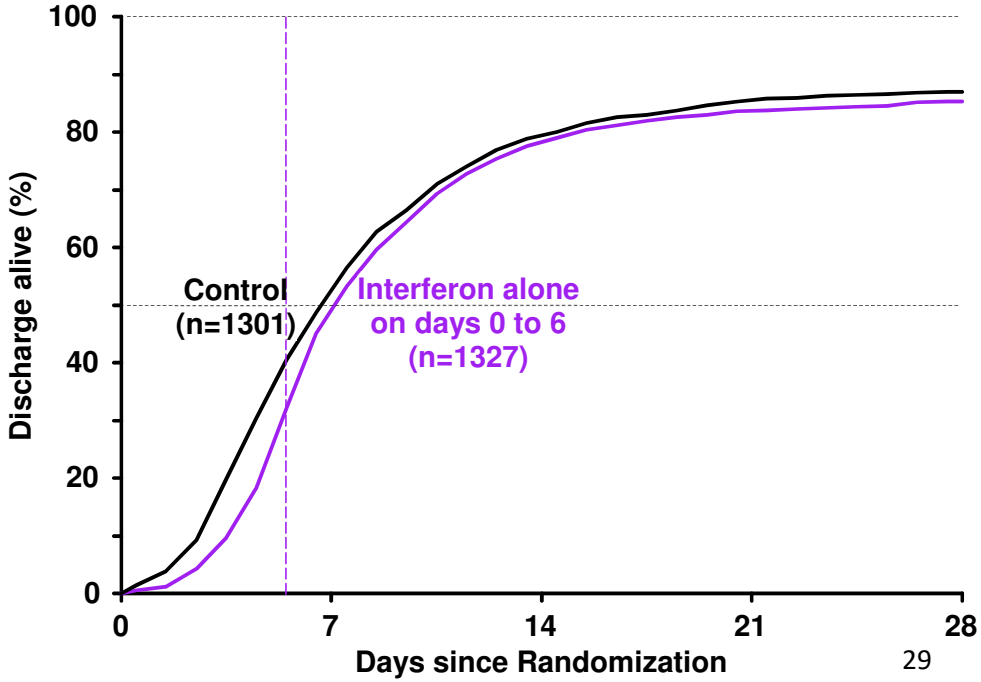
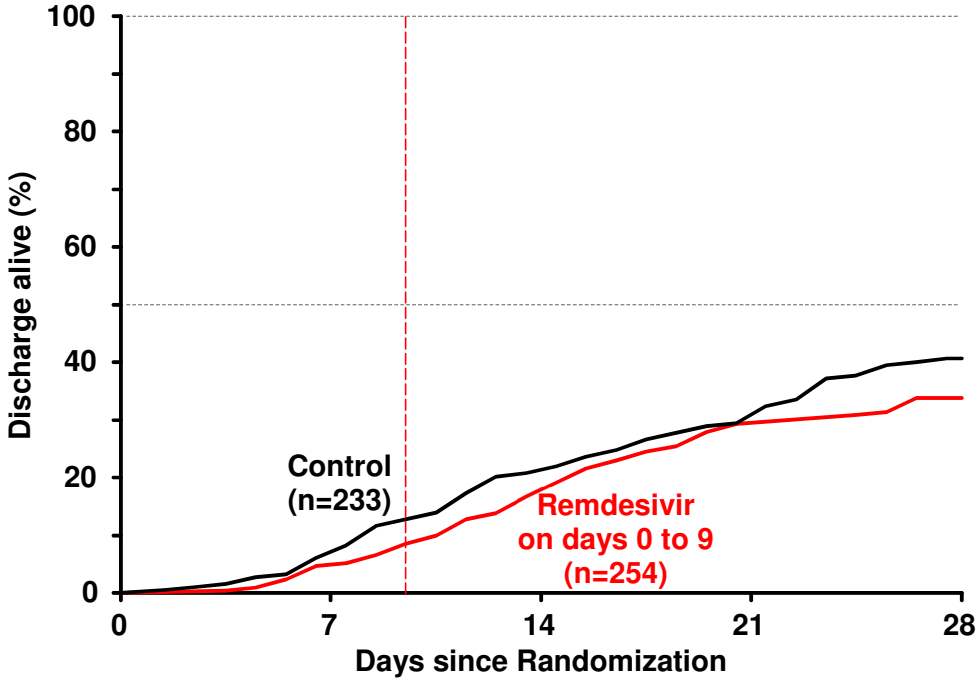
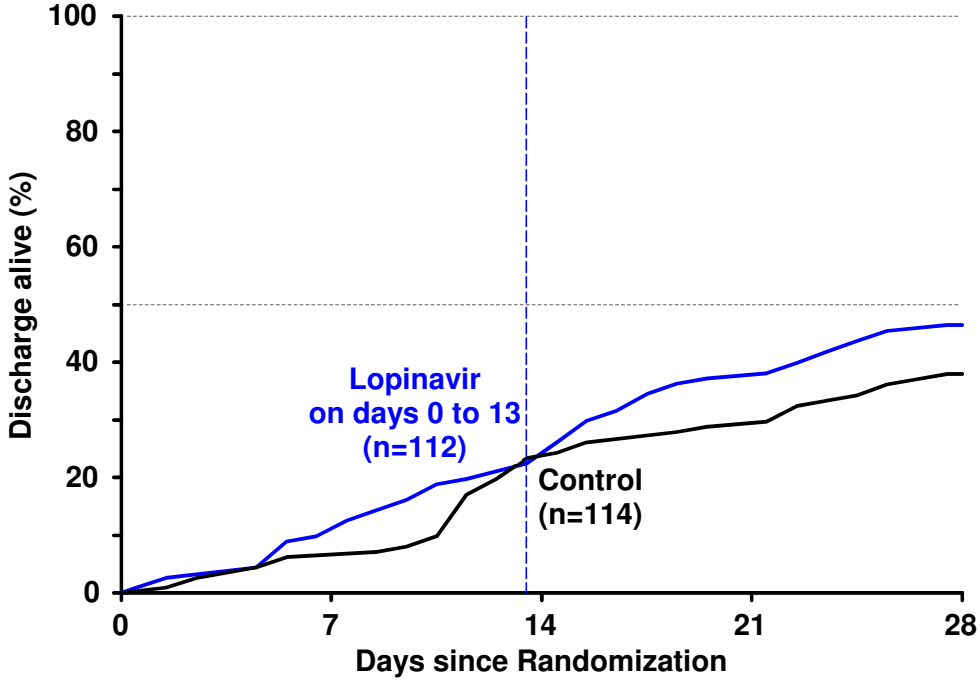
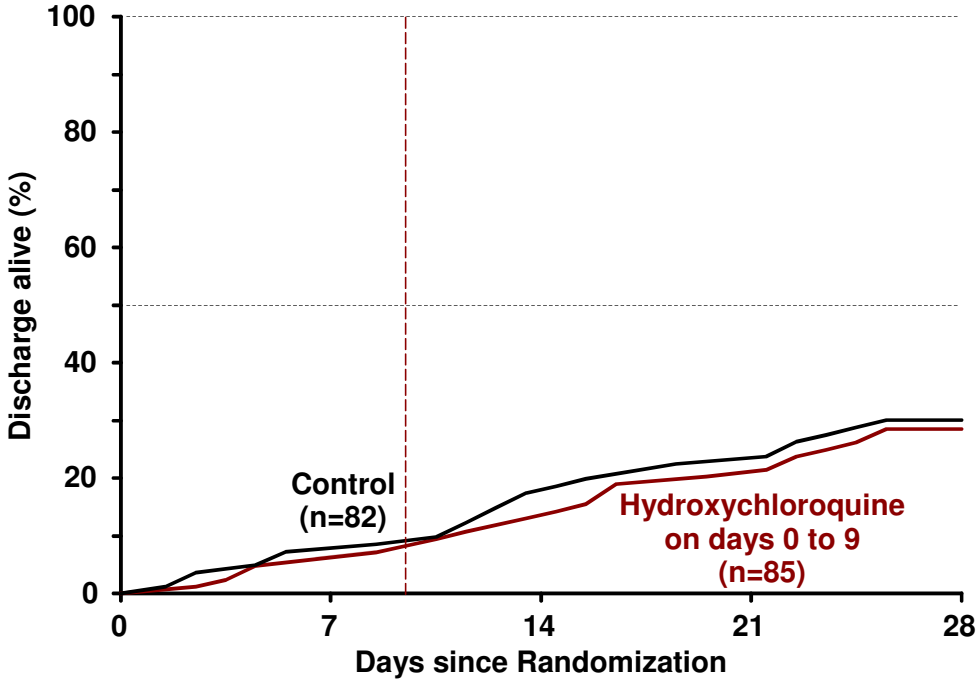


Figure S12. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own control - effects on time to discharge alive in patients already being ventilated at entry Those who die in hospital remain in the analyses until after day 28.







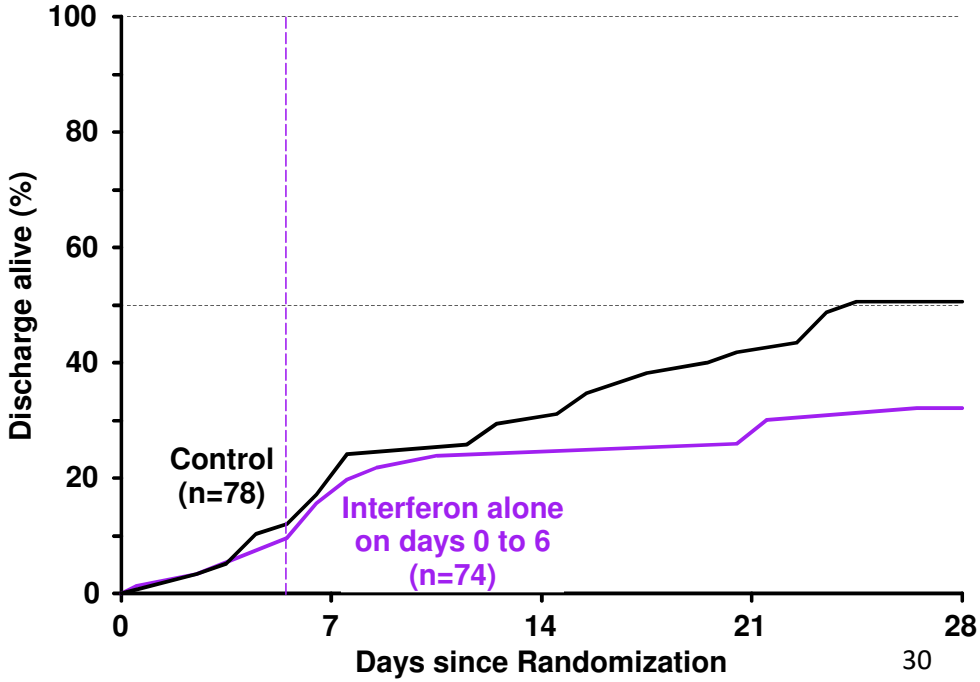
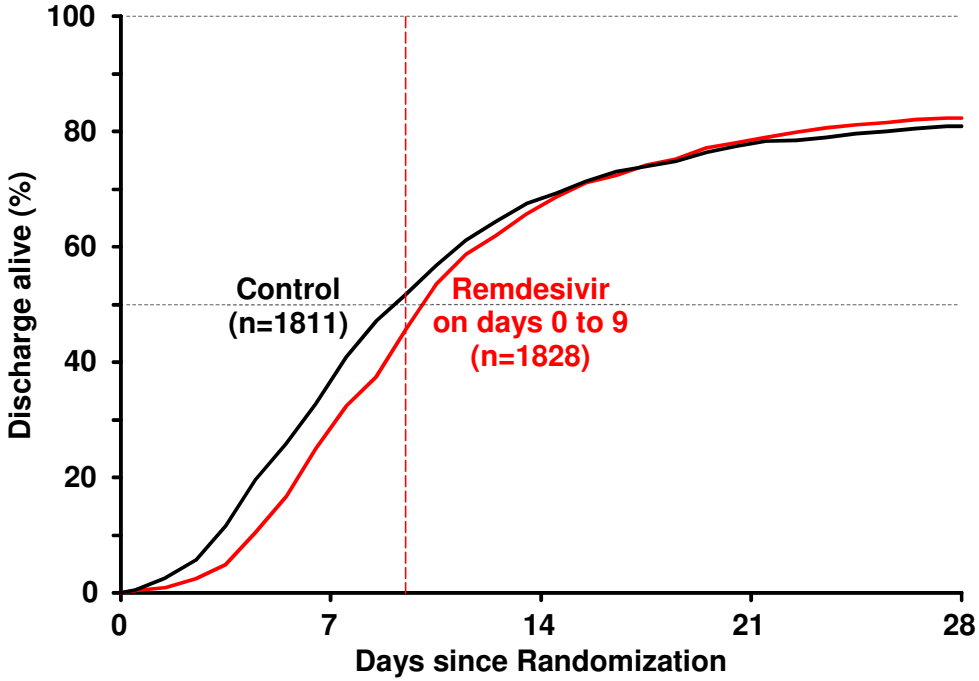
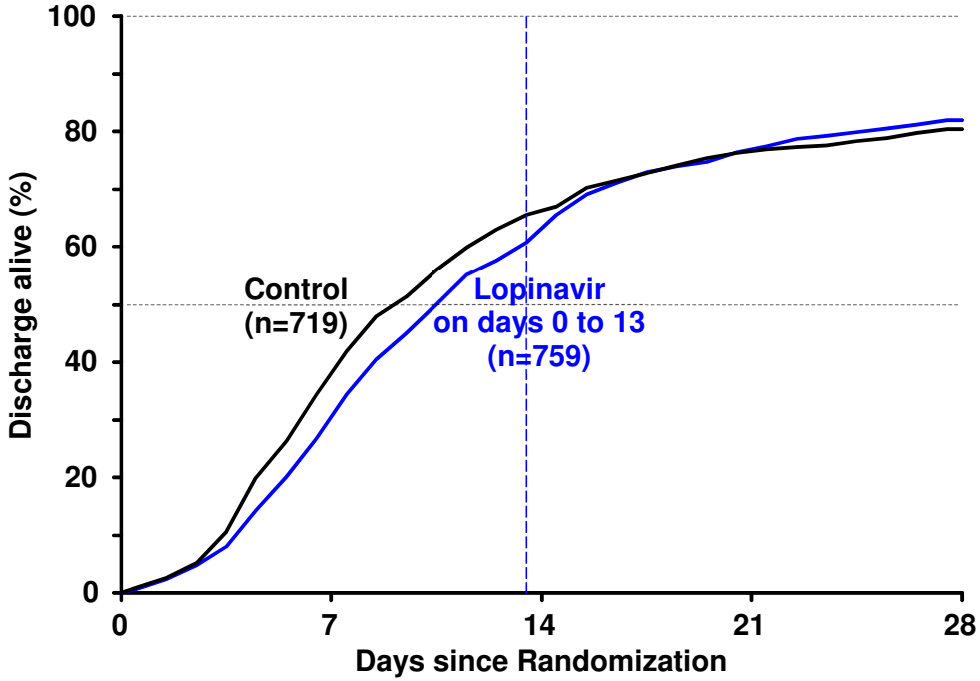
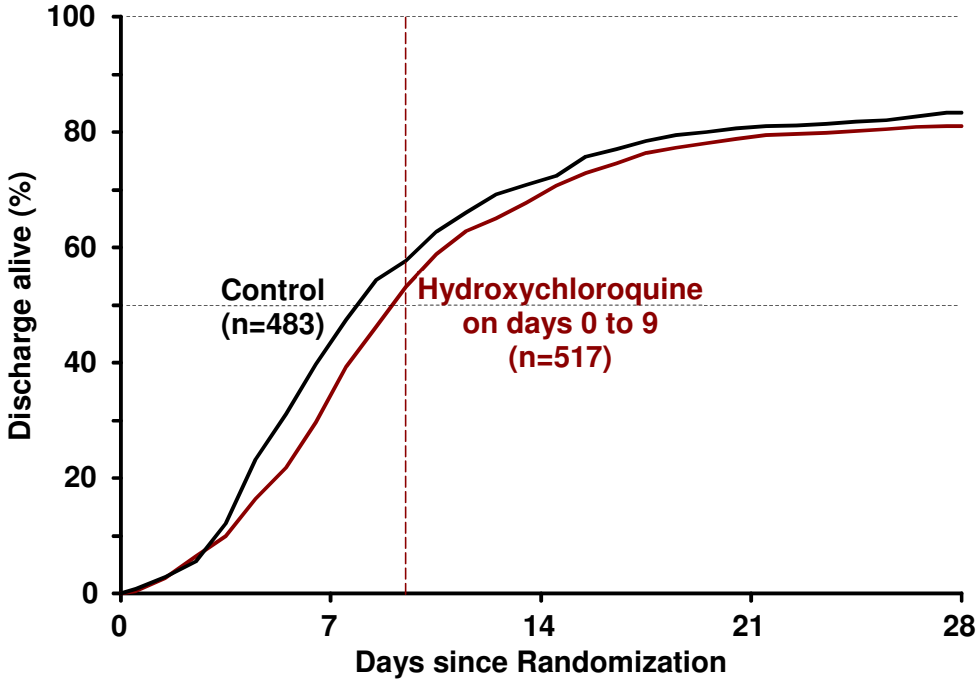


Figure S13. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients being given low-flow O2 / high-flow O2 at entry Those who die in hospital remain in the analyses until after day 28.







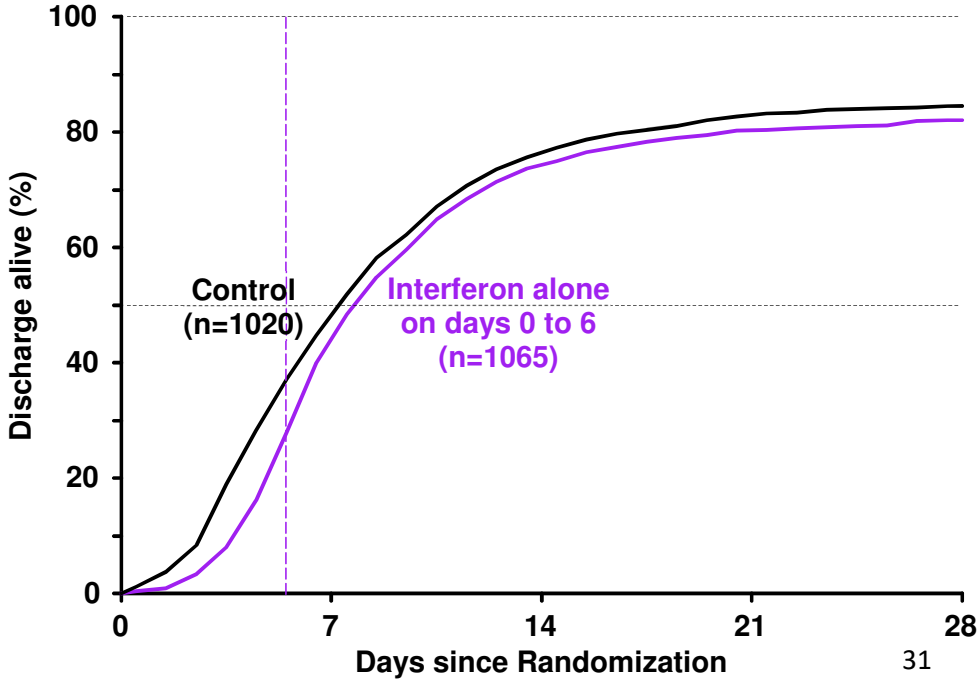
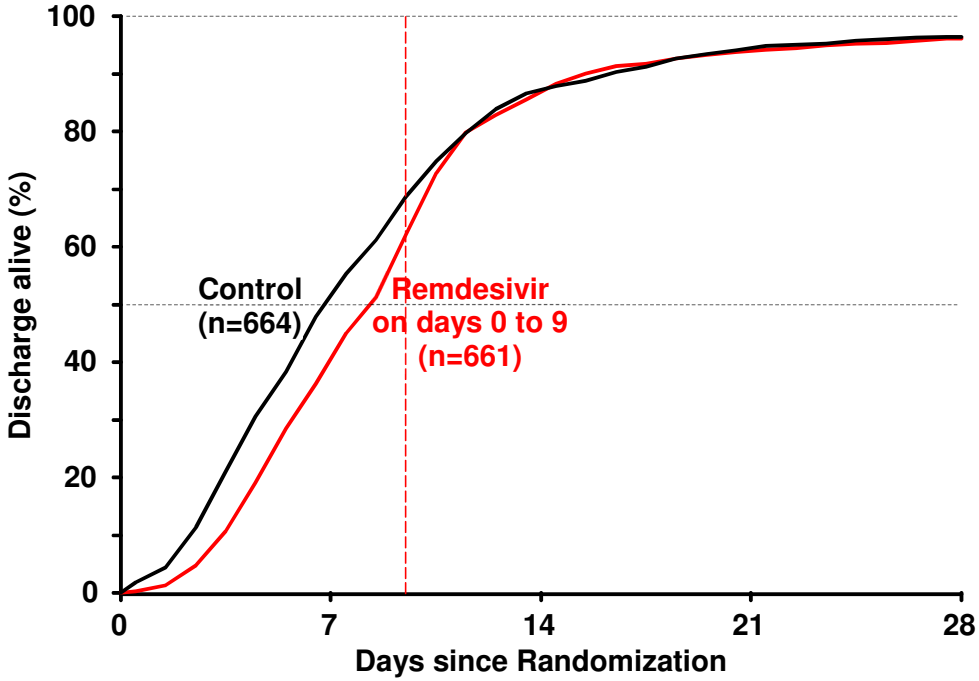
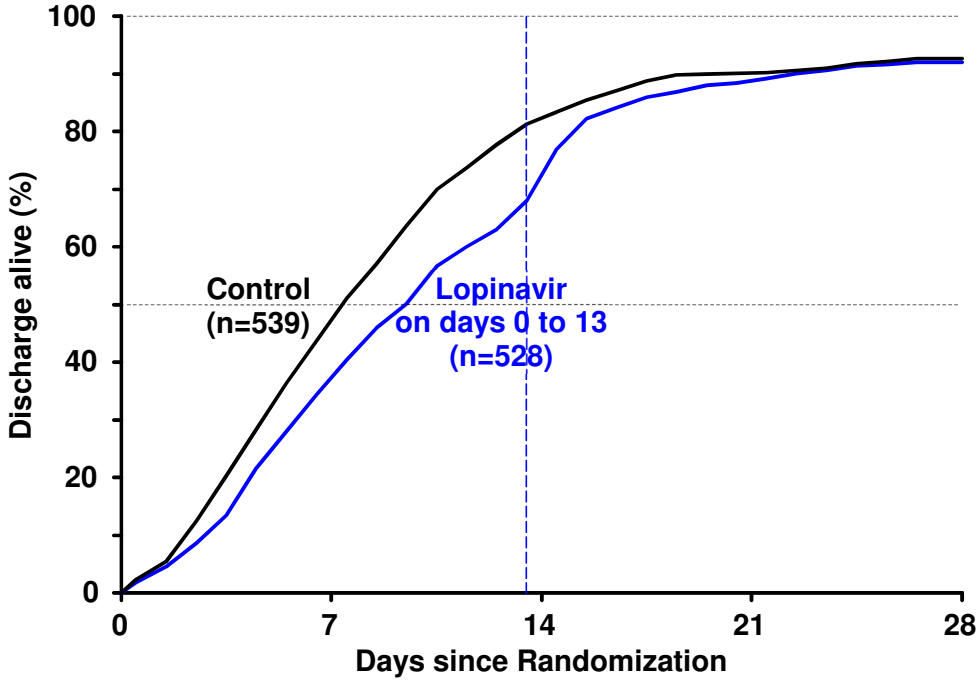
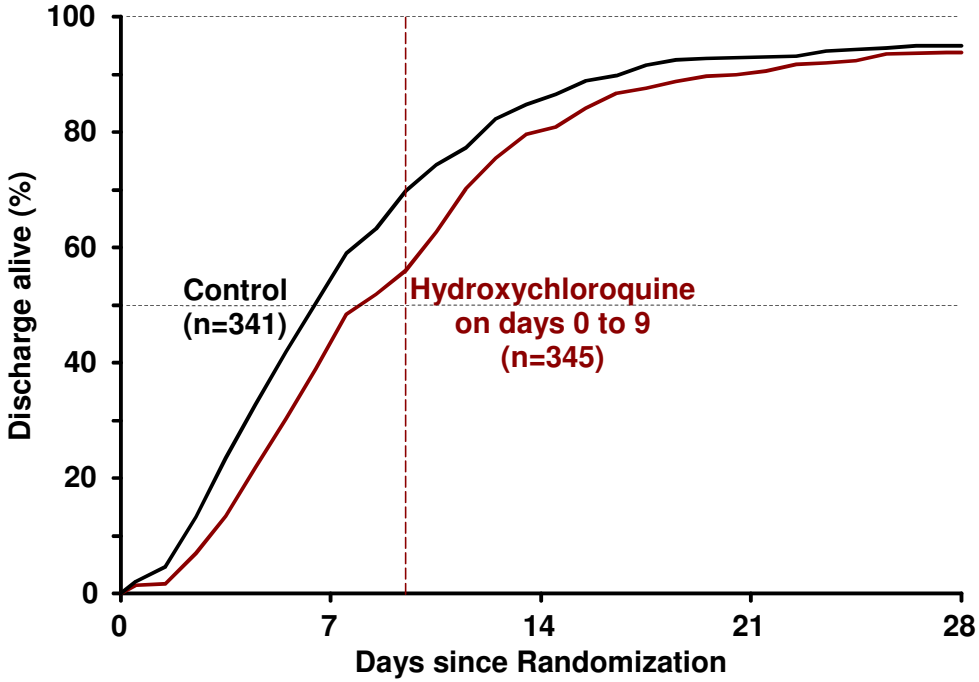


Figure S14. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients being given no O2 at entry (Approximates "mild-to-moderate" in ACTT-1/FDA reports) Those who die in hospital remain in the analyses until after day 28.







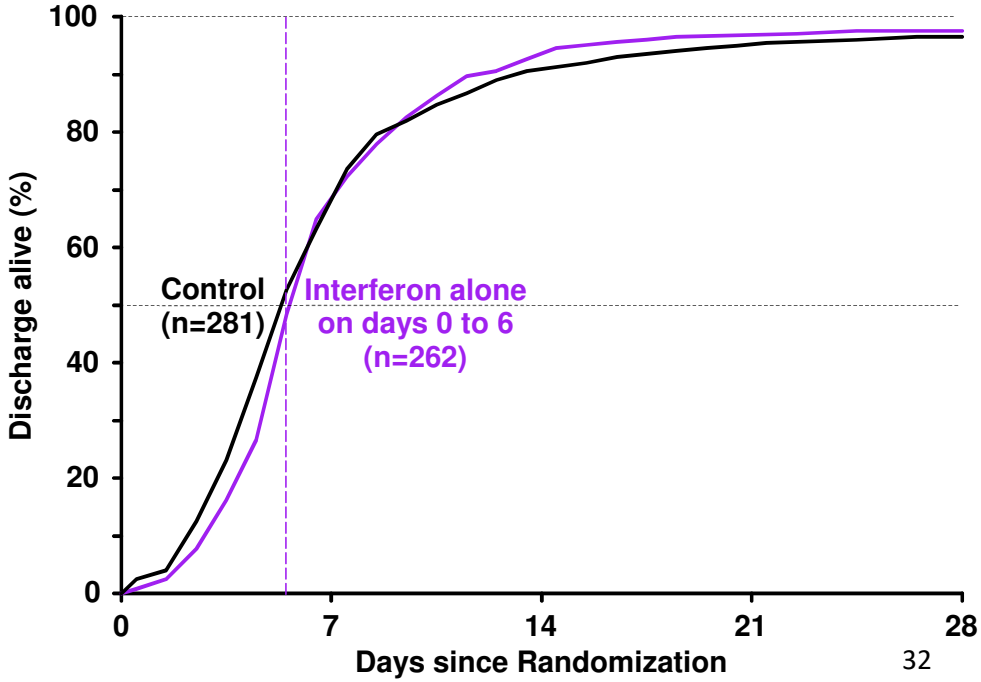
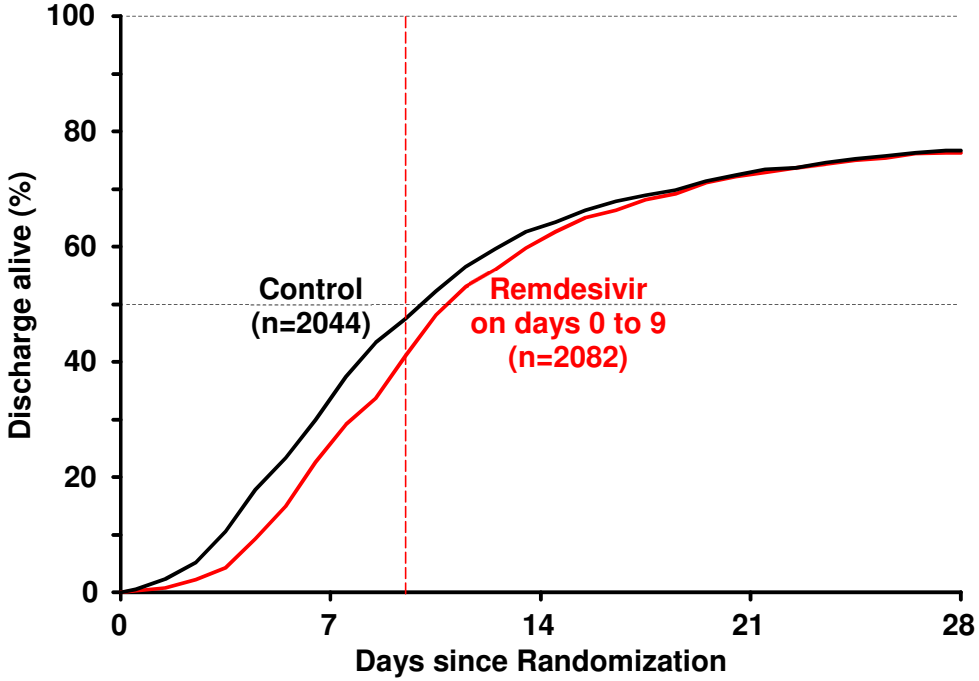
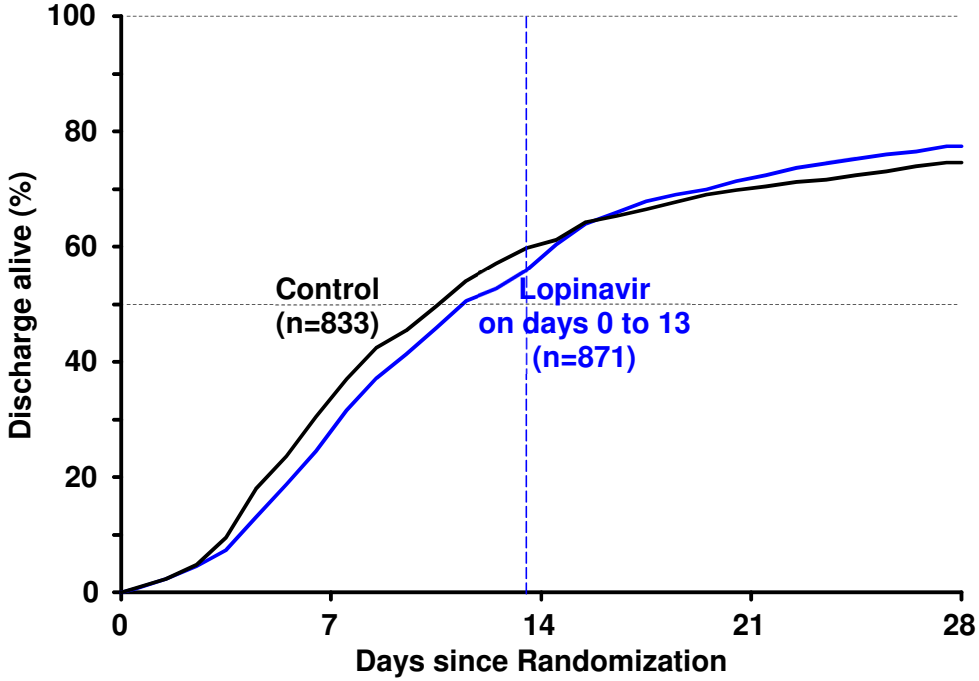
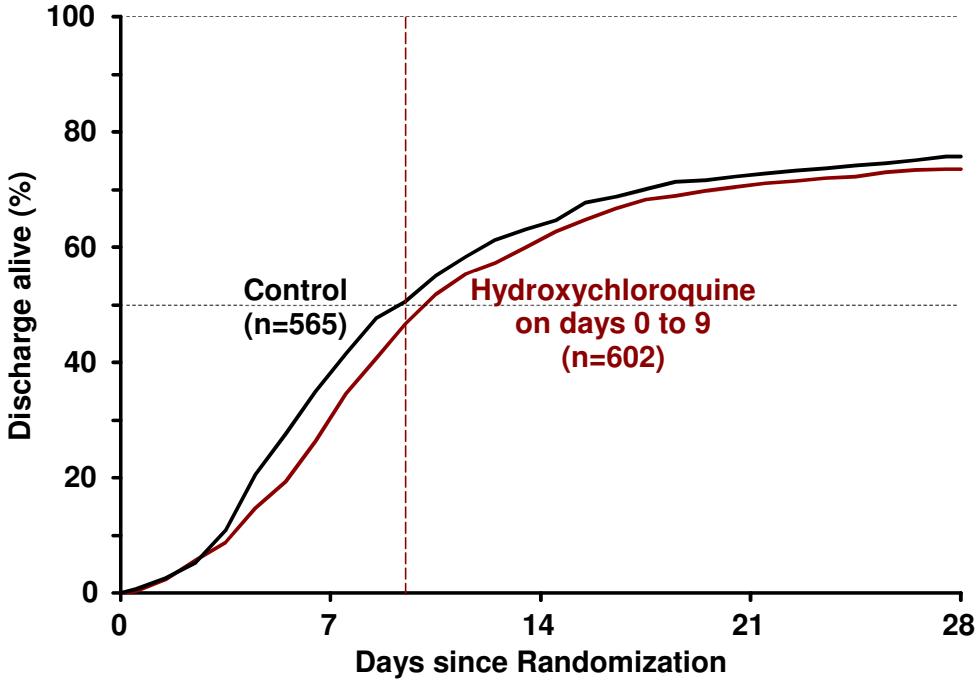


Figure S15. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in patients on low-/high-flow O2 or ventilated (Approximates "severe" in ACTT-1/FDA reports.) Those who die in hospital remain in the analyses until after day 28.







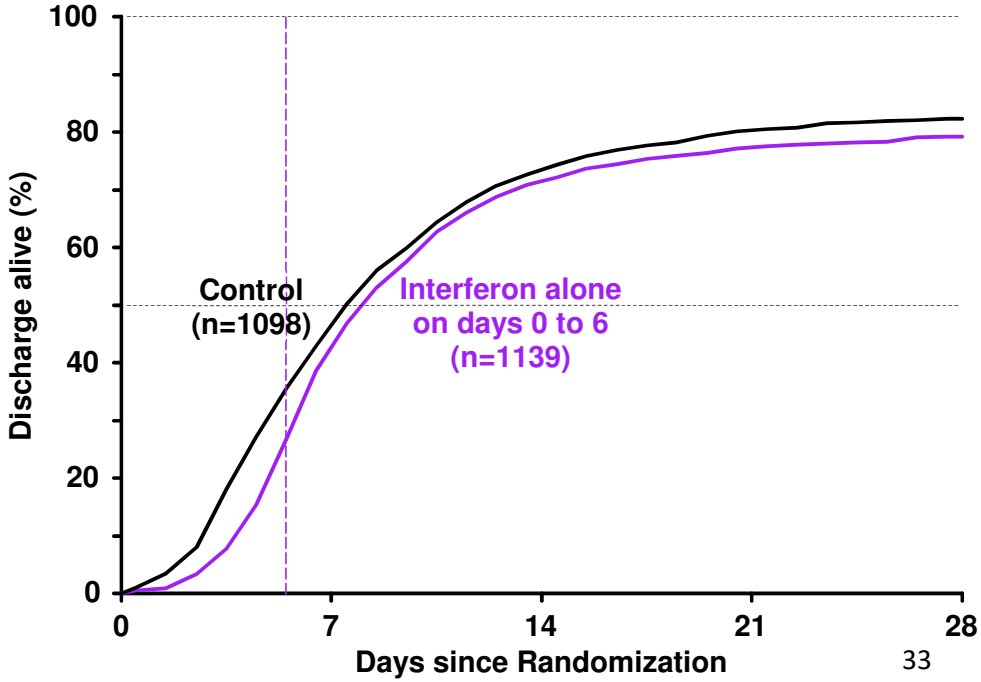
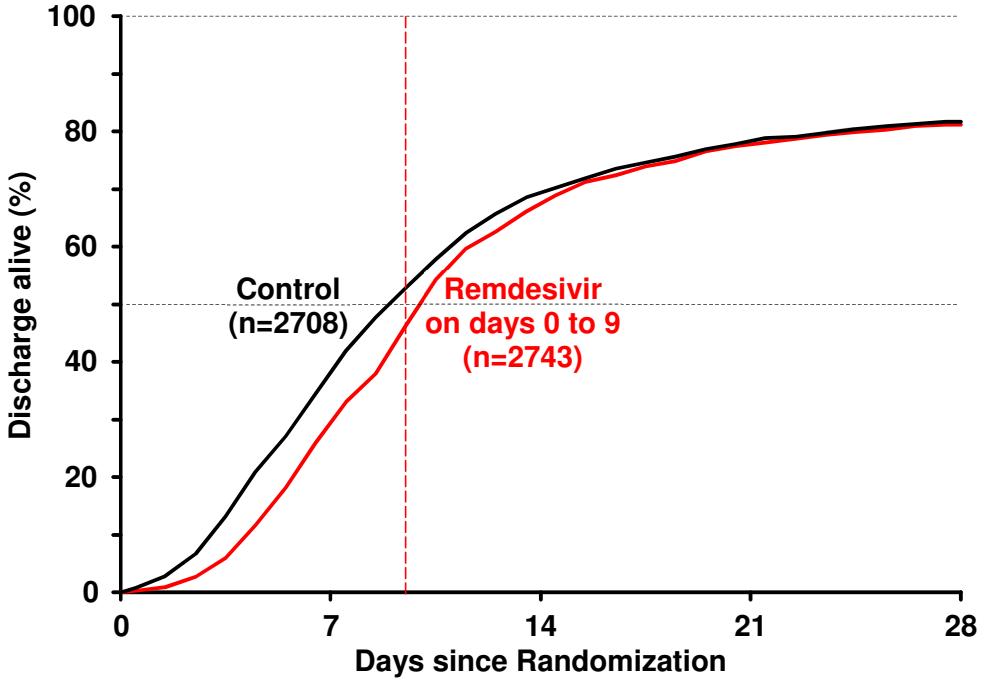
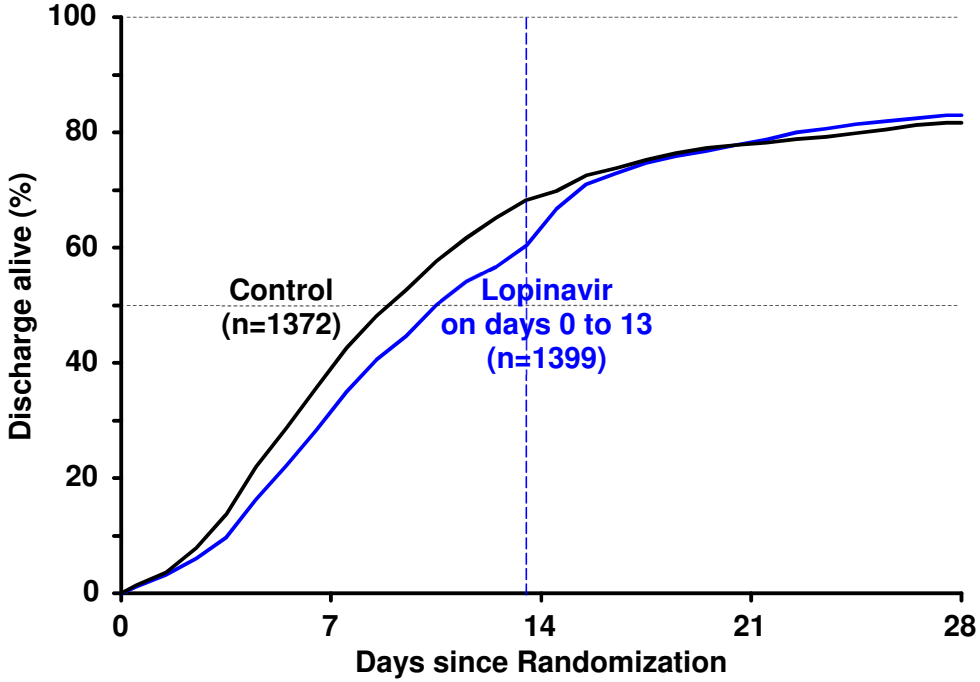
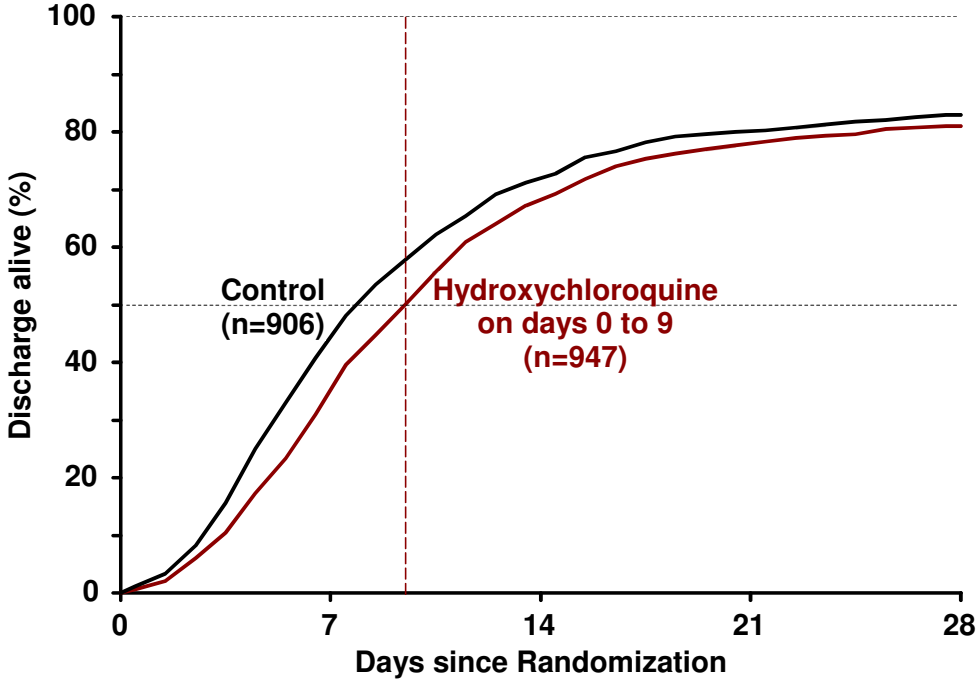


Figure S16. Remdesivir, hydroxychloroquine, lopinavir & interferon, each vs its own controls - effects on time to discharge alive in <u>all patients, regardless of respiratory support at entry</u> Those who die in hospital remain in the analyses until after day 28.







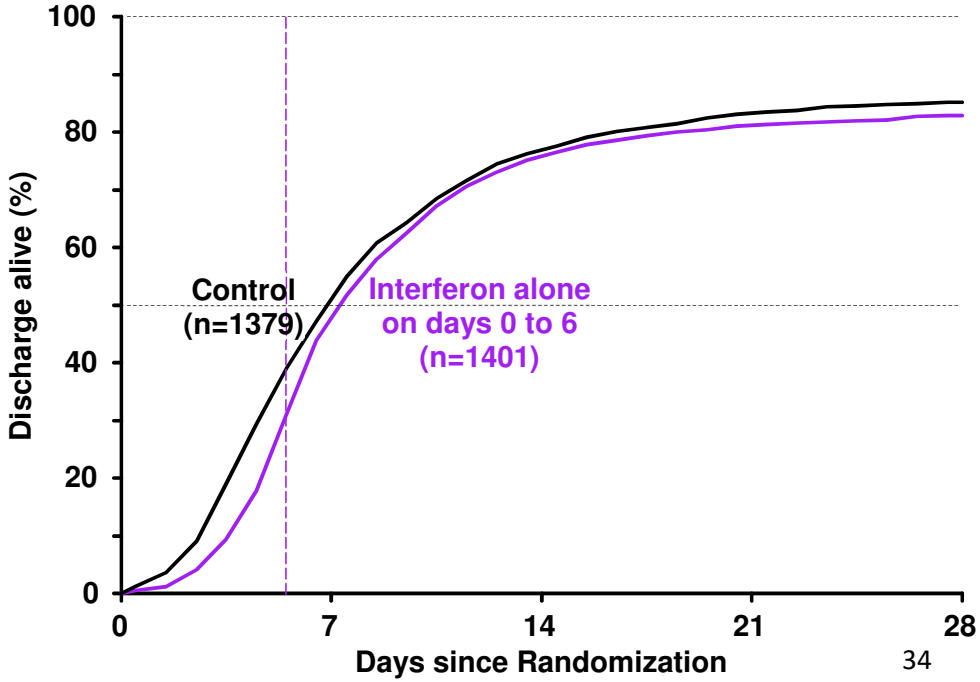


Figure S17. Pairwise randomized comparisons between pairs of study drugs - effects on time to discharge alive, restricted to patients randomized when and where both of the two drugs were available Those who die in hospital remain in the analyses until after day 28.

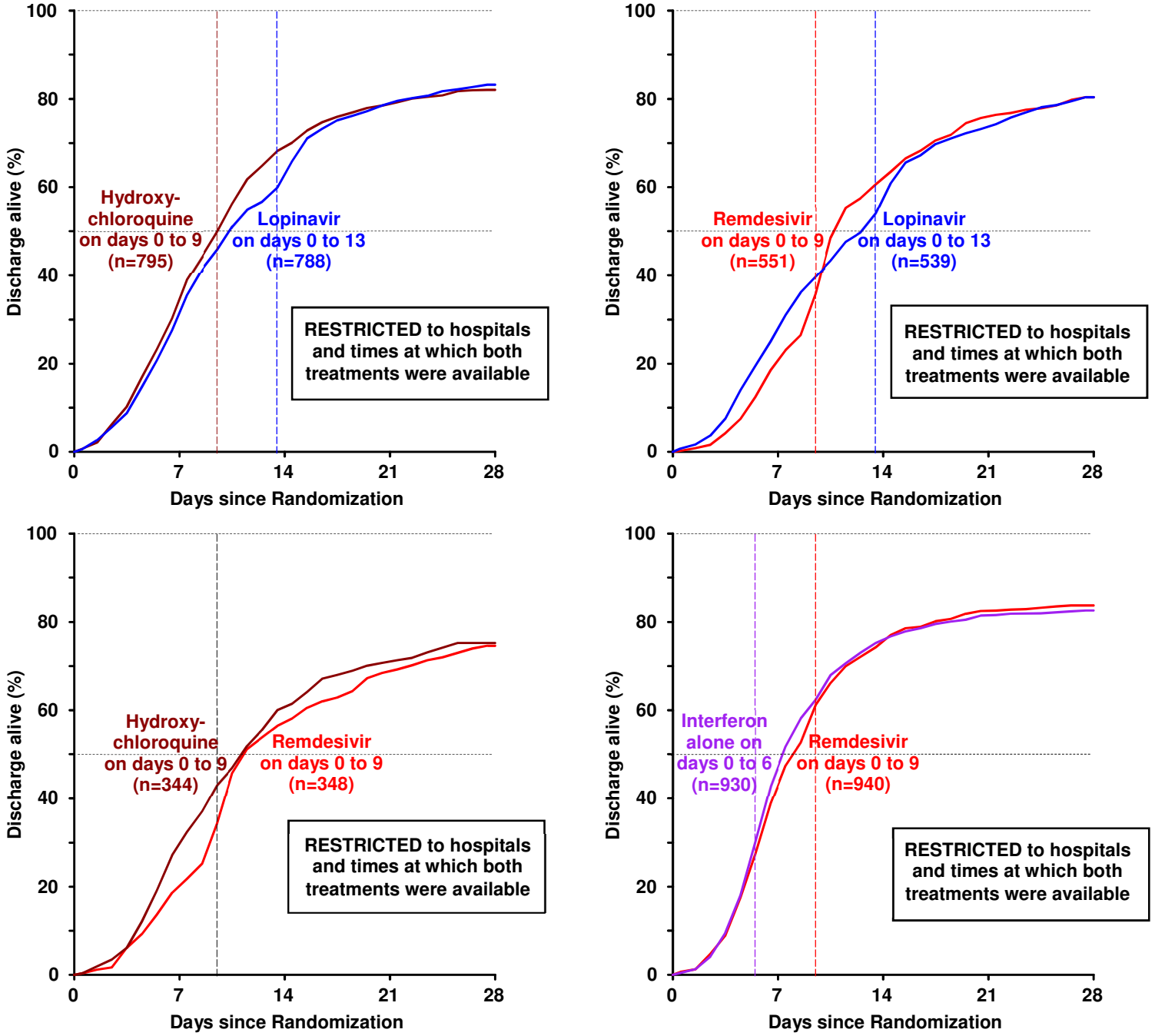
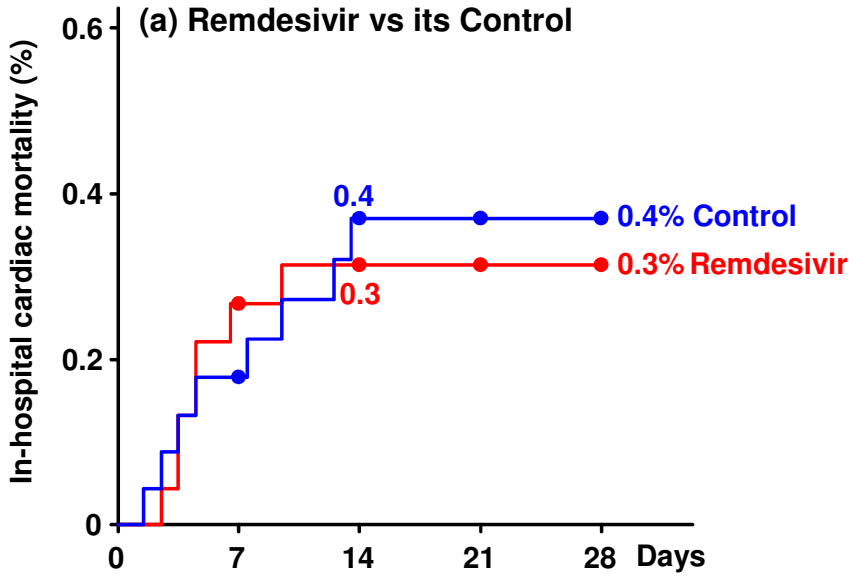
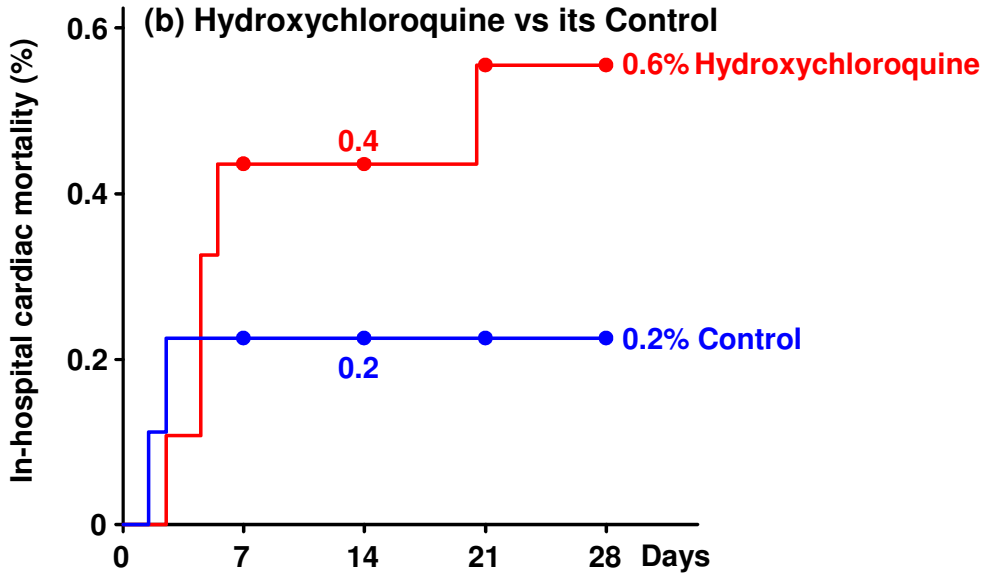


Figure S18. Effects of (a) remdesivir, (b) hydroxychloroquine, (c) lopinavir, (d) interferon on cardiac death in hospital
(any death in hospital for which the trial's electronic death report included a cardiac cause)



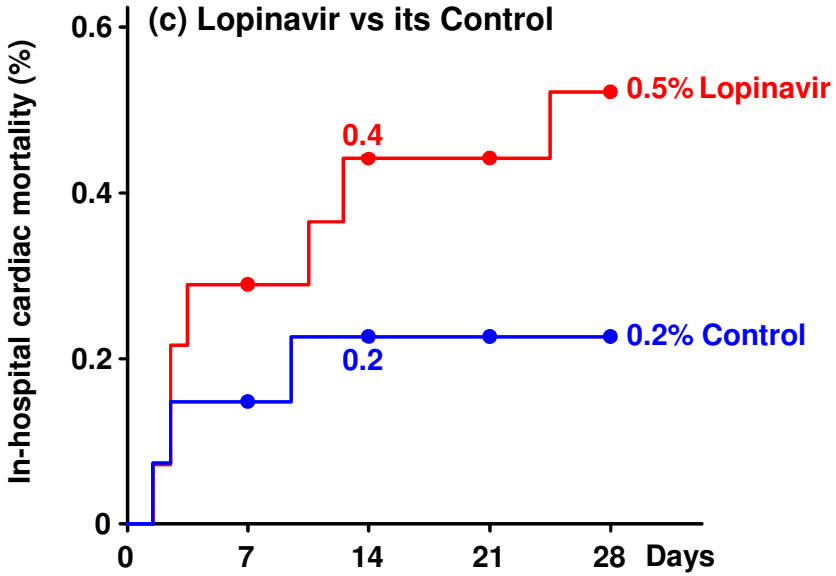
No. randomized, nos. of cardiac deaths, and denominators

Remdesivir	2743	6	2159	1	2029	0	1918	0	1838	0
Control	2708	4	2138	4	2004	0	1908	0	1833	0



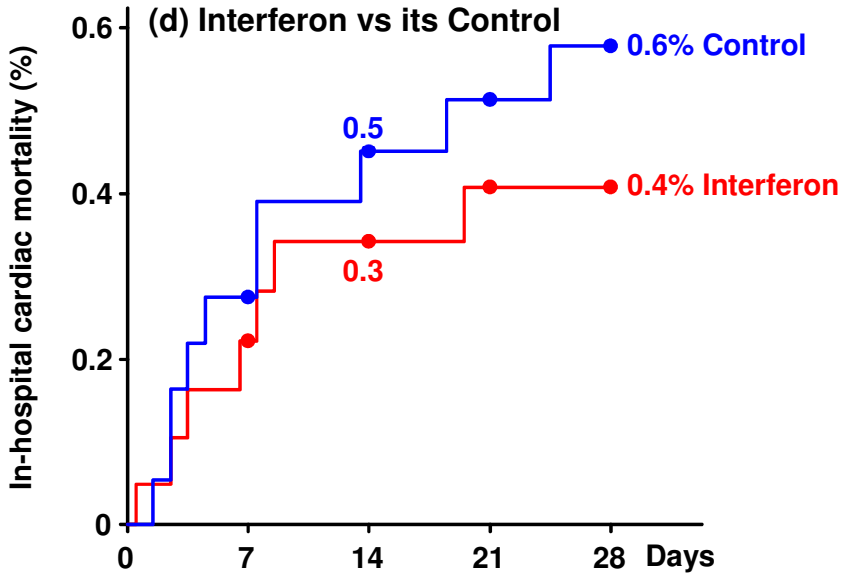
No. randomized, nos. of cardiac deaths, and denominators

Hydroxychlor.	947	4	889	0	854	1	838	1	833	3
Control	906	2	853	0	823	0	814	0	809	1



No. randomized, nos. of cardiac deaths, and denominators

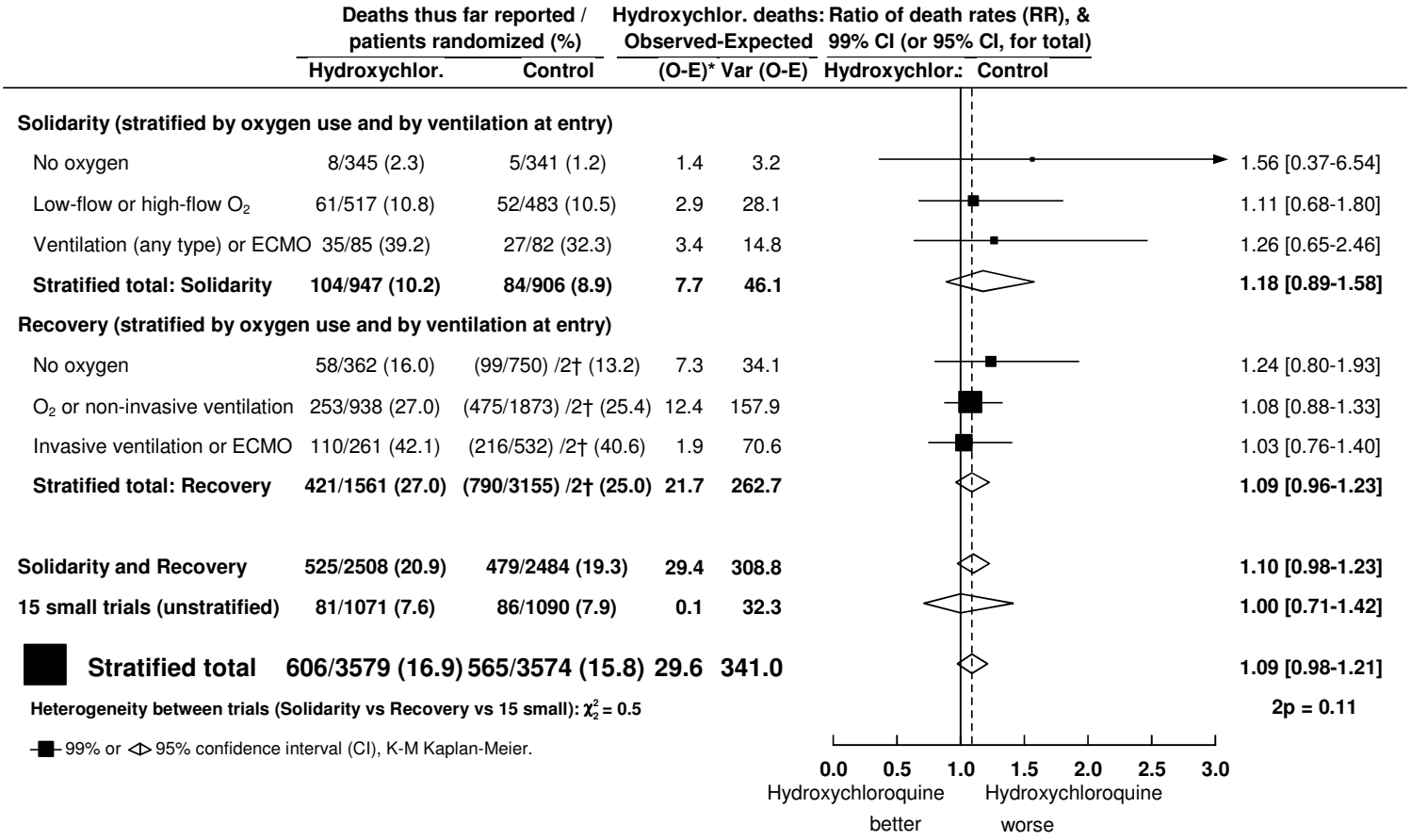
Lopinavir	1399	4	1333	2	1282	0	1257	1	1243	0
Control	1372	2	1293	1	1239	0	1216	0	1203	0



No. randomized, nos. of cardiac deaths, and denominators

Interferon	2050	4	1669	2	1554	1	1483	0	1410	1
Control	2050	5	1725	3	1636	1	1563	1	1498	0

Figure S19. Hydroxychloroquine vs its control in hospitalized COVID – Meta-analysis of mortality in the Solidarity, Recovery and other trials

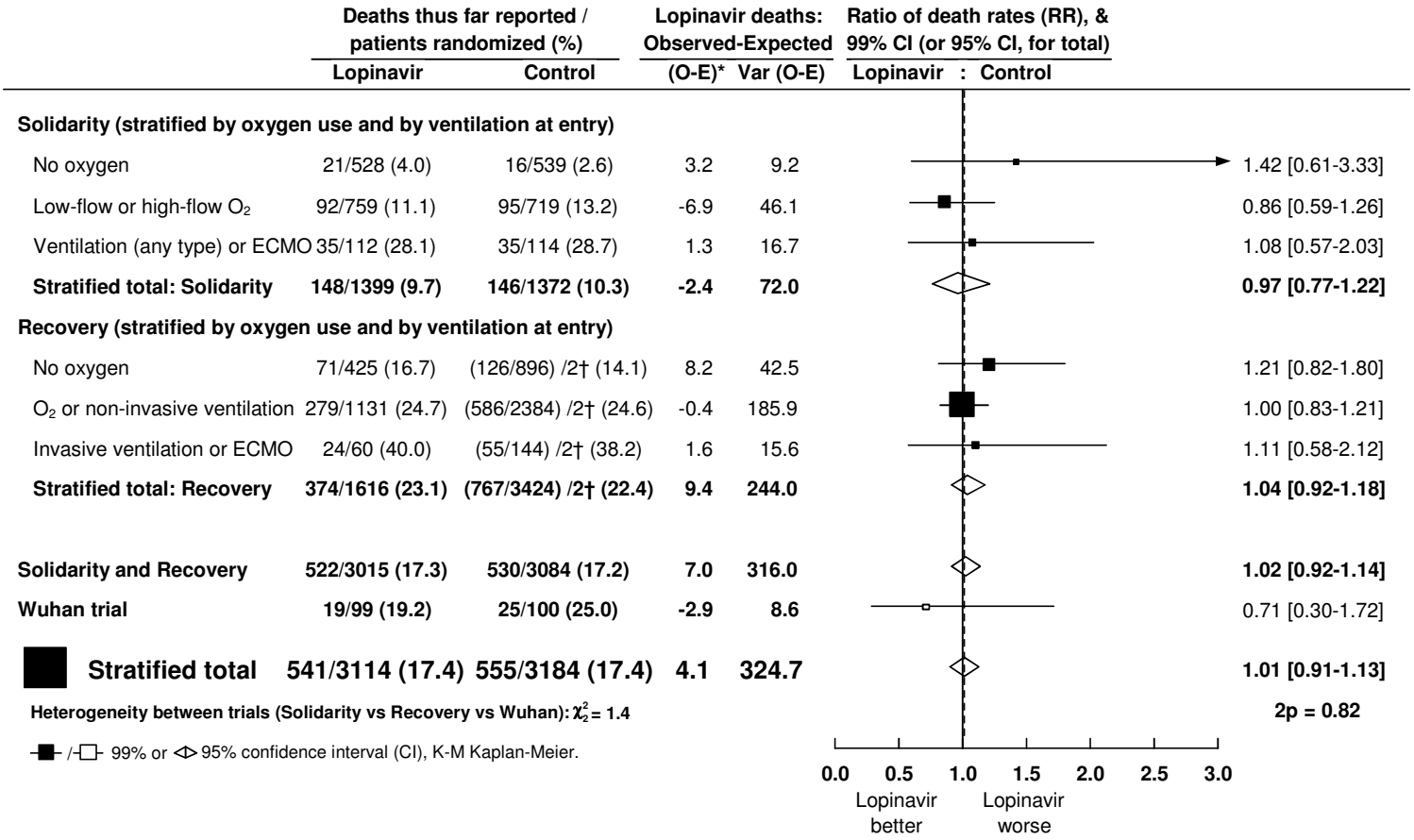


* Log-rank O-E for Solidarity and Recovery, and sum of O-E from 2x2 tables for small trials.

RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Similar use of subtotals or of totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

† For balance, only half the control numbers in Recovery are added into totals and subtotals.

Figure S20. Lopinavir versus its control in hospitalized COVID – Meta-analysis of mortality in the Solidarity, Recovery & Wuhan trials

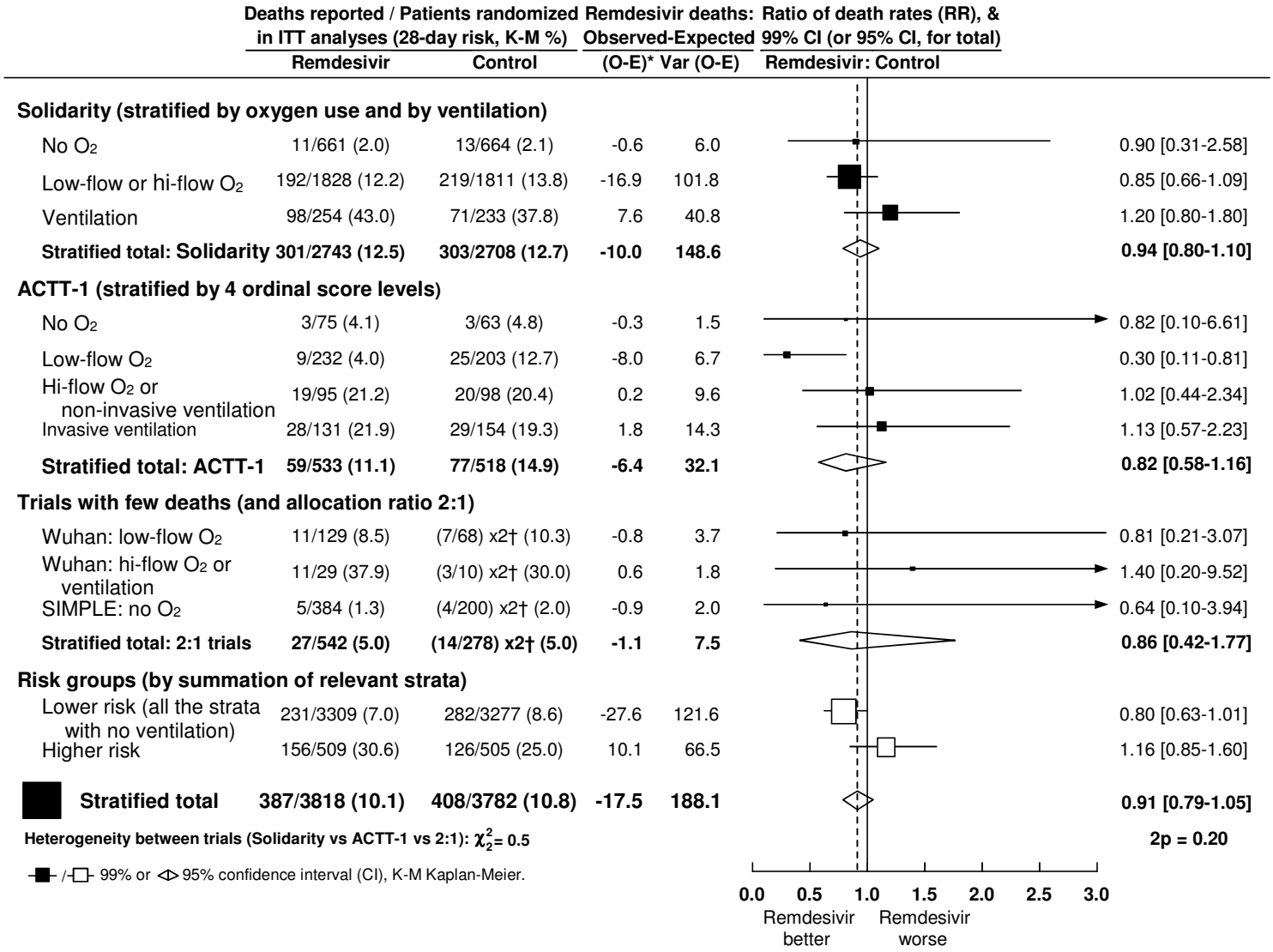


* Log-rank O-E for Solidarity and Recovery, and O-E from a 2x2 table for the Wuhan trial.

RR is got by taking $\log_e$RR to be (O-E)/V with Normal variance 1/V. Similar use of subtotals or of totals of (O-E) and of V yield inverse-variance-weighted averages of the $\log_e$RR values.

† For balance, only half the control numbers in Recovery are added into totals and subtotals.

Figure S21. Remdesivir vs control – Meta-analysis of mortality in trials of random allocation of hospitalised COVID-19 patients between remdesivir and its control



* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log$_e$HR for ACTT strata (with the weight w being the inverse of the variance of log$_e$HR, which is got from the HR's CI). RR is got by taking log$_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log$_e$RR values.

† For balance, controls in the 2:1 studies count twice in the control totals and subtotals.