Supplementary Tables and Figures

Meta-Analysis of 16S rRNA Microbial Data Identified Alterations of the Gut Microbiota in COVID-19 Patients during the Acute and Recovery Phases

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Table S1. The search strategy

Information sources	Search terms
	("COVID-19"[Title/Abstract] OR "coronavirus disease 19"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "severe acute
	respiratory syndrome coronavirus 2"[Title/Abstract]) AND ("microbio*"[Title/Abstract] OR "microflora*"[Title/Abstract] OR
	"bacteria*"[Title/Abstract] OR "microbiome*"[Title/Abstract] OR "flora*"[Title/Abstract] OR "bacterial*"[Title/Abstract] OR
Publyled	"microorganism"[Title/Abstract] OR "dysbiosis"[Title/Abstract]) AND ("gut"[All Fields] OR "intestine*"[All Fields] OR
	"bowel*"[All Fields] OR "gastrointestinal*"[All Fields] OR "feces*"[All Fields] OR "stool*"[All Fields] OR "rectal*"[All Fields])
	AND "16S"[All Fields]
	(TS=(COVID-19 OR "Coronavirus Disease 19" OR SARS-CoV-2 OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR
Wah of Science	2019-nCoV OR "2019 Novel Coronavirus") AND TS=(microbiota* OR microflora* OR bacteria* OR microbiome* OR flora* OR
web of Science	bacterial* OR bacteria* OR microorganism OR dysbiosis) AND TS=(gut* OR intestine* OR bowel* OR gastrointestinal* OR feces*
	OR stool* OR rectal*) AND TS=(16S))
	('covid-19' OR 'coronavirus disease 19' OR 'sars-cov-2' OR 'severe acute respiratory syndrome coronavirus 2' OR '2019 ncov' OR
Embase	'2019 novel coronavirus') AND (microbiota* OR microflora* OR microbiome* OR flora* OR bacterial* OR bacteria* OR
	microorganism OR dysbiosis) AND (gut* OR intestine* OR bowel* OR gastrointestinal* OR feces* OR stool* OR rectal*) AND 16s
	(TITLE-ABS-KEY("COVID-19" OR "Coronavirus Disease 19" OR "SARS-CoV-2" OR "Severe Acute Respiratory Syndrome
	Coronavirus 2" OR "2019 nCoV" OR "2019 Novel Coronavirus") AND TITLE-ABS-KEY("microbiota*" OR "microflora*" OR
Scopus	"bacteria*" OR "microbiome*" OR "flora*" OR "bacterial*" OR "bacteria*" OR "microorganism" OR "dysbiosis") AND ALL(gut*
	OR intestine* OR bowel* OR gastrointestinal* OR feces* OR stool* OR rectal*) AND ALL("16S")) AND (EXCLUDE
	(DOCTYPE,"re"))AND (LIMIT-TO (LANGUAGE,"English"))
SD A	("COVID-19" OR "SARS-CoV-2") [AND] (microbiota* OR microflora* OR bacteria* OR microbiome* OR flora* OR bacterial*
SKA	OR bacteria* OR microorganism OR dysbiosis) [AND] (gut* OR intestine* OR bowel* OR gastrointestinal* OR feces* OR stool*)

Author, Year [Ref]	Country	Design	Study Population	Sample Type	16S region	Sequencing	Differential	Reasons for exclusion
						Platform	analysis	
Jagielski 2022 [34]	Poland	Case-control	8 COV, 14 non-COV	Fecal samples	NM	NM	NM	Raw data cannot be obtained
Junior 2022 [35]	Brazil	Case-control	149 post-COV, 70 non-COV	Fecal samples	V3-V4	MiSeq	corncob	Unpublished and disease
								status is ambiguity
Mizutani 2022 [36]	Japan	Case-control	22 COV (39 samples),	Fecal samples	V3–V4	MiSeq	LEfSe	Unable to distinguish the raw
			40 non-COV, 6 RP					data of COV and RP
Schult 2022 [37]	Germany	Case-control	107 COV (210 samples),	Fecal samples	V3–V4	MiSeq	adonis	Disease status was not reported
			37 non-COV (41 samples)					in the metadata
Wu 2021 [17]	China	Case-control	13 COV, 30 non-COV	Fecal samples	V3–V4	MiSeq	Wilcoxon	Raw data cannot be obtained
			(15 HCs,15 NC-PCs)					
Venzon 2021 [38]	USA	Cross-sectional	101 COV	Fecal samples	V4	MiSeq	NM	Lacked non-COV
Xu 2021 [39]	China	Cross-sectional	19 COV	Fecal samples	V4	MiSeq	NM	Lacked non-COV

Table S2. Characteristics of	of studies not	included in	Meta-Analysis
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NM, not mentioned; HCs, healthy controls; NC-PCs, non-COVID-19 pneumonia controls.

Bacterial taxa ^{<i>a</i>}	Pooled	95% Pooled lower	95% Pooled upper	Pooled p-value	FDR adjusted pooled
	estimate(log(OR))	limit	limit		p-value
fRuminococcaceae.gRuminococcus	-0.33	-0.48	-0.19	0	2.00E-04
f_Lachnospiraceae.g_Lachnospira	-0.63	-0.82	-0.44	0	0
fStreptococcaceae.gStreptococcus	0.43	0.24	0.63	0	3.00E-04
f_Ruminococcaceae.g_Faecalibacterium	-0.6	-0.93	-0.26	5.00E-04	0.0063
f_Lachnospiraceae.g_Coprococcus	-0.52	-0.81	-0.23	5.00E-04	0.0063
fLachnospiraceae.gRoseburia	-0.58	-0.92	-0.23	0.001	0.0093
f_Prevotellaceae.g_Prevotella	-0.4	-0.64	-0.16	0.001	0.0093
fVeillonellaceae.gDialister	-0.48	-0.79	-0.17	0.0025	0.0203
fVeillonellaceae.gMegasphaera	-0.52	-0.87	-0.18	0.0029	0.0204
fPasteurellaceae.gHaemophilus	-0.34	-0.57	-0.1	0.0049	0.0311
fVeillonellaceae.gMegamonas	-0.4	-0.68	-0.12	0.0056	0.0326
f_Erysipelotrichaceae.g_Catenibacterium	-0.46	-0.85	-0.07	0.0202	0.0931
fParaprevotellaceae.gParaprevotella	-0.28	-0.51	-0.04	0.0203	0.0931
f_Enterococcaceae.g_Enterococcus	0.33	0.05	0.6	0.0204	0.0931
f_Corynebacteriaceae.g_Corynebacterium	0.4	0.06	0.75	0.0222	0.0946
fTuricibacteraceae.gTuricibacter	-0.33	-0.62	-0.04	0.0269	0.1075
fErysipelotrichaceae.gBulleidia	-0.59	-1.12	-0.06	0.0295	0.1109
fVeillonellaceae.gPhascolarctobacterium	-0.21	-0.41	-0.02	0.0315	0.112
fCoriobacteriaceae.gEggerthella	0.21	0	0.41	0.0454	0.1531
gFaecalibacterium.sprausnitzii	-0.52	-0.83	-0.22	8.00E-04	0.0507
gPrevotella.scopri	-0.45	-0.74	-0.17	0.0017	0.0523
gClostridium.s_lavalense	0.33	0.08	0.58	0.0098	0.1462
gBifidobacterium.sadolescentis	-0.22	-0.38	-0.05	0.0101	0.1462

Table S3. Meta-analysis of all included studies for gut bacterial taxa with differential relative abundances between COV vs. non-COV.

Table S3. Continued

Bacterial taxa ^a	Pooled estimate(log(OR))	95% Pooled lower	95% Pooled upper	Pooled p-value	FDR adjusted pooled
		limit	limit		p-value
g_Bacteroides.s_caccae	0.18	0.04	0.32	0.0143	0.1462
g_Eubacterium.s_dolichum	0.26	0.05	0.47	0.0166	0.1462
gHaemophilus.sparainfluenzae	-0.28	-0.51	-0.05	0.0191	0.1462
gRuminococcus.sbromii	-0.30	-0.55	-0.05	0.0192	0.1462
gStreptococcus.sanginosus	0.34	0.03	0.65	0.0297	0.2012
gRoseburia.sfaecis	-0.34	-0.66	-0.01	0.0411	0.2316
gClostridium.sspiroforme	0.55	0.02	1.08	0.0418	0.2316
gVeillonella.sdispar	0.19	0	0.37	0.0479	0.2437

Bacterial taxa ^{<i>a</i>}	Pooled	95% Pooled lower	95% Pooled upper	Pooled p-value	FDR adjusted pooled
	estimate(log(OR))	limit	limit		p-value
fLachnospiraceae.gLachnospira	-0.62	-0.87	-0.38	0	0
f_Prevotellaceae.g_Prevotella	-0.51	-0.8	-0.21	7.00E-04	0.0236
fPasteurellaceae.gHaemophilus	-0.48	-0.79	-0.17	0.0026	0.049
f_Pseudomonadaceae.g_Pseudomonas	-1.16	-1.93	-0.38	0.0033	0.049
fRuminococcaceae.gOscillospira	-0.3	-0.51	-0.1	0.0041	0.049
fParaprevotellaceae.gParaprevotella	-0.4	-0.68	-0.13	0.0041	0.049
fRuminococcaceae.gRuminococcus	-0.25	-0.43	-0.08	0.0053	0.0508
fAlcaligenaceae.gSutterella	-0.36	-0.61	-0.1	0.0057	0.0508
fRuminococcaceae.gFaecalibacterium	-0.61	-1.12	-0.11	0.0169	0.1335
fStreptococcaceae.gStreptococcus	0.3	0.03	0.56	0.0292	0.1902
fErysipelotrichaceae.gBulleidia	-0.59	-1.12	-0.06	0.0295	0.1902
fVeillonellaceae.gMegasphaera	-0.45	-0.87	-0.02	0.0382	0.1993
fVeillonellaceae.gMegamonas	-0.49	-0.95	-0.02	0.0392	0.1993
f_Enterococcaceae.g_Enterococcus	0.33	0.01	0.65	0.0413	0.1993
fVeillonellaceae.gDialister	-0.43	-0.85	-0.02	0.0421	0.1993
f_Corynebacteriaceae.g_Corynebacterium	0.4	0.01	0.79	0.0454	0.2017
gPrevotella.scopri	-0.56	-0.91	-0.21	0.0019	0.1128
gRuminococcus.salbus	-1.05	-1.92	-0.17	0.0187	0.3392
gFaecalibacterium.sprausnitzii	-0.52	-0.96	-0.08	0.0216	0.3392
gClostridium.scelatum	-0.24	-0.45	-0.03	0.0275	0.3392
gBifidobacterium.sadolescentis	-0.19	-0.36	-0.02	0.0283	0.3392
gHaemophilus.sparainfluenzae	-0.34	-0.66	-0.01	0.0441	0.4414

Table S4. Differential abundance analysis between COV vs. non-COV: sensitivity analysis removing the four Chinese studies.

		patients.			
Bacterial taxa ^{<i>a</i>}	Pooled	95% Pooled lower	95% Pooled upper	Pooled p-value	FDR adjusted pooled
	<pre>estimate(log(OR))</pre>	limit	limit		p-value
f_Lachnospiraceae.g_Roseburia	-0.31	-0.57	-0.05	0.0184	0.9621
f_Ruminococcaceae.g_Faecalibacterium	-0.49	-0.98	-0.01	0.0456	0.9621
g_Coprococcus.s_eutactus	-0.22	-0.22	-0.21	0	0

Table S5. Meta-analysis of all included studies for gut bacterial taxa with differential relative abundances between severe vs. non-severe COVID-19

Bacterial taxa ^a	Pooled	95% Pooled lower	95% Pooled upper	Pooled p-value	FDR adjusted pooled
	estimate(log(OR))	limit	limit		p-value
fRuminococcaceae.gRuminococcus	-0.49	-0.72	-0.26	0	6.00E-04
f_Ruminococcaceae.g_Faecalibacterium	-0.75	-1.05	-0.44	0	0
f_Lachnospiraceae.g_Roseburia	-0.63	-0.87	-0.38	0	0
f_Lachnospiraceae.g_Coprococcus	-0.72	-1.09	-0.36	1.00E-04	0.0014
fFusobacteriaceae.gFusobacterium	0.7	0.29	1.1	7.00E-04	0.0084
fStreptococcaceae.gStreptococcus	0.34	0.08	0.59	0.0092	0.0893
fCoriobacteriaceae.gCollinsella	-0.36	-0.67	-0.06	0.0206	0.1708
f_Erysipelotrichaceae.g_Clostridium	0.39	0.01	0.76	0.042	0.2761
fPasteurellaceae.gHaemophilus	0.35	0	0.69	0.0471	0.2761
gFaecalibacterium.sprausnitzii	-0.72	-1.02	-0.42	0	1.00E-04
gParabacteroides.sdistasonis	0.49	0.18	0.8	0.0019	0.0563
g_Coprococcus.s_eutactus	-1.23	-2.09	-0.38	0.0048	0.095
gClostridium.shathewayi	0.84	0.21	1.48	0.0093	0.1163
gClostridium.scitroniae	0.54	0.13	0.95	0.0103	0.1163
gClostridium.sramosum	0.38	0.08	0.67	0.0118	0.1163
gPrevotella.sstercorea	-0.87	-1.6	-0.15	0.0184	0.155
gRuminococcus.sgnavus	0.27	0.03	0.52	0.0268	0.1974
gRoseburia.sfaecis	-0.28	-0.55	-0.01	0.039	0.2556

Table S6. Meta-analysis of all included studies for gut bacterial taxa with differential relative abundances between RP/post-RP vs. non-COV.

Bacterial taxa ^{<i>a</i>}	Pooled	95% Pooled lower	95% Pooled upper	Pooled p-value	FDR adjusted pooled
	estimate(log(OR))	limit	limit		p-value
fActinomycetaceae.gActinomyces	0.39	0.12	0.67	0.0055	0.1972
fClostridiaceae.gSMB53	-0.76	-1.31	-0.22	0.0058	0.1972
f_Enterobacteriaceae.g_Citrobacter	0.84	0.04	1.64	0.0406	0.7727
gBifidobacterium.sbreve	1.55	1.38	1.72	0	0
gClostridium.sclostridioforme	-0.77	-1.19	-0.36	3.00E-04	0.0081
gRuminococcus.s_lactaris	-0.72	-1.38	-0.05	0.0354	0.6093
gBacteroides.splebeius	-0.54	-1.06	-0.01	0.0448	0.6093

Table S7. Meta-analysis of all included studies for gut bacterial taxa with differential relative abundances between RP/post-RP vs. COV.

Table 58. The raw data detai	IS
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Author, Year	Accession number
Al 2021	PRJNA769052
Cervino 2022	PRJNA787810
Chen 2022	PRJNA703303
Gaibani 2021	PRJNA700830, mgp17761, PRJNA247489
Gu 2020	PRJNA636824
Kim 2021	a
Khan 2021	PRJNA705797
Mazzarelli 2021	PRJNA681516
Moreira-Rosario 2021	PRJNA734646
Newsome 2021	PRJNA678695
Rafiqul 2022	PRJNA767939
Reinold 2021	PRJNA747262
Ren 2021	PRJNA660302
Tian 2021	PRJNA683685
Wu 2021	PRJNA684070
Zhou 2021	PRJNA736160

^{*a*} The raw sequencing data are available on reasonable request from the corresponding author of Kim 2021



Fig. S1 Flowchart for study search and selection.

а				Standardised Mean			Weight	Weight
	Study	cov	non-COV	Difference	SMD	95%-CI	(Fixed)	(random)
	AI 2021	78	50		0.40	[0.04; 0.76]	12.4%	9.1%
	Cervino 2022	55	76		-0.83	[-1.19; -0.46]	12.2%	9.0%
	Chen 2022	26	30		-0.99	[-1.54; -0.43]	5.1%	8.1%
	Gaibani 2021	69	65 -	•••• <u>i</u> i	-1.38	[-1.76; -1.00]	11.2%	9.0%
	Gu 2020	30	30		-0.67	[-1.19; -0.15]	5.9%	8.3%
	Khan 2021	30	10		-0.63	[-1.36; 0.10]	3.0%	7.2%
	Mazzarelli 2021	12	8		-0.41	[-1.31; 0.50]	1.9%	6.3%
	Newsome 2021	49	34	:	-0.20	[-0.64; 0.24]	8.3%	8.7%
	Rafiqul 2022	44	30 -		-1.24	[-1.75; -0.73]	6.2%	8.4%
	Reinold 2021	117	95	· · · · ·	0.08	[-0.19; 0.36]	21.7%	9.4%
	Ren 2021	36	72 —	— :i	-1.82	[-2.29; -1.35]	7.2%	8.5%
	Wu 2021	24	32		-1.02	[-1.59; -0.46]	5.0%	8.1%
	Fixed offect med				0.59	1 0 70: 0 451	400.0%	
	Fixed effect mod	ei			-0.58	[-0.70; -0.45]	100.0%	
	Random effects i	model			-0.72 T	[-1.10; -0.34]		100.0%
	Heterogeneity: $I^{-} = 9$	90%, t = 0	.3746, p < 0.01	-1 0 1	2			
		Enriche	d in non-COV	· →	Enriched ir	n COV		
b				Standardised Mean			Weight	Weight
b	Study	cov	non-COV	Standardised Mean Difference	SMD	95%-CI	Weight (Fixed)	Weight (random)
b	Study AI 2021	COV 78	non-COV	Standardised Mean Difference	SMD -0.25	95%-Cl [-0.61: 0.11]	Weight (Fixed) 12.1%	Weight (random) 9.0%
b	Study Al 2021 Cervino 2022	COV 78 55	non-COV 50 76	Standardised Mean Difference	SMD -0.25 -0.29	95%-Cl [-0.61; 0.11] [-0.64: 0.06]	Weight (Fixed) 12.1% 12.6%	Weight (random) 9.0% 9.0%
b	Study Al 2021 Cervino 2022 Chen 2022	COV 78 55 26	non-COV 50 76 30 —	Standardised Mean Difference	SMD -0.25 -0.29 -1.07	95%-CI [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51]	Weight (Fixed) 12.1% 12.6% 4.8%	Weight (random) 9.0% 9.0% 8.1%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021	COV 78 55 26 69	non-COV 50 76 30 — 65	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60: 0.08]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3%	Weight (random) 9.0% 9.0% 8.1% 9.1%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020	COV 78 55 26 69 30	non-COV 50 76 30 — 65 30	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37 -0.31]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5%	Weight (random) 9.0% 8.1% 9.1% 8.2%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021	COV 78 55 26 69 30 30	non-COV 50 76 30 — 65 30 10	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021	COV 78 55 26 69 30 30 30	non-COV 50 76 30 — 65 30 10 8	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01: 0.78]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021	COV 78 55 26 69 30 30 12 49	non-COV 50 76 30 — 65 30 10 8 34	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [-0.34; 1.25]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5%	Weight (random) 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafinul 2022	COV 78 55 26 69 30 30 12 49 44	non-COV 50 76 30 — 65 30 10 8 34 30 —	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -110	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2%	Weight (random) 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.6%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafiqul 2022 Beinold 2021	COV 78 55 26 69 30 30 12 49 44 117	non-COV 50 76 30 — 65 30 10 8 34 34 30 —	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60] [-0.20: 0.34]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0%	Weight (random) 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.4% 9.3%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafiqul 2022 Reinold 2021 Ren 2021	COV 78 55 26 69 30 30 12 49 44 117 36	non-COV 50 76 30 65 30 10 8 34 34 30 95 72	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07 -1.49	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60] [-0.20; 0.34] [-1.04; -1.04]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0% 21.0%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.6% 8.4% 9.3% 8.6%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafiqul 2022 Reinold 2021 Ren 2021	COV 78 55 26 69 30 30 12 49 44 117 36 24	non-COV 50 76 30 65 30 10 8 34 34 30 95 72 32	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07 -1.49 -1.37	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60] [-0.20; 0.34] [-1.94; -1.04] [-1.94; -0.78]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0% 7.7% 4.4%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.6% 8.4% 9.3% 8.6%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Refiqul 2022 Reinold 2021 Ren 2021 Wu 2021	COV 78 55 26 69 30 30 12 49 44 117 36 24	50 76 30 65 30 10 8 34 30 72 32	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07 -1.49 -1.37	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60] [-0.20; 0.34] [-1.94; -1.04] [-1.96; -0.78]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0% 7.7% 4.4%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.4% 9.3% 8.6% 8.0%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafigul 2022 Reinold 2021 Ren 2021 Wu 2021 Fixed effect mod	COV 78 55 26 69 30 30 12 49 44 117 36 24	50 76 30 65 30 10 8 34 30 72 32	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07 -1.49 -1.37 -0.37	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60] [-0.20; 0.34] [-1.94; -1.04] [-1.96; -0.78] [-0.49; -0.25]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0% 7.7% 4.4%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.6% 8.6% 8.0%
b	Study Al 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafiqul 2022 Reinold 2021 Ren 2021 Wu 2021 Fixed effect mod Random effects of	COV 78 55 26 69 30 30 12 49 44 117 36 24 el model	non-COV 50 76 30 65 30 10 8 34 34 30 	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07 -1.49 -1.37 -0.37 -0.49	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.60; -0.60] [-0.20; 0.34] [-1.94; -1.04] [-1.96; -0.78] [-0.49; -0.25] [-0.88; -0.10]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0% 7.7% 4.4%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.6% 8.6% 8.0%
b	Study AI 2021 Cervino 2022 Chen 2022 Gaibani 2021 Gu 2020 Khan 2021 Mazzarelli 2021 Newsome 2021 Rafiqul 2022 Reinold 2021 Ren 2021 Wu 2021 Fixed effect mod Random effects of Heterogeneity: J ² = 4	COV 78 55 26 69 30 30 12 49 44 117 36 24 el model 88%, $\hat{\tau} = 0$	non-COV 50 76 30 65 30 10 8 34 34 30 95 72 32	Standardised Mean Difference	SMD -0.25 -0.29 -1.07 -0.26 -0.84 0.06 -0.12 0.79 -1.10 0.07 -1.49 -1.37 -0.37 -0.49	95%-Cl [-0.61; 0.11] [-0.64; 0.06] [-1.64; -0.51] [-0.60; 0.08] [-1.37; -0.31] [-0.65; 0.78] [-1.01; 0.78] [0.34; 1.25] [-1.06; -0.60] [-0.20; 0.34] [-1.94; -1.04] [-1.96; -0.78] [-0.49; -0.25] [-0.88; -0.10]	Weight (Fixed) 12.1% 12.6% 4.8% 13.3% 5.5% 3.0% 1.9% 7.5% 6.2% 21.0% 7.7% 4.4% 100.0%	Weight (random) 9.0% 9.0% 8.1% 9.1% 8.2% 7.3% 6.4% 8.6% 8.6% 8.6% 8.0%

Fig. S2 Forest plot of the differences in alpha diversity between COV and non-COV by (a) Pielou's evenness, and (b) Faith's phylogenetic diversity.



Fig. S3 Sensitivity analysis for the differences in alpha diversity between COV and non-COV after the removal of either of the included studies. (a) Shannon's diversity index, (b) observed species, (c) Pielou's evenness, and (d) Faith's phylogenetic diversity. Random-effects models (red diamonds) with 95% CI above or below 0 were considered statistically significant.



Fig. S4 Funnel plot for publication for the differences in alpha diversity between COV and non-COV. (a) Shannon's diversity index, (b) observed species, (c) Pielou's evenness, and (d) Faith's phylogenetic diversity. Begg's correlation test and Egger's regression test were also used to detect the publication biases, with a P value < 0.1 indicating a potential bias.

а				Standardised Mean			Weight	Weight
	Study	severe	non-severe	Difference	SMD	95%-CI	(Fixed)	(random)
	Khan 2021	10	10 -		0.18	[-0.70; 1.06]	8.6%	9.6%
	Moreira-Rosario 2021	57	54 —		-0.42	[-0.80; -0.04]	47.0%	46.3%
	Reinold 2021	38	79		-0.12	[-0.51; 0.26]	44.4%	44.1%
	Fixed effect model				-0.24	[-0.49; 0.02]	100.0%	
	Random effects mode	el			-0.23	[-0.51; 0.05]		100.0%
	Heterogeneity: $I^2 = 6\%$, f^2	= 0.0061,	p = 0.35	-0.5 0 0.5				
	Enric	hed in no	on-severe 🔶	·····	Enriched ir) severe		

b

Study	severe	non-severe	Standardised Mean Difference	SMD	95%-CI	Weight (Fixed)	Weight (random)
Khan 2021	10	10 ——	*	-0.23	[-1.11; 0.65]	8.6%	11.8%
Moreira-Rosario 202	21 57	54		-0.40	[-0.78; -0.02]	47.0%	44.9%
Reinold 2021	38	79		0.00	[-0.39; 0.39]	44.4%	43.3%
Fixed effect model				-0.21	[-0.47; 0.05]	100.0%	
Random effects mo	del			-0.21	[-0.52; 0.11]		100.0%
Heterogeneity: $I^2 = 6\%$,	f = 0.021	16, <i>p</i> = 0.35					
		-1	-0.5 0 0.5	1			
Enrie	ched in n	ion-severe 🔶		Enriched in	severe		

С				Standardised Mean			Weight	Weight
	Study	severe	non-severe	Difference	SMD	95%-CI	(Fixed)	(random)
	Khan 2021	10	10		- 0.36	[-0.53; 1.24]	8.5%	8.5%
	Moreira-Rosario 202	1 57	54		-0.38	[-0.76; 0.00]	47.2%	47.2%
	Reinold 2021	38	79		-0.15	[-0.53; 0.24]	44.3%	44.3%
	Fixed effect model				-0.21	[-0.47; 0.04]	100.0%	
	Random effects mod	lel			-0.21	[-0.47; 0.04]		100.0%
	Heterogeneity: $I^2 = 19\%$, ² < 0.000	p = 0.29					
	Enric	hed in no	n-severe 🛶	• • • • •	Enriched in	severe		

d	Study	severe	non-severe	Standa Dif	rdised Me fference	ean		SMD	95%	-CI	Weight (Fixed)	Weight (random)
	Khan 2021	10	10 —					-0.22	[-1.10; 0	.66]	8.6%	15.9%
	Moreira-Rosario 20	21 57	54		_			-0.42	[-0.80; -0	.04]	47.0%	42.5%
	Reinold 2021	38	79			_		0.12	[-0.26; 0	.51]	44.4%	41.6%
	Fixed effect model							-0.16	[-0.42; 0.	.10]	100.0%	
	Random effects mo	odel						-0.16	[-0.56; 0.	.24]		100.0%
	Heterogeneity: $I^2 = 49\%$	o, ℓ = 0.0€	620, p = 0.14	-0.5	0	0.5	1					
	Enri	iched in	non-severe ┥				En	riched in	severe			

Fig. S5 Forest plot of the differences in alpha diversity between severe and non-severe COVID-19 patients by (a) Shannon's diversity index, (b) observed species, (c) Pielou's evenness, and (d) Faith's phylogenetic diversity.

а				Standardised Mean			Weight	Weight
	Study	RP/post-RP	non-COV	Difference	SMD	95%-CI	(Fixed)	(random)
	Chen 2022A	20	30	— <u>—</u> — I	-0.91	[-1.50; -0.31]	17.3%	15.8%
	Chen 2022B	30	30		-1.08	[-1.62; -0.53]	20.7%	16.7%
	Newsome 202	1 9	34	Ç	0.11	[-0.62; 0.85]	11.3%	13.6%
	Ren 2021	18	72 —	• <u>·</u> !	-1.68	[-2.25; -1.11]	18.6%	16.2%
	Tian 2021	7	7 —		-1.04	[-2.18; 0.10]	4.7%	8.7%
	Wu 2021	20	32		-1.27	[-1.88; -0.65]	16.3%	15.5%
	Zhou 2021	15	14	- č	-0.57	[-1.31; 0.18]	11.0%	13.5%
				·. !				
	Fixed effect m	odel		*	-1.00	[-1.25; -0.75]	100.0%	
	Random effec	ts model	_	<u> </u>	-0.94	[-1.37; -0.52]		100.0%
1	Heterogeneity: I ² =	= 63%, f = 0.20	182, p = 0.01		1			
		Enrichad	in non COV	-1 0 1 2	Z Enriched i	n BB/n ant BB		
		Enriched	III IIOII-COV		Enriched I	II KP/post-RP		
b								
b				Standardised Mean			Weight	Weight
b	Study	RP/post-RP	non-COV	Standardised Mean Difference	SMD	95%-CI	Weight (Fixed)	Weight (random)
b	Study Chen 2022A	RP/post-RP	non-COV 30 —	Standardised Mean Difference	SMD -1.39	95%−Cl [−2.03; −0.76]	Weight (Fixed) 14.9%	Weight (random) 15.1%
b	Study Chen 2022A Chen 2022B	RP/post-RP 20 30	non-COV 30 30	Standardised Mean Difference	SMD -1.39 -1.02	95%-Cl [-2.03; -0.76] [-1.56; -0.48]	Weight (Fixed) 14.9% 20.5%	Weight (random) 15.1% 16.7%
b	Study Chen 2022A Chen 2022B Newsome 202	RP/post-RP 20 30 1 9	non-COV 30 30 34	Standardised Mean Difference	SMD -1.39 -1.02 0.36	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09]	Weight (Fixed) 14.9% 20.5% 11.0%	Weight (random) 15.1% 16.7% 13.4%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021	RP/post-RP 20 30 1 9 18	non-COV 30 30 34 72	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2%	Weight (random) 15.1% 16.7% 13.4% 16.7%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021	RP/post-RP 20 30 1 9 18 7	non-COV 30 30 34 72 7	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62] [-1.74; 0.43]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1%	Weight (random) 15.1% 16.7% 13.4% 16.7% 8.9%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021 Wu 2021	RP/post-RP 20 30 1 9 18 7 20	non-COV 30	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65 -0.81	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62] [-1.74; 0.43] [-1.40; -0.23]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1% 17.7%	Weight (random) 15.1% 16.7% 13.4% 16.7% 8.9% 16.0%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021 Wu 2021 Zhou 2021	RP/post-RP 20 30 19 18 7 20 15	non-COV 30	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65 -0.81 -0.64	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62] [-1.74; 0.43] [-1.40; -0.23] [-1.39; 0.11]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1% 17.7% 10.6%	Weight (random) 15.1% 16.7% 13.4% 16.7% 8.9% 16.0% 13.2%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021 Wu 2021 Zhou 2021	RP/post-RP 20 30 11 9 18 7 20 15	non-COV 30	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65 -0.81 -0.64	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62] [-1.74; 0.43] [-1.40; -0.23] [-1.39; 0.11]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1% 17.7% 10.6%	Weight (random) 15.1% 16.7% 13.4% 16.7% 8.9% 16.0% 13.2%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021 Wu 2021 Zhou 2021 Fixed effect m	RP/post-RP 20 30 19 18 7 20 15 00del	non-COV 30	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65 -0.81 -0.64 -0.86	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62] [-1.74; 0.43] [-1.40; -0.23] [-1.39; 0.11] [-1.10; -0.61]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1% 17.7% 10.6% 100.0%	Weight (random) 15.1% 16.7% 13.4% 16.7% 8.9% 16.0% 13.2%
b	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021 Wu 2021 Zhou 2021 Fixed effect m Random effect	RP/post-RP 20 30 1 9 18 7 20 15 model ts model	non-COV 30	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65 -0.81 -0.64 -0.86 -0.80	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.71; -0.62] [-1.74; 0.43] [-1.40; -0.23] [-1.39; 0.11] [-1.10; -0.61] [-1.21; -0.39]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1% 17.7% 10.6% 100.0%	Weight (random) 15.1% 16.7% 13.4% 16.7% 8.9% 16.0% 13.2%
b H	Study Chen 2022A Chen 2022B Newsome 202 Ren 2021 Tian 2021 Wu 2021 Zhou 2021 Fixed effect m Random effec eterogeneity: /² =	RP/post-RP 20 30 1 9 18 7 20 15 model ts model 60%, ℓ = 0.186	non-COV 30 30 34 72 32 14 34, p = 0.02	Standardised Mean Difference	SMD -1.39 -1.02 0.36 -1.16 -0.65 -0.81 -0.64 -0.86 -0.80	95%-Cl [-2.03; -0.76] [-1.56; -0.48] [-0.38; 1.09] [-1.74; 0.43] [-1.74; 0.43] [-1.40; -0.23] [-1.39; 0.11] [-1.39; 0.11] [-1.21; -0.39]	Weight (Fixed) 14.9% 20.5% 11.0% 20.2% 5.1% 17.7% 10.6% 100.0%	Weight (random) 15.1% 16.7% 16.7% 16.7% 8.9% 16.0% 13.2%

Fig. S6 Forest plot of the differences in alpha diversity between RP/post-RP and non-COV by (a) Pielou's evenness, and (b) Faith's phylogenetic diversity.



Fig. S7 Sensitivity analysis for the differences in alpha diversity between RP/post-RP and non-COV after the removal of either of the included studies. (a) Shannon's diversity index, (b) observed species, (c) Pielou's evenness, and (d) Faith's phylogenetic diversity. Random-effects models (red diamonds) with 95% CI above or below 0 were considered statistically significant.

Fig. S8 Funnel plot for publication for the differences in alpha diversity between RP/post-RP and non-COV. (a) Shannon's diversity index, (b) observed species, (c) Pielou's evenness, and (d) Faith's phylogenetic diversity.

Fig. S9 Tests for subgroup differences demonstrated no significance when studies stratified by RP and post-RP in alpha diversity. (a) Shannon's diversity index, (b) observed species, (c) Pielou's evenness, and (d) Faith's phylogenetic diversity. The random effects model results were emphasized.

Fig. S10 Boxplots showing standardized alpha diversity by SARS-CoV-2 infection status. (a) Standardized observed species, (b) Standardized Pielou's evenness, and (c) Standardized Faith's phylogenetic diversity. Red = COV, purple = RP, blue = post-RP, and green = non-COV.

Fig. S11 Differential abundance analysis between COV vs. non-COV (a) at genus level, and (b) at species level: sensitivity analysis removing the four Chinese studies. Heatmap showed log(OR) of relative abundances of bacterial taxa between COV and non-COV across each study. The bacterial taxa unavailable in a particular study were in white in heatmap. Forest plot indicated pooled log(OR) estimate and 95% CI of relative abundances of bacterial taxa between COV and non-COV across all studies included. Log(OR) estimates were from GAMLSS-BEZI and Random Effects Meta-analysis. Only bacterial taxa with pooled *P* of pooled log(OR) estimates below 0.05 were displayed. Pooled log(OR) estimates with FDR-adjusted pooled *P* < 0.1 were showed as red triangles. Log(OR) > 0 denoted an increase and log(OR) < 0 denoted a decrease of taxa relative abundance in COV compared with non-COV.