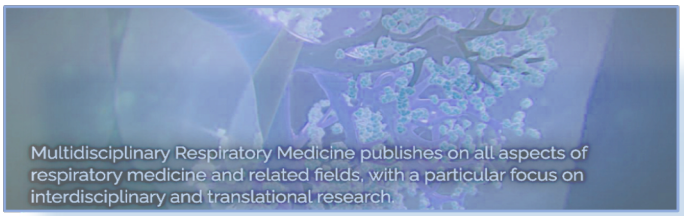

SUPPLEMENTARY MATERIAL

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Outcomes comparison between the first and the subsequent SARS-CoV-2 waves – a systematic review and meta-analysis

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Supplementary Table 1. Search strategy for Ovid MEDLINE.

Search: ((COVID-19) OR (SARS-COV-2)) AND ((critical care) OR (intensive care unit)) AND (waves) ("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 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 "sars cov 2"[All Fields] OR "sars cov 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 ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[All Fields])) AND ("critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] OR ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields] AND "unit"[All Fields]) OR "intensive care unit"[All Fields])) AND ("wave s"[All Fields] OR "waves"[All Fields])
Translations
COVID-19: ("COVID-19" OR "COVID-19"[MeSH Terms] OR "COVID-19 Vaccines" OR "COVID-19 Vaccines"[MeSH Terms] OR "COVID-19 serotherapy" OR "COVID-19 serotherapy"[Supplementary Concept] OR "COVID-19 Nucleic Acid Testing" OR "covid-19 nucleic acid testing"[MeSH Terms] OR "COVID-19 Serological Testing" OR "covid-19 serological testing"[MeSH Terms] OR "COVID-19 Testing" OR "covid-19 testing"[MeSH Terms] OR "SARS-CoV-2" OR "sars-cov-2"[MeSH Terms] OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR (("coronavirus"[MeSH Terms] OR "coronavirus" OR "COV") AND 2019/11/01[PDAT] : 3000/12/31[PDAT])) **SARS-COV-2**: "sars-cov-2"[MeSH Terms] OR "sars-cov-2"[All Fields] OR "sars cov 2"[All Fields] **critical care**: "critical care"[MeSH Terms] OR ("critical"[All Fields] AND "care"[All Fields]) OR "critical care"[All Fields] intensive care unit: "intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields] AND "unit"[All Fields]) OR "intensive care unit"[All Fields] **waves**: "wave's"[All Fields] OR "waves"[All Fields]

Supplementary Table 2. Assessment of risk of bias using the "Tool to Assess Risk of Bias in Cohort Studies" developed by the CLARITY Group at McMaster University.

Author	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8
Aries[1]	High	Low	Low	Low	Moderate	Moderate	High	High
Asghar[2]	High	Low	Low	High	Moderate	High	High	High
Begum[3]	High	Low	Low	Moderate	Low	Low	Low	High
Carbonell[4]	High	Low	Low	Low	Low	Low	Moderate	High
Contou[5]	High	Low	Low	High	High	High	High	High
Demoule[6]	High	Low	Low	Low	Moderate	Moderate	Low	High
Dongelmans[7]	High	Low	Low	Low	Low	Low	High	High
Haase[8]	High	Low	Low	Low	Moderate	Moderate	Moderate	High
Hosoda[9]	High	Low	Low	High	Moderate	High	High	High
Kerai[10]	High	Low	Low	High	Moderate	High	High	High
Kieninger[11]	High	Low	Low	High	Moderate	Low	High	High
Lalla[12]	High	Low	Low	High	Moderate	Low	High	High
Lazaro[13]	High	Low	Low	High	Moderate	Moderate	High	High
Le Terrier[14]	High	Low	Low	High	Moderate	High	High	High
Lopez[15]	High	Low	Low	Low	High	High	High	High
Mayerhofer[16]	High	Low	Low	Low	Low	Low	Moderate	High
Namendis-Silva[17]	High	Low	Low	High	High	Low	High	High
Perez-Acosta[18]	High	Low	Low	High	Moderate	High	High	High
Piagnerelli[19]	High	Low	Low	High	High	High	High	High
Ritchie[20]	High	Low	Low	Low	Moderate	High	High	High
Routsie[21]	High	Low	Low	High	Moderate	High	High	High
Szakmany[22]	High	Low	Low	High	High	High	Moderate	High
Taxbro[23]	High	Low	Low	High	Moderate	Moderate	High	High
Wilcox[24]	High	Low	Low	High	High	Moderate	High	High
Zirpe[25]	High	Low	Low	High	High	High	High	High

Each question addresses bias risk of different causes. High = high risk, Moderate = moderate risk, Low = low or no risk of bias.

Supplementary Table 3. Demographics of included patients from the selected studies (part 1).

Study	Age (median and IC range)		Female (%)		HP (%)		DM (%)		Smoking (%)		Prior CVA (%)		Prior MI (%)		Prior PCI (%)		Renal failure (%)		COPD (%)	
	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.
Aries	60(51-67)	57(46-66)	36.6	36.5	61	54.8	53.7	51.3	2.4	4.3	NR	NR	NR	NR	NR	NR	19.5	9.6	2.4	6.6
Asghar	56(19)*	65(18.5)*	37	38.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Begum	64(54-72)	54(41-65)[$]	31	38	NR	NR	28	29.8	13	19.8	NR	NR	NR	NR	NR	NR	6	5.3	9	6
Carbonell	64(55-71)	63(53-71)	29.6	28.4	44.4*	49.4*	20.9*	26.7*	NR	NR	NR	NR	6.7	6.3	NR	NR	4.6*	6.8*	6.9	7.4
Countou	62(55-70)	65(61-69)	19	24	63	60	43	44	NR	NR	9	6	10	10	NR	NR	9	10	23	28
Demoule	63(55-71)*	67(58-73)*	25	29	51	51	30	30	NR	NR	NR	NR	NR	NR	NR	NR	12	10	8	10
Dongelmans	63(11.3)*	61(11.7)[$]*	28	33[$]*	NR	NR	19.1	22*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Haase	69(59-75)	66(57-64)	27*	34*	50	54	21	25	NR	NR	NR	NR	13	15	NR	NR	12	15	20	19
Hosoda	60(52-73)	67(57-74)[$]	10.8	29[$]	59.5	67	45.9	53	NR	NR	13.5	8.8	18.9*	14.3*	NR	NR	5.4	19.8	13.5	12
Kerai	56.8(16.3)*	49.5(13.5)*	37.7*	55.5*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kieninger	60[#]	58[#]	32.2	22.4	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lalla	54.1(45.7-61.7)	53.8(46.4-59.7)	44.6*	67.1*	59.5	57.4	49.9	50	3.7	5.6	NR	NR	NR	NA	NR	NR	4.8	0	3.3	0
Lazaro	59.8(15.2)*	57.1(14.9)*	39.7	43.4	64.8	59.2	38.6	31.8	NR	NR	NR	NR	NR	NR	NR	NR	14.8	18	3.4	2.3
Le Terrier	64.5(57-63)	68(59-74)	23.4	25.3	48.4	47.5	26.6*	40.4*	15.3	21.4	NR	NR	NR	NR	NR	NR	8.1	9.1	7.3	7.1
Lopez	62(52-72)	67(60-73)	23	28	69	53	43	29	23	15	NR	NR	26	20	NR	NR	3	7	11	15
Mayerhofer	64(54-74)*	72(62-78)*	28	30.4	66.4	63.8	18.7	28.5	12.8	9.1	10.3	14	NR	NR	NR	NR	19.6	21.7	13.1	14
Namendis-Silva	61(51-70)[&]	60(50-70)[&]	35.1	37.3[&]	41.2*	42.8*[&]	35.3	35.2[&]	NR	NR	NR	NR	NR	NR	NR	NR	5.6*	4.7*[&]	4.1	3.2*[&]
Perez-Acosta	65.2(9.9)	62(14.3)	38.5	26.1	65.4	65.2	46.2	34.8	19.2	18.2	NR	NR	19.2	18.2	NR	NR	NR	NR	15.4	6.5
Piagnerelli	60(55-67)	66(59-73)	28	32	54	54	36	36	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Ritchie	59.2(10.1)*	61.5(11.2)*	28*	43.5*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Routsie	NR	NR	24	30	28	42	18	28.8	NR	NR	NR	NR	12*	28.8*	NR	NR	2.0	7.5	8.0	12.7
Szakmany	57(51-63)*	61(53-67)*	33.8	26.5	43	37	28	20	NR	NR	NR	NR	4.6*	23*	NR	NR	3	9.7	1.5	5.3
Taxbro	63[#]	67[#]	34	27	50	58	27	30	27	30	NR	NR	20	21	NR	NR	50	63	7.3	9.5
Wilcox	59(13)	59(13)	30	44	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zirpe	57.6(14.6)	56.7(15.5)	26.5*	31.6*	45	50	40	45	NR	NR	NR	NR	14*	17*	NR	NR	5.3*	9.8*	4.6*	10.3*

CVA= cerebrovascular accident; DM= diabetes; HP= hypertension; MI= myocardial infarction; NR= not reported; PCI= percutaneous coronary intervention; SD= standard deviation Subs.= subsequent; *p<0.05; [$]Data from third wave; [#]Interquartile range NR; [&]Data from second wave

Supplementary Table 3. Demographics of included patients from the selected studies (part 2).

Study	Charlson Index (mean±SD)		Vaccination (%)		SAPS (median/range)		APACHE (median/range)		SOFA (median/range)		Oxygenation Index (median/range)		Corticosteroids use (%)		Remdesivir use (%)		IL-6 use (%)	
	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.	First	Subs.
Aries	NR	NR	NR	NR	NR	NR	NR	NR	3(2-5)	3(2-4)	129(84-180)	99.5(78-128)	20*	100*	NR	NR	NR	NR
Asghar	NR	NR	NR	NR	NR	NR	15(7.5)*	13(5.5)*	4(2.5)	3(2)	NR	NR	NR	NR	NR	NR	NR	NR
Begum	1(0-3)	1(0-2)	0	20	NR	NR	14(10-18)	13(9-17)$	NR	NR	NR	NR	30	95	1	17	0	10.5
Carbonell	NR	NR	NR	NR	NR	NR	14(10-19)*	12(9-16)*	5(3-7)	4(3-6)	NR	NR	58.2*	95.9*	1.7*	16.1*	28.9*	6.2*
Countou	NR	NR	NR	NR	33(24-41)	29(22-37)	NR	NR	4(3-7)	4(3-4)	NR	NR	12*	100*	0	0	0	0
Demoule	NR	NR	NR	NR	NR	NR	NR	NR	4(3-7)*	3(2-6)*	118(81-181)*	96(70-147)*	31*	95*	NR	NR	4*	1*
Dongelmans	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	85*	75.6$*	NR	NR	NR	NR	NR	NR
Haase	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hosoda	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	48.6*	100*	2.7*	88*	NR	NR
Kerai	NR	NR	NR	NR	NR	NR	NR	NR	3.5(2.2)	3.4(1.3)	NR	NR	NR	NR	NR	NR	11,.3	4.2
Kieninger	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lalla	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	76	72	NR	NR	NR	NR	NR	NR
Lazaro	NR	NR	NR	NR	70*	59*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Le Terrier	NR	NR	NR	NR	52.5(40.5-65)*	60(43-72)*	22(14-29)*	26(18-30)*	6(4-7)	6(4-8)	140.2*	96.7*	0*	95*	7.3	11.1	NR	NR
Lopez	NR	NR	NR	NR	31(23-38)	34(30-42)	NR	NR	3(2-5)	3(2-4)	145(108-190)	123(93-165)	NR	NR	NR	NR	NR	NR
Mayerhofer	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	29.1	88.3	NR	NR	NR	NR

Namendis-Silva	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Perez-Acosta	2.96(1.6)	3(2)	NR	NR	NR	NR	14.2(4.1)	17(8)	8.3(4.5)	7(4)	NR	NR	65.4*	89.1*	NR	NR	NR	NR
Piagnerelli	NR	NR	NR	NR	NR	NR	13(12-19)	14(11-17)	6(5-8)	6(4-8)	NR	NR	18	99	NR	NR	NR	NR
Ritchie	NR	NR	NR	NR	NR	NR	14.9*	17*	6.4(2.9)	6.1(3.4)	135,8(79)*	105,8(47)*	50.9*	99.2*	2.9*	41.6*	6.3	31.8
Routsie	NR	NR	NR	NR	NR	NR	12(8-17)	13(9-20)	7(3-9)	6(2-9)	121(86-171)	124(90-180)	10*	100*	6*	42*	10*	0*
Szakmany	NR	NR	NR	NR	NR	NR	NR	NR	10(7-12)*	8(5-9)*	NR	NR	21.5*	100*	NR	NR	3.1	63.7
Taxbro	NR	NR	NR	NR	57(48-62)	58(51-64)	NR	NR	NR	NR	NR	NR	56.3*	96.4*	1*	11*	3.1	1.8
Wilcox	NR	NR	NR	NR	NR	NR	15(5)	14(5)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zirpe	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	99*	100*	NR	NR	NR	NR

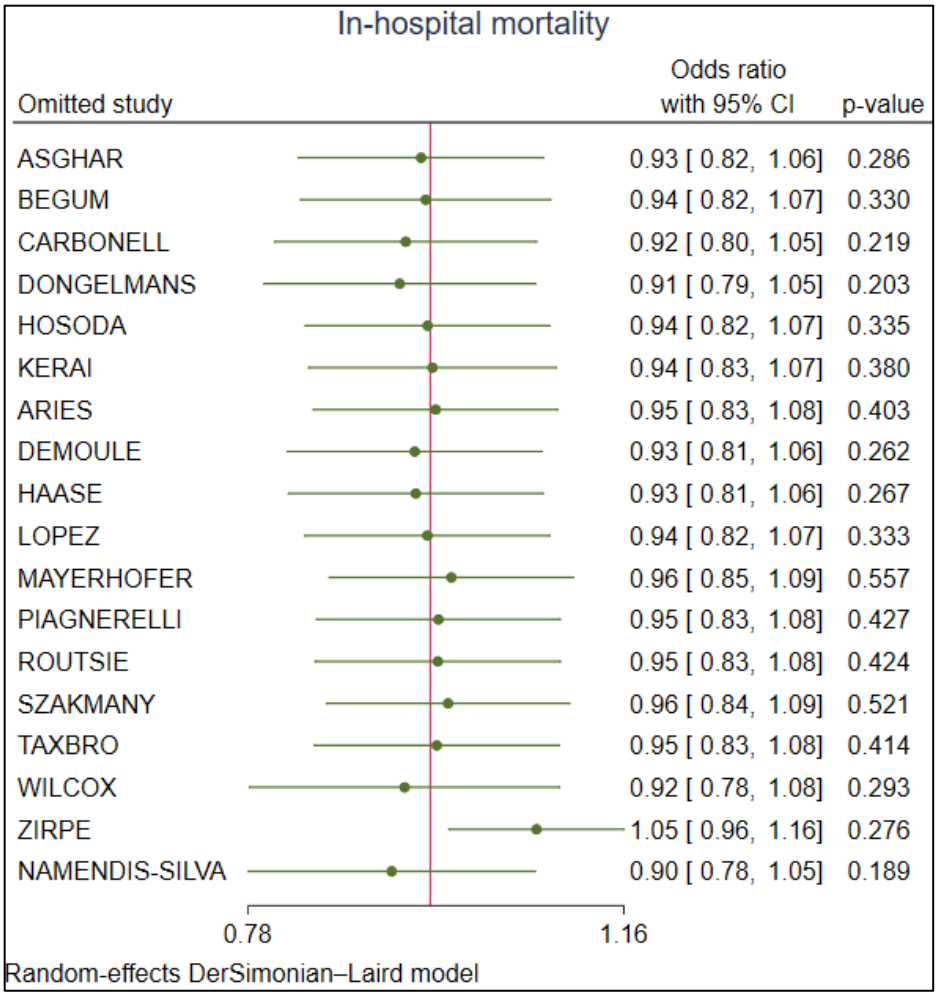
APACHE= Acute Physiology and Chronic Health Evaluation, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, Subs.= subsequent. *p<0.05; $Data from third wave;

Supplementary Table 4. Waves period, vaccination start date, use of respiratory support.

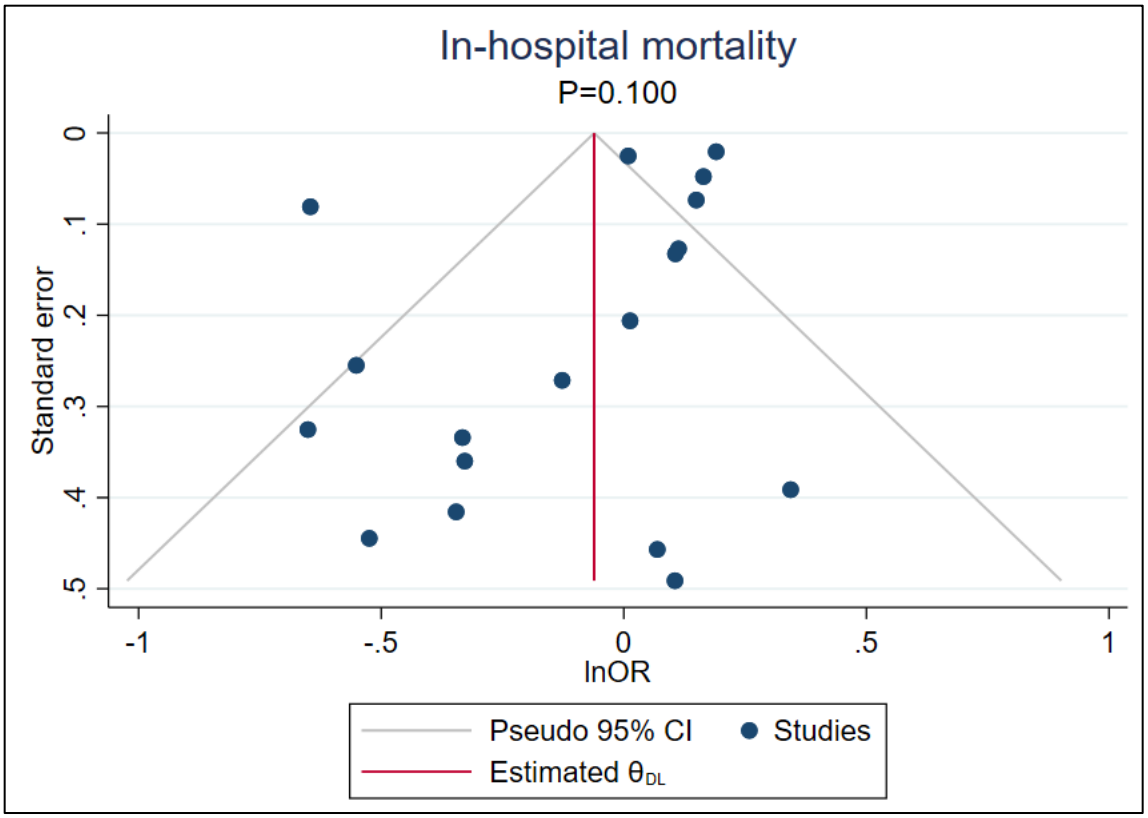
Author	First wave period		Subsequent waves period		Vaccination starting	HFNC First wave (%)	HFNC Subs. Waves (%)	NIV First wave (%)	NIV subs. Waves (%)	IMV first wave (%)	IMV subs. Waves (%)
Aries	03/15/2020 09/27/2020	to	02/01/2021 03/01/2021	to	December 2020	NR	NR	NR	NR	NR	NR
Asghar	03/01/2020 05/31/2020	to	10/01/2020 11/30/2020	to	February 2021	NR	NR	30	34	27	16
Begum	02/27/2020 06/30/2020	to	07/01/2020 11/01/2021	to	February 2021	43	79	7	42	58	50
Carbonell	02/01/2020 06/30/2020	to	07/01/2020 05/31/2021	to	December 2020	18	49	5	7	79	71
Countou	03/13/2020 05/27/2020	to	08/19/2020 12/07/2020	to	December 2020	NR	NR	NR	NR	88	64
Demoule	02/01/2020 06/30/2020	to	07/01/2020 12/31/2020	to	December 2020	NR	NR	NR	NR	69	46
Dongelmans	02/01/2020 05/24/2020	to	10/05/2020 06/30/2021	to	December 2020	NR	NR	NR	NR	NR	NR
Haase	03/10/2020 05/19/2020	to	05/20/2020 06/30/2021	to	December 2020	NR	NR	NR	NR	81	58
Hosoda	03/01/2020 06/30/2020	to	07/01/2020 02/28/2021	to	February 2021	0	7	NR	NR	NR	NR
Kerai	04/01/2020 04/30/2020	to	08/15/2020 09/15/2020	to	January 2021	NR	NR	NR	NR	NR	NR
Kieninger	03/14/2020 06/02/2020	to	10/01/2020 02/28/2021	to	December 2020	NR	NR	NR	NR	NR	NR
Lalla	03/27/2020 10/29/2020	to	11/04/2020 02/10/2021	to	February 2021	NR	NR	NR	NR	14	39
Lazaro	03/01/2020 10/31/2020	to	11/01/2020 06/30/2021	to	January 2021	NR	NR	1	26	81	67
Le Terrier	03/09/2020 05/15/2020	to	05/16/2020 01/09/2021	to	December 2020	NR	NR	NR	NR	100	100
Lopez	03/01/2020 06/30/2020	to	09/01/2020 01/31/2021	to	December 2020	71	88	NR	NR	66	48
Mayerhofer	02/01/2020 07/17/2020	to	07/18/2020 02/22/2021	to	December 2020	22	53	75	79	67	51
Namendis-Silva	02/27/2020 09/30/2020	to	10/01/2020 08/20/2021	to	December 2020	NR	NR	NR	NR	100	100

Perez-Acosta	03/01/2020 07/31/2020	to	08/01/2020 12/31/2020	to	December 2020	NR	NR	4	50	84	73
Piagnerelli	03/01/2020 08/31/2020	to	09/01/2020 12/31/2020	to	December 2020	NR	NR	NR	NR	72	71
Ritchie	02/23/2020 10/31/2020	to	11/01/2020 02/23/2021	to	December 2020	2	14	6	25	95	82
Routsie	03/01/2020 07/31/2020	to	09/01/2020 01/31/2021	to	December 2020	28	55	4	2	82	66
Szakmany	03/09/2020 06/05/2020	to	11/17/2020 03/15/2021	to	December 2020	NR	NR	NR	NR	99	91
Taxbro	03/14/2020 09/13/2020	to	09/14/2020 03/13/2021	to	December 2020	NR	NR	NR	NR	85	73
Wilcox	03/01/2020 08/31/2020	to	09/01/2020 02/28/2021	to	December 2020	NR	NR	NR	NR	NR	NR
Zirpe	03/01/2020 11/30/2020	to	03/01/2021 05/31/2021	to	January 2021	NR	NR	NR	NR	26	40

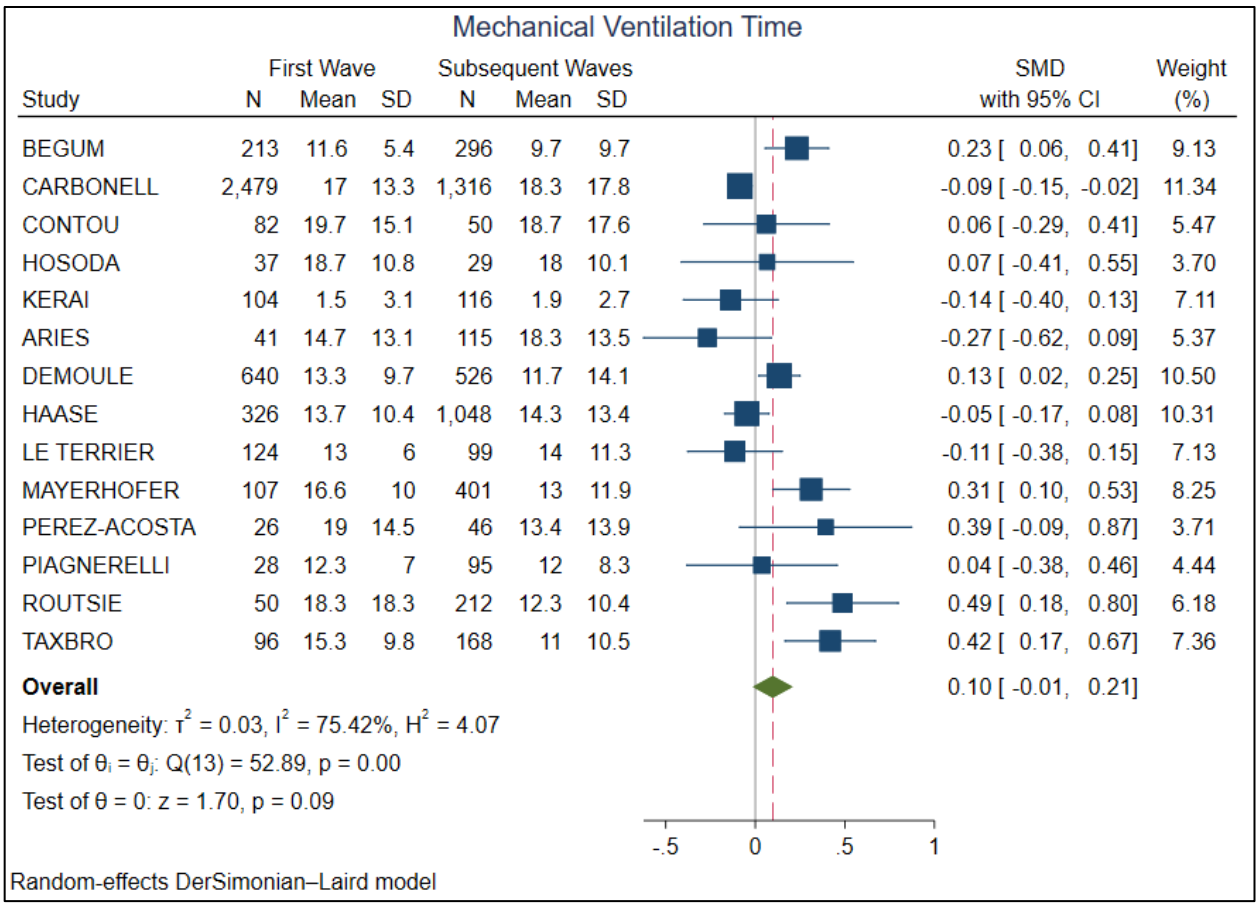
Supplementary Figure 1. Leave-one-out analysis for in-hospital mortality.



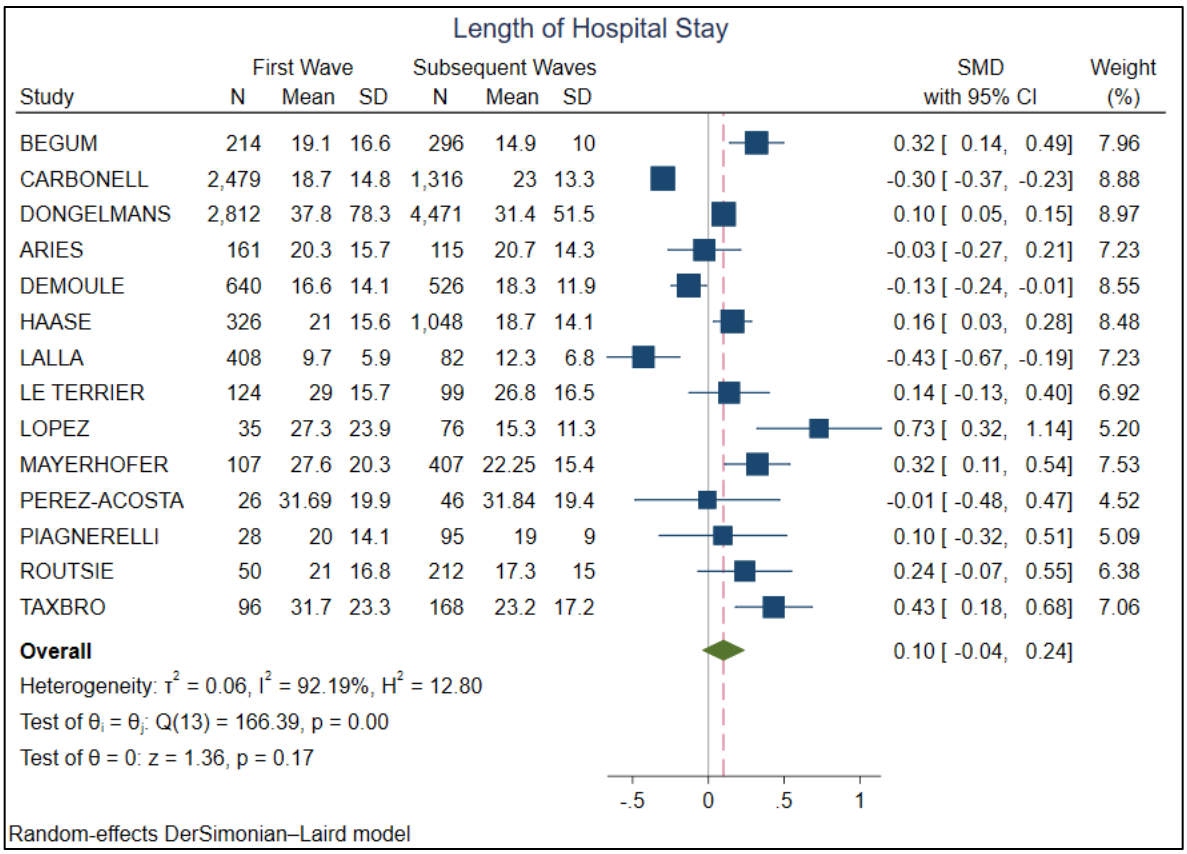
Supplementary Figure 2. Funnel plot for in-hospital mortality.



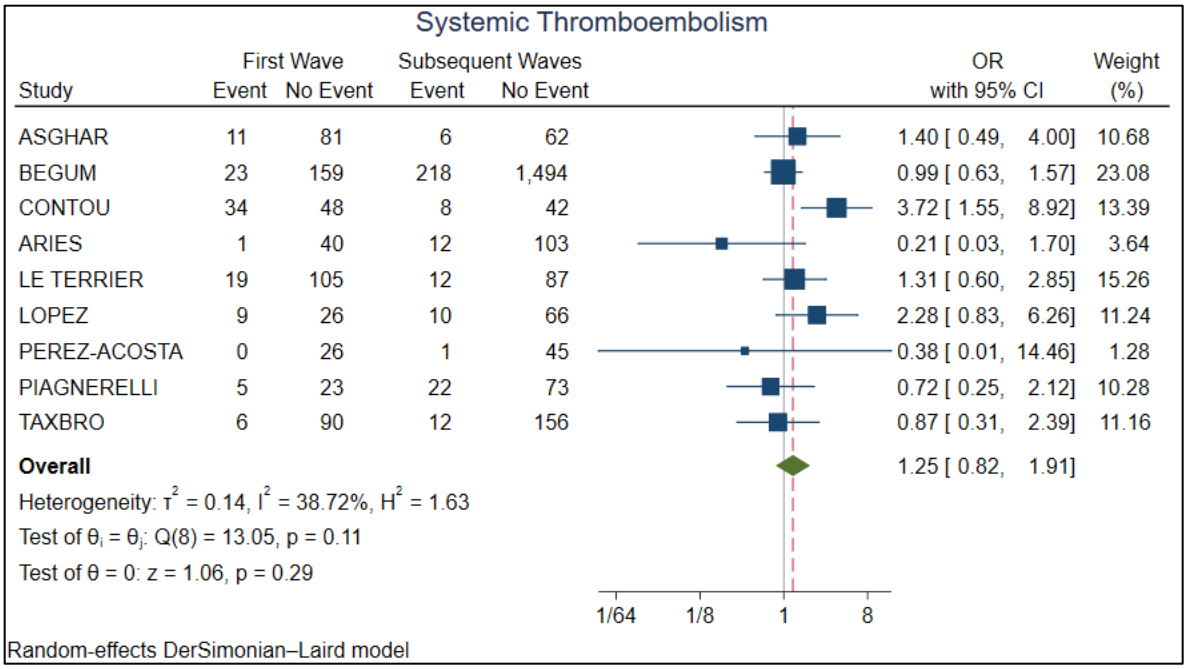
Supplementary Figure 3. Forest plot for mechanical ventilation time.



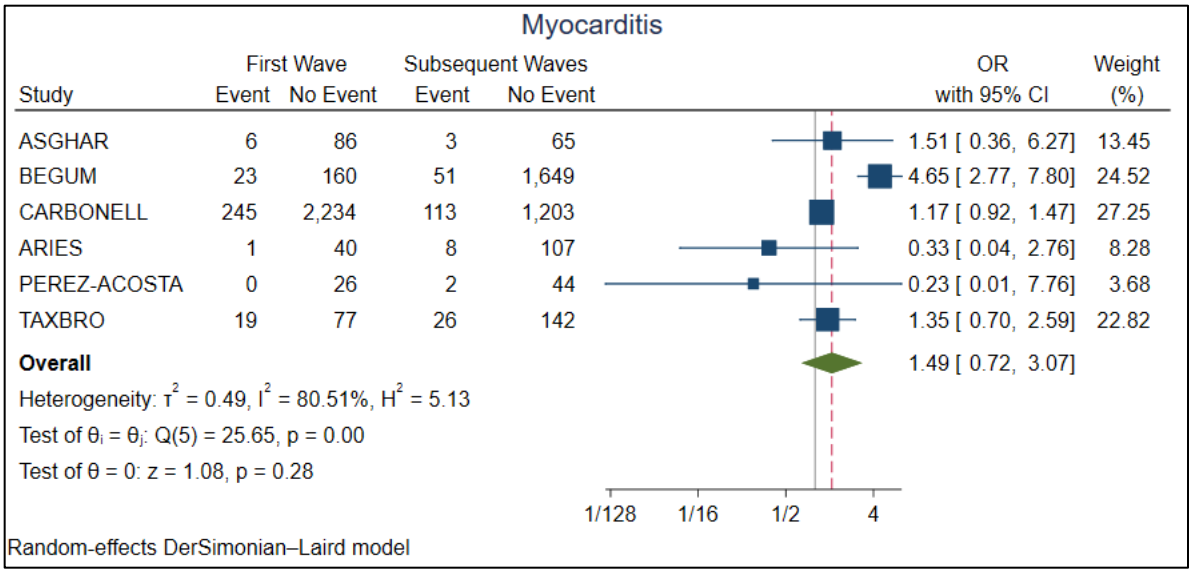
Supplementary Figure 4. Forest plot for length of hospital stay.



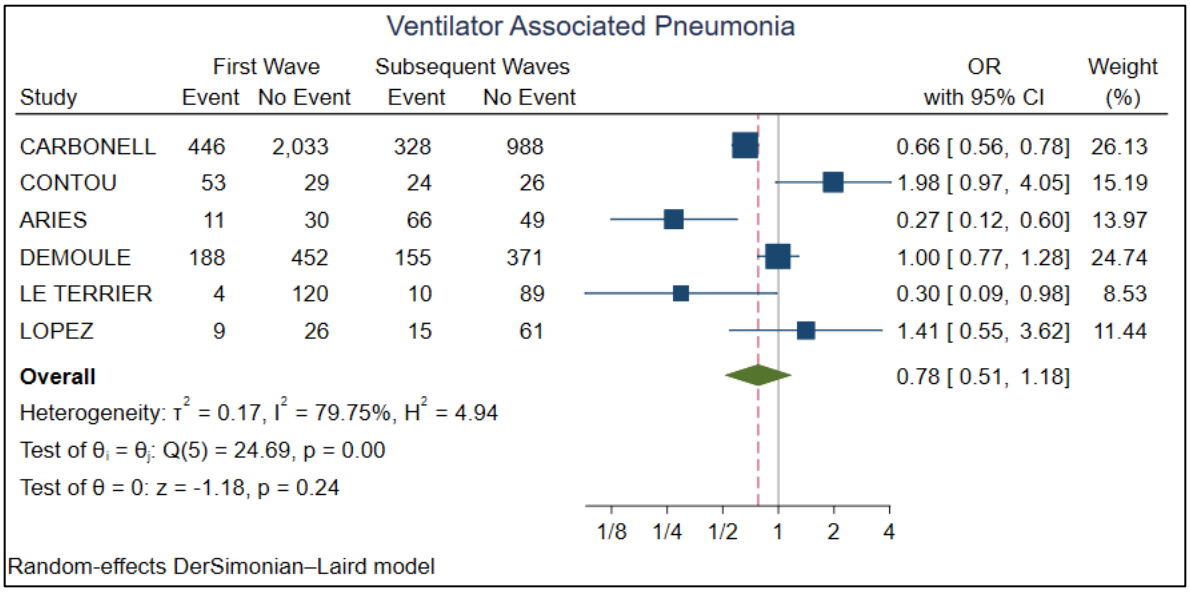
Supplementary Figure 5. Forest plot for systemic thromboembolism.



Supplementary Figure 6. Forest plot for myocarditis.



Supplementary Figure 7. Forest plot for ventilator associated pneumonia.



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