Supplementary information to:

Review article:

THE ASSOCIATION OF *ACE1*, *ACE2*, *TMPRSS2*, *IFITM3* AND *VDR* POLYMORPHISMS WITH COVID-19 SEVERITY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Zorana Dobrijević¹⁰, Dragana Robajac¹⁰, Nikola Gligorijević¹⁰, Miloš Šunderić¹⁰, Ana Penezić¹⁰, Goran Miljuš¹⁰, Olgica Nedić¹⁰

University of Belgrade – Institute for the Application of Nuclear Energy (INEP), Belgrade, Serbia

* Corresponding author: Zorana Dobrijević, Department for Metabolism, Institute for the Application of Nuclear Energy (INEP), University of Belgrade, Belgrade, Serbia Tel: +381 11 2618 666, E-mail: <u>zorana.dobrijevic@inep.co.rs</u>

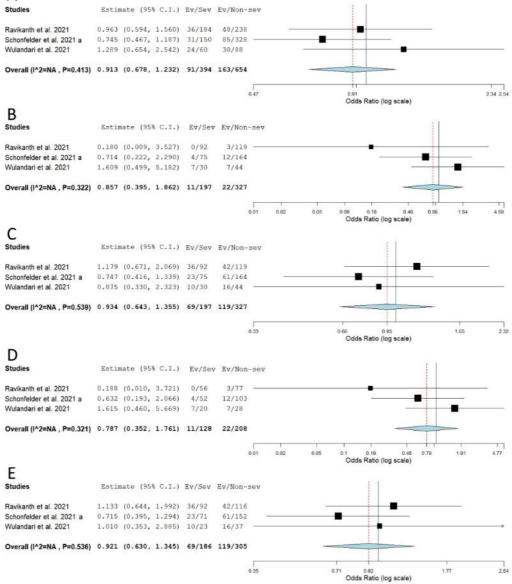
https://dx.doi.org/10.17179/excli2022-4976

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<u>http://creativecommons.org/licenses/by/4.0/</u>).

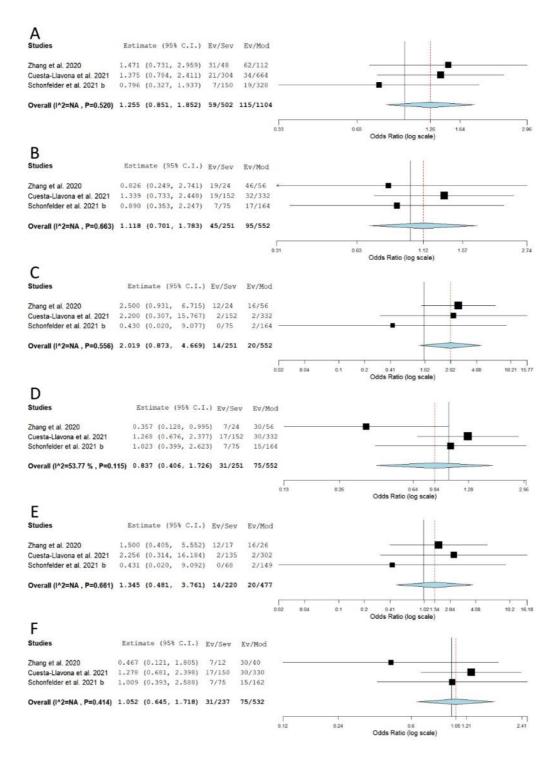
Studies	Estima	ate (95%	C.I.)	Ev/Sev	Ev/Non-sev								
Aladag et al. 2021	1.484 ((0.625,	3,5191	10/24	65/200					_			
		1			106/238	_							
Gunal et al. 2021		(0.408,		20/60	22/60				-				
Mohlendick et al. 2021	0.994 ((0.698,	1.415)	78/180	180/414								
Saad et al. 2021	0.625 ((0.399,	0.978)	36/122	130/324		-	-	-				
Overall (I^2=NA , P=0.373)	0.856 ((0.683,	1.072)	171/456	503/1236			-	-				
В						0.4		0.8	Odds Ratio	(log scale)	2		3.6
Studies	Estin	mate (9	5% C.I.)	Ev/Sev	Ev/Non-se	₽V							
Aladag et al. 2021	3.772	(0.786,	18.111)	10/12	57/100			-		-	<u>.</u>		
Karakas Celik et al. 2021	0.600	(0.274,	1.315)	21/35	85/119	-		-					
Gunal et al. 2021			1.624)	11/30	15/30	-							
Mohlendick et al. 2021			1,780)	59/90	133/207			_					
Saad et al. 2021	0.608	(0.335,	1.102)	31/61	102/162			-	_				
Overall (I^2=NA , P=0.158)	0.834	(0.606,	1.146)	132/220	8 392/618			\langle	٨				
С					0	1.21	0.41	0.83 1			13	10.32	18.1
Studies	Estim	ate (95	% C.I.)	Ev/Sev	Ev/Non-sev	7			Odds Ratio (log scale)			
Aladam et al. 2024	0.425	10.004	0.0101	0/10	0/1100				_				
Aladag et al. 2021 Karakas Celik et al. 2021			8.012) 2.618)	0/12	8/100 4								
Karakas Celik et al. 2021 Gunal et al. 2021			4.453)	6/35 9/30	21/119 7/30								
Gunal et al. 2021 Mohlendick et al. 2021			4.453)		47/207								
Saad et al. 2021			1.163)	5/61	28/162			-	-	-			
Overall (I^2=NA , P=0.573)	0.803	(0.530,	1.218)	39/228	111/618				V	4			
D					Г			- (1	i			- 1
D					0.0	4 0	0.08	0.2	0.39 Odds Ratio (I	0.79 og scale)	1.97	3.93	7.87
Studies	E	stimate	(95% C.	I.) Ev/Se	ev Ev/Non-	sev							
Aladag et al. 2021	5.2	04 (1.0	85, 24.9	64) 10/1	2 49/100	0					-		
Karakas Celik et al. 2021				79) 15/3				_	-	<u> </u>			
		96 (0.0	38 1 0										
Gunal et al. 2021			201 710	20) 2/3	0 8/30	-							
Mohlendick et al. 2021	0.1	26 (0.6	83, 1.8	54) 40/9	86/207			•	_				
Mohlendick et al. 2021	0.1	26 (0.6	83, 1.8		86/207	,		•	_	-			
Mohlendick et al. 2021 Saad et al. 2021	0.1 1.1 0.8	26 (0.6 83 (0.4	83, 1.8 88, 1.6	54) 40/9 00) 26/6	0 86/207 51 74/162	2			-				
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0	0.1 1.1 0.8	26 (0.6 83 (0.4	83, 1.8 88, 1.6	54) 40/9 00) 26/6	0 86/207 51 74/162	2	1	0.19	38 0.76	1.89	1 3.78	1 7.57	18.92
	0.1 1.1 0.8 049) 0.9	26 (0.6) 83 (0.4) 17 (0.5)	83, 1.8 88, 1.6 15, 1.6	54) 40/9 00) 26/6 34) 93/2	0 86/207 51 74/162	2 3 0.04	0.06	0.19	038 076 Odds Ratio		1 3.78	7.57	18.92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies	0.1 1.1 0.8 049) 0.9 Estim	26 (0.6) 83 (0.4) 17 (0.5)	83, 1.8 88, 1.6 15, 1.6 % C.I.)	54) 40/9 00) 26/6 34) 93/2	0 86/207 51 74/162 28 281/618	2 3 0.04	0.06	0.19 c			1 3.78	1 7.57	18.92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021	0.1 1.1 0.8 049) 0.9 Estim	26 (0.6 83 (0.4) 17 (0.5) nate (95 (0.045,	83, 1.8 88, 1.6 15, 1.6 % C.I.) 23.274)	54) 40/9 00) 26/6 34) 93/2 Ev/Sev	0 86/207 51 74/162 28 281/618 Ev/Non-sev	2 3 0.04	0.08	1 0.19 c			1 3.78	7.57	16.92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021	0.1 1.1: 0.8 0.9 0.9 Estim 1.024 (0.694 (26 (0.6 83 (0.4) 17 (0.5) nate (95 (0.045,	83, 1.8 88, 1.6 15, 1.6 % C.I.) 23.274) 2.085)	54) 40/9 00) 26/6 34) 93/2 Ev/Sev 0/2	0 86/207 51 74/162 28 281/618 Ev/Non-sev 8/51	2 3 0.04	0.06	0.19			1 3.78	1 7.57	16.92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Mohlendick et al. 2021	0.1 1.1: 0.8: 049) 0.9: Estim 1.024 (0.694 (1.015 (0.965 (26 (0.6) 83 (0.4) 17 (0.5) 17 (0.5) 10 (0.5) (0.045, (0.231, (0.307, (0.490,	83, 1.8 88, 1.6 15, 1.6 % C.I.) 23.274) 2.085) 3.361) 1.901)	54) 40/9 00) 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121	2 3 0.04	0.08	1 0.19 (3.78	7 57	18 92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Mohlendick et al. 2021	0.1 1.1: 0.8: 049) 0.9: Estim 1.024 (0.694 (1.015 (0.965 (26 (0.6 83 (0.4) 17 (0.5) nate (95 (0.045, (0.231, (0.307,	83, 1.8 88, 1.6 15, 1.6 % C.I.) 23.274) 2.085) 3.361) 1.901)	54) 40/9 00) 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22	2 3 0.04	1 0.08	0.19			3.78	1 7.57	16.92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021	0.1 1.1 0.8 649) 0.9 Estim 1.024 (0.694 (0.965 (0.357 (26 (0.6) 83 (0.4) 17 (0.5) mate (95 (0.045, (0.231, (0.307, (0.490, (0.125,	<pre>83, 1.8 88, 1.6 15, 1.6 % C.I.) 23.274) 2.085) 3.361) 1.901) 1.018)</pre>	54) 40/9 00) 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35	0 86/207 11 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88	2 3 0.04	0.06	0.19			3.78	7.57	18.92
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021	0.1 1.1 0.8 649) 0.9 Estim 1.024 (0.694 (0.965 (0.357 (26 (0.6) 83 (0.4) 17 (0.5) mate (95 (0.045, (0.231, (0.307, (0.490, (0.125,	<pre>83, 1.8 88, 1.6 15, 1.6 % C.I.) 23.274) 2.085) 3.361) 1.901) 1.018)</pre>	54) 40/9 00) 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35	0 86/207 11 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88	2 3 0.04	0.06	1 0.19 0 	Odds Ratio	(log scale)	1 3.78		,
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=NA , P=0.592) F	0.1 1.1: 0.8: 049) 0.9: Estim 1.024 (0.694 (1.015 (0.965 (0.357 (0.723 (26 (0.6) 83 (0.4) 17 (0.5) mate (95 (0.045, (0.231, (0.307, (0.307, (0.490, (0.125, (0.458,	<pre>83, 1.8 888, 1.6 15, 1.6 15, 1.6 14 C.I.) 23.274) 2.085) 3.361) 1.901) 1.018) 1.141)</pre>	54) 40/9 00) 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135	0 86/207 11 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88	7 2 3 0.04 7		-	Odds Ratio	(log scale)			,
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=NA , P=0.592) F Studies	0.1 1.1 0.8 Estim 1.024 (0.694 (1.015 (0.965 (0.357 (0.723 (26 (0.6) 83 (0.4) 17 (0.5) 17 (0.5) 10,045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate	<pre>83, 1.8 88, 1.6 15, 1.6 (% C.I.) 23.274) 2.085) 3.361) 1.901) 1.018) 1.141) (95% C.</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/Set 	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88 111/337 ev Ev/Non-	7 2 3 0.04 7		-	Odds Ratio	(log scale)			
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=NA , P=0.592) E Studies Aladag et al. 2021	0.1 1.1 0.8 Estim 1.024 (0.694 (1.015 (0.357 (0.357 (0.723 (E: 4.3)	26 (0.6) 83 (0.4) 17 (0.5) nate (95 (0.045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate 88 (0.9)	<pre>83, 1.8 88, 1.6 15, 1.6 15, 1.6 15, 1.6 15, 1.6 123.274) 2.085) 3.361) 1.901) 1.018) 1.141) (95% C. 11, 21.1</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/S 42) 10/1 	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88 111/337 ev Ev/Non- 2 49/92	7 2 3 0.04 7		-	Odds Ratio	(log scale)			
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=NA , P=0.592) E Studies Aladag et al. 2021 Karakas Celik et al. 2021	0.1 1.1 0.8 Estim 1.024 (0.694 (1.015 (0.965 (0.357 (0.723 (E. 4.3 0.5	26 (0.6) 83 (0.4) 17 (0.5) nate (95 (0.045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate 88 (0.9) 69 (0.2)	<pre>83, 1.8 88, 1.6 15, 1.6 15, 1.6 15, 1.6 15, 1.6 123.274) 2.085) 3.361) 1.901) 1.901) 1.141) (95% C. 11, 21.1 46, 1.3</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/St 12,10/1 17) 15/2 	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88 111/337 ev Ev/Non- 2 49/92 9 64/98	7 2 3 0.04 7		-	Odds Ratio	(log scale)			
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Saad et al. 2021 Overall (I^2=NA , P=0.592) E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021	0.1 1.1 0.8 Estim 1.024 (0.694 (1.015 (0.965 (0.357 (0.723 (Estim 1.035 (0.723 (0	26 (0.6) 83 (0.4) 17 (0.5) 17 (0.5) 10,045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate 88 (0.9) 69 (0.2) 97 (0.0)	<pre>83, 1.8 83, 1.8 888, 1.6 15, 1.6 (% C.I.) 23.274) 2.085) 3.361) 1.901) 1.018) 1.141) (95% C. 11, 21.1 46, 1.3 36, 1.0</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/St 12,10/1 17) 15/2 	0 86/201 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88 111/337 ev Ev/Non- 2 49/92 9 64/98 1 8/23	7 2 3 0 005 5 5 8 7		-	Odds Ratio	(log scale)			
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Saad et al. 2021 Overall (I^2=NA , P=0.592)	0.11 1.11 0.83 Estim 1.024 (0.694 (1.015 (0.357 (0.357 (0.723 (E: 4.33 0.55 0.11 1.11	26 (0.6 83 (0.4 17 (0.5 17 (0.5 (0.045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate 88 (0.9, 69 (0.2) 99 (0.2) 99 (0.2)	<pre>83, 1.8 83, 1.8 888, 1.6 15, 1.6 15, 1.6 14, 0.1 23.274) 2.085) 3.361) 1.901) 1.018) 1.141) (95% C. 11, 21.1 46, 1.3 36, 1.0 33, 1.9</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/Si 42) 10/1 17) 15/2 71) 2/2 	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/68 111/337 ev Ev/Non- 2 49/92 9 64/98 1 86/160 1 86/160	0004 0004		-	Odds Ratio	(log scale)			,
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Overall (I^2=NA , P=0.592) F Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Mohlendick et al. 2021 Saad et al. 2021	0.11 1.11 0.89 Estim 1.024 (0.694 (1.015 (0.965 (0.965 (0.357 (0.723 (Estim 1.015 (0.965 (0.923 (0.723 (0.711 (0.911 (26 (0.6) 83 (0.4) 17 (0.5) 17 (0.5) 17 (0.5) (0.045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate 88 (0.9) 69 (0.2) 97 (0.0) 10 (0.6) 03 (0.3)	<pre>83, 1.8 83, 1.8 888, 1.6 15, 1.6 15, 1.6 15, 1.6 15, 1.6 1,2085) 3.361) 1.901) 1.901) 1.141) (95% C. 11, 21.1 46, 1.3 36, 1.0 33, 1.9 76, 1.3</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/Si 42) 10/1 17) 15/2 71) 2/2 49) 40/7 14) 26/5 	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88 111/337 ev Ev/Non- 2 49/92 9 64/98 1 8/23 1 86/160 6 74/134	, 2 3 004 , 005 		-	Odds Ratio	(log scale)			,
Mohlendick et al. 2021 Saad et al. 2021 Overall (I^2=58.05 % , P=0.0 E Studies Aladag et al. 2021 Karakas Celik et al. 2021 Gunal et al. 2021 Overall (I^2=NA , P=0.592) F Studies Aladag et al. 2021 Karakas Celik et al. 2021 Mohlendick et al. 2021 Mohlendick et al. 2021	0.11 1.11 0.89 Estim 1.024 (0.694 (1.015 (0.965 (0.965 (0.357 (0.723 (Estim 1.015 (0.965 (0.923 (0.723 (0.711 (0.911 (26 (0.6) 83 (0.4) 17 (0.5) 17 (0.5) 17 (0.5) (0.045, (0.231, (0.307, (0.490, (0.125, (0.458, stimate 88 (0.9) 69 (0.2) 97 (0.0) 10 (0.6) 03 (0.3)	<pre>83, 1.8 83, 1.8 888, 1.6 15, 1.6 15, 1.6 15, 1.6 15, 1.6 1,2085) 3.361) 1.901) 1.901) 1.141) (95% C. 11, 21.1 46, 1.3 36, 1.0 33, 1.9 76, 1.3</pre>	 54) 40/9 26/6 34) 93/2 Ev/Sev 0/2 6/20 9/28 19/50 5/35 39/135 I.) Ev/Si 42) 10/1 17) 15/2 71) 2/2 49) 40/7 14) 26/5 	0 86/207 1 74/162 28 281/618 Ev/Non-sev 8/51 21/55 7/22 47/121 28/88 111/337 ev Ev/Non- 2 49/92 9 64/98 1 8/23 1 86/160 6 74/134	, 2 3 004 , 005 		023	Odds Ratio	(log scale)			16.92 , 8.4

Supplementary Figure 1: Meta-analysis of the association between rs1799752 in *ACE1* and COVID-19 severity: comparison severe vs. non-severe. A) allelic model; B) dominant model; C) recessive model; D) overdominant model; E) II vs. DD; F) DI vs. DD. The results of the included studies presented as ORs, with 95 CI, and the overall effect with 95 % CI are shown in the forest plot. *P* values given are derived from heterogeneity tests.

А



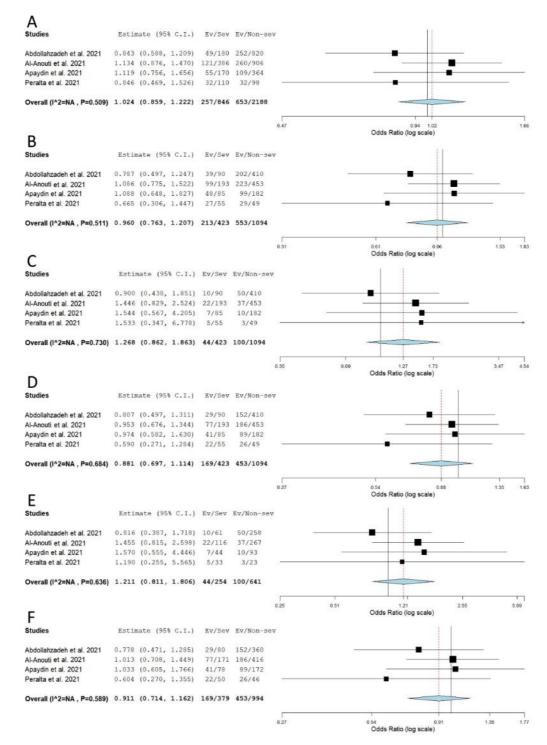
Supplementary Figure 2: Meta-analysis of the association between rs12329760 in *TMPRSS2* and COVID-19 severity, after the exclusion of asymptomatic SARS-CoV-2 infected participants: comparison severe vs. non-severe. **A**) allelic model; **B**) recessive model; **C**) overdominant model; **D**) AA vs. GG; **E**) GA vs. GG. The results of the included studies presented as ORs, with 95 % CI, and the overall effect with 95 % CI are shown in the forest plot. *P* values given are derived from heterogeneity tests.



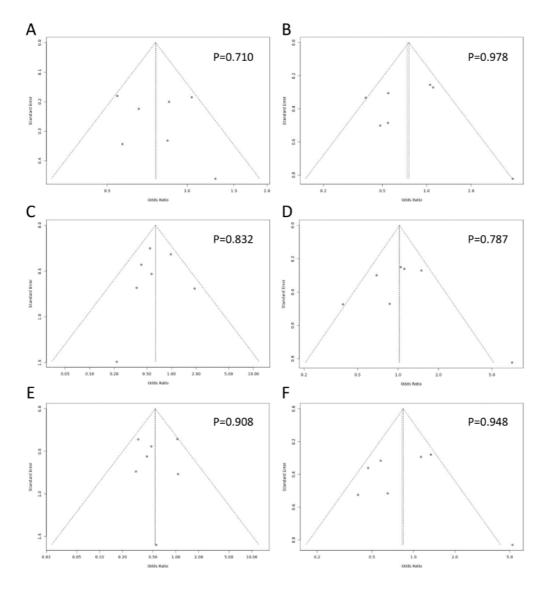
Supplementary Figure 3: Meta-analysis of the association between rs12252 in *IFITM3* and COVID-19 severity: comparison severe vs. moderate. A) allelic model; B) dominant model; C) recessive model; D) overdominant model; E) CC vs. TT; F) TC vs. TT. The results of the included studies presented as ORs, with 95 % CI, and the overall effect with 95 % CI are shown in the forest plot. *P* values given are derived from heterogeneity tests.

A Estimate (95% C.I.) Ev/Sev Ev/Non-sev Abdollahzadeh et a 1.354 (0.976, 1.878) 78/180 296/820 1.067 (0.718, 1.586) 52/170 107/366 Apaydin et al. Kotur et al. 0,945 (0,424, 2,106) 12/34 41/112 n (1^2=NA , P=0.548) 1.199 (0.943, 1.525) 142/384 444/1298 Subgroup C 0.751 (0.512, 1.101) 39/386 118/906 Subgroup Mixed (I^2=NA , P=NA) 0.751 (0.512, 1.101) 39/386 118/906 Overall (I^2=NA , P=0.149) 1.044 (0.853, 1.278) 181/770 562/2204 0.42 2.11 В Odds Ratio (log scale Studies Estimate (95% C.I.) Ev/Sev Ev/Non-sev 1.431 (0.885, 2.313) 60/90 239/410 Abdollahzadeh et al Apaydin et al. 1.167 (0.697, 1.954) 0.996 (0.330, 3.000) 92/183 33/56 46/85 . 10/17 Kotur et al Subgroup Caucasian (I^2=NA , P=0.768) 1.272 (0.911, 1.776) 116/192 364/649 0.803 (0.529, 1.217) 38/193 106/453 Al-Anouti Subgroup Mixed (I^2=NA , P=NA) 0.803 (0.529, 1.217) 38/193 106/453 Overall (I^2=NA . P=0.339) 1.060 (0.820, 1.371) 154/385 470/1102 0.33 0.66 1.65 C Odds Ratio (log sca Estimate (95% C.I.) Ev/Sev Ev/Non-set Abdollabzadeh et al 1.548 (0.860, 2.786) 18/90 57/410 0.851 (0.318, 2.275) Apaydin et al. 6/85 15/183 Kotur et al. 0.800 (0.153, 4.184) 2/17 8/56 casian (I^2=NA , P=0.502) Subgroup Ca 1.246 (0.770, 2.015) 26/192 80/649 AL-Anout 0.191 (0.025, 1.482) 1/193 12/453 Subgroup Mixed (I^2=NA , P=NA) 0.191 (0.025, 1.482) 1/193 12/453 Overall (I^2=NA , P=0.198) 1.035 (0.655, 1.637) 27/385 92/1102 4. 0.0 1.04 2.47 D Odds Ratio (log scale) Estimate (95% C.I.) Ev/Sev Ev/Non-sev Studies 1.096 (0.694, 1.732) 42/90 182/410 zadeh et al Apaydin et al. 1.224 (0.730, 2.053) 1.102 (0.371, 3.273) 40/85 77/183 Kotur et al 8/17 25/56 Subgroup Caucasian (I^2=NA , P=0.950) 1.146 (0.826, 1.589) 90/192 284/649 0.906 (0.593, 1.385) 37/193 Al-Anouti 94/453 Subgroup Mixed (I^2=NA , P=NA) 0.906 (0.593, 1.385) 37/193 94/453 Overall (I^2=NA , P=0.839) 1.049 (0.810, 1.358) 127/385 378/1102 0.5 2.23 E Odds Ratio (log scale) Studies Estimate (95% C.I.) Ev/Sev Ev/Non-set Abdoliahzadeh et al 1.800 (0.933, 3.471) 18/48 57/228 0.933 (0.337, 2.584) Apaydin et al. 6/45 15/106 Kotur et al. 0.821 (0.141, 4.800) 2/9 8/31 Subgroup Caucasian (I^2=NA , P=0.467) 1.388 (0.823, 2.339) 26/102 80/365 Al-Anout 0.187 (0.024, 1.447) 1/156 12/359 Subgroup Mixed (I^2=NA , P=NA) 0.187 (0.024, 1.447) 1/156 12/359 Overall (I^2=NA , P=0.155) 1.100 (0.675, 1.794) 27/258 92/724 4.8 F 0.04 2.4 Odds Ratio (log scale) Estimate (95% C.I.) Ev/Sev Ev/Non-sev Studie Abdollahzadeh et al 1,315 (0,788, 2,197) 42/72 182/353 1.212 (0.710, 2.070) Apaydin et al. 40/79 77/168 Kotur et al. 1.051 (0.329, 3.360) 8/15 25/48 roup Caucasian (I^2=NA , P=0.935) 1.244 (0.874, 1.770) 90/166 284/569 Subg Al-Anouti 0.881 (0.576, 1.348) 37/192 94/441 Subgroup Mixed (I^2=NA , P=NA) 0.881 (0.576, 1.348) 37/192 94/441 Overall (I^2=NA , P=0.653) 1.080 (0.825, 1.413) 127/358 378/1010 0.4 0.79 1.06 Odds Ratio (log scale) 1.98 2.95

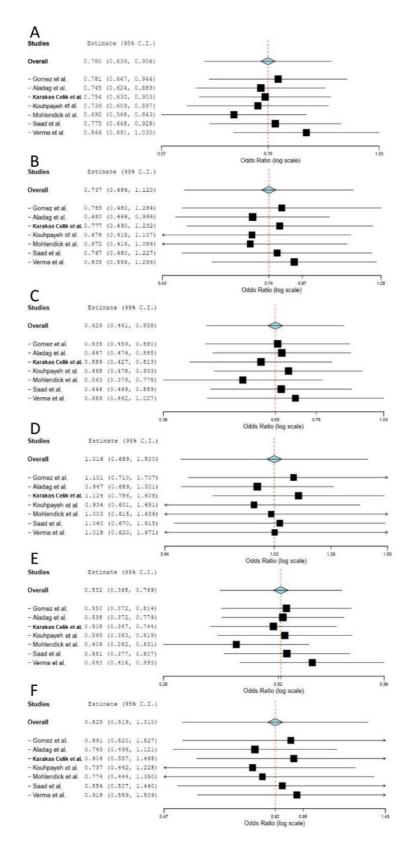
Supplementary Figure 4: Meta-analysis of the association between rs2228570 in *VDR* and COVID-19 severity: comparison severe vs. non-severe. **A**) allelic model; **B**) dominant model; **C**) recessive model; **D**) overdominant model; **E**) AA vs. GG; **F**) GA vs. GG. The results of the included studies presented as ORs, with 95 % CI, and the overall effect with 95 % CI are shown in the forest plot. *P* values given are derived from heterogeneity tests.



Supplementary Figure 5: Meta-analysis of the association between rs731236 in *VDR* and COVID-19 severity: comparison severe vs. non-severe. **A**) allelic model; **B**) dominant model; **C**) recessive model; **D**) overdominant model; **E**) GG vs. AA; **F**) AG vs. AA. The results of the included studies presented as ORs, with 95 % CI, and the overall effect with 95 % CI are shown in the forest plot. *P* values given are derived from heterogeneity tests.



Supplementary Figure 6: Funnel plots for meta-analyses of the association between rs1799752 in *ACE1* and COVID-19 severity: comparison severe vs. moderate. **A**) allelic model; **B**) dominant model; **C**) recessive model; **D**) overdominant model; **E**) II vs. DD; **F**) DI vs. DD. *P* values presented are derived from Egger's tests.



Supplementary Figure 7: Forest plots representing the results of sensitivity testing by leave-one-out meta-analysis of the association between rs1799752 in *ACE1* and COVID-19 severity: comparison severe vs. moderate. **A**) allelic model; **B**) dominant model; **C**) recessive model; **D**) overdominant model; **E**) II vs. DD; **F**) DI vs. DD. ORs with their 95 % CIs were used as risk estimates.

Authors*	Year	Selection				Comparability Outcome)	Score
		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	
Gómez et al.	2020	*	*	*	*	*	*	*	*	8
Zhang et al.	2020	*	*	*	*	*	*	*	*	8
Abdollahzadeh et al.	2021	*	*	*			*	*	*	6
Akin et al.	2022	*	*	*	*	*	*	*	*	8
Aladag et al.	2021	*	*	*	*	*	*	*	*	8
Al-Anouti et al.	2021	*	*	*	*	**	*	*	*	9
Alghamdi et al.	2021	*	*	*	*	**	*	*	*	9
Apaydin et al.	2021	*	*	*	*	*	*	*	*	8
Cafiero et al.	2021	*	*	*	*	*	*	*	*	8
Cuesta-Llavona et al.	2021	*	*	*	*		*	*	*	7
Gómez et al.	2021	*	*	*	*	**	*	*	*	9
Gunal et al.	2021	*	*	*	*		*	*	*	7
Hubacek et al.	2021	*	*	*	*		*	*	*	7
Íñiguez et al.	2021	*	*	*	*	**	*	*	*	9
Karakaş Çelik et al.	2021	*	*	*	*		*	*	*	7
Kotur et al. (adults)	2021	*	*	*	*	**	*	*	*	9
Kouhpayeh et al.	2021	*	*	*	*	**	*	*	*	9
Mir et al.	2021	*	*	*	*		*	*	*	7
Möhlendick et al.	2021	*	*	*	*		*	*	*	7
Monticelli et al.	2021	*	*	*			*	*	*	6
Peralta et al.	2021	*	*	*	*		*	*	*	7
Ravikanth et al.	2021	*	*	*	*	**	*	*	*	9
Saad et al.	2021	*	*	*	*	**	*	*	*	9
Schönfelder et al.	2021a	*	*	*	*		*	*	*	7
Schönfelder et al.	2021b	*	*	*	*		*	*	*	7
Verma et al.	2021	*	*	*	*	**	*	*	*	9
Wulandari et al.	2021	*	*	*	*		*	*	*	7
Akbari et al.	2022	*	*	*	*	**	*	*	*	9
Akin et al.	2022	*	*	*	*	*	*	*	*	8
Wang et al.	2022	*	*	*	*		*	*	*	7

Supplementary Table 1: Newcastle-Ottawa scale quality assessment of the studies included in the qualitative synthesis

* References see main document