## 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

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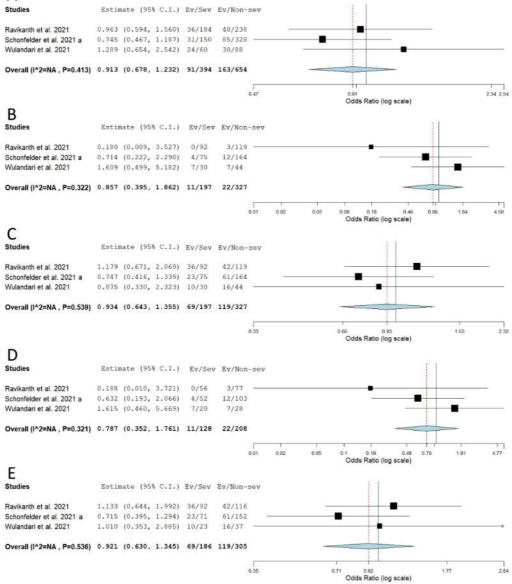
https://dx.doi.org/10.17179/excli2022-4976

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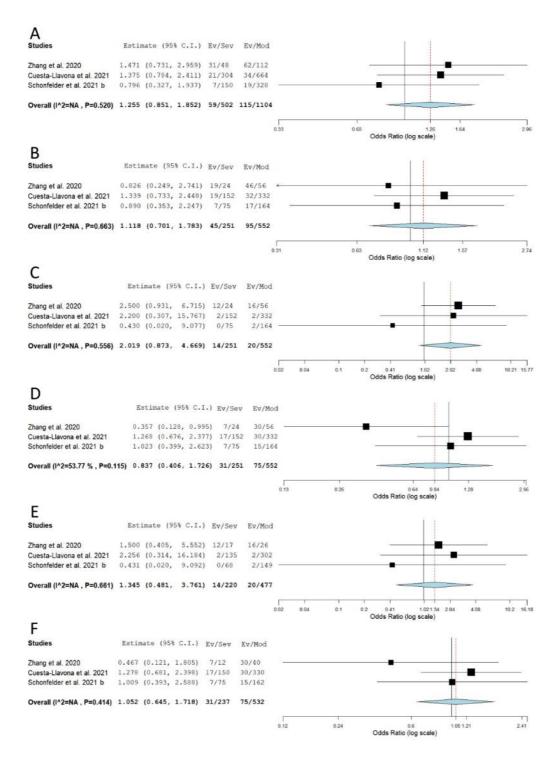
Studies	Estima	ate (95%	C.I.)	Ev/Sev	Ev/Non-sev								
Aladag et al. 2021	1.484 (	(0.625,	3,5191	10/24	65/200					_			
		1			106/238	_							
Gunal et al. 2021		(0.408,		20/60	22/60				-				
Mohlendick et al. 2021	0.994 (	(0.698,	1.415)	78/180	180/414								
Saad et al. 2021	0.625 (	(0.399,	0.978)	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			
<b>D</b>					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) <b>17 (0.5</b> ) 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) <b>17 (0.5</b> ) 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>	<ul> <li>54) 40/9</li> <li>26/6</li> <li>34) 93/2</li> <li>Ev/Sev</li> <li>0/2</li> <li>6/20</li> <li>9/28</li> <li>19/50</li> <li>5/35</li> <li>39/135</li> <li>I.) Ev/Set</li> </ul>	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)			
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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>	<ul> <li>54) 40/9</li> <li>26/6</li> <li>34) 93/2</li> <li>Ev/Sev</li> <li>0/2</li> <li>6/20</li> <li>9/28</li> <li>19/50</li> <li>5/35</li> <li>39/135</li> <li>I.) Ev/St</li> <li>12,10/1</li> <li>17) 15/2</li> </ul>	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)			
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**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.

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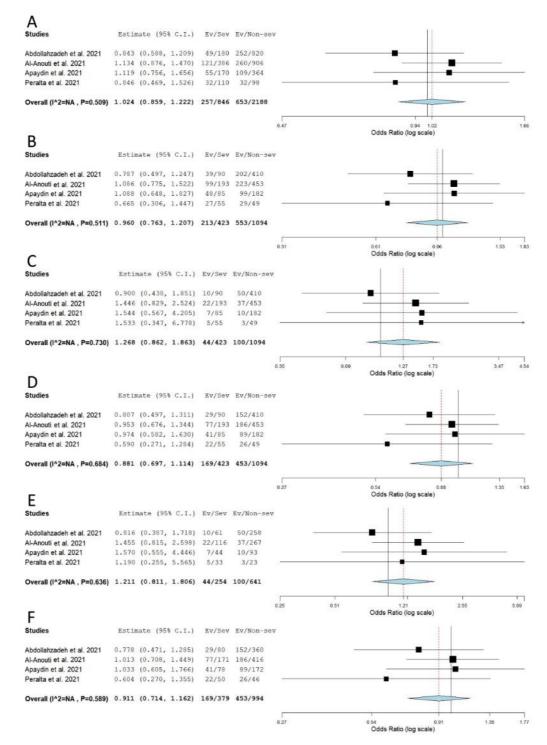
**Supplementary Figure 2:** Meta-analysis of the association between rs12329760 in *TMPRSS2* and COVID-19 severity, after the exclusion of asymptomatic SARS-CoV-2 infected participants: comparison severe vs. non-severe. **A**) allelic model; **B**) recessive model; **C**) overdominant model; **D**) AA 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.



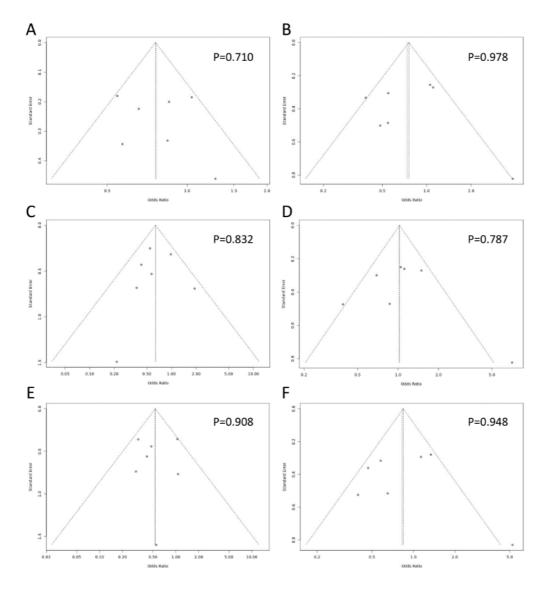
**Supplementary Figure 3:** Meta-analysis of the association between rs12252 in *IFITM3* and COVID-19 severity: comparison severe vs. moderate. A) allelic model; B) dominant model; C) recessive model; D) overdominant model; E) CC vs. TT; F) TC vs. TT. The results of the included studies presented as 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

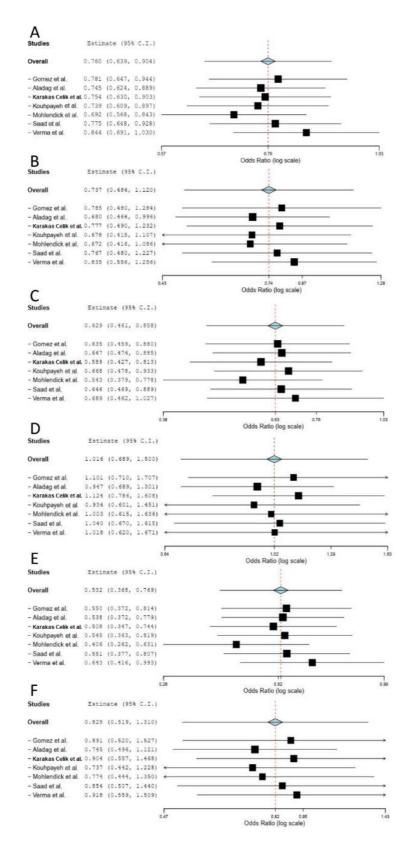
**Supplementary Figure 4:** Meta-analysis of the association between rs2228570 in *VDR* and COVID-19 severity: comparison severe vs. non-severe. **A**) allelic model; **B**) dominant model; **C**) recessive model; **D**) overdominant model; **E**) AA vs. GG; **F**) GA vs. GG. The results of the included 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