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Letter to the Editor

Regdanvimab improves disease mortality and morbidity in patients with COVID-19: Too optimistic and too early to say?

Dear Editor,

Α

We have read with great interest the recently published metaanalysis by Yang, M. et al.¹ in the *Journal of Infection* on the topic of regdanvimab use in COVID-19 patients. The authors included 7 studies in their meta-analysis and concluded that regdanvimab administration significantly reduced COVID-19 mortality and risk of disease progression according to a composite outcome. This publication is of particular interest and significance as it is currently the only meta-analysis published on the topic, however some of the authors' presented results and conclusions may potentially be misleading.

In the original meta-analysis (recreated on Fig. 1A) the authors included 4 studies in their mortality outcome analysis and concluded that regdanvimab use was associated with statistically significant lower mortality (OR = 0.14, 95% CI: 0.03 to 0.56, P = 0.006; I2 = 0%). In the meta-analysis, the study by Park, S. et al.² with a weight of 75.5% and an OR of 0.04 (95% CI: 0.00 to 0.64) contributed disproportionately more to the pooled result in comparison to other included studies. The Park, S. et al.² study was an observational retrospective study which explored outcomes of 377 regdanvimab treated patients and 520 standard of care com-

trols in an overall primary cohort from which a propensity score matched cohort of 754 patients, 377 in each group, was created and analysed. In their meta-analysis, Yang, M. et al.¹ included the outcomes from the unmatched primary cohort, instead of the PSmatched cohort, which in our opinion was incorrect due to statistically significant differences between the two unmatched groups, as reported by Park, S. et al.², which favoured the treatment group. Patients in the control group: 1) were older (median age 65 [IQR, 57–75] vs. 61 [53–68] years, *P* < 0.001), 2) had a higher proportion of moderate COVID-19 pneumonia (54.1% vs. 45.9%, P = 0.049), 3) chronic lung disease (78.9% vs. 21.1%, P = 0.007) and 4) cardiovascular disease (73.9% vs. 26.1%, P < 0.001), which were all accounted for and no longer statistically significant in the PSmatched cohort. Thus, the decision to include the outcomes of the unmatched cohort seems inappropriate and presents a significant potential source of bias in the meta-analysis, especially when considering the significant weight of the Park, S. et al^2 study. In order to eliminate the source of bias, we recreated the metaanalysis using the outcomes from the PS-matched cohort, Fig. 1B (OR = 0.49, 95% CI: 0.10 to 2.28, P = 0.38; I2 = 0%) and we also excluded the Park, S. et al.² study altogether due to the zero event rate, Fig. 1C (OR = 0.44, 95% CI: 0.08 to 2.53, P = 0.38; I2 = 0%) and we found no statistically significant impact of regdanvimab on COVID-19 mortality in either analysis. Moreover, we also recre-

A								
		etion/		ontrol		Odds Ra		Odds Ratio
	Events					MH, Fixed,		MH, Fixed, 95% CI
Choi 2022	0	65	5					
JY Lee 2021	0	234	1	544		0.77 [0.03;		
Park 2022	0	377	17					
S Lee 2022	0	113	2	161	10.6%	0.28 [0.01;	5.91]	
Total (95% CI) Prediction inte	0	789	25	1558	100.0%	0.14 [0.03; [0.01; 5		
Heterogeneity: Ta			70 # -	0 /D - /	a 401, 12 -		.99]	
Test for overall e					J.43); I [_] =	0%		0.01 0.1 1 10 100
rescior overall e	11ect. Z -	-2.11 (- < 0.01)					0.01 0.1 1 10 100
в								
	Interv	etion	C	ontrol		Odds Ra	atio	Odds Ratio
Study	Events	Total	Events	Total	Weight	MH, Fixed,	95% CI	MH, Fixed, 95% CI
Choi 2022	0	65	5	333	34.3%	0.46 [0.02;	8.35]	<u>_</u>
JY Lee 2021	0	234	1	544	17.2%	0.77 [0.03;	19.03]	
Park 2022	0	377	0		9.5%	1.00 [0.02;	50.53]	
S Lee 2022	0	113	2	161	39.1%	0.28 [0.01;	5.91]	
Total (95% CI)	0	789	8	1415	100.0%	0.49 [0.10;	2.381	
Prediction inte	rval					[0.02: 17		
Heterogeneity: Ta		$chi^2 = 0$	33 df =	3 (P = ($(95) \cdot 1^2 =$			
Test for overall e								0.1 0.51 2 10
С								
	Interv	etion	C	ontrol		Odds Ra	atio	Odds Ratio
Study	Events	Total	Events	Total	Weight	MH, Fixed,	95% CI	MH, Fixed, 95% CI
Choi 2022	0	65	5	333	37.8%	0.46 [0.02;	8.35]	- <u>-</u>
JY Lee 2021	0	234	1	544	19.0%	0.77 [0.03;	19.03]	— <u> </u>
S Lee 2022	0	113	2	161	43.2%	0.28 [0.01;	5.91]	
Total (95% CI)	0	412	8	1038	100.0%	0.44 [0.08;	2.53]	
Prediction inte Heterogeneity: Ta		$hi^2 = 0$	20 df -	2 (P - (0 00)· 1 ² -	[0.00; 405	44.40]	
Test for overall el					5.50),1 =	070		0.001 0.1 1 10 1000
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D	Inter	vetion	C	ontrol		Odds Ratio	Odds Ratio
Study	Events	Total	Events	Total	Weight	MH, Random, 95% CI	MH, Random, 95% Cl
Cercel 2022	8	203	9	104	14.9%	0.43 [0.16; 1.16]	
Choi 2022	4	65	67	333	14.2%	0.26 [0.09; 0.74]	
Hong 2022	20	256	31	251	19.5%	0.60 [0.33; 1.09]	- -
JY Lee 2021	5	234	52	544	15.5%	0.21 [0.08; 0.52]	
Kim 2022	12	89	9	63	15.5%	0.94 [0.37; 2.37]	
Park 2022	19	377	132	520	20.5%	0.16 [0.09; 0.26]	
Total (95% CI)	68	1224	300	1815	100.0%	0.35 [0.19; 0.65]	-
Prediction inte	erval					[0.05; 2.65]	
Heterogeneity: T					5 (P < 0.0	1); I ² = 74%	
Test for overall e	effect: Z =	-3.29 (P < 0.01)				0.1 0.5 1 2 10
E	Interv	vetion	C	ontrol		Odds Ratio	Odds Ratio
E Study					Weight	Odds Ratio MH, Random, 95% CI	Odds Ratio MH, Random, 95% CI
Study	Events	Total	Events	Total	14.4%	MH, Random, 95% CI	
Study Cercel 2022	Events 8	Total 203 65	Events 9	Total 104	14.4%	MH, Random, 95% CI 0.43 [0.16; 1.16] 0.26 [0.09; 0.74]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022	Events 8 4	Total 203 65	Events 9 67	Total 104 333 251	14.4% 13.5% 20.4%	MH, Random, 95% CI 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022 Hong 2022	Events 8 4 20	Total 203 65 256 234	Events 9 67 31	Total 104 333 251	14.4% 13.5% 20.4%	MH, Random, 95% CI 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022 Hong 2022 JY Lee 2021	Events 8 4 20 5	Total 203 65 256 234 89	Events 9 67 31 52	Total 104 333 251 544	14.4% 13.5% 20.4% 15.1%	MH, Random, 95% CI 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09] 0.21 [0.08; 0.52]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022 Hong 2022 JY Lee 2021 Kim 2022	Events 8 4 20 5 12	Total 203 65 256 234 89	Events 9 67 31 52 9	Total 104 333 251 544 63	14.4% 13.5% 20.4% 15.1% 15.1%	MH, Random, 95% Cl 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09] 0.21 [0.08; 0.52] 0.94 [0.37; 2.37]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022 Hong 2022 JY Lee 2021 Kim 2022	Events 8 4 20 5 12 19	Total 203 65 256 234 89	Events 9 67 31 52 9 81	Total 104 333 251 544 63 377	14.4% 13.5% 20.4% 15.1% 15.1%	MH, Random, 95% Cl 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09] 0.21 [0.08; 0.52] 0.94 [0.37; 2.37]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022 Hong 2022 JY Lee 2021 Kim 2022 Park 2022	Events 8 4 20 5 12 19 68	Total 203 65 256 234 89 377	Events 9 67 31 52 9 81	Total 104 333 251 544 63 377	14.4% 13.5% 20.4% 15.1% 15.1% 21.5%	MH, Random, 95% CI 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09] 0.21 [0.08; 0.52] 0.94 [0.37; 2.37] 0.19 [0.11; 0.33]	MH, Random, 95% CI
Study Cercel 2022 Choi 2022 Hong 2022 JY Lee 2021 Kim 2022 Park 2022 Total (95% CI)	Events 8 4 20 5 12 19 68 erval	Total 203 65 256 234 89 377 1224	Events 9 67 31 52 9 81 249	Total 104 333 251 544 63 377 1672	14.4% 13.5% 20.4% 15.1% 15.1% 21.5% 100.0%	MH, Random, 95% CI 0.43 [0.16; 1.16] 0.26 [0.09; 0.74] 0.60 [0.33; 1.09] 0.21 [0.08; 0.52] 0.94 [0.37; 2.37] 0.19 [0.11; 0.33] 0.37 [0.21; 0.63] [0.07; 1.96]	MH, Random, 95% CI

Fig. 1. Forest plots recreating the original meta-analysis results by Yang, M. et al.¹ regarding the mortality (Fig. 1A) and composite (Fig. 1D) outcomes. Reanalysis of the mortality (Fig. 1B) and composite (Fig. 1E) outcome meta-analysis using outcomes from the propensity score matched cohort from the Park, S. et al.² Mortality outcome meta-analysis (Fig. 1C) with the Park, S. et al.² study excluded due to a zero event rate.

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ated the composite outcome analysis, Fig. 1D and conducted an additional analysis with the PS-matched Park, S. et al.² cohort and

found no significant difference between the results. In conclusion, while it seems that regdanvimab may have a potential beneficial effect on COVID-19 patients based on the composite outcome, in our view, the conclusion made by Yang, M. et al.¹ that regdenvimab reduced patient mortality seems exaggerated. Finally, in all meta-analyses shown on Fig. 1, a considerable uncertainty of the results is perhaps best illustrated by the wide prediction intervals, which were present even in the original mortality outcome analysis by Yang, M. et al.¹, Fig. 1A. As the number of published studies remains small and with most current studies being retrospective in design, additional high quality, prospective, randomised trials exploring the potential beneficial effects of regdanvimab in COVID-19 patients are urgently needed.

Conflict of interest

No conflicts of interest to declare.

Authors' contributions

All authors participated equally in all parts of the manuscript.

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Data disclosure statement

All analysed data is presented in the manuscript.

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