Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Conceptual interpretation and clinical applicability of a systematic review and meta-analysis about prognostic value of apolipoproteins in COVID-19 patients

Dear Editor,

Prognostic value of Apolipoproteins in COVID-19 patients conducted by Ulloque-Badaracco and colleagues striked a great interest to us with its innovative research exploration and synthesising high-level evidence [1]. COVID-19 is a pan system disease with a manifold attack on vital organs and the research on covid19 continues to evolve. The key highlights of this systematic review and meta-analysis comprises the detailed documentation of association of apolipoproteins (A and B) with severity in hospitalized COVID-19 patients, however there are a few lacunae dampening its clinical applicability.

The authors conclude in their results "ApoB/ApoA1 ratio revealed no statistically significant association with higher odds of severity." It must be noted that the statistical significance of odds ratio is not adequate to be considered as an independent indicator for evaluating the pooled estimated effect size of meta-analysis, considering it is a binary interpretation [2]. Elaboration of pooled estimated effect size (here we refer Odds Ratio or Standard Mean Difference) provides additional clinical utility as it scrutinizes the validity of prognostic value or intervention in a wide variety of contexts [3] and enhance the results presented in the study. Merely 12 cohort studies offering a low range of statistical significance can make these results difficult to translate in the clinical setting.

Table 1
Publication bias indicators and Hypothesis Testing and Heterogeneity Testing analysis performed in Ulloque-Badaracco and colleagues's study.

		Publication Bias Indicators									
		Classic fail-safe N		Orwin fail-safe N	Begg and Mazumdar test			Dual and Tweedie (Random effects)			
	Groups	Z value	P-value	HR in observed	Tau	Z value	P-value	Observed	Q value	Adjusted	Q value
1	Association of ApoA1 and COVID-19 severity	−13.25	0.00	0.74	−0.44	1.79	0.07	0.35	128.69	0.35	128.69
2	Risk of Bias - Association between ApoA1 and severity in COVID-19 patients	−5.18	0.00	0.82	−0.83	1.70	0.09	0.82	1.18	0.82	1.18
3	Association of ApoB and COVID-19 Severity	−5.48	0.00	0.81	0.00	0.00	1.00	0.88	8.55	0.88	8.55
4	Association of ApoB/ApoA1 ratio and COVID-19 severity	2.17	0.03	1.03	−0.10	0.24	0.81	1.18	7.55	1.05	12.12
5	Association of ApoA1 ratio and COVID-19 mortality				0.67	1.04	0.30				
6	Association of ApoB and COVID-19 mortality	−2.00	0.05	0.69	−0.83	1.70	0.09	0.62	5.22	0.62	5.22

		Heterogeneity Testing and Hypothesis Testing															
					Fixed			Mixed/random			Hypothesis test						
	Group	**Heterogeneity**			**HR**	**95% CI**		**HR**	**95% CI**		**Fixed effects model**			**Random effects model**			
		Q	**P**	**I^2**		**Low**	**High**		**Low**	**High**	**Z**	**P**	**Studies**	**Z**	**P**	**Studies**
1	Association of ApoA1 and COVID-19 severitiy	128.69	0.00	93.01	0.74	0.70	0.79	0.35	0.24	0.49	−9.06	0.00	10	−5.98	0.00	10
2	Risk of Bias - Association between ApoA1 and severity in COVID-19 patients	1.18	0.76	0.00	0.82	0.76	0.87	0.82	0.76	0.87	−5.82	0.00	04	−5.82	0.00	04
3	Association of ApoB and COVID-19 Severity	8.55	0.38	6.44	0.81	0.75	0.88	0.79	0.71	0.87	−5.21	0.00	9	−4.64	0.00	09
4	Association of ApoB/ApoA1 ratio and COVID-19 severity	7.55	0.11	47.02	1.03	0.95	1.12	1.18	0.95	1.46	0.68	0.50	05	1.49	0.14	05
5	Association of ApoA1 ratio and COVID-19 mortality	1.22	0.55	0.00	0.34	0.21	0.57	0.34	0.21	0.57	−4.15	0.00	03	−4.15	0.00	03
6	Association of ApoB and COVID-19 mortality	5.22	0.16	42.53	0.69	0.43	1.10	0.62	0.32	1.22	−1.54	0.13	04	−1.38	0.17	04

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Mortality should be Hazard Ratio instead of Odds Ratio or Standard Mean Difference. We also noted that the authors fail to define the pooled estimated effect size to calculate the results of the prognostic value of apolipoproteins for COVID-19 severity and mortality. An odds ratio (OR) is a measure of association between an exposure and an outcome. The methodology of the study describes about "Standardized Mean Differences (SMD) that were converted to the natural logarithm of Odds Ratio". Standardized Mean Differences is ideal for comparison of RCT studies as it emphasises the variance in the effect of treatment and control [4]. However, prognostic value of any marker is generally assessed by the Hazard Ratio and the use of Hazard Ratio is considered as the preferred effect size metric of mortality, rather than Standard Mean Difference or Odds Ratio.

The inclusion of key publication bias indicators such as Orwin and Classic Fail-Safe N Test and Begg and Mazumdar Rank Correlation Test will elucidate the potential publication bias of the included studies due to small or missing studies (Table 1). These indicators are the regular parameters of "publication based meta-analysis" and is used for calculation of publication bias [5–7].

Replicating the aforementioned recommendations into the study can significantly improve its clinical feasibility and can be a template to future similar studies.

Declaration

Authors' contributions

R.J. predominantly conceived this review and led the development of the manuscript. MSR, SS, RS, SSS, SS, RRM. wrote the first draft of the letter, and all authors critically revised and edited successive drafts of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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