Clinical Validity and Conceptual Interpretation of Impact of alcohol consumption on COVID-19 severity

Rama Jayaraj[1], Sameep Shetty[2], Devi A[3], Suja S[4], and Yash Merchant[5]

[1]OP Jindal Global University
[2]Manipal Academy of Higher Education
[3]Valliammai Society
[4]Bharathiar University
[5]Dr D Y Patil Vidyapeeth University

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Rama Jayaraj [1]*, Sameep Shetty [2], A Devi[3], Suja S[4], Yash Merchant[5]

Author's affiliations

***Corresponding author**

1. Jindal Institute of Behavioral Sciences (JIBS), Jindal Global Institution of Eminence Deemed to be University, Sonipat 131001, India ; rama.jayaraj@jgu.edu.in and Director of Clinical Sciences, Northern Territory Institute of Research and Training, Darwin 0909, NT, Australia * Correspondence: Prof Rama Jayaraj, Email: jramamoorthi@gmail.com
2. Department of Oral and Maxillofacial Surgery, College of Dental Sciences Manipal, Manipal Academy of Higher Education, A Constituent of MAHE, Mangalore, 575001, India; sameep.shetty@manipal.edu
3. Department of Biotechnology, College of Engineering & Technology, Kattankulathur – Chennai, Tamil Nadu, India; devia@srmist.edu.in
4. Bharathiar Univ, Dept Biochem, Coimbatore, Tamil Nadu, India; suja.s@buc.edu.in
5. Dept Oral and Maxillofacial Surgery, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune, Maharashtra, Email:merchantyash@gmail.com

Excellent Clinical Research Approach and Adaptation of Systematic Review Guidelines and Registrations: It is with interest that we read the relevant systematic review and meta-analysis on the impact of alcohol consumption on severity of COVID-19 infection. We laud the efforts of the authors to contribute to this global research output and provide myth busting evidence on the contemporary issue. This study is of great clinical and timely relevance, also adhered the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Furthermore, it is also recommended that the Protocol OF A Systematic Review and Meta-Analysis be registered in the International Prospective Register of Systematic Reviews (PROSPERO) to identify any replication of the study and act as guide for other similar studies. We would like to take the opportunity to offer our perspective and constructive critique in their analysis.

Alcohol and confounding factors (tobacco in the smoked or smokeless form) : Patients partaking alcohol often smoke during drinking and alcohol as a solvent has a synergistic and additive deleterious effect.

It is recommended to note that in the subset of patients partaking alcohol whether confounding factors like other habits (tobacco in the smoked or smokeless form) and co-morbidities were taken into consideration.

Contradicting findings of another impact of alcohol consumption on COVID-19 severity: It is undisputed that moderate to heavy alcohol consumption impairs immunity and has no benefits during a pandemic or otherwise. However, a recent prospective study noted that COVID-19 risk appears to vary across different alcoholic beverage subtypes, frequency, and amount. Red wine, white wine, and champagne may reduce the risk of COVID-19 when consumed in moderation and occasionally[1].

Attempts to inform clinical decision making and Future directions: It is believed that the higher polyphenolic content of these beverages enhanced plasma antioxidant activity and reduces the level of low-density lipoprotein[2]. Authors of this study strongly proposed that people do not drink alcohol during the COVID-19 pandemic and attempts to inform clinical decision during this crisis. Public health guidance should focus on reducing the risk of COVID-19 by advocating healthy lifestyle habits and preferential policies among consumers of beer and cider and spirits.

Conceptual Interpretation of Conclusions from Literature-Based Meta-Analysis: We would like to recommend that conclusions by Wei and colleagues should better reflect the indecision of a literature based Systematic Review and Meta-Analysis. In this scenario, elaborating that "Alcohol consumption intensifies COVID-19 severity and deteriorates its clinical outcomes" should be potentially replaced by "alcohol consumption are likely associated with COVID-19 severity and may be or could be deteriorate its clinical outcomes."

Publication bias of the included studies: Publication bias is a corollary of the publication process. Small sample studies or negative findings often fail to get published. Abiding the PRISMA, authors have piloted the publication bias analysis using Egger's test for continuous variables but evaded other publication bias indicators in the manuscript or as supplementary material, which could derail peer-appraisal of the study (Figure 1). Therefore, a suggestion would be to inculcate Classic Fail-Safe N, Orwin Fail-Safe N, Duval and Begg and Mazumdar's rank correlation test in such studies for comprehensive analysis of publication bias indicators (Table 1).[3,4] Although this is the first systematic review and meta-analysis on Impact of alcohol consumption on COVID-19 severity, not assessing the full scale of publication bias leads to the findings being uncertain in term of actual clinical utility.

Comparison of Heterogeneity with Hypothesis testing: A robust statistical analysis can be interpreted with the addition of Tau- Square in addition to Chi-Square and I-Square static (measures of statistical heterogeneity). The authors have estimated the Z value, a test static for the null hypothesis and to obtain the *P*- value, but fail to compare the Heterogeneity with Hypothesis testing (Table 2). The ordered heterogeneity test, that permits testing against simply ordered alternative hypotheses in the context of almost any nondirectional test[5]. Therefore, we recommend comparing the results of all statistical syntheses including heterogeneity and hypothesis testing of the included study, conducted according to PRISMA.

We feel that above points should be addressed. Given the current relevance of this field to medical virology, it is important that this study that feeds it is free of any possible reproach when under scientific analysis.

Authors' Contributions

R.J. predominantly conceived this review and led the development of the manuscript. SSS, and YM 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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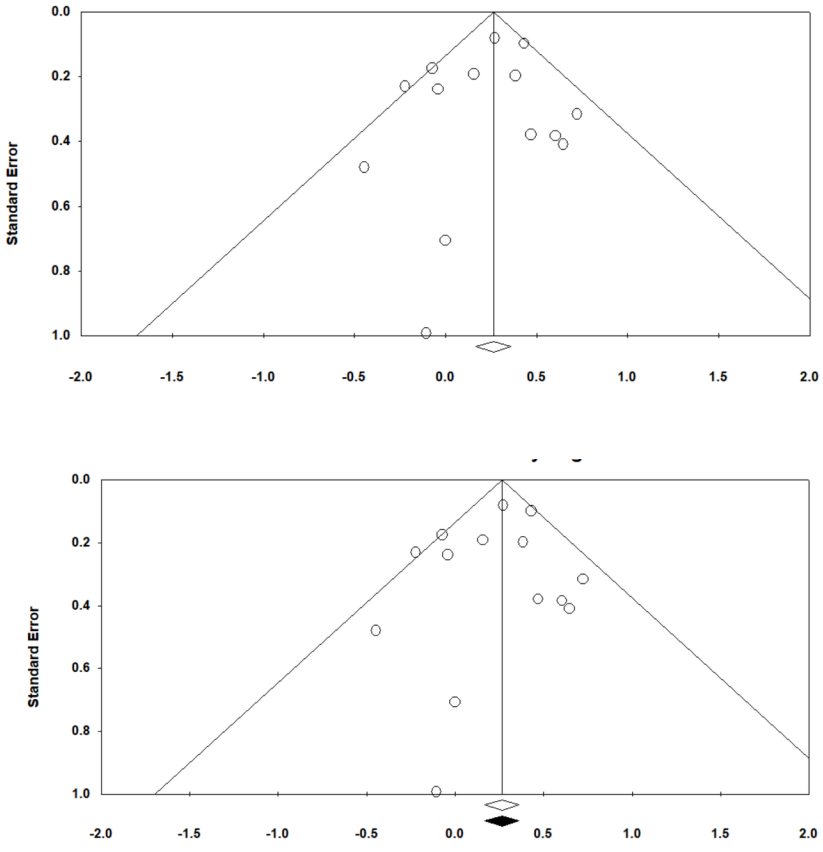

Figure 1. A. Funnel plot of observed studies ofImpact of alcohol consumption on COVID-19 severity.

Figure 1. A. Funnel plot of observed and imputed studies of Impact of alcohol consumption on COVID-19 severity.

Large studies appear toward the top of the graph and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph, and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values. In the absence of publication bias we would expect the studies to be distributed symmetrically about the combined effect size. By contrast, in the presence of bias, we would expect that the bottom of the plot would show a higher concentration of studies on one side of the mean than the other. This would reflect the fact that smaller studies (which appear toward the bottom) are more likely to be published if they have larger than average effects, which makes them more likely to meet the criterion for statistical significance. These figures represent unlikely or no bias between the included studies concerning Impact of alcohol consumption on COVID-19 severity. Each plot represents an individual cohort or study and this plot has been constructed using CMA software (Version 3.3.070) USA.

Heterogeneity testing and hypothesis testing

Subgroups	**Heterogeneity Q**	**Heterogeneity** P	**Heterogeneity I^2**	**Point estimate (Fixed)**	**95% CI Low**
Symptomatic COVID-19	3.989	0.136	49.891	1.3666	1.197
COVID-19 progression	2.764	0.251	27.649	1.502	0.841
COVID-19 Hospitalization	0.417	0.519	0	1.79	1.76
ICU admissions	7.405	0.192	32.477	1.395	1.221
IMV requirements	4.347	0.114	53.989	1.869	1.354
COVID-19 Mortality	12.542	0.324	12.295	0.923	0.82
COVID-19 Severity	19.906	0.098	34.692	1.3	1.181

Table 1: Heterogeneity testing and hypothesis testing of the included studies comparing impact of alcohol consumption and COVID19 severity.

Table 2: Publication based indicators of the included studies comparing impact of alcohol consumption and COVID19 severity.

Publication based indicators

Classic Fail-Safe N	**Classic Fail-Safe N**	**Orwin Fail-Safe N**	**Begg and Mazumdar Test**	**Begg and Mazumdar Test**	**Begg and Mazumdar Test**	**Begg and Mazumdar Test**	**Begg and Mazumdar Test**	**Begg and Mazumdar Test**	**Egger's regression intercept**	**Egger's regression intercept**	**Egger's regression intercept**	**Egger's regression intercept**	**Egger's regression intercept**	**Eg re gr si in te ce**
			Kendall Tau without continuity correction	**Kendall Tau with continuity correction**	**Kendall Tau without continuity correction**	**Kendall Tau with continuity correction**	**Kendall Tau with continuity correction**	**Kendall's Tau with continuity correction**						

Groups	Z value	P Value	Ratio in observed	Tau	Z value	P Value (1-tailed)	Tau	Z value	P Value (1-tailed)	Intercept	95% lower limit	95% upper limit	t-value	df	P-Va (1 ta
	3.89	0.0001	1.30	0.01	0.05	0.47	0.00	0.0000	0.50000	-0.39372	-1.67840	0.89096	0.66775	12.00000	0.2