Heliyon 10 (2024) e22746

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Can mild COVID-19 infection represent the entire Clinical Spectrum of COVID-19?

To the editor

I would like to share my views on the recent article titled “A systematic review of the effect of COVID-19 on semen parameters” authored by Xiucheng Lan and colleagues [1]. The study draws a conclusion that COVID-19 can lead to reduced semen quality and impaired male fertility. However, I believe there might be some inappropriate data handling in Lan’s analysis of Holtmann et al.’s research [2]. Lan [1] performed a meta-analysis, considering the “mild infections” as the representative COVID-19 group, which, in my opinion, could introduce biases. While mild cases may currently represent a significant proportion of COVID-19 cases due to ongoing mutations of SARS-CoV-2 and vaccination efforts, the physical changes observed in mild patients may not entirely represent the entire spectrum of COVID-19 patients. Moreover, the other four included studies did not explicitly specify that the COVID-19 group consisted solely of mild patients. In light of this, I combined Holtmann’s research data, which included both 14 mild and 4 moderate patients, to calculate the mean and standard deviation of male semen parameters, as illustrated in Fig. 1. Despite the smaller number of moderate patients in the merged group, I believe this approach is more reasonable than solely relying on the “mild group” as the COVID-19 group in the meta-analysis.

Additionally, I have identified several issues with the forest plots presented in Lan’s research:

1. In Fig. 2, the interquartile range (IQR) of the experimental and control groups from the study by Temiz [3] was mistakenly used as the standard deviation (SD), where the IQR is approximately 1.35 times the SD.
2. In Fig. 3, the SD of the control group from the study by Temiz [3] should be 147.25 ($\times 10^6$).
3. I have reservations about the SD calculations for the experimental and control groups from the study by Li [4] in Fig. 4.
4. In Fig. 5, the IQR of the experimental and control groups from the study by Temiz [3] was mistakenly used as the SD.

1. Revised meta-analysis results

1 To observe the impact of COVID-19 on semen volume (mL) in patients, the results indicate no heterogeneity among the four included studies ($I^2 = 0$ %, $P = 0.58$) [2,3,5,6]. The fixed effect model was utilized for the analysis, and the results showed that RR $= -0.18$ [-0.53, 0.16], $Z = 1.05$, $P = 0.29$, as shown in Fig. 2. These findings align with Lan’s conclusions [1].

2 Total sperm number ($\times 10^6$) , a critical indicator of male fertility, was also investigated.The results demonstrate no heterogeneity among the four included studies ($I^2 = 0$ %, $P = 0.42$) [2,3,5,6]. The fixed effect model was employed for the analysis, and the results showed that RR $= -46.39$ [-67.48, -25.30], $Z = 4.31$, $P < 0.0001$, as shown in Fig. 3. While the conclusion aligns with Lan’s findings, merging Holtmann study’s mild and moderate patients as the COVID-19 group eliminates heterogeneity among the studies, suggesting that this might have been a source of heterogeneity in Lan’s study [1].

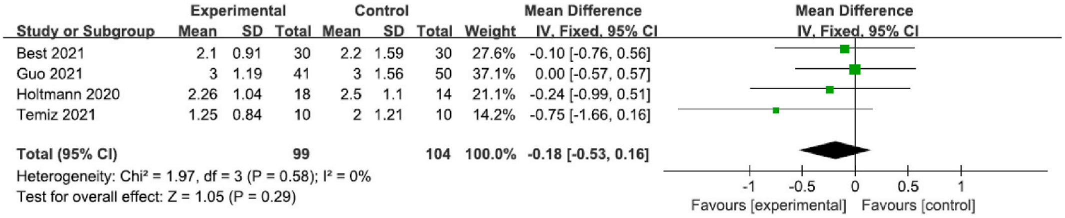
3 Sperm concentration ($\times 10^6$/mL), another parameter influenced by COVID-19, exhibited significant heterogeneity among the five included studies ($I^2 = 64$ %, $P = 0.02$) [2–6]. The fixed effect model was used for the analysis, and the results showed that RR $= -14.81$ [-22.15, -7.47], $Z = 3.95$, $P < 0.0001$, as shown in Fig. 4. The conclusion aligns with Lan’s findings, and merging Holtmann study’s mild and moderate infections as the COVID-19 group reduced heterogeneity among the studies, suggesting this might have been one of the sources of heterogeneity in Lan’s study, requiring further investigation into other sources of heterogeneity.

4 Progressive sperm motility (%) was found to be affected by COVID-19, exhibiting significant heterogeneity among the three included studies. ($I^2 = 70$ %, $P = 0.13$) [2,3,5]. The fixed effect model was used for the analysis, and the results showed that RR $= -3.79$ [-8.70, 1.11], $Z = 1.52$, $P = 0.13$, as shown in Fig. 5, which aligns with Lan’s findings. Subsequently, a sensitivity analysis reveals that Guo et al.’s study has the greatest impact on heterogeneity [5]. After excluding this study, the remaining two studies

https://doi.org/10.1016/j.heliyon.2023.e22746
Received 22 July 2023; Accepted 17 November 2023

	Combined groups
Sample size	$N_1 + N_2$
Mean	$\frac{N_1 M_1 + N_2 M_2}{N_1 + N_2}$
SD	$\sqrt{\frac{(N_1-1)\mathrm{SD}_1^2 + (N_2-1)\mathrm{SD}_2^2 + \frac{N_1 N_2}{N_1+N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1+N_2-1}}$

Fig. 1. The Mean and SD of combined groups.

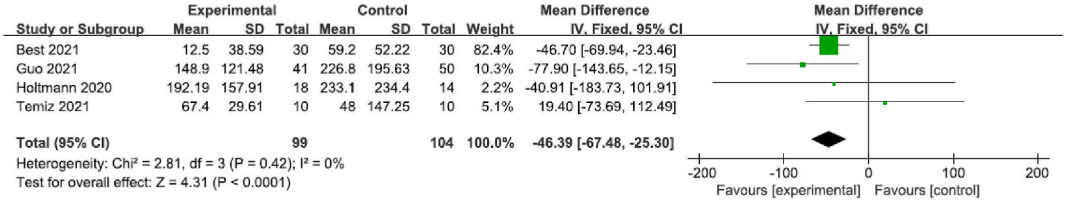


	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Best 2021	2.1	0.91	30	2.2	1.59	30	27.6%	-0.10 [-0.76, 0.56]
Guo 2021	3	1.19	41	3	1.56	50	37.1%	0.00 [-0.57, 0.57]
Holtmann 2020	2.26	1.04	18	2.5	1.1	14	21.1%	-0.24 [-0.99, 0.51]
Temiz 2021	1.25	0.84	10	2	1.21	10	14.2%	-0.75 [-1.66, 0.16]
Total (95% CI)			**99**			**104**	**100.0%**	**-0.18 [-0.53, 0.16]**

Heterogeneity: Chi² = 1.97, df = 3 (P = 0.58); I² = 0%

Test for overall effect: Z = 1.05 (P = 0.29)

Fig. 2. Forest plot of effects of COVID-19 on semen volume.

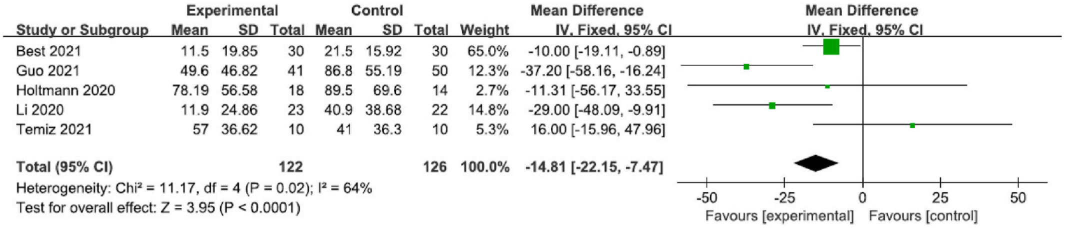


	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Best 2021	12.5	38.59	30	59.2	52.22	30	82.4%	-46.70 [-69.94, -23.46]
Guo 2021	148.9	121.48	41	226.8	195.63	50	10.3%	-77.90 [-143.65, -12.15]
Holtmann 2020	192.19	157.91	18	233.1	234.4	14	2.2%	-40.91 [-183.73, 101.91]
Temiz 2021	67.4	29.61	10	48	147.25	10	5.1%	19.40 [-73.69, 112.49]
Total (95% CI)			**99**			**104**	**100.0%**	**-46.39 [-67.48, -25.30]**

Heterogeneity: Chi² = 2.81, df = 3 (P = 0.42); I² = 0%

Test for overall effect: Z = 4.31 (P < 0.0001)

Fig. 3. Forest plot of effects of COVID-19 on total sperm number.



	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Best 2021	11.5	19.85	30	21.5	15.92	30	65.0%	-10.00 [-19.11, -0.89]
Guo 2021	49.6	46.82	41	86.8	55.19	50	12.3%	-37.20 [-58.16, -16.24]
Holtmann 2020	78.19	56.58	18	89.5	69.6	14	2.7%	-11.31 [-56.17, 33.55]
Li 2020	11.9	24.86	23	40.9	38.68	22	14.8%	-29.00 [-48.09, -9.91]
Temiz 2021	57	36.62	10	41	36.3	10	5.3%	16.00 [-15.96, 47.96]
Total (95% CI)			**122**			**126**	**100.0%**	**-14.81 [-22.15, -7.47]**

Heterogeneity: Chi² = 11.17, df = 4 (P = 0.02); I² = 64%

Test for overall effect: Z = 3.95 (P < 0.0001)

Fig. 4. Forest plot of effects of COVID-19 on sperm concentration.

showed no heterogeneity ($I^2 = 0$ %, P = 0.44), and the results showed that RR = 2.77 [-4.38, 9.92], Z = 0.76, P = 0.45, as shown in Fig. 6. The conclusion aligns with Lan's findings.

In conclusion, the above presents my personal views on this paper. I welcome constructive peer criticism and correction to enhance the understanding of this crucial research area.

Sincerely,

During the preparation of this work the author used ChatGPT in order to improve language and readability. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

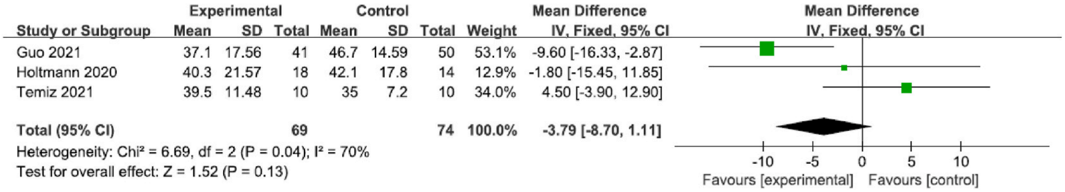


Fig. 5. Forest plot of effects of COVID-19 on progressive sperm motility.

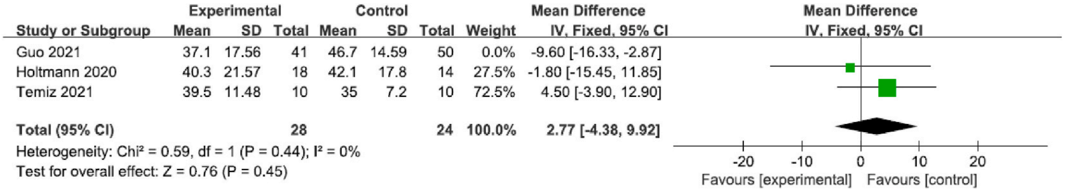


Fig. 6. Forest plot after sensitivity analysis of COVID-19 on progressive sperm motility.

Declaration of competing interest

The authors declare no competing interests.

References

[1] X. Lan, M. Wang, X. Yu, L. Dong, J. Li, D. Chang, et al., A systematic review of the effect of COVID-19 on semen parameters, Heliyon 9 (4) (2023), e14776.

[2] N. Holtmann, P. Edimiris, M. Andree, C. Doehmen, D. Baston-Buest, O. Adams, et al., Assessment of SARS-CoV-2 in human semen-a cohort study, Fertil. Steril. 114 (2) (2020) 233–238.

[3] M.Z. Temiz, M.M. Dincer, I. Hacibey, R.O. Yazar, C. Celik, S.H. Kucuk, et al., Investigation of SARS-CoV-2 in semen samples and the effects of COVID-19 on male sexual health by using semen analysis and serum male hormone profile: a cross-sectional, pilot study, Andrologia 53 (2) (2021), e13912.

[4] H. Li, X. Xiao, J. Zhang, M.I. Zafar, C. Wu, Y. Long, et al., Impaired spermatogenesis in COVID-19 patients, EClinicalMedicine 28 (2020), 100604.

[5] T.H. Guo, M.Y. Sang, S. Bai, H. Ma, Y.Y. Wan, X.H. Jiang, et al., Semen parameters in men recovered from COVID-19, Asian J. Androl. 23 (5) (2021) 479–483.

[6] J.C. Best, M. Kuchakulla, K. Khodamoradi, T.F.N. Lima, F.S. Frech, J. Achua, et al., Evaluation of SARS-CoV-2 in human semen and effect on total sperm number: a prospective observational study, World J Mens Health 39 (3) (2021) 489–495.

Yao Lin
The First Affiliated Hospital of Dalian Medical University, Xigang District, Dalian, Liaoning, 116014, China
E-mail address: yao19862021@126.com.