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Monitoring population-level viral load proxies from cycle threshold values for COVID-19 transmission surveillance: a systematic review and meta-analysis

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Background

The COVID-19 pandemic has brought unprecedented challenges to global healthcare, prompting the need for efficient surveillance strategies. Increasingly, studies are using cycle threshold (Ct) values to estimate the transmission levels of COVID-19, yet a unified understanding is lacking.

Objectives

We conducted a systematic review and meta-analysis that synthesized the estimates on the relationship between population-level Ct values and COVID-19 transmission.

Methods

We categorized the types of Ct measurements, surveillance scopes, and transmission indicators to determine the correlation between these data streams with different lags in surveillance. We also performed out-of-sample predictions to determine the generalizability of using Ct values as a tool of COVID-19 transmission.

Results

Out of the 36 identified studies, 27 studies used quantitative approaches, with 11 studies attempted to predict COVID-19 transmission using Ct distributions. These studies consistently revealed associations between Ct values and transmission indicators. For Ct measurements, our analyses indicated that maintaining excessive rolling Ct values was suboptimal. In terms of out-of-sample predictions, we verified the generalizability of Ct-based framework but emphasized the necessity for further calibration to accommodate the epidemic characteristics of various regions. Our findings also highlight the model trained on the data from public surveillance is more stable compared with models trained on data from lab-based surveillance.

Table 1. Factors affecting the correlation between population-level Ct means and COVID-19 transmission by meta regression.

	Lag 0	Lag 3	Lag 7	Lag 14	Lag 21	Lag 28	Overall (lag 0~28)ᵃ
Case counts							
Ct distributions							
Daily mean	Reference	Reference	Reference	Reference	Reference	Reference	Reference
3-day rolling mean	0.13 (-0.07, 0.34)	-0.04 (-0.22, 0.13)	-0.30 (-0.54, -0.06)	0.00 (-0.20, 0.20)	-0.04 (-0.32, 0.25)	0.04 (-0.32, 0.40)	-0.04 (-0.14, 0.06)
7-dat rolling mean	0.06 (-0.15, 0.26)	-0.10 (-0.28, 0.07)	-0.35 (-0.60, -0.11)	-0.04 (-0.24, 0.16)	-0.05 (-0.34, 0.24)	0.04 (-0.31, 0.40)	-0.08 (-0.18, 0.02)
14-day rolling mean	0.00 (-0.20, 0.20)	-0.15 (-0.32, 0.02)	-0.39 (-0.64, -0.15)	-0.06 (-0.26, 0.14)	-0.04 (-0.32, 0.25)	0.02 (-0.34, 0.38)	-0.11 (-0.21, -0.01)
Surveillance types							
Public	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Lab-based data	0.15 (0.00, 0.30)	0.24 (0.12, 0.37)	0.19 (0.01, 0.37)	0.35 (0.20, 0.49)	0.34 (0.13, 0.54)	0.26 (0.00, 0.52)	0.24 (0.17, 0.32)
Lag							
Overall (lag 0~28)ᵃ	Reference	-0.01 (-0.14, 0.11)	0.03 (-0.10, 0.15)	-0.12 (-0.25, 0.00)	-0.08 (-0.21, 0.04)	-0.02 (-0.15, 0.10)	N/A
Rt							
Ct distributions							
Daily mean	Reference	Reference	Reference	Reference	Reference	Reference	Reference
3-day rolling mean	-0.05 (-0.27, 0.16)	-0.02 (-0.24, 0.21)	-0.01 (-0.25, 0.23)	0.03 (-0.25, 0.30)	0.07 (-0.21, 0.35)	0.05 (-0.21, 0.31)	0.01 (-0.09, 0.11)
7-dat rolling mean	-0.02 (-0.24, 0.19)	0.02 (-0.21, 0.25)	0.04 (-0.20, 0.28)	0.10 (-0.18, 0.37)	0.13 (-0.15, 0.41)	0.07 (-0.19, 0.33)	0.06 (-0.04, 0.16)
14-day rolling mean	0.05 (-0.17, 0.26)	0.10 (-0.13, 0.32)	0.12 (-0.12, 0.36)	0.16 (-0.11, 0.43)	0.13 (-0.15, 0.41)	0.00 (-0.26, 0.26)	0.09 (-0.01, 0.19)
Surveillance types							
Public	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Lab-based data	0.06 (-0.11, 0.23)	0.01 (-0.16, 0.18)	-0.04 (-0.22, 0.14)	-0.07 (-0.27, 0.14)	-0.12 (-0.32, 0.09)	-0.23 (-0.42, -0.04)	-0.06 (-0.14, 0.01)
Lag							
Overall (lag 0~28)ᵃ	Reference	0.07 (-0.05, 0.19)	0.16 (0.04, 0.29)	0.30 (0.17, 0.42)	0.38 (0.26, 0.50)	0.40 (0.28, 0.53)	N/A

a Included lags 0, 3,7,14,21 and 28 in one meta-regression model.

Table 2. Factors affecting the correlation between population-level Ct skewness and COVID-19 transmission by meta-regression.

	Lag 0	Lag 3	Lag 7	Lag 14	Lag 21	Lag 28	Overall (lag 0~28)ᵃ
Case counts							
Ct distributions							
Daily skewness	Reference	Reference	Reference	Reference	Reference	Reference	Reference
3-day rolling skewness	0.02 (-0.18, 0.22)	0.04 (-0.17, 0.26)	0.04 (-0.18, 0.26)	0.04 (-0.19, 0.26)	0.04 (-0.20, 0.28)	0.01 (-0.24, 0.26)	0.03 (-0.06, 0.12)
7-day rolling skewness	0.06 (-0.13, 0.26)	0.08 (-0.13, 0.29)	0.08 (-0.15, 0.30)	0.05 (-0.17, 0.28)	0.06 (-0.18, 0.30)	0.04 (-0.21, 0.28)	0.06 (-0.03, 0.15)
14-day rolling skewness	0.08 (-0.11, 0.28)	0.09 (-0.12, 0.30)	0.08 (-0.14, 0.31)	0.05 (-0.17, 0.27)	0.04 (-0.20, 0.28)	0.05 (-0.20, 0.30)	0.06 (-0.02, 0.15)
Surveillance types							
Public	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Lab-based	-0.17 (-0.31, -0.02)	-0.26 (-0.41, -0.11)	-0.31 (-0.47, -0.16)	-0.40 (-0.56, -0.24)	-0.36 (-0.53, -0.19)	-0.34 (-0.52, -0.16)	-0.31 (-0.37, -0.24)
Lag							
Overall (lag 0~28)ᵃ	Reference	0.04 (-0.07, 0.15)	0.09 (-0.02, 0.20)	0.15 (0.04, 0.26)	0.15 (0.04, 0.26)	0.13 (0.02, 0.24)	N/A
Rt							
Ct distributions							
Daily skewness	Reference	Reference	Reference	Reference	Reference	Reference	Reference
3-day rolling skewness	-0.01 (-0.23, 0.21)	0.01 (-0.20, 0.23)	0.01 (-0.21, 0.24)	-0.01 (-0.26, 0.24)	-0.05 (-0.33, 0.24)	-0.01 (-0.32, 0.30)	-0.01 (-0.11, 0.09)
7-day rolling skewness	-0.03 (-0.25, 0.18)	-0.02 (-0.24, 0.20)	-0.03 (-0.26, 0.20)	-0.06 (-0.31, 0.19)	-0.09 (-0.37, 0.19)	0.00 (-0.31, 0.31)	-0.04 (-0.14, 0.06)
14-day rolling skewness	-0.11 (-0.33, 0.11)	-0.09 (-0.31, 0.12)	-0.10 (-0.33, 0.13)	-0.09 (-0.34, 0.15)	-0.07 (-0.35, 0.21)	0.06 (-0.25, 0.37)	-0.07 (-0.17, 0.03)
Surveillance types							
Public	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Lab-based	-0.16 (-0.32, 0.00)	-0.10 (-0.26, 0.07)	-0.04 (-0.21, 0.13)	0.01 (-0.18, 0.19)	0.06 (-0.15, 0.27)	0.20 (-0.03, 0.43)	0.00 (-0.08, 0.07)
Lag							
Overall (lag 0~28)ᵃ	Reference	-0.07 (-0.19, 0.06)	-0.14 (-0.26, -0.01)	-0.24 (-0.36, -0.12)	-0.30 (-0.42, -0.17)	-0.32 (-0.45, -0.20)	N/A

a COVID-19 transmission data (e.g., case counts and Rt) were reported by national or regional public organizations.

b Included lags 0, 3,7,14,21 and 28 in one meta-regression model.

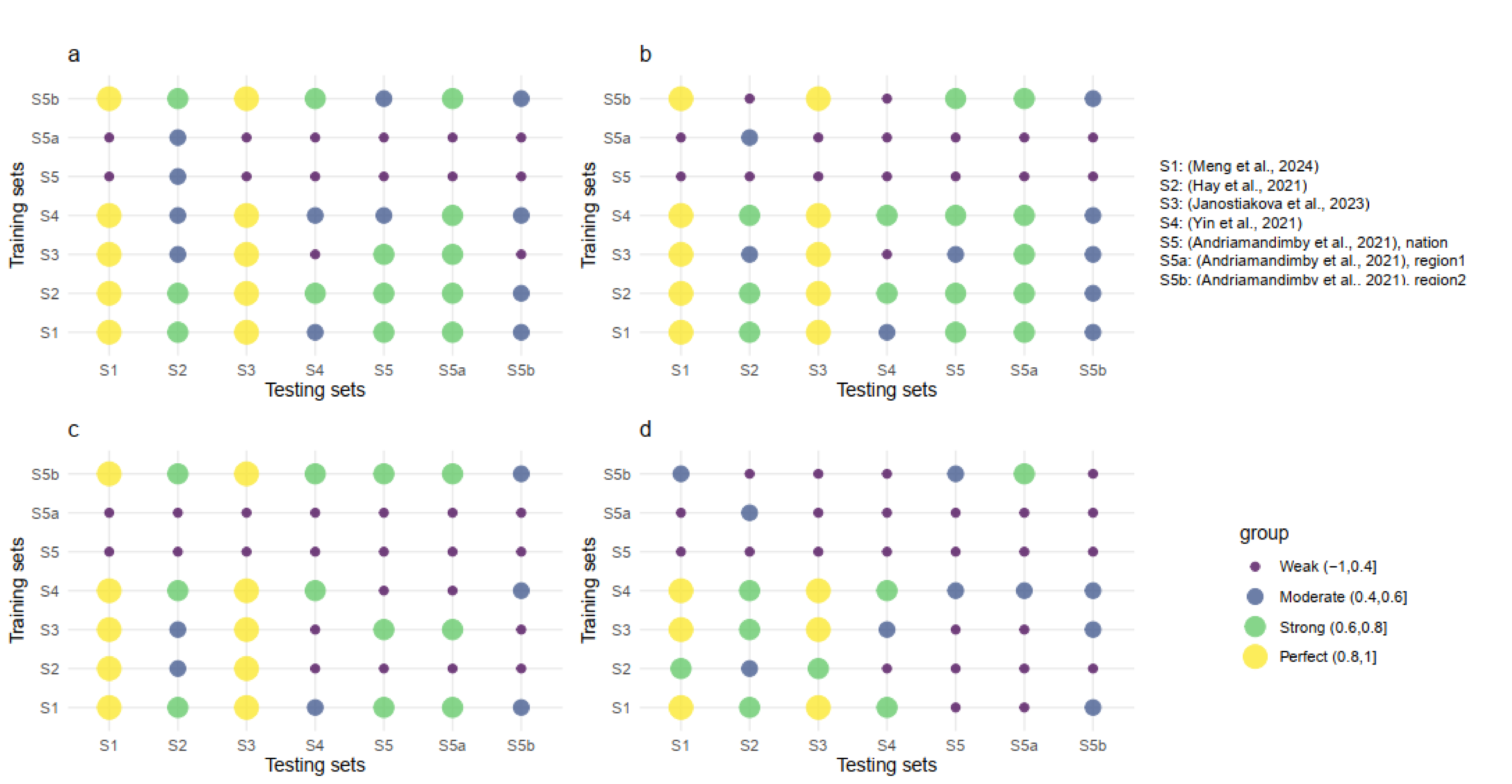

Figure 3. The heatmap of out-of-sample predictions on case counts/positive tests across 5 studies. Spearman rank correlation coefficients between observed case counts/positive tests and predicted case counts/positive tests using linear regression model fitted on 31-day peak data from 5 studies. The linear regression model was fitted on daily Ct distributions (panel A), 3-day rolling Ct distributions (panel B), 7-day rolling Ct distributions (panel C) and 14-day rolling Ct distributions (panel D) to predict daily case counts/positive tests.

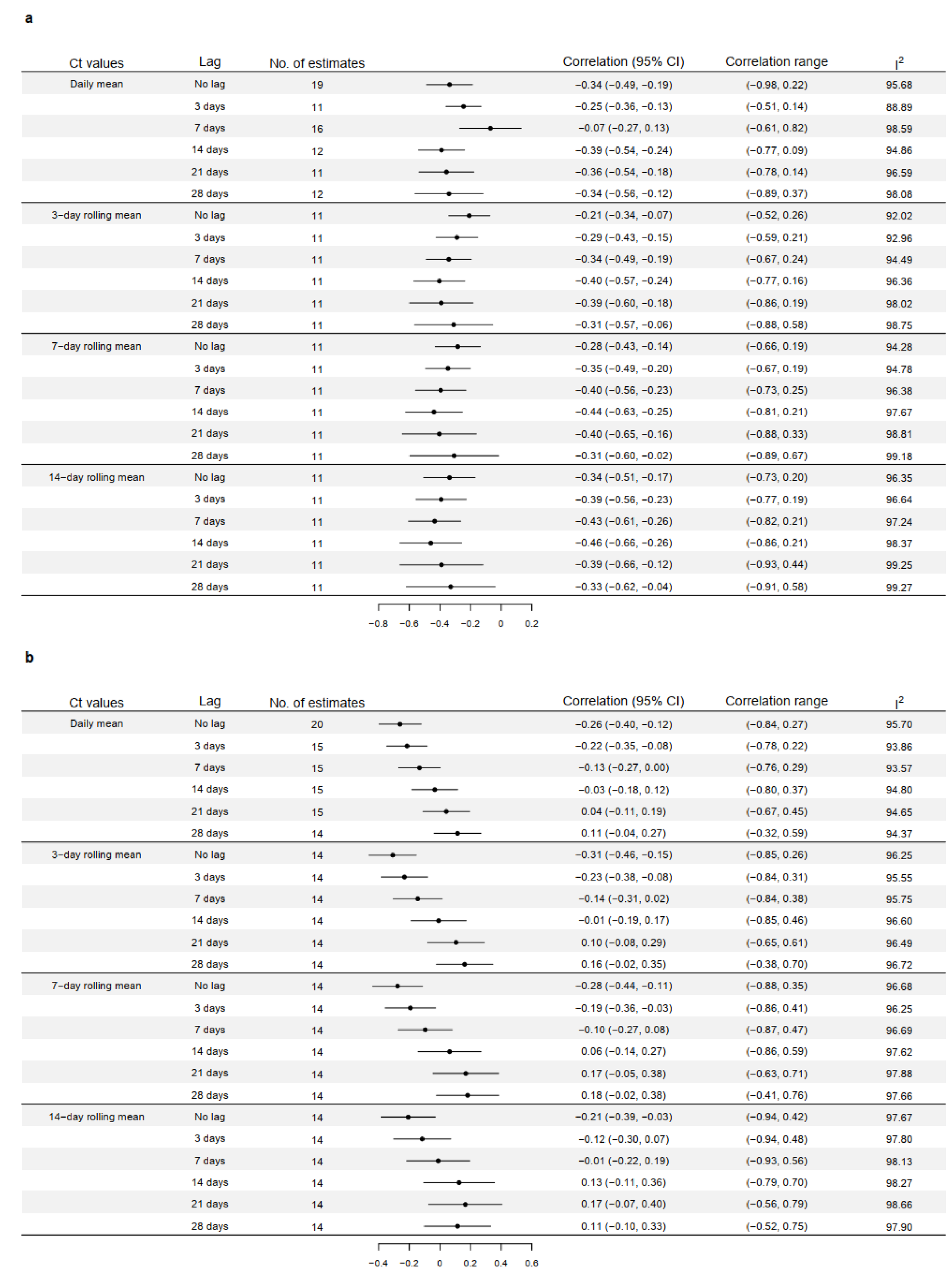

Figure 1. The pooled estimate of correlation between population-level Ct means and COVID-19 transmission (panel a, case counts; panel b, Rt).

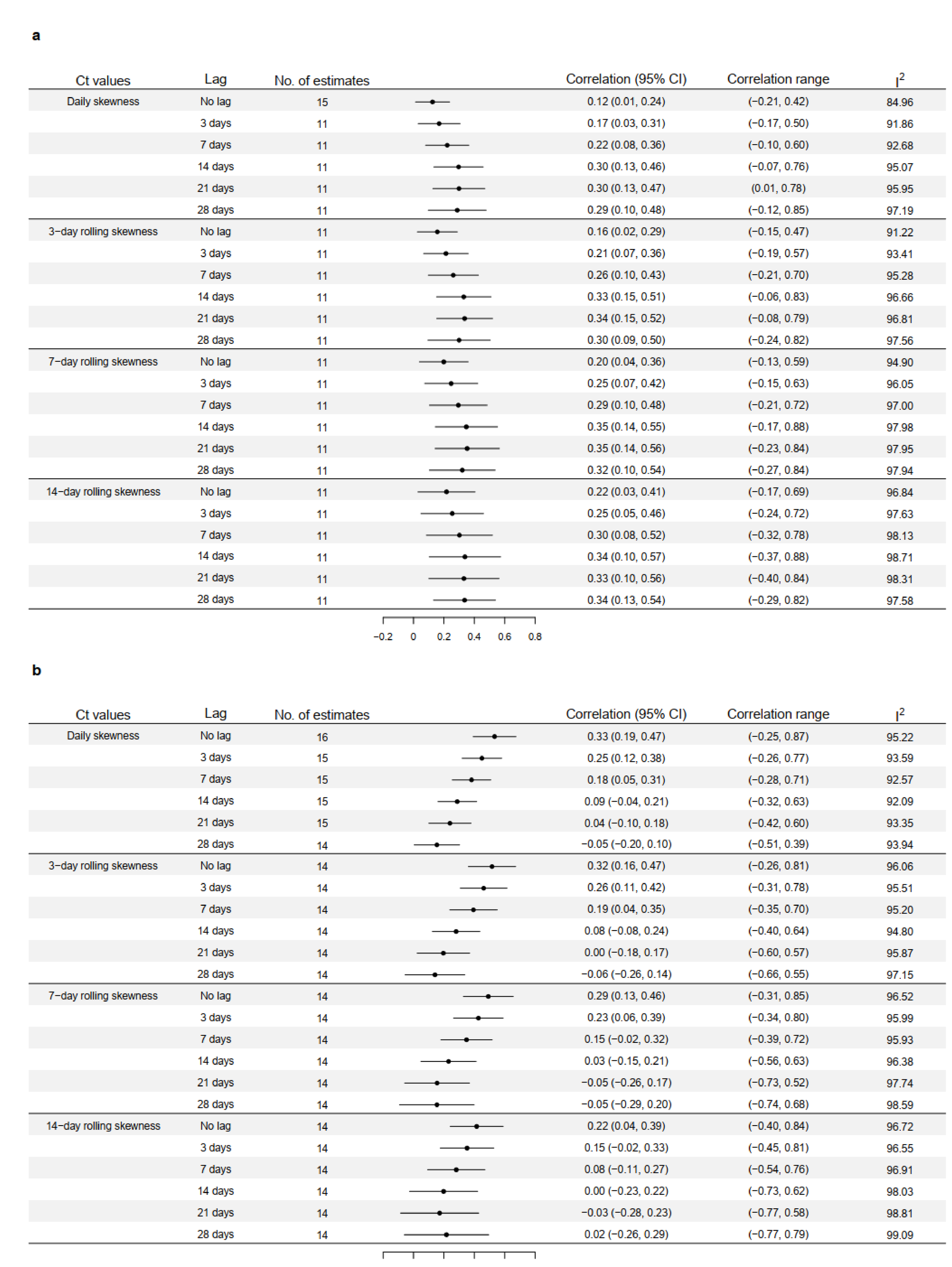

Figure 2. The pooled estimate of correlation between population-level Ct skewness and COVID-19 transmission (panel a, case counts; panel b, Rt).

Conclusion

Our study supports the importance of conducting viral loads surveillance to monitor changes in SARS-CoV-2 transmission. These observations are instrumental to plan for future COVID-19 waves.

References

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