Front. Med. 2022, 16(4): 661−665
https://doi.org/10.1007/s11684-021-0907-9

Answer for questions of repeated measurements of variance analysis and distribution test of data — Authors' reply

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Thank the journal for sending us the Correspondence of Dr. Jie Wei for our article "Effects of Shuanghuanglian oral liquids on patients with COVID-19: a randomized, open-label, parallel-controlled, multicenter clinical trial" published in Frontiers of Medicine [1]. We appreciate Dr. Jie Wei for agreeing with most of the conclusions in our paper and we address Dr. Jie Wei's comments carefully as below.

For Dr. Jie Wei's first comment, "repeated measurements of variance analysis should be used in the random control trial when repeated measurements of the same observation indicator are required at different times." To investigate whether the repeated measurements of variance analysis was needed, we did repeated measures ANCOVA in this study, using changes from baseline at different time points after the intervention as outcome, and the interventions and time as independent variables. The interaction between interventions and time was also examined. The results showed that the treatment time could independently affect the outcomes, but interaction between interventions and time were not significantly different among the treatment groups (Tables 1−5). Therefore, it would unlikely affect the authenticity of the original conclusions of the article.

For Dr. Jie Wei's second comment, "the SW test is the most powerful test for all types of distribution and sample size." We appreciate this comment. In this study, we used Kolmogorov–Smirnov test to determine the distribution of continuous data. According to the above comment, we used Shapiro–Wilk (SW) test conducted with SPSS (version 22.0, Armonk, USA) to check for normality and distribution of continuous data in our study again (Tables 6−9), and there were no much difference between these two tests. In addition, in our study, all continuous variables were tested by nonparametric statistical methods, which could be used for both normal distribution data and non-normal distribution data. It would not affect the results and conclusions in this study. We would like to thank Dr. Jie Wei for Dr. Jie Wei's interests in our paper and for Dr. Jie Wei's comments that we have addressed above.

Table 1 The interaction between interventions and time in effects of SHL treatment on the symptoms scores as compared with standard care

		F-statistic	*P* value
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.795	0.498
Time	Day 0 vs. 2 vs. 4 vs. 7 vs. 10 vs. 14	71.185	<0.001
Interaction	Time & intervention	1.630	0.134

Control, standard care; low dose, low dose of SHL; mid dose, middle dose of SHL; high dose, high dose of SHL; SHL, Shuanghuanglian.

Table 2 The interaction between interventions and time in reduction of density of infection focus on CT imaging from baseline

		F-statistic	*P* value
Intervention	Standard care vs. combined dose groups	1.749	0.190
Time	Day 7 vs. day 14	8.285	0.005
Interaction	Time & intervention	0.722	0.398
Intervention	Control vs. low dose vs. mid dose vs. high dose	2.795	0.05
Time	Day 7 vs. day 14	15.02	<0.001
Interaction	Time & intervention	0.943	0.424

Control, standard care; low dose, low dose of SHL; mid dose, middle dose of SHL; high dose, high dose of SHL.

Received: August 15, 2021; accepted: November 8, 2021

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Acknowledgements

We would like to thank Prof. Jingxin Li of Laboratory of Enteric

Table 3 The interaction between interventions and time in the analysis of serum inflammatory factors

		F-statistic	*P* value
IL-6			
Intervention	Standard care vs. combined dose groups	2.234	0.157
Time	Day 0 vs. day 7 vs. day 14	1.686	0.215
Interaction	Time & intervention	0.766	0.401
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.738	0.550
Time	Day 0 vs. day 7 vs. day 14	3.992	0.066
Interaction	Time & intervention	1.427	0.281
IL-8			
Intervention	Standard care vs. combined dose groups	0.033	0.859
Time	Day 0 vs. day 7 vs. day 14	4.640	0.018
Interaction	Time & intervention	0.700	0.505
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.306	0.820
Time	Day 0 vs. day 7 vs. day 14	3.068	0.065
Interaction	Time & intervention	0.389	0.879
IL-10			
Intervention	Standard care vs. combined dose groups	0.353	0.562
Time	Day 0 vs. day 7 vs. day 14	1.275	0.295
Interaction	Time & intervention	0.078	0.925
Intervention	Control vs. low dose vs. mid dose vs. high dose	1.062	0.402
Time	Day 0 vs. day 7 vs. day 14	0.903	0.419
Interaction	Time & intervention	0.238	0.959
TNF-α			
Intervention	Standard care vs. combined dose groups	0.074	0.789
Time	Day 0 vs. day 7 vs. day 14	0.099	0.906
Interaction	Time & intervention	0.122	0.886
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.925	0.458
Time	Day 0 vs. day 7 vs. day 14	0.171	0.844
Interaction	Time & intervention	0.149	0.987
IL-1b			
Intervention	Standard care vs. combined dose groups	0.031	0.863
Time	Day 0 vs. day 7 vs. day 14	0.503	0.526
Interaction	Time & intervention	0.877	0.384
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.704	0.568
Time	Day 0 vs. day 7 vs. day 14	0.265	0.660
Interaction	Time & intervention	0.737	0.570

(*Continued*)

		F-statistic	*P* value
IL-2R			
Intervention	Standard care vs. combined dose groups	1.311	0.271
Time	Day 0 vs. day 7 vs. day 14	1.434	0.255
Interaction	Time & intervention	1.762	0.204
Intervention	Control vs. low dose vs. mid dose vs. high dose	1.238	0.339
Time	Day 0 vs. day 7 vs. day 14	2.547	0.127
Interaction	Time & intervention	0.625	0.641

Control, standard care; low dose, low dose of SHL; mid dose, middle dose of SHL; high dose, high dose of SHL.

Table 4 The interaction between interventions and time in the analysis of markers of myocardial injury

		F-statistic	*P* value
NT-proBNP			
Intervention	Standard care vs. combined dose groups	1.898	0.180
Time	Day 0 vs. day 7 vs. day 14	1.524	0.230
Interaction	Time & intervention	1.909	0.170
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.588	0.629
Time	Day 0 vs. day 7 vs. day 14	0.348	0.638
Interaction	Time & intervention	0.823	0.527
cTnI			
Intervention	Standard care vs. combined dose groups	0.445	0.509
Time	Day 0 vs. day 7 vs. day 14	0.466	0.500
Interaction	Time & intervention	0.419	0.523
Intervention	Control vs. low dose vs. mid dose vs. high dose	0.607	0.616
Time	Day 0 vs. day 7 vs. day 14	0.684	0.415
Interaction	Time & intervention	0.644	0.593

Control, standard care; low dose, low dose of SHL; mid dose, middle dose of SHL; high dose, high dose of SHL.

Table 5 The interaction between interventions and time in the analysis of antibodies of SARS-CoV-2

		F-statistic	*P* value
IgM			
Intervention	Standard care vs. combined dose groups	0.026	0.873
Time	Day 0 vs. day 7 vs. day 14	1.523	0.234
Interaction	Time & intervention	0.470	0.518
Intervention	Control vs. low dose vs. mid dose vs. high dose	1.605	0.227
Time	Day 0 vs. day 7 vs. day 14	4.169	0.052
Interaction	Time & intervention	1.891	0.163
IgG			
Intervention	Standard care vs. combined dose groups	5.831	0.027
Time	Day 0 vs. day 7 vs. day 14	5.039	0.032
Interaction	Time & intervention	1.232	0.287
Intervention	Control vs. low dose vs. mid dose vs. high dose	1.871	0.175
Time	Day 0 vs. day 7 vs. day 14	3.596	0.070
Interaction	Time & intervention	0.735	0.560

Control, standard care; low dose, low dose of SHL; mid dose, middle dose of SHL; high dose, high dose of SHL.

Table 6 Tests of normality for the continuous data of characteristics at baseline

	Kolmogorov–Smirnov[a]		Shapiro–Wilk	
	Statistic	*P* value	Statistic	*P* value
Age	0.067	0.017	0.974	<0.001
Onset day	0.137	<0.001	0.947	<0.001
temp	0.126	<0.001	0.926	<0.001
SBP	0.108	<0.001	0.972	<0.001
HR	0.121	<0.001	0.960	<0.001
RR	0.239	<0.001	0.797	<0.001
WBC	0.132	<0.001	0.932	<0.001
Lymph	0.062	0.041	0.969	<0.001
PLT	0.096	<0.001	0.909	<0.001
ALT	0.242	<0.001	0.568	<0.001
AST	0.260	<0.001	0.412	<0.001
Crea	0.095	<0.001	0.906	<0.001
LDH	0.174	<0.001	0.739	<0.001
TBIL	0.133	<0.001	0.844	<0.001
PT	0.273	<0.001	0.320	<0.001

[a]Lilliefors Significance Correction.
Onset day, days from illness onset to randomization; temp, body temperature; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; WBC, white-cell count; Lymph, lymphocyte count; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Crea, serum creatinine; LDH, lactate dehydrogenase; TBIL, total bilirubin; PT, prothrombin time.

Table 7 Tests of normality for the continuous data of serum inflammatory factors

	Kolmogorov–Smirnov[a]		Shapiro–Wilk	
	Statistic	*P* value	Statistic	*P* value
IL-6_0 d	0.275	0.002	0.730	<0.001
IL-10_0 d	0.433	<0.001	0.566	<0.001
IL-8_0 d	0.165	0.200*	0.933	0.275
TNF-α_0 d	0.156	0.200*	0.955	0.579
IL-1b_0 d	0.378	<0.001	0.580	<0.001
IL-2R_0 d	0.160	0.200*	0.843	0.011
IL-6_7 d	0.273	0.002	0.763	0.001
IL-10_7 d	0.496	<0.001	0.358	<0.001
IL-8_7 d	0.178	0.187	0.902	0.086
TNF-α_7 d	0.215	0.046	0.895	0.068
IL-1b_7 d	0.331	<0.001	0.697	<0.001
IL-2R_7 d	0.124	0.200*	0.942	0.373
IL-6_14 d	0.298	<0.001	0.690	<0.001
IL-10_14 d	0.424	<0.001	0.318	<0.001
IL-8_14 d	0.153	0.200*	0.901	0.082
TNF-α_14 d	0.183	0.156	0.879	0.037
IL-1b_14 d	0.507	<0.001	0.285	<0.001
IL-2R_14 d	0.135	0.200*	0.944	0.406

*This is a lower bound of the true significance.
[a]Lilliefors Significance Correction.

Table 8 Tests of normality for the continuous data of markers of myocardial injury

	Kolmogorov–Smirnov[a]		Shapiro–Wilk	
	Statistic	*P* value	Statistic	*P* value
NTproBNP_0 d	0.220	0.005	0.843	0.002
NTproBNP_7 d	0.278	<0.001	0.590	<0.001
NTproBNP_14 d	0.286	<0.001	0.671	<0.001
cTnI_0 d	0.343	<0.001	0.578	<0.001
cTnI_7 d	0.223	0.004	0.776	<0.001
cTnI_14 d	0.340	<0.001	0.531	<0.001
CRP_0 d	0.310	<0.001	0.550	<0.001
CRP_7 d	0.289	<0.001	0.602	<0.001
CRP_14 d	0.334	<0.001	0.534	<0.001

[a]Lilliefors Significance Correction.

Table 9 Tests of normality for the continuous data of antibodies of SARS-CoV-2

	Kolmogorov–Smirnov[a]		Shapiro–Wilk	
	Statistic	*P* value	Statistic	*P* value
IgM_0 d	0.373	<0.001	0.373	<0.001
IgG_0 d	0.120	0.200*	0.918	0.089
IgM_7 d	0.381	<0.001	0.487	<0.001
IgG_7 d	0.237	0.005	0.858	0.007
IgM_14 d	0.406	<0.001	0.424	<0.001
IgG_14 d	0.218	0.014	0.896	0.034

[a]Lilliefors Significance Correction.

Pathogenic Microbiology, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China, for her constructive comments and great help in the statistical analysis.

Compliance with ethics guidelines

Dao Wen Wang, Li Ni, and Hualiang Jiang declare no conflicts of interest. This manuscript is a correspondence and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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