

Supplementary data for

Effects of Shuanghuanglian oral liquids on patients with COVID-19: a randomized, open-label, parallel-controlled, multicenter clinical trial

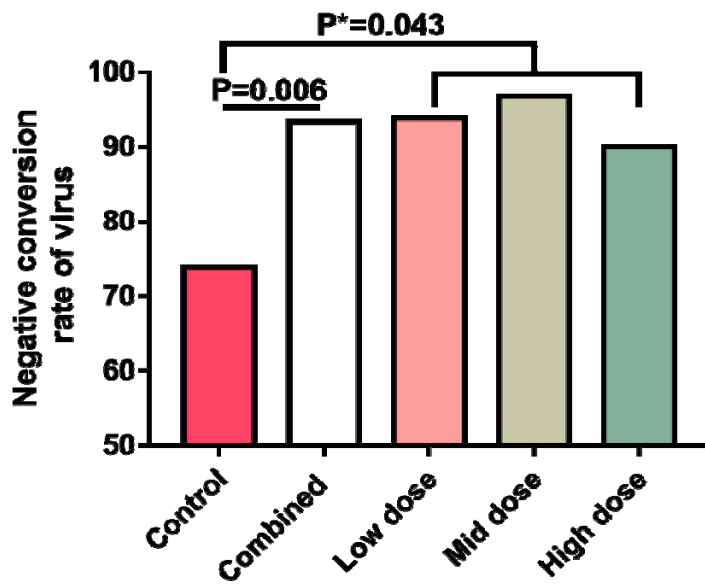
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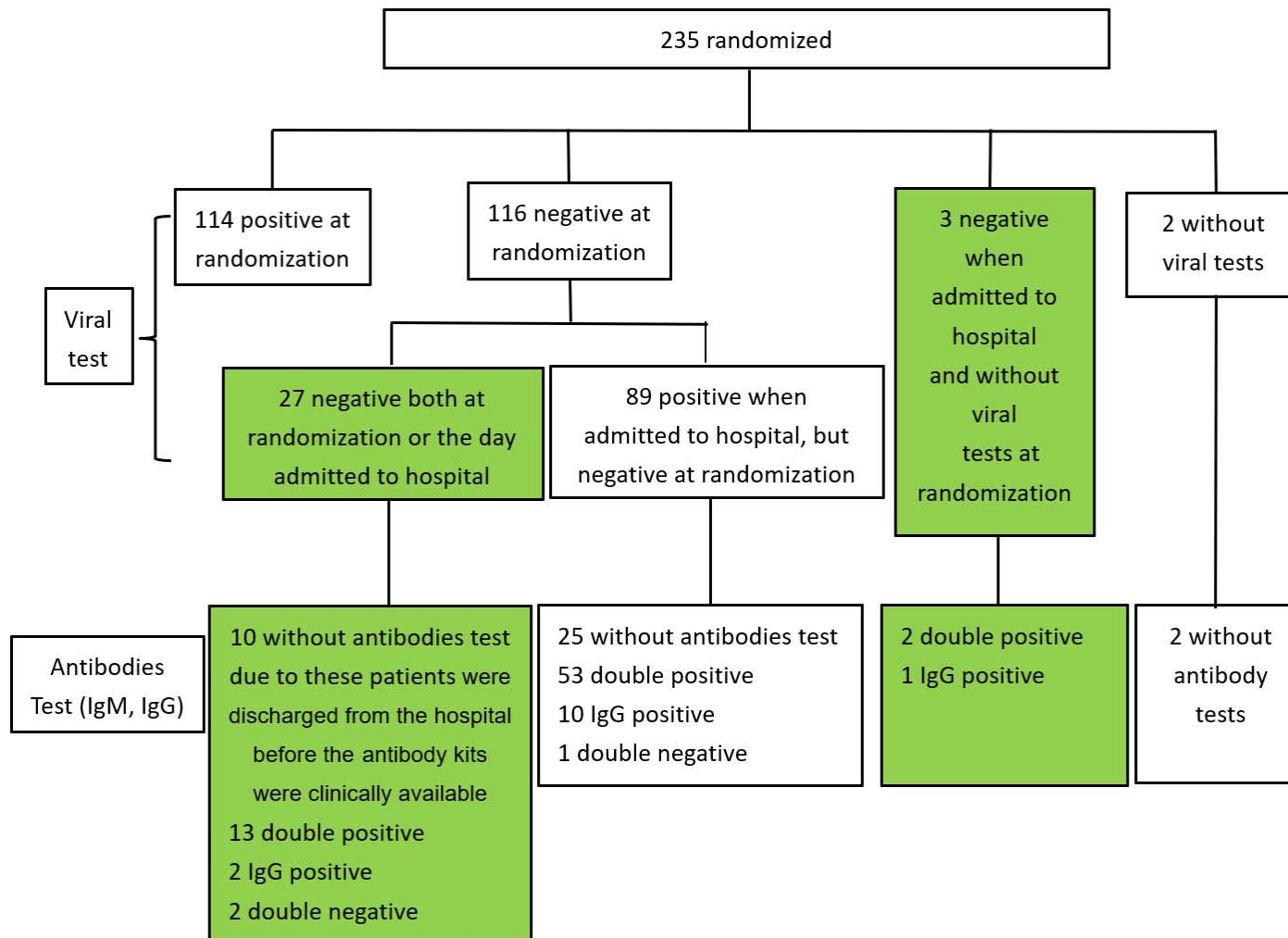
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Supplementary Figures 1 and 2

Supplementary Tables 1–7



Supplementary Figure 1. Rate of negative conversion of viral tests. Control: standard care; Low dose: low dose of SHL; Mid dose: middle dose of SHL; High dose: high dose of SHL. *P value trend across the SHL groups as compared with control group.



Supplementary Figure 2. Status of nucleic acid and antibody tests and for the enrolled patients prior to the treatment.

Supplementary Table 1. Primary outcomes.

	Standard Care	SHL			P value		
	(N=59)	Low dose SHL	Middle dose SHL	High dose SHL	Combined	For Trend	For Combined
		(N=56)	(N=61)	(N=59)	(N=176)	across Doses	Dose Groups
					vs. Standard Care	vs. Standard Care	
Recovery Time, d	13.00 [9.00, 19.00]	13.00 [9.00, 20.00]	13.00 [10.00, 20.00]	15.00 [9.00, 22.00]	13.00 [9.75, 20.00]	0.986	0.86
Hazard Ratio (95% CI)	-	1.16 (0.79-1.68)	1.27 (0.87-1.83)	1.071 (0.74-1.55)	1.16 (0.85-1.57)		
P value	-	0.866	0.79	0.934	0.864		

Values are presented as median [interquartile range, IQR] or n (%).

Supplementary Table 2. Criteria for scoring primary symptoms.

Primary symptoms	Scoring criteria
Fever	0: body temperature $\leq 37.2^{\circ}\text{C}$ 3: body temperature $37.3^{\circ}\text{C}\sim 37.9^{\circ}\text{C}$ 6: body temperature $38^{\circ}\text{C}\sim 38.5^{\circ}\text{C}$ 9: body temperature $> 38.5^{\circ}\text{C}$
Fatigue	0: no fatigue 3: occasional slight fatigue 6: fatigue at general activity 9: sustaining fatigue even at rest
Cough	0: no cough 3: occasional cough 6: often cough 9: heavy cough all the time

Supplementary Table 3. Criteria for scoring secondary symptoms.

Secondary symptoms	Scoring criteria
Diarrhea	0: no diarrhea 1: <4 times per day 2: 4-6 times per day 3: >6 times per day
Nausea or vomiting	0: no nausea or vomiting 1: <4 times per day 2: 4-6 times per day 3: >6 times per day
Feeling of cold	0: no feeling of cold 1: feeling of cold but no need to put on more clothes 2: feeling of cold and needing to put on more clothes 3: chilling
Chest pain	0: no chest pain 1: slight chest pain 2: tolerable chest pain 3: severe chest pain when breathing or coughing

Polydipsia	<p>0: no thirst</p> <p>1: slight thirst</p> <p>2: need drink water because of thirsty</p> <p>3: drinking water frequently</p>
Hypohidrosis	<p>0: normal sweating</p> <p>1: slight sweating</p> <p>2: abnormal sweating</p> <p>3: no sweat</p>
Chest tightness	<p>0: no chest tightness</p> <p>1: slight chest tightness</p> <p>2: remarkable chest tightness</p> <p>3: sense of asphyxia</p>
Shortless of breath	<p>0: no shortless of breath</p> <p>1: slight shortless of breath</p> <p>2: remarkable shortless of breath</p> <p>3: out of breath</p>

Supplementary Table 4. Analysis of serum inflammatory factors.

	Standard Care	SHL			P value		
		Low Dose SHL	Middle Dose SHL	High Dose SHL	Combined Dose Groups	For Trend across Doses vs. Standard Care	For Combined Dose Groups vs. Standard Care
Day 0	N=43	N=40	N=40	N=37	N=117		
IL-6 (pg/mL)	2.83 [1.71, 4.27]	3.27 [1.79, 10.18]	2.82 [1.50, 4.96]	3.46 [1.77, 8.33]	3.07 [1.66, 7.83]	0.519	0.391
IL-10 (pg/mL)	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	0.76	0.964
IL-8 (pg/mL)	8.60 [6.25, 16.90]	9.35 [7.50, 17.47]	10.05 [6.30, 17.50]	9.40 [6.40, 21.70]	9.50 [6.40, 18.10]	0.841	0.39
TNF- α (pg/mL)	7.40 [5.45, 9.55]	7.40 [5.92, 9.32]	7.45 [5.18, 10.20]	7.50 [5.60, 9.80]	7.50 [5.50, 9.80]	0.998	0.934
IL-1b (pg/mL)	5.00 [5.00, 6.55]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	0.265	0.07
IL-2R (U/mL)	390.00 [276.50, 520.50]	380.50 [272.50, 533.75]	394.50 [272.50, 529.50]	438.00 [348.00, 635.00]	412.00 [284.00, 562.00]	0.434	0.404
Day 7	N=15	N=16	N=18	N=18	N=52		
IL-6 (pg/mL)	1.50 [1.50, 3.87]	2.94 [1.50, 8.22]	2.29 [1.50, 7.24]	2.17 [1.50, 7.11]	2.30 [1.50, 7.94]	0.677	0.263
IL-10 (pg/mL)	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	0.583	0.172
IL-8 (pg/mL)	5.00 [5.00, 9.10]	8.20 [5.00, 9.75]	8.05 [5.00, 10.88]	5.45 [5.00, 8.80]	7.25 [5.00, 9.75]	0.643	0.452

	TNF- α (pg/mL)	6.40 [5.05, 9.25]	6.80 [5.87, 8.38]	7.15 [4.88, 9.62]	7.60 [5.73, 10.05]	7.20 [5.58, 9.65]	0.974	0.662
	IL-1b (pg/mL)	5.00 [5.00, 7.30]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.68]	5.00 [5.00, 5.00]	0.528	0.264
	IL-2R (U/mL)	303.00 [171.00, 394.00]	357.50 [287.00, 642.75]	423.50 [273.00, 458.75]	408.00 [195.25, 523.25]	408.00 [279.00, 561.50]	0.449	0.127
Day 14		N=10	N=10	N=8	N=9	N=27		
	IL-6 (pg/mL)	1.96 [1.50, 2.75]	2.19 [1.54, 3.88]	1.86 [1.50, 6.86]	3.12 [1.50, 7.21]	2.19 [1.50, 6.00]	0.73	0.292
	IL-10 (pg/mL)	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	0.875	0.42
	IL-8 (pg/mL)	14.00 [7.67, 18.38]	9.65 [6.20, 12.60]	10.10 [8.40, 11.08]	13.60 [10.80, 21.10]	10.80 [6.80, 14.20]	0.32	0.411
	TNF- α (pg/mL)	8.95 [6.95, 10.68]	7.10 [4.00, 7.80]	8.50 [7.05, 10.57]	7.50 [4.00, 8.20]	7.45 [4.17, 9.35]	0.203	0.156
	IL-1b (pg/mL)	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	5.00 [5.00, 5.08]	5.00 [5.00, 5.00]	5.00 [5.00, 5.00]	0.898	0.632
	IL-2R (U/mL)	332.50 [255.50, 371.50]	274.50 [177.75, 393.00]	426.00 [239.00, 549.25]	330.00 [204.00, 421.00]	330.00 [190.00, 478.00]	0.603	0.864

Values are presented as median [IQR]. TNF- α , tumor necrosis factor α . IL-6, interleukin 6; IL-10, interleukin 10; IL-8, interleukin 8; IL-1b, interleukin 1 beta; IL-2R, interleukin 2 receptor.

Supplementary Table 5. Markers of myocardial injury analysis.

	Standard Care		SHL			Combined Dose Groups	P value	
		Low dose SHL	Middle dose SHL	High dose SHL	For Trend across Doses vs. Standard Care		For Combined Dose Groups vs. Standard Care	
Day 0								
NT-proBNP (pg/mL)	N=35	N=35	N=38	N=36	N=109			
	37.00 [14.00, 100.50]	67.00 [34.00, 170.50]	38.00 [20.00, 139.75]	64.50 [22.00, 123.00]	61.00 [22.00, 149.00]	0.135	0.066	
cTNI (pg/mL)	N=38	N=36	N=41	N=39	N=116			
	1.90 [1.90, 2.82]	3.45 [1.90, 5.03]	1.90 [1.90, 5.20]	2.10 [1.90, 4.75]	2.20 [1.90, 5.03]	0.34	0.144	
Day 7								
NT-proBNP (pg/mL)	N=24	N=23	N=22	N=22	N=67			
	55.00 [32.75, 298.75]	52.00 [33.50, 122.50]	28.50 [13.25, 115.00]	41.00 [17.50, 62.75]	43.00 [18.00, 116.50]	0.209	0.063	
cTNI (pg/mL)	N=24	N=25	N=25	N=23	N=73			
	2.00 [1.90, 2.90]	1.90 [1.90, 2.80]	1.90 [1.90, 3.30]	2.20 [1.90, 3.40]	1.90 [1.90, 3.30]	0.775	0.784	
Day 14								
NT-proBNP (pg/mL)	N=16	N=16	N=13	N=14	N=43			
	59.00 [14.25, 114.75]	63.50 [43.50, 139.25]	53.00 [26.00, 94.00]	39.00 [19.00, 133.25]	54.00 [21.50, 121.50]	0.733	0.714	
cTNI (pg/mL)	N=17	N=18	N=14	N=14	N=46			

1.90 [1.90, 3.30]	1.90 [1.90, 2.60]	2.45 [1.90, 3.40]	2.25 [1.90, 2.48]	2.15 [1.90, 2.75]	0.85	0.855
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Values are presented as median [IQR]. cTnI, cardiac troponin I; NT-proBNP, N-terminal Pro-B-type natriuretic peptide.

Supplementary Table 6. Antibodies of SARS-Cov-2 analysis.

	Standard Care		SHL			Combined Dose Groups	P value	
			Low dose SHL	Middle dose SHL	High dose SHL		For Trend	For Combined
							across Doses vs. Standard Care	Dose Groups vs. Standard Care
Day 0	N=19	N=18	N=15	N=18	N=51			
IgM (AU/mL) (pg/mL)	44.86 [23.32, 80.93]	68.92 [8.82, 165.03]	49.53 [19.82, 91.79]	33.23 [12.44, 57.14]	45.95 [11.39, 94.69]	0.539	0.72	
IgG (AU/mL) (pg/mL)	163.98 [109.75, 204.80]	178.01 [121.34, 250.00]	172.13 [93.41, 231.38]	195.12 [156.37, 253.31]	184.77 [112.90, 252.60]	0.448	0.782	
Day 7	N=19	N=18	N=15	N=15	N=48			
IgM (AU/mL) (pg/mL)	33.80 [16.36, 140.84]	5.83 [2.29, 21.20]	22.11 [8.56, 59.37]	9.04 [3.12, 33.75]	10.39 [3.66, 41.18]	0.011	0.016	
IgG (AU/mL) (pg/mL)	128.91 [81.98, 294.86]	95.52 [82.59, 113.62]	90.14 [64.15, 201.31]	89.49 [71.74, 132.12]	92.00 [70.17, 144.97]	0.068	0.295	
Day 14	N=19	N=21	N=18	N=20	N=59			
IgM (AU/mL) (pg/mL)	40.71 [11.71, 60.84]	28.07 [7.99, 60.64]	25.41 [13.87, 35.03]	59.70 [21.63, 135.11]	29.12 [10.05, 66.94]	0.775	0.259	
IgG (AU/mL) (pg/mL)	97.54 [78.54, 175.05]	149.81 [90.21, 175.09]	146.74 [83.38, 189.64]	149.70 [88.06, 188.00]	149.81 [87.54, 184.36]	0.228	0.676	

Values are presented as median [IQR].

Supplementary Table 7. Percentage of nucleic acid test negative rate at the time of enrollment in each group.

group	n	positive	without viral test report	negative	negative (percentage)
control	59	23	0	36	61.0%
low dose	56	28	3	25	44.6%
middle dose	61	34	0	27	44.3%
high dose	59	29	2	28	47.5%