Online Supplement to

Long-term outcomes of patients with COVID-19 treated with helmet noninvasive ventilation or usual respiratory support: Follow-up study of the Helmet-COVID randomized clinical trial

Contents

Supplementary Methods

Data

We collected the following baseline data: demographics, severity of illness, chronic comorbidities, respiratory rate, arterial blood gases, location before ICU admission, chest radiograph findings (number of quadrants with infiltrates), respiratory support and awake prone positioning before randomization, number of days from symptom onset to emergency department visit and ICU admission and number of days from ICU admission to randomization. We also recorded data on the intervention and co-interventions in the ICU up to 28 days after randomization, including respiratory support modalities, settings of the helmet and mask noninvasive ventilation [pressure support level and positive end-expiratory pressure (PEEP)], the number of hours of helmet noninvasive ventilation and other respiratory support modalities, awake prone positioning, dexmedetomidine use, vasopressor therapy and renal replacement therapy. We recorded data on the frequency and duration of invasive mechanical ventilation, the frequency of use of neuromuscular blocker infusion, tracheostomy and therapies with corticosteroids, tocilizumab and COVID-19 antiviral agents. We also recorded the ICU length of stay and hospital length of stay.

Post hoc sample size calculation and statistical analysis:

The sample size of the original trial (n=320) was estimated to provide 80% power to detect a reduction in the primary outcome of 28-day mortality from 40% to 25% accounting for a 5% loss to follow-up. A post hoc analysis indicates that the sample size of the current analysis (n=317) would detect a 15% difference in 180-day mortality considering the observed baseline event rate of 41% with a power of 80%.

Although we have originally planned to use generalized linear mixed models to compare EQ-5D-5L index values and VAS scores between the two groups, we decided to use quantile

regression in order to calculate the median difference which cannot be carried out using GLMM.

Table S1: Helmet COVID management and writing committees, Data Safety & Monitoring Board and Helmet COVID site collaborators.

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Table S2: Additional information on 180-day outcome.

Timing of death	Helmet noninvasive ventilation (N=159)	Usual respiratory support (N=158)
Within the first 28 days	43	42
Between 28-90 days	20	23
In the hospital	18	23
After hospital discharge	2	0

Table S3: Additional baseline characteristics and additional treatments received.

	Non-survivors by 180 days		HRQoL respondents	
Characteristic	**Helmet noninvasive ventilation (N=63)**	**Usual respiratory support (N=65)**	**Helmet noninvasive ventilation (N=96)**	**Usual respiratory support (N=93)**
Location prior to ICU admission, No. (%)				
Emergency department	30 (47.6)	28 (43.1)	56 (58.3)	57 (61.3)
Hospital ward	24 (38.1)	25 (38.5)	22 (22.9)	27 (29.0)
Transfer from outside hospital ICU or ward	9 (14.3)	12 (18.5)	18 (18.8)	9 (9.7)
Quadrants with infiltrates on chest radiograph, median (IQR)	4 (3, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)
Awake prone positioning	14 (22.2)	7 (10.8)	80 (83.3)	74 (79.6)
Days from onset of symptoms to the emergency room, median (IQR)	4 (2, 8)	5 (3, 8)	6 (4, 9)	5 (3, 8)
Days from onset of symptoms to ICU admission, median (IQR)	6 (4, 10)	7 (5, 11)	8 (5, 10.5)	7 (4, 10)
Days from ICU admission to randomization, median (IQR)	2 (1, 2)	2 (1, 3)	1 (1, 2)	2 (1, 2)
Days from hospital admission to randomization, median (IQR)	3 (2, 5)	3 (2, 6)	2 (2, 4)	2 (2, 4)
Days from hospital admission to ICU admission, median (IQR)	2 (1, 3)	2 (1, 4)	2 (1, 3)	2 (1, 3)
Additional treatments				
Macrolide	45 (71.4)	42 (64.6)	66 (68.8)	61 (65.6)
Beta-lactam/Beta-lactamase inhibitor	32 (50.8)	42 (64.6)	59 (61.5)	50 (53.8)
Favipiravir	17 (27.0)	20 (30.8)	24 (25.0)	24 (25.8)
Remdesivir	5 (7.9)	6 (9.2)	5 (5.2)	5 (5.4)
Chloroquine	0 (0)	0 (0)	1 (1.0)	1 (1.1)
Hydroxychloroquine	1 (1.6)	0 (0)	0 (0)	0 (0)
Convalescent plasma	0 (0)	0 (0)	1 (1.0)	0 (0)
Lopinavir/Ritonavir	0 (0)	0 (0)	0 (0)	0 (0)
Ribavirin	0 (0)	0 (0)	0 (0)	0 (0)
Intravenous immunoglobulin	0 (0)	0 (0)	0 (0)	0 (0)
Interferon	0 (0)	0 (0)	0 (0)	0 (0)

ICU, intensive care unit; IQR, interquartile range; NIV

Table S4: Per-protocol analysis of outcome measures at 180 days among patients in the helmet noninvasive ventilation and usual respiratory support groups.

	Helmet noninvasive ventilation (N=146)	Usual respiratory support (N=154)	Risk difference or median difference (95%, CI)	P value
Per-protocol analysis				
Death by 180 days, n/N (%)	61/146 (41.8)	63/154 (40.9)	0.87 (−10.28, 12.02)	0.88
EQ-5D-5L index values				
Median (IQR)	0.64 (0, 1)	0.67 (0.00, 1.00)	−0.02 (−0.35, 0.31)	0.84
Mean ± SD	0.5 (0.45)	0.50 (0.45)	-	-
EQ-VAS				
Median (IQR)	70 (0, 93)	70.0 (0.0, 90.0)	0 (−32.26, 32.26)	0.79
Mean ± SD	49.9 (43.83)	49.4 (43.06)	-	-
Analysis of the HRQoL population				
EQ-5D-5L index values				
Median (IQR)	1 (0.72, 1)	1 (0.72, 1)	0 (−0.08, 0.08)	0.96
Mean ± SD	0.86 (0.19)	0.85 (0.21)	-	-
EQ-VAS				
Median (IQR)	90 (76, 100)	85 (75, 100)	5 (−1.41, 11.41)	0.38
Mean ± SD	85.7 (14.60)	83.6 (16.15)	-	-

Table S5: Sensitivity analyses of EQ-5D-5L index values using France and Japan set values in the modified intention-to-treat population.

	Helmet noninvasive ventilation (N=159)	Usual respiratory support (N=158)	Risk difference or median difference (95%, CI)	P value
EQ-5D-5L index values using France EQ-5D-5L set values				
Intention-to-treat analysis				
Median (IQR)	0.41 (0, 1)	0.38 (0, 1)	0.02 (−0.29,0.33)	0.71
Mean ± SD	0.46 ± 0.44	0.44 ± 0.45		
Analysis of the HRQoL population				
Median (IQR)	0.96 (0.46, 1)	1.00 (0.45, 1)	0.00 (−0.14,0.14)	0.95
Mean ± SD	0.76 ± 0.31	0.75 ± 0.34		
EQ-5D-5L index values using Japan EQ-5D-5L set values				
Intention-to-treat analysis				
Median (IQR)	0.59 (0, 1)	0.58 (0, 1)	0.006 (−0.30,0.31)	0.93
Mean ± SD	0.49 ± 0.43	0.48 ± 0.44		
Analysis of the HRQoL population				
Median (IQR)	0.92 (0.61, 1)	1 (0.63, 1)	0.00 (−0.13,0.13)	0.88
Mean ± SD	0.82 ± 0.21	0.81 ± 0.23		

Table S6: Individual EQ-5D-5L dimension levels at 180 days between patients who received helmet noninvasive ventilation and patients who received usual respiratory support.

Dimensions	Helmet noninvasive ventilation (N=96)	Usual respiratory support (N=93)	P value*
Mobility, No. (%)			
No problems walking	57 (59.4)	58 (62.4)	0.83
Slight problems walking	22 (22.9)	19 (20.4)	
Moderate problems walking	10 (10.4)	8 (8.6)	
Severe problems walking	6 (6.3)	5 (5.4)	
Unable to walk	1 (1)	3 (3.2)	
Self-care, No. (%)			
No problems washing or dressing	67 (69.8)	64 (68.8)	0.65
Slight problems washing or dressing	22 (22.9)	17 (18.3)	
Moderate problems washing or dressing	3 (3.1)	7 (7.5)	
Severe problems washing or dressing	2 (2.1)	2 (2.2)	
Unable to wash or dress	2 (2.1)	3 (3.2)	
Usual activities, No. (%)			
No problems doing usual activities	62 (64.6)	58 (62.4)	0.91
Slight problems doing usual activities	24 (25)	21 (22.6)	
Moderate problems doing usual activities	6 (6.3)	9 (9.7)	
Severe problems doing usual activities	2 (2.1)	2 (2.2)	
Unable to do usual activities	2 (2.1)	3 (3.2)	
Pain or discomfort, No. (%)			
No pain or discomfort	59 (61.5)	56 (60.2)	0.58
Slight pain or discomfort	21 (21.9)	26 (28)	
Moderate pain or discomfort	14 (14.6)	9 (9.7)	
Severe pain or discomfort	1 (1)	2 (2.2)	
Extreme pain or discomfort	1 (1)	0	
Anxiety or depression, No. (%)			
Not anxious or depressed	68 (70.8)	66 (71)	0.24
Slightly anxious or depressed	17 (17.7)	18 (19.4)	
Moderately anxious or depressed	11 (11.5)	6 (6.5)	
Severely anxious or depressed	0	3 (3.2)	
Extremely anxious or depressed	0	0	

EQ-5D-5L, EuroQol, 5 dimensions, 5 levels

* P value was calculated using Freeman-Halton extension of Fisher test except for the mobility dimension, which was calculated using Chi-square test

Table S7: Predictors of EuroQol-5D-5L and VAS at day 180 of enrollment among 180-survivors (HRQoL population) and among 28-survivors in the modified intention-to-treat population. The following variables were included in the multivariable model: receipt of helmet noninvasive ventilation or usual respiratory support, sex, APACHE II score, intubation, age, PaO2:FiO2 ratio at baseline and receipt of dexmedetomidine.

	180-day survivors (HRQoL population)		**28-survivors in the modified intention-to-treat population**	
Variable	EuroQol-5D-5L index median difference (95% CI)	P value	EuroQol-5D-5L index median difference (95% CI)	P value
Helmet noninvasive ventilation versus usual respiratory support	0.0 (−0.06, 0.06)	>0.99	0.0 (−0.04, 0.04)	>0.99
Female versus male	−0.008 (−0.07, 0.06)	0.81	−0.05 (−0.099, 0.001)	0.055
APACHE >13 versus ≤12	−0.06 (−0.13, 0.003)	0.06	−0.08 (−0.15, 0.002)	0.056
Intubation versus not	−0.21 (−0.26, −0.154)	<0.0001	−0.32 (−0.52, −0.12)	0.0018
Age >58 versus ≤58*	−0.11 (−0.20, −0.02)	0.013	−0.20 (−0.28, −0.11)	<0.0001
PaO2:FiO2 >100 versus ≤100 at baseline	0.004 (−0.07, 0.07)	0.91	0.05 (0.002, 0.096)	0.04
Dexmedetomidine use versus not	−0.004 (−0.07, 0.06)	0.91	−0.05 (−0.114, 0.016)	0.14

Variable	**VAS median difference (95% CI)**	**P value**	**VAS median difference (95% CI)**	**P value**
Helmet noninvasive ventilation versus usual respiratory support	0.5 (−3.9, 4.9)	0.82	4 (−2.76, 10.76)	0.25
Female versus male	−7.83 (−11.93, −3.74)	0.0002	−5 (−11.48, 1.48)	0.13
APACHE >13 versus ≤12	−3.33 (−7.71, 1.04)	0.134	−4 (−10.90, 2.90)	0.25
Intubation versus not	−11.68 (−16.41, −6.92)	< 0.0001	−35 (−58.70, −11.31)	0.004
Age >58 versus ≤58	−8.33 (−13.31, −3.35)	0.0012	−11 (−17.99, −4.01)	0.002
PaO2:FiO2 >100 versus ≤100 at baseline	−0.500 (−4.96, 3.96)	0.83	−0 (−6.48,−6.48)	>0.99
Dexmedetomidine use versus not	−7.88 (-13.33, −2.34)	0.006	−10 (−16.78, −3.23)	0.004

* The age cut-off of 58 years is the median age of the cohort

Table S8: EuroQol-5D-5L at 180 days between patients who were intubated or not intubated.

	Intubated (N=155)	Not intubated (N=162)	P value
Intention-to-treat analysis			
EQ-5D-5L index values			
Median (IQR)	0 (0, 0.42)	1 (0.72, 1)	<0.0001
Mean ± SD	0.19 ± 0.34	0.81 ± 0.31	
EQ VAS			
Median (IQR)	0 (0, 50)	90 (75, 100)	<0.0001
Mean ± SD	19.9 ± 34.15	79.2 ± 28.26	
Analysis of the HRQoL population			
EQ-5D-5L index values			
Median (IQR)	0.70 (0.64, 0.85)	1 (0.81, 1)	<0.0001
Mean ± SD	0.71 ± 0.21	0.89 ± 0.17	
EQ VAS			
Median (IQR)	80 (60, 85)	90 (80, 100)	<0.0001
Mean ± SD	73.6 ± 18.41	87.3 ± 13.06	

EQ-5D-5L, EuroQol-5 dimensions-5 levels; IQR, interquartile range; SD, standard deviation; VAS visual analogue scale.

Table S9: Individual EQ-5D-5L dimension levels at 180 days between patients who were intubated or not intubated.

Dimensions	Intubated (N=42)	Not intubated (N=147)	P value
Mobility, No. (%)			
No problems walking	10 (23.8)	105 (71.4)	
Slight problems walking	15 (35.7)	26 (17.7)	
Moderate problems walking	10 (23.8)	8 (5.4)	< 0.0001
Severe problems walking	5 (11.9)	6 (4.1)	
Unable to walk	2 (4.8)	2 (1.4)	
Self-care, No. (%)			
No problems washing or dressing	16 (38.1)	115 (78.2)	
Slight problems washing or dressing	17 (40.5)	22 (15)	
Moderate problems washing or dressing	4 (9.5)	6 (4.1)	< 0.0001
Severe problems washing or dressing	3 (7.1)	1 (0.7)	
Unable to wash or dress	2 (4.8)	3 (2)	
Usual activities, No. (%)			
No problems doing usual activities	11 (26.2)	109 (74.1)	
Slight problems doing usual activities	20 (47.6)	25 (17)	
Moderate problems doing usual activities	6 (14.3)	9 (6.1)	< 0.0001
Severe problems doing usual activities	3 (7.1)	1 (0.7)	
Unable to do usual activities	2 (4.8)	3 (2)	
Pain or discomfort, No. (%)			
No pain or discomfort	12 (28.6)	103 (70.1)	
Slight pain or discomfort	18 (42.9)	29 (19.7)	
Moderate pain or discomfort	10 (23.8)	13 (8.8)	< 0.0001
Severe pain or discomfort	2 (4.8)	1 (0.7)	
Extreme pain or discomfort	0	1 (0.7)	
Anxiety or depression, No. (%)			
Not anxious or depressed	20 (47.6)	114 (77.6)	
Slightly anxious or depressed	11 (26.2)	24 (16.3)	
Moderately anxious or depressed	8 (19)	9 (6.1)	< 0.0001
Severely anxious or depressed	3 (7.1)	0	
Extremely anxious or depressed	0	0	

* All p values were calculated using Freeman-Halton extension of Fisher test

Figure S1: Flow diagram.