Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods.

Inclusion and exclusion criteria

Inclusion Criteria	1. Adults ≥ 18 years of age.
	2. Suspected or confirmed Covid-19 (i.e., a positive PCR for SARS CoV-2 or pending PCR results).
	3. Hypoxemia requiring oxygen supplementation ≥ 0.4 FiO2 or ≥ 5L nasal cannula.
	4. Bilateral or unilateral chest infiltrates on x-ray as interpreted by the treating team.
	5. Admitted to the ICU or an acute care unit where hemodynamic and respiratory monitoring is feasible.
Exclusion Criteria	1. Immediate need for intubation as determined by the treating team.
	2. Decreased level of consciousness (Glasgow Coma Scale score <10), or significant cognitive impairment hat may interfere with compliance (delirium, dementia)
	3. Contraindication to proning including, but not limited to any of the following:
	4. Open chest or abdomen, abdominal surgery (i.e., laparotomy) within the 4 days,
	5. Unstable spine, facial, cervical, femur, or pelvic fractures.
	6. Limited neck mobility or inability to lie prone comfortably
	7. Skeletal deformities that interfere with proning.
	8. Complete bowel obstruction.
	9. Active upper gastrointestinal bleeding.
	10. Patient is unlikely/unable to prone, or to be compliant as indicated by the treating team.
	11. Body mass index > 40 kg/m^2

Abbreviations: ICU: Intensive care unit; PCR: Polymerase chain reaction; SARS CoV-2: severe acute respiratory syndrome coronavirus-2

List of trial outcomes and definitions

Outcome	Definition	
Primary outcome	Endotracheal Intubation within 30 days	Endotracheal Intubation within 30 days of randomization
Secondary outcomes	Mortality at 60 days	Status of life at 60-days
	Invasive mechanical ventilation free days at 30 days	Number of days alive and not receiving mechanical ventilation
	Non-invasive ventilation free days at 30 days	Number of days alive and not receiving non-invasive mechanical ventilation
	Days alive and outside the Intensive Care Unit	Number of days alive and outside the Intensive Care Unit
	Days alive and outside of the hospital truncated at 60 days	Number of days alive and outside of hospital
Safety outcomes	Complications from proning	Includes any of the following: accidental removal of intravenous access, hypotension, pressure injuries, or other occurring during the proning intervention.
	Adverse Events	Any adverse event occurring following study mandated procedures, directly related to the treatment or intervention. a) Any serious adverse event occurring following study mandated procedures, directly related to the treatment or intervention that results in any of the following outcomes: (death, life-threatening adverse event, disability, or incapacity) b) Any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above, which the attending physician perceives may be directly related to enrolment
Protocol deviation	Intervention arm	A protocol deviation in the Intervention arm (prone) is defined as the number of patients with zero proning hours across all days before meeting the stopping criteria.
	Control arm	A protocol deviation in the control arm is defined as the number of patients with any proning hours before meeting the stopping criteria

eTable 1. Screening and enrollment by site

Country	Center	Randomized patients			Total Per Country
		Proning	Control	Total Per Site	
Canada	St Joseph's Healthcare Hamilton	17	16	**33**	**161**
	Juravinski Hospital	5	4	**9**	
	Hamilton General Hospital	1	0	**1**	
	Niagara Health St. Catharine's General	2	6	**8**	
	South Health Campus	7	4	**11**	
	Foothills Medical Centre	15	13	**28**	
	Rockyview General Hospital	6	4	**10**	
	Peter Lougheed Centre	21	22	**43**	
	Mount Sinai Hospital	8	4	**12**	
	CHU de Québec-Université Laval	2	3	**5**	
	University Health Network	1	0	**1**	
Saudi Arabia	King Abdulaziz Medical City, Riyadh	31	31	**62**	**162**
	King Abdulaziz Medical City, Jeddah	5	7	**12**	
	King Fahd Hospital of the University, Khobar	20	19	**39**	
	King Faisal Specialist Hospital and Research Centre, Riyadh	18	18	**36**	
	Prince Mohammad Bin Abdulaziz Hospital Madinah	0	2	**2**	
	King Abdulaziz Hospital, NGHA	6	5	**11**	
Kuwait	Jaber AL Ahmed hospital	11	11	**22**	**49**
	Al-Amiri Hospital	15	12	**27**	
United States	Lyndon B Johnson Hospital, Houston	15	13	**28**	**28**

eTable 2. Adverse events and serious adverse events

Adverse Events n **(%)**	**Proning Group (n=205)**		**Control Group (n=195)**	
	Patients	**Events**	**Patients**	**Events**
All Events	21 (10)	26	0 (0)	0
Musculoskeletal and Other Pain	13 (62)	16 (62)	0 (0)	0 (0)
Desaturation	2 (10)	4 (15)	0 (0)	0 (0)
Coughing	1 (5)	1 (4)	0 (0)	0 (0)
Dizziness & Shortness of Breath	1 (5)	1 (4)	0 (0)	0 (0)
Hypotension & Desaturation	1 (5)	1 (4)	0 (0)	0 (0)
Accidental Intravenous Access Removal	1 (5)	1 (4)	0 (0)	0 (0)
Nausea	1 (5)	1 (4)	0 (0)	0 (0)
Shortness of breath	1 (5)	1 (4)	0 (0)	0 (0)
Serious Adverse Events n (%)	0 (0)		0 (0)	

eTable 3. Additional characteristics of patients at baseline

Category	Proning Group (n=205)	Control Group (n=195)
Comorbidities		
Cardiac n (%)		
Hypertension	94 (46)	96 (49)
CAD	12 (6)	17 (9)
Arrhythmia	6 (3)	8 (4)
CHF	6 (3)	5 (3)
Stroke	5 (2)	9 (5)
Respiratory n (%)		
Asthma	16 (8)	17 (9)
COPD	7 (3)	8 (4)
Others	2 (1)	1 (0.50)
ILD	1 (0.5)	1 (0.50)
Gastrointestinal n (%)		
IBD	1 (0.5)	2 (1)
Cirrhosis	0 (0)	0 (0)
Hematologic n (%)	4 (2)	0 (0)
Immunocompromised n (%)	6 (3)	6 (3)
Endocrine n (%)		
Diabetes	83 (40)	76 (39)
Hypothyroidism	14 (7)	19 (10)
Morbid obesity	0 (0)	1 (0.5)
Renal n (%)		
CKD	13 (6)	7 (4)
ESRD on dialysis	2 (1)	5 (3)
Solid Organ Malignancy n (%)	2 (1)	3 (2)
Hematological malignancy n (%)	8 (4)	3 (2)
Rheumatological Diseases n (%)	9 (4)	9 (5)
Transplant n (%)	6 (3)	3 (2)
None n (%)	47 (23)	41 (21)
Other comorbidities n (%)	71 (35)	74 (38)
Pharmacologic interventions		
Medication n (%)		
Statin	58 (28)	61 (31)
ARB	33 (16)	30 (15)
ACE-I	20 (10)	22 (11)
Inotropes n (%)	1 (0.5)	0 (0)
Dopamine	1 (0.5)	0 (0)
Vasopressors n (%)	1 (0.5)	1 (0.5)
Norepinephrine	1 (0.5)	1 (0.5)
Vasopressin	0 (0)	0 (0)
Phenylephrine	0 (0)	0 (0)
Sedatives n (%)	8 (4)	11 (6)
Dexmedetomidine	4 (2)	5 (3)
Benzodiazepines	3 (1)	3 (2)

Haloperidol	1 (0.50)	0 (0)
Fentanyl	0 (0)	1 (0.5)
Zopiclone	0 (0)	1 (0.5)
Ketamine	0 (0)	1 (0.5)
Corticosteroids n (%)	194 (95)	186 (95)
Dexamethasone	186 (91)	178 (91)
Methylprednisolone	5 (2)	6 (3)
Prednisone	2 (1)	0 (0)
Hydrocortisone	1 (0.5)	1 (0.5)
Fluticasone[a]	0 (0)	1 (0.5)
Prednisolone	0 (0)	1 (0.5)
Antibiotics n (%)	163 (80)	154 (79)
Cephalosporins	103 (50)	99 (51)
Macrolides	85 (41)	80 (41.)
Others	52 (25)	57 (29)
Quinolones	10 (5)	6 (3)
Tetracyclines	15 (7)	11 (6)
Penicillins	9 (4)	8 (4)
Carbapenem	7 (3)	9 (5)
Anticoagulation n (%)	181 (88)	179 (92)
Prophylactic dosing		
Enoxaparin	94 (46)	90 (46)
Tinzaparin	37 (18)	37 (19)
Heparin	15 (7)	15 (8)
Dalteparin	12 (6)	13 (7)
Therapeutic Dosing		
Enoxaparin	9 (4)	8 (4)
Heparin	5 (2)	9 (5)
Dalteparin	3 (1)	1 (0.5)
Warfarin	3 (1)	0 (0)
Rivaroxaban	2 (1)	2 (1)
Apixaban	1 (0.5)	4 (2)

Abbreviations: ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CAD – coronary artery disease; CHF – congestive heart failure; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; ESRD – end-stage renal disease; IBD – inflammatory bowel disease; ILD – interstitial lung disease.
[a]Participant on Fluticasone also receiving Dexamethasone

eTable 4. Interventions and cointerventions after randomization

Variable	Proning Group (n= 205)	Control Group (n=195)
Prone positioning		
Duration of daily proning as randomized cohort (day 1) — hours/day, median (IQR)	5 (2 to 8)	0 (0 - 0)
Duration of daily proning per-protocol cohort [a] (day 1) — hours/day, median (IQR)	6 (2.5 – 8)	–
Duration of daily proning as randomized cohort (days 1 to 4) — hours/day, median (IQR)	4.8 (1.8 – 8)	0 (0 – 0)
Duration of daily proning per-protocol cohort [a] (days 1 to 4) — hours/day, median (IQR)	5 (2.6 – 8)	–
Days of proning — days, median (IQR)	3 (1 to 5)	0 (0 – 0)
Patients who underwent awake proning — no. (%)	184 (90)	38 (19)
Respiratory support — no. (%) [b]		
High-flow oxygen	176 (86)	165 (85)
Low-flow oxygen [c]	143 (70)	122 (63)
Noninvasive positive pressure ventilation	53 (26)	60 (31)
Kidney replacement therapy — no. (%) [d]	5 (2)	10 (5)
Vasoactive agents — no. (%) [d]	29 (14)	37 (19)
Median daily fluid balance (days 1 to 4) — ml, median (IQR) [e]	-176 (-474 to 300) n=182	- 50 (-434 to 346) n=178
Pharmacologic interventions — no. (%) [d]		
Corticosteroids	202 (99)	193 (99)
Prophylactic dose anticoagulation	184 (90)	176 (90)
Tocilizumab	30 (15)	24 (12)
Remdesivir	28 (14)	21 (11)
Therapeutic dose anticoagulation	24 (12)	21 (11)
Hydroxychloroquine or chloroquine	7 (3)	7 (4)

Convalescent plasma — no. (%)	1 (0.5)	4 (2)

IQR: interquartile range

[a] Per-protocol analysis excluded 21 patients from the intervention group who did not undergo any prone positioning and 38 patients from the control group who underwent any hours of prone positioning

[b] Representing the number of patients who received respiratory support during intensive care or acute care stay.

[c] Low-flow oxygen includes oxygen delivery via any device other than high-flow nasal cannula or non-invasive ventilation regardless of the fraction of oxygen delivered to the patient.

[d] These frequencies represent the number of patients who received an intervention before meeting proning stopping criteria during daily data collection, it does not include periods after meeting the stopping criteria (i.e., death, improvement in the fraction of inspired Oxygen requirement by 40% from baseline value that is sustained for 24 hours; intubation; or the patient is discharged from the ICU or monitored setting).

[e] The mean daily fluid balance was derived from 182 patients in the intervention group and 178 patients in the control group.

eTable 5. Protocol deviations

Variable	Proning Group (n=205)	Control Group (n=195)
Protocol deviation, n (%)	21 (10)	38 (19)
Reasons, n (%)		
Patient Preference	15 (71)	21 (55)
Care Team Preference	0 (0)	19 (50)
Not Documented	3 (14)	0 (0)
Oxygenation Mode[a]	1 (5)	0 (0)
Agitation	1 (5)	0 (0)
Desaturation	1 (5)	0 (0)
Patient was randomized late in the day	1 (5)	0 (0)
Allocation miscommunication to care team	0 (0)	1 (3)

[a] Oxygenation delivery mode was deemed as a barrier to prone positioning
The proportion of patients with a protocol deviation of the entire group is described. A protocol deviation in the proning group was defined as any patient with zero hours of proning across all days before meeting intervention stopping criteria. Each patient may have more than 1 reason for the protocol deviation. A protocol deviation in the control arm is defined as any prone positioning after randomization before meeting intervention stopping criteria.

eTable 6. Additional co-interventions after randomization

Category	Proning Group (n=205)	Control Group (n=195)
Anticoagulation n (%)	204 (100) [a]	191 (98) [a]
Prophylactic dosing	184 (90)	176 (90)
Enoxaparin	110 (54)	105 (54)
Tinzaparin	47 (23)	41 (21)
Heparin	18 (9)	20 (10)
Dalteparin	17 (8)	16 (8)
Therapeutic dosing	24 (12)	21 (11)
Heparin	19 (9)	17 (9)
Dalteparin	4 (2)	3 (2)
Apixaban	3 (1)	7 (4)
Warfarin	3 (1)	1 (0.5)
Tinzaparin	2 (1)	2 (1)
Rivaroxaban	2 (1)	1 (0.5)
Corticosteroids n (%)	202 (99) [a]	193 (99) [a]
Dexamethasone	197 (96)	186 (95)
Methylprednisolone	9 (4)	11 (6)
Prednisone	7 (3)	8 (4)
Hydrocortisone	3 (1)	6 (3)
Prednisolone	0 (0)	1 (0.5)
COVID-19 Interventions n (%)	75 (37) [a]	63 (32) [a]
Remdesivir	28 (14)	21 (11)
Favipravir	19 (9)	13 (7)
Lopinavir/ Ritonavir	10 (5)	12 (6)
CQ/ HCQ	7 (3)	7 (4)
CQ/ HCQ plus azithromycin	5 (2)	3 (2)
Azithromycin	4 (2)	3 (2)
Vitamin C	4 (2)	6 (3)
Ribavirin	3 (1)	3 (2)
Convalescent plasma	1 (0.5)	4 (2)
LSALT Peptide	1 (0.5)	0 (0)
Vadadustat	1 (0.5)	0 (0)
Ivermectin	0 (0)	1 (0.5)

Abbreviations: CQ – chloroquine; HCQ – hydroxychloroquine.
[a] Total number of participants includes some patients receiving multiple co-interventions at any time during 30-day study period.

eTable 7. Duration of oxygenation modality use after randomization

Variable	Proning Group	Control Group
Days on HFO median	4.0 (interquartile range 2 to 6) n=176	4.0 (interquartile range 2 to 6) n=165
Days on LFO median	3.0 (interquartile range 2 to 5) n=143	3.0 (interquartile range 2 to 6) n=122
Days on NIPPV median	2.0 (interquartile range 1 to 5) n=53	2.0 (interquartile range 1 to 4) n=60

Abbreviations: LFO: low flow oxygen; HFO: high flow oxygen; NIPPV: non-invasive positive pressure ventilation
For those patients on the specified oxygen modality, the duration of oxygenation modality post randomization during the trial intervention period is described. Patients may have received more than one modality during the trial intervention period.

eTable 8. Additional analysis for study outcomes

Outcome	Adjusted Relative Effect or Difference (95% CI)	P Value
Primary outcome [a] Endotracheal intubation at 30 days	HR 0.79 (0.57 to 1.09)	0.16
Secondary outcomes [a]		
Mortality at 60 days	HR 0.93 (0.62 to 1.40)	0.73
Ventilation free days at 30 days	MD 2.04 (-0.41 to 4.49)	0.10
Invasive ventilation free days at 30 days	MD 2.03 (-0.39 to 4.44)	0.10
Intensive Care Unit free days at 60 days	MD 4.12 (-0.44 to 8.69)	0.08
Hospital free days at 60 days	MD 3.41 (-0.98 to 7.79)	0.13
Post hoc outcomes		
Composite of intubation or death at 30 days [b]	HR 0.75 (0.55 to 1.02) [c]	0.07
	RR 0.82 (0.67 to 1.00) [d]	0.05
Mixed effect modelling [e]	HR 0.80 (0.58 to 1.11)	0.18

Abbreviations: CI – Confidence interval, HR – hazard ratios, MD – Mean Difference, RR – Relative risk

[a] Analysis were adjusted for center and severity of hypoxemia.

[b] 74 patients (36%) in the proning group and 89 patients (46%) in the control group developed the outcome

[c] Analysis for this *post hoc* composite outcome was done using unadjusted Cox regression (proportional hazard) analysis

[d] Analysis for this *post hoc* composite outcome was done using $\chi 2$ test.

[e] Mixed effect modelling using site as random effect

eTable 9. Subgroup analyses for endotracheal intubation outcome

Subgroup	Awake Proning Events/total	Control Events/total	Hazard Ratio (95% CI)	Absolute difference (95% CI)	P-Interaction	FDR%
Severity of hypoxia at baseline					0.03	12
SpO_2:FiO_2 >150	13/84 (15)	25/78 (32)	0.44 (0.23 to 0.87)	-16.58% (-29.50 to -3.65)		
SpO_2:FiO_2 ≤150	57/121 (47)	54/117 (46)	1.02 (0.70 to 1.48)	0.95% (-11.72 to 13.63)		
Respiratory Support at baseline					0.54	73
Low flow oxygen	14/45 (31)	10/43 (23)	1.35 (0.60 to 3.05)	7.86% (-10.65 to 26.36)		
High flow oxygen	49/148 (33)	65/132 (49)	0.61 (0.42 to 0.88)	-16.13% (-27.55 to -4.72)		
NIPPV	7/12 (58)	4/20 (20)	3.69 (1.07 to 12.70)	38.33% (5.39 to 71.28)		
Age					0.73	73
<70 years	60/174 (34)	63/152 (41)	0.78 (0.55 to 1.12)	-6.96% (-17.5 to 3.58)		
≥70 years	10/31 (32)	16/43 (37)	0.90 (0.41 to 1.99)	-4.95% (-26.8 to 16.9)		
Sex					0.64	73
Male	51/149 (34)	56/134 (42)	0.77 (0.53 to 1.12)	-7.56% (-18.87 to 3.74)		
Female	19/56 (34)	23/61 (38)	0.92 (0.50 to 1.68)	-3.78% (-21.15 to 13.59)		

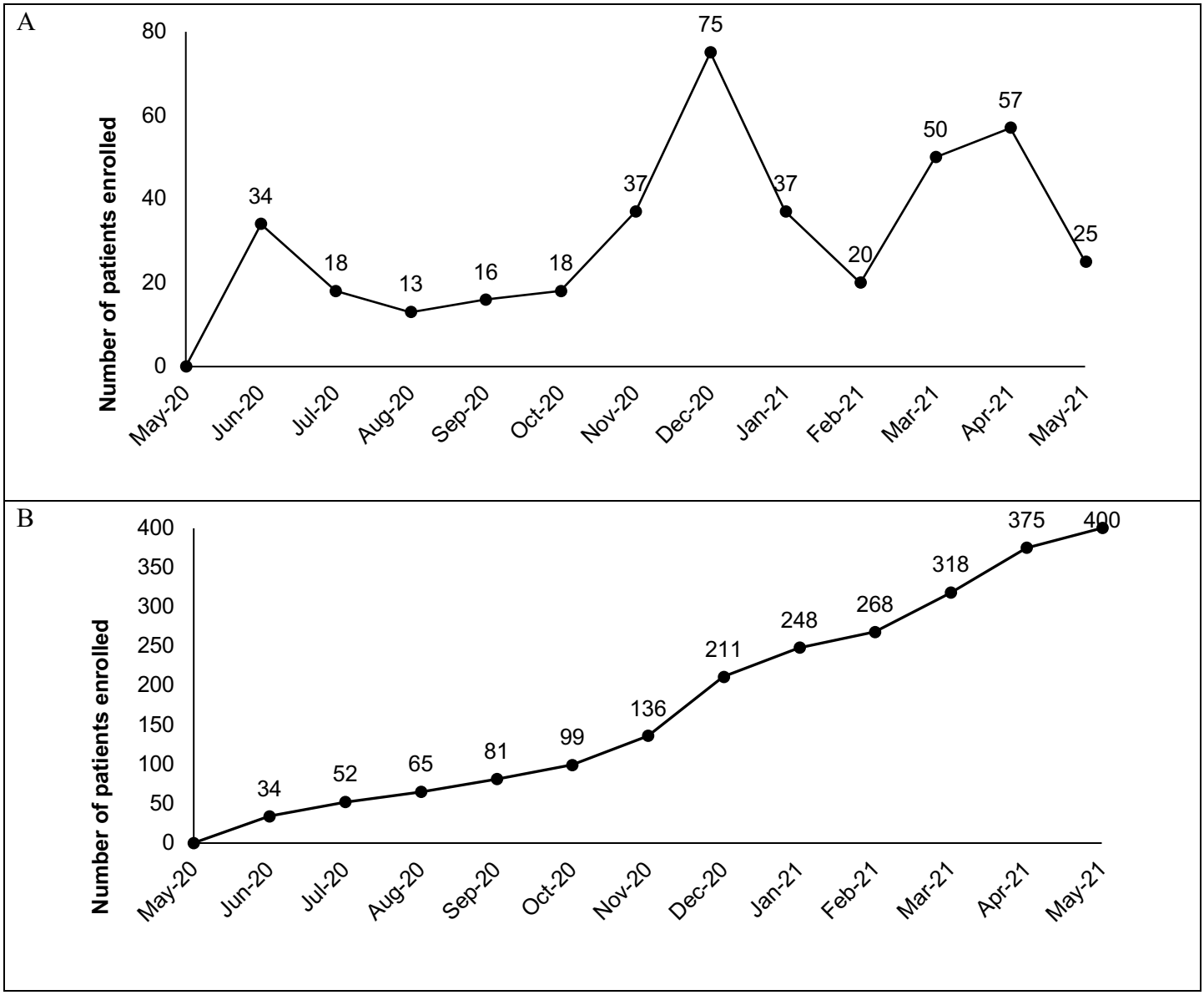
Abbreviations: CI: Confidence interval; FDR: false discovery rate; HFO: High flow oxygen; HR: Hazard ratio; LFO: Low flow oxygen; NIPPV: Non-invasive positive pressure ventilation; SpO_2:FiO_2: pulse oximetric saturation to fraction of inspired oxygen.
Two-sided P values for interaction are reported. The false discovery rate accounts for multiplicity by calculating the expected proportion of tests with false positives at a specified rank of a set of tests.

eTable 10. Reasons for proning interruption (less than 8 hours) in the proning group

Reason	Number of patients (n=205) [b]
Patient Preference	140 (68)
Late Randomization	33 (16)
Not Documented	18 (9)
Desaturation	8 (4)
Oxygenation Mode [a]	5 (2)
Lack of care team support	5 (2)
Agitation	4 (2)
Patient transferred within hospital	4 (2)
Procedure	1 (0.5)
Discharged from Hospital	1 (0.5)
Delirium	1 (0.5)

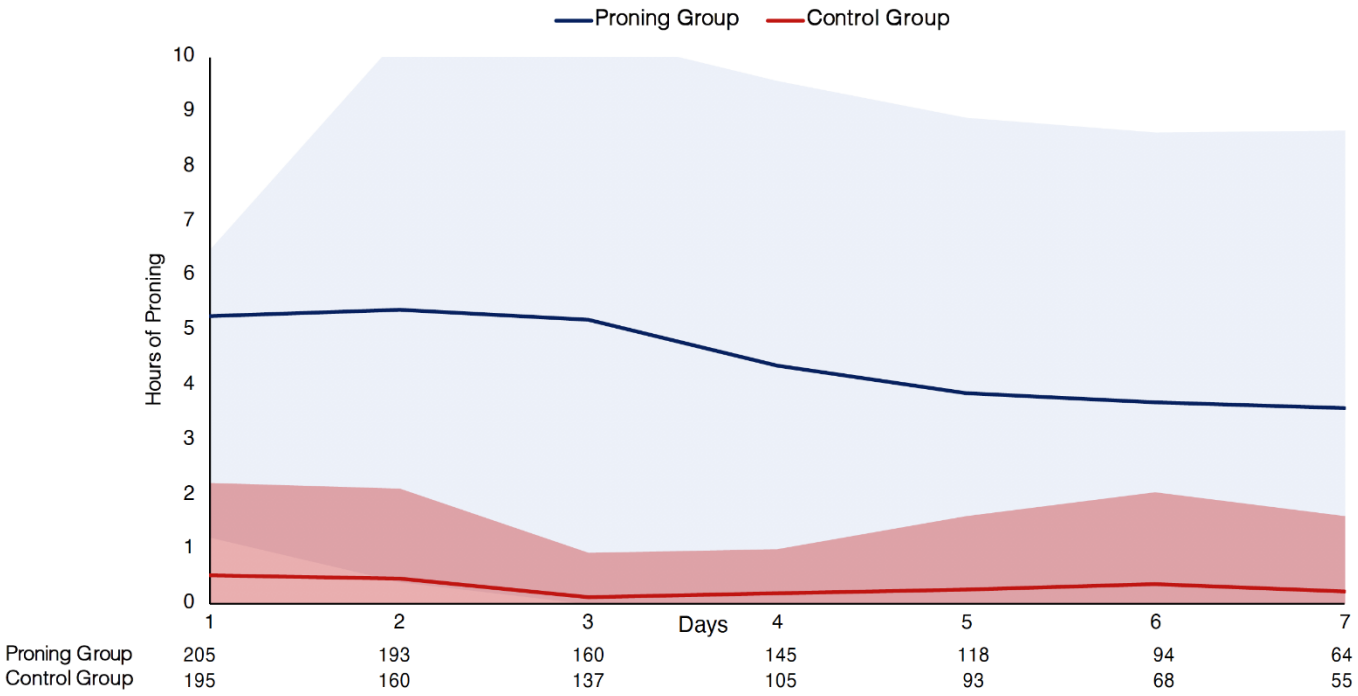
[a] Oxygenation mode was deemed as a barrier to prone positioning that day.
[b] Each patient may have more than 1 reason for the incomplete proning. The second column indicate the number of patients with a specific reason at least once.

eFigure 1. Monthly and cumulative enrollment



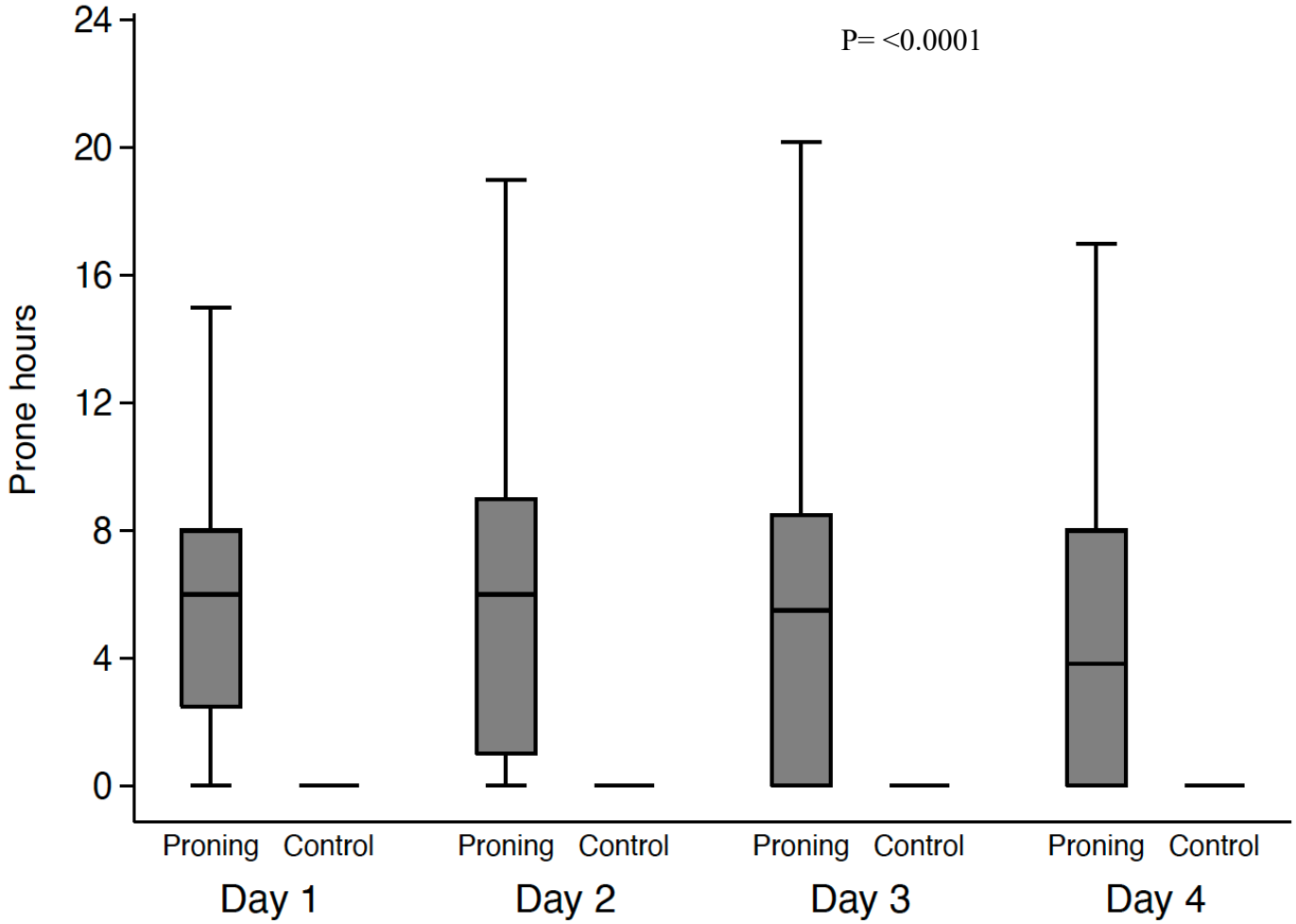
Panel A: Monthly enrollment. Panel B: Cumulative enrollment.

eFigure 2. Duration of proning over time



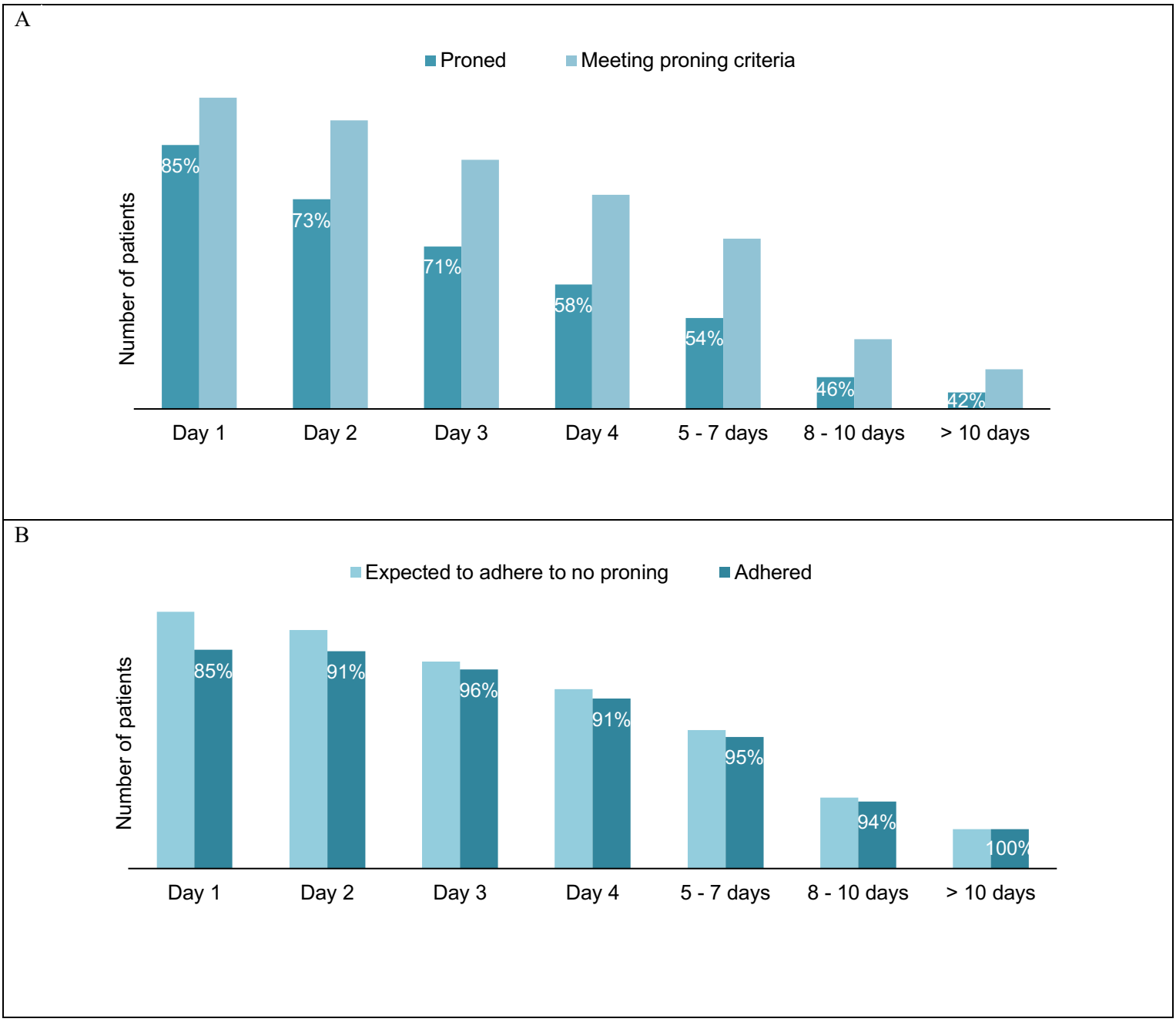
The means and standard deviations are displayed for the daily proning hours in the proning group (blue line) and in the control group (red line) over the first 7 days after randomization.

eFigure 3. Duration of proning in the per protocol population on days 1-4



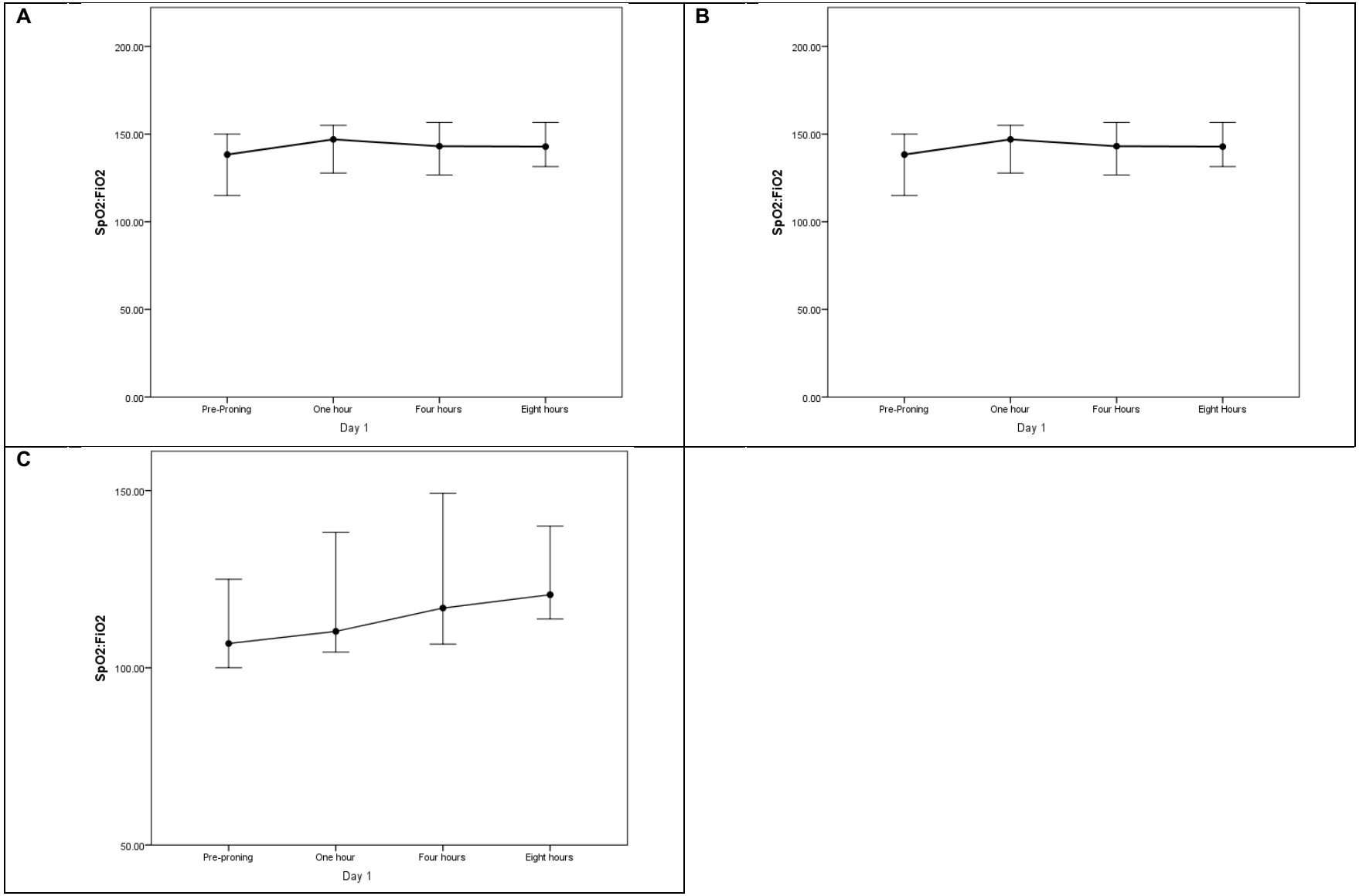
Excluding patients who did not prone in the intervention arm [n=21], and patients who did any proning in the control arm [n= 38]. Box plots are displayed with medians and quartiles 1 and 3. The error bars refer to 1.5x interquartile range. The P-value for the difference between the two groups over time is reported using a mixed linear model.

eFigure 4. Adherence to any prone positioning in the prone positioning group and control group



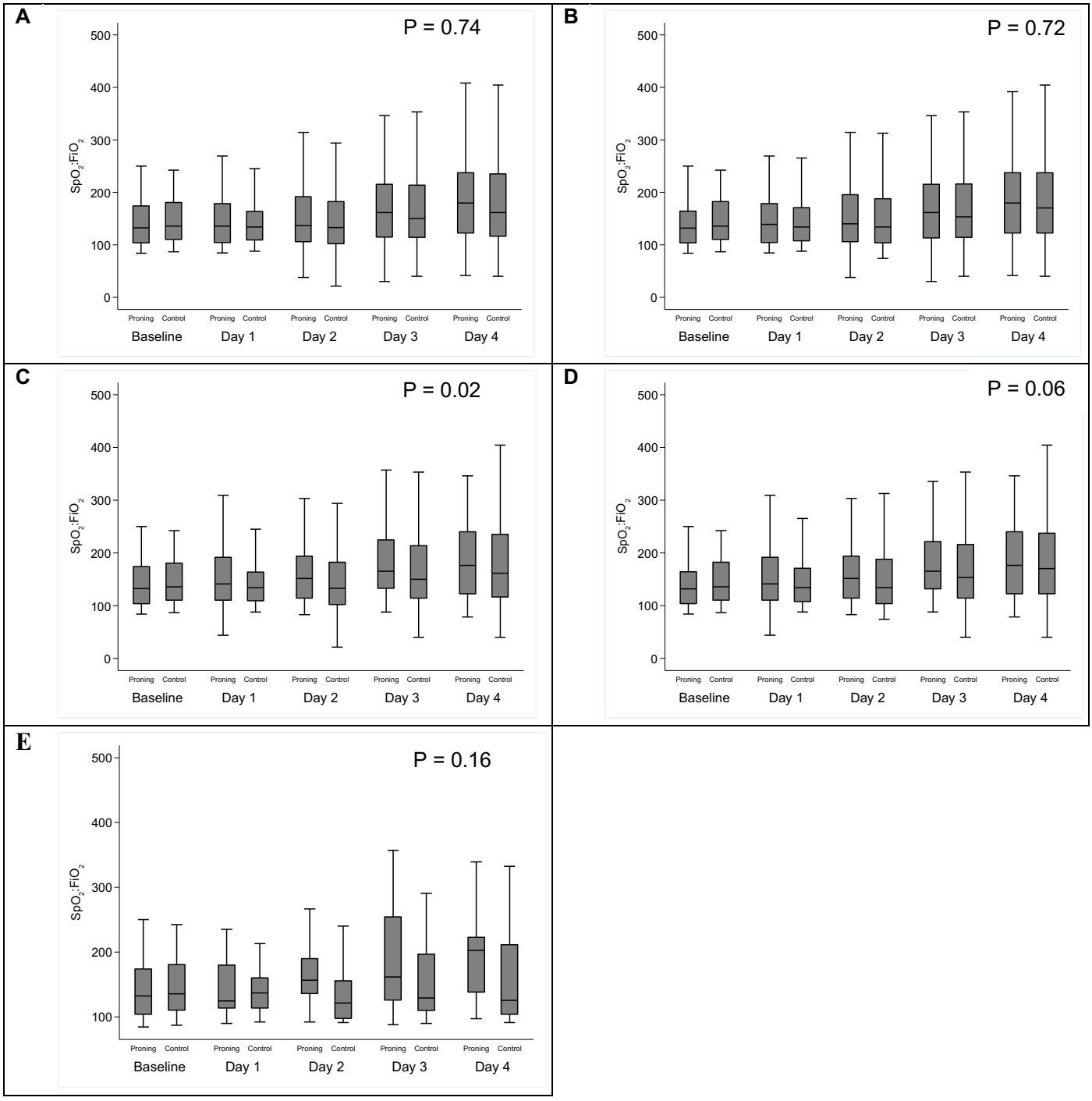
Panel A: Adherence to any prone positioning in the prone positioning group: Proportion of patients in the prone positioning group who performed proning (dark blue labeled: Proned) daily in relation to the total number of patients who did not meet stopping criteria (light blue labeled: Meeting proning criteria) that day. **Panel B:** Adherence to no prone positioning in the control group: Proportion of patients in the control group who did not perform any prone positioning dark blue (labeled: Adhered to no proning) in relation to the total number of patients who did not meet study stopping criteria (light blue labeled: Expected to adhere to proning).

eFigure 5. Mean SpO_2:FiO_2 and standard deviations (error bars) pre and post proning (on day 1)



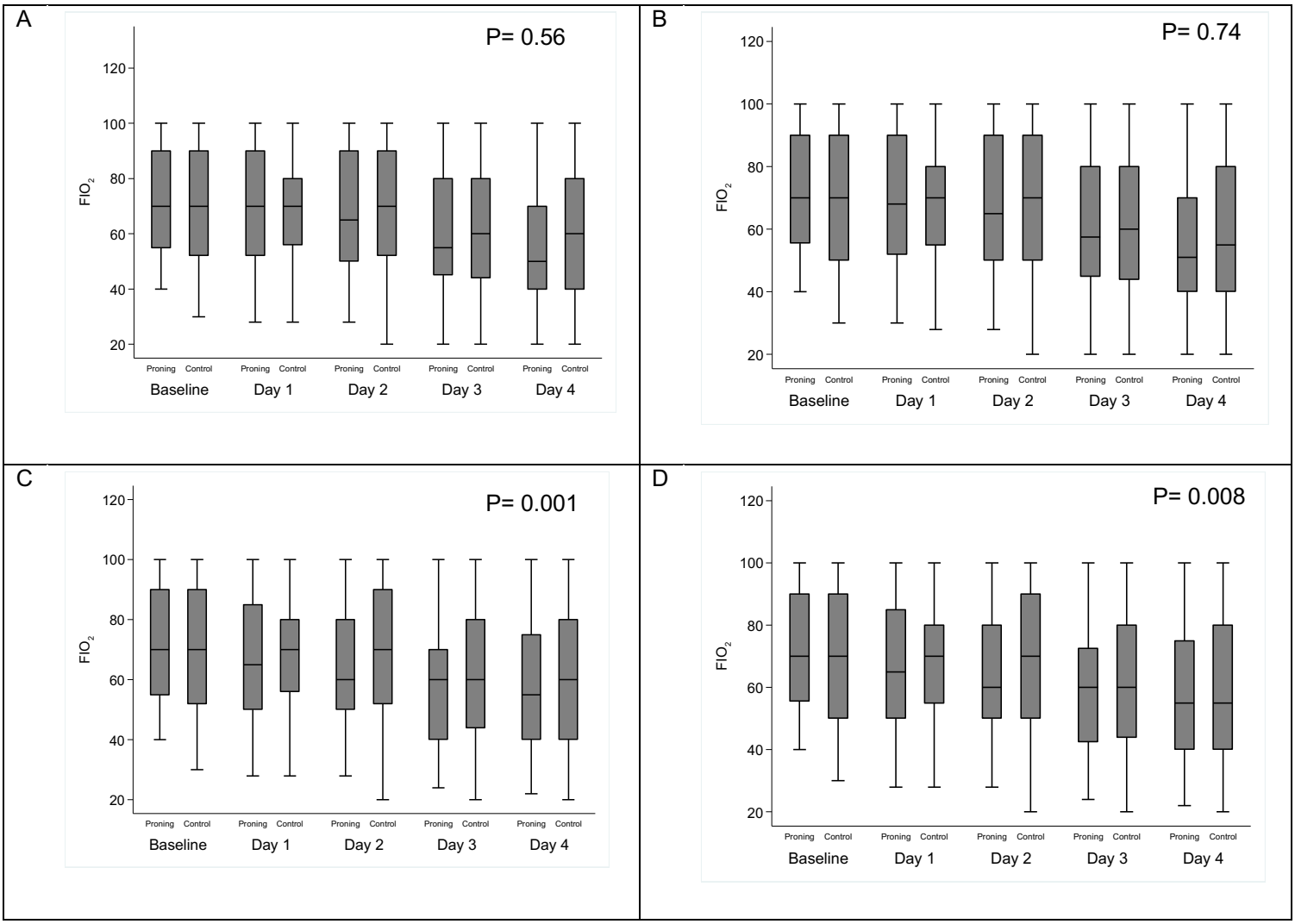
Abbreviations: SpO_2:FiO_2 – peripheral oxygen saturation to fraction of inspired oxygen ratio.
Panel A: SpO_2:FiO_2 values pre-proning, 1 hour after proning, 4 hours after proning, and 8 hours after proning in the intention-to-treat cohort. **Panel B:** SpO_2:FiO_2 values pre-proning, 1 hour after proning, 4 hours after proning, and 8 hours after proning in the per protocol cohort. **Panel C:** SpO_2:FiO_2 pre-proning, 1 hour after proning, 4 hours after proning, and 8 hours after proning while proning.

eFigure 6. SpO2:FiO2 over time



Abbreviations: SpO_2:FiO_2 – peripheral oxygen saturation to fraction of inspired oxygen ratio.
The box plots are displayed with medians and quartiles 1 and 3. The error bars refer to 1.5x interquartile range. The P-value for the difference between the two groups over time is reported using a mixed linear model. **Panel A:** SpO2:FiO2 over time in the intention-to-treat cohort in the prone positioning (pre-proning values) and control groups. **Panel B:** SpO2:FiO2 over time in the per protocol cohort in the prone positioning (pre-proning values) and control groups. **Panel C:** SpO2:FiO2 over time in the intention-to-treat cohort in the prone positioning (8 hours post proning values) and control groups. **Panel D:** SpO2:FiO2 over time in the Per protocol cohort in the prone positioning (8 hours post proning values) and control groups. **Panel E:** SpO2:FiO2 over time while in prone positioning the prone positioning (8 hours post proning values) group versus control group.

eFigure 7. Fraction of inspired oxygen in study groups over time



Abbreviations: FiO2 – Fraction of inspired oxygen.
Box plots are displayed with medians and quartiles 1 and 3. The error bars refer to 1.5x interquartile range. The P-value for the difference between the two groups over time is reported using a mixed linear model. **Panel A:** Fraction of inspired oxygen in the proning (pre-proning values) and control groups on days 1 to 4 by in the intention-to-treat cohort. **Panel B:** Fraction of inspired oxygen in the proning (pre-proning values) and control groups on days 1 to 4 by in the per protocol cohort. **Panel C:** Fraction of inspired oxygen in the proning (8 hours after proning) and control groups on days 1 to 4 by in the intention-to-treat cohort. **Panel D:** Fraction of inspired oxygen in the proning (8 hours after proning) and control groups on days 1 to 4 by in the per protocol cohort.