

Supplementary Online Content

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

eAppendix. Supplemental Methods

Rationale for the inclusion and exclusion criteria

Older patients and longer expected duration of surgery are well known major risk factors for the development of postoperative respiratory complications, thus, we aimed to enroll an ‘enriched’ population where the rate of the primary outcome would be expected to be higher. ‘Major surgery’ was defined as an expected duration of surgery greater than 2 hours and an expected hospital stay of at least one night. In addition, the use of an arterial line during surgery also denotes a higher risk procedure, and permits sampling of arterial blood gases for evaluation of PaO₂. The exclusion criteria are related to situations where: 1) ventilation practice differs markedly (one-lung ventilation in thoracic surgery and no ventilation during cardiopulmonary bypass in cardiac surgery); 2) the use of low tidal volume and consequent hypercapnia can induce harm (intracranial surgery); and 3) the outcome and management is expected to be different from usual (pregnancy and use of nitrous oxide).

Sensitivity analyses

Since the primary outcome of the present study is a composite one, the choice of the statistical method is an important part of design because various methods provide different power, depending on the situation. In addition to the standard analysis described, the following pre-specified analyses were performed to test the robustness of the trial findings:

- Count analysis: the number of positive component events (i.e., ‘count’) across the composite was assessed. The groups were compared on the count using a Wilcoxon rank–sum test, and the odds ratio with the 95%

confidence interval was assessed with a proportional odds logistic regression model;

- Individual component analysis: the effect of the intervention in each component was analysed using a generalized linear model using a Bonferroni correction for multiple comparisons. The 99.37% Bonferroni-corrected confidence intervals are reported ($1 - 0.05/8 = 0.9937$);
- Common effect test: A multivariate (i.e., multiple outcomes per subject) generalized estimating equations (GEE) model was used to estimate a common effect odds ratio across the components;
- Average relative effect test: The average relative effect test was assessed by averaging the component-specific treatment effect from the distinct effects model, and testing whether the average is equal to zero. In the GEE distinct effect model a distinct treatment effect is estimated for each component;
- Heterogeneity of treatment effect: Heterogeneity of treatment effect across components was assessed by a treatment-by-component interaction test in the distinct effects GEE model.

eTable 1. Definition of the Primary Outcome

	Definition
Pneumonia	Defined as need of antibiotics for a suspected respiratory infection and one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever and/or white blood cell count $> 12 \times 10^9/L$
Bronchospasm	Defined as newly detected expiratory wheeze treated with bronchodilators
Atelectasis	Defined as lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
Pulmonary congestion	Defined as clinical signs of congestion, including dyspnoea, oedema, rales, and jugular venous distention, with or without chest x-ray demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates
Respiratory failure	Defined as a postoperative $PaO_2 < 60$ mmHg on room air, a PaO_2 / FiO_2 ratio < 300 mmHg or arterial oxyhaemoglobin saturation measured with pulse oximetry $< 90\%$ and requiring oxygen therapy
Pleural effusion	Defined as chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Pneumothorax	Defined as air in the pleural space with no vascular bed surrounding the visceral pleura
Requirement for mechanical ventilation	Defined as unplanned need of non-invasive or invasive ventilation

eTable 2. Definitions of the Secondary Outcomes	
Outcome	Definition
Postoperative pulmonary complications during hospital stay	As defined in eTable 1 but considering the whole hospital stay
Pulmonary embolism	Presence of segmental or subsegmental pulmonary embolus diagnosed on computerized tomography or high probability pulmonary embolus on ventilator-perfusion scan
Acute respiratory distress syndrome	According to Berlin definition
SIRS	Two or more of the following: <ul style="list-style-type: none"> • Temperature < 36 °C or > 38 °C; or • Heart rate > 90 beats per minute; or • Respiratory rate > 20 breaths per minute; or, PaCO₂ < 32 mmHg; or • White blood cell count < 4000 cells/mm³ or > 12000 cells/mm³; or more than 10% immature neutrophils (band forms).
Sepsis	SIRS criteria plus a definitive or presumed infectious foci
Acute kidney injury	According to RIFLE criteria: <ul style="list-style-type: none"> • Risk: 1.5-fold increase in the serum creatinine, GFR decrease by 25%, or urine output < 0.5 mL/kg per hour for 6 hours; or • Injury: Two-fold increase in the serum creatinine, or GFR decrease by 50%, or urine output < 0.5 mL/kg per hour for 12 hours; or • Failure: Three-fold increase in the serum creatinine, or GFR decrease by 75%, or urine output of < 0.3 mL/kg per hour for 24 hours, or no urine output (anuria) for 12 hours; or • Loss: Complete loss of kidney function (e.g., need for renal replacement therapy) for more than four weeks; or • End-stage kidney disease: Complete loss of kidney function (e.g., need for renal replacement therapy) for more than three months.
Wound infection	Superficial or deep surgical site infection according to CDC definition in the first seven days
Intraoperative need of vasopressor	Defined as the need of aramine, norepinephrine, ephedrine, phenylephrine, epinephrine and/or vasopressin in the intraoperative period
Unplanned ICU admission	Any admission that was not previously planned in the plan of care
Need for rapid response team call	Any call for the rapid response team while in the ward
ICU length of stay	Days from ICU admission to ICU discharge
Hospital length of stay	Days from hospital admission to hospital discharge
Hospital mortality	Death from any cause during hospital stay
<i>ICU: intensive care unit; SIRS: systemic inflammatory response syndrome; CDC: Centers for Disease Control; GFR: glomerular filtration rate</i>	

eTable 3. Missing Values for Study Variables

	Total (n = 1206)	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)
Age	3 (0.2)	1 (0.2)	2 (0.3)
Gender	0 (0.0)	0 (0.0)	0 (0.0)
Weight	7 (0.6)	2 (0.3)	5 (0.8)
ARISCAT	134 (11.1)	60 (9.8)	74 (12.5)
Preoperative SpO ₂	13 (1.1)	6 (1.0)	7 (1.2)
Preoperative HCO ₃	37 (3.1)	13 (2.1)	24 (4.1)
Preoperative hemoglobin	29 (2.4)	8 (1.3)	21 (3.5)
Preoperative creatinine	356 (29.5)	172 (28.0)	184 (31.1)
Diabetes mellitus	2 (0.2)	1 (0.2)	1 (0.2)
Hypertension	2 (0.2)	1 (0.2)	1 (0.2)
Coronary artery disease	2 (0.2)	1 (0.2)	1 (0.2)
Chronic renal disease	2 (0.2)	1 (0.2)	1 (0.2)
Chronic liver disease	2 (0.2)	1 (0.2)	1 (0.2)
Current smoker	0 (0.0)	0 (0.0)	0 (0.0)
COPD	0 (0.0)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease	0 (0.0)	0 (0.0)	0 (0.0)
Bronchiectasis	0 (0.0)	0 (0.0)	0 (0.0)
Obstructive sleep apnea	0 (0.0)	0 (0.0)	0 (0.0)
Obesity	49 (4.1)	19 (3.1)	30 (5.1)
Recent LRTI	0 (0.0)	0 (0.0)	0 (0.0)
Type of Surgery	1 (0.1)	0 (0.0)	1 (0.2)
Tidal volume	24 (2.0)	14 (2.3)	10 (1.7)
PEEP	0 (0.0)	0 (0.0)	0 (0.0)
Highest peak pressure	43 (3.6)	23 (3.7)	20 (3.4)
Lowest respiratory rate	29 (2.4)	20 (3.3)	9 (1.5)
Highest respiratory rate	27 (2.2)	17 (2.8)	10 (1.7)
Lowest SpO ₂	22 (1.8)	15 (2.4)	7 (1.2)
Lowest FiO ₂	28 (2.3)	17 (2.8)	11 (1.9)
Highest FiO ₂	27 (2.2)	17 (2.8)	10 (1.7)
Highest etCO ₂	27 (2.2)	15 (2.4)	12 (2.0)
pH after induction	76 (6.3)	39 (6.4)	37 (6.2)
PaO ₂ after induction	76 (6.3)	37 (6.0)	39 (6.6)
PaCO ₂ after induction	74 (6.1)	37 (6.0)	37 (6.2)

eTable 3. Missing Values for Study Variables

	Total (n = 1206)	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)
HCO ₃ after induction	85 (7.0)	44 (7.2)	41 (6.9)
PaO ₂ / FiO ₂ after induction	101 (8.4)	48 (7.8)	53 (9.0)
Hemoglobin after induction	74 (6.1)	38 (6.2)	36 (6.1)
Base excess after induction	88 (7.3)	43 (7.0)	45 (7.6)
Lactate after induction	119 (9.9)	55 (9.0)	64 (10.8)
pH prior closure	114 (9.5)	60 (9.8)	54 (9.1)
PaO ₂ prior closure	115 (9.5)	60 (9.8)	55 (9.3)
PaCO ₂ prior closure	112 (9.3)	58 (9.4)	54 (9.1)
HCO ₃ prior closure	115 (9.5)	61 (9.9)	54 (9.1)
PaO ₂ / FiO ₂ prior closure	138 (11.4)	71 (11.6)	67 (11.3)
Hemoglobin prior closure	110 (9.1)	57 (9.3)	53 (9.0)
Base excess prior closure	120 (10.0)	63 (10.3)	57 (9.6)
Lactate prior closure	154 (12.8)	76 (12.4)	78 (13.2)
Duration of surgery	19 (1.6)	10 (1.6)	9 (1.5)
Use of regional anesthesia	21 (1.7)	14 (2.3)	7 (1.2)
Aramine	21 (1.7)	14 (2.3)	7 (1.2)
Ephedrine	21 (1.7)	13 (2.1)	8 (1.4)
Phenylephrine	20 (1.7)	13 (2.1)	7 (1.2)
Norepinephrine	22 (1.8)	14 (2.3)	8 (1.4)
Epinephrine	22 (1.8)	15 (2.4)	7 (1.2)
Vasopressin	21 (1.7)	14 (2.3)	7 (1.2)
Morphine	24 (2.0)	14 (2.3)	10 (1.7)
Fentanyl	24 (2.0)	14 (2.3)	10 (1.7)
Remifentanyl	24 (2.0)	14 (2.3)	10 (1.7)
Highest SpO ₂ at PACU	51 (4.2)	30 (4.9)	21 (3.5)
Lowest SpO ₂ at PACU	50 (4.1)	30 (4.9)	20 (3.4)
Highest respiratory rate at PACU	49 (4.1)	29 (4.7)	20 (3.4)
Lowest respiratory rate at PACU	49 (4.1)	29 (4.7)	20 (3.4)
Highest oxygen flow at PACU	53 (4.4)	30 (4.9)	23 (3.9)
Lowest oxygen flow at PACU	53 (4.4)	30 (4.9)	23 (3.9)
Ventilatory support	45 (3.7)	28 (4.6)	17 (2.9)
Anesthesiologist review at PACU	32 (2.7)	21 (3.4)	11 (1.9)
Morphine at PACU	33 (2.7)	20 (3.3)	13 (2.2)
Fentanyl at PACU	34 (2.8)	19 (3.1)	15 (2.5)

eTable 3. Missing Values for Study Variables

	Total (n = 1206)	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)
Remifentanyl at PACU	35 (2.9)	19 (3.1)	16 (2.7)
Pethidine at PACU	33 (2.7)	19 (3.1)	14 (2.4)
Other opioid at PACU	35 (2.9)	20 (3.3)	15 (2.5)
pH at PACU	152 (12.6)	80 (13.0)	72 (12.2)
PaO ₂ at PACU	153 (12.7)	80 (13.0)	73 (12.3)
PaCO ₂ at PACU	151 (12.5)	79 (12.9)	72 (12.2)
HCO ₃ at PACU	156 (12.9)	82 (13.4)	74 (12.5)
PaO ₂ / FiO ₂ at PACU	199 (16.5)	100 (16.3)	99 (16.7)
Hemoglobin at PACU	159 (13.2)	83 (13.5)	76 (12.8)
Base excess at PACU	151 (12.5)	80 (13.0)	71 (12.0)
Lactate at PACU	194 (16.1)	95 (15.5)	99 (16.7)
ICU admission after PACU	30 (2.5)	19 (3.1)	11 (1.9)
Components of the primary outcome	8 (0.7)	6 (1.0)	2 (0.3)
Pneumonia	5 (0.4)	4 (0.7)	1 (0.2)
Respiratory failure	4 (0.3)	2 (0.3)	2 (0.3)
Pleural effusion	5 (0.4)	3 (0.5)	2 (0.3)
Atelectasis	7 (0.6)	6 (1.0)	1 (0.2)
Pneumothorax	4 (0.3)	3 (0.5)	1 (0.2)
Bronchospasm	4 (0.3)	2 (0.3)	2 (0.3)
Pulmonary congestion	3 (0.2)	2 (0.3)	1 (0.2)
Unplanned non-invasive or invasive ventilation	3 (0.2)	2 (0.3)	1 (0.2)
Composite respiratory complications during hospital stay	29 (2.4)	16 (2.6)	13 (2.2)
Pulmonary embolism	38 (3.2)	19 (3.1)	19 (3.2)
Acute respiratory distress syndrome	38 (3.2)	20 (3.3)	18 (3.0)
SIRS	3 (0.2)	2 (0.3)	1 (0.2)
Sepsis	3 (0.2)	2 (0.3)	1 (0.2)
Acute kidney injury	392 (32.5)	194 (31.6)	198 (33.4)
Wound infection	34 (2.8)	17 (2.8)	17 (2.9)
Intraoperative need of vasopressor	22 (1.8)	14 (2.3)	8 (1.4)
Unplanned ICU admission	34 (2.8)	19 (3.1)	15 (2.5)
Need for MET call	3 (0.2)	2 (0.3)	1 (0.2)
ICU length of stay	24 (2.0)	16 (2.6)	8 (1.4)
Hospital length of stay	0 (0.0)	0 (0.0)	0 (0.0)
Hospital mortality	2 (0.2)	0 (0.0)	2 (0.3)

eTable 4. Detailed Description of Surgical Procedures

	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)
Biliary drainage	2 (0.3)	0 (0.0)
Any biopsy or excision	7 (1.2)	9 (1.6)
Carotid surgery	5 (0.9)	6 (1.1)
Closure of ileostomy	4 (0.7)	4 (0.7)
Colostomy	3 (0.5)	3 (0.5)
Endoscopic urological surgery	4 (0.7)	3 (0.5)
Parotid excision	2 (0.3)	1 (0.2)
Tongue excision	1 (0.2)	1 (0.2)
Incisional hernia	10 (1.7)	5 (0.9)
Kidney transplant	4 (0.7)	11 (2.0)
Laparoscopic division of adhesions	2 (0.4)	4 (0.7)
Laparoscopic appendectomy	0 (0.0)	1 (0.2)
Laparoscopic bariatric surgery	9 (1.6)	11 (2.0)
Laparoscopic cholecystectomy	4 (0.7)	3 (0.5)
Laparoscopic colorectal surgery	34 (5.9)	33 (6.0)
Laparoscopic small bowel resection	1 (0.2)	1 (0.2)
Laparoscopic hernia repair	1 (0.2)	2 (0.4)
Laparoscopic hiatus hernia repair	2 (0.3)	4 (0.7)
Laparoscopic lymphadenectomy	0 (0.0)	1 (0.2)
Laparoscopic nephrectomy	20 (3.5)	30 (5.5)
Laparoscopic pancreatectomy	1 (0.2)	1 (0.2)
Laparoscopic pelvic surgery	1 (0.2)	0 (0.0)
Laparoscopic prostatectomy	21 (3.6)	17 (3.1)
Laparoscopic pyeloplasty	1 (0.2)	0 (0.0)
Laparoscopic splenectomy	1 (0.2)	2 (0.4)
Mastectomy	17 (3.0)	16 (2.9)
Mediastinotomy	1 (0.2)	0 (0.0)
Neck lymphadenectomy	2 (0.3)	4 (0.7)
Open division of adhesions	3 (0.5)	3 (0.5)
Open adrenalectomy	3 (0.5)	2 (0.4)
Open bariatric	1 (0.2)	2 (0.4)
Open biliary procedures	8 (1.4)	4 (0.7)
Open bladder surgery	12 (2.1)	5 (0.9)
Open cholecystectomy	1 (0.2)	1 (0.2)
Open colorectal surgery	59 (10.2)	51 (9.3)
Open tumor debulking surgery	1 (0.2)	0 (0.0)
Open small bowel resection	6 (1.0)	6 (1.1)
Open esophagectomy	1 (0.2)	0 (0.0)
Open gastrectomy	3 (0.5)	5 (0.9)
Open partial hepatectomy	32 (5.6)	33 (6.0)
Open hernia repair	2 (0.3)	7 (1.3)
Open hiatus hernia repair	0 (0.0)	1 (0.2)
Open hysterectomy	3 (0.5)	0 (0.0)
Open lymphadenectomy	2 (0.3)	0 (0.0)
Open nephrectomy	5 (0.9)	2 (0.4)
Open pancreatectomy	23 (4.0)	20 (3.6)
Open pelvic surgery	1 (0.2)	0 (0.0)
Open prostatectomy	32 (5.6)	32 (5.8)
Peripheral orthopedic surgery	43 (7.0)	46 (7.8)
Parathyroidectomy	1 (0.2)	1 (0.2)
Other peripheral surgery	7 (1.2)	4 (0.7)
Breast reconstruction	12 (2.1)	10 (1.8)
Repair of enterocutaneous fistula	2 (0.3)	0 (0.0)
Head and neck resection	5 (0.9)	3 (0.6)
Spinal surgery	125 (20.4)	120 (20.3)

eTable 4. Detailed Description of Surgical Procedures

	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)
Stoma correction	1 (0.2)	4 (0.7)
Thyroidectomy	7 (1.2)	4 (0.7)
Vascular procedure	29 (4.7)	28 (4.7)

eTable 5. Additional Intraoperative Data			
	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)	p value
Use of vasoactive drugs			
Metaraminol, bolus	451 (75.2)	457 (78.1)	.26
Metaraminol, infusion	7 (1.1)	12 (2.0)	.32
Ephedrine	256 (42.6)	251 (43.0)	.94
Dose, mg	16.9 ± 11.6	16.3 ± 11.6	.55
Phenylephrine	2 (0.3)	2 (0.3)	.99
Dose, µg	5.4 ± 3.7	2.5 ± 3.5	.51
Norepinephrine	40 (6.7)	26 (4.5)	.12
Dose, µg/kg	9.0 ± 7.0	6.9 ± 4.7	.19
Epinephrine	6 (1.0)	1 (0.2)	.14
Dose, µg/kg	6.7 ± 7.8	1.0	---
Vasopressin	3 (0.5)	0 (0.0)	.26
Dose, U/min	1.0 ± 0.9	---	---
Use of opioids			
Morphine	140 (23.3)	121 (20.8)	.32
Dose, mg	10.1 ± 4.9	9.6 ± 4.5	.45
Fentanyl	465 (77.5)	452 (77.7)	.99
Dose, µg	362.7 ± 184.0	364.6 ± 186.4	.88
Remifentanyl	121 (20.2)	115 (19.8)	.92

Data are presented as mean ± standard deviation or N (%)

eTable 6. Postoperative Characteristics

	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)	Absolute Difference (95% CI)	p value
Vital signs at PACU				
SpO ₂ , %				
Highest	99.8 ± 1.0	99.8 ± 0.7	-0.0 (-0.1 to 0.0)*	.31
Lowest	98.1 ± 2.8	98.3 ± 2.3	-0.2 (-0.5 to 0.1)*	.19
Respiratory rate, bpm				
Highest	18.4 ± 3.4	18.6 ± 3.6	-0.2 (-0.6 to 0.2)*	.24
Lowest	11.7 ± 2.6	12.1 ± 3.0	-0.3 (-0.7 to -0.0)*	.03
Oxygen flow, L/min				
Highest	6.1 ± 0.9	6.1 ± 1.2	0.0 (-0.1 to 0.1)*	.72
Lowest	4.0 ± 2.0	4.0 ± 2.1	0.1 (-0.2 to 0.3)*	.60
Ventilatory support at PACU				
CPAP	3 (0.5)	7 (1.2)	-0.7 (-1.9 to 0.4)**	.19
NIV	1 (0.2)	3 (0.5)	-0.3 (-1.2 to 0.4)**	.31
Reintubation	0 (0.0)	2 (0.3)	-0.3 (-0.8 to 0.1)**	.15
Anesthesiologist review at PACU	169 (28.5)	147 (25.3)	3.2 (-1.9 to 8.3)**	.22
Use of opioids at PACU				
Morphine	98 (16.5)	109 (18.8)	-2.3 (-6.7 to 2.0)**	.30
Dose, mg	7.8 ± 4.9	8.0 ± 5.2	-0.3 (-1.6 to 1.1)*	.72
Fentanyl	215 (36.1)	201 (34.8)	1.3 (-4.2 to 6.8)**	.64
Dose, µg	88.5 ± 60.7	90.9 ± 63.8	-2.4 (-14.4 to 9.6)*	.69
Remifentanyl	1 (0.2)	0 (0.0)	0.2 (-0.2 to 0.5)**	.32
Pethidine	1 (0.2)	0 (0.0)	0.2 (-0.2 to 0.5)**	.32
Other opioid	85 (14.3)	96 (16.6)	-2.3 (-6.5 to 1.8)**	.27
ABG at PACU admission				
pH	7.34 ± 0.05	7.34 ± 0.05	0.00 (-0.01 to 0.00)*	.39
PaO ₂ , mmHg	160.9 ± 59.9	159.2 ± 56.1	1.7 (-5.3 to 8.7)*	.64
PaCO ₂ , mmHg	45.3 ± 6.9	44.9 ± 6.8	0.4 (-0.4 to 1.2)*	.33
HCO ₃ , mmol/L	23.7 ± 2.3	23.7 ± 2.6	-0.0 (-0.3 to 0.3)*	.93
PaO ₂ / FiO ₂	414.1 ± 143.2	411.6 ± 131.5	2.4 (-14.6 to 19.4)*	.78
Base excess	-1.4 ± 2.5	-1.3 ± 2.7	-0.1 (-0.4 to 0.2)*	.62
Hemoglobin, g/dL	12.3 ± 2.0	12.3 ± 1.8	-0.1 (-2.4 to 2.2)*	.96
Lactate, mmol/L	1.6 ± 0.9	1.6 ± 1.1	-0.1 (-0.2 to 0.1)*	.35
Hypoxemia ^a	3 (0.6)	1 (0.2)	0.4 (-0.4 to 1.3)**	.33
Acidosis ^b	87 (16.3)	75 (14.4)	1.9 (-2.5 to 6.2)**	.40

eTable 6. Postoperative Characteristics

	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)	Absolute Difference (95% CI)	p value
Hypercapnia ^c	9 (1.7)	12 (2.3)	-0.6 (-2.4 to 1.1)**	.47
ICU admission after PACU				
Planned	136 (22.9)	120 (20.7)	2.2 (-2.5 to 6.9)**	.36
Unplanned	11 (1.9)	13 (2.2)	-0.4 (-2.1 to 1.3)**	.64

Data are presented as mean ± standard deviation or N (%)

ABG: arterial blood gas; CI: confidence interval; FiO₂: inspired fraction of oxygen; HCO₃⁻: bicarbonate; PaO₂: partial pressure of oxygen. PaCO₂: partial pressure of carbon dioxide; SpO₂: pulse oximetry; PACU: post-anaesthesia care unit; CPAP: continuous positive airway pressure; NIV: non-invasive ventilation

* absolute difference is mean difference from a generalized linear model considering a Gaussian distribution

** absolute difference is risk difference from a generalized linear model considering a Binomial distribution with an identity link

^a defined as PaO₂ < 60 mmHg

^b defined as pH < 7.30

^c defined as PaCO₂ > 60 mmHg

eTable 7. Protocol Violations and Reason for Violations

	Total (n=75)	Low Tidal Volume (n = 41)	Conventional Tidal Volume (n = 34)
Protocol violations			
Incorrect tidal volume*	44	22	22
Incorrect PEEP	6	4	2
Use of recruitment manoeuvre	3	2	1
Multiple protocol violations	3	2	1
Reasons for protocol violations*			
Hypercapnia	13	10	3
Hypoxia	3	3	0
High peak inspiratory pressure	9	2	7

* defined as a tidal volume different from the one calculated according to the randomization group in more than ± 1 mL/kg predicted body weight
** when available

eTable 8. Adjusted P Values for the Secondary Outcomes		
	Unadjusted p value	Adjusted p value*
SIRS	0.089942	0.989362
Sepsis	0.256753	1.000000
Hospital LOS	0.396800	1.000000
Intraoperative need of vasopressor	0.551830	1.000000
Composite respiratory complications during hospital stay	0.565142	1.000000
Unplanned ICU admission	0.565970	1.000000
Pulmonary embolism	0.714534	1.000000
ICU LOS	0.841244	1.000000
In-hospital mortality	0.855448	1.000000
Need for rapid response team call	0.872292	1.000000
Wound infection	0.893860	1.000000
<i>ICU: intensive care unit;</i>		
* Holm-Bonferroni correction to control the family-wide error rate to the p-values for all 11 secondary outcomes was done		

eTable 9. Additional Sensitivity Analyses for the Primary Outcome

	Low Tidal Volume (n = 614)	Conventional Tidal Volume (n = 592)	Odds Ratio (95% CI)	p value
Adjusted analysis*	---	---	0.92 (0.71 to 1.20)	.54
Count events	0.6 ± 1.0	0.6 ± 1.0	0.94 (0.75 to 1.18)**	.62
Median (IQR)	0 (0 – 1)	0 (0 – 1)		
Common effect GEE	---	---	0.94 (0.81 to 1.09)***	.41
Treatment–component interaction GEE	---	---	---	.72 ^a
Average relative effect GEE	---	---	0.98 (0.94 to 1.03) ^b	.54

Data are presented as mean ± standard deviation or N (%)
 GEE: *generalized estimating equations*
 * adjusted for age, gender, baseline SpO₂, ARISCAT and hypertension
 ** 95% confidence intervals calculated with proportional odds logistic regression and p values calculated Wilcoxon rank-sum test
 *** 95% confidence intervals and p values calculated in a common effect GEE model (estimating a single treatment effect across all 8 components)
^a p value calculated in a GEE model (test whether the treatment effect differs across the 8 components)
^b p value calculated in a GEE model (estimating, then averaging, the 8 distinct treatment effects)

eTable 10. Primary and Secondary Outcomes Only in Patients Undergoing Laparoscopic Surgery				
	No. of Events / Total No. (%)			
	Low Tidal Volume (n = 158)	Conventional Tidal Volume (n = 170)	Absolute Difference (95% CI)	p value^c
Primary outcome				
Composite respiratory complications within seven days	52 / 157 (33.1)	72 / 169 (42.6)	-9.5 (-19.9 to 1.0)**	0.08
Components of the primary outcome				
Pneumonia	6 / 158 (3.8)	6 / 169 (3.6)	0.2 (-4.0 to 4.6)**	0.91
Respiratory failure ^a	21 / 158 (13.3)	33 / 169 (19.5)	-6.2 (-14.3 to 1.8)**	0.13
Pleural effusion	15 / 158 (9.5)	16 / 169 (9.5)	-0.0 (-6.5 to 6.5)**	0.99
Atelectasis ^b	36 / 157 (22.9)	48 / 170 (28.2)	-5.3 (-14.7 to 4.2)**	0.27
Pneumothorax	0 / 158 (0.0)	0 / 169 (0.0)	---	---
Bronchospasm	2 / 158 (1.3)	3 / 169 (1.8)	-0.5 (-3.6 to 2.5)**	0.71
Pulmonary congestion	2 / 158 (1.3)	4 / 169 (2.4)	-1.1 (-4.4 to 2.0)**	0.45
Unplanned non-invasive or invasive ventilation	3 / 158 (1.9)	4 / 169 (2.4)	-0.5 (-3.9 to 3.0)**	0.77
Secondary outcomes				
Composite respiratory complications during hospital stay	53 / 157 (33.8)	75 / 167 (44.9)	-11.1 (-21.6 to -0.5)**	0.04
Pulmonary embolism	1 / 158 (0.6)	1 / 166 (0.6)	0.0 (-2.2 to 2.3)**	0.97
Acute respiratory distress syndrome	0 / 158 (0.0)	0 / 166 (0.0)	---	---
SIRS	0 / 157 (0.0)	1 / 169 (0.6)	-0.6 (-1.8 to 0.6)**	0.34
Sepsis	7 / 158 (4.4)	4 / 169 (2.4)	2.1 (-1.9 to 6.4)**	0.30
Acute kidney injury ^d	11 / 115 (9.6)	13 / 113 (11.5)	-1.9 (-10.1 to 6.1)**	0.63
Risk	8 / 11 (7.0)	10 / 13 (8.8)		

eTable 10. Primary and Secondary Outcomes Only in Patients Undergoing Laparoscopic Surgery

	No. of Events / Total No. (%)		Absolute Difference (95% CI)	p value ^c
	Low Tidal Volume (n = 158)	Conventional Tidal Volume (n = 170)		
Injury	1 / 11 (0.9)	0 / 13 (0.0)		
Failure	2 / 11 (1.7)	3 / 13 (2.7)		
Wound infection	3 / 158 (1.9)	3 / 167 (1.8)	0.1 (-3.1 to 3.4)**	0.94
Intraoperative need of vasopressor	130 / 156 (83.3)	139 / 166 (83.7)	-0.4 (-8.6 to 7.7)**	0.92
Unplanned ICU admission	8 / 155 (5.2)	7 / 165 (4.2)	0.9 (-3.8 to 5.9)	0.70
Need for rapid response team call	12 / 158 (7.6)	14 / 169 (8.3)	-0.7 (-6.7 to 5.3)	0.82
Length of stay				
In ICU, mean (SD), days	0.2 (0.8)	0.3 (0.9)	3.3 (-15.1 to 21.8)*	0.72
In hospital, mean (SD), days	7.0 (6.4)	6.3 (5.7)	0.6 (-0.7 to 2.0)*	0.33
In-hospital mortality	3 / 158 (1.9)	2 / 170 (1.2)	0.7 (-1.9 to 3.4)**	0.60

Abbreviations: CI: confidence interval; ICU: intensive care unit;

^a Defined as a postoperative PaO₂ < 60 mmHg on room air, a PaO₂ / FiO₂ ratio < 300 mmHg or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy

^b Defined as lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung

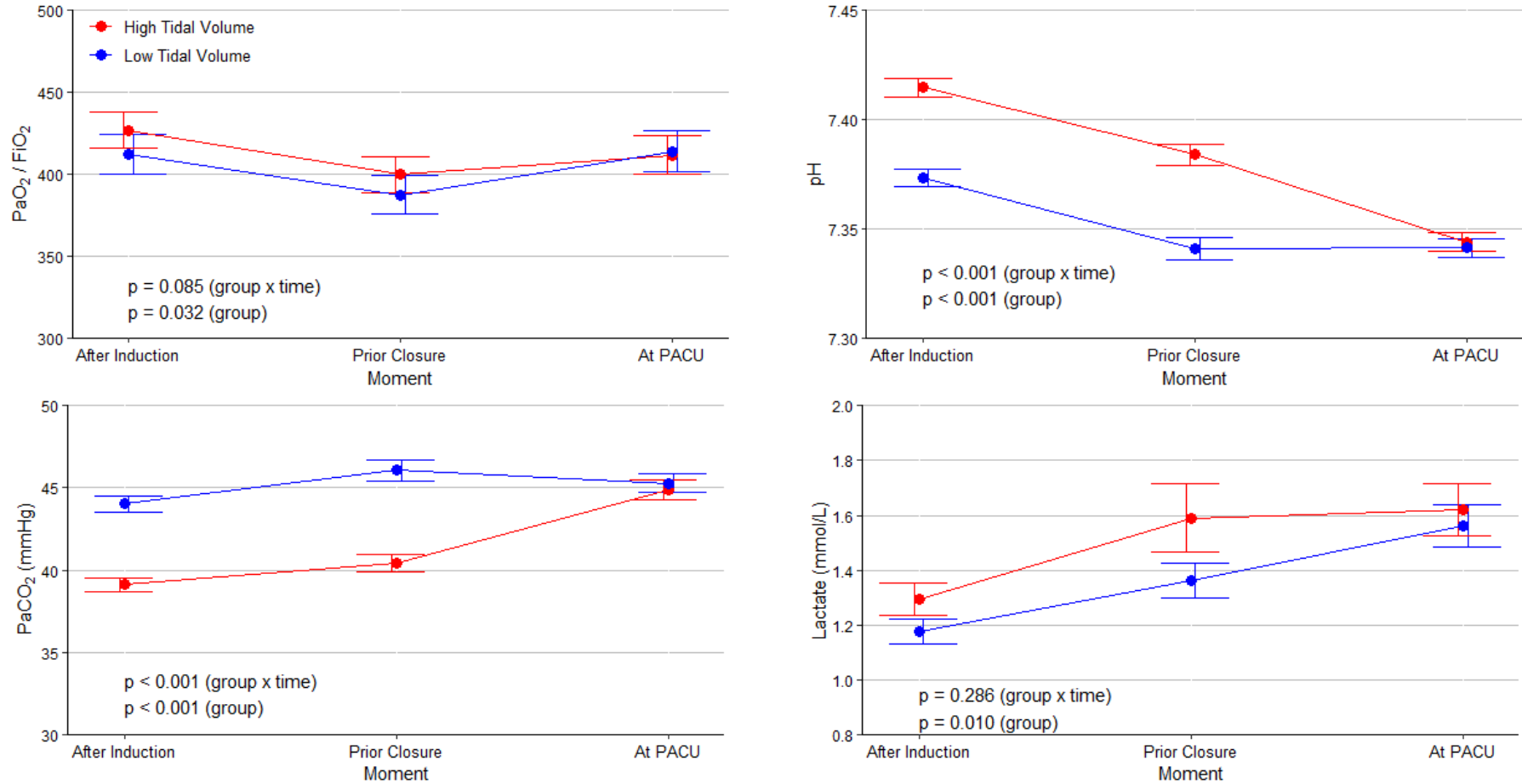
^c Calculated using the χ^2 test for categorical variables or from a generalized linear model considering an inverse Gaussian distribution for the continuous variables

^d Classified in 3 categories according to the stage of kidney injury. Acute kidney failure risk defined as an increase in creatinine level 1.5 times the baseline creatinine; injury, an increase in creatinine level 2 times the baseline creatinine; failure, an increase in creatinine level 3 times the baseline creatinine, or an increase in creatinine level \geq 0.5 mg/dL if baseline creatinine \geq 4 mg/dL

* absolute difference is mean difference from a generalized linear model considering a Gaussian distribution

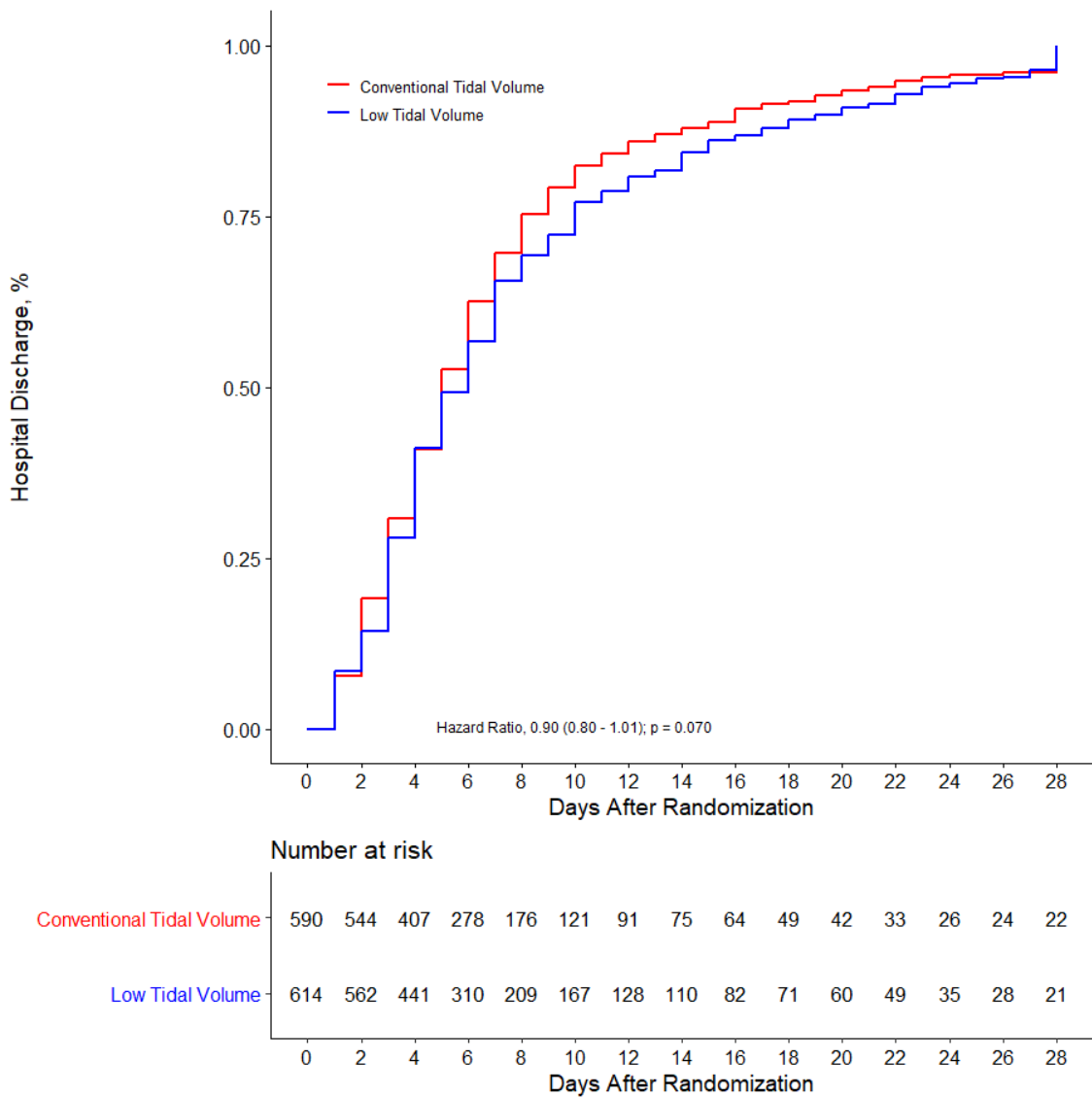
** absolute difference is risk difference from a generalized linear model considering a Binomial distribution with an identity link

eFigure 1. Trend Over Time for Arterial Blood Gases



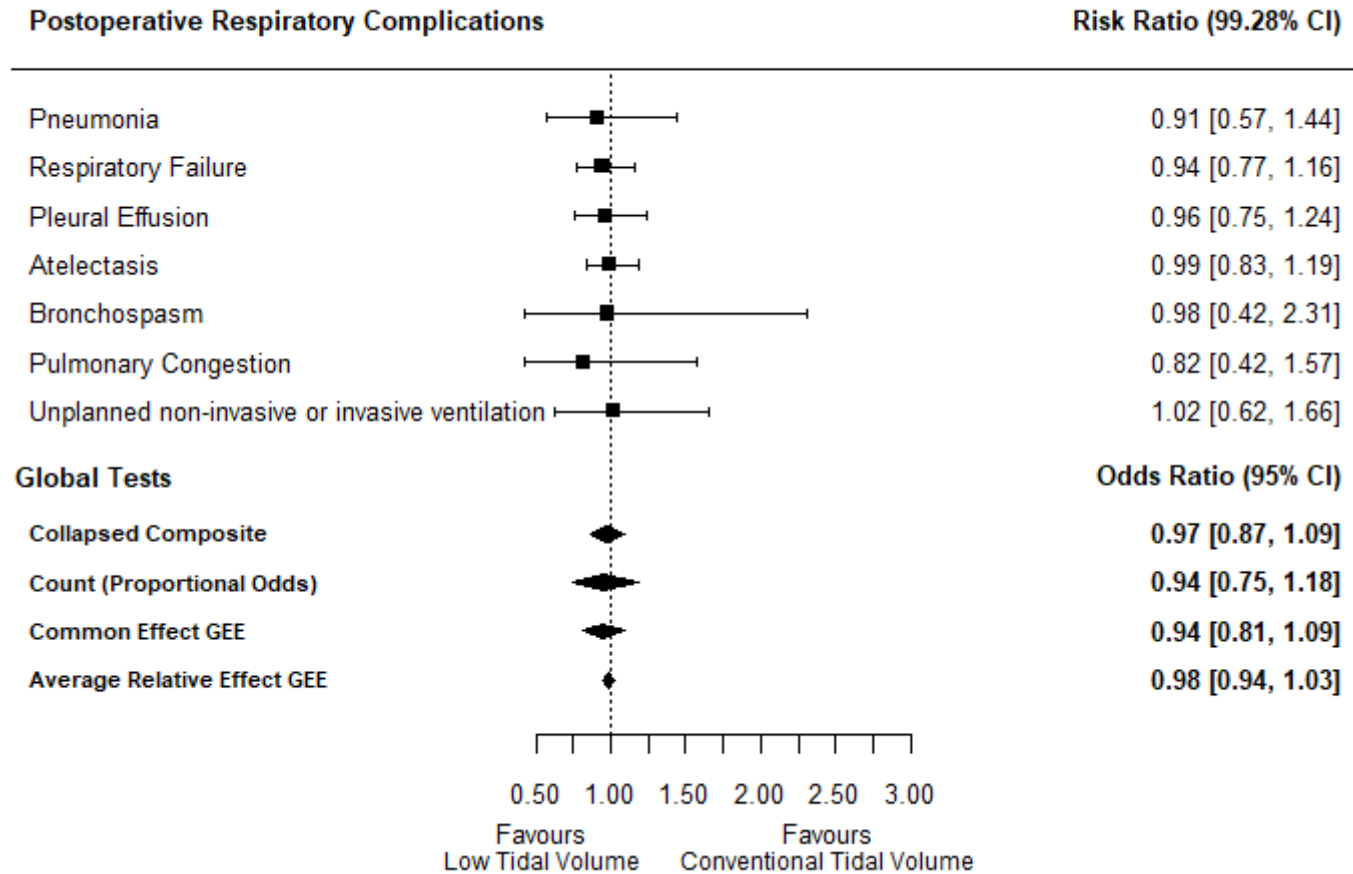
Circles are the mean and error bars the 95% confidence interval. Unadjusted mixed-effect longitudinal models with random intercept for patients and with group, time and the interaction of group x time as fixed effects. *P* values for the group reflect the overall test for difference between groups across the three periods while *p* values for the group x time interaction evaluate if change over time differed by group.

eFigure 2. Kaplan-Meier Estimates for Patients in the Low Tidal Volume and Conventional Tidal Volume Groups



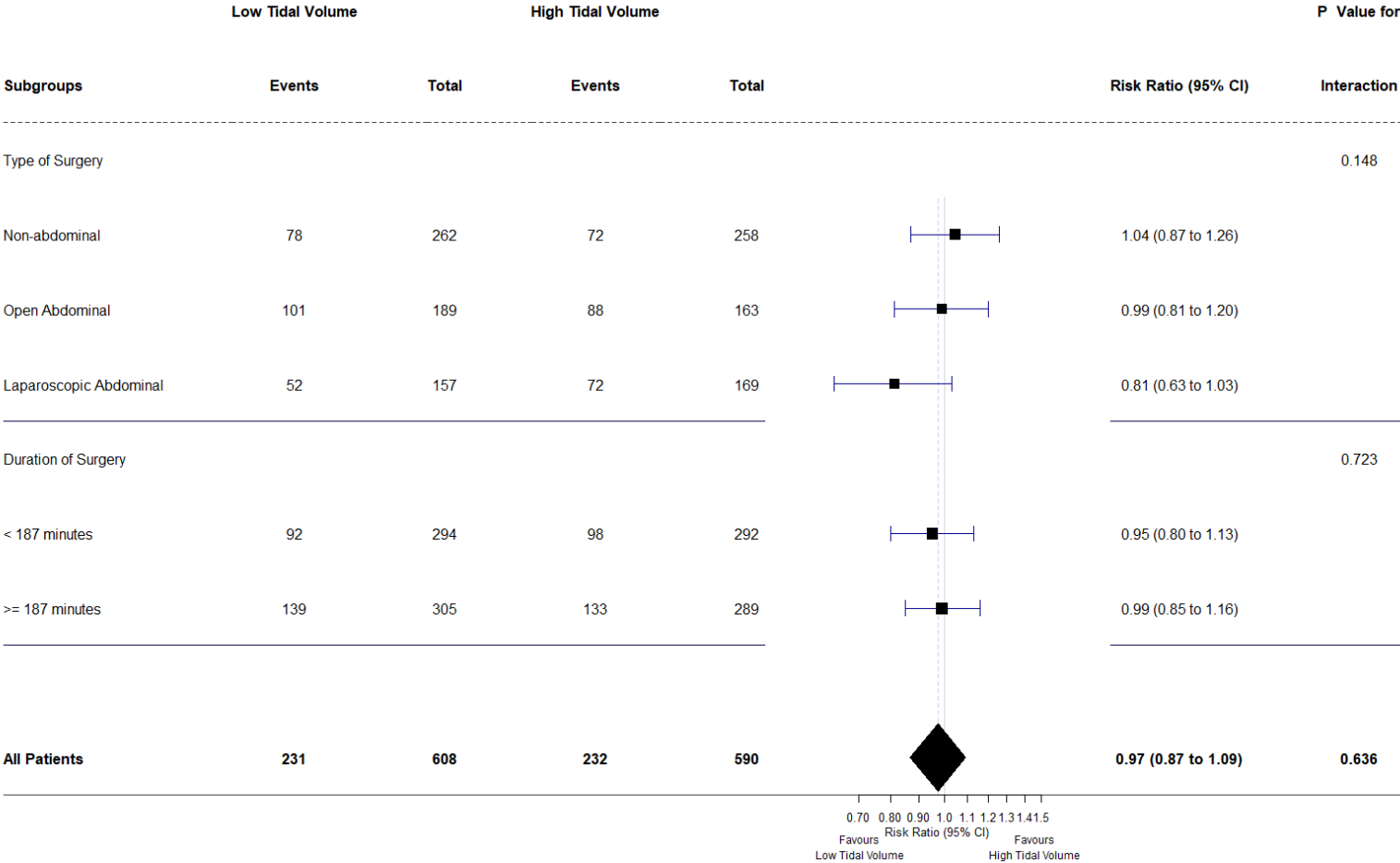
Median (IQR) observation period for hospital length of stay was 6 (3 to 10) days for the low tidal volume group and 5 (3 to 8) days for the conventional tidal volume group; P value for the Schoenfeld residuals was 0.664.

eFigure 3. Results of the Sensitivity Analyses for the Primary Outcome



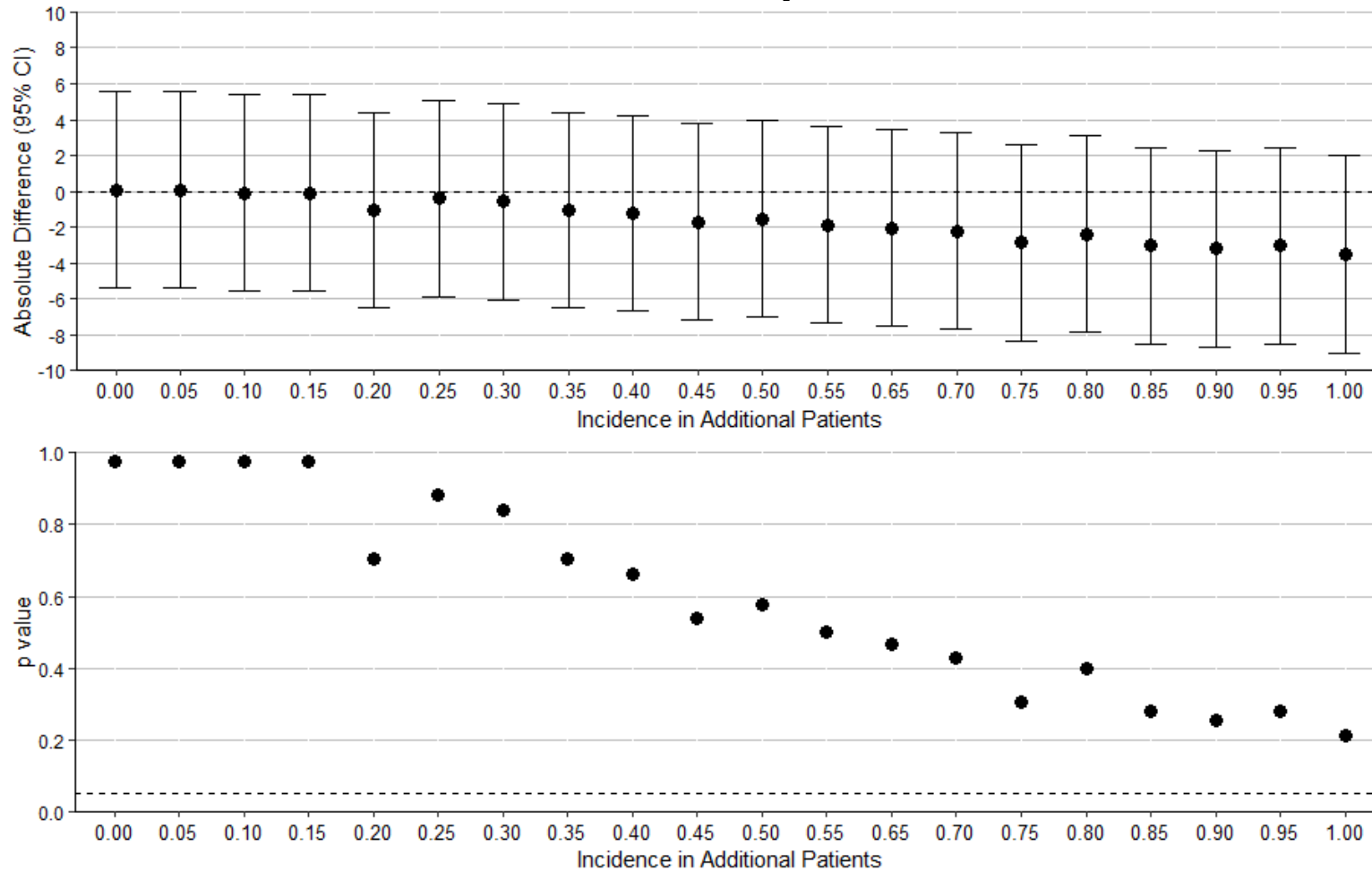
The effect of the intervention in each component was analyzed using a generalized linear model using a Bonferroni correction for multiple comparisons. The 99.28% Bonferroni-corrected confidence intervals is reported ($1 - 0.05/7 = 0.9928$). Pneumothorax was excluded from this analysis due to the absence of events in one group.
CI: confidence interval; GEE: generalized estimating equations

eFigure 4. Risk Ratio for Postoperative Respiratory Complications in Post Hoc Subgroups



The data marker sizes are proportional to the numbers of patients entering the analysis.
 CI: confidence interval.

eFigure 5. Results of the Sensitivity Analysis Allocating 22 Additional Patients in the Conventional Arm With Different Incidences of the Primary Outcomes



Worst-case scenario (all 22 additional patients developing PPCs): absolute difference, -3.51 (-9.00 to 2.00); $p = 0.210$. Best-case scenario (none of the 22 additional patients developing PPCs): absolute difference, 0.08 (-5.35 to 5.52); $p = 0.975$. Similar scenario (incidence of PPCs in additional patients similar to patients included in the conventional arm, 39.3%): absolute difference, -1.54 (-7.00 to 3.92); $p = 0.578$