KINETICS OF PLASMA BIOMARKERS OF INFLAMMATION AND LUNG INJURY IN SURGICAL PATIENTS WITH OR WITHOUT POSTOPERATIVE PULMONARY COMPLICATIONS

ONLINE SUPPLEMENT

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eTable 1 – Definitions of postoperative pulmonary complications

PPCs	Definition
Unexpected need for supplementary oxygen	PaO_2 < 60 mmHg or SpO_2 < 90% in room air but responding to supplemental oxygen
Severe hypoxemia	Need for non-invasive or invasive mechanical ventilation or a PaO_2 < 60 mmHg or SpO_2 < 90% despite supplemental oxygen
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Suspected pulmonary infection	Patient receives antibiotics and meets at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest X-ray when clinically indicated, tympanic temperature > 38.3°C, WBC count > 12,000/μl in the absence of other infectious focus
Pulmonary infiltrate	Chest X-ray demonstrating unilateral or bilateral infiltrates
Aspiration pneumonitis	Respiratory failure after the inhalation of regurgitated gastric contents
ARDS	According to AECC[1]
Atelectasis	Suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung
Pleural effusion	Chest X-ray demonstrating blunting of the costophrenic angle, loss of the 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 hemi-thorax with preserved vascular shadows
Cardiopulmonary edema	Clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest X-ray demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura

PPCs: postoperative pulmonary complications; ARDS: acute respiratory distress syndrome; AECC: America-European Consensus Conference

1. Bernard GR, *et al*. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med 1994, 20:225–232.

eTable 2 – Baseline characteristics of included patients according to randomization group and outcome group

	High PEEP (n = 120)	Low PEEP (n = 122)	PPCs (n = 135)	No PPC (n = 97)
Demographic and clinical variables				
Men	70 / 120 (58.3)	71 / 122 (58.2)	81 / 135 (60.0)	52 / 97 (53.6)
Age, years	66.0 (56.2 – 73.0)	65.0 (55.0 – 73.2)	68.0 (60.0 – 74.0)	61.0 (52.0 – 71.5)
Body mass index, kg m^{-2}	22.2 (19.3 – 24.6)	22.6 (19.4 – 24.5)	22.6 (19.3 – 24.8)	22.0 (19.2 – 24.3)
Weight, kg	73.5 (64.0 – 85.0)	75.0 (64.0 – 85.0)	77.0 (64.0 – 85.0)	72.0 (63.5 – 82.0)
ARISCAT score*	41.0 (38.0 – 42.0)	41.0 (38.0 – 48.0)	41.0 (38.0 – 48.0)	41.0 (38.0 – 44.0)
Intermediate (26 – 44)	94 / 120 (78.3)	88 / 122 (72.1)	100 / 135 (74.1)	74 / 97 (76.3)
High (> 44)	26 / 120 (21.7)	34 / 122 (27.9)	35 / 135 (25.9)	23 / 97 (23.7)
Smoking status				
Never	68 / 120 (56.7)	63 / 122 (51.6)	71 / 135 (52.6)	55 / 97 (56.7)
Former	23 / 120 (19.1)	23 / 122 (18.9)	29 / 135 (21.5)	16 / 97 (16.5)
Current	29 / 120 (24.2)	36 / 122 (29.5)	35 / 135 (25.9)	26 / 97 (26.8)
Alcohol status (past 2 weeks)				
None	64 / 120 (53.3)	72 / 122 (59.0)	77 / 135 (57.0)	52 / 97 (53.6)
0 – 2 units	52 / 120 (43.3)	45 / 122 (36.9)	52 / 135 (38.5)	42 / 97 (43.3)
> 2 units	4 / 120 (3.3)	5 / 122 (4.1)	6 / 135 (4.4)	3 / 97 (3.1)
ASA physical status classification system				
1	2 / 119 (1.7)	10 / 122 (8.2)	2 / 135 (1.5)	8 / 97 (8.2)
2	62 / 119 (52.1)	61 / 122 (50.0)	68 / 135 (50.4)	51 / 97 (52.6)
3	55 / 119 (46.2)	50 / 122 (41.0)	64 / 135 (47.4)	38 / 97 (39.2)
4	0 / 119 (0.0)	1 / 122 (0.8)	1 / 135 (0.7)	0 / 97 (0.0)
5	0 / 119 (0.0)	0 / 122 (0.0)	0 / 135 (0.0)	0 / 97 (0.0)
New York Heart Association classification				
No cardiac failure	96 / 120 (80.0)	97 / 122 (79.5)	103 / 135 (76.3)	82 / 97 (84.5)
I	23 / 120 (19.2)	24 / 122 (19.7)	31 / 135 (23.0)	14 / 97 (14.4)
II	1 / 120 (0.8)	1 / 122 (0.8)	1 / 135 (0.7)	1 / 97 (1.0)
III	0 / 120 (0.0)	0 / 122 (0.0)	0 / 135 (0.0)	0 / 97 (0.0)
IV	0 / 120 (0.0)	0 / 122 (0.0)	0 / 135 (0.0)	0 / 97 (0.0)
Functional status				
Independent	118 / 120 (98.3)	120 / 122 (98.4)	132 / 135 (97.8)	96 / 97 (99.0)
Partially dependent	2 / 120 (1.7)	2 / 122 (1.6)	3 / 135 (2.2)	1 / 97 (1.0)
Totally dependent	0 / 120 (0.0)	0 / 122 (0.0)	0 / 135 (0.0)	0 / 97 (0.0)

History of active cancer	62 / 120 (51.7)	62 / 122 (50.8)	75 / 135 (55.6)	45 / 97 (46.4)
Chronic kidney failure	6 / 120 (5.0)	6 / 122 (4.9)	7 / 135 (5.2)	5 / 97 (5.2)
Chronic obstructive pulmonary disease	11 / 120 (9.2)	5 / 122 (4.1)	11 / 135 (8.1)	4 / 97 (4.1)
Inhalation therapy**	7 / 120 (5.8)	3 / 122 (2.5)	8 / 135 (5.9)	2 / 97 (2.1)
Systemic steroids	5 / 120 (4.2)	1 / 122 (0.8)	4 / 135 (3.0)	1 / 97 (1.0)
Diabetes mellitus	22 / 120 (18.3)	28 / 122 (23.0)	30 / 135 (22.2)	18 / 97 (18.6)
Oral medication	14 / 120 (11.7)	11 / 122 (9.0)	16 / 135 (11.9)	7 / 97 (7.2)
Insulin	6 / 120 (5.0)	13 / 122 (10.7)	10 / 135 (7.4)	9 / 97 (9.3)
Systemic steroids	4 / 120 (3.3)	3 / 122 (2.5)	6 / 135 (4.4)	0 / 97 (0.0)
Statins	29 / 120 (24.2)	29 / 122 (23.8)	38 / 135 (28.1)	18 / 97 (18.6)
Preoperative transfusion	1 / 120 (0.8)	0 / 122 (0.0)	1 / 135 (0.7)	0 / 97 (0.0)
Preoperative tests				
Hemoglobin, g dl^{-1}	13.5 (12.2 – 14.5)	13.4 (12.2 – 14.6)	13.2 (12.1 – 14.4)	13.7 (12.4 – 14.6)
Creatinine, mg dl^{-1}	0.8 (0.7 – 1.0)	0.8 (0.7 – 1.0)	0.8 (0.7 – 1.0)	0.8 (0.7 – 1.0)
Urea, mg dl^{-1}	25.9 (16.0 – 36.9)	23.2 (16.0 – 35.1)	25.3 (16.0 – 36.7)	25.3 (16.6 – 36.3)
White blood cells, $x10^9$ cells per litre	7.3 (5.7 – 8.9)	6.7 (5.7 – 8.5)	7.0 (5.7 – 9.0)	6.8 (5.7 – 8.4)
Oxyhemoglobin saturation, %***	97.0 (96.0 – 98.0)	97.0 (96.0 – 98.2)	97.0 (96.0 – 98.0)	98.0 (96.5 – 99.0)
Abnormalities on chest radiography	7 / 78 (9.0)	8 / 90 (8.9)	10 / 91 (11.0)	4 / 72 (5.6)
Perioperative variables				
Duration of anesthesia, minutes	300.0 (240.0 – 400.0)	275.0 (210.0 – 360.0)	325.0 (255.0 – 417.0)	245.0 (193.5 – 305.0)
Duration of surgery, minutes¶	240.0 (165.0 – 330.0)	215.0 (150.0 – 300.0)	259.0 (190.0 – 355.0)	188.0 (140.0 – 237.5)
Surgical procedure				
Gastric	4 / 120 (3.3)	7 / 122 (5.7)	8 / 135 (5.9)	2 / 97 (2.1)
Pancreatic	31 / 120 (25.8)	35 / 122 (28.7)	36 / 135 (26.7)	29 / 97 (29.9)
Biliary	9 / 120 (7.5)	3 / 122 (2.5)	8 / 135 (5.9)	3 / 97 (3.1)
Liver	15 / 120 (12.5)	6 / 122 (4.9)	14 / 135 (10.4)	6 / 97 (6.2)
Colonic	13 / 120 (10.8)	10 / 122 (8.2)	13 / 135 (9.6)	10 / 97 (10.3)
Rectal	11 / 120 (9.2)	10 / 122 (8.2)	10 / 135 (7.4)	11 / 97 (11.3)
Bladder	2 / 120 (1.7)	3 / 122 (2.5)	5 / 135 (3.7)	0 / 97 (0.0)
Kidney	5 / 120 (4.2)	6 / 122 (4.9)	7 / 135 (5.2)	3 / 97 (3.1)
Vascular	11 / 120 (9.2)	13 / 122 (10.7)	12 / 135 (8.9)	9 / 97 (9.3)
Other	19 / 120 (15.8)	29 / 122 (23.8)	22 / 135 (16.3)	24 / 97 (24.7)
Antibiotic prophylaxis	113 / 114 (99.1)	116 / 117 (99.1)	132 / 133 (99.2)	95 / 96 (99.0)
Type of anesthesia				
Total intravenous	16 / 117 (13.7)	15 / 118 (12.7)	16 / 135 (11.9)	14 / 97 (14.4)
Mixed (volatile and intravenous)	101 / 117 (86.3)	103 / 118 (87.3)	119 / 135 (88.1)	83 / 97 (85.6)

Epidural				
Thoracic	64 / 111 (57.7)	73 / 115 (63.5)	85 / 130 (65.4)	50 / 94 (53.2)
Lumbar	1 / 111 (0.9)	0 / 115 (0.0)	0 / 130 (0.0)	1 / 94 (1.1)

PPCs, postoperative pulmonary complications; PEEP, positive end-expiratory pressure; ASA, American Society of Anesthesiology
Data are median (interquartile range), or number / total number of patients (%)
* ARISCAT score measures risk of postoperative pulmonary complications
** inhaled bronchodilators, steroids or both
*** measured by pulse oximetry
¶ defined as the time between skin incision and closure of incision

eTable 3 – Intraoperative characteristics of included patients

	High PEEP (n = 120)	Low PEEP (n = 122)
Tidal volumes, ml kg^{-1} PBW*	7.9 (7.6 – 8.1)	8.0 (7.8 – 8.1)
After 1 hour	7.9 (7.7 – 8.2)	7.9 (7.7 – 8.1)
Before extubation	7.9 (7.6 – 8.1)	8.0 (7.8 – 8.3)
PEEP, cmH_2O*	12.0 (12.0 – 12.0)	2.0 (1.0 – 2.0)
After 1 hour	12.0 (12.0 – 12.0)	2.0 (0.0 – 2.0)
Before extubation	12.0 (12.0 – 12.0)	2.0 (1.0 – 2.0)
Peak pressure, cmH_2O*	21.7 (20.0 – 23.1)	15.5 (13.7 – 18.0)
After 1 hour	21.0 (19.5 – 23.5)	15.0 (13.0 – 18.0)
Before extubation	22.0 (20.0 – 24.0)	16.0 (14.0 – 19.0)
Dynamic compliance, ml cmH_2O^{-1}*	50.0 (40.5 – 59.4)	37.5 (28.3 – 45.6)
After 1 hour	50.0 (40.0 – 67.1)	38.4 (28.6 – 49.1)
Before extubation	50.0 (40.5 – 59.4)	36.7 (28.1 – 42.5)
Respiratory rate, breaths $minute^{-1}$*	12.0 (10.0 – 13.0)	12.0 (10.0 – 12.0)
After 1 hour	11.0 (10.0 – 12.0)	12.0 (10.0 – 12.0)
Before extubation	12.0 (10.0 – 14.0)	11.0 (10.0 – 12.0)
Minute ventilation, l min^{-1}*	5.9 (5.1 – 6.7)	5.7 (4.9 – 6.6)
After 1 hour	5.7 (4.9 – 6.3)	5.5 (4.7 – 6.2)
Before extubation	6.1 (4.8 – 7.3)	5.6 (4.8 – 6.6)
Inspired fraction of oxygen*	0.43 (0.40 – 0.49)	0.43 (0.40 – 0.50)
After 1 hour	0.42 (0.40 – 0.50)	0.44 (0.40 – 0.50)
Before extubation	0.42 (0.40 – 0.47)	0.43 (0.40 – 0.48)
Oxyhemoglobin saturation, %*,**	100.0 (99.0 – 100.0)	100.0 (99.0 – 100.0)
After 1 hour	100.0 (99.0 – 100.0)	99.0 (98.2 – 100.0)
Before extubation	100.0 (99.0 – 100.0)	100.0 (98.0 – 100.0)
$P_{ET}CO_2$, mmHg*	34.0 (32.0 – 36.0)	33.7 (31.6 – 35.2)
After 1 hour	35.2 (33.0 – 37.0)	34.0 (31.5 – 35.2)
Before extubation	35.2 (33.0 – 37.4)	35.2 (33.4 – 37.0)
Recruitment maneuver		
After intubation	113 / 116 (97.4)	3 / 117 (2.6)
Before extubation	101 / 117 (86.3)	1 / 118 (0.8)

PEEP, positive end-expiratory pressure; PBW, predicted body weight; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide

Data are median (interquartile range), or number / total number of patients (%). PBW calculated as 50 + 0.91 × (height [cm] – 152.4) for men and 45.5 + 0.91 × (height [cm] – 152.4) for women. Dynamic compliance calculated as tidal volume / (peak pressure – PEEP)

* Averaged during surgery

** Measured by pulse oximetry

eTable 4 – Incidence of PPCs

	High PEEP (n = 120)	**Low PEEP (n = 122)**
Postoperative pulmonary complications		
Total	76 / 116 (65.5)	59 / 116 (50.9)
Total (excluding hypoxemia)	52 / 116 (44.8)	48 / 117 (41.0)
Hypoxemia	60 / 116 (51.7)	44 / 117 (37.6)
Severe hypoxemia	11 / 116 (9.5)	10 / 117 (8.5)
Bronchospasm	6 / 116 (5.2)	8 / 117 (6.8)
Suspected pulmonary infection	25 / 116 (21.6)	19 / 117 (16.2)
Pulmonary infiltrate	10 / 112 (8.9)	8 / 112 (7.1)
Aspiration pneumonitis	0 / 116 (0.0)	3 / 117 (2.6)
Acute respiratory distress syndrome	1 / 111 (0.9)	2 / 112 (1.8)
Atelectasis	11 / 111 (9.9)	14 / 112 (12.5)
Pleural effusion	32 / 111 (28.8)	32 / 112 (28.6)
Cardiogenic pulmonary edema	7 / 112 (6.3)	8 / 114 (7.0)
Pneumothorax	2 / 110 (1.8)	0 / 112 (0.0)

PPCs, postoperative pulmonary complications; PEEP, positive end-expiratory pressure
Data are median (interquartile range), or number / total number of patients (%). Complications were counted as soon as an event occurred

eTable 5 – Receiver operator characteristic–area under curve for development of PPCs

	AUC (95% CI)
Absolute value	
TNF-α	0.592 (0.515 – 0.669)
IL-6	0.700 (0.630 – 0.769)
SP-D	0.539 (0.462 – 0.615)
CC-16	0.580 (0.503 – 0.657)
Relative change	
TNF-α	0.604 (0.527 – 0.681)
IL-6	0.652 (0.577 – 0.726)
SP-D	0.585 (0.509 – 0.661)
CC-16	0.526 (0.450 – 0.603)

AUC, area under the curve; CI, confidence interval; PPCs, postoperative pulmonary complications; TNF, tumor necrosis factor; IL, interleukin; SP-D, surfactant protein D; CC-16, clara cell protein.
Absolute value directly after surgery
% change: (postoperative *divided* by preoperative)

eTable 6 – Analyses from the false discovery rate using the Benjamini-Hochberg procedure with a false discovery rate of 0.2 for results of Figure 3

Variable	*P* value	Benjamini-Hochberg *P* value	Significant*
CC–16 (Day 1)	0.009	0.1260	Yes
sRAGE (Day 1)	0.098	0.5203	No
IL–6 (Day 1)	0.153	0.5203	No
SP–D (Day 1)	0.158	0.5203	No
IL–8 (Day 1)	0.213	0.5203	No
CC–16 (Day 5)	0.223	0.5203	No
TNF–α (Day 1)	0.331	0.6172	No
sRAGE (Day 5)	0.389	0.6172	No
SP–D (Day 5)	0.440	0.6172	No
IL–6 (Day 5)	0.466	0.6172	No
TNF–α (Day 5)	0.485	0.6172	No
IL–8 (Day 5)	0.574	0.6696	No
KL6 (Day 5)	0.684	0.7366	No
KL6 (Day 5)	0.848	0.8480	No

TNF, tumor necrosis factor; IL, interleukin; sRAGE, soluble receptor for advanced glycation end–products; SP-D, surfactant protein D; CC–16, Clara cell protein; KL6, Krebs von den Lungen-6.

*: significance according to the false discovery rate of 0.2

eTable 7 – Plasma level of biomarkers of inflammation and lung injury according to diagnosis of severe PPCs

	TNF–α (pg ml^{-1})	IL–6 (pg ml^{-1})	IL–8 (pg ml^{-1})	sRAGE (µg ml^{-1})	SP–D (µg ml^{-1})	CC–16 (µg ml^{-1})	KL6 (units ml^{-1})
Severe PPCs							
Preoperative	8.6 (3.9 – 11.1)	3.0 (1.9 – 4.9)	6.6 (3.9 – 9.5)	1.8 (1.4 – 2.4)	8.8 (4.6 – 15.3)	14.3 (7.7 – 22.7)	17.3 (9.9 – 26.3)
Postoperative	8.5 (3.5 – 11.8)	95.4 (37.5 –	14.9 (8.0 – 32.6)	1.8 (1.4 – 2.5)	5.3 (3.4 – 9.8)	16.7 (10.1 – 26.3)	13.0 (7.3 – 20.8)
Postoperative day 5	8.5 (4.5 – 11.6)	205.1)	9.1 (5.6 – 13.1)	1.9 (1.4 – 2.5)	5.9 (3.5 – 8.8)	10.3 (6.9 – 17.2)	12.4 (6.3 – 18.3)
P–value*	0.025	11.0 (5.8 – 21.4)	< 0.001	0.713	< 0.001	< 0.001	< 0.001
		< 0.001					
No Severe PPC							
Preoperative	9.0 (5.5 – 11.5)	3.8 (2.6 – 6.5)	7.1 (5.0 – 11.3)	2.1 (1.7 – 2.4)	9.7 (5.3 – 1.7)	16.3 (11.6 – 23.9)	18.8 (13.3 – 27.4)
Postoperative	9.0 (5.1 – 13.3)	153.7 (71.7 –	21.4 (12.4 – 45.4)	2.1 (1.5 – 2.5)	6.3 (3.2 – 10.5)	18.4 (13.5 – 30.2)	14.2 (8.7 – 19.0)
Postoperative day 5	10.2 (5.5 – 12.9)	335.7)	10.7 (7.7 – 20.9)	2.0 (1.5 – 2.7)	6.7 (4.3 – 13.0)	14.1 (8.8 – 21.7)	13.4 (7.4 – 19.0)
P–value*	0.044	19.0 (10.6 – 50.7)	< 0.001	0.798	< 0.001	< 0.001	< 0.001
		< 0.001					
P–value**	0.233		0.719	0.715	0.407	0.017	0.504
		0.032					

PPCs, postoperative pulmonary complications; TNF, tumor necrosis factor; IL, interleukin; sRAGE, soluble receptor for advanced glycation end-products; SP-D, surfactant protein D; CC-16, clara cell protein; KL-6, Krebs von den Lungen-6.

Values are medians (interquartile range)

*, value is for comparison over time (postoperative vs. preoperative and postoperative day 5 vs. postoperative [repeated contrast])

**, comparison between groups over time (PPCs vs. no PPC and High PEEP vs. Low PEEP)

eTable 8 – Plasma level of biomarkers of inflammation and lung injury according to level of PEEP and development of PPC

	TNF–α (pg ml^{-1})	IL–6 (pg ml^{-1})	IL–8 (pg ml^{-1})	sRAGE (µg ml^{-1})	SP–D (µg ml^{-1})	CC–16 (µg ml^{-1})	KL6 (units ml^{-1})
High PEEP and PPC							
Preoperative	8.8 (5.0 – 11.3)	3.3 (2.3 – 5.0)	7.2 (4.7 – 9.5)	2.0 (1.7 – 2.4)	10.5 (6.6 – 19.4)	15.0 (9.8 – 21.9)	17.8 (12.2 – 25.5)
Postoperative	9.7 (5.1 – 13.6)	153.7 (82.9 –	23.1 (11.8 – 47.9)	2.2 (1.6 – 2.8)	5.9 (3.7 – 11.8)	18.1 (12.2 – 30.4)	12.9 (9.1 – 17.6)
Postoperative day 5	10.2 (5.8 – 12.7)	344.8)	10.6 (7.2 – 20.0)	2.2 (1.7 – 2.8)	6.9 (4.3 – 13.3)	13.9 (8.0 – 23.2)	12.7 (7.1 – 17.3)
P–value*	0.006	16.9 (10.3 – 53.7)	< 0.001	0.222	< 0.001	< 0.001	< 0.001
		< 0.001					
High PEEP and No PPC	5.9 (3.1 – 9.9)	2.6 (2.0 – 4.1)	6.8 (4.5 – 12.8)	1.7 (1.2 – 2.2)	7.6 (3.9 – 16.7)	17.0 (6.7 – 24.6)	17.4 (9.1 – 31.0)
Preoperative	6.2 (3.0 – 10.5)	61.5 (29.3 –	14.4 (8.7 – 29.0)	1.9 (1.3 – 2.4)	4.7 (2.2 – 9.0)	17.2 (9.7 – 28.0)	13.3 (7.7 – 22.5)
Postoperative	6.4 (4.3 – 10.9)	166.0)	8.3 (4.3 – 13.4)	1.7 (1.3 – 2.5)	5.4 (3.4 – 8.4)	9.7 (6.6 – 16.9)	12.7 (6.0 – 20.6)
Postoperative day 5	0.787	7.6 (5.4 – 15.4)	< 0.001	0.376	< 0.001	< 0.001	< 0.001
P–value*		< 0.001					
Low PEEP and PPC							
Preoperative	9.1 (5.7 – 11.5)	4.5 (2.4 – 6.6)	7.1 (5.4 – 12.9)	1.9 (1.5 – 2.5)	9.0 (4.5 – 15.6)	16.3 (12.1 – 24.5)	19.9 (11.7 – 29.6)
Postoperative	8.5 (5.4 – 12.9)	147.3 (71.7 –	19.4 (13.7 – 43.8)	2.0 (1.4 – 2.4)	5.6 (2.8 – 10.1)	19.1 (13.1 – 26.5)	14.1 (7.9 – 20.0)
Postoperative day 5	9.9 (5.5 – 13.0)	326.6)	10.5 (7.7 – 14.5)	1.9 (1.4 – 2.5)	5.9 (4.2 – 12.7)	13.8 (8.8 – 21.5)	13.2 (7.4 – 17.4)
P–value*	0.060	19.0 (9.4 – 45.2)	< 0.001	0.989	< 0.001	< 0.001	< 0.001
		< 0.001					
Low PEEP and No PPC							
Preoperative	8.1 (3.8 – 11.6)	3.3 (1.6 – 5.0)	6.0 (3.1 – 9.4)	1.8 (1.4 – 2.4)	8.4 (4.9 – 14.2)	13.0 (7.7 – 22.1)	18.6 (9.7 – 27.7)
Postoperative	8.5 (3.5 – 11.6)	64.3 (32.9 –	12.7 (7.1 – 23.9)	1.7 (1.4 – 2.1)	5.7 (3.6 – 10.4)	16.2 (8.8 – 24.2)	13.7 (6.8 – 23.5)
Postoperative day 5	7.5 (3.7 – 12.0)	144.4)	8.0 (4.2 – 12.1)	1.8 (1.3 – 2.2)	5.9 (3.1 – 9.0)	10.3 (6.6 – 17.3)	12.8 (5.6 – 21.9)
P–value*	0.402	10.2 (6.5 – 18.8)	< 0.001	0.845	< 0.001	< 0.001	< 0.001
		< 0.001					
P–value**	0.308		0.690	0.512	0.121	0.050	0.721
		0.085					

PPCs, postoperative pulmonary complications; TNF, tumor necrosis factor; IL, interleukin; sRAGE, soluble receptor for advanced glycation end-products; SP-D, surfactant protein D; CC-16, clara cell protein; KL-6, Krebs von den Lungen-6.

Values are medians (interquartile range)

*, value is for comparison over time (postoperative vs. preoperative and postoperative day 5 vs. postoperative [repeated contrast])

**, comparison between groups over time (High PEEP and PPC vs. High PEEP and No PPC vs. Low PEEP and PPC vs. Low PEEP and No PPC)

eTable 9 – Relative changes in plasma level of biomarkers of inflammation and lung injury according to level of PEEP and development of PPC

	High PEEP and PPC	High PEEP and No PPC	Low PEEP and PPC	Low PEEP and No PPC	*P* value
Day 01					
TNF–α	1.1 (1.0 – 1.2)	0.9 (0.7 – 1.0)	1.0 (0.9 – 1.1)	1.0 (0.9 – 1.1)	0.001
IL–6	47.9 (20.2 – 134.8)	21.7 (14.1 – 38.4)	43.4 (14.3 – 96.6)	20.4 (7.8 – 58.9)	0.001
IL–8	3.2 (1.7 – 5.6)	2.1 (1.4 – 3.6)	2.6 (1.7 – 7.3)	2.0 (1.2 – 3.7)	0.019
sRAGE	1.0 (0.9 – 1.2)	0.9 (0.8 – 1.2)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.415
SP–D	0.6 (0.5 – 0.7)	0.7 (0.5 – 0.8)	0.6 (0.5 – 0.9)	0.7 (0.6 – 0.9)	0.098
CC–16	1.2 (1.0 – 1.5)	1.2 (1.0 – 1.6)	1.1 (0.9 – 1.5)	1.1 (0.9 – 1.3)	0.109
KL6	0.72 (0.6 – 0.8)	0.7 (0.6 – 0.9)	0.7 (0.5 – 0.9)	0.7 (0.6 – 0.9)	0.261
Day 05					
TNF–α	1.1 (1.0 – 1.4)	1.1 (0.9 – 1.2)	1.1 (1.0 – 1.4)	1.0 (0.9 – 1.1)	0.117
IL–6	4.9 (2.8 – 15.8)	3.0 (2.0 – 4.7)	4.5 (2.2 – 9.6)	3.5 (1.7 – 6.1)	0.010
IL–8	1.6 (1.1 – 2.4)	1.3 (0.7 – 1.8)	1.4 (0.9 – 2.0)	1.5 (0.9 – 2.1)	0.279
sRAGE	1.1 (0.8 – 1.3)	1.0 (0.7 – 1.2)	1.0 (0.8 – 1.3)	1.0 (0.8 – 1.2)	0.354
SP–D	0.6 (0.5 – 1.0)	0.5 (0.4 – 0.9)	0.8 (0.5 – 1.1)	0.6 (0.5 – 0.8)	0.246
CC–16	0.9 (0.8 – 1.2)	0.8 (0.5 – 1.0)	0.8 (0.6 – 1.0)	0.8 (0.6 – 1.0)	0.045
KL6	0.7 (0.5 – 0.8)	0.7 (0.5 – 0.8)	0.6 (0.5 – 0.8)	0.7 (0.6 – 0.9)	0.610

PPCs, postoperative pulmonary complications; TNF, tumor necrosis factor; IL, interleukin; sRAGE, soluble receptor for advanced glycation end-products; SP-D, surfactant protein D; CC-16, clara cell protein; KL-6, Krebs von den Lungen-6.

Values are medians (interquartile range)

*, value is for comparison over time (postoperative vs. preoperative and postoperative day 5 vs. postoperative [repeated contrast])

**, comparison between groups over time (High PEEP and PPC vs. High PEEP and No PPC vs. Low PEEP and PPC vs. Low PEEP and No PPC)

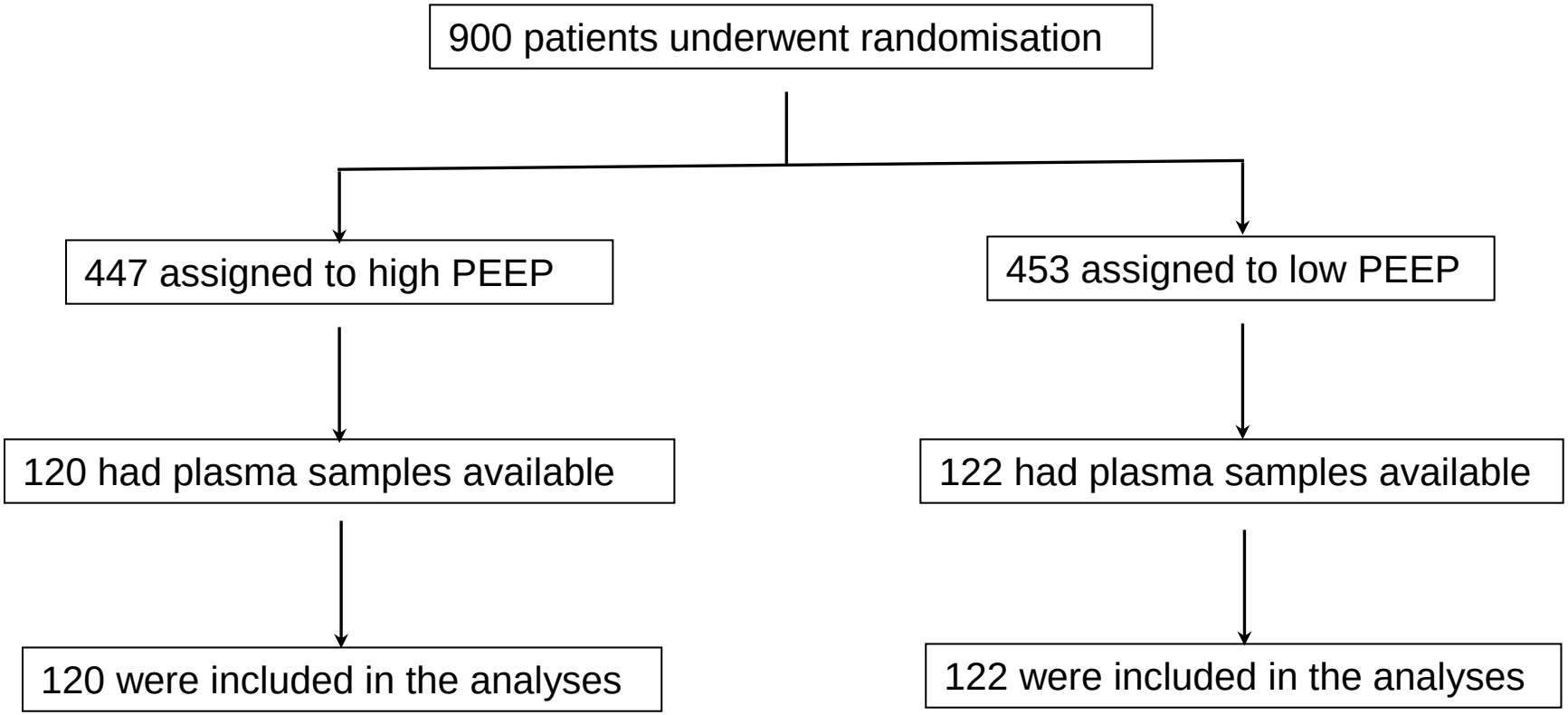
eTable 10 – Analyses from the false discovery rate using the Benjamini-Hochberg procedure with a false discovery rate of 0.2 for results of eTable 8

Variable	*p* value	Benjamini-Hochberg *p* value	Significant*
TNF–α (Day 1)	0.00068	0.0076	Yes
IL–6 (Day 1)	0.00109	0.0076	Yes
IL–6 (Day 5)	0.01000	0.0466	Yes
IL–8 (Day 1)	0.01900	0.0665	Yes
CC–16 (Day 5)	0.04500	0.1260	Yes
SP–D (Day 1)	0.09800	0.2047	No
CC–16 (Day 1)	0.10900	0.2047	No
TNF–α (Day 5)	0.11700	0.2047	No
SP–D (Day 5)	0.24600	0.3550	No
KL6 (Day 1)	0.26100	0.3550	No
IL–8 (Day 5)	0.27900	0.3500	No
sRAGE (Day 5)	0.35400	0.4130	No
sRAGE (Day 1)	0.41500	0.4469	No
KL6 (Day 5)	0.6100	0.6100	No

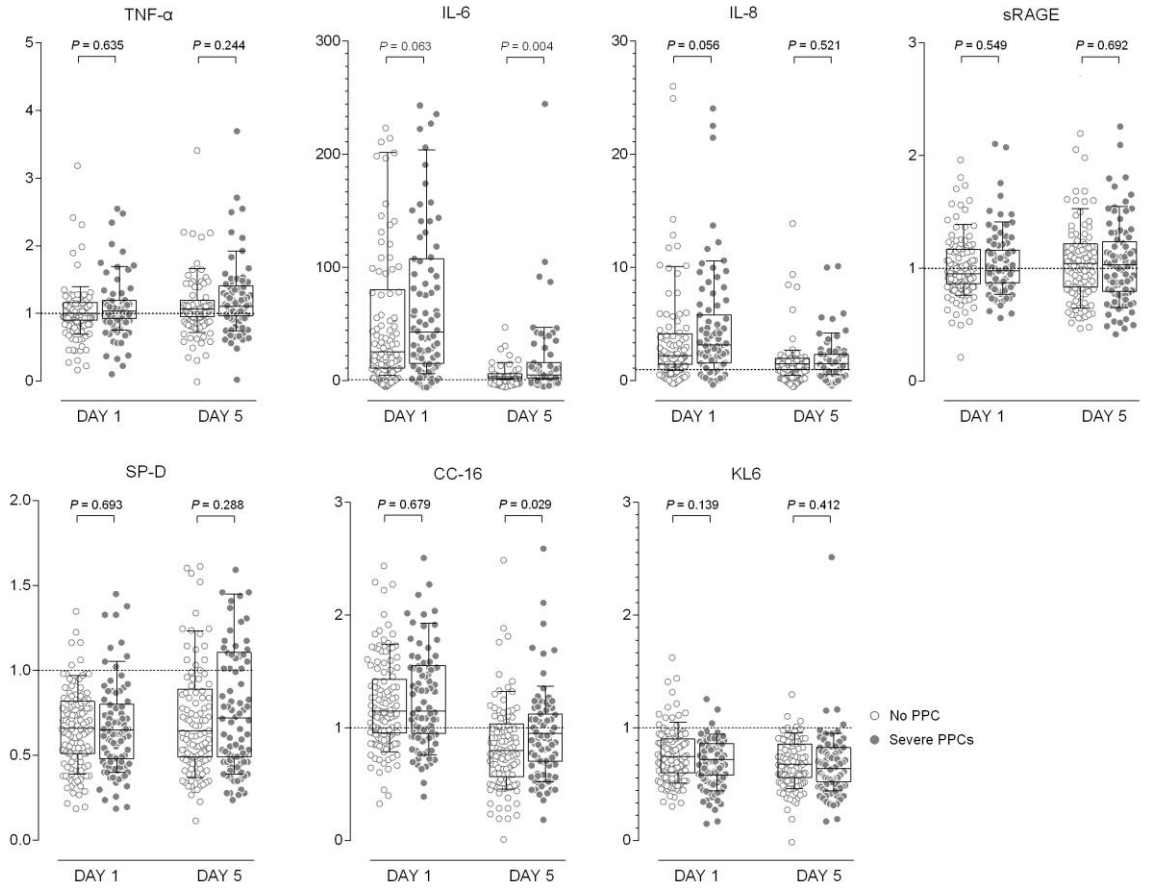
TNF, tumor necrosis factor; IL, interleukin; sRAGE, soluble receptor for advanced glycation end–products; SP-D, surfactant protein D; CC–16, Clara cell protein; KL6, Krebs von den Lungen-6.

*: significance according to the false discovery rate of 0.2

eFigure 1 – Flowchart of the trial



eFigure 2 – Relative changes in plasma levels of biomarkers in patients with (closed circles) and patients without PPC, restricted to severe PPCs (i.e., excluding unexpected need for supplementary oxygen) (open circles)



Analysis of relative change of plasma levels of biomarkers of inflammation according to development (gray circles) or not (white circles) of severe postoperative pulmonary complications. *Line represents the median, the box the interquartile range and the bars the 10% and 90% range.*