Role of biomarkers in acute traumatic lung injury

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Traumatic lung injury

- Pulmonary contusion /
  Parenchymal injury (pneumatocele, hematocele)

- Transmission of kinetic energy (with or without overlying rib fractures and subsequent laceration) results in bruising of the lung, characterized by interstitial and alveolar edema, hemorrhage, and subsequent alveolar collapse.

Traumatic lung injury

- Direct chest trauma or inflammatory response
  - Lung tissue injury & microvascular damage
  - Inflammatory response; toll like receptors(TLRs)

    → activation of NFkB, inflammatory response

Traumatic lung injury

- Clinically, hypoxia and ventilatory embarrassment develop within 24 to 48 hours
- Complication(50%); ARDS, pneumonia

- The treatment is generally supportive.
  - Iv volume restricted
  - Colloid solutions appear to aggravate pulmonary dysfunction
  - Diuresis
  - No role for prophylactic antibiotics

Measurement of traumatic lung injury

- CXR; patchy changes
- CT; grade the degree of injury
- ABGA; depend on O_2 supply

- Biomarker

Biomarkers for traumatic lung injury

- Markers of epithelial damage
- Markers of endothelial damage
- Inflammatory biomarkers
- Coagulation/fibrinolysis related biomarkers

Markers of epithelial damage

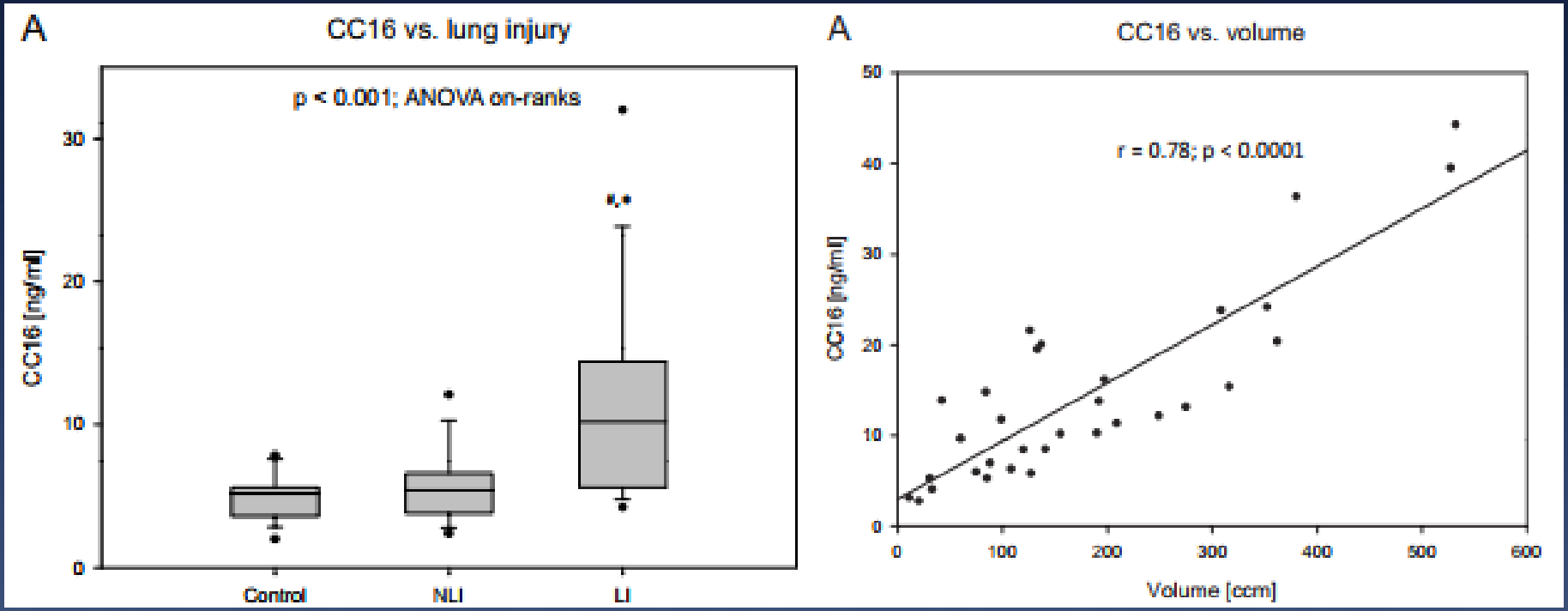
- Club cell protein 16
- Leukotriene B-4
- Soluble receptor for advanced glycation end products (sRAGE)
- Surfactant proteins

Biomarker	Author	Year	Patients	Conclusion
CC-16	Wutzler et al. [28]	2011	104	Potential biomarker in severely injured patients with lung injury, correlates with volume of PC.
	Wutzler et al. [33]	2012	44	Values in case of thoracic trauma elevated, decline during first 24 h, second peak indicates respiratory complications.
	Wu et al. [32]	2016	42	CC-16 serum levels are increased in case of pulmonary contusion during first 24 h, correlate with degree of injury.
	Negrin et al. [34]	2017	101	Elevated CC-16 serum levels exceeding 30.51 ng/ml at day 2 post trauma predict pneumonia.
LTB − 4	Auner et al. [41]	2012	100	High levels of LTB − 4 indicate development of PC in severely injured patients.
sRAGE	Negrin et al. [47]	2016	130	sRAGE levels increased in patients with thoracic trauma, promising tool to asses the severity of lung injury shortly after trauma.
	Uhle et al. [46]	2014	77	Early and transiently release after trauma, associated with extend of injury and inflammatory response.
	Cohen et al. [48]	2010	168	sRAGE levels increased 30 min after injury, correlate with Injury Severity Score, no significant correlation to development of ALI ($p = 0.11$).
	Fremont et al. [49]	2010	192	Most valuable marker out of seven tested to distinguish patients with from patients without ALI.
Surfactant proteins	Kurt et al. [58]	2016	60	Elevated serum SP-D levels could be used as a marker in follow − up complications after blunt chest trauma.

Club cell protein 16

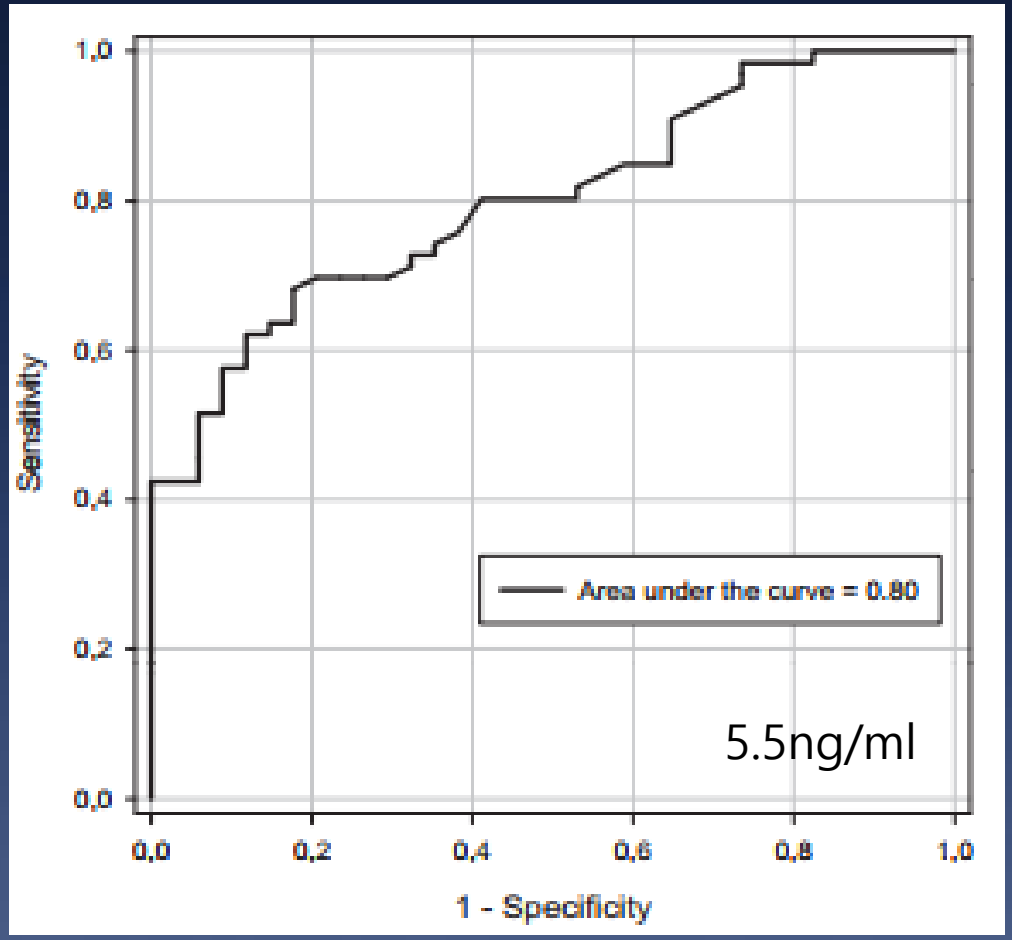
- Clara cell protein
- Secreted by Club cells of the terminal bronchial epithelium
- Anti-oxidant & anti-inflammatory protein
- Modulation of phospholipase A2, INF-γ, TNF-α

Club cell protein 16



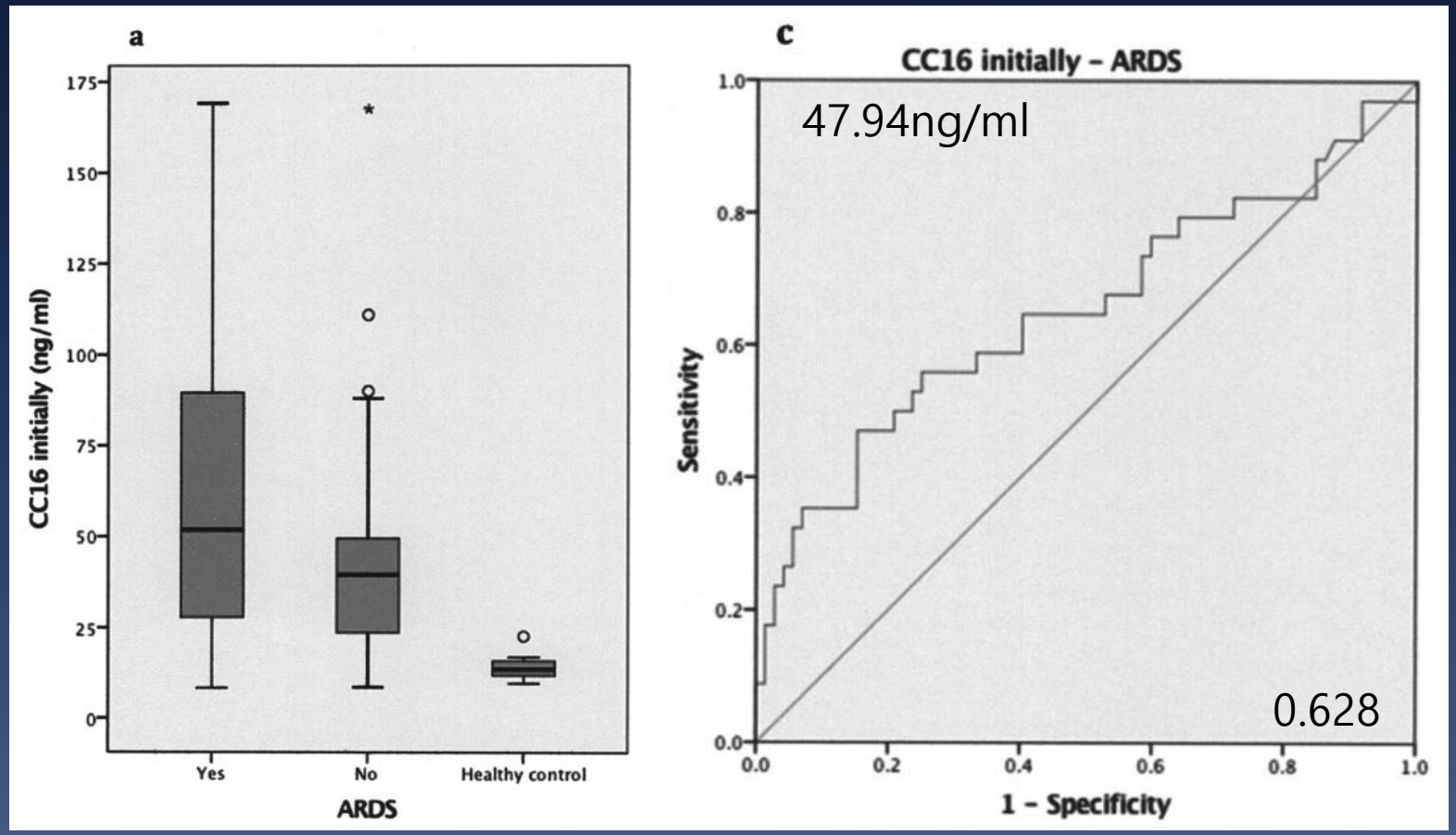
Wutzler et al. J Trauma 2011;71:E31-6

Club cell protein 16 ~ severe Lung Injury



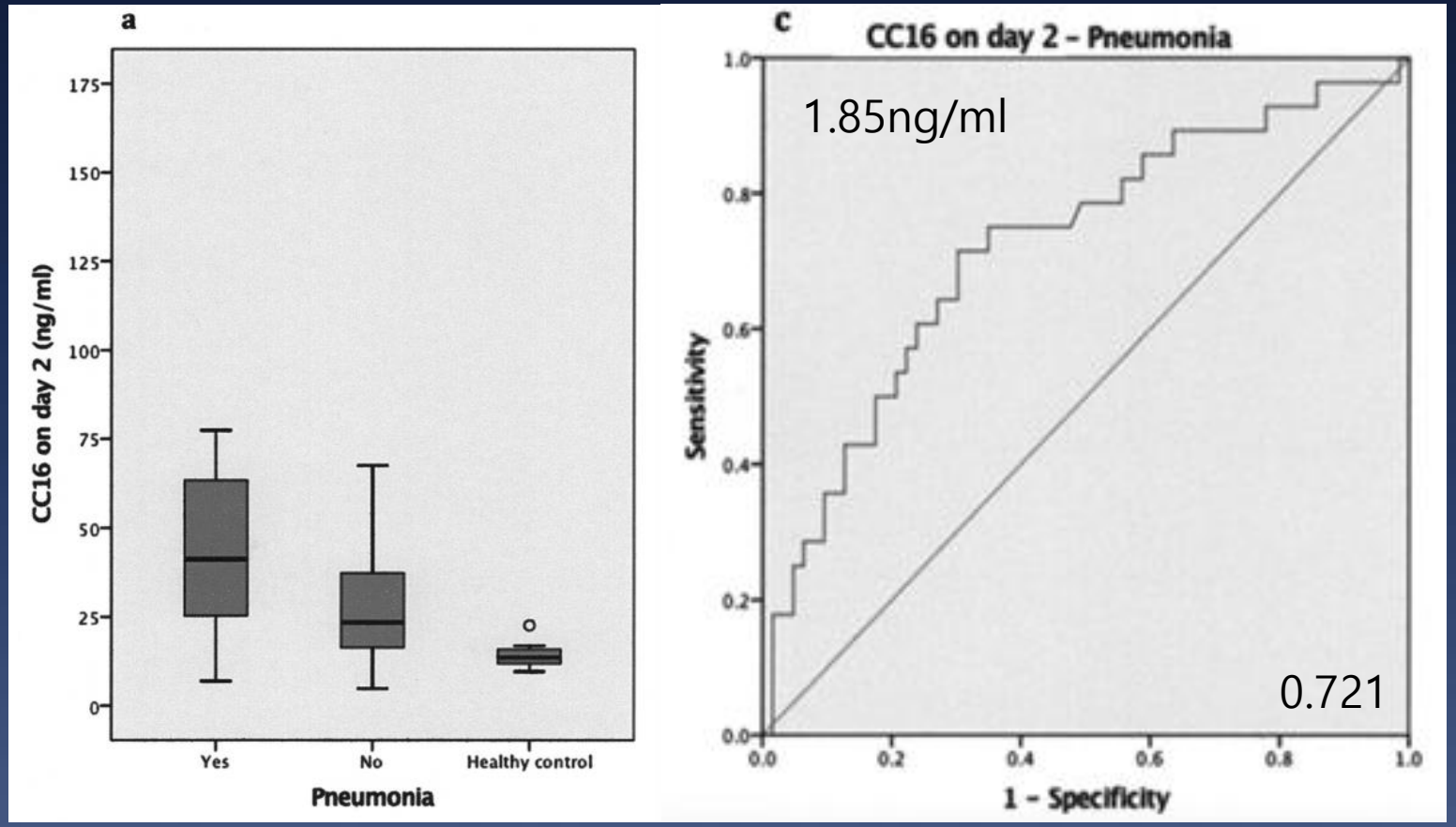
Wutzler et al. J Trauma 2011;71:E31-6

Club cell protein 16 ~ ARDS



Negrin et al. PLoS One 2017;(12):e003

Club cell protein 16 ~ pneumonia at PTD 2#

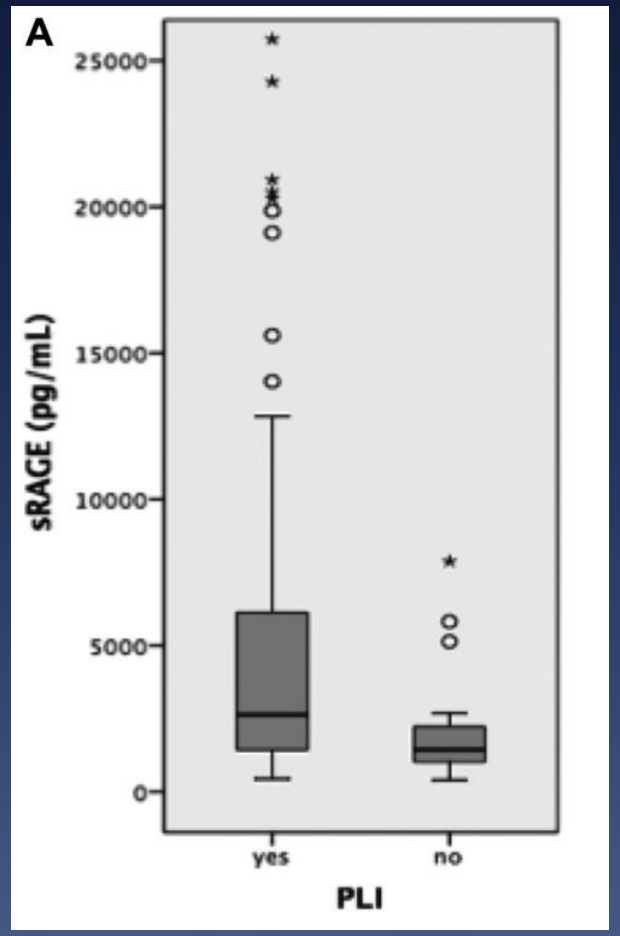


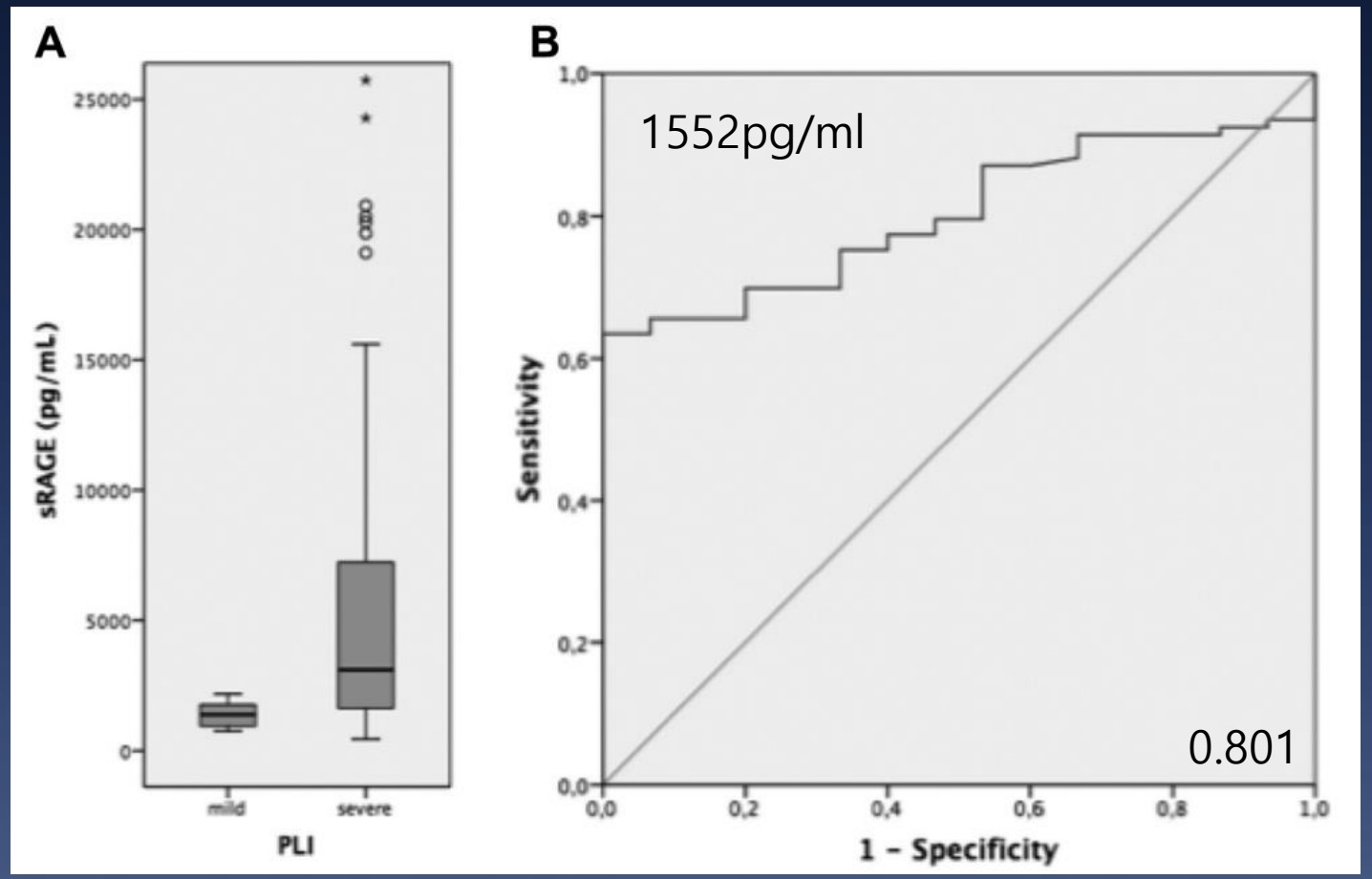
Negrin et al. PLoS One 2017;(12):e003

Soluble receptor for advanced glycation end products (sRAGE)

- Basal Mb of alveolar cell type 1
- Pro-inflammatory response by activation of cytokines, reactive oxygen species, protease
- Major mediator in the inflammatory activation in ARDS

sRAGE





Negrin et al. Ann Thorac Surg 2017;103:1587-93

Leukotrien B-4

- 5-lipoxygenase of the arachidonic acid metabolism
- Strong chemoattractant;
  adherence of neutrophils to endothelial cells
- Well correlate with acute phase of ARDS

Circulating Leukotriene B4 Identifies Respiratory Complications after Trauma

Auner et al. Mediators Inflamm 2012;2012;536156-8

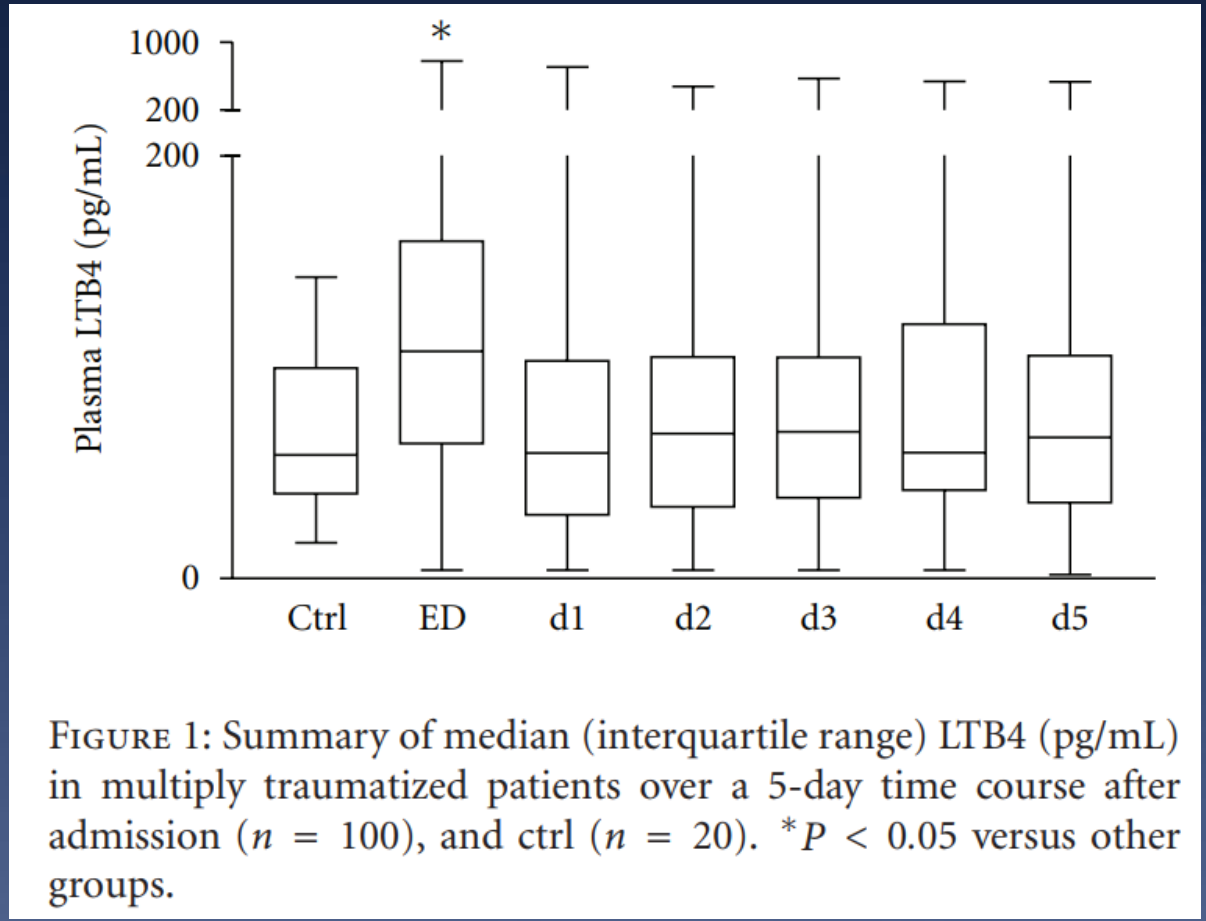


FIGURE 1: Summary of median (interquartile range) LTB4 (pg/mL) in multiply traumatized patients over a 5-day time course after admission ($n = 100$), and ctrl ($n = 20$). $^*P < 0.05$ versus other groups.

Leukotriene B-4

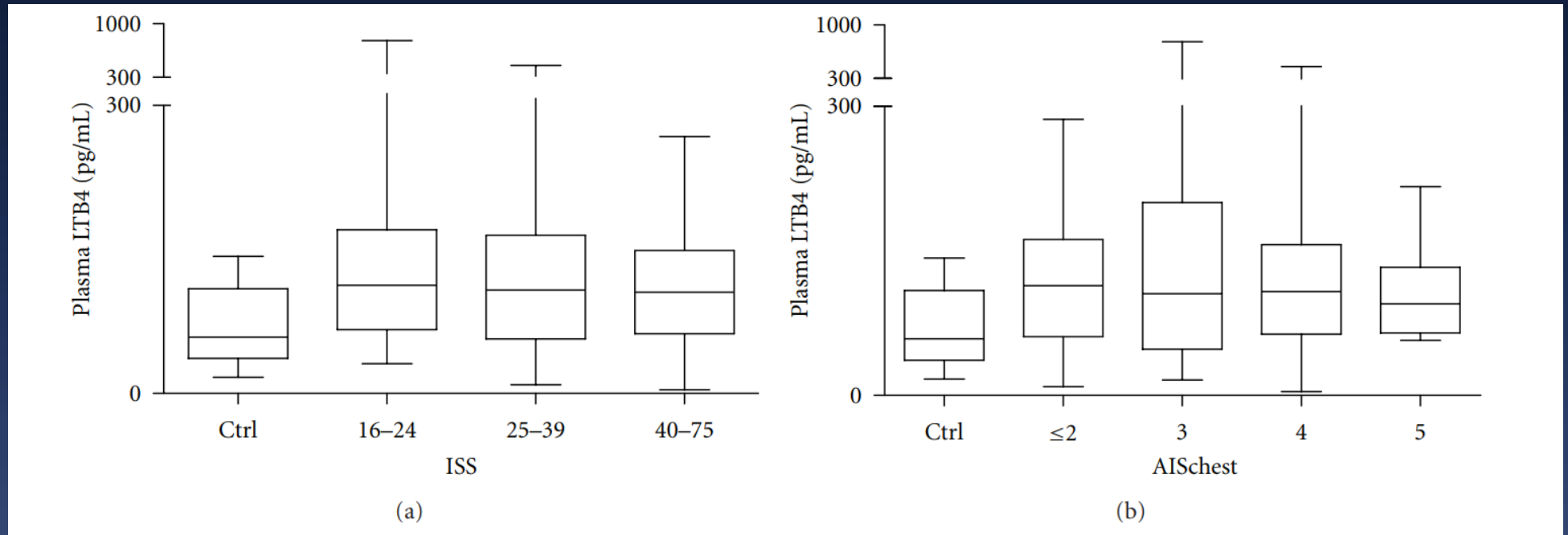


FIGURE 2: Summary of median (interquartile range) LTB4 (pg/mL) in ED samples in different groups of patients based on the overall injury severity (a) and the severity of chest injury (b). (a) ISS: 16–24, $n = 17$, ISS: 25–39, $n = 54$, ISS: ≥40, $n = 29$ and ctrl group, $n = 10$. (b) $AIS_{chest} \leq 2$, $n = 21$, $AIS_{chest} = 3$, $n = 23$, $AIS_{chest} = 4$, $n = 49$, $AIS_{chest} = 5$, $n = 7$ and ctrl, $n = 20$.

Auner et al. Mediators Inflamm 2012;2012;536156-8

Leukotriene B-4

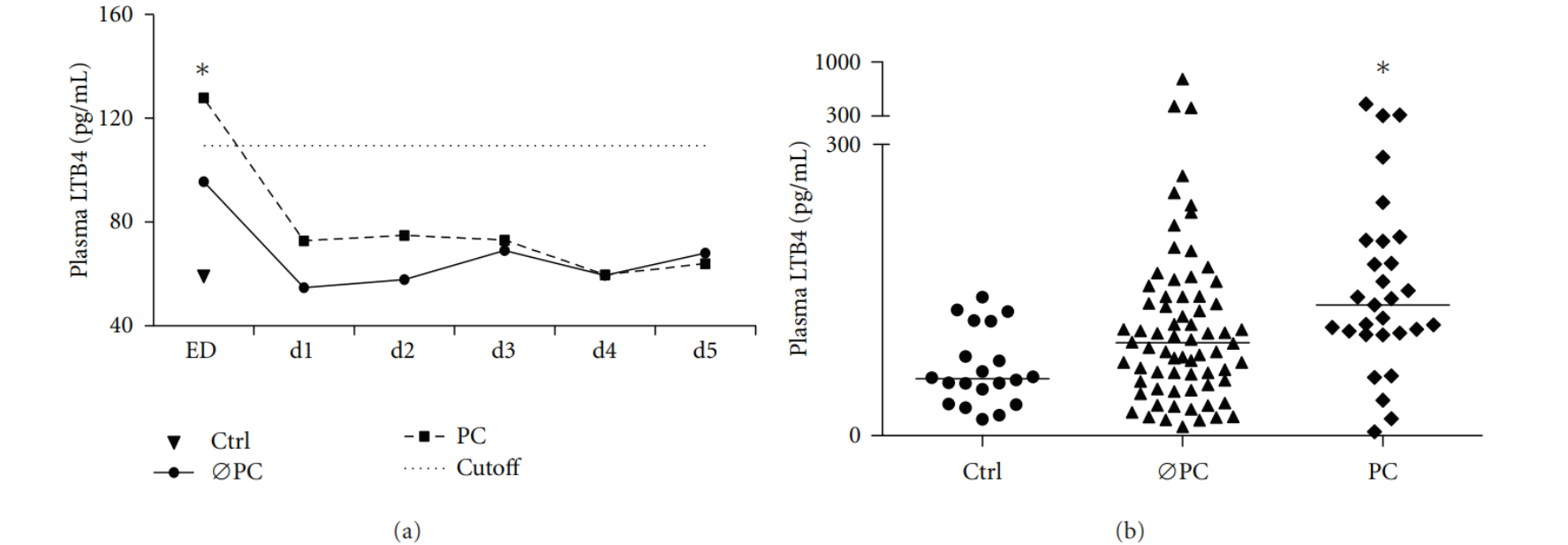


FIGURE 3: Summary of median LTB4 (pg/mL) in two patient groups based on the development of pulmonary complications (ØPC: no pulmonary complications, $n = 70$, and PC: pulmonary complications, $n = 30$) and ctrl, $n = 20$, $^*P < 0.05$ versus other groups: (a) time course in both groups, (b) LTB4 levels at the ED.

Auner et al. Mediators Inflamm 2012;2012;536156-8

Leukotriene B-4

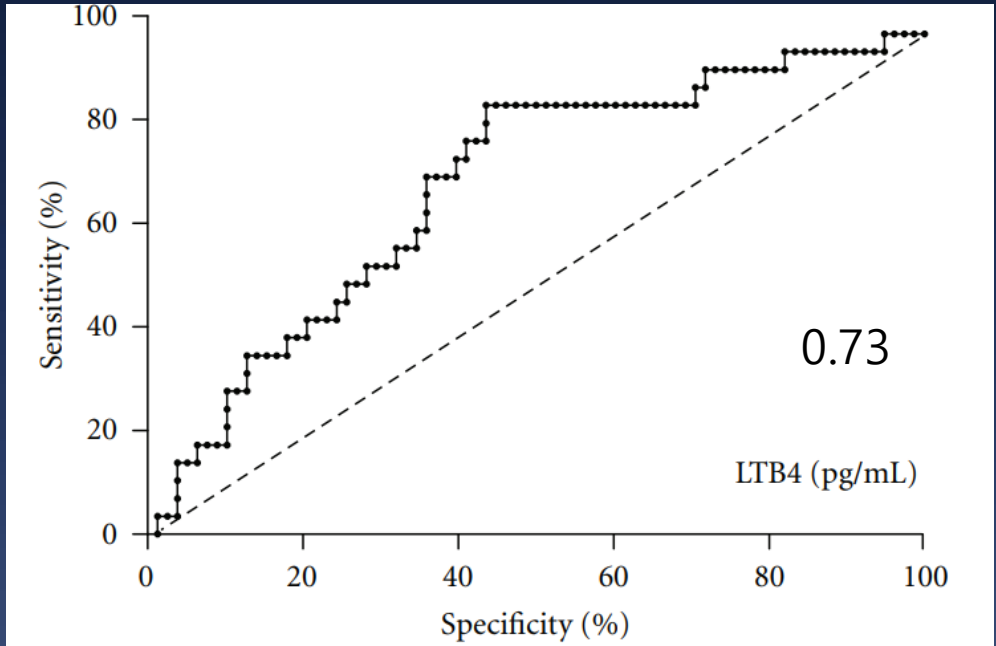


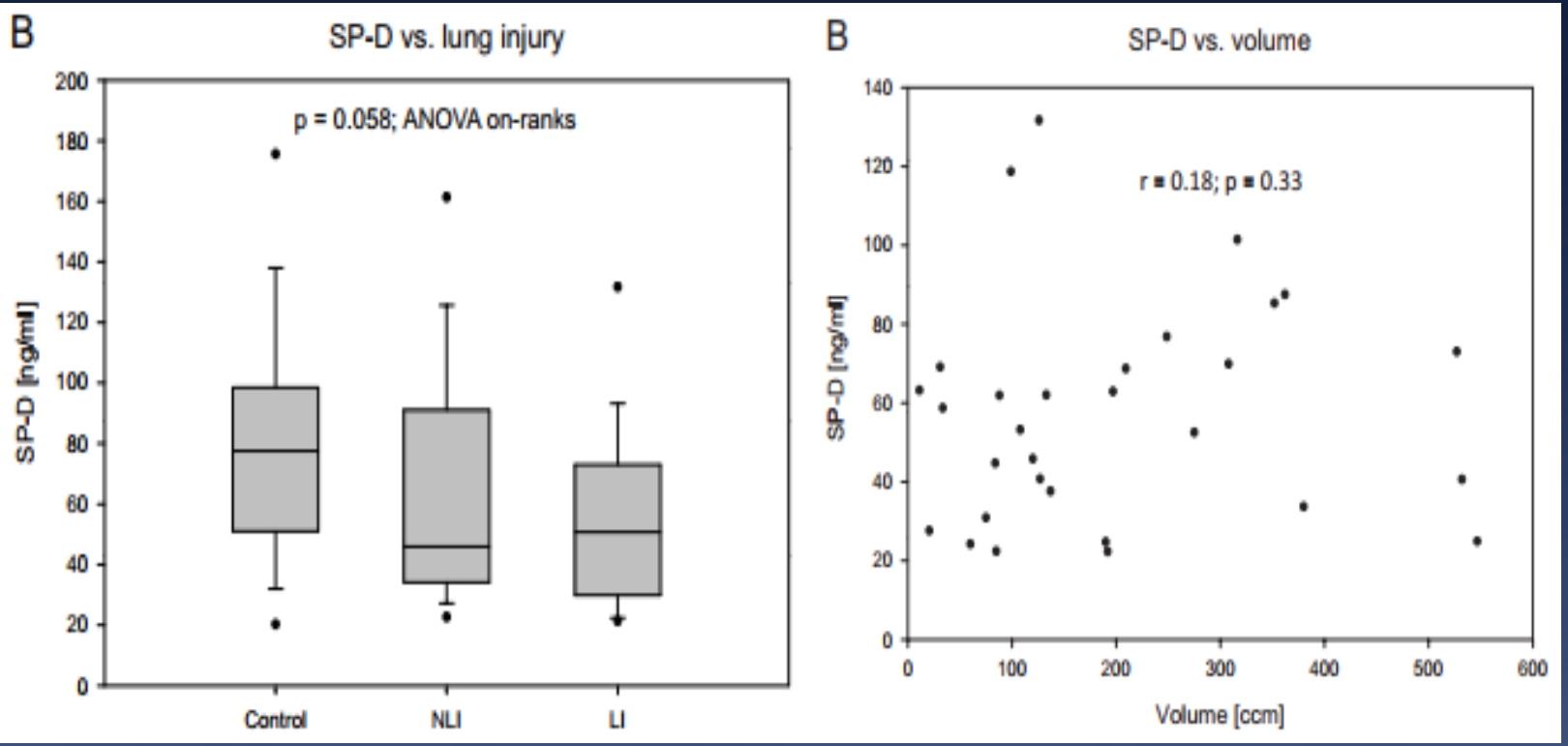
FIGURE 4: Receiver operating curve showing the optimal cutoff for LTB4 levels (109.6 pg/mL in predicting the presence or absence of postinjury pulmonary complications with 72% specificity and 67% sensitivity).

Auner et al. Mediators Inflamm 2012;2012;536156-8

Surfactant proteins

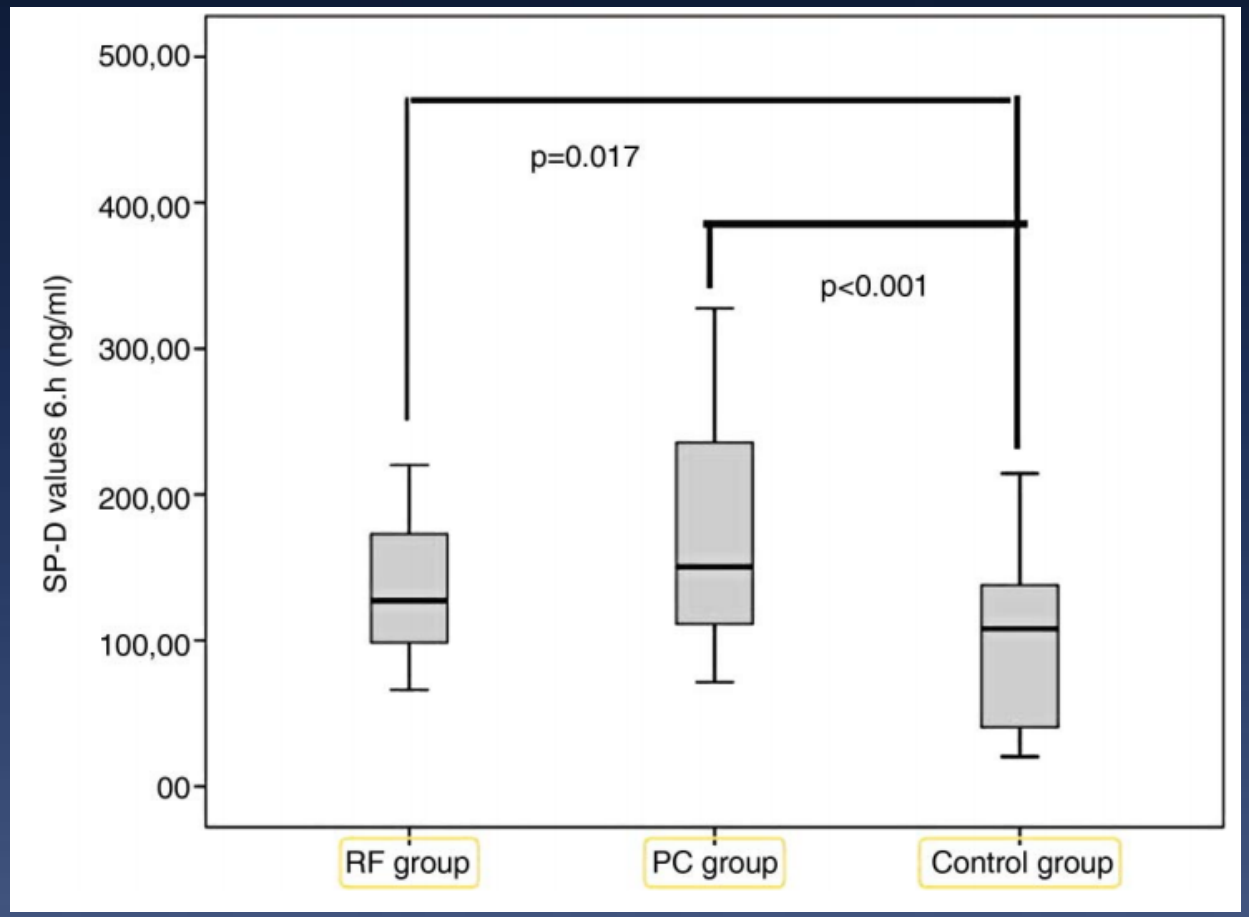
- Type II alveolar endothelial cells
- Prevent an end-expiratory alveolar collapse
- Essential for the integrity of the alveolar Mb permeability

Surfactant proteins



Wutzler et al. J Trauma 2011;71:E31-6

Surfactant proteins



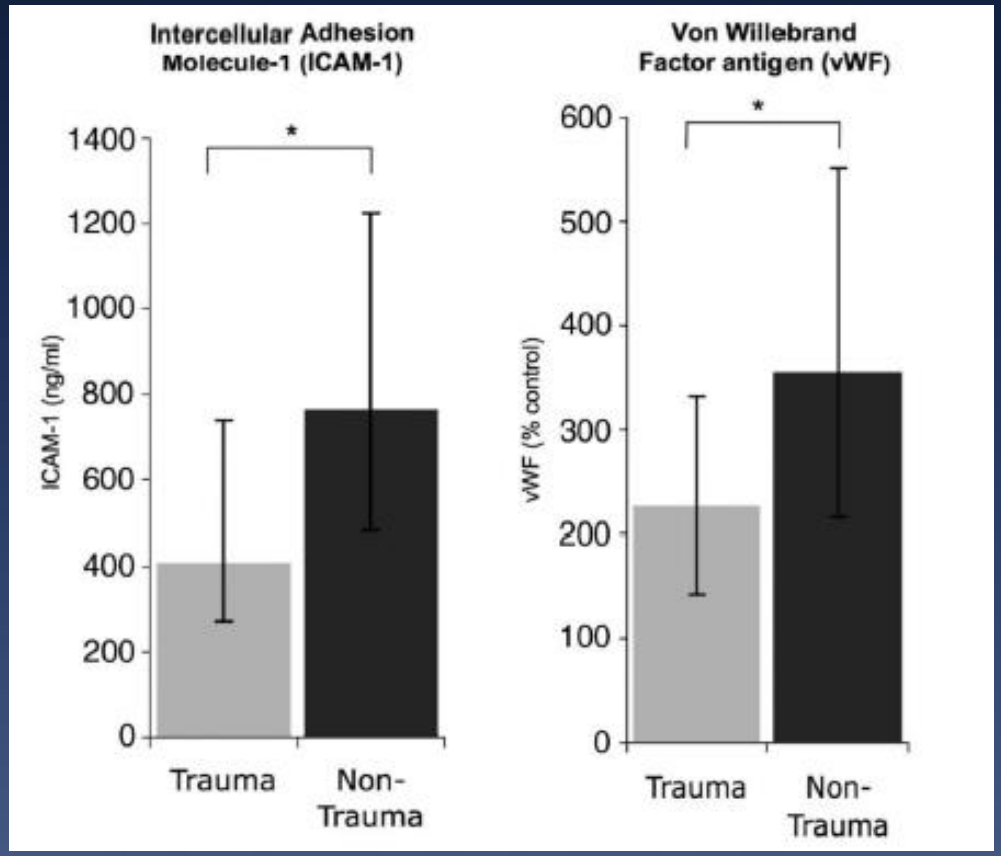
Kurt et al. BMJ 2016;6:E011797

Markers of endothelial damage

- von Willebrand factor
- Soluble intracellular adhesion molecule-1 (sICAM-1)
- Vasoendothelial growth factor (VEGF)
- Angiopoietin-2

Biomarker	Author	Year	Patients	Conclusion
vWF	Calfee et al. [6]	2007	1451[a]	vWF serum levels significantly lower than for patients with ALI without trauma, trauma associated ALI possibly with less endothelial damage.
VEGF	Guo et al. [63]	2017	60	Increase of sVEGFR1 and decrease of sVEGFR2 in early trauma is associated with development of late ARDS.
	Wada et al. [64]	2013	159[b]	Levels of sVEGFR1 are higher in patients with ALI/ARDS, could be valuable prognostic biomarker.
Ang-2	Reilly et al. [66]	2014	636	Suitable to distinguish trauma patients with early from those with late onset ARDS.
sICAM-1	Gando et al. [71]	2002	58	Correlation of high serum levels and poor outcome but no correlation to development of ALI.
	Calfee et al. [6]	2007	1451[a]	Serum levels of trauma patients significantly lower than for ALI patients with no association to trauma, possible reason for better outcome of trauma patients.
	Sousa et al. [70]	2015	99	Elevated plasma levels associated to MODS but not to death.

vWF / ICAM-1



Calfee et al. Crit Care Med 2007 October;35(10):2243-2250

Vasoendothelial growth factor (VEGF)

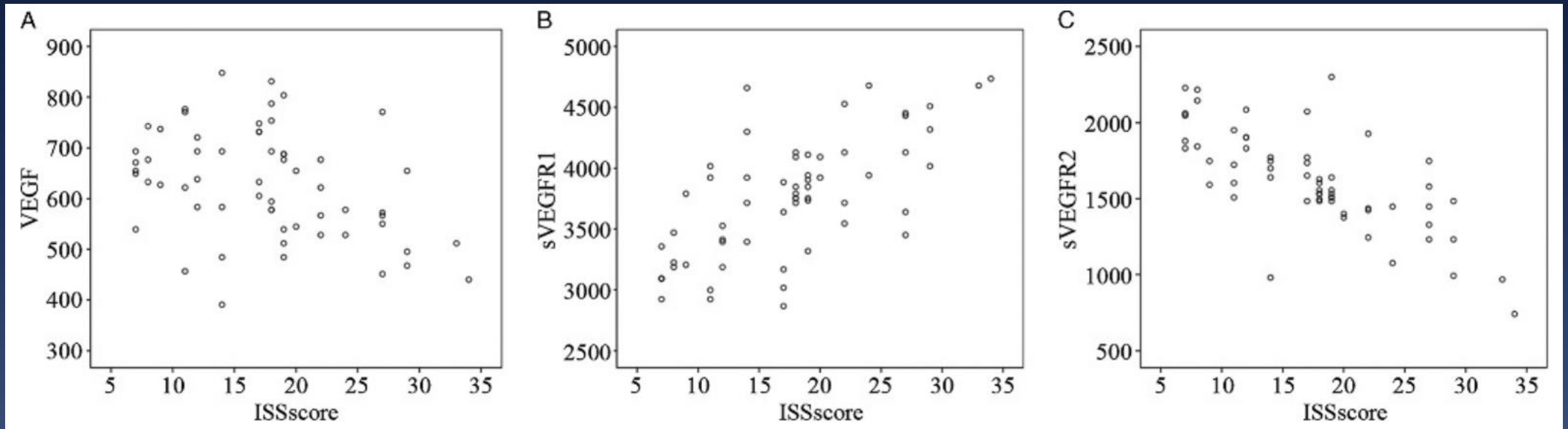


Figure 1. Scatter plot showing relationship between ISS and the level of serum VEGF (*A*) and the level of serum sVEGFR1 (*B*) and the level of serum sVEGFR2 (*C*). (*A*) No correlation; (*B*) $r^2 = 0.459$, $p < 0.0001$; (*C*) $r^2 = 0.510$, $p < 0.0001$.

Guo et al. J Trauma Acute Care Surg 2017;82:766-70

Monitoring of vascular endothelial growth factor and its soluble receptor levels in early trauma

Jianying Guo, MD, Wenwen Yan, MD, Yong Yang, MD,
Zhiyong Wang, MD, *and* **Fengjun Tian, MD**, *Shijiazhuang, China*

TABLE 2. The Rate of ARDS and the Level of Serum VEGF and Their Soluble Receptors

	Control Group	Non-ARDS	ARDS	*p*
Patients (n)	10	42	18	
Age, y	34 ± 7	33 ± 9	34 ± 7	0.231
Sex (male)	9/10	37/42	15/18	0.846
Time, h		1.6 ± 0.5	1.5 ± 0.4	0.665
VEGF, pg/mL	684.1 ± 96.6	644.8 ± 106.5	591.3 ± 98.8	0.061
sVEGFR1, pg/mL	2967.4 ± 411.9	3640.1 ± 489.0*	4005.8 ± 424.8*, **	<0.0001
sVEGFR2, pg/mL	2067.8 ± 399.1	1684.7 ± 287.3*	1462.3 ± 357.7*, **	<0.0001

*Different from control group ($p < 0.05$).
**Different between ARDS group and non-ARDS group ($p < 0.05$).

Angiopoietin-2

- Induce vascular infiltration
- Increase endothelial junction instability & vascular leakage

Heterogeneous Phenotypes of Acute Respiratory Distress Syndrome after Major Trauma

John P. Reilly[1,2], Scarlett Bellamy[2], Michael G. S. Shashaty[1,2], Robert Gallop[2], Nuala J. Meyer[1], Paul N. Lanken[1], Sandra Kaplan[1], Daniel N. Holena[3], Addison K. May[4], Lorraine B. Ware[5], and Jason D. Christie[1,2]

Table 4. Plasma biomarker levels by acute respiratory distress syndrome onset class

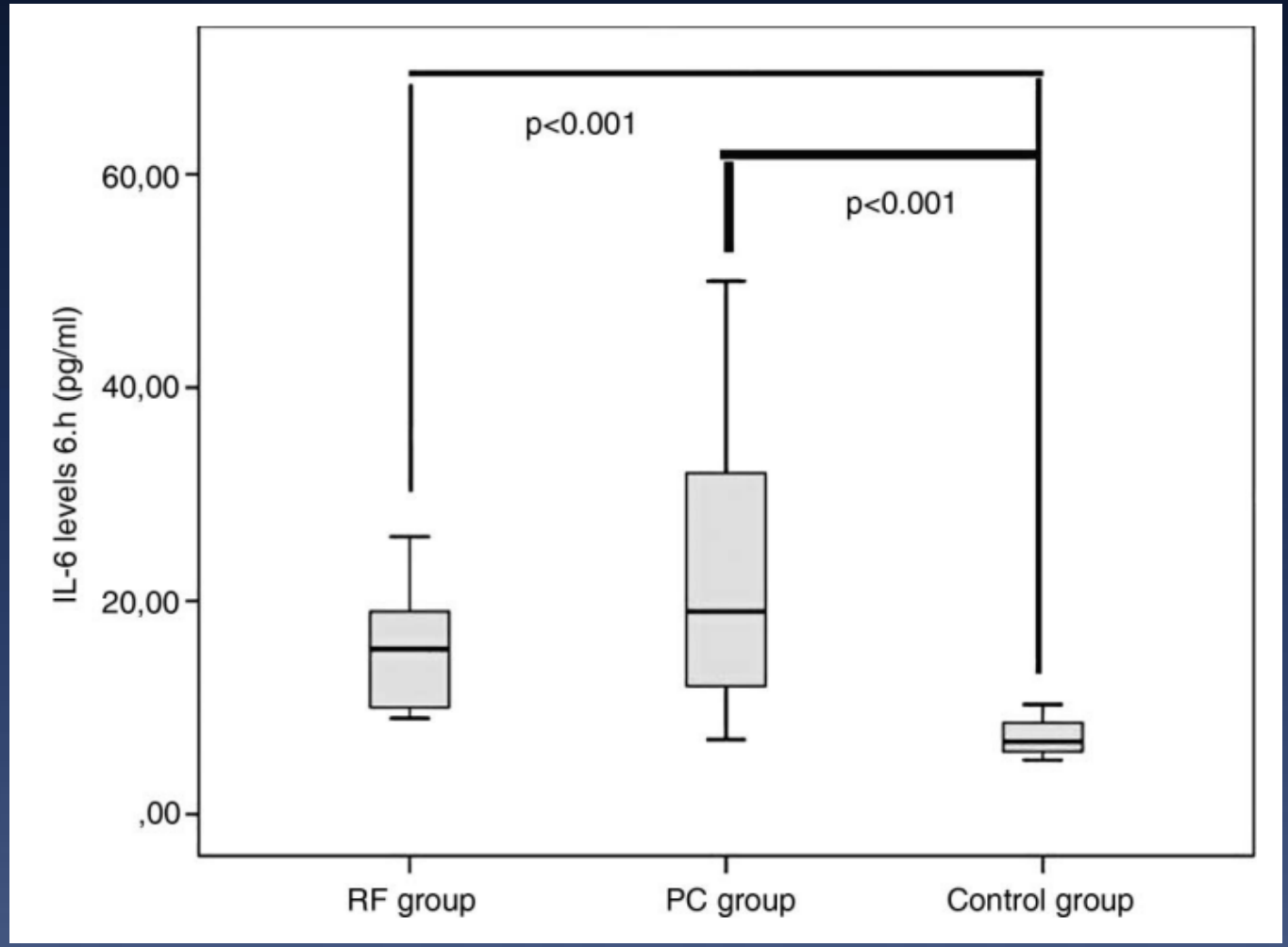
Biomarker	Early-Onset ARDS (n = 66; 59%)	Late-Onset ARDS (n = 46; 41%)	*P* Value
IL-8, pg/ml	15.6 (15.6–58.2)	15.6 (15.6–85.5)	0.644
VWF, % control	231 (168–351)	248 (194–353)	0.219
SP-D, ng/ml	57 (37–88)	63 (42–80)	0.927
PAI-1, ng/ml	138 (40–266)	87 (40–197)	0.271
CC16, ng/ml	6.9 (4.1–12.4)	5.8 (4.4–8.3)	0.187
sRAGE, pg/ml	1,773 (949–3,227)	1,226 (773–1,944)	0.025
Ang-2, pg/ml	5,684 (4,190–7,773)	4,365 (2,957–5,647)	0.002
BNP, ng/ml	0.41 (0.31–0.67)	0.33 (0.26–0.56)	0.123
PCP III, ng/ml	3.5 (2.8–4.9)	3.2 (2.7–4.2)	0.249
IL-10, pg/ml	16 (9–86)	21 (9–70)	0.703
TNF-α, pg/ml	1.03 (0.61–3.47)	0.67 (0.61–4.83)	0.535

Inflammatory biomarkers

- Cytokines

Biomarker	Author	Year	Patients	Conclusion
IL-6	Calfee et al. [6]	2007	1451[a]	Significantly increased values of IL-6 on day 0 in trauma patients with ALI when compared to trauma-independent ALI.
IL-8	Hildebrand et al. [73]	2007	97	Elevated plasma levels of IL-8 from day 3 in patients with ARDS, may point to a genetic predisposition for IL-8-synthesis and development of ARDS.
HMGB-1	Cohen et al. [77]	2009	168	Significantly higher values 30 min after severe trauma in non survivors, high amounts correlate with development of ALI during the clinical course.
IL-6	Frink et al. [75]	2009	143	Increased plasma levels of IL-6 predict mortality and multi organ dysfunction syndrome, no specific data for ALI/ARDS.
IL-8	Raymondos et al. [74]	2012	24	BAL-F IL-8 levels >200 pg/ml 2–6 h after trauma identify patients at high risk to develop ARDS.
IL-6	Holloway et al. [76]	2015	21	Markedly greater levels of plasma and BAL-F levels of IL-6 in patients with development of ARDS. Pro-inflammatory milieu might contribute ALI/ARDS.

IL-6



Kurt et al. BMJ 2016;6:E011797

Association of IL-8-251A/T polymorphism with incidence of Acute Respiratory Distress Syndrome (ARDS) and IL-8 synthesis after multiple trauma

Frank Hildebrand [a,*], Manfred Stuhrmann [b], Martijn van Griensven [c], Sven Meier [a], Sandra Hasenkamp [b], Christian Krettek [a], Hans-Christoph Pape [d]

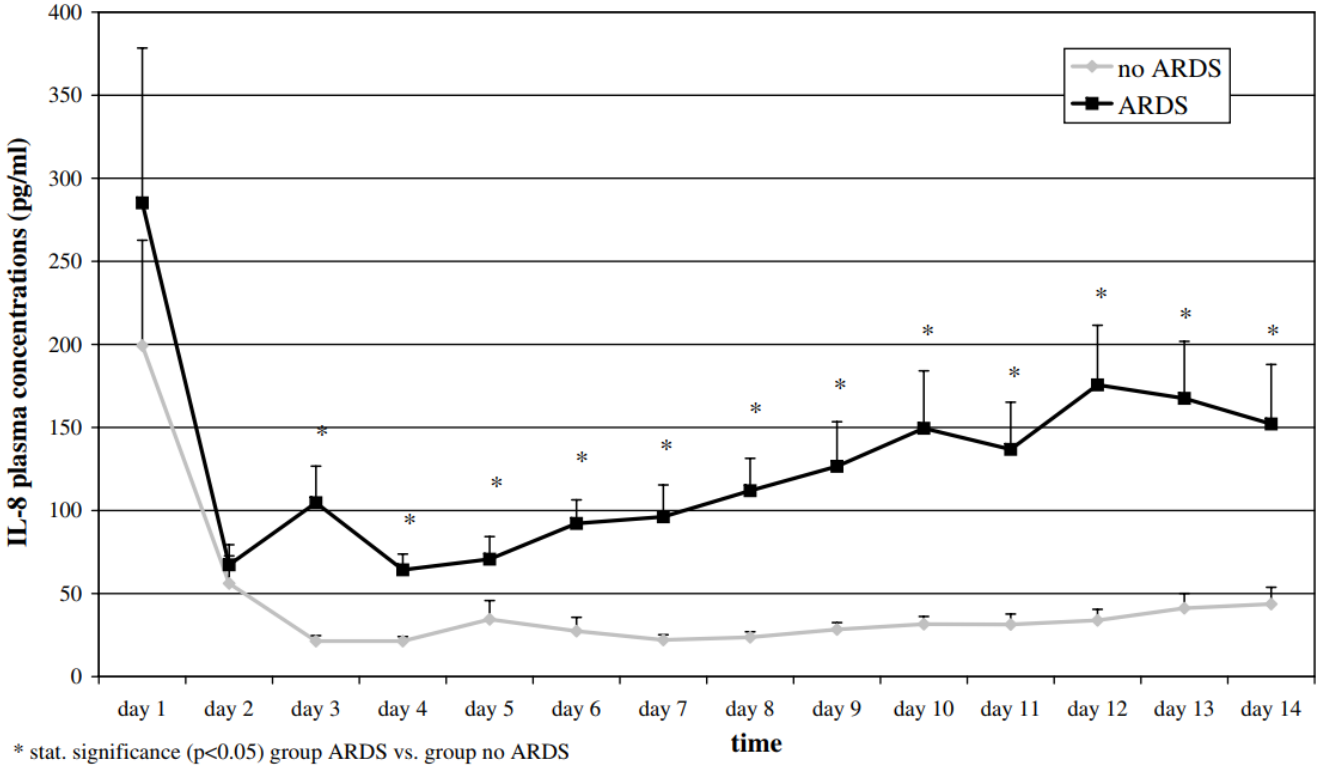
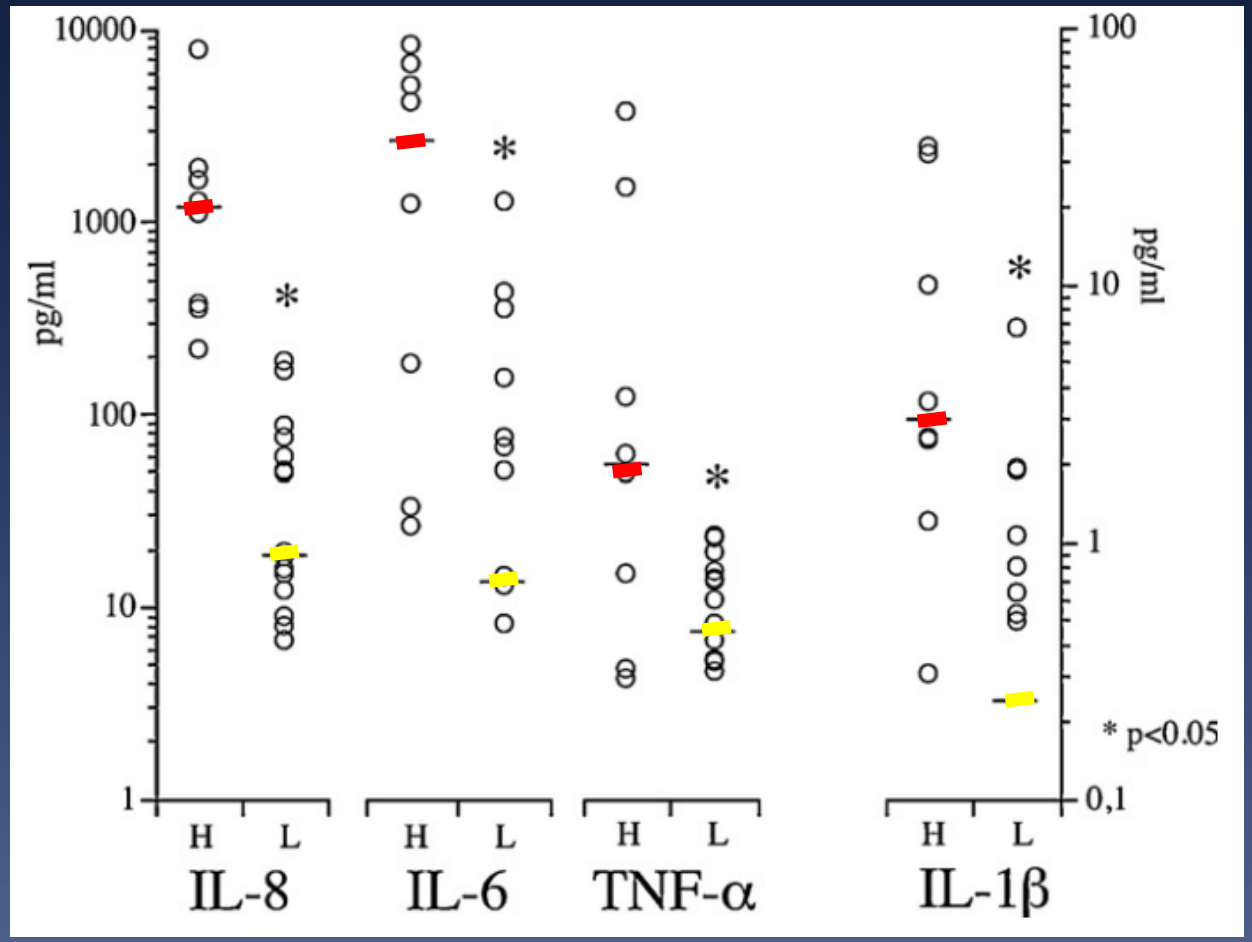


Fig. 1. Comparison of IL-8 plasma concentrations over the observation period between group +ARDS and group −ARDS (according to American-European Consensus Conference on ARDS), Students *t*-test, $^{*}p < 0.05$.

Early alveolar and systemic mediator release in patients at different risks for ARDS after multiple trauma

Konstantinos Raymondos [a,*], Michael U. Martin [b], Tanja Schmudlach [a], Stefan Baus [c], Christian Weilbach [a], Tobias Welte [d], Christian Krettek [e], Michael Frink [e], Frank Hildebrand [e]



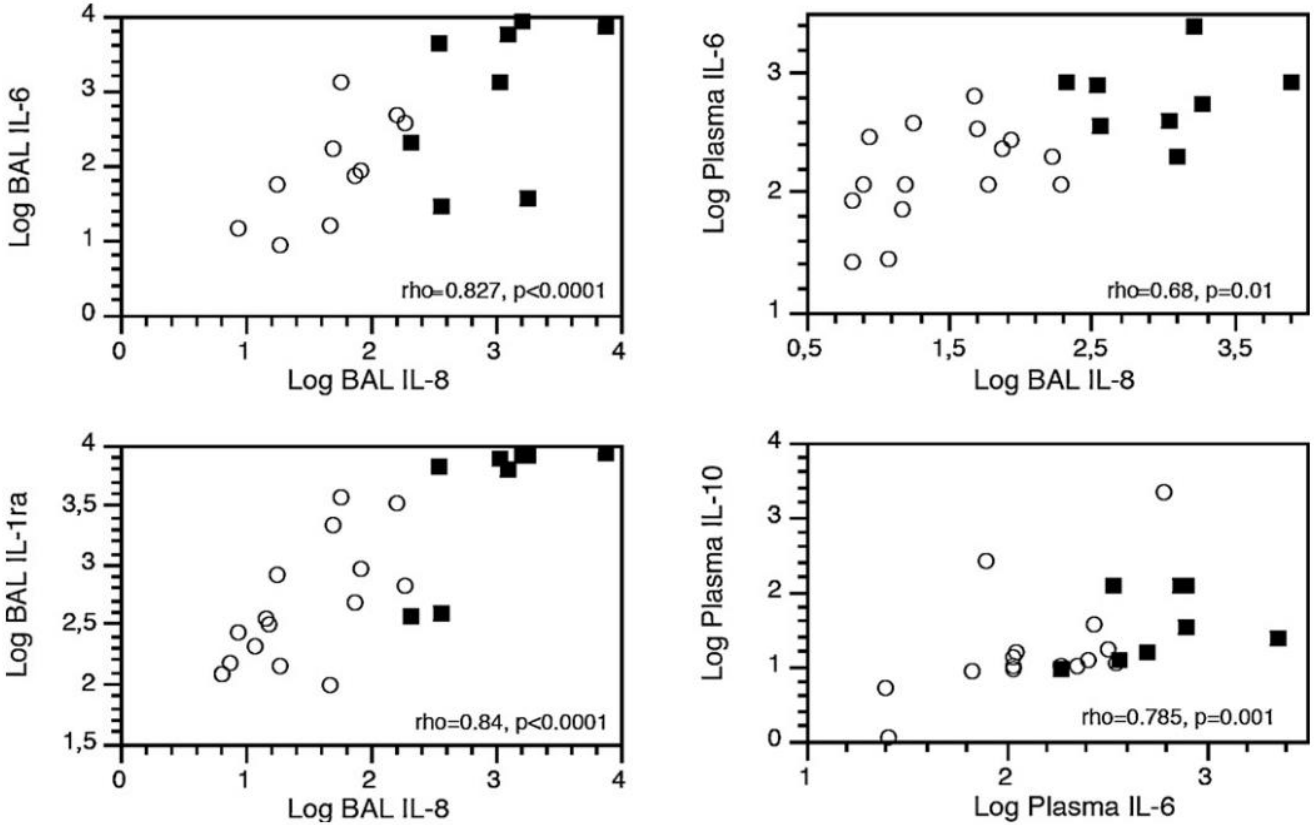
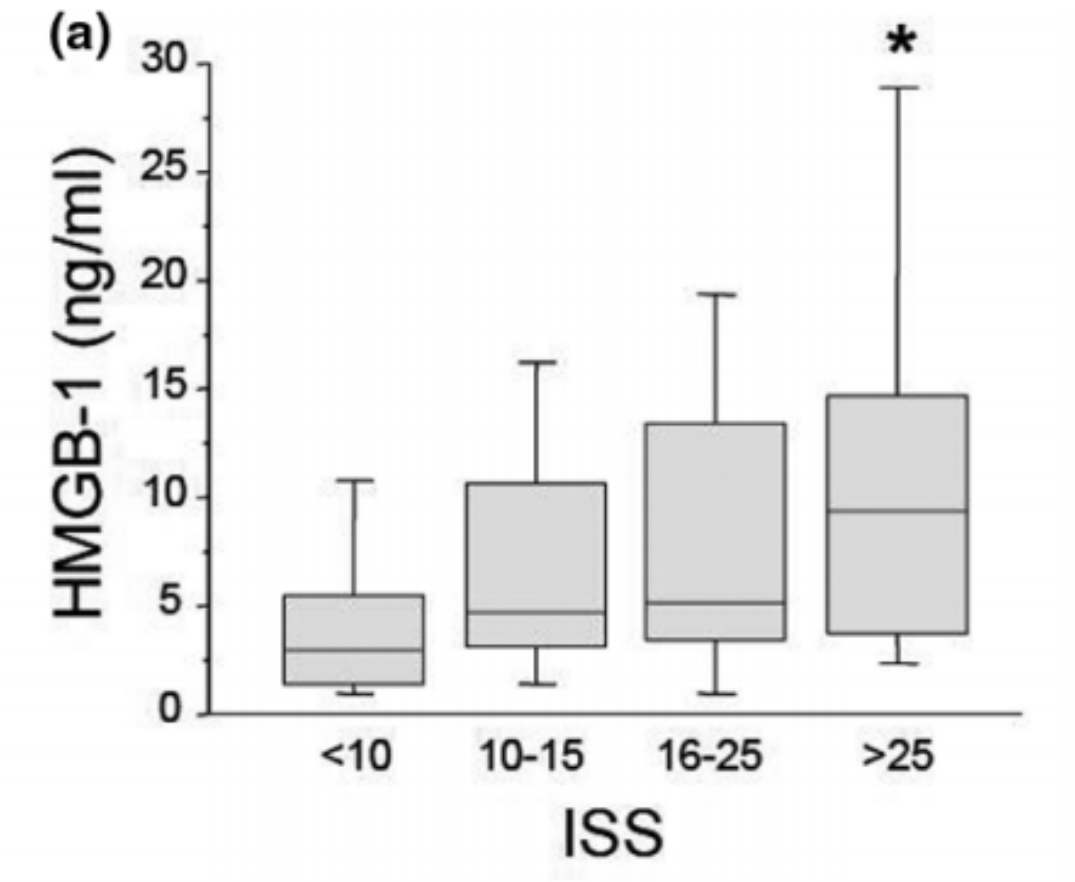


Fig. 2. Regression plots for mediators in bronchoalveolar lavage (BAL) and plasma from patients at high (■) and low (○) risk for ARDS after multiple trauma. Only detectable mediator levels were included.

Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion

Mitchell J Cohen[1], Karim Brohi[2], Carolyn S Calfee[3], Pamela Rahn[1], Brian B Chesebro[4], Sarah C Christiaans[1], Michel Carles[4], Marybeth Howard[4] and Jean-François Pittet[4]



Coagulation/fibrinolysis related biomarkers

- Potential biomarkers (plasminogen activation inhibitor-1, protein C, plasmamodulin)
- No clinical study