



11. Anästhesie Forum Linz

# Organversagen in der Sepsis – sind wir weitergekommen?

Michael Bauer

Klinik für Anästhesiologie &  
Intensivmedizin  
UK Jena



# Battle of Trafalgar (1805)

Courtesy Mervyn Singer

## Casualties and prisoners:

- French & Spanish 14,000
  - British 1,500

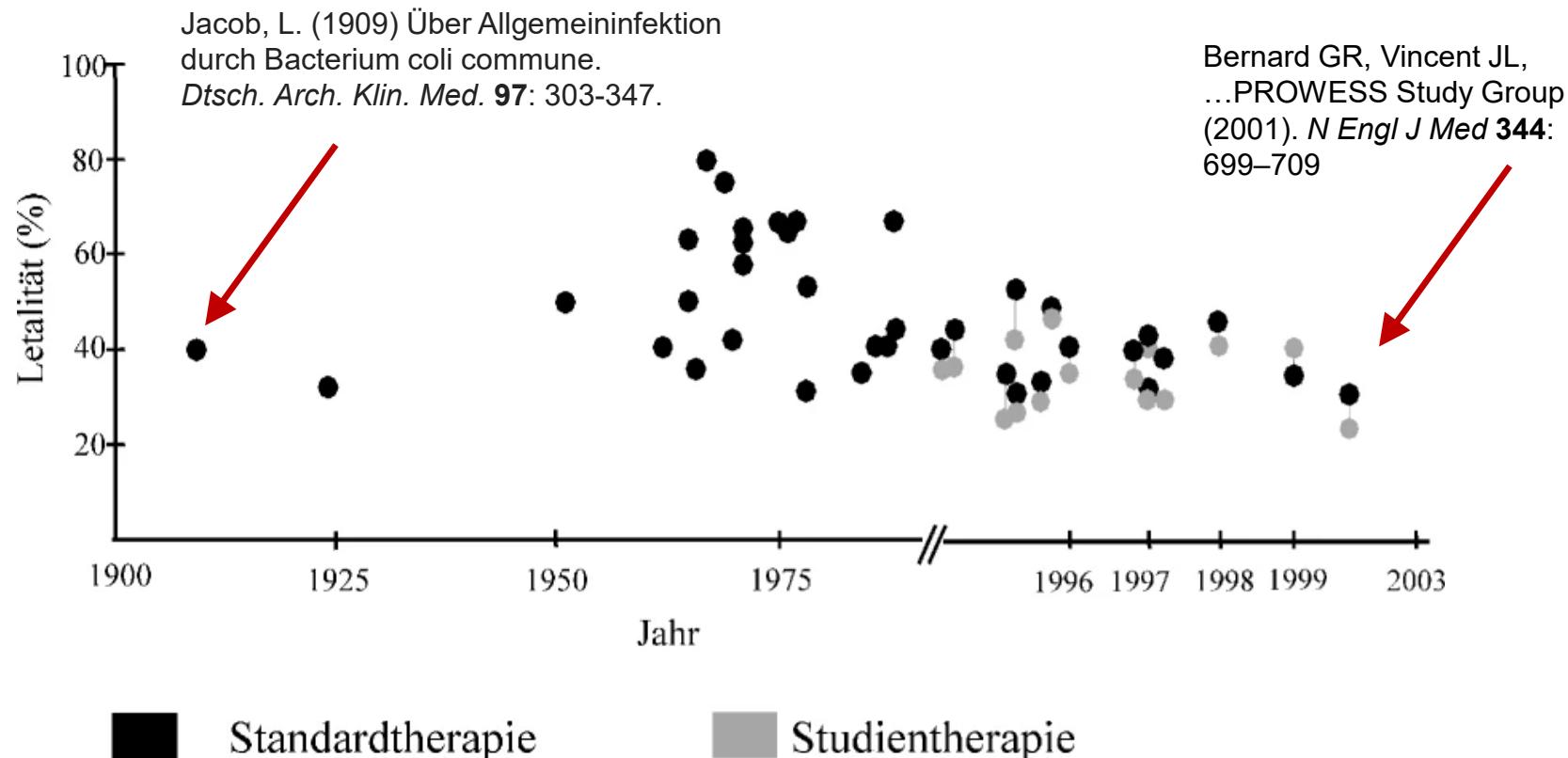
57 crew killed/died soon after battle

- 102 wounded:
  - performed 10 amputations (mainly leg)
  - later deaths from gangrene & tetanus

HMS Victory medical report (Dr Beatty)

.. only six subsequently died

# Sepsis und Organdysfunktion – Kein Fortschritt in den letzten 100 Jahren?

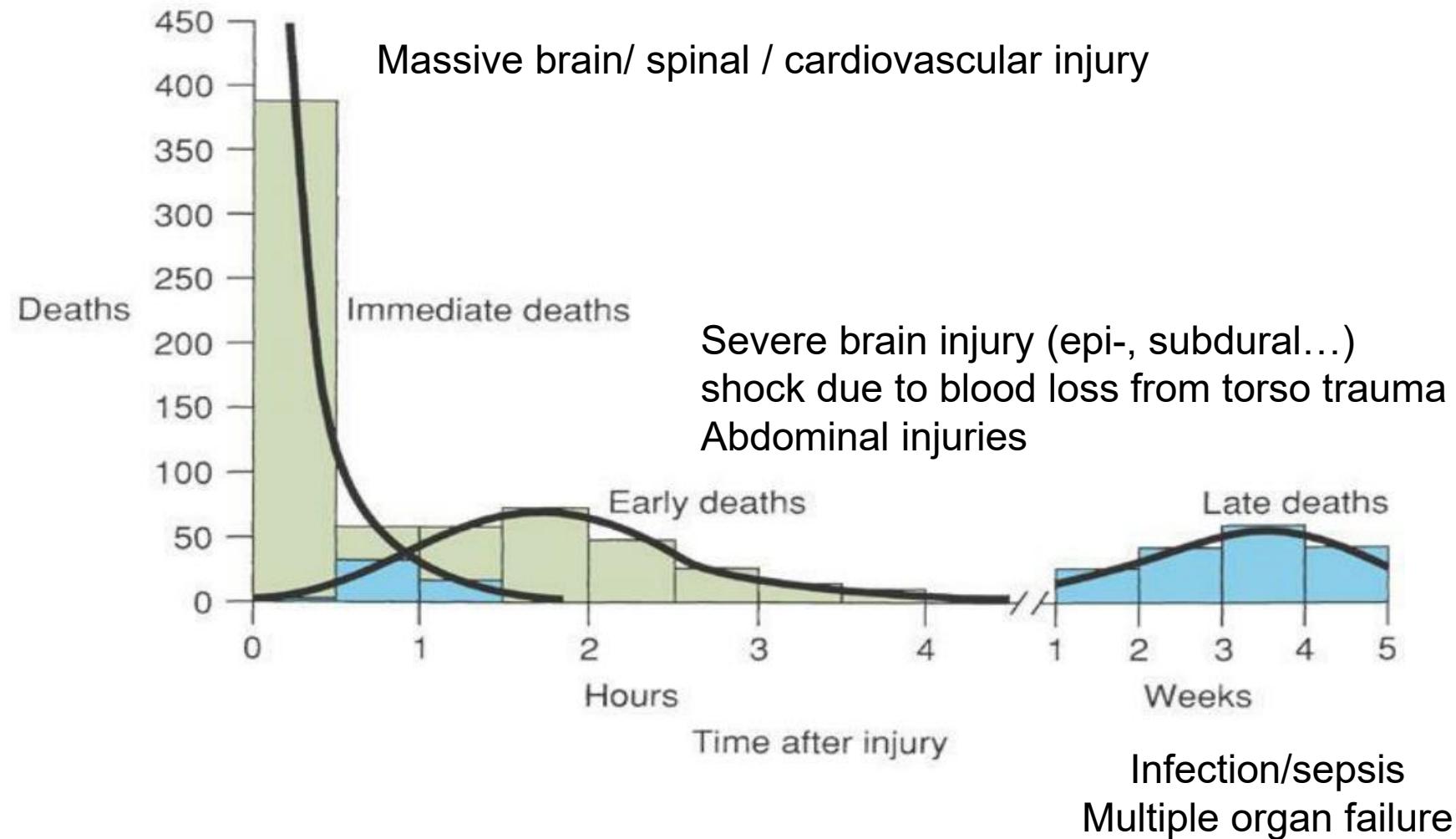


Letalität von schwerer Sepsis und septischem Schock—Entwicklung der letzten hundert Jahre. Das Diagramm schildert die Letalität klinischer Sepsisstudien seit der Erstpublikation einer Serie mit gramnegativer Sepsis 1909. Die wesentlichen, bis 1999 durchgeführten placebo-kontrollierten Studien mit Substanzen zur Blockade der überschießenden Inflammationsreaktion sind mit offenen und geschlossenen Kreisen markiert



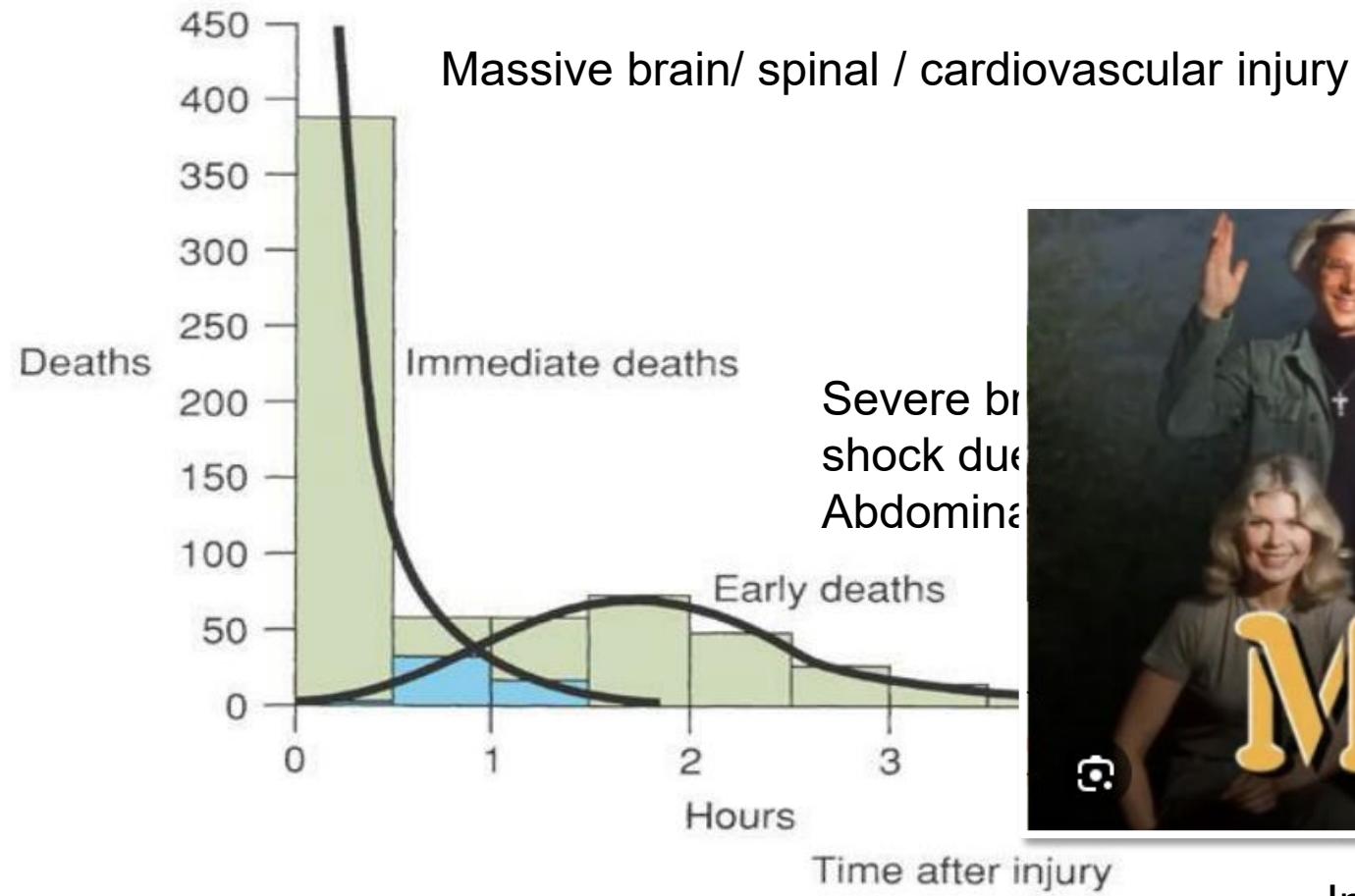
**Jetzt  
mal im  
Ernst!**

# Sepsis und Organdysfunktion – Kein Fortschritt in den letzten 100 Jahren?



Sobrino J and Shafi S (2013) Timing and causes of death after injuries. *Proc (Bayl Univ Med Cent)* **26**: 120-3. doi: 10.1080/08998280.2013.11928934

# Sepsis und Organdysfunktion – Kein Fortschritt in den letzten 100 Jahren?



Infection/sepsis  
Multiple organ failure

Sobrino J and Shafi S (2013) Timing and causes of death after injuries. *Proc (Bayl Univ Med Cent)* **26**: 120-3. doi: 10.1080/08998280.2013.11928934

# Sepsis und Organdysfunktion – Kein Fortschritt in den letzten 100 Jahren?

Historical trends combating mortality of U.S. soldiers

	Killed in action	Died of Wounds
<b>Mexican War (1846-1848)</b>		15.0 %
<b>American War (1861-1864)</b>		14.0 %
<b>Spanish-American War (1898)</b>		7.0 %
<b>World War I (1914-18) excluding gas</b>	19.6 %	8.1 %
<b>World War II (European campaign, 1945)</b>	19.8 %	3.0 %
<b>Korean War (1953)</b>	19.5 %	2.4 %
<b>Vietnam War (1965 – 1975)</b>	20.2 %	3.5 %

Donald D. Trunkey: The Development of Trauma systems, Chapter 1, The Development of Trauma Systems, Anesthesia key, abgerufen am 7.4.2025; [www.aneskey.com/the-development-of-trauma-systems/](http://www.aneskey.com/the-development-of-trauma-systems/)

Bellamy RF, Maningas PA, Vayer SJ (1986) Epidemiology of trauma: military experience. *Ann Emerg Med.* **15:** 1384-8. doi: 10.1016/s0196-0644(86)80920-9.  
Bzik KD, Bellamy RF (1984) A note on combat casualty statistics. *Milit Med* **143:** 143-161.

# Therapie der Organdysfunktion – Krisen als Treiber der Innovation

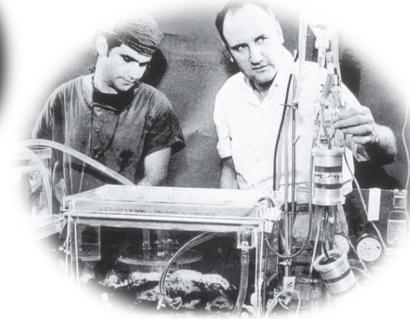
(Supportive Therapie / „Organersatz“



Irreversibler Schock



ANV



ARDS  
(„Da Nang Lung“)

MOV

Therapielimitierung

1. WW

1900

1925

2. WW

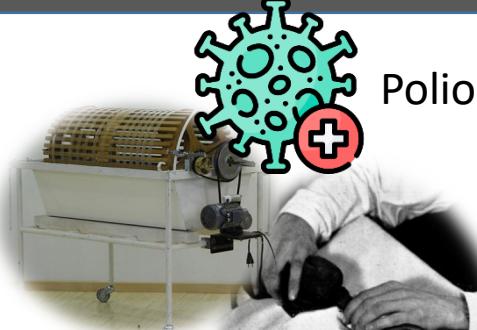
1950

Vietnam

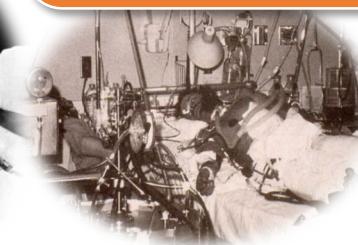
1975

2000

2025



Polio

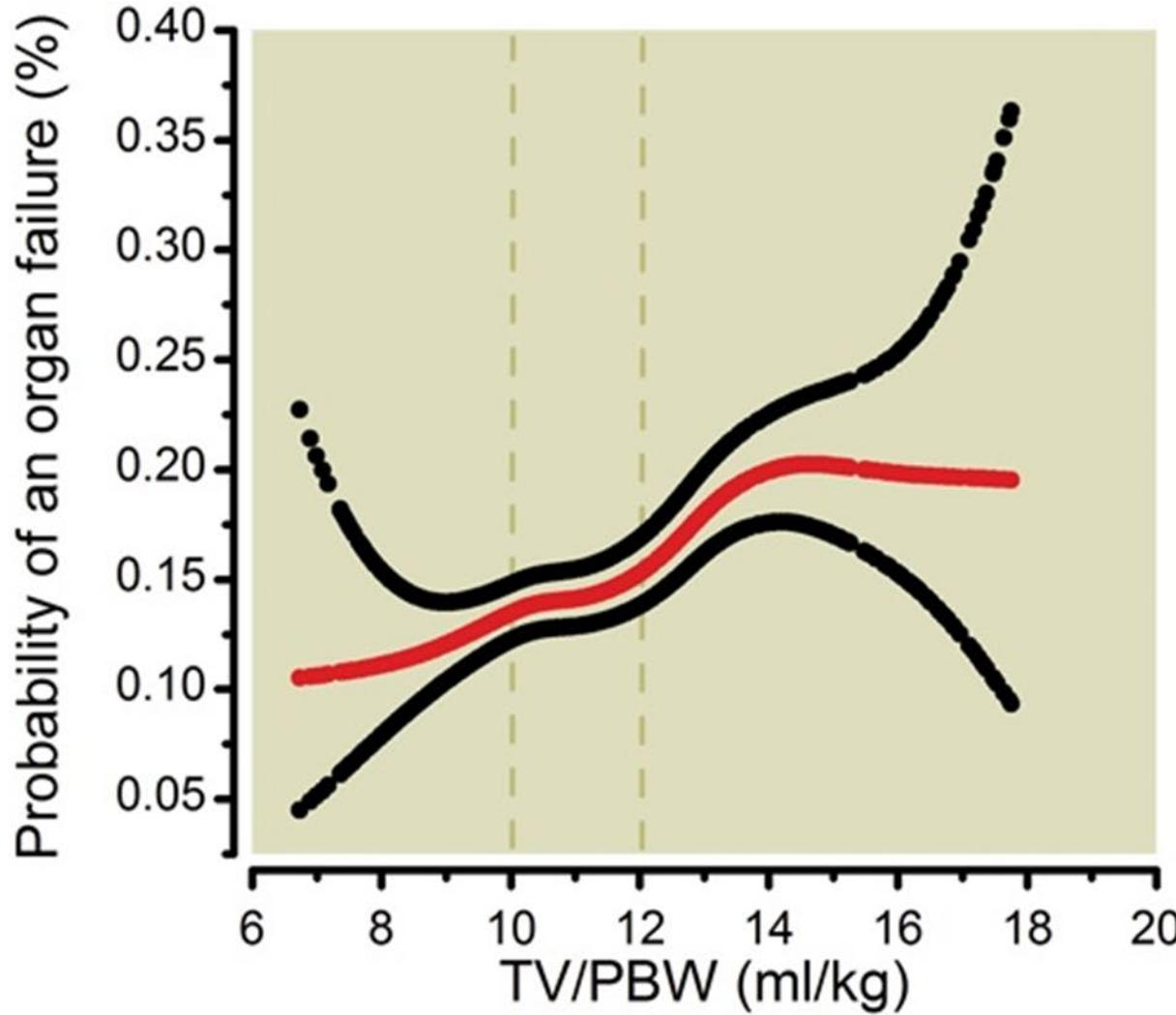


Fortschritte in der allgemeinen  
Intensivmedizin / Organsupport



**Paradebeispiel ARDS**

# Therapie der Organdysfunktion – Tidalvolumen, Beatmung und Outcome

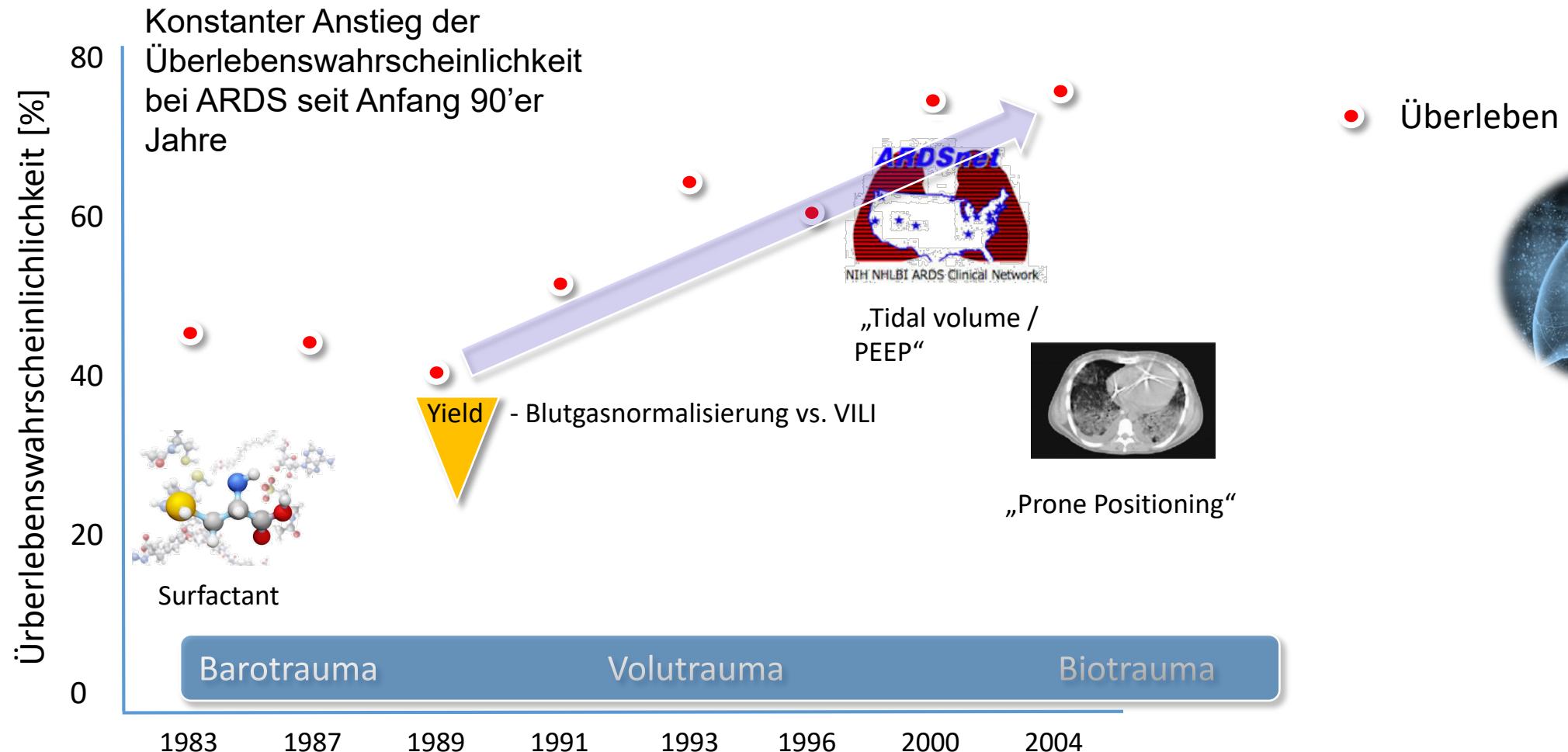


Statistical model of a nonparametric logistic regression showing the dose-response relationship between the tidal volume at intensive care unit admission (mL/kg of predicted body weight) and the probability of an organ failure. TV/PBW = tidal volume/predicted body weight.



High Tidal Volumes in Mechanically Ventilated Patients Increase Organ Dysfunction after Cardiac Surgery  
Anesthesiology 116(5):1072-1082, May 1, 2012.

# Therapie der Organdysfunktion – Tidalvolumen, Beatmung und Outcome



Mod. nach Bernard GR (2005) Acute Respiratory Distress Syndrome - A Historical Perspective. *Am J Respir Crit Care Med* 172:798–806. doi: 10.1164/rccm.200504-663OE

# Therapie der Organdysfunktion – Tidalvolumen, Beatmung und Outcome

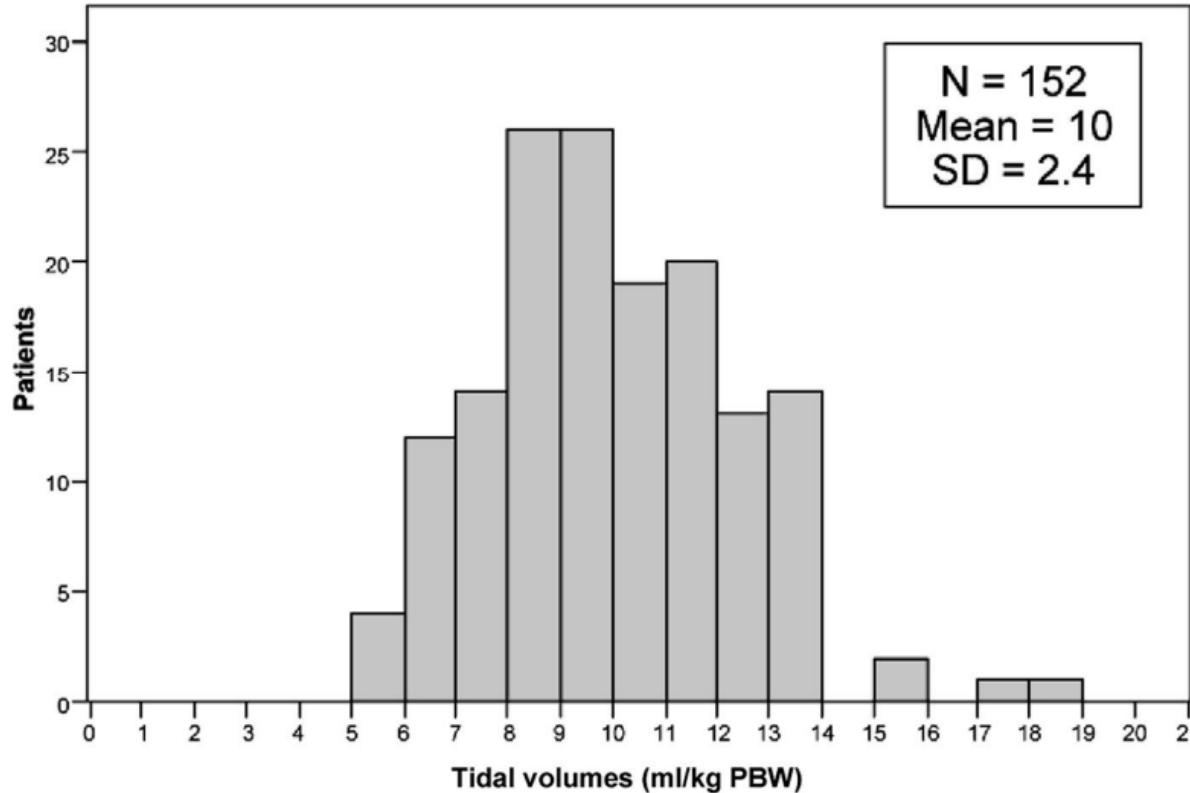


Figure 1. Range of tidal volumes in patients with severe sepsis/septic shock and acute lung injury/acute respiratory distress syndrome. Maximal tidal volumes (mL/kg predicted body weight [PBW]) in 152 patients with severe sepsis and septic shock.



” A total of 17.1% patients had tidal volume between 6 and 8 mL/kg predicted body weight and 80.3% >8 mL/kg predicted body weight. Mean tidal volume was 10.0 mL/kg predicted body weight. Perceived adherence to low-tidal volume ventilation was 79.9%...

# Therapie der Organdysfunktion – Tidalvolumen, Beatmung und Outcome

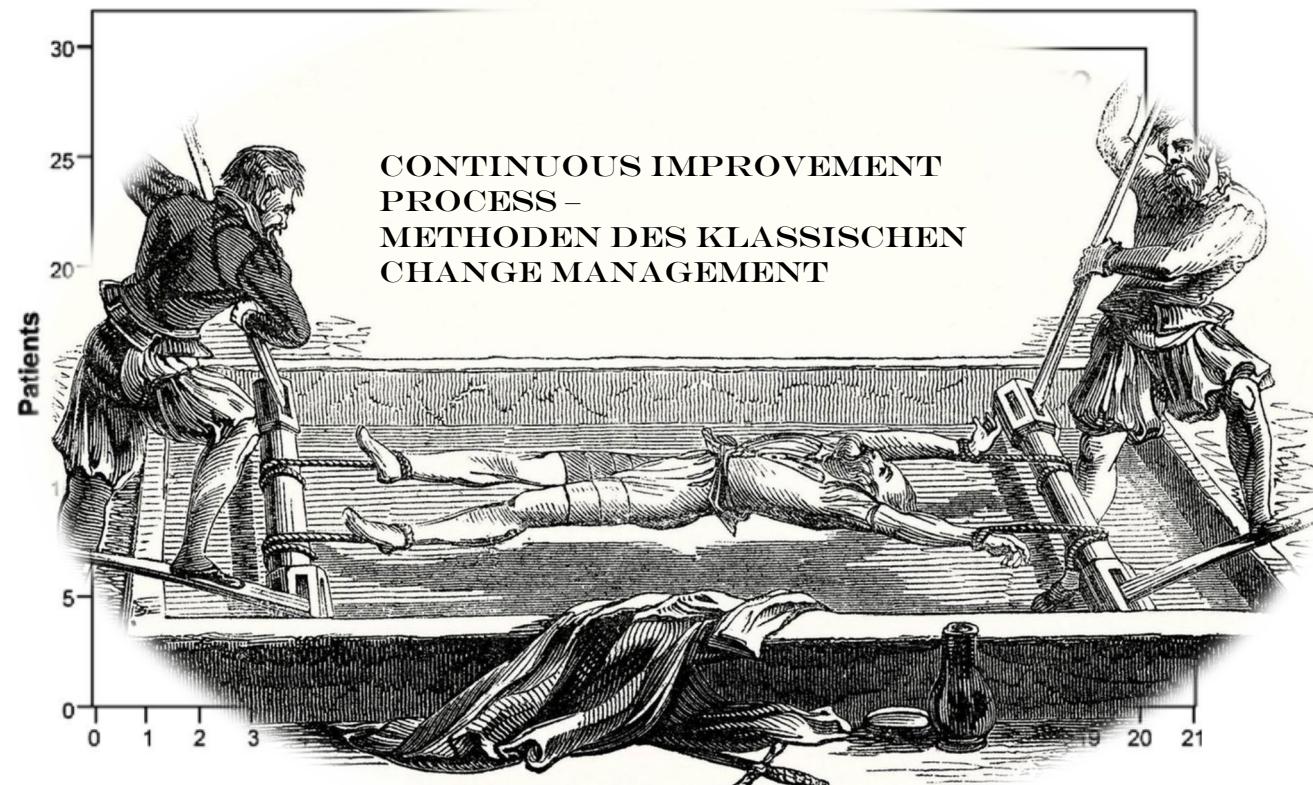
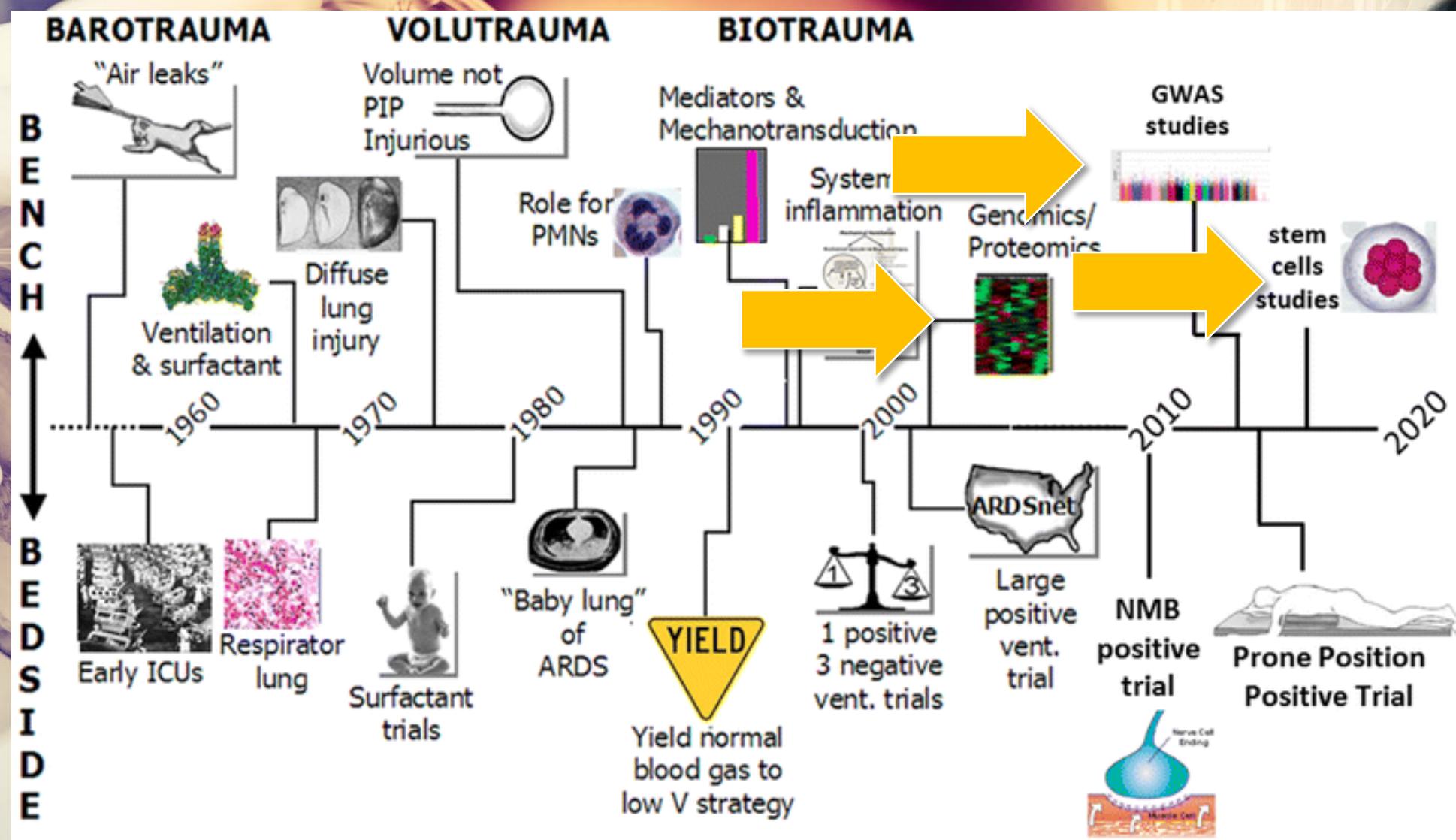


Figure 1. Range of tidal volumes in patients with severe sepsis/septic shock and acute lung injury/acute respiratory distress syndrome. Maximal tidal volumes (mL/kg predicted body weight [PBW]) in 152 patients with severe sepsis and septic shock.



” A total of 17.1% patients had tidal volume between 6 and 8 mL/kg predicted body weight and 80.3% >8 mL/kg predicted body weight. Mean tidal volume was 10.0 mL/kg predicted body weight. Perceived adherence to low-tidal volume ventilation was 79.9%...

# Molekularmedizin – die stille Revolution

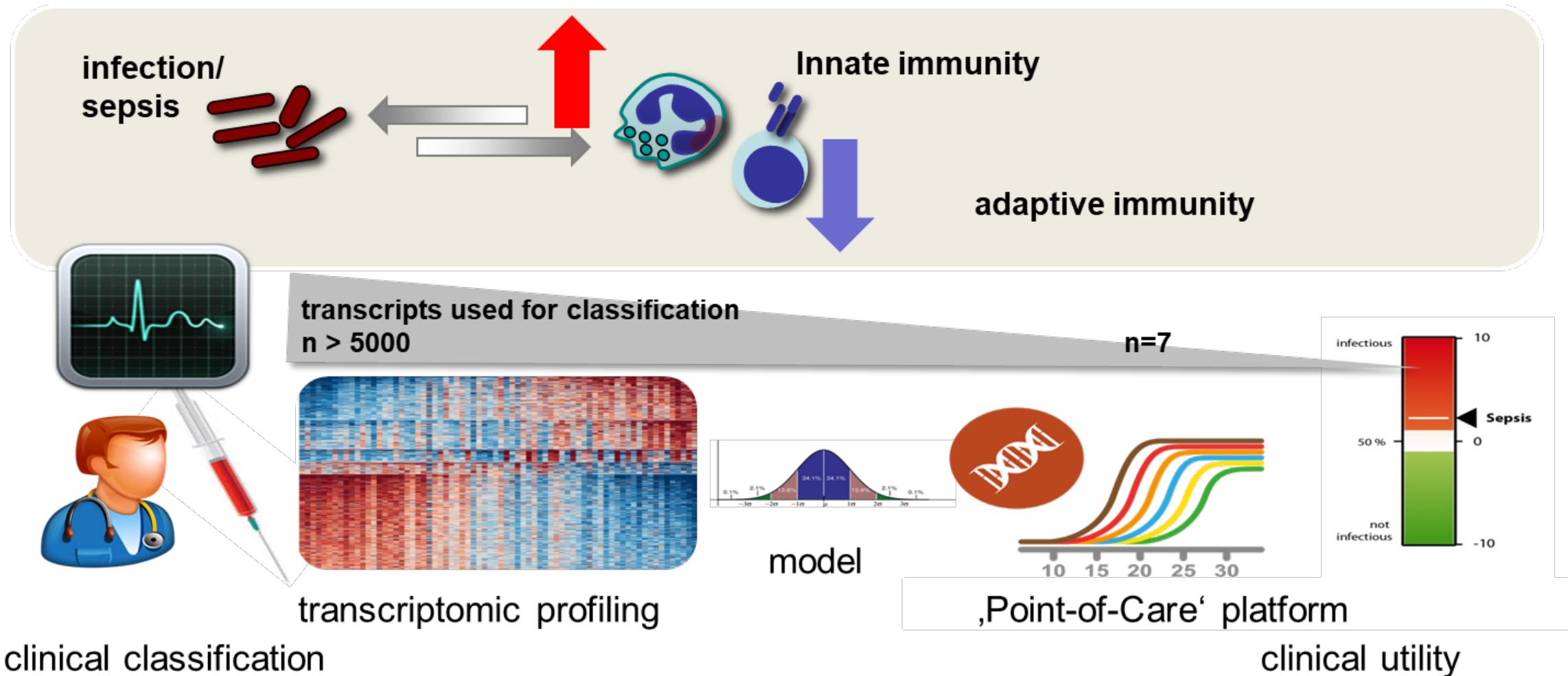


Slutsky AS, Villar J & Pesenti A (2016) Happy 50th birthday ARDS! *Int Care Med* 42: 637-639.

Tremblay LN, Slutsky AS (2006) Ventilator-induced lung injury: from the bench to the bedside. *Int Care Med* 1: 24–33.

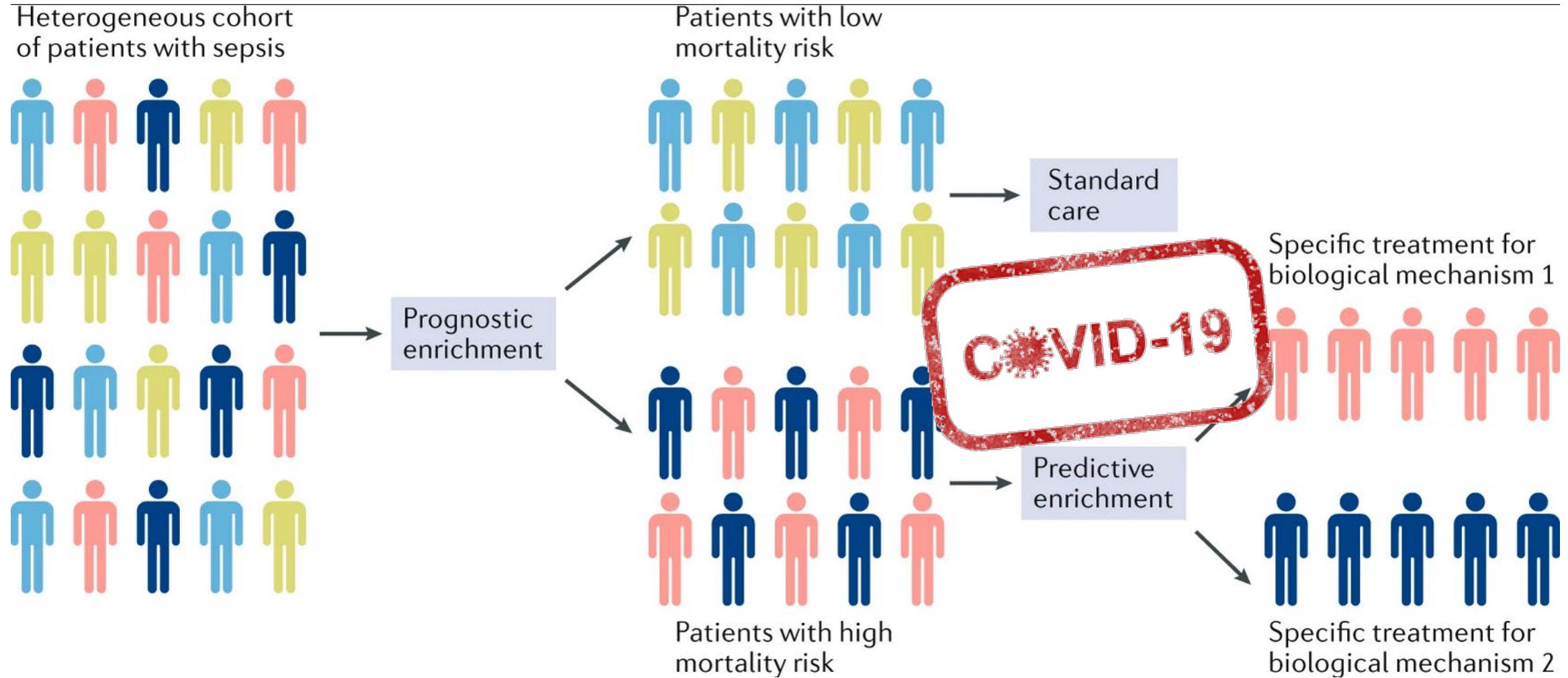


# Zur Rolle von Biomarkern/ “Theranostik”



A Transcriptomic Biomarker to Quantify Systemic Inflammation in Sepsis — A Prospective Multicenter Phase II Diagnostic Study  
Bauer et al. EBioMedicine 6 (2016) 114–125

# Zur Rolle von Biomarkern/ “Theranostik”



# Therapie der Organdysfunktion – Krisen als Treiber der Innovation

Fortschritte in der kausalen  
Therapie / „Theranostics“

Endophänotyp und  
kausale Therapie

1900

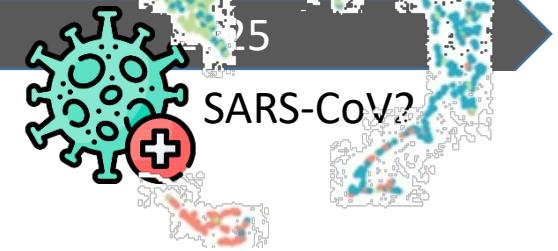
1925

1950

1975

2000

25



SARS-CoV?

# Warp speed – auch bei den klin. Studien!

Beispiel Anakinra für COVID-19

## Phase 2 study SAVE

- April 2020-November 2020; 13 sites in Greece
- Open-label with SoC comparators
- Almost 1,000 patients enrolled
- Interim published data on 130

Kyriazopoulou E et al.

Nat Med. 2021;27(10):1752-60.

## Phase 3 study SAVE-MORE

- December 2020-June 2021; 29 sites in Greece; 8 sites in Italy
- Double-blind randomized
- 594 patients enrolled

Samaras C et al.

Cytokine. 2023;162:156111.

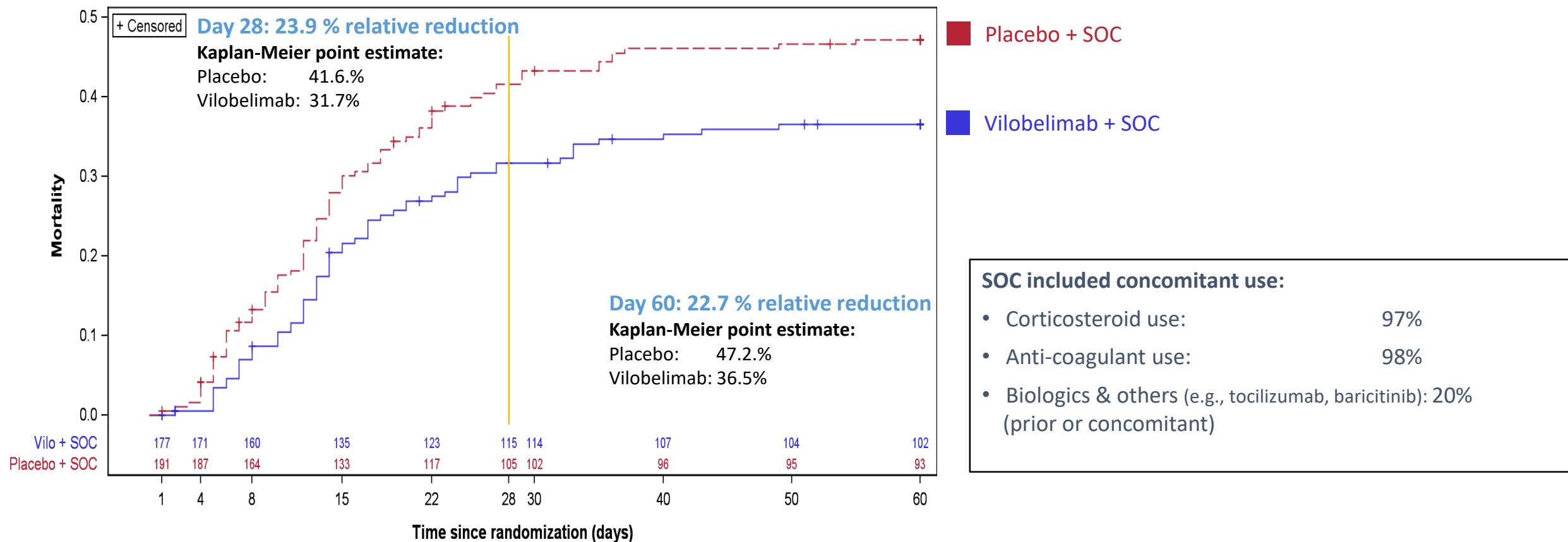
1  
2  
/  
2  
0  
2  
1

## Zulassung Anakinra

für COVID-19 bei  
suPAR > 6ng/ml

# PANAMO Study: Phase III – Primary Endpoint

## 28- and 60-Day All-Cause Mortality

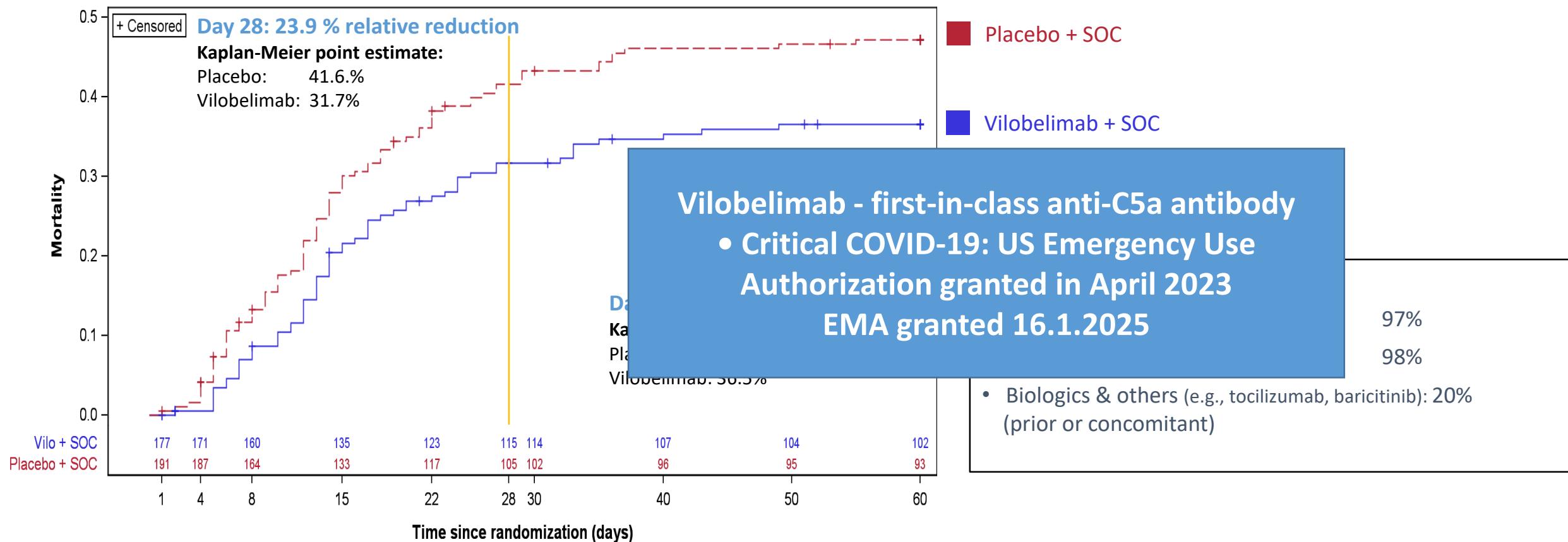


➤ One additional life was saved for every 10 vilobelimab-treated patients at day 28

➤ One additional life was saved for every 9 vilobelimab-treated patients at day 60

# PANAMO Study: Phase III – Primary Endpoint

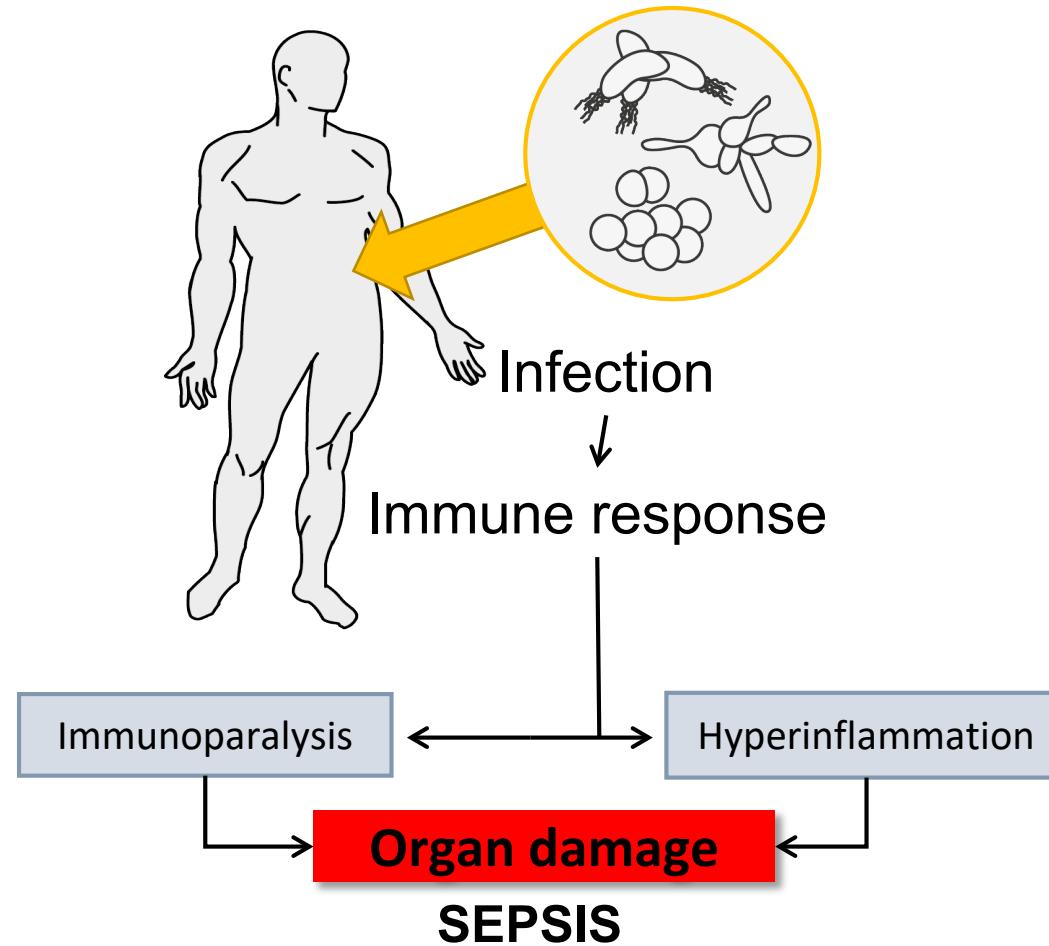
## 28- and 60-Day All-Cause Mortality



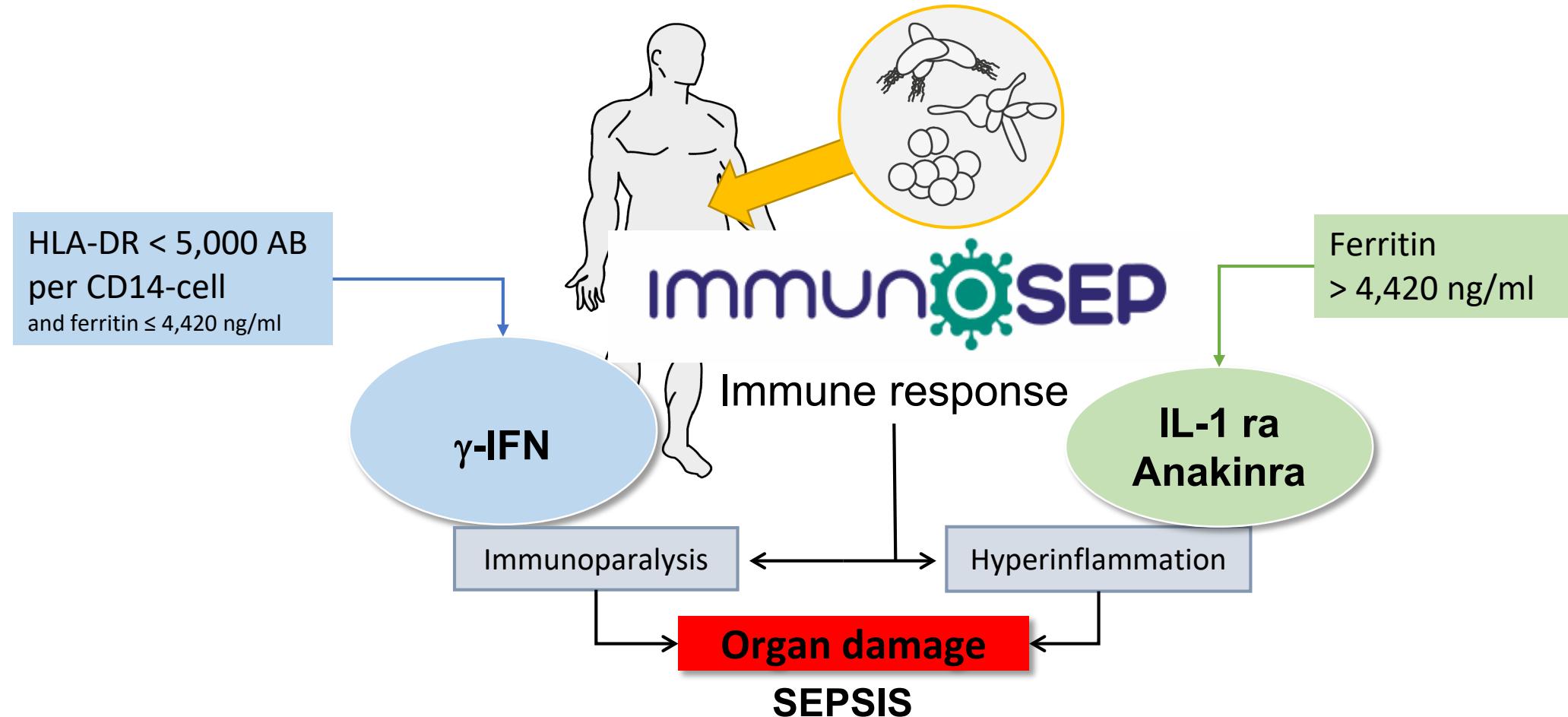
➤ One additional life was saved for every 10 vilobelimab-treated patients at day 28

➤ One additional life was saved for every 9 vilobelimab-treated patients at day 60

# Sepsis-3: Fehlregulierte (statt „überschießende“) Wirtsantwort auf Infektion als Ursache der Organdysfunktion!



# Sepsis-3: Fehlregulierte (statt „überschießende“) Wirtsantwort auf Infektion als Ursache der Organdysfunktion!



# ImmunoSep - a first randomized clinical trial for precision immunotherapy



Precision immunotherapy +  
standard-of-care

Anakinra for MALS  
rhIFN $\gamma$  for immunoparalysis

## Patient population:

- Lung infection or primary bacteremia
- Sepsis-3
- MALS or immunoparalysis
- Within 72 hours

**Primary endpoint:**  
Change of mean SOFA score  
by day 9  
Powered for 280 patients

Of 657 patients screened  
by April 2024

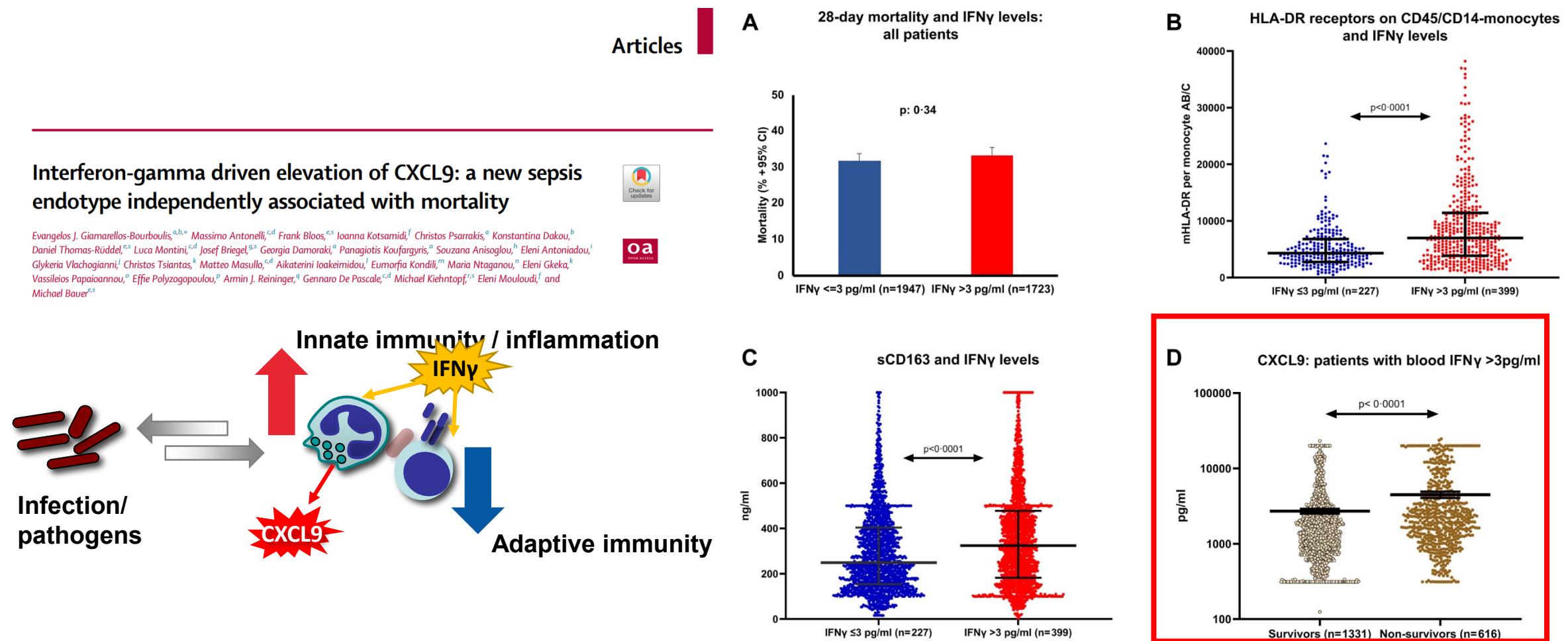
→ Immunoparalysis: n=224

→ MALS: n=46

Placebo  
+ standard-of-care

# Weitere potenzielle Endophänotypen zur Immunmodulation

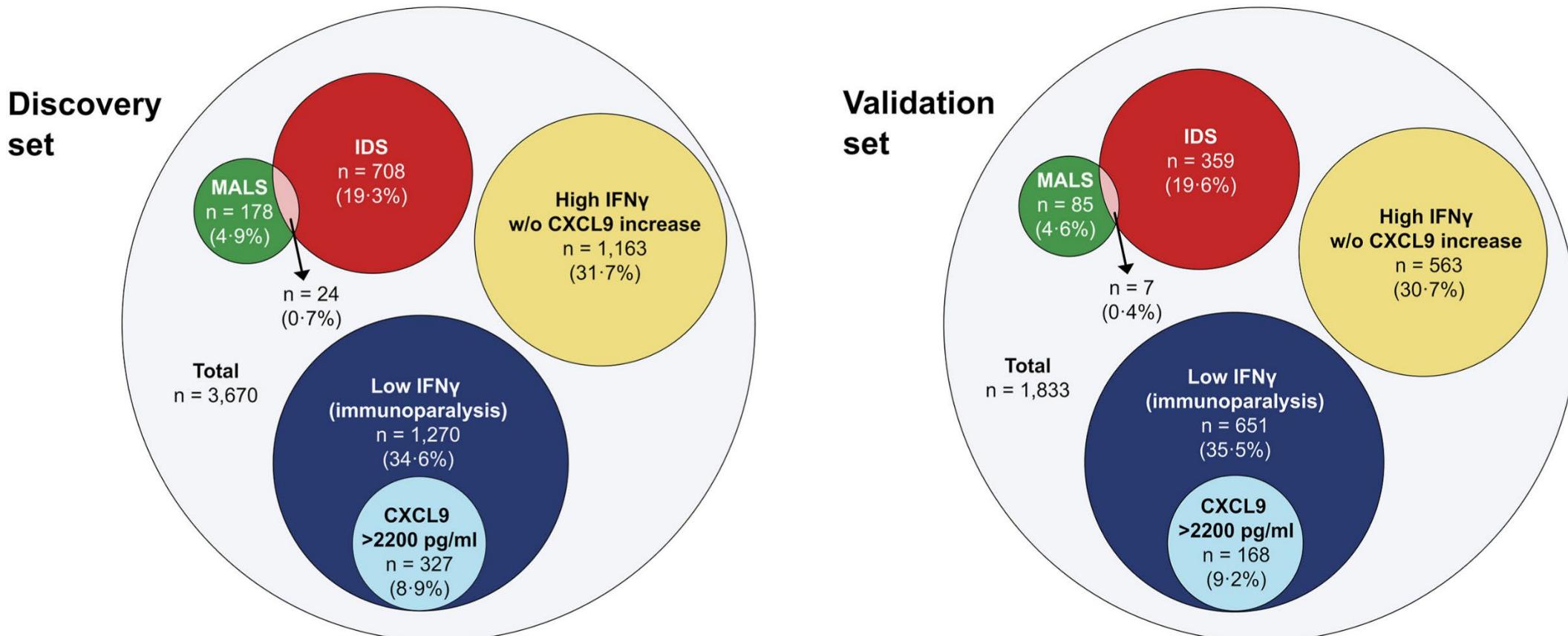
## Development of the IFN $\gamma$ -driven sepsis (IDS) endotype in the discovery set



# Weitere potenzielle Endophänotypen zur Immunmodulation

## Interferon-stimulierte CXCL-9 Antwort – ein eigener Sepsisphänotyp?

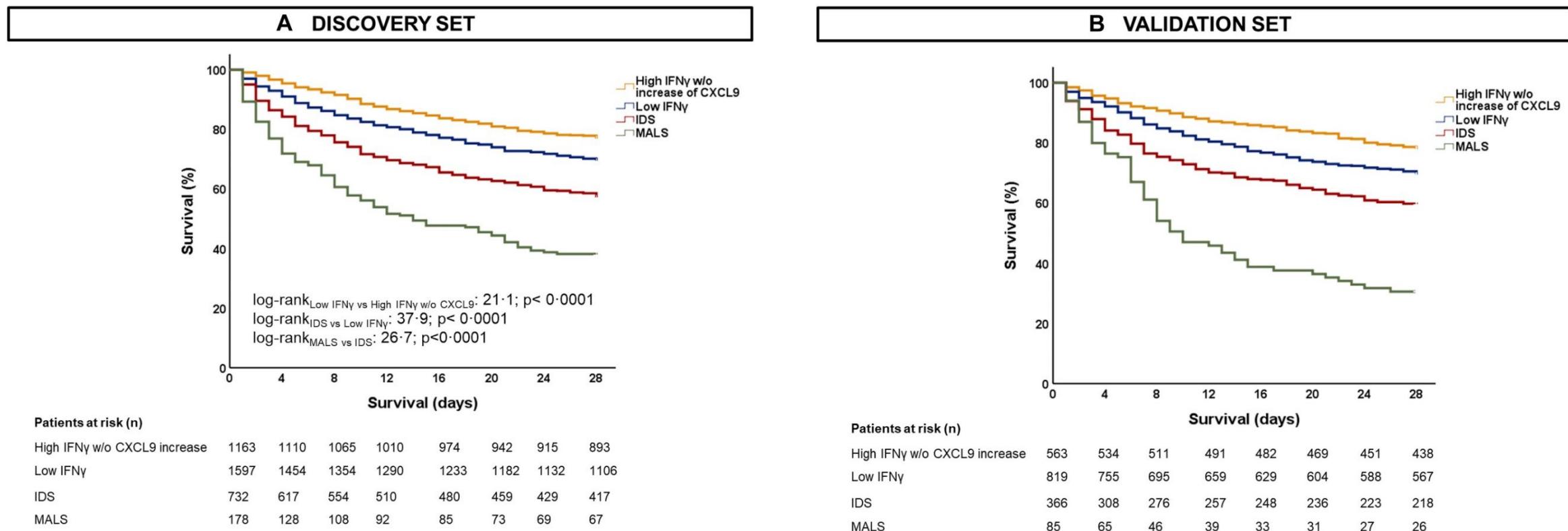
- Distribution of endotypes in the discovery and the validation sets of patients



# Weitere potenzielle Endophänotypen zur Immunmodulation

## Interferon-stimulierte CXCL-9 Antwort – ein eigener Sepsisphänotyp?

- The impact of the endotype of IFN $\gamma$ -driven sepsis on mortality the first 28 days



# Zusammenfassung



Entgegen der allgemeinen Wahrnehmung war das letzte Jahrhundert von einer dramatischen Verbesserung der Prognose beim Organversagen geprägt

Diese verlief in zwei Wellen –

- eine erste der Verbesserung der supportiven Möglichkeiten
- eine zweite - (die noch voll im Laufen ist) mit der Revolution der Molekularmedizin

Beide wurden durch die großen Gesundheitskrisen und Kriege des 20. Jahrhunderts angetrieben, oder mit ...

... Winston Churchill:

**Never waste a good crisis!**