La *speckle-tracking echocardiography* nella diagnosi precoce e gestione della cardiomiopatia sepsi-relata

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MoKeMED

DOMANDE

Perché parlare di ***speckle-tracking echocardiography***?

Cosa sono la **sepsi**, lo **shock settico** e la **cardiomiopatia sepsi-relata**?

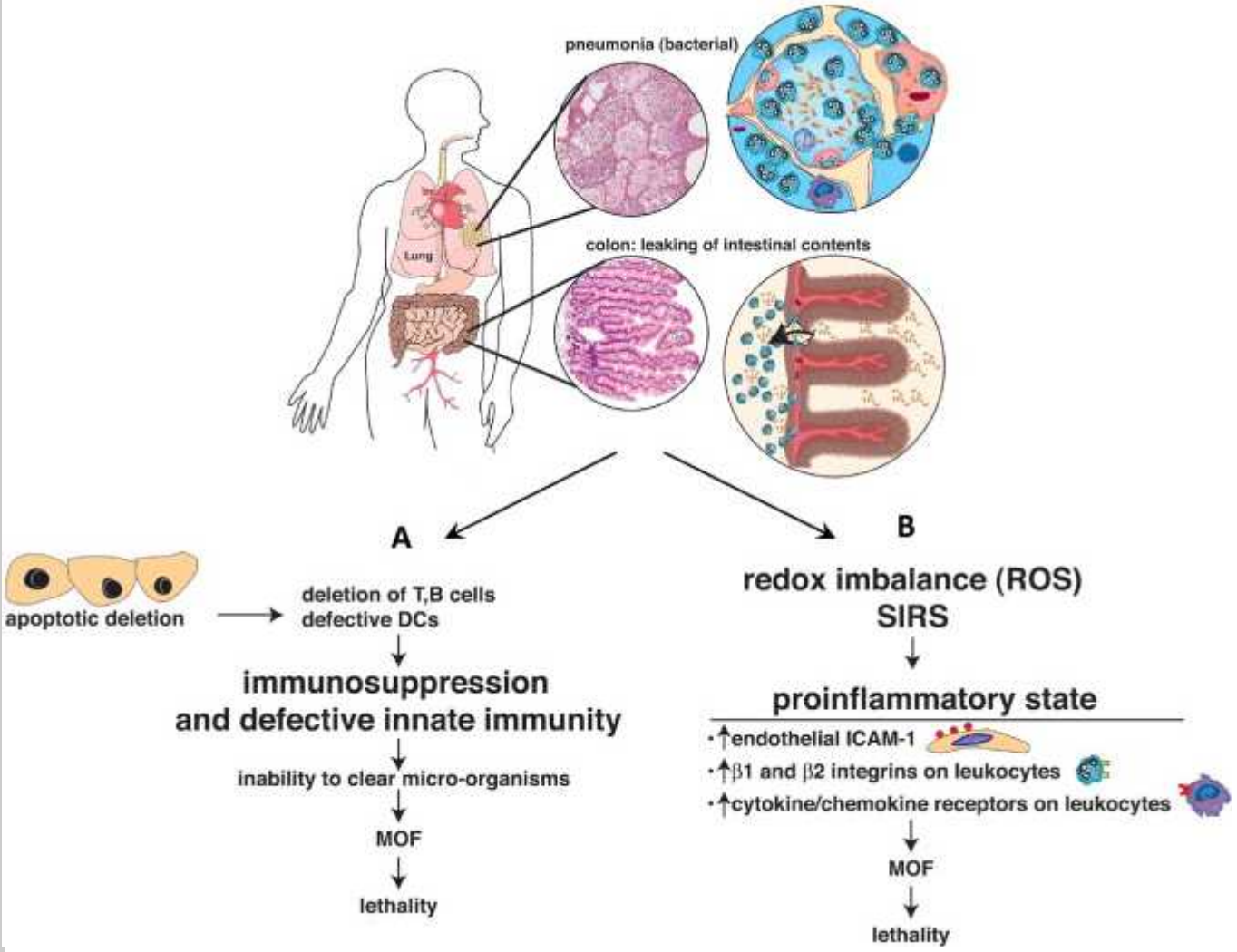
Quali dati e risultati emergono dai **clinical trials**?

Qual è l'impiego attuale e quali le **prospettive** future della speckle-tracking nella diagnosi di cardiomiopatia sepsi-relata?

SHOCK SETTICO

Dysregulated host response to infection & circulatory and cellular/metabolic abnormalities

Life-threatening organ dysfunction



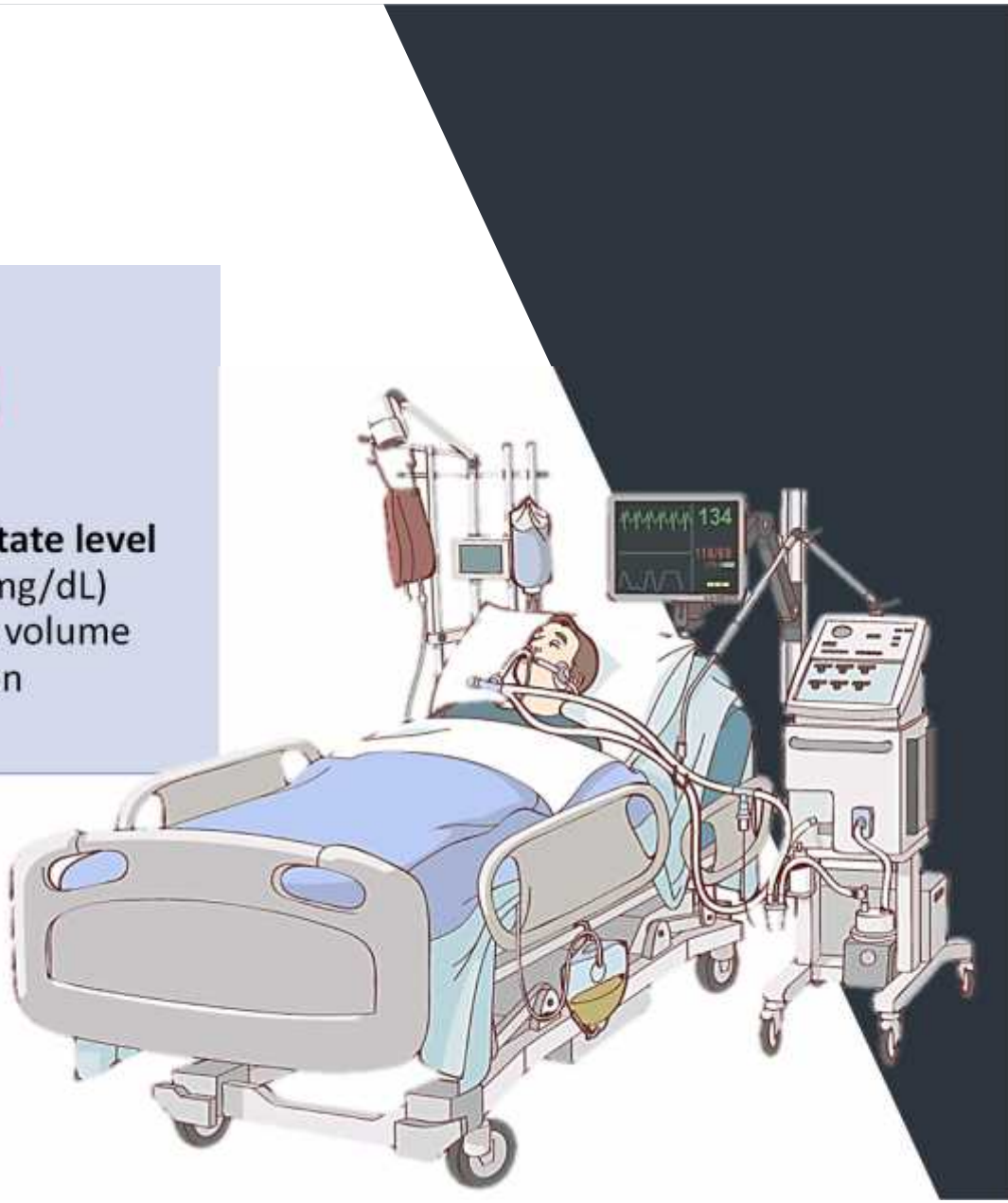
SHOCK SETTICO

1

Persisting hypotension requiring vasopressors to maintain **MAP ≥65 mmHg**

2

Having a **serum lactate level >2 mmol/L** (18 mg/dL) despite adequate volume resuscitation



Mervyn Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016

SOFA score

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

System	Score 0	1	2	3	4
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FIO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

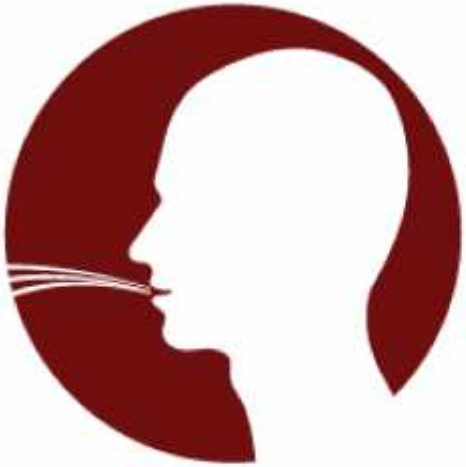
[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Mervyn Singer et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016

qSOFA

Score prognostico in SHOCK SETTICO: **quickSOFA**

A. Respiratory rate ≥ 22/min
B. Altered mentation
C. Systolic blood pressure ≤ 100mmHg



FAST RESPIRATORY RATE

ALTERED MENTAL STATUS

LOW BLOOD PRESSURE

DISFUNZIONE CARDIACA

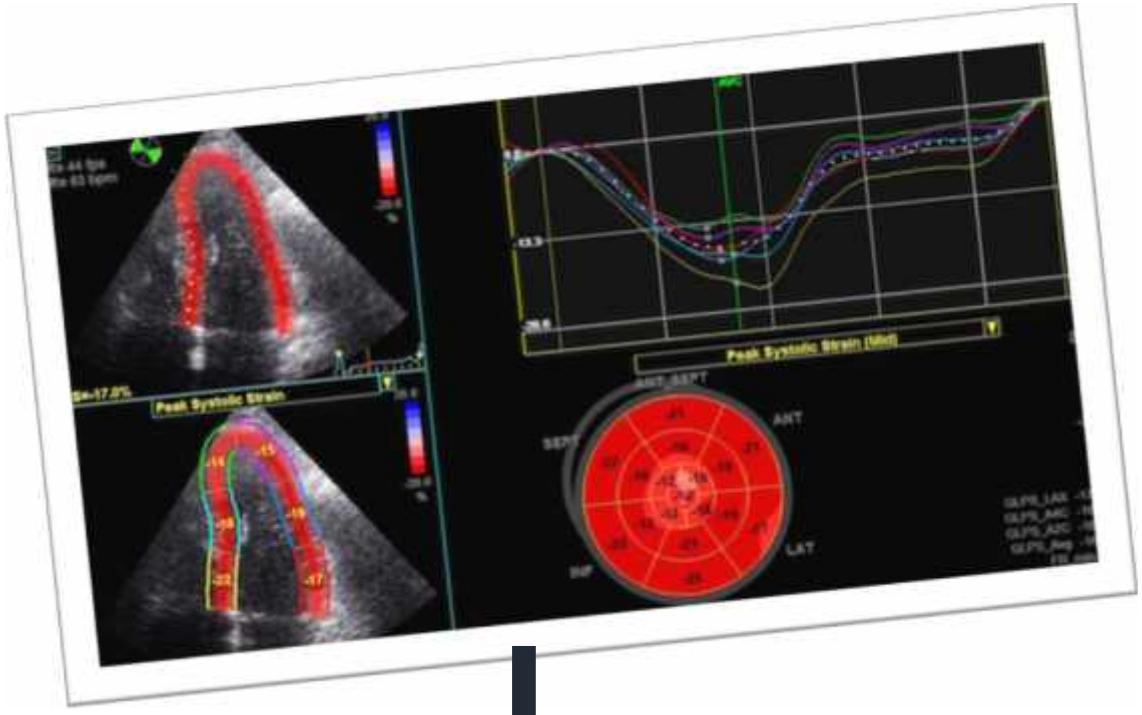
- Reversibilità
- Disfunzione sistolica e diastolica del ventricolo sinistro
- Disfunzione sistolica del ventricolo destro
- Dilatazione delle camere ventricolari

CARDIOMIOPATIA SEPSI-RELATA

Noxa patogena → Disfunzioni metaboliche, infiammatorie ed adrenergiche → Risposta dell'ospite → Misure terapeutiche

Modes of cardiac dysfunction	Mechanisms	Future treatments or areas of research
Inflammation	TNF-α, IL-1β, IL-6, IL-8, IL-12, IFN-γ, toll-like receptors, matrix metalloproteinase, heat shock proteins, nitric oxide, reactive oxygen species	TLR antagonists MMP inhibitors HSP augmentation
Mitochondrial dysfunction	Nitric oxide, reactive oxygen species	
Abnormal calcium utilization	Decreased calcium current, decreased number of L-type calcium channels, abnormal calcium sequestration, decreased myofilament sensitivity to calcium, decreased ryanodine receptor calcium sensitivity	Levosimendan
Decreased β adrenergic signalling	Downregulation of the number of β receptors, β receptors less sensitive to circulating catecholamines	
Excess catecholamines	Direct cardiac dysfunction, alterations in calcium metabolism	Selective β_1 blockade (i.e. esmolol)

ECOCARDIOGRAFIA



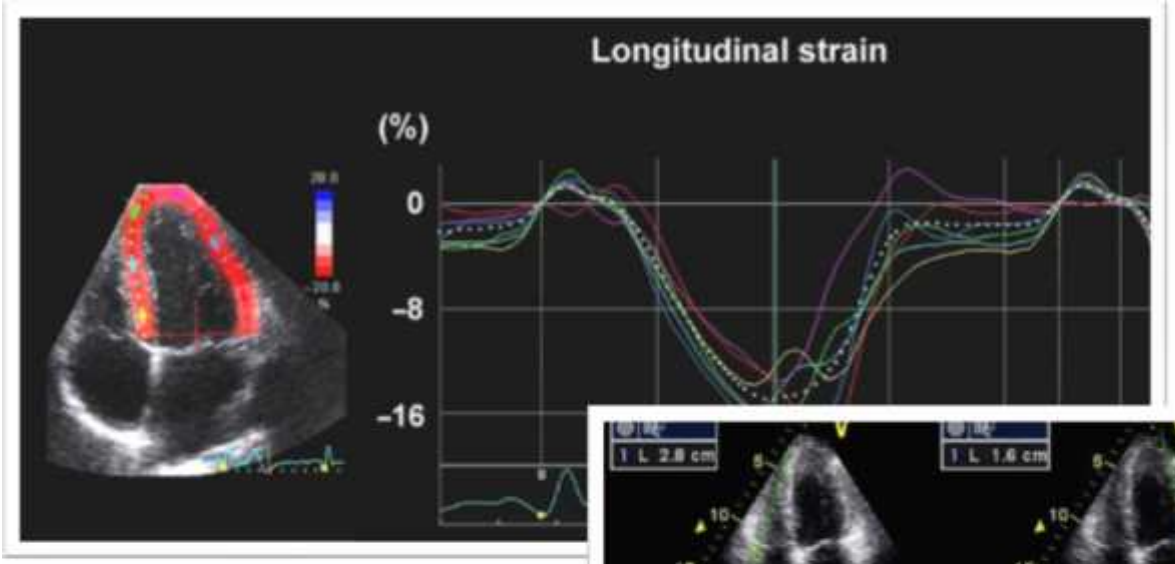
Diagnosi precoce

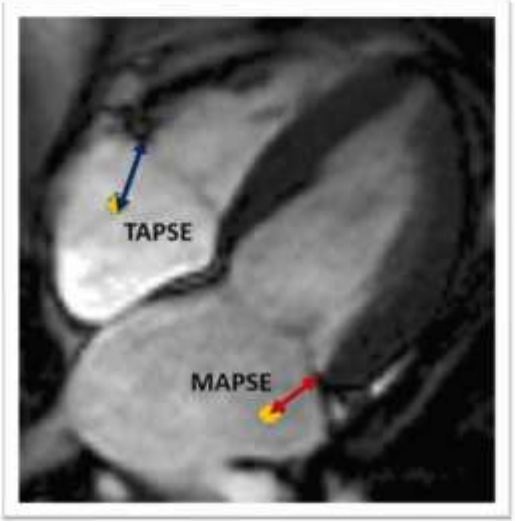
Ottimizzare le misure terapeutiche

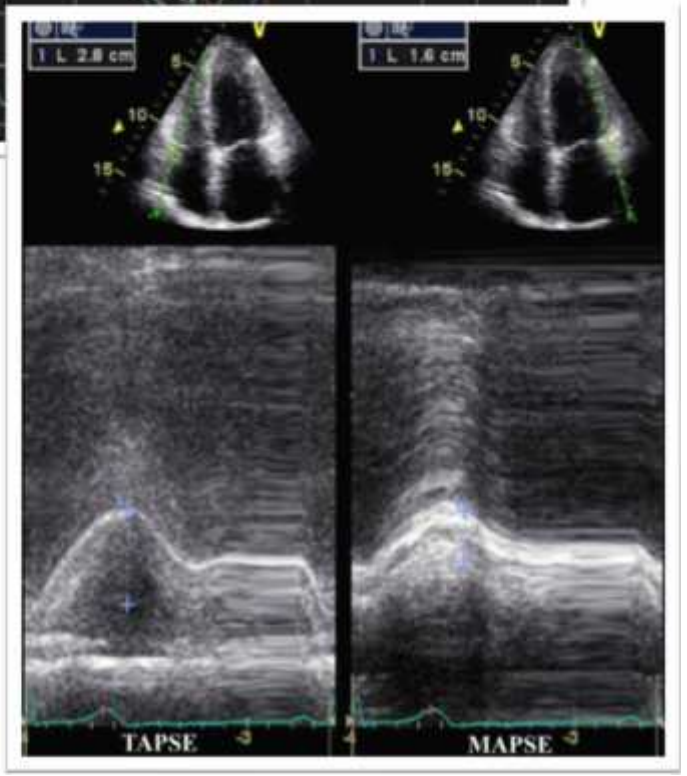
Predire il rischio di mortalità del paziente

ECOCARDIOGRAFIA

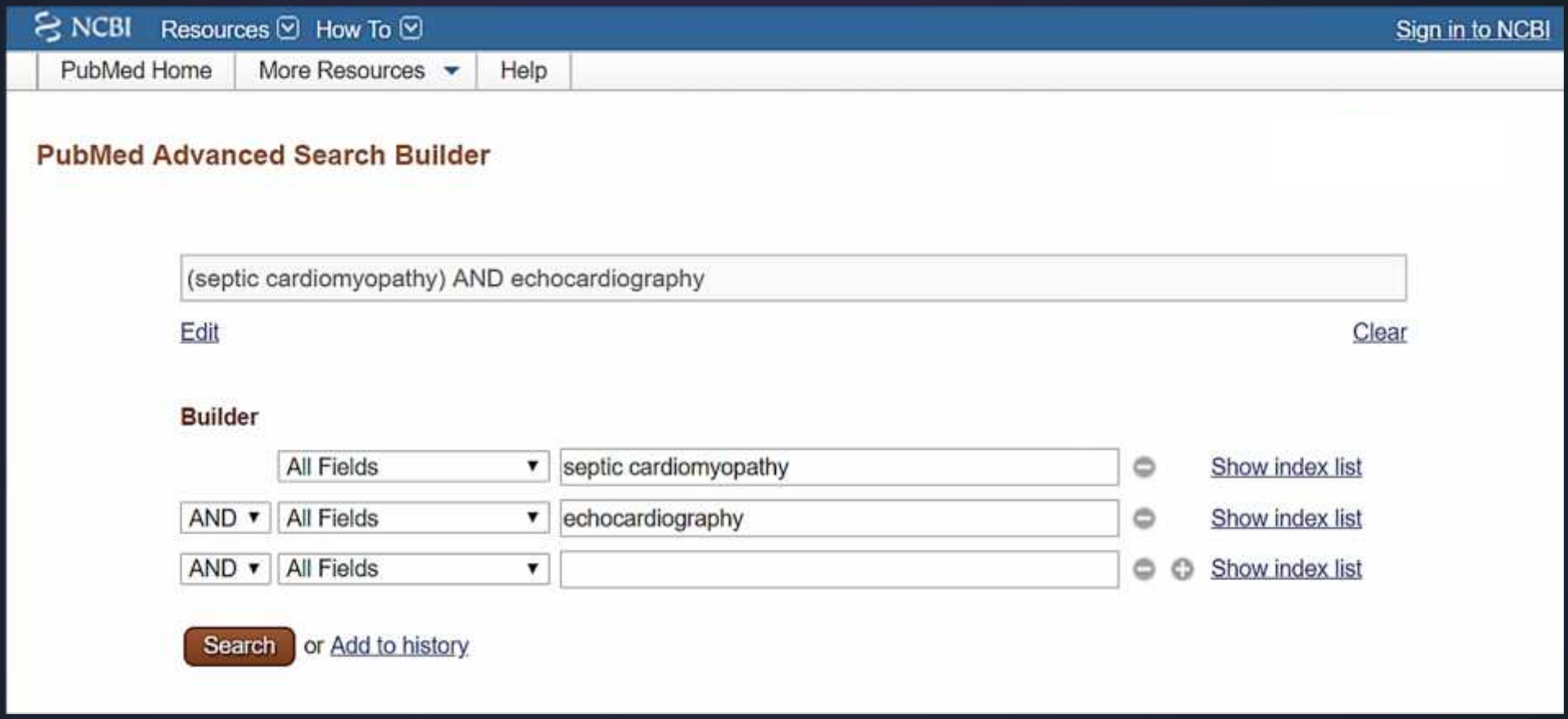
- **Speckle-tracking** → GLOBAL LONGITUDINAL STRAIN
- **Immagini Doppler** → MAPSE, TAPSE







MATERIALI E METODI



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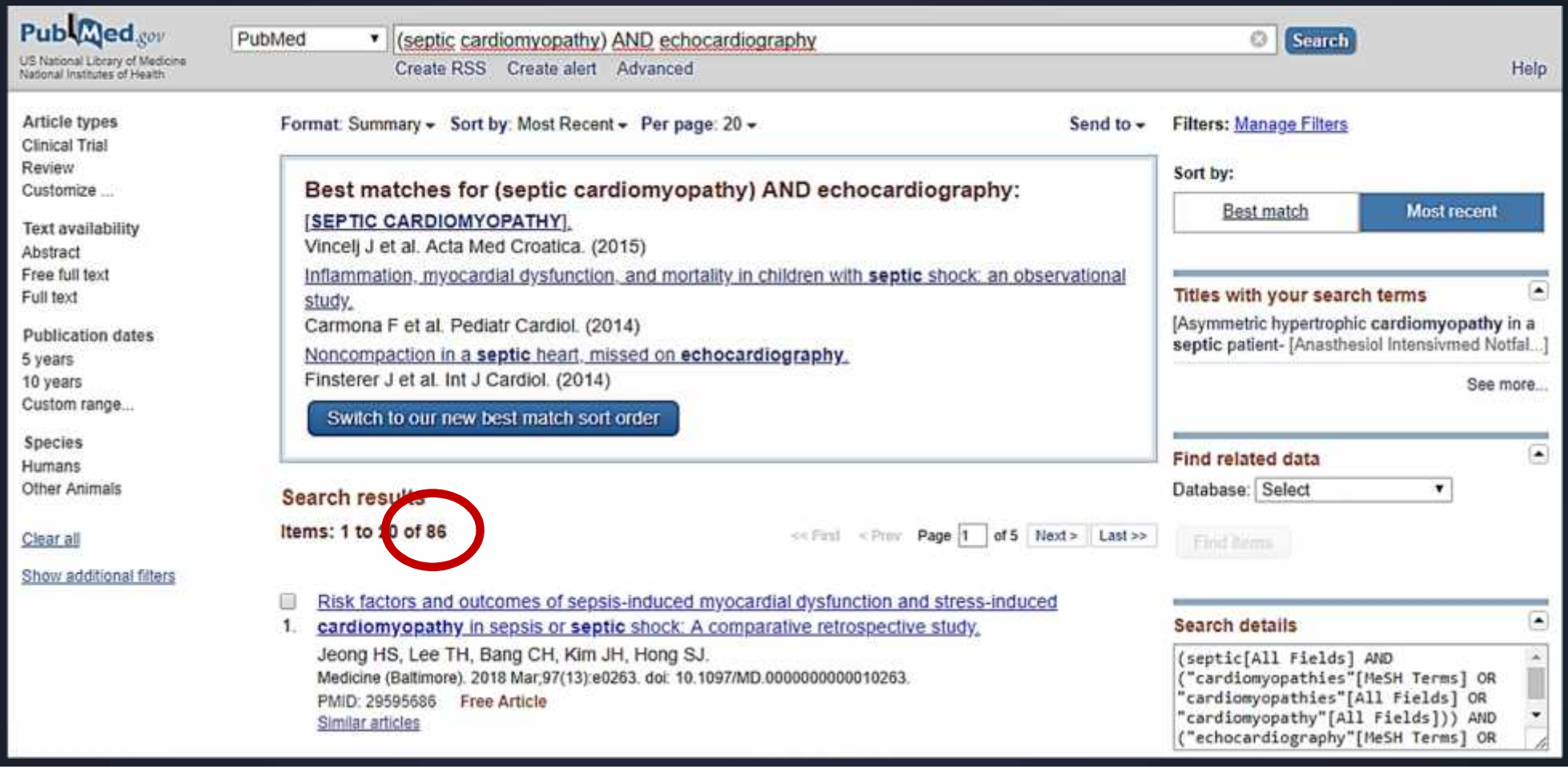


Criterio clinico:

utilizzo diagnostico e prognostico dell'ecocardiografia nella cardiomiopatia sepsi-correlata

+

Criterio temporale:

articoli dal 2014 al 2018

→

Risultato:

16 articoli selezionati

RISULTATI - OVERVIEW

	GLS > LVEF	Shock vs Sepsi	Mortalità	Infiammazione
Cinotti	X			
Shahul	X	X		
Ng	X	X		
Dalton	X			
Zaky	X		X	
Basu	X	X		
Lanspa 2015	X	X		
Lanspa 2017		X		
Haileselassie		X	X	X
Orde			X	
Chang			X	
Zhang	(Altri markers)			
Guérin	(Altri markers)			
Totale:	7 / 13	6 / 13	4 / 13	1 / 13

Frazione d'eiezione del ventricolo sinistro

Controlli – Pz. con sepsi

Studio – Pz. con shock settico

p = 0,319

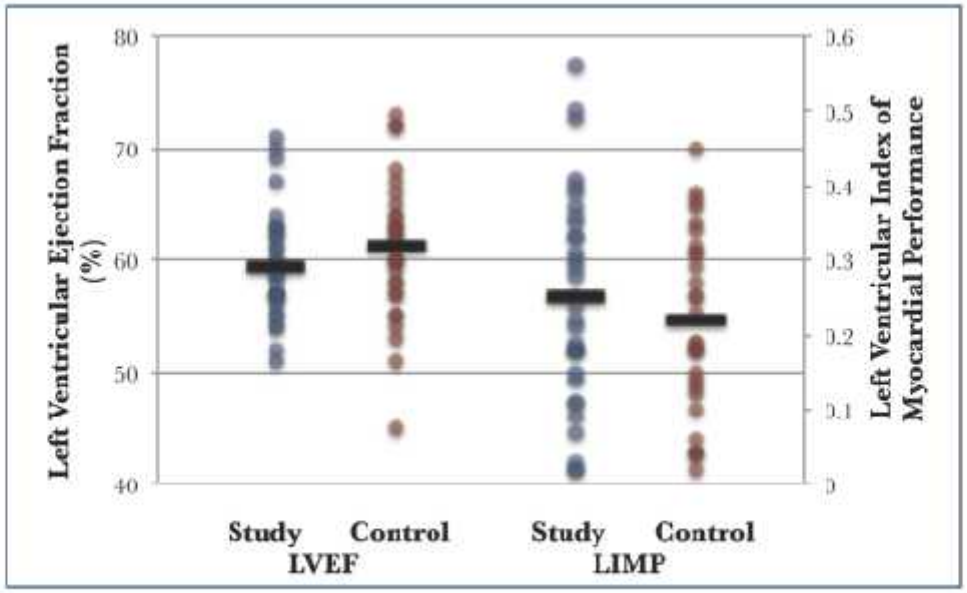


Fig. 2 Standard echocardiographic indices of left ventricular function. Left ventricular ejection fraction (*LVEF*): mean 59 % vs 61 %, $P = 0.169$. Left ventricular index of myocardial performance (*LMP*): mean 0.25 vs 0.22, $P = 0.319$

Ng, P. Y. et al. (2016). Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). *Critical Care*

Global Longitudinal Strain del ventricolo sinistro

Controlli – Pz. con sepsi

Studio – Pz. con shock settico

p < 0,001

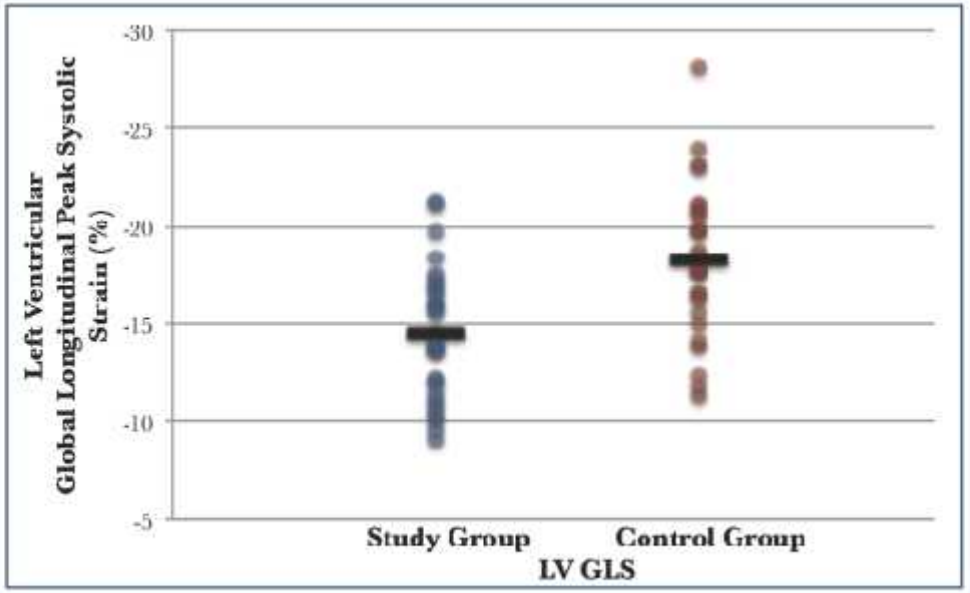


Fig. 3 Left ventricular global longitudinal strain in the study and control groups at diagnosis of sepsis. Left ventricular global longitudinal peak systolic strain (*LV GLS*): mean −14.5 % vs −18.3 %, $P < 0.001$

Ng, P. Y. et al. (2016). Speckle tracking echocardiography in patients with septic shock: a case control study (SPECKSS). *Critical Care*

Mortalità

RV strain
> -13%

↓

Disfunzione sistolica severa

↓

↑ Mortalità a un anno

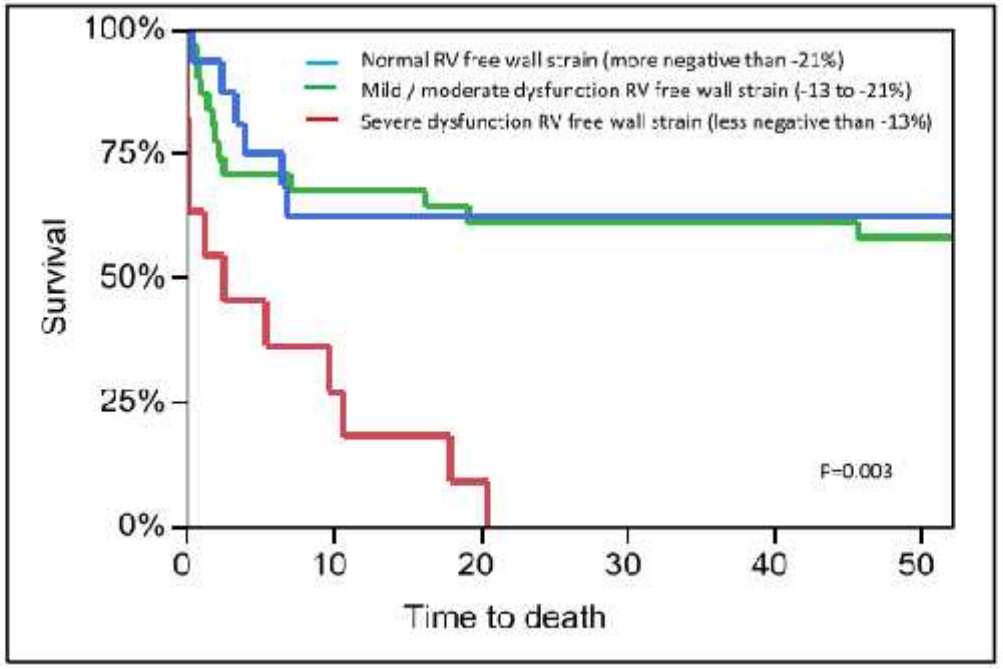


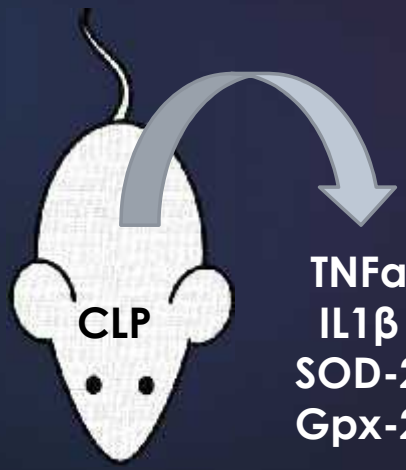
Figure 4 Kaplan–Meier 1-year survival curves based on right ventricle free wall strain. RV, right ventricle.

Orde, S. R. et al. (2014). Outcome prediction in sepsis: speckle tracking echocardiography based assessment of myocardial function. *Critical Care*

Infiammazione

Aumento di citochine infiammatorie nei topi CLP (Cecal Ligation and Puncture)

Stress ossidativo miocardico



TNFa
IL1β
SOD-2
Gpx-2

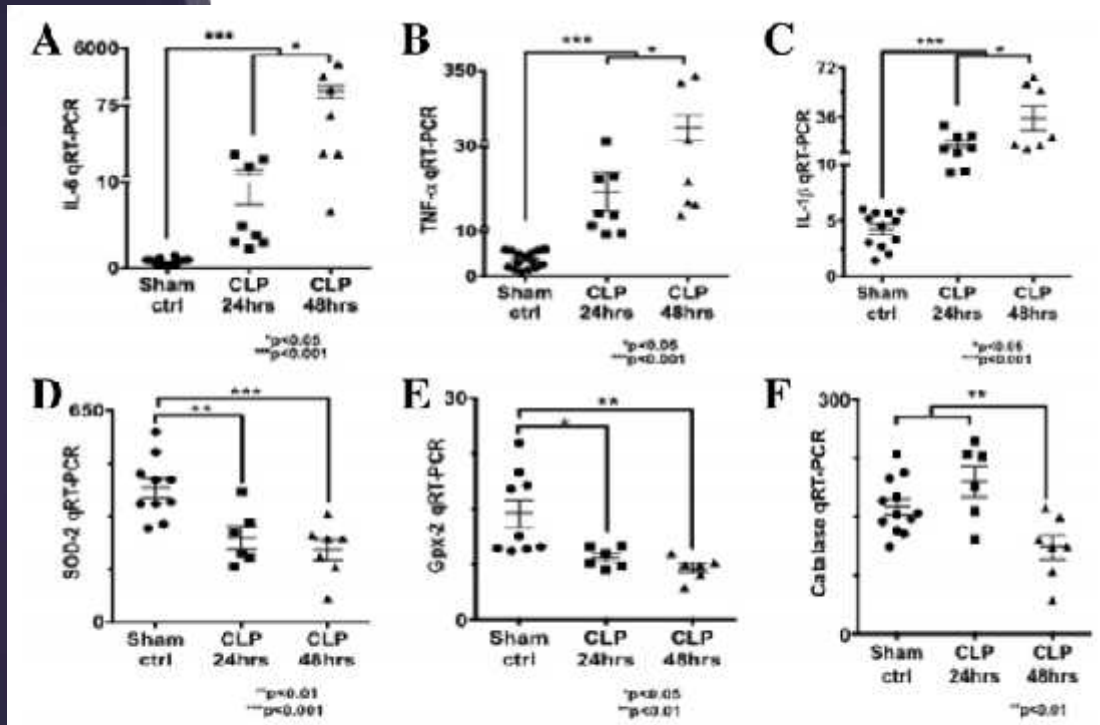
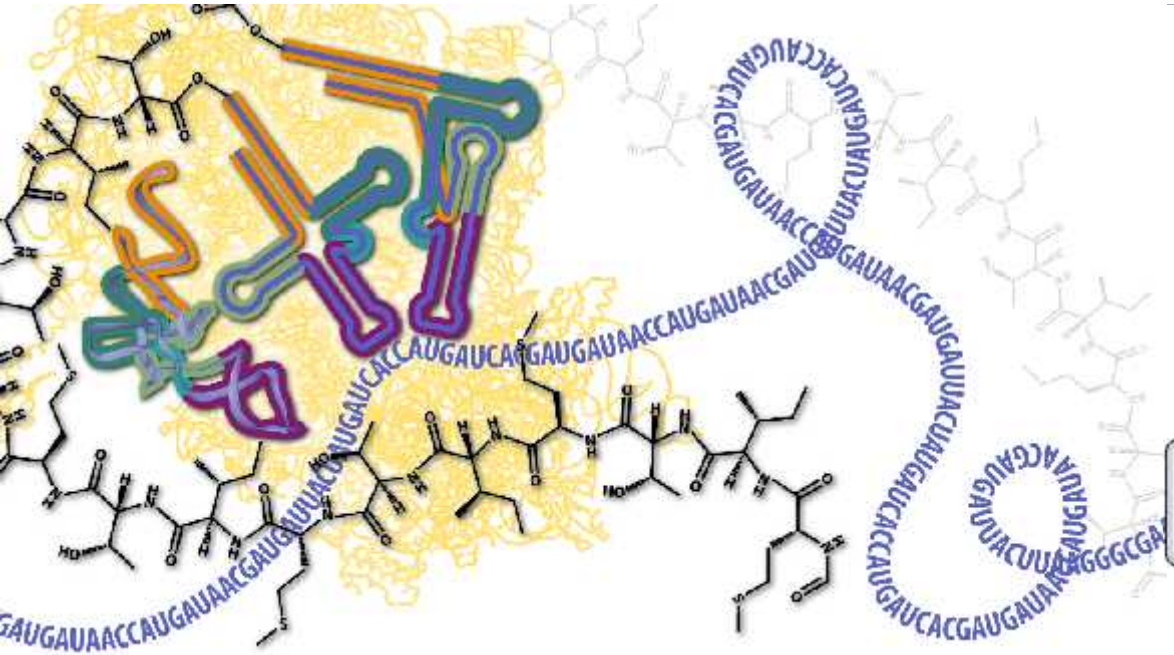


Fig. 3 Quantitative real-time PCR of pro-inflammatory cytokines (TNF-α, IL-1, and Il-6) and mitochondrial free radical scavengers (SOD-2, GPX-2, Catalase) at 24 and 48 h following CLP. Significant increase in TNF-α, IL-1, and Il-6 is seen at 24 and 48 h in the CLP group when compared to sham and control (**a–c**) Significant decrease in mitochondrial ROS scavengers is seen at 24 and 48 h post-surgery in the CLP group when compared to sham and control (**d–f**)



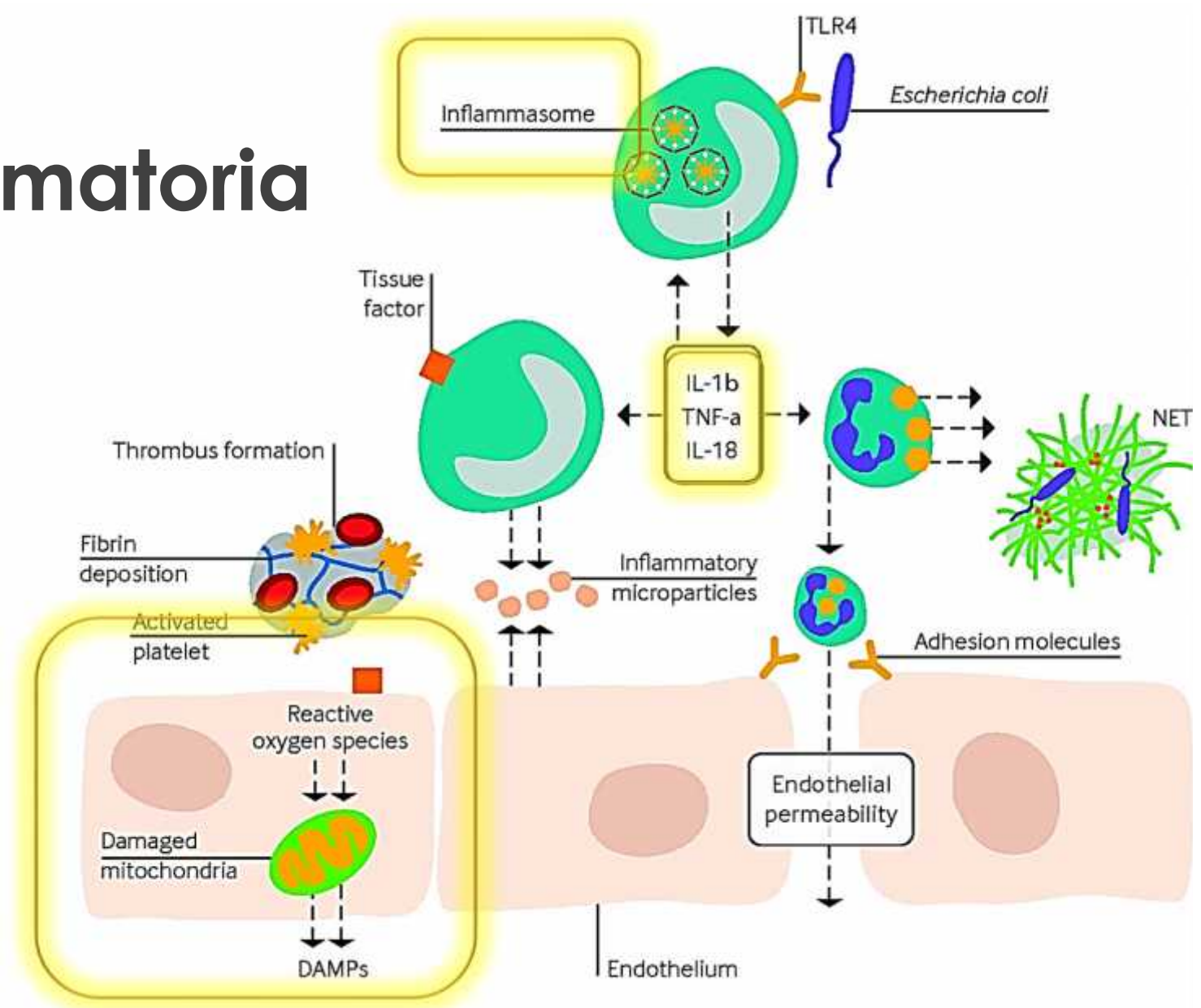
DISCUSSIONE

Sepsi: processo bifasico

Infiammazione

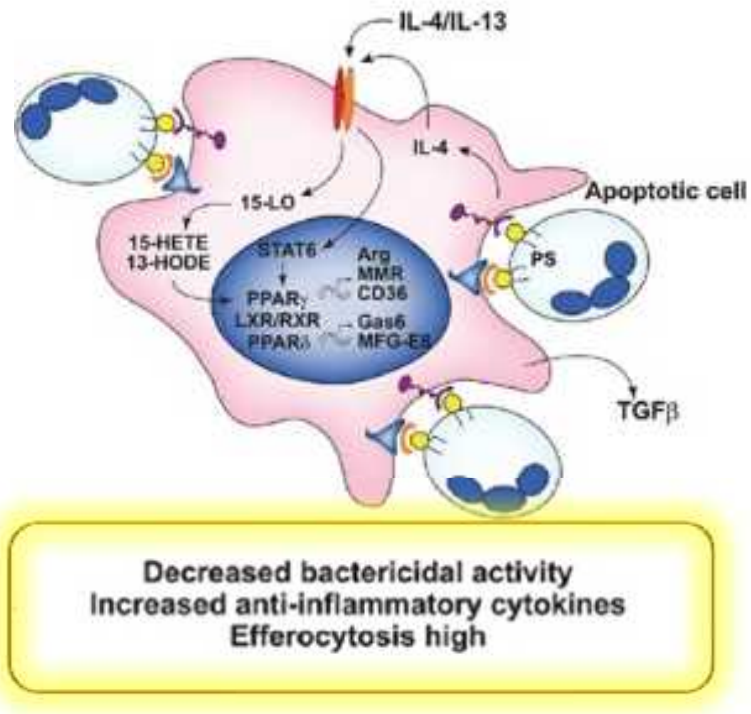
Immunosoppressione

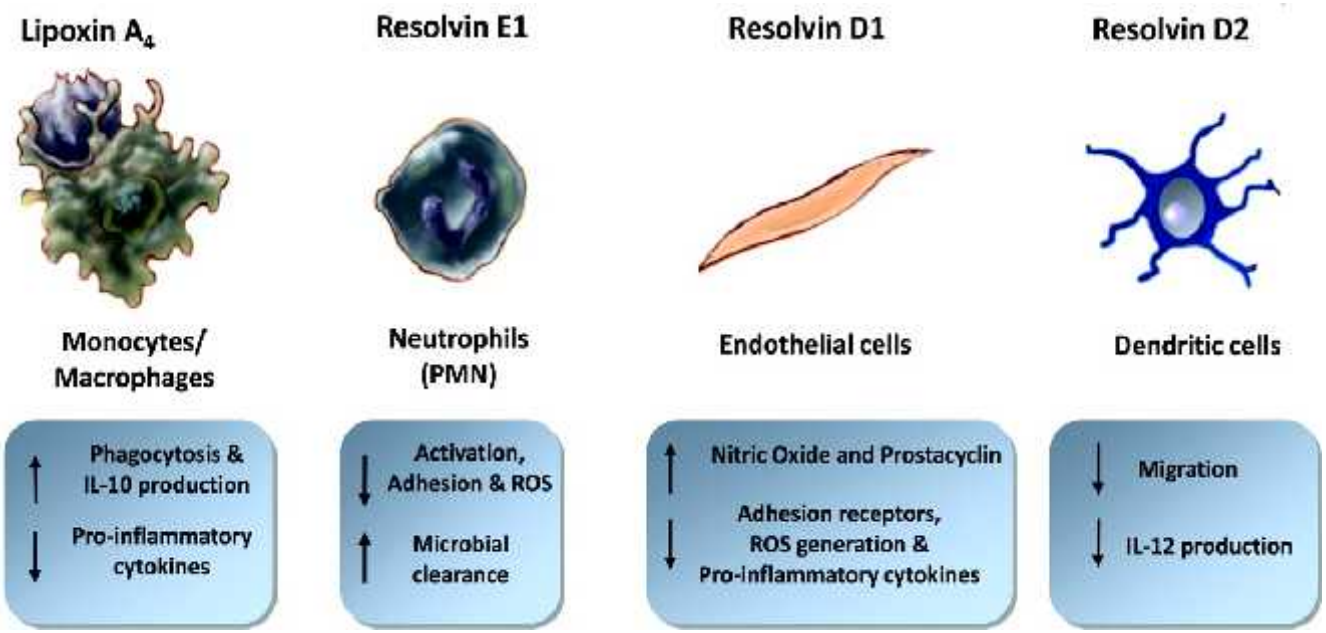
Fase infiammatoria



Jeffrey E Gotts, Michael A Matthay (2016) Sepsis: pathophysiology and clinical management. *BMJ*

Fase immunosoppressiva





Darlynn Korns et al. (2011). Modulation of macrophage efferocytosis in inflammation. *Frontiers in immunology*

Matthew Spite and Charles N. Serhan (2010). Novel Lipid Mediators Promote Resolution of Acute Inflammation. *Circulation Research*

Pazienti e ricoveri: grande eterogeneità!

- Età e sesso
- Genetica
- Comorbidità
- Stile di vita
- Patogeno
- Sito d'infezione

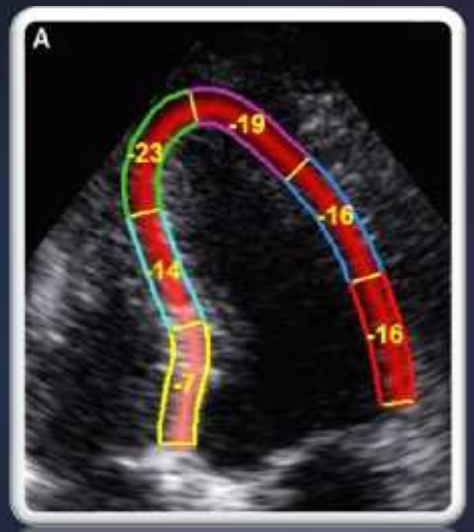
TABLE 1: Demographics and baseline characteristics for early and delayed ICU admission ($n = 287$).

	Early admission <6 hours ($n = 137$)	Delayed admission ≥6 hours ($n = 150$)
Age (mean, SD)	73.0 (13.6)	72.4 (16.0)
Sex (% male)	53.3	48.0
Admission per calendar quarter (%)		
Q1 (January–March)	25.55	34.00
Q2 (April–June)	36.50	29.33
Q3 (July–September)	18.98	20.00
Q4 (October–December)	18.98	16.67
SOFA score (mean, SD)	7.2 (3.2)	7.0 (3.3)
MAP (mean, SD)	70.1 (19.5)	72.0 (18.6)
Initial lactate (mean, SD)	3.9 (2.6)	3.2 (2.2)
Patient with initial lactate ≥ 4 (%)	39.4	30.0
Hypotension (MAP < 65) on initial presentation	49.64	40.67
Code status		
Full	73.72	75.33
DNR/DNI	26.28	24.67
Median ED time (hours) [25th, 75th percentile]	4.6 [3.8, 5.3]	8.1 [7.1, 10.8]

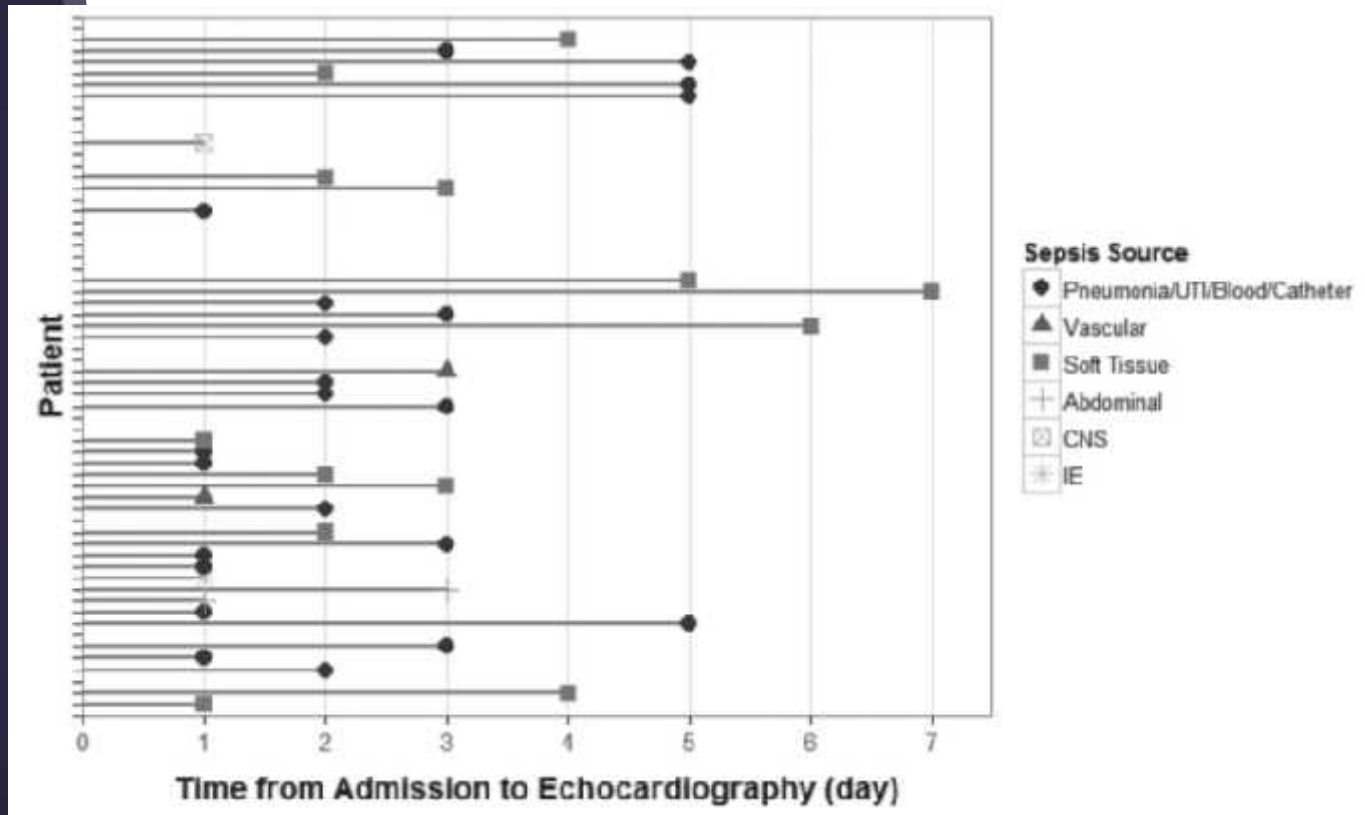
MAP, mean arterial pressure; SOFA, Sequential Organ Failure Assessment; DNR, do not resuscitate; DNI, do not intubate.

Michael Agustin et al. (2017) *Critical Care Research and Practice*

Pazienti e ricoveri: grande eterogeneità!



Patrick Collier et al. (2017) *JACC*



A. Zaky et al (2016) *Anaesth Intensive Care*

ANTI-CYTOKINES				
Etanercept[118]	Escalating doses of a fusion protein of Fc and extracellular domain of TNF receptor that neutralizes the potent inflammatory cytokine TNF	141 septic shock	28 day mortality	**Harm** Significant dose response† for mortality (P=0.02)
Afelimomab[184]	Monoclonal antibody fragments against TNF-α Stratified by IL-6 level at enrollment	2634 severe sepsis stratified by IL-6	28 day mortality	**Mild improvement in patients with raised IL-6** OR 0.74 (0.56 to 0.99)
Anakinra[185]	Recombinant IL-1ra, a monocyte/ macrophage protein that specifically inhibits the potent inflammatory cytokine IL-1	696 severe sepsis	28 day mortality	**No improvement** 36.4% placebo *v* 33.1% anakinra (P=0.36)
ANTI-VIRULENCE FACTORS				
HA-1A CHESS[187]	Monoclonal antibody against the lipid A portion of LPS	2199 septic shock	14 day mortality	**No improvement** RR 1.08 (0.97 to 1.21)
E5[186]	Monoclonal antibody against a broad range of Gram negative endotoxins	1090 severe sepsis	14 day mortality	**No improvement** 29.7% E5 *v* 31.1% placebo (P=0.67)
Eritoran ACCESS[189]	Lipid A-like molecule that blocks LPS binding to TLR4	1961 severe sepsis	28 day mortality	**No improvement** HR 1.05 (0.88 to 1.26)

Jeffrey E Gotts, M. A. Matthay (2016) Sepsis: pathophysiology and clinical management. *BMJ*

Target therapy inefficace!

Markers di disfunzione miocardica

- Troponine
- NT-proBNP
- CK e CK-MB
- Mioglobina
- PCR

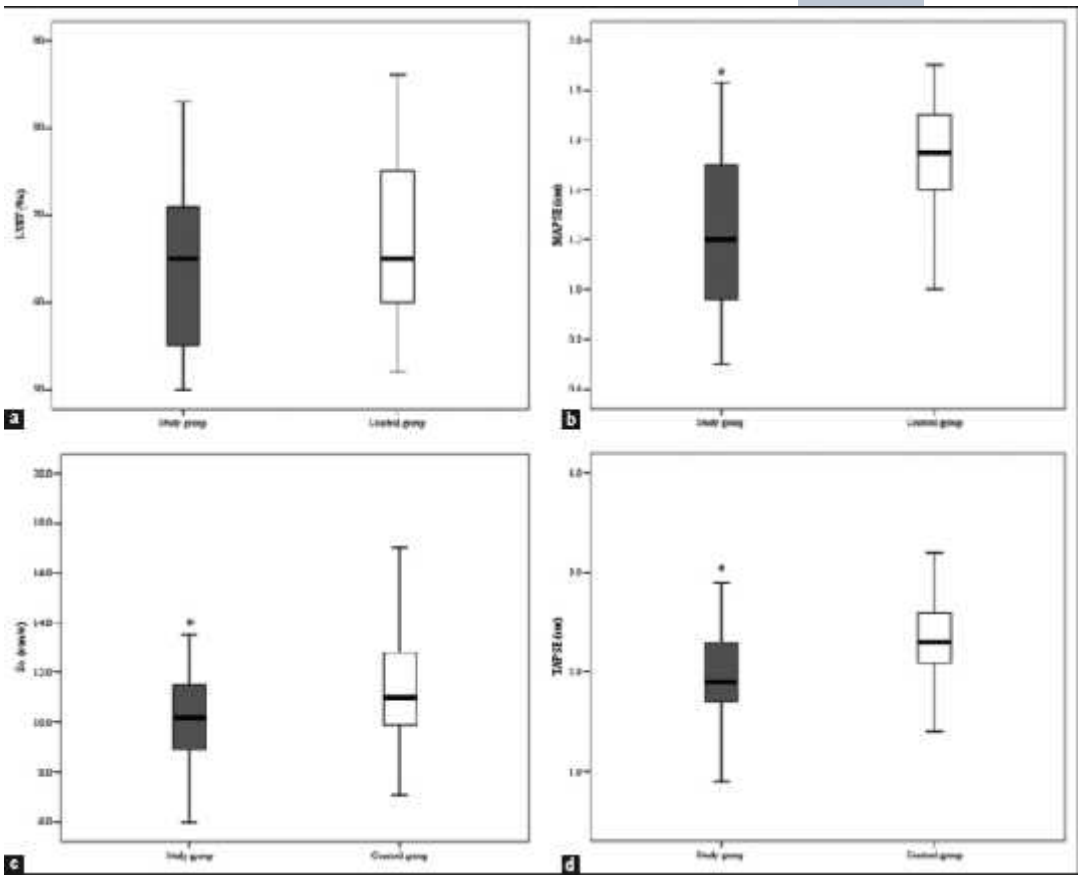
Allison Dalton and Sajid Shahul (2018). Cardiac disfunction in critical illness. *Current Opinion in Anesthesiology*

Markers di disfunzione miocardica

Mediante STE

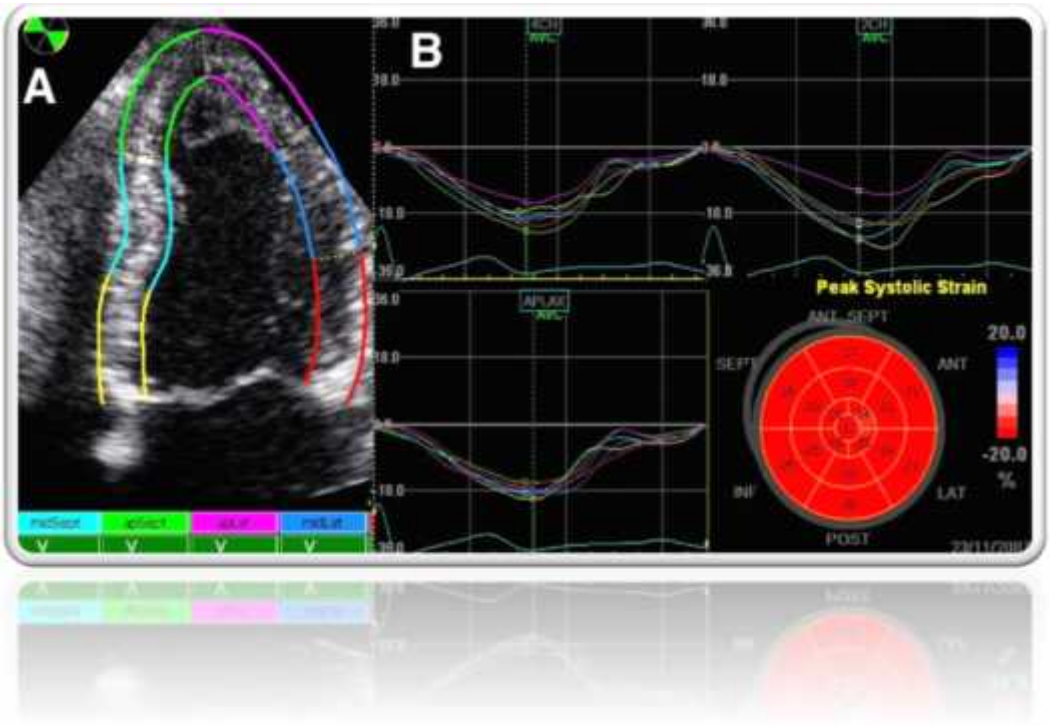
Table 2: Echocardiographic parameters the sepsis shock group and nonsepsis group (n = 45)

Categories	Study group	Control group	t	P
LVDD (mm)	47.6 ± 6.2	47.9 ± 2.7	−0.220	0.826
LVSD (mm)	29.8 ± 6.5	28.4 ± 3.8	1.105	0.274
LVEF (%)	64.6 ± 9.3	67.2 ± 8.8	−1.426	0.161
E-wave (cm/s)	73.4 ± 20.9	73.7 ± 20.1	−0.016	0.961
A-wave (cm/s)	84.8 ± 24.2	80.2 ± 12.1	0.842	0.518
e' (cm/s)	9.8 ± 3.0	10.8 ± 2.3	−1.812	0.073
E/e'	7.7 ± 2.1	8.1 ± 2.1	−0.506	0.614
TAPSE (cm)	1.9 ± 0.4	2.3 ± 0.4	−4.216	<0.001
Sa (cm/s)	10.2 ± 2.7	11.8 ± 2.9	−2.796	0.014
MAPSE (cm)	1.2 ± 0.4	1.5 ± 0.2	−4.945	<0.001



Hong-Min Zhang et al. (2017). Left Ventricular Longitudinal Systolic Function in Septic Shock Patients with Normal Ejection Fraction: A Case-control Study. *Chinese Medical Journal*

GLS: guida per impostare la terapia



Thomas H. Marwick et al. (2009). *JACC: Cadiovascular imaging*

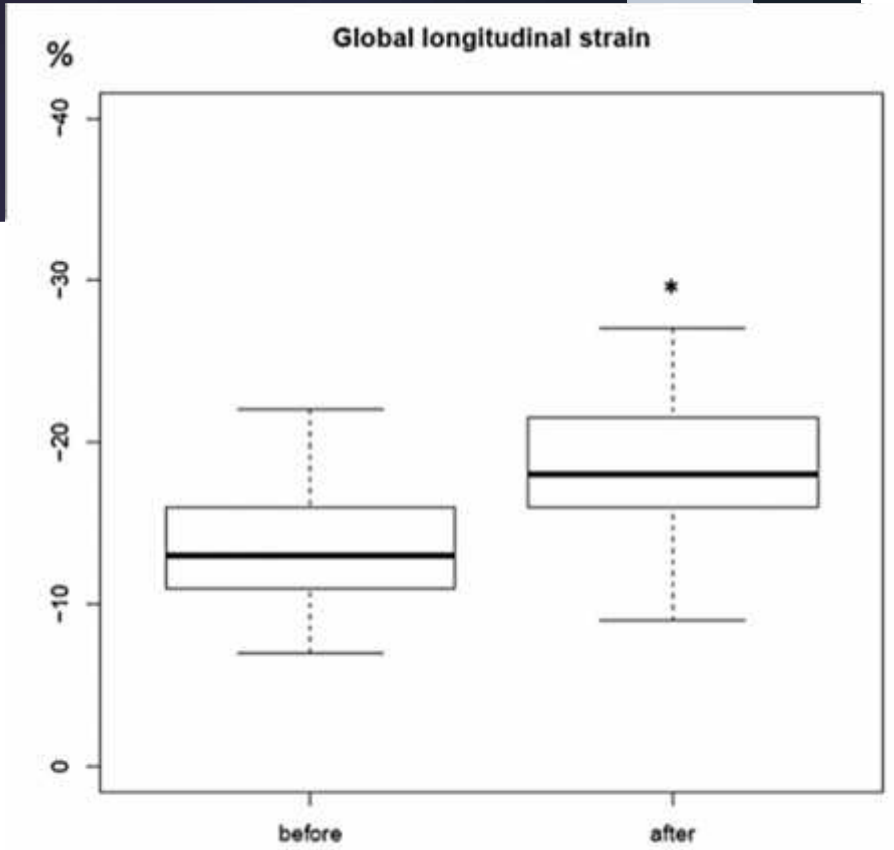
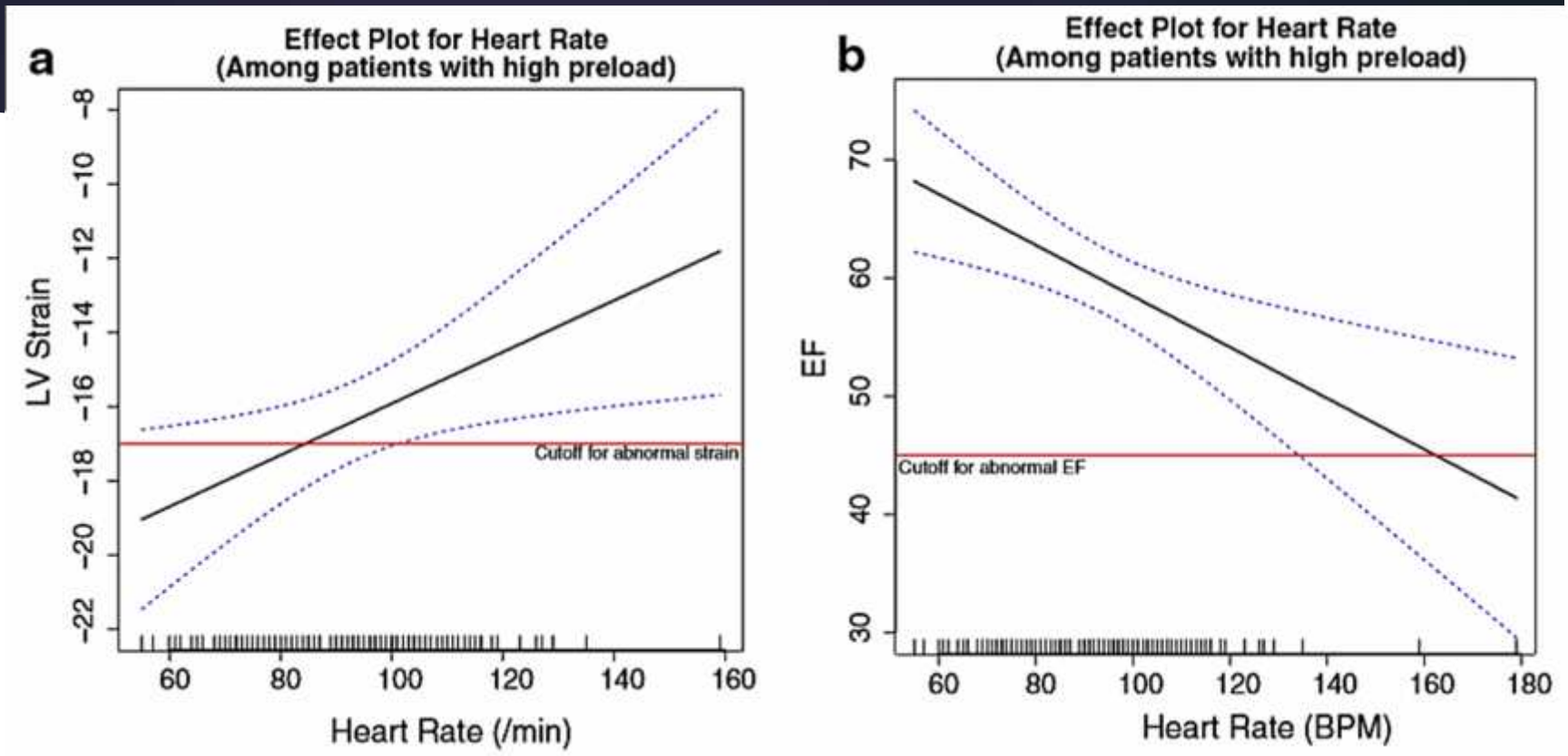


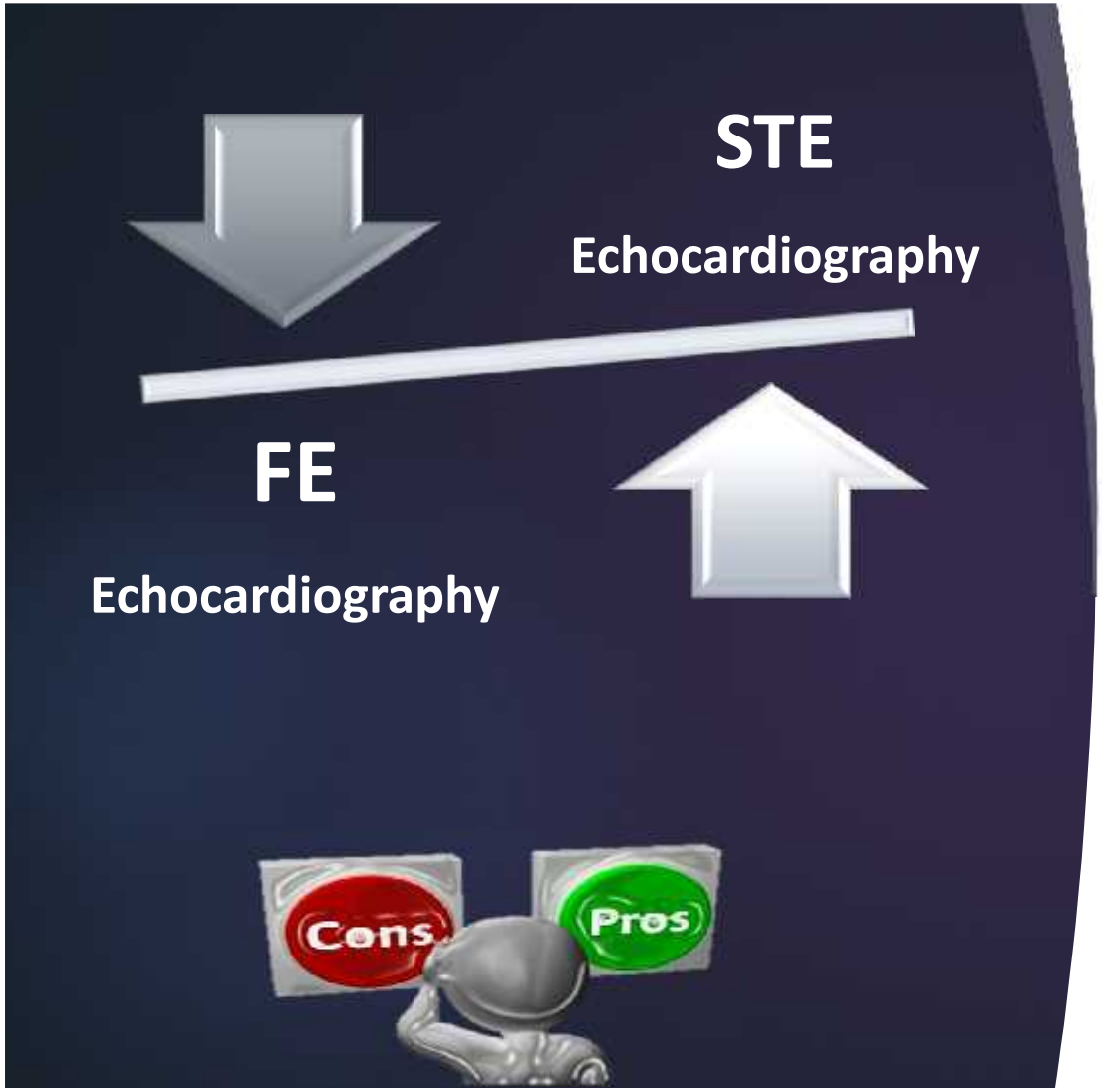
Fig. 3 Significant increase of absolute value in GLS: − 13.3 ± 3.5 versus − 18.4 ± 4.5% ($p < 0.01$)

Nafati et al. (2018). *Annals of Intensive Care*

Se pre-load elevato … relazione con FC!



Michael J. Lanspa et al. (2017). Associations among left ventricular systolic function, tachycardia, and cardiac preload in septic patients. *Annals of Intensive Care*



CONCLUSIONI


PROS
CONS
Maggiore sensibilità e specificità
• Diagnosi precisa e precoce
• Terapia mirata
Monitoraggio
• Adattamento e modificazione della terapia
Prognosi
• Maggiore sicurezza per il medico
• Maggiore sicurezza per il paziente e i familiari
Lunga curva di apprendimento
• Non immediatamente utilizzabile
Ulteriori trials clinici
• Maggiore numerosità campionaria
Necessità di studi retrospettivi
• Nuovi studi e revisione della letteratura precedente

Grazie per l'attenzione

M. Lucenteforte, S. Doria, L. G. Remore, G. Anguissola

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