

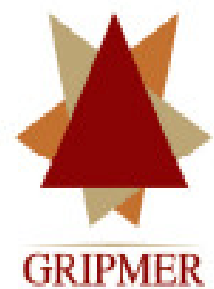
SHOULD THERAPEUTIC AGENTS FOR SEPSIS TARGET THE GLYCOCALYX?



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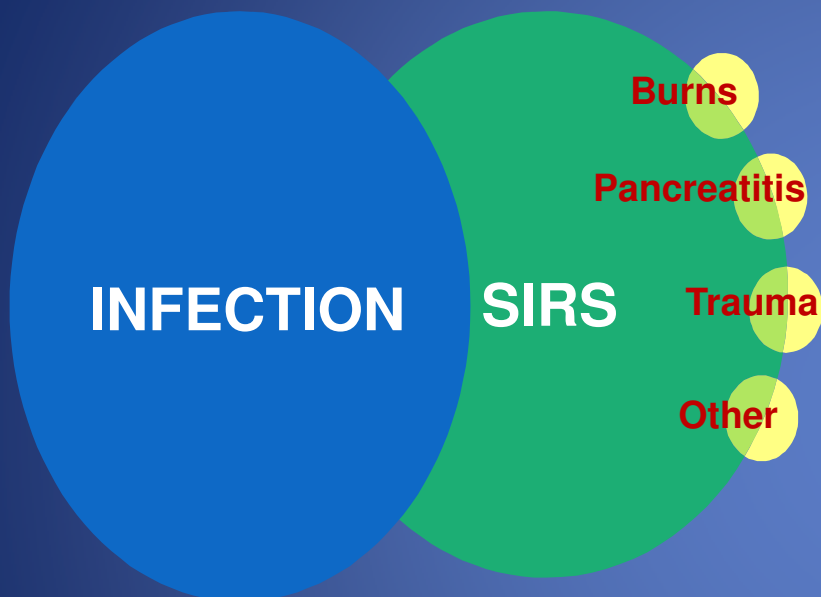


**Ganga Ram Institute of
Postgraduate Medical
Education and
Research**

Systemic Inflammatory Response Syndrome (SIRS)/Sepsis

ACCP/SCCM Consensus Conference (1992) *Crit Care Med* 1992; 20:864–874

Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis.



Sepsis

=

Known or suspected infection

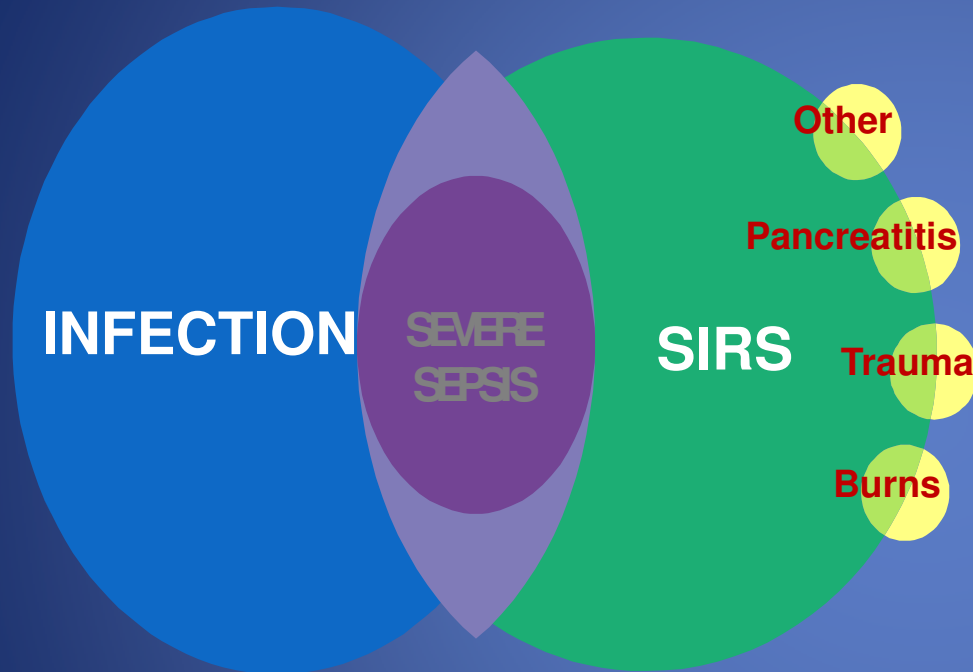
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≥2 SIRS criteria

Criteria for Dx of SIRS

- Core temperature $>38.3^{\circ}\text{C}$ / $<36^{\circ}\text{C}$
- Heart rate >90 bpm / $>2\text{SD}$
- Respiratory rate >30 bpm
or
PaCO₂ <32 mm Hg
- WBC count $>12,000$ cells/mm³
or
 $<4,000$ cells/mm³
or
 $>10\%$ immature neutrophils

SIRS, Sepsis, Severe Sepsis and Septic shock



Severe Sepsis

Sepsis + ≥ 1 organ dysfunction

Septic Shock

Severe Sepsis

+

Hypotension despite fluid resuscitation

ACCP/SCCM Consensus Conference (1992)

Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864–874

SOFA Score

Variables/Points	1	2	3	4
Neurological Coma Score: Glasgow	13-14	10-12	6-9	< 6
Pulmonary PaO ₂ (mmHg) / FiO ₂	< 400	< 300	< 200 with respiratory support	< 100 with respiratory support
Cardiological Mean Systolic Arterial Pressure (mmHg)	< 70	Dopamine \leq 5 or Dobutamine (whatever dose)	Dopamine > 5 or Adrenaline \leq 0.1 or Noradrenaline \leq 0.1	Dopamine > 15 or Adrenaline > 0.1 or Noradrenaline > 0.1
Renal Blood creatinine μ mol/L (mg/L) or Diuresis mL/day	110-170 (1.2-1.9)	171-299 (2.0-3.4)	300-440 (3.5-4.9) or < 500	> 440 (> 5.0) or < 200
Haematological Platelets 10 ⁹ /L	< 150	< 100	< 50	< 20
Hepatic Blood bilirubin μ mol/L (mg/dL)	20-32 (1.2-1.9)	33-101 (2.0-5.9)	102-204 (6.0-11.9)	> 204 (> 12.0)

Crit Care Med 1998;26:1793-1800

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The APACHE II Score

Physiologic Variable	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Rectal Temp (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥100	140-179	110-139		70-109		50-69	40-54	≤39
Respiratory Rate	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation a) FIO ₂ ≥0.5 record A-aDO ₂ b) FIO ₂ <0.5 record PaO ₂	≥500	350-499	200-349		<200 PO ₂ >70	PO ₂ 61-70		PO ₂ 55-60	PO ₂ <55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
HCO₃ (mEq/l)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
K (mEq/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Na (mEq/l)	≥100	160-179	155-159	150-154	130-149		120-129	111-119	≤110
S. Creat (mgm/dl)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
TLC (10³/cc)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS									

Age -score

<44 → 0
45-54 → 2
55-64 → 3
65-74 → 5
≥75 → 6

GCS:

15 → 0	14 → 1	13 → 2
12 → 3	11 → 4	10 → 5
9 → 6	8 → 7	7 → 8
6 → 9	5 → 10	4 → 11
3 → 12		

JAMA 1993;270(24):2957-2963

Dilemmas in sepsis

- **Early diagnosis**
- **Segregation into sepsis and SIRS**
- **Differentiation between sepsis, severe sepsis and septic shock**
- **Prognosis**
- **Increased morbidity and mortality**
- **Refractory hypotension and organ failure**

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Procalcitonin as a rapid diagnostic biomarker to differentiate between culture-negative bacterial sepsis and systemic inflammatory response syndrome: A prospective, observational, cohort study[☆]



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Salient findings:

- PCT differentiates culture-negative sepsis from SIRS at a cut off of 1.43 ng/ml, with 92% sensitivity and 83% negative predictive value (AUC 0.892)
- PCT differentiates culture-positive sepsis from SIRS at a cut off of 2.49 ng/ml, with 94.4% sensitivity and 91.5% negative predictive value (AUC 0.959)

Next Question

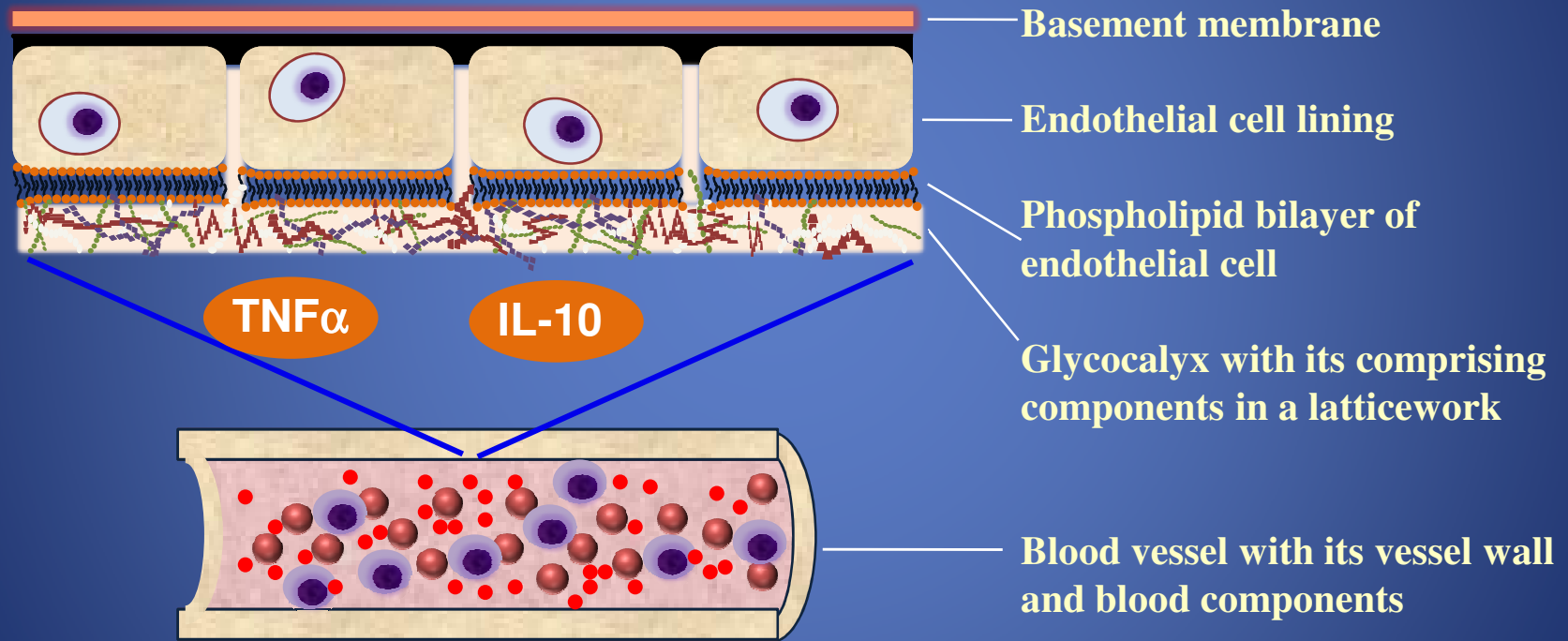
Identification of a marker or markers to effectively differentiate between sepsis, severe sepsis and septic shock

HOW?

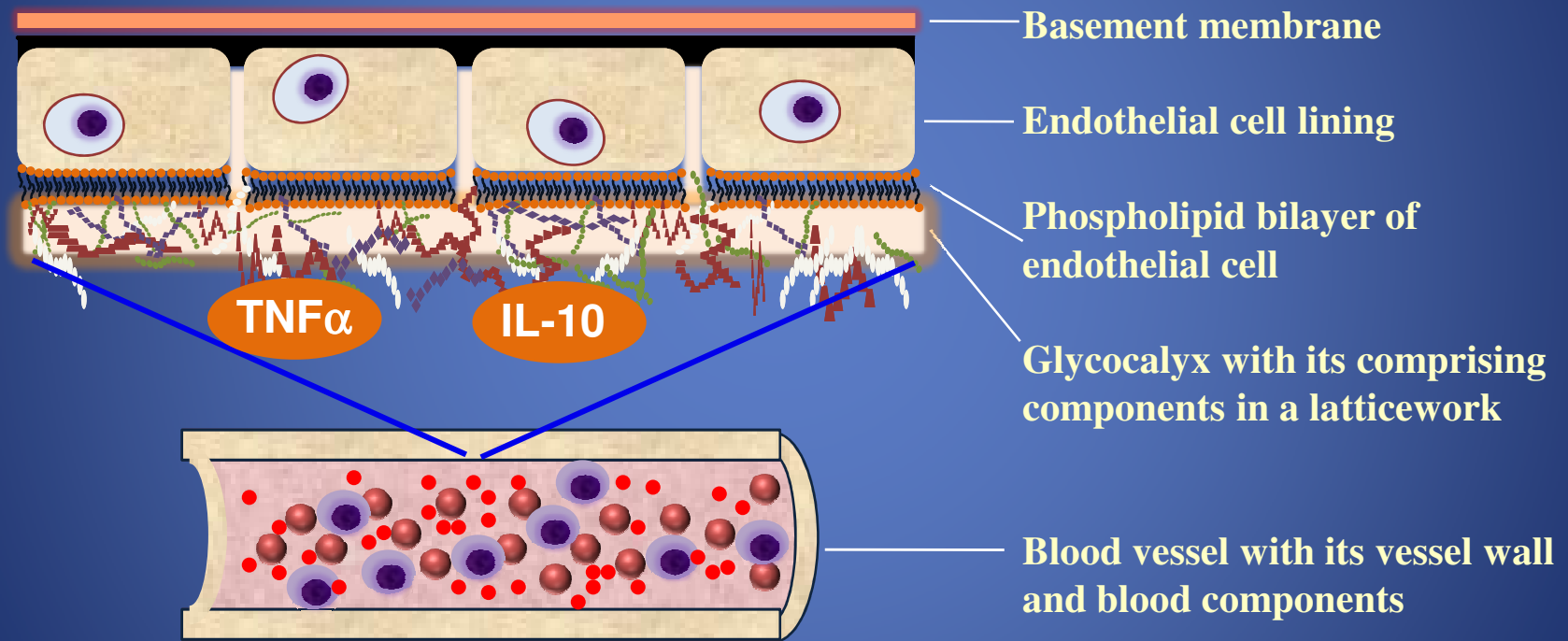
Pathophysiology of sepsis

Disruption of the glycocalyx is a known event

The Glycocalyx

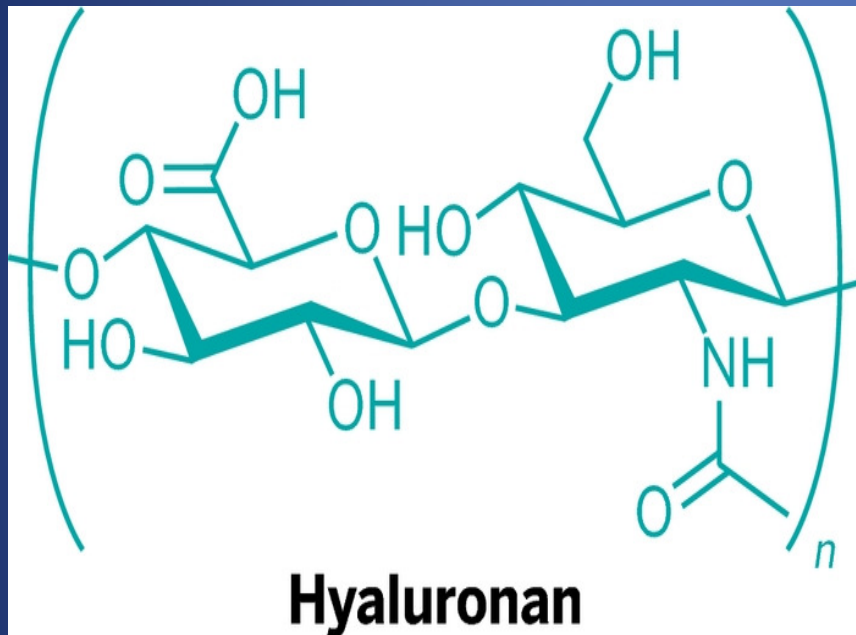


The Glycocalyx

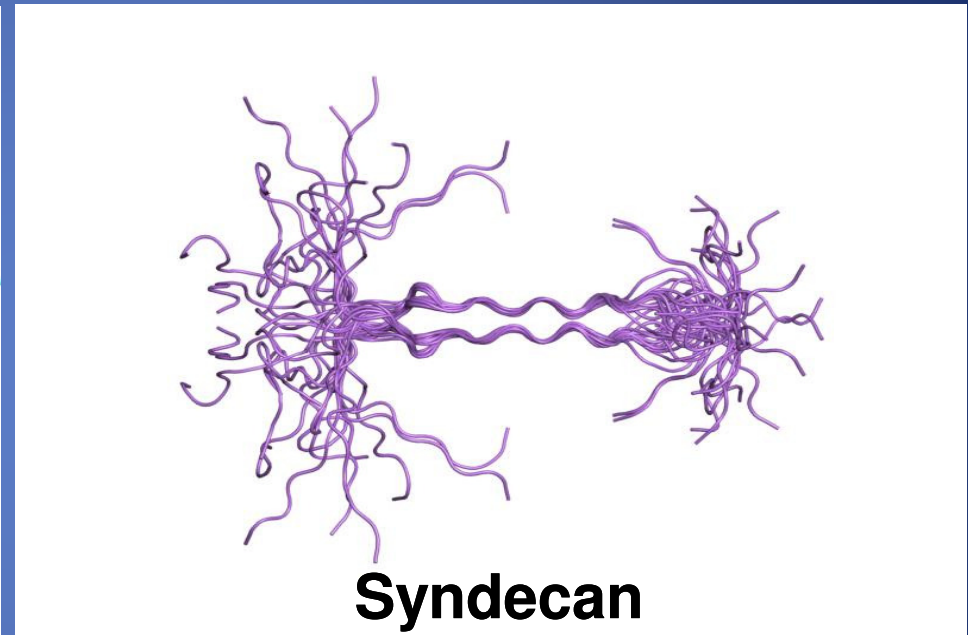


Hyaluronan & Syndecan

Glycocalyx components



Widely distributed anionic
non-sulphated GAG



Single transmembrane domain GAG
G-protein coupled receptors

Study Objectives

1. To study the evolution of hyaluronan and syndecan (glycocalyx components) as prognostic markers for sepsis

2. To correlate their serum levels with

- a) Progression of disease**
- b) Survival status**
- c) Organ failure**
- d) Inflammatory mediators**

Methods: Inclusion & Exclusion criteria

- **Inclusion Criteria**

- Age ≥ 18 years
- Patients admitted to the intensive care unit with community acquired Sepsis, Severe sepsis or Septic shock

- **Exclusion Criteria**

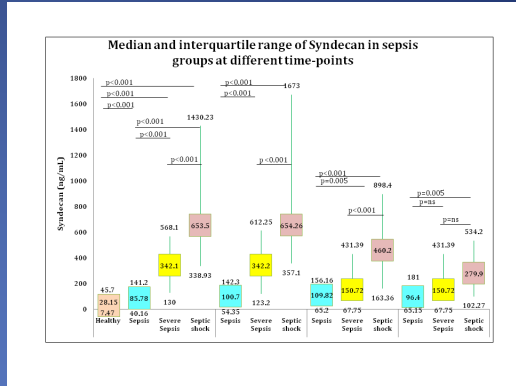
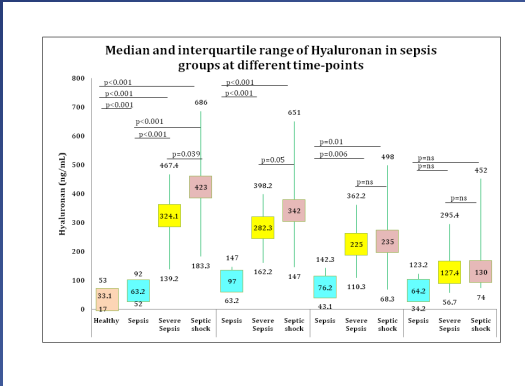
- Post-operative patients
- Lethal condition
- Malignancy
- Immunocompromised
- Transferred from other ICU's

Methodology

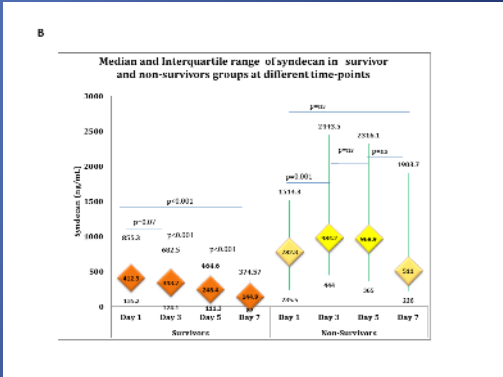
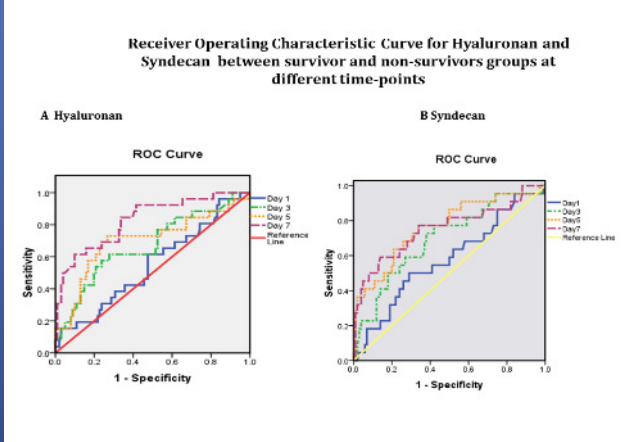
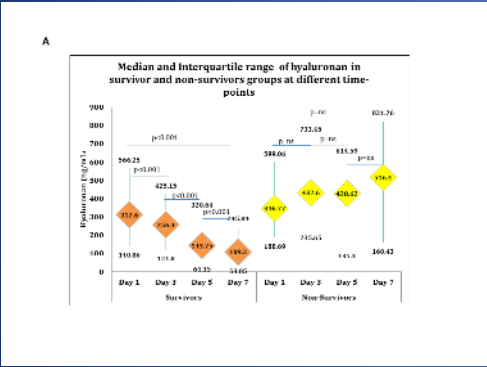
Days 1,3,5, and 7 → Blood drawn from all subjects

Following analytes estimated in serum:

- Hyaluronan- Competitive Enzyme Linked Immunosorbent Assay
(Teco Medical, Switzerland)
- Syndecan- Solid Phase Sandwich Elisa
(Diacclone, Besancom Cedex, France)
- TNF- α - Chemiluminescent Immunoassay (Immulite, Siemens)
- Interleukin-10 - Solid Phase Sandwich Elisa
(Diacclone, Besancom Cedex, France)
- SOFA and APACHE II scores



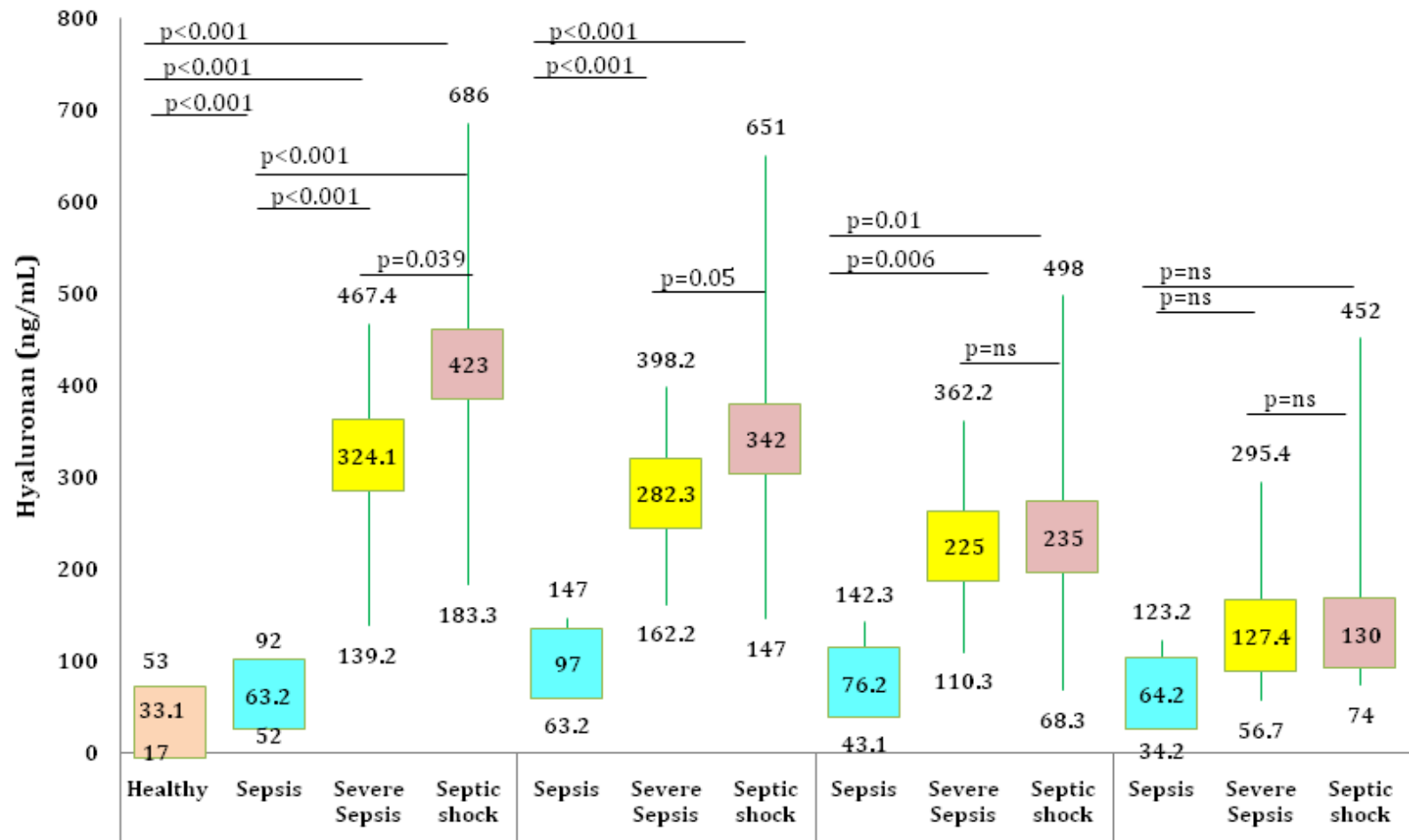
RESULTS



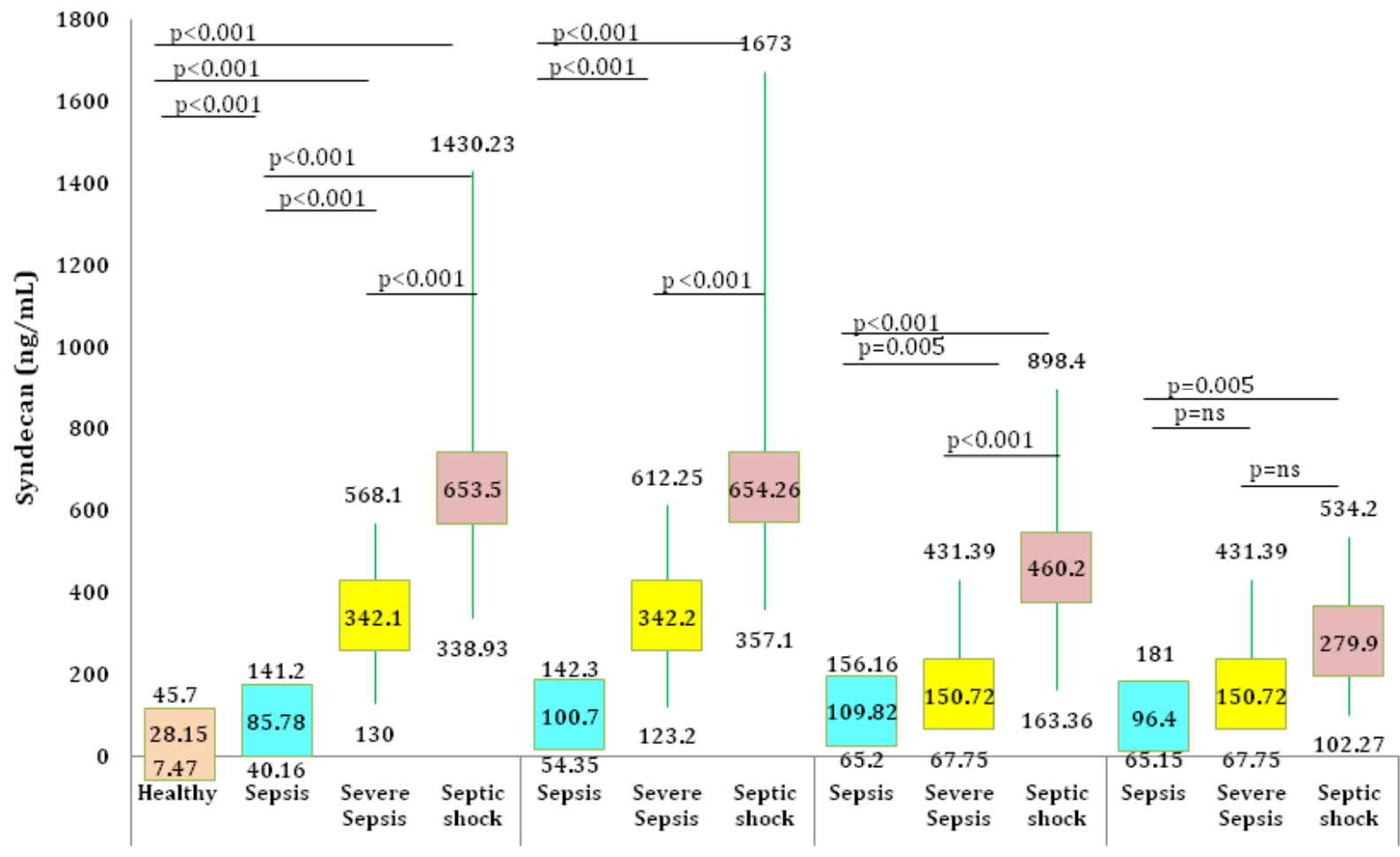
Patient baseline characteristics

	Sepsis (N = 15)	Severe Sepsis (N = 45)	Septic Shock (N = 90)	p Value
Age, Mean \pm S.D	52.2 \pm 16.3	53.4 \pm 16	54 \pm 16.5	ns
Gender (M/F)	8/7	27/18	56/34	ns
Mortality– N (%)	1 (6.66%)	6 (13.3%)	34 (37.7%)	0.002
APACHE II Mean \pm S.D.	9 + 6.2	20.1 + 7.0	25.1 + 7.4	0.004
SOFA SCORE Mean \pm S.D.	4.8 + 2.1	8.5 + 3.7	12.1 + 3.5	<0.001

Median and interquartile range of Hyaluronan in sepsis groups at different time-points



Median and interquartile range of Syndecan in sepsis groups at different time-points



DAY 1

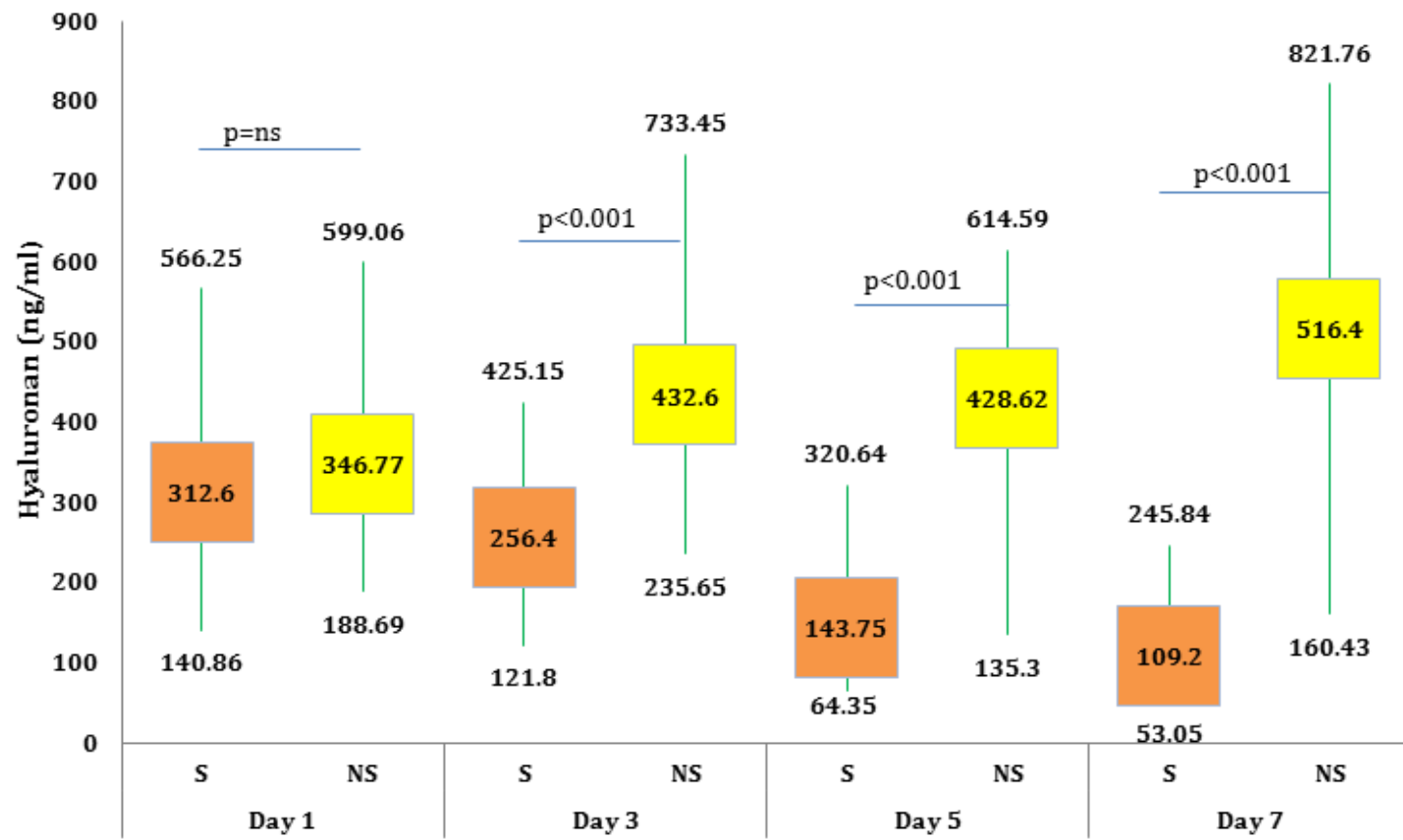
DAY 3

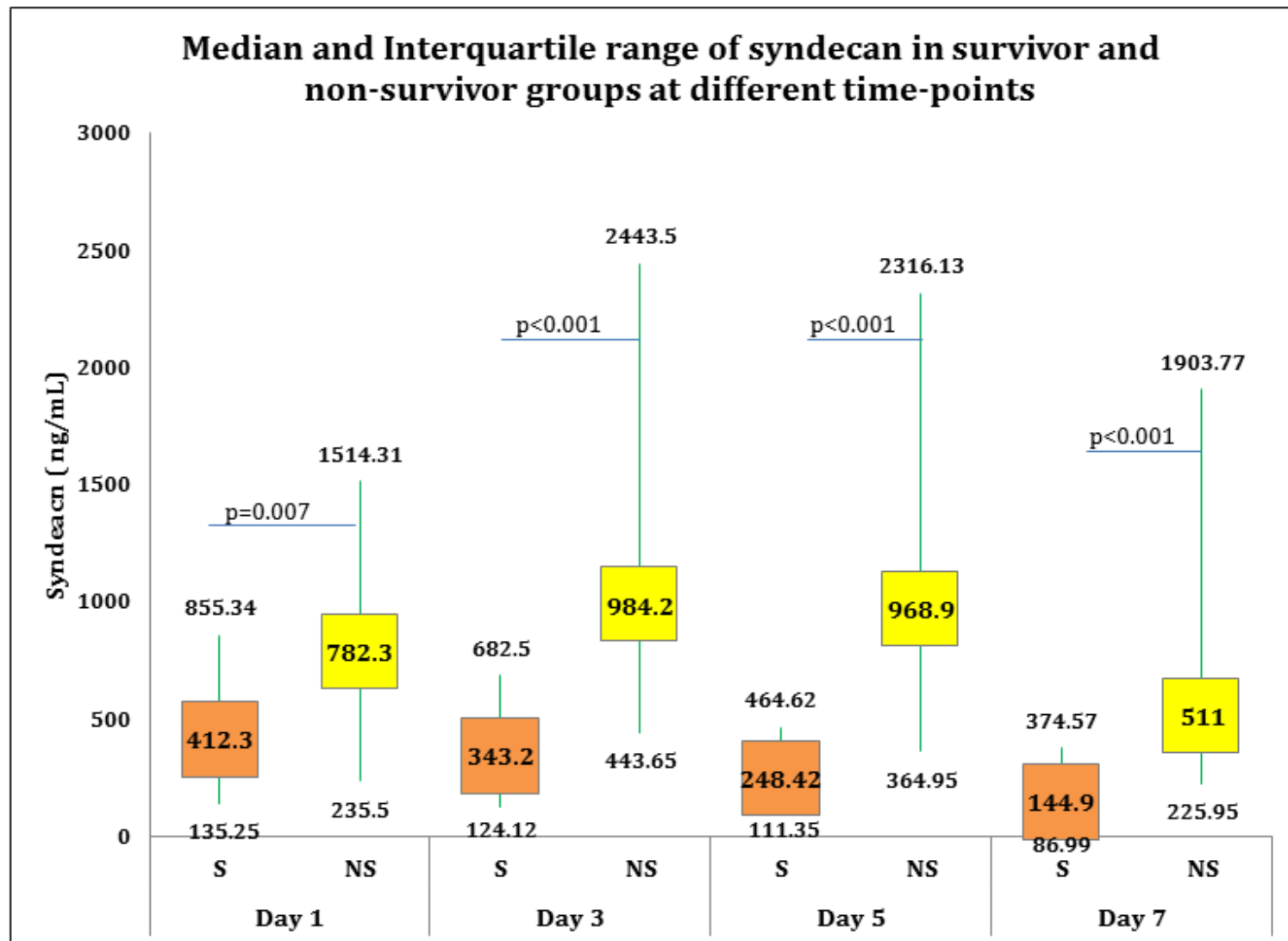
DAY 5

DAY 7

A

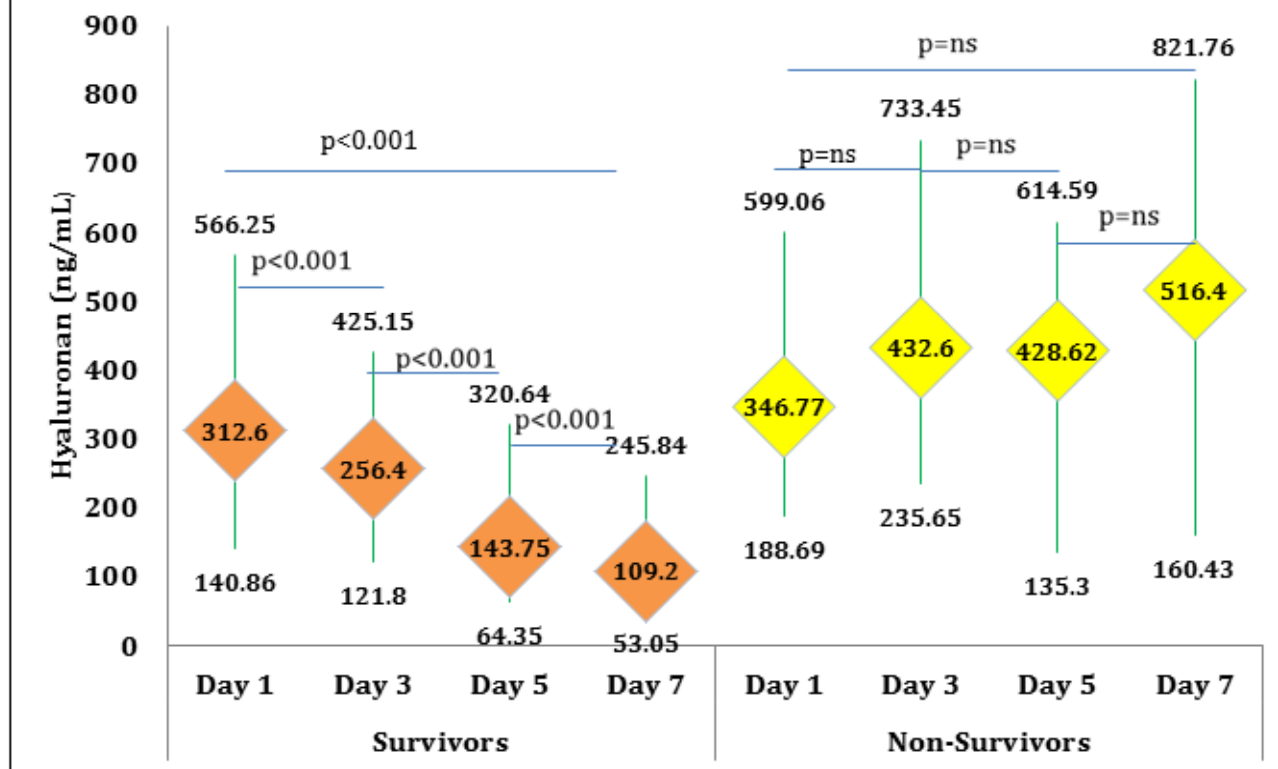
Median and interquartile range of hyaluronan in survivor and non-survivor groups at different time-points

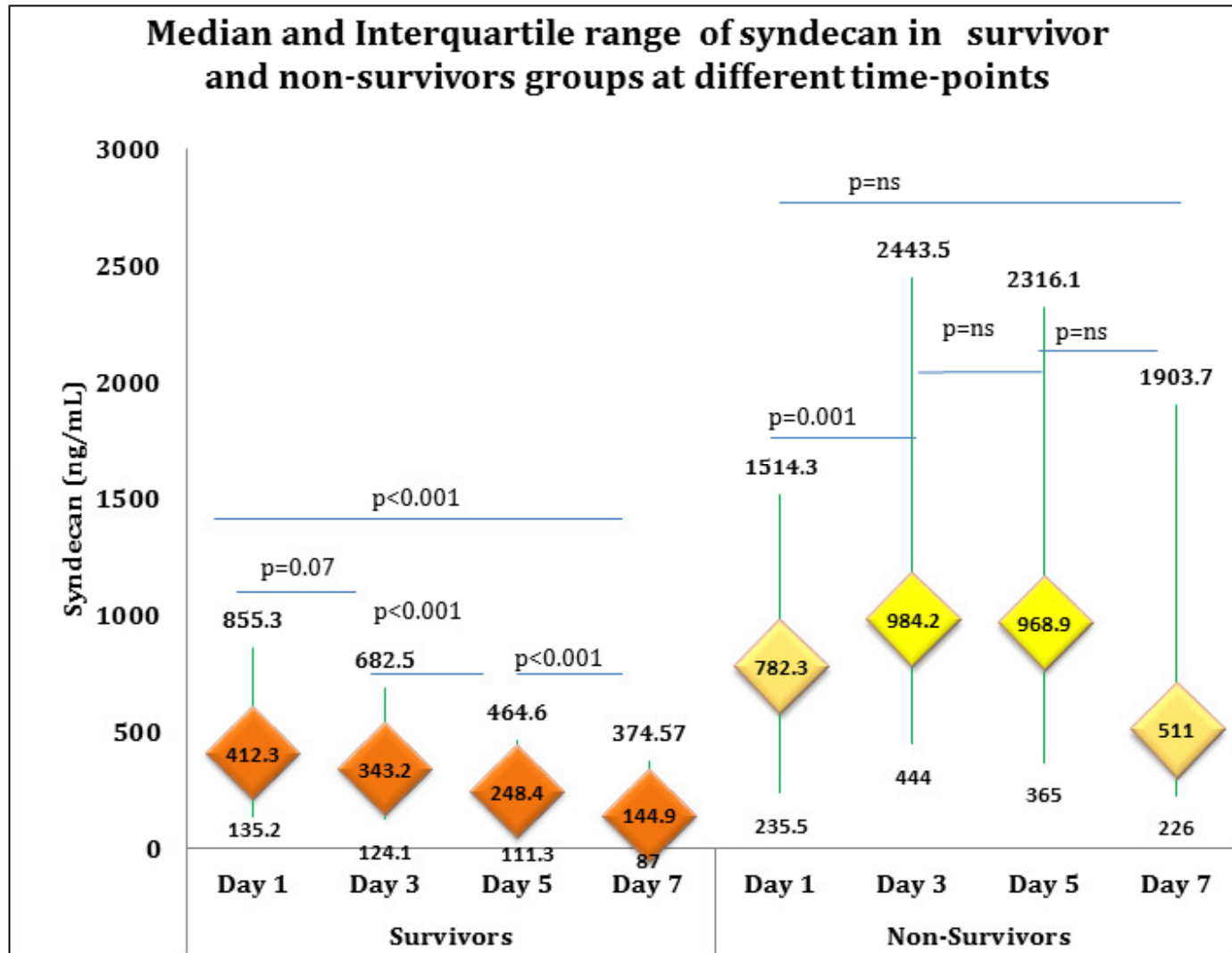


B

A

Median and Interquartile range of hyaluronan in survivor and non-survivors groups at different time-points

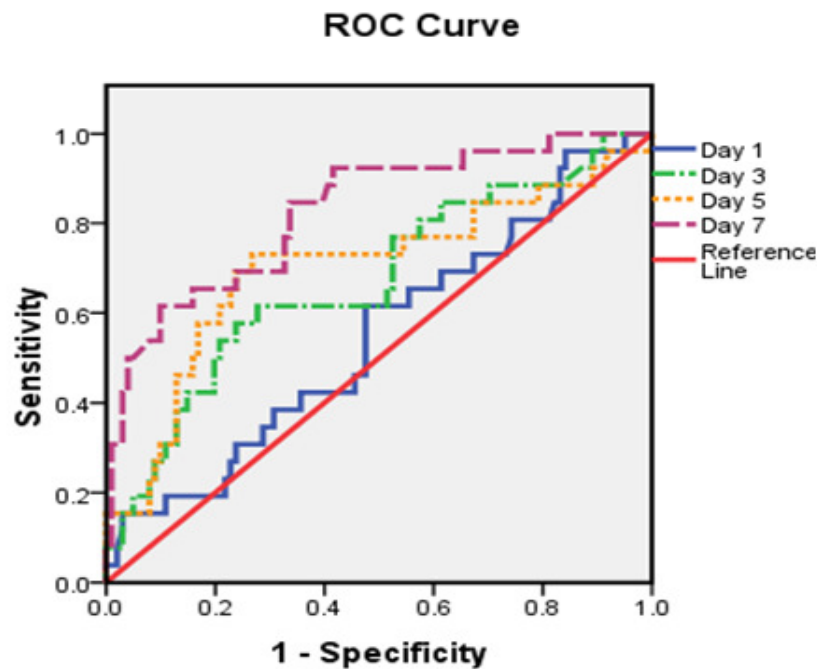


B

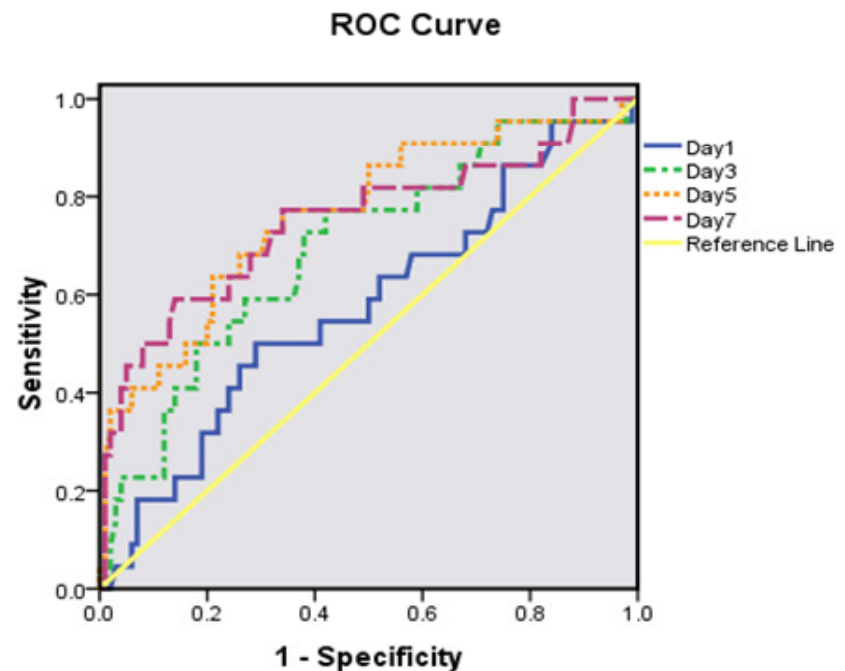
Receiver Operating Characteristic Curve

Receiver Operating Characteristic Curve for Hyaluronan and Syndecan between survivor and non-survivors groups at different time-points

A Hyaluronan



B Syndecan



Receiver Operating Characteristics of Hyaluronan

Survivors vs Non-Survivors

Days	Variable	Cut Off	Sensitivity %	Specificity %	PPV %	NPV %
Day 1	220	0.573 (0.47-0.67)	73	44	33	81.3
Day 3	344	0.671 (0.55-0.79)	64	71.3	47	84
Day 5	321	0.720 (0.61-0.82)	71	76	49.02	89.1 3
Day 7	441	0.827 (0.73-0.91)	61	90	62	90

Receiver Operating Characteristics of Syndecan

Survivors vs Non-Survivors

Days	AUC	Cut Off	Sensitivity %	Specificity %	PPV %	NPV %
Day 1	625	0.644 (0.54-0.74)	56	71	42	81
Day 3	389	0.756 (0.66-0.84)	85.4	55	41.7	91
Day 5	898	0.801 (0.71-0.98)	52.9	94	72	86.3
Day 7	455	0.751 (0.621-0.881)	59	86	48.1	91

Hyaluronan: Association with Mortality, Organ Dysfunction scores and inflammatory markers at all Time-points

Hyaluronan	Day 1	Day 3	Day 5	Day 7
APACHE II	r=0.387 p<0.001			
SOFA	r=0.387 p<0.001	r=0.406 p<0.001	r=0.327 p<0.001	r=0.289 p=0.002
TNF- α	r=0.338 p=0.001	r=0.341 p=0.002	r=0.258 p=0.043	r=0.256 p=0.033
IL-10	r=0.232 p=0.032	r=0.264 p=0.017	r=0.260 p=0.023	r=0.256 p=0.049

Syndecan: Association with Mortality, Organ Dysfunction scores and inflammatory markers at all Time-points

Syndecan	Day 1	Day 3	Day 5	Day 7
APACHE II	r=0.294 p<0.001			
SOFA	r=0.437 p<0.001	r=0.354 p=0.003	r=0.494 p<0.001	r=0.217 p=0.026
TNF- α	r=0.234 p=0.029	r=0.321 p=0.010	r=0.382 p=0.001	p=ns
IL-10	r=0.215 p=0.05	r=0.229 p=0.050	r=0.354 p=0.004	r=0.266 p=0.044

Summary

Serum levels of Hyaluronan and Syndecan

Serum levels on admission categorize the patient into sepsis, severe sepsis and septic shock

Both markers show a significant positive correlation with –

- Organ dysfunction
- Mortality scores
- Pro- & Anti-inflammatory markers

Serial measurements differentiate survivors from non-survivors with the following:

	Cut-off	Specificity	NPV
H	441 ng/ml	90%	90%
S	898 ng/ml	94%	86%

Conclusions

- **Glycocalyx components [hyaluronan and syndecan] could be used for diagnosis i.e. to differentiate between sepsis, severe sepsis and septic shock.**
- **Hyaluronan and syndecan could also be used for prognosis i.e. to identify survivors and non-survivors.**
- **Required: Further multicentric studies on these as well as other glycocalyx components to demonstrate comparative clinical utility of these markers. Also this would give further direction as to the usefulness of therapy targetting these markers**

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Patients

Enrolled subjects

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THANK YOU