

# Presepsin workshop Evaluation Results in Japan

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Yoshikazu Okamura  
Research and development division  
Mitsubishi Chemical Medience Corporation  
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## What is presepsin ?

- sCD14-ST was renamed as “**presepsin**” in 2011.
- Soluble CD14-subtype (sCD14-ST) is a 13-kDa protein that is a truncated N-terminal fragment of CD14
  - CD14 is the receptor for lipopolysaccharide (LPS)/LPS binding protein (LBP) complexes

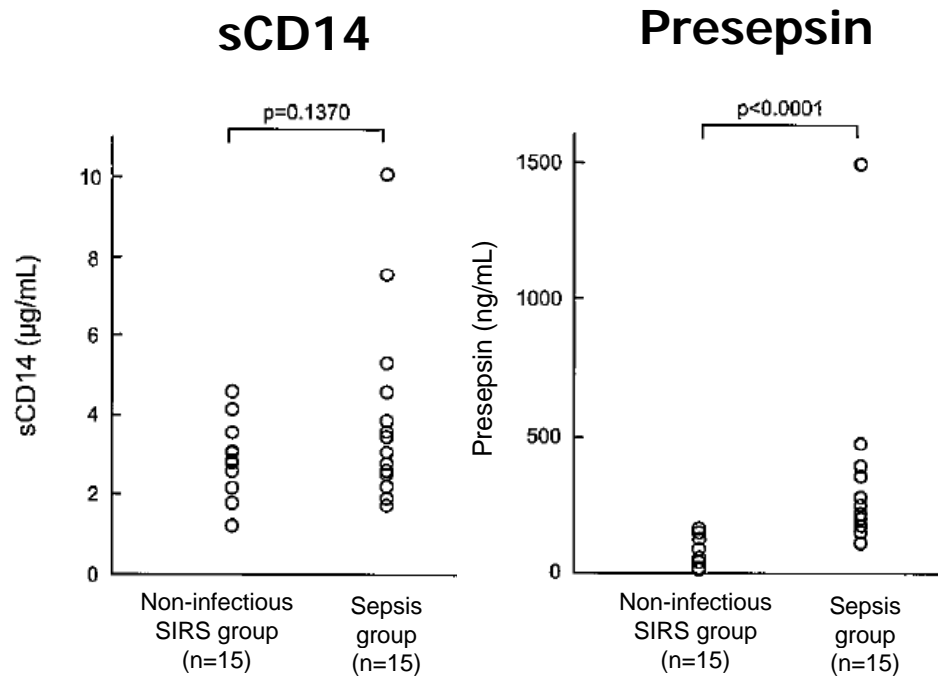


## History of presepsin (sCD14-ST)

- 1989~ Conventional sCD14 assays are available.
- 2002 Assay kit (ELISA) and antibody of low-molecular weight CD14 (sCD14-ST, presepsin) whose levels increase specifically in the blood of sepsis patients was developed. (Shirakawa et al.)
- **2003** **The usefulness of presepsin for the diagnosis of sepsis was published.**  
**(S. Endo et al. Iwate Medical Univ.)**
- 2005 Presepsin molecule was identified.
- 2009 PATHFAST Presepsin for POCT use was developed
- **2011** **“PATHFAST Presepsin” was launched.**

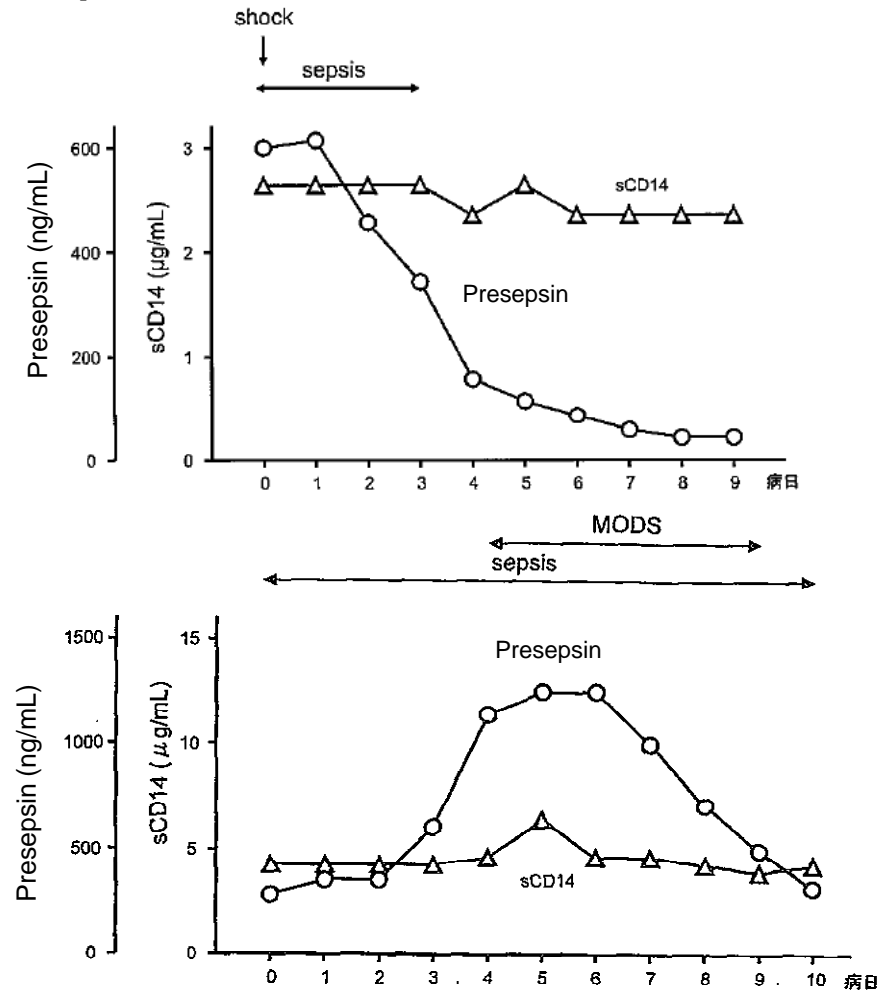
# Comparison of presepsin with sCD14

## Distribution of conventional sCD14, and presepsin in patients with non-infectious SIRS, and sepsis



Reference: Endo S et al., Medical Postgraduates 44:381-385,2006

## Time course of presepsin in sepsis patient

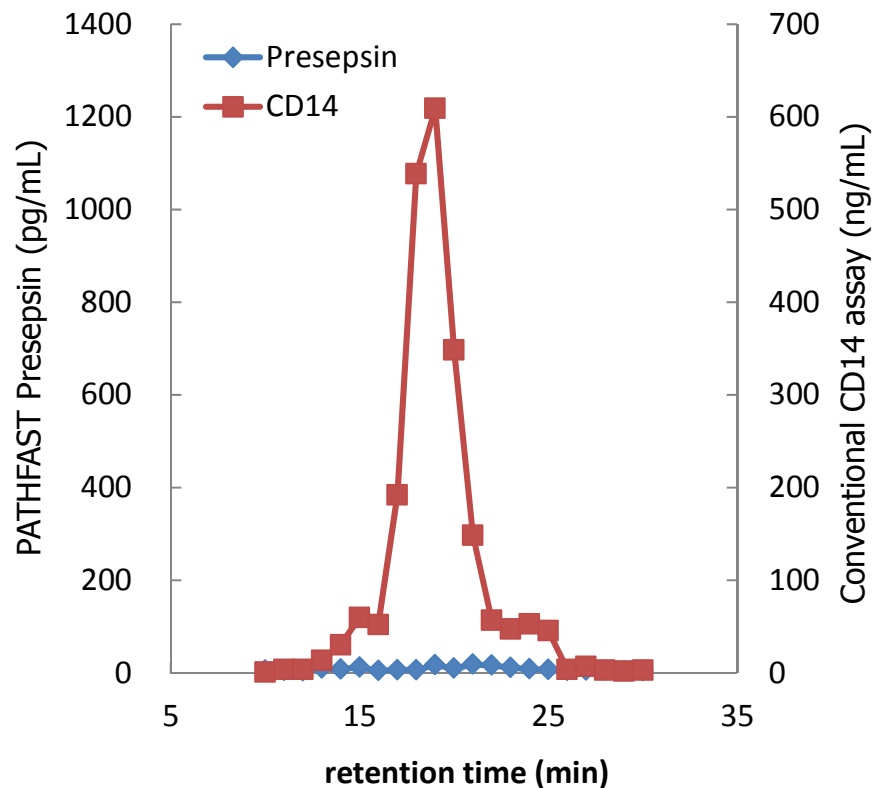


**Presepsin assay was superior to diagnose sepsis in comparison with conventional sCD14-ELISA.**



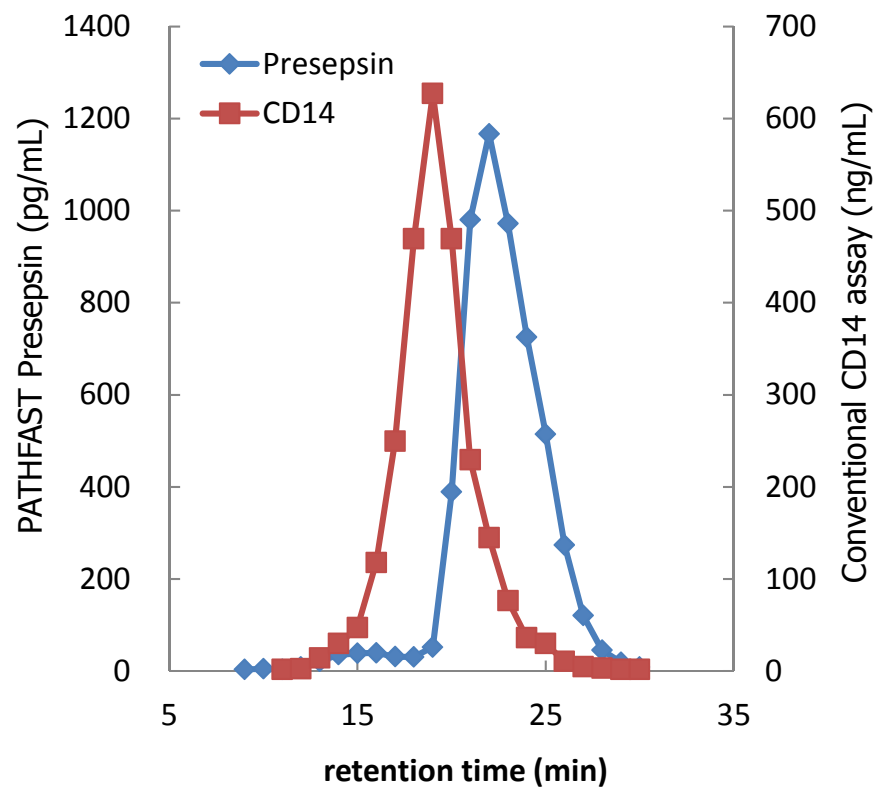
# Gel filtration of normal and patient samples

## Normal



CD14 : 4.76 ug/mL  
Presepsin: 105 pg/mL

## Patient



CD14 : 2.98 ug/mL  
Presepsin: 8048 pg/mL

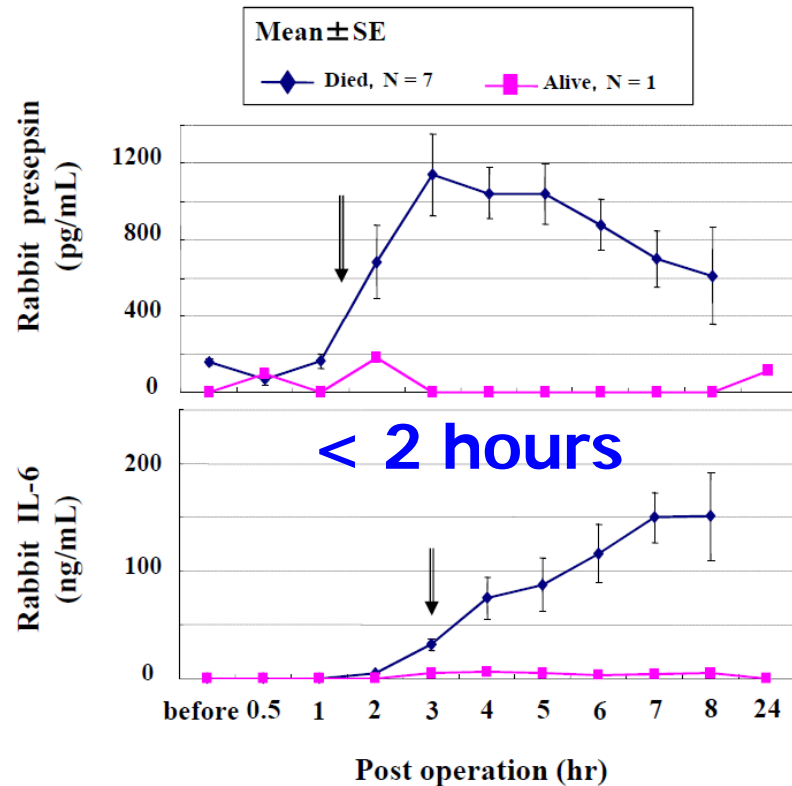
**PATHFAST detected presepsin significantly.**



# Kinetics and half-life of presepsin in blood

## Induction time

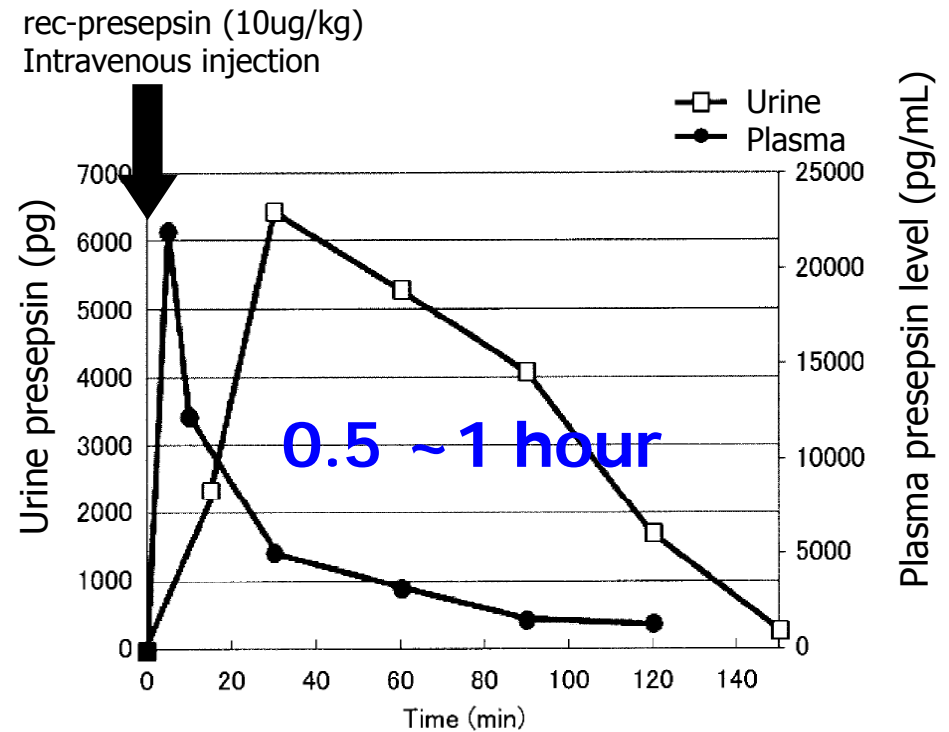
(Model: Cecal ligation and puncture (CLP) sepsis rabbit model)



Reference: Katsuki Naitoh et al., Poster of SEPSIS 2010

## Half-life

(Model: Normal beagle dog)



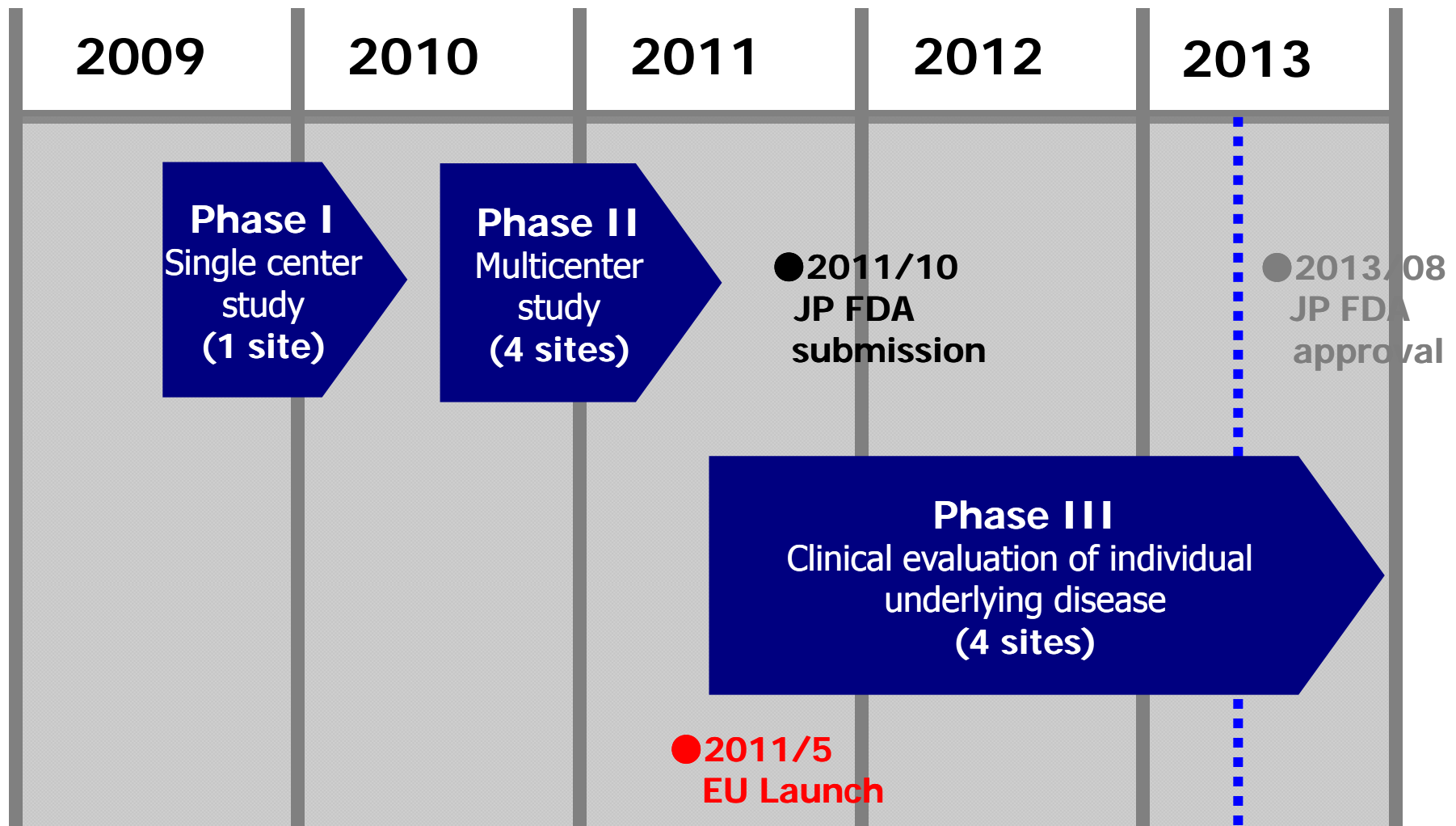
Reference: Shirakawa K. PCT patent WO 2012/157751 A1

- The presepsin levels were elevated sharply prior to IL-6.
- Presepsin protein was mainly metabolized in the kidney.



# Time table of clinical evaluation of PATHFAST Presepsin in Japan

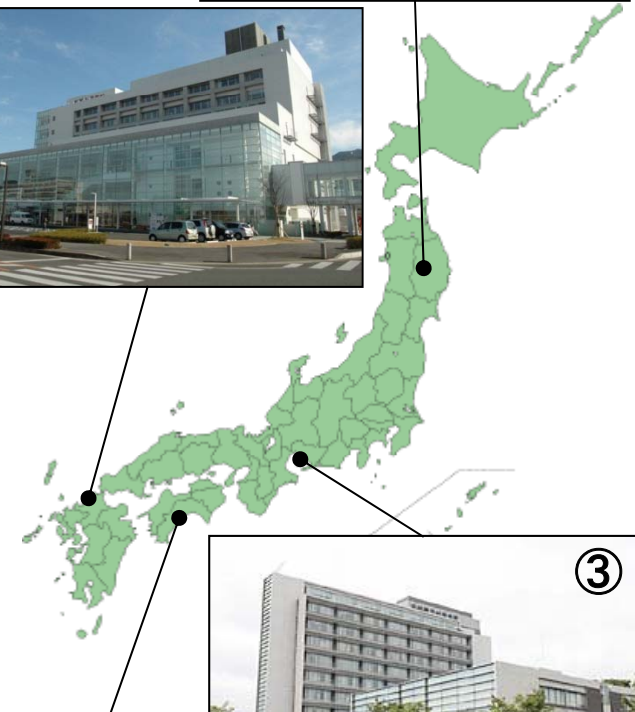
(year)





# Evaluators in Japan

- ① **Shigeatsu Endo, MD, Professor**
  - Department of Critical Care Medicine, Iwate Medical University
  - Past chairperson of the Japanese Association for Acute Medicine (JAAM)
- ② **Hiroyasu Ishikura, MD, Professor**
  - Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University
- ③ **Masanao Miura, MD**
  - Anesthesiology, Emergency and Critical Care Center, Kariya Toyota General Hospital
- ④ **Yasuo Fukui, MD**
  - Department of Gastroenterological Surgery, Kochi Health Sciences Center







## **Outcome of presepsin clinical study in Japan (2009-2013)**

- **Diagnosis of sepsis**
- **The assessment of the degree of septic severity**
- **Monitoring of sepsis patients**
- **Monitoring of patients with the following diseases**
  - Following surgical trauma
  - Severe mechanical trauma
  - Severe burns

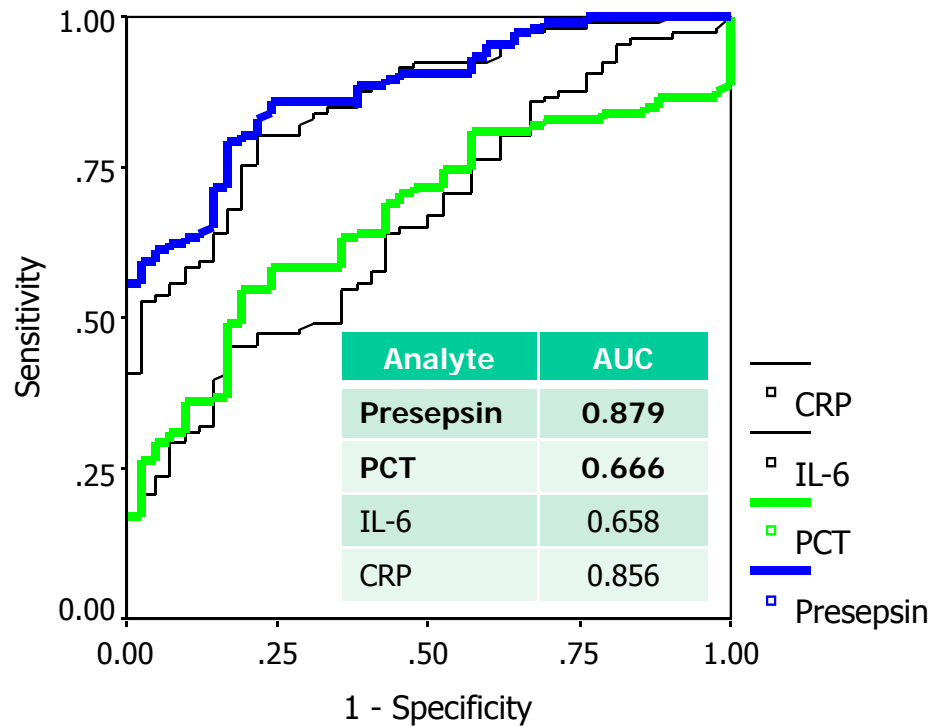


# [Diagnosis of sepsis]

## ROC analysis

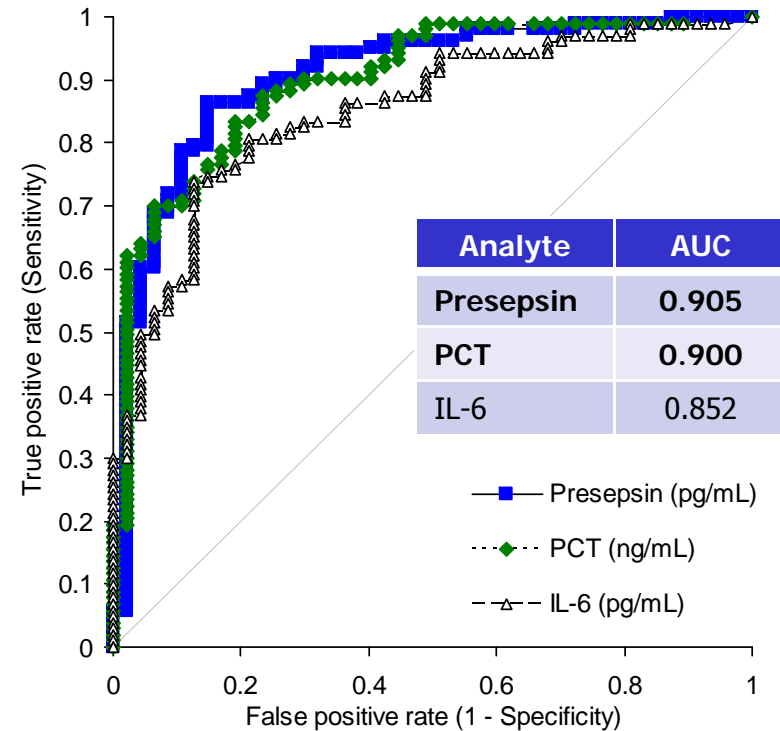
### Phase I single center study

Non-infectious SIRS group : n=41  
Sepsis group : n=101



### Phase II multicenter study

Non-infectious SIRS group : n=47  
Sepsis group : n=103



J Infect Chemother. 2011, 17(6); 764-769.

**AUC of presepsin was higher than PCT in two clinical studies.**



# 【Diagnosis of sepsis】

## Determination of cut-off level

SIRS group (n=47) vs Sepsis group (n=103)

### Phase II multicenter study

Analyte	Cut-off	Sensitivity	Specificity	Efficiency	Positive predictive value	Negative predictive value
Presepsin	500 pg/mL	94.2%	68.1%	86.0%	86.6%	84.2%
PCT	0.5 ng/mL	88.3%	72.3%	83.3%	87.5%	73.9%
Presepsin	1000 pg/mL	68.0%	93.6%	76.0%	95.9%	57.1%
PCT	2.0 mg/mL	68.0%	93.6%	76.0%	95.9%	57.1%

### Cut-off value

<b>Presepsin</b>		<b>PCT</b>
<b>500 pg/mL</b>	≐	<b>0.5 ng/mL</b>
<b>1000 pg/mL</b>	≐	<b>2.0 ng/mL</b>

# 【Diagnosis of sepsis】

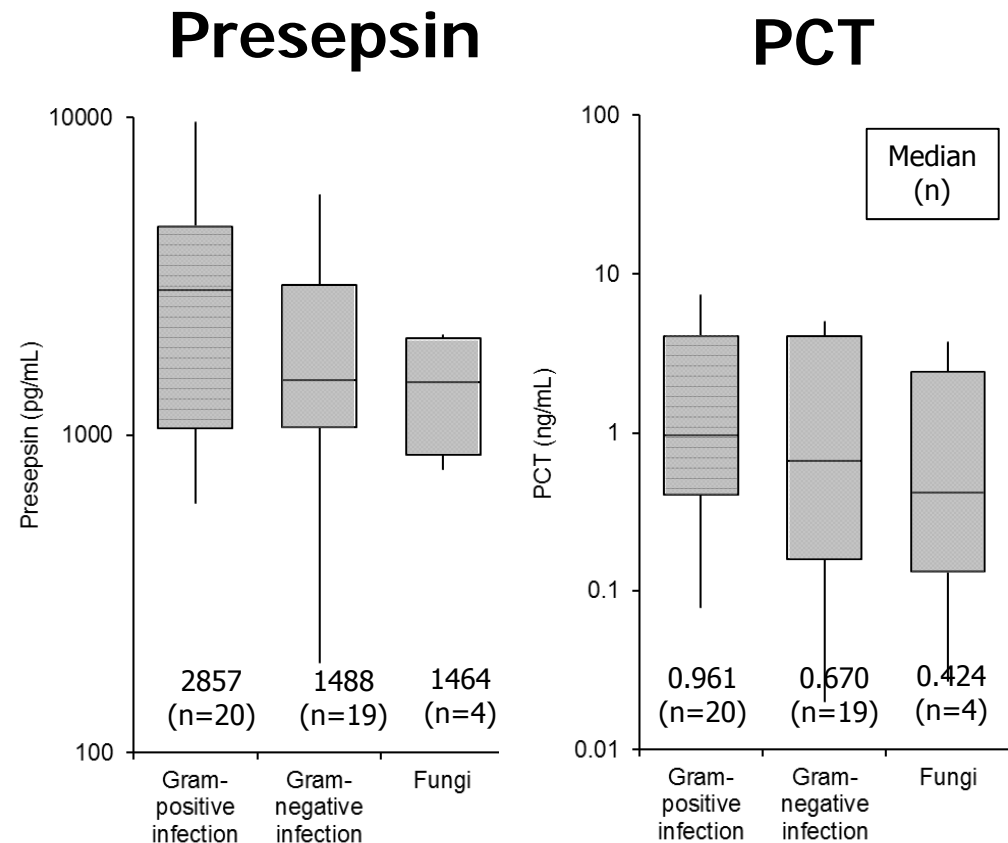
## Sensitivity of presepsin using blood culture as positive control

Phase III clinical evaluation

\* The result published by Y. Fukui in 2013

In patients admitted hospital with blood culture positive (n=43)

Type of infection	Presepsin		PCT	
	600 pg/mL		0.5 ng/mL	
	Ratio	n	Ratio	n
Gram-positive infection	95.0%	19/20	50.0%	10/20
Gram-negative infection	100%	19/19	68.4%	13/19
Fungi	100%	4/4	50.0%	2/4
Total	97.6%	42/43	58.1%	25/43

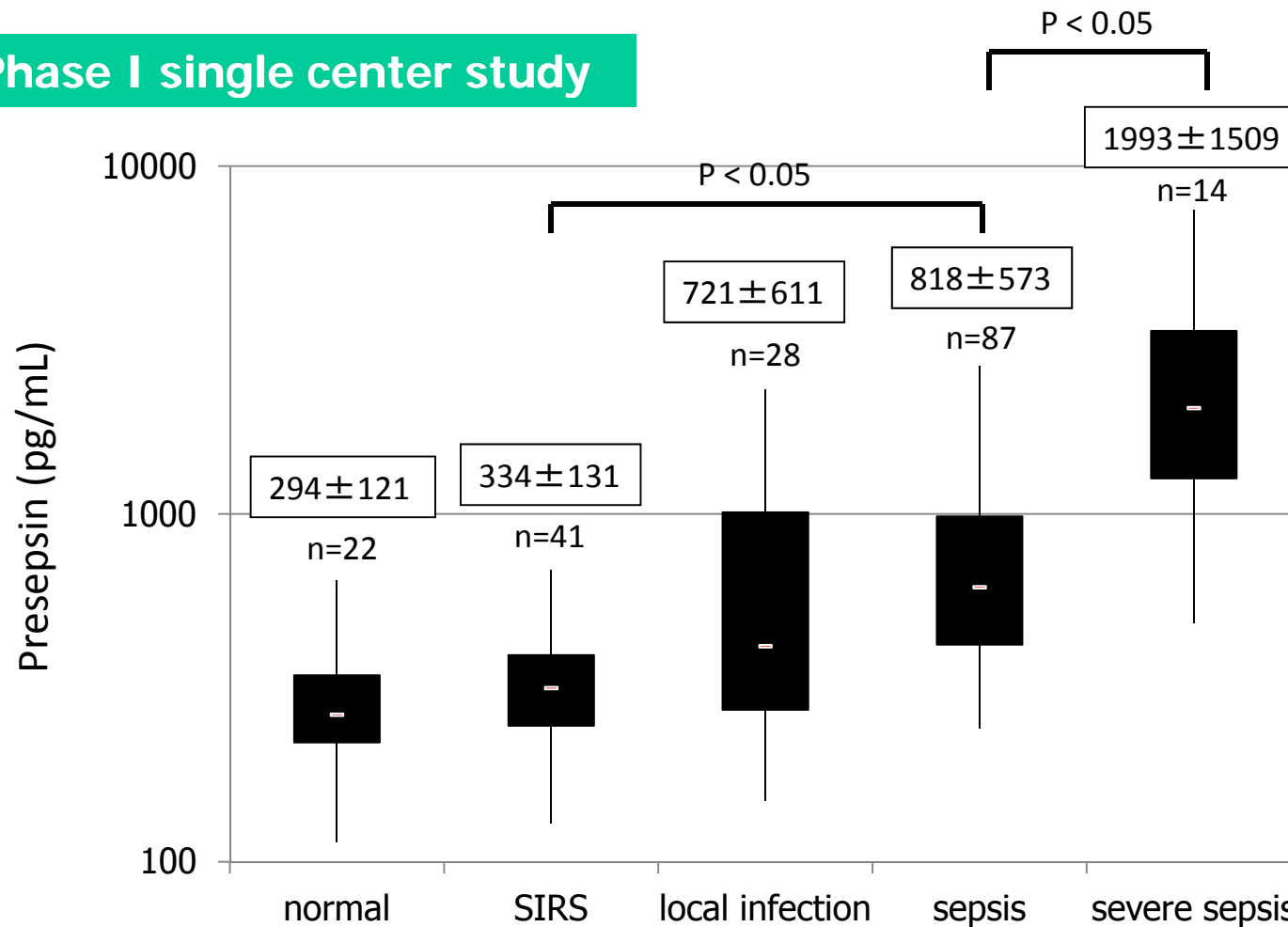


Presepsin showed significantly higher concordance with blood culture than PCT.

# 【The assessment of the degree of septic severity】

## Presepsin values in each disease phase

### Phase I single center study

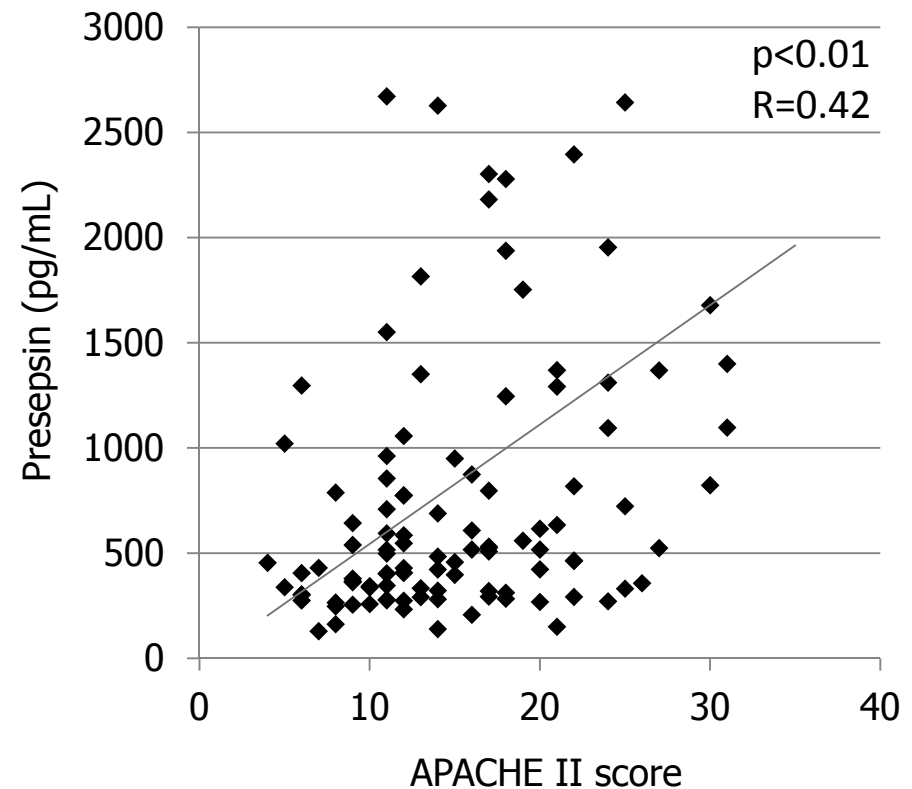
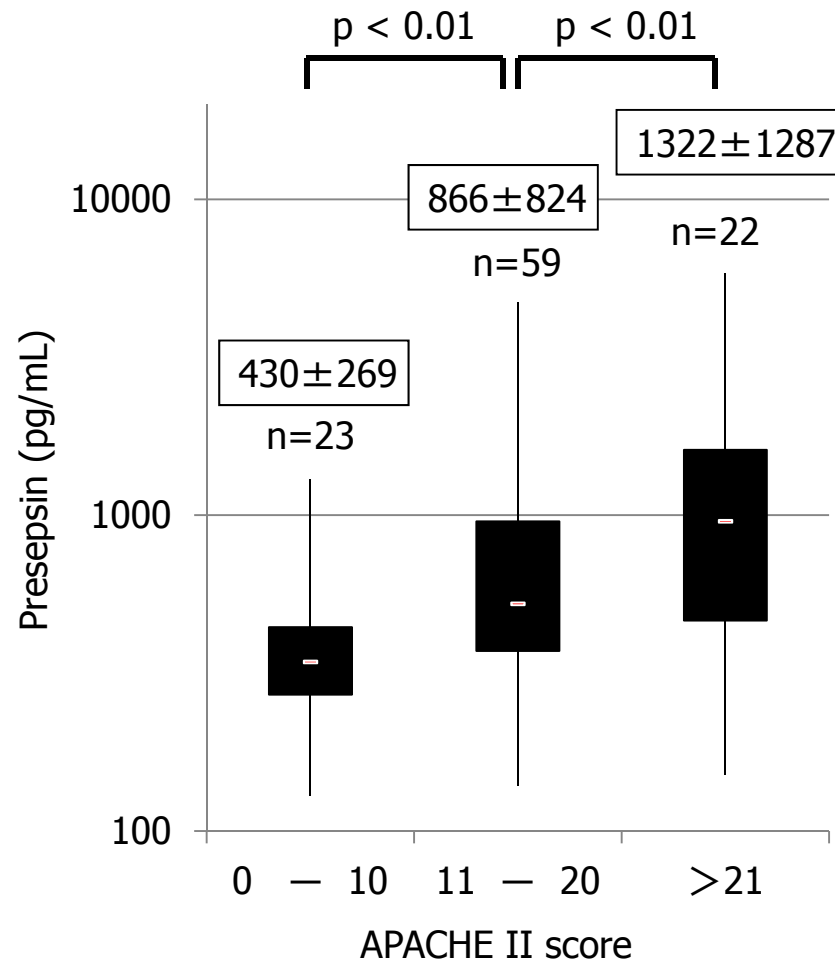


J Infect Chemother. 2011, 17(6); 764-769.

**Presepsin reflected the degree of septic severity.**

# 【The assessment of the degree of septic severity】 Relevance between presepsin and severity scores

## Phase I single center study



J Infect Chemother. 2011, 17(6); 764-769.

**Presepsin correlated well with APACHE II score used as septic severity.**

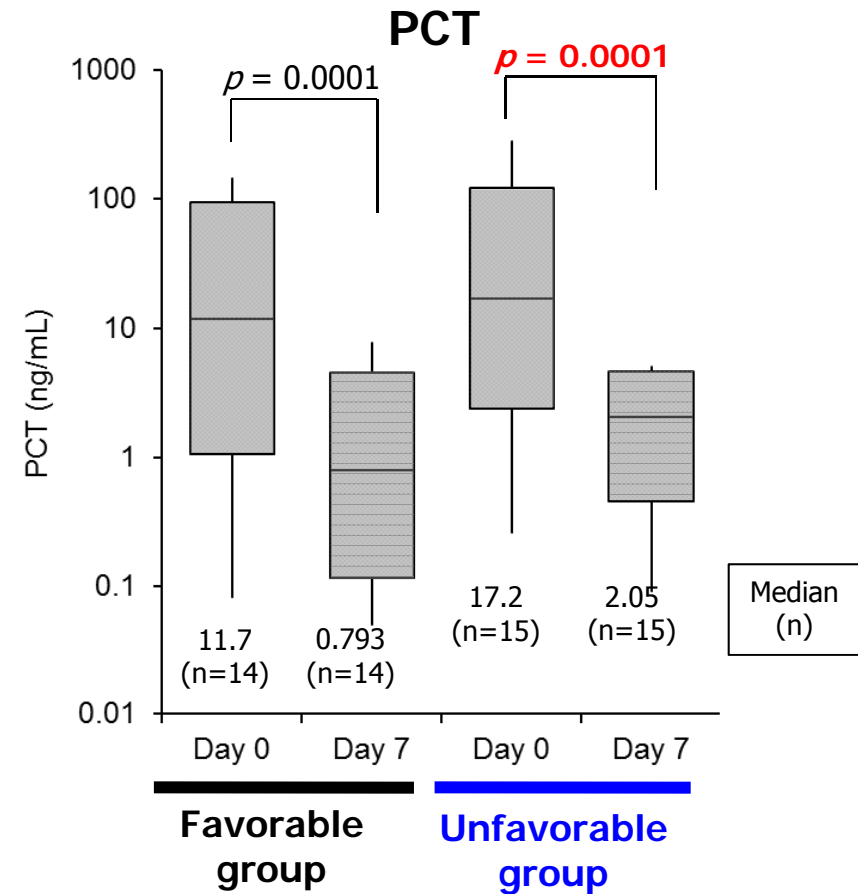
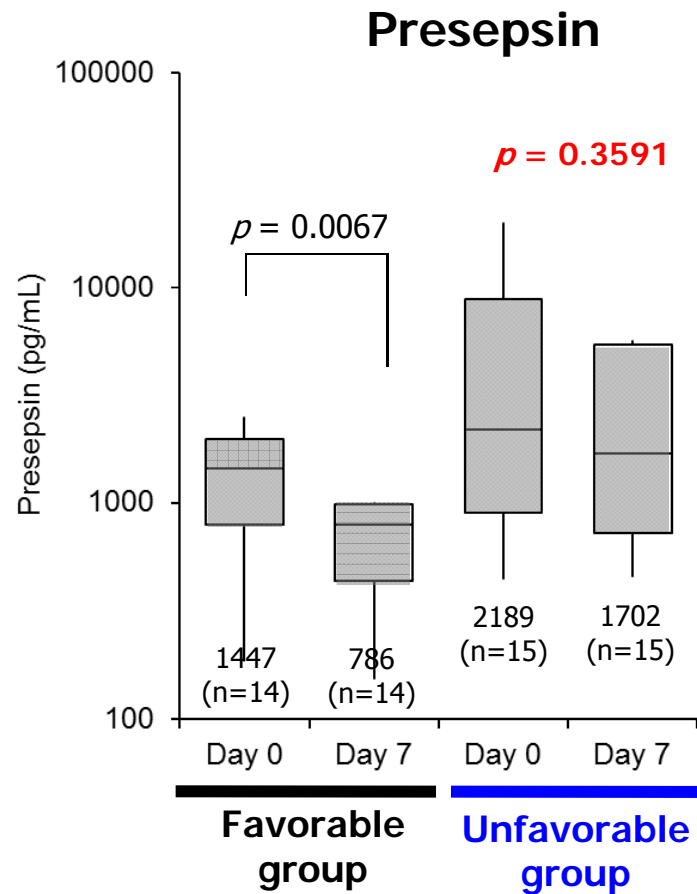
# Monitoring of sepsis patients

## Relevance of SIRS criteria and biomarkers during follow-up

### Phase III clinical evaluation

\* The result published by A. Murai in 2013

**Favorable prognosis group** : Septic patients with SIRS criteria < 2 on day7  
**Unfavorable prognosis group**: Septic patients with SIRS criteria ≥2 on day 7



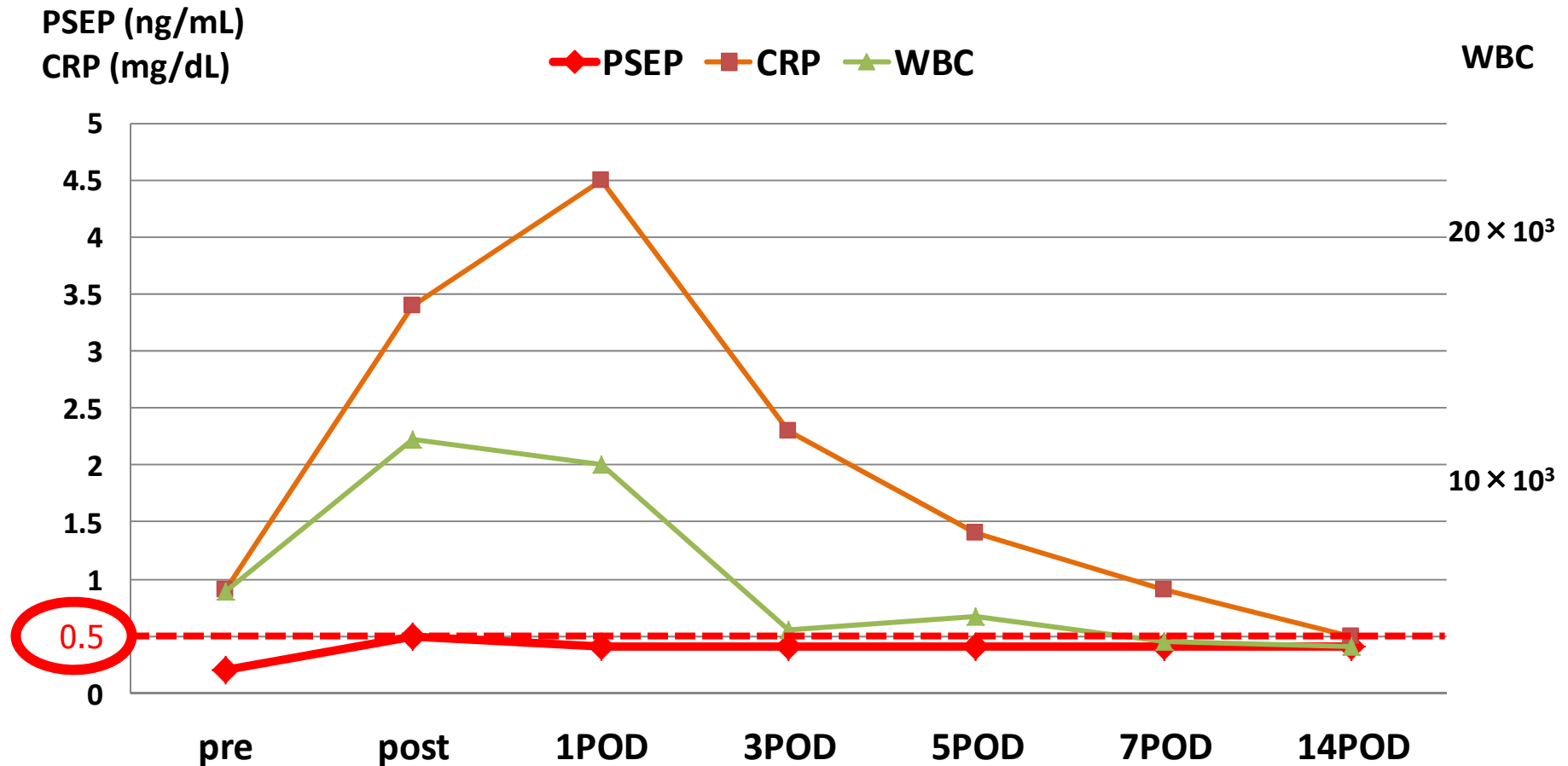
15 Presepsin reflected clinical condition of septic patients during follow-up.



# Non-infectious spine scoliosis surgery patients (n=12)

Phase III clinical evaluation

\* The result published by G. Takahashi in 2013



Unlike CRP and WBC, presepsin wasn't affected under severe surgical condition.

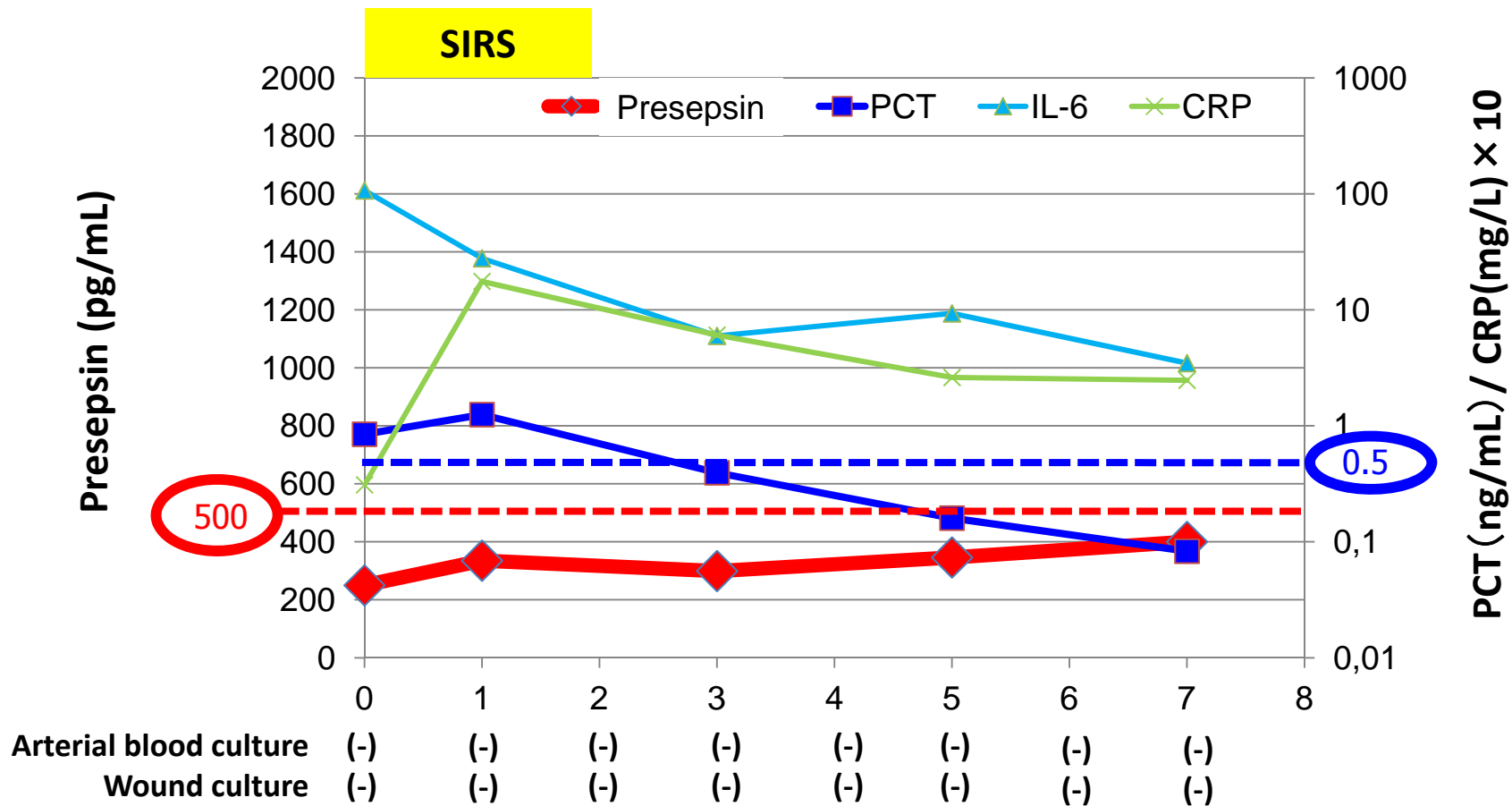


# Trauma

## Phase III clinical evaluation

\* The result published by G. Takahashi in 2013

<b>Case</b>	Age: 19	APACHE II score: 22	Temperature	38.7 °C
	Sex: men	SOFA score: 7	heart rate	89 /min
	Multiple trauma		respiratory rate	18 /min
			WBC	30100 mm <sup>3</sup>



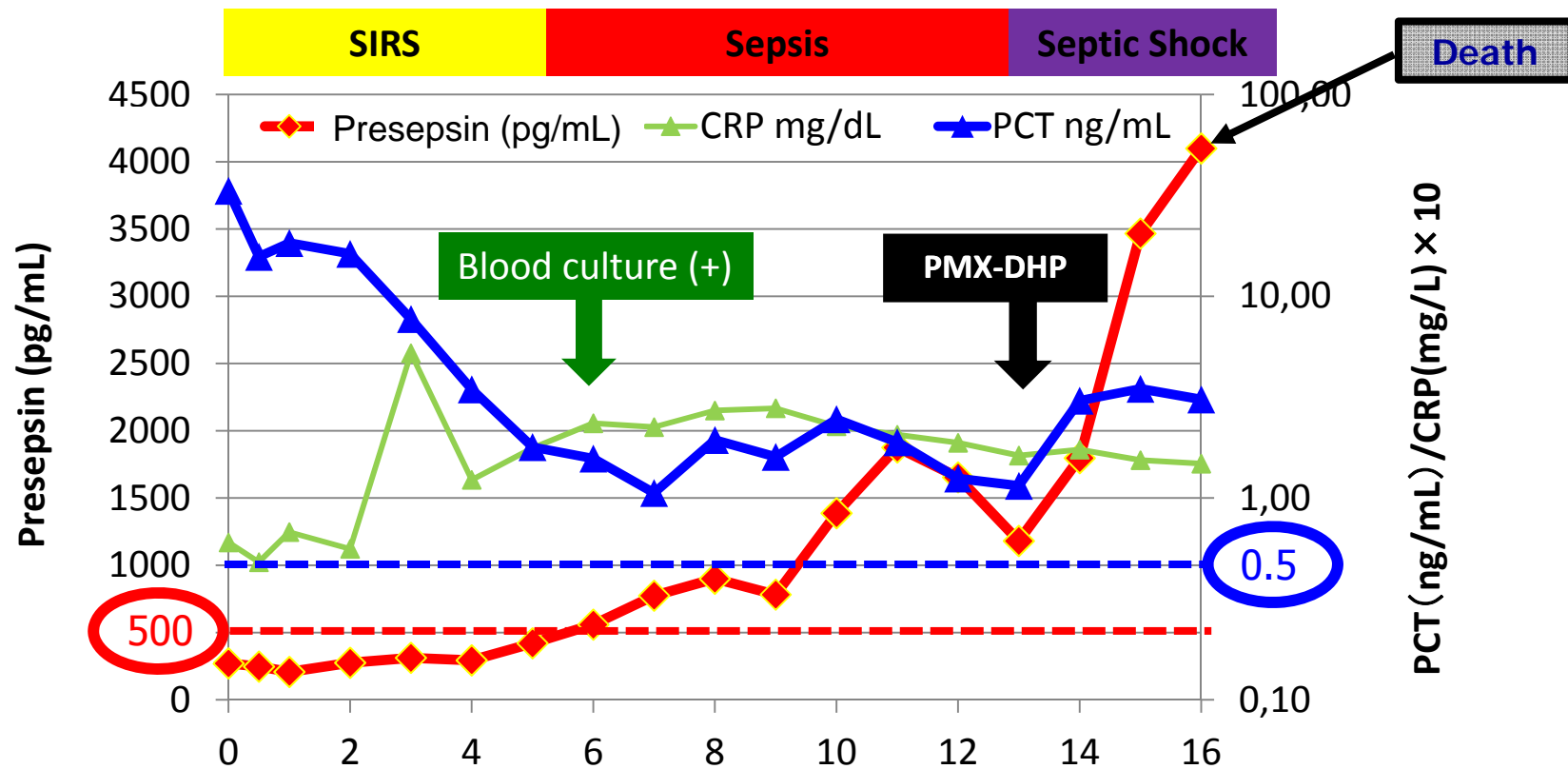
Unlike PCT, IL-6 and CRP, presepsin wasn't affected under severe trauma.

# Severe burn

## Phase III clinical evaluation

\* The result published by G. Takahashi in 2013

<b>Case</b>	Age: 83	APACHE II score: 24	Temperature	38.4 °C
	Sex: female	SOFA score: 7	heart rate	122 /min
	55% of body was burned. (burn index 50)		respiratory rate	36 /min
			WBC	21850 mm <sup>3</sup>

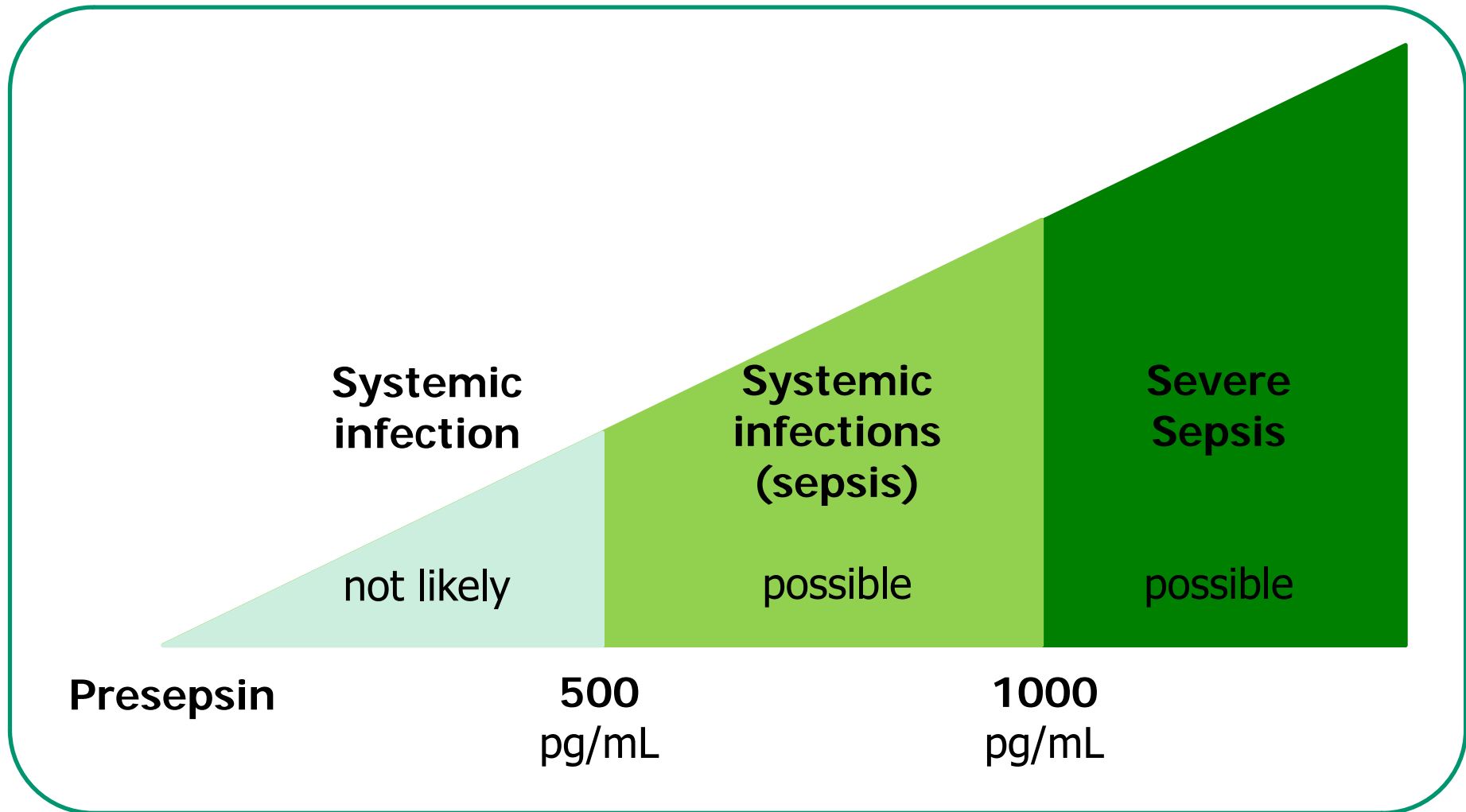


Arterial blood culture	(-)	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(+)
Wound culture	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(+)	(+)

Unlike PCT and CRP, presepsin wasn't affected under severe burn.



# Recommended cutoff values for PATHFAST Presepsin assay at admission to ER





# Comparison of presepsin with PCT

Property	Presepsin	PCT
Molecular weight	13 kDa	13 kDa
Expression	Granulocyte	Parenchymal cells (e.g. liver, kidney, adipocytes and muscle)
Induction factor	Bacteria (not LPS)	Bacteria, cytokine, LPS etc.
Induction time after the inflammatory response	< 2 hour	2 ~ 3hour
Half-life	0.5 ~ 1.0 hour	20 ~ 24 hour
Disease specificity	Infection and sepsis	Infection, sepsis, severe trauma, severe burn etc.

- Secretion of presepsin may be triggered by microbial infection.
- The presepsin levels may be elevated prior to PCT.



# Conclusions

- Presepsin is a powerful monitoring tool for diagnosis and prognosis of sepsis.
- Presepsin is a highly specific marker for diagnosis of sepsis in comparison with PCT, IL-6 and CRP.
- **PATHFAST Presepsin that have the following features is a new tool for the early diagnosis of sepsis.**
  - Assay time: 17min
  - Using whole blood
  - Detecting presepsin level of healthy volunteer



# Acknowledgement

- **Shigeatsu Endo, MD, Professor**
  - Department of Critical Care Medicine, Iwate Medical University
- **Hiroyasu Ishikura, MD, Professor**
  - Department of Emergency and Critical Care Medicine, Faculty of Medicine, Fukuoka University
- **Masanao Miura, MD**
  - Anesthesiology, Emergency and Critical Care Center, Kariya Toyota General Hospital
- **Yasuo Fukui, MD**
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