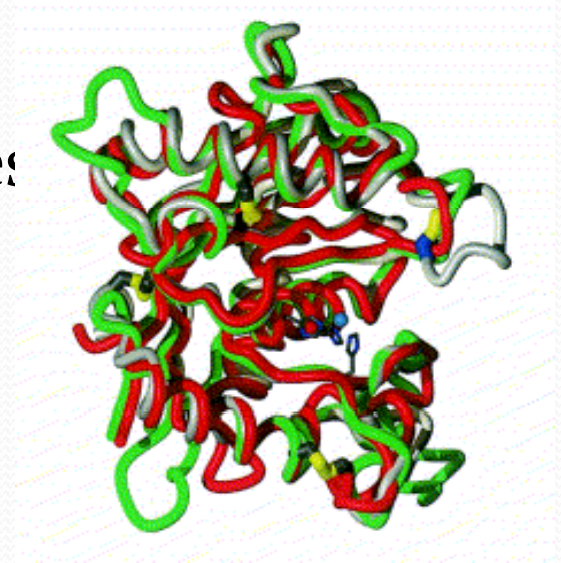


Deficiency Of ADAMTS-13 in Pediatric Patients With Severe Sepsis

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Adil, Anwar-ul-Haq

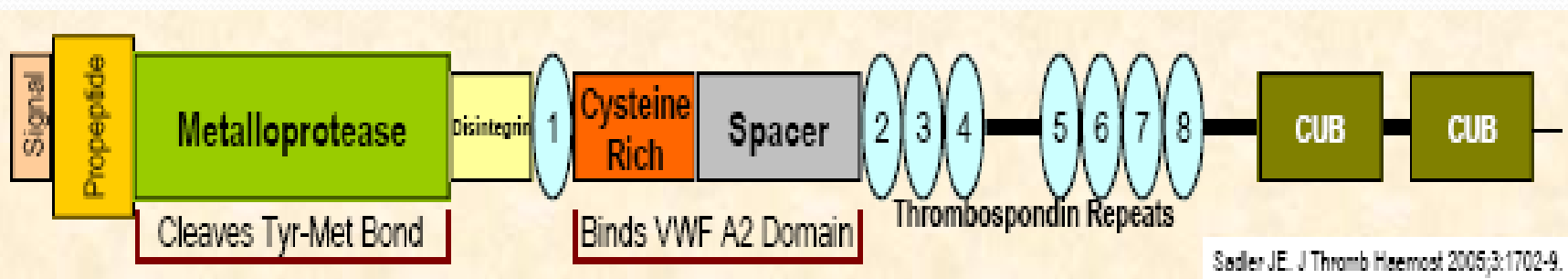
Introduction

- ADAMTS-13 = A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif
- “The molecule formerly known as vWf-CP”
- Processes vWf multimers and cleaves thrombogenic potential

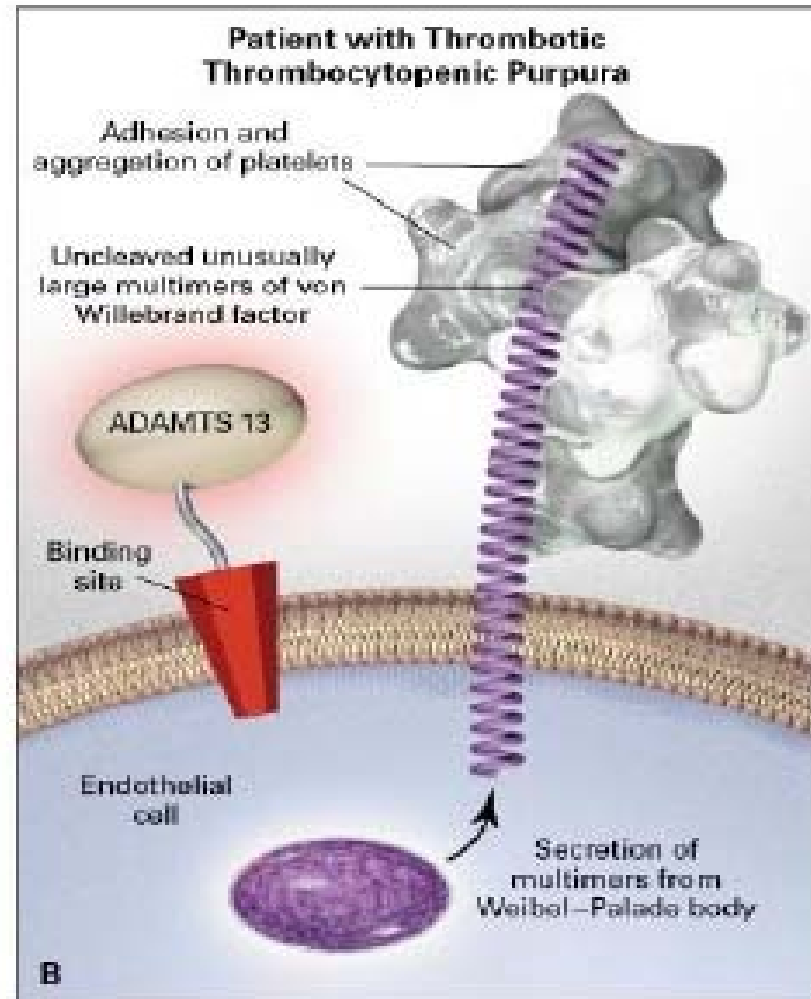
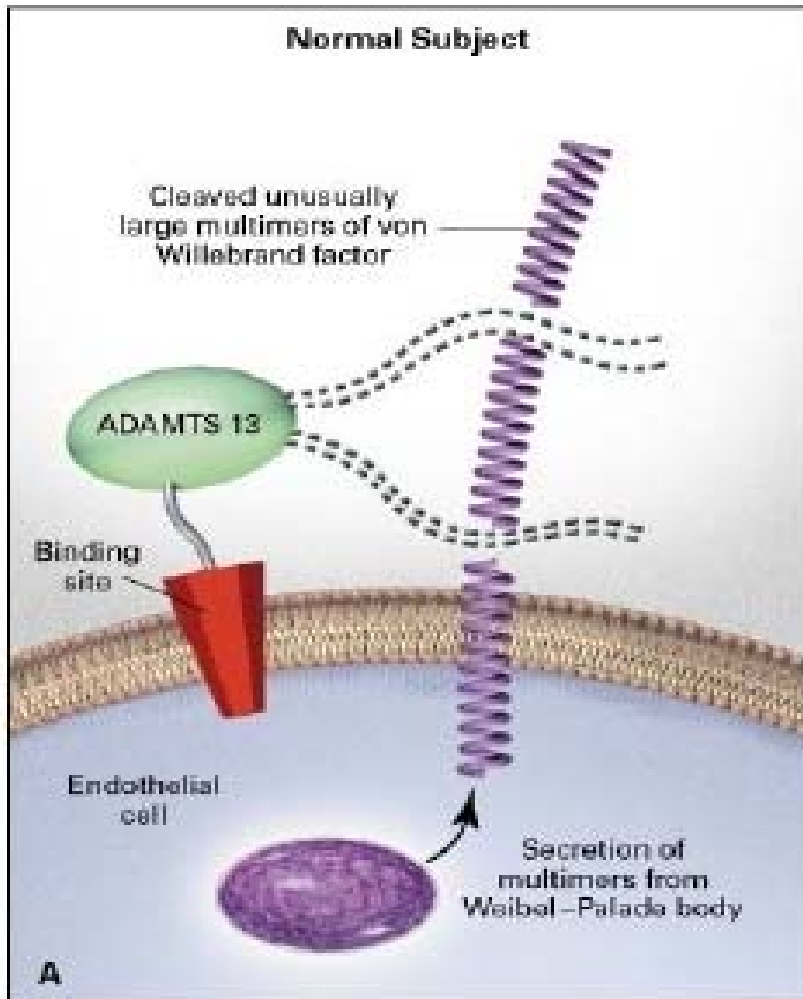


Introduction

- Synthesized in liver and endothelial cells as a zymogen and becomes activated upon propeptide cleavage.
- Plasma half-life is ~ 2-3 days
- Cleaves its substrate, von Willebrand Factor (VWF), in the A2 domain at Tyr₁₆₀₅—Met₁₆₀₆



Role Of ADAMTS-13 In Normal And Disease States





Link Of ADAMTS-13 With Sepsis

- Abnormalities of vWf cleaving protease.
- Disseminated platelet-rich thrombi in the microcirculation.
- Thrombotic microangiopathy (TMA)
→ predispose to MOF



Objective

- To evaluate ADAMTS-13 levels in pediatric patients with severe sepsis.
- To determine outcome of pediatric patients with severe ADAMTS-13 deficiency.



Materials And Methods

- Study setting: Aga Khan University Hospital, karachi.
- Study design: observational study.
- Study period: October 2008 – March 2009



- Inclusion criteria:

- Pediatric patients with age 1 day to 15 years.
- Diagnosed as severe sepsis according to criteria of Critical Care Consensus Conference Committee 2005.

- Exclusion criteria:

- Blood product transfusion within a week of sample collection.
- Known thrombotic or bleeding disorder.

Definition of Severe Sepsis

Table 2. Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock

SIRS^a

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core^b temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$.
- Tachycardia, defined as a mean heart rate >2 sd above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1 yr old: bradycardia, defined as a mean heart rate <10 th percentile for age in the absence of external vagal stimulus, β -blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.
- Mean respiratory rate >2 sd above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or $>10\%$ immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Table 4.

Variables:

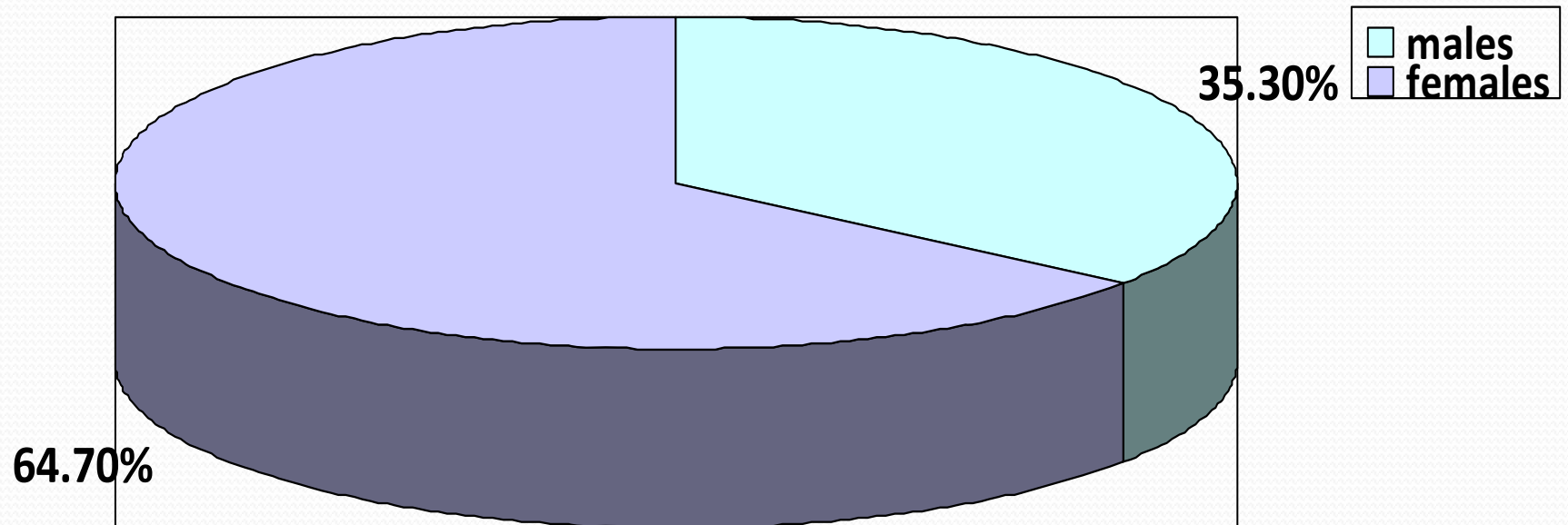
- Age
- Gender
- ADAMTS-13 levels:
 - ELISA technique (IMUBIND by American Diagnostica)
 - Normal range: 650-850 ng/dl




Results

- Sample size : 17 patients
- Age (Median) : 1.5 years
(Range: 2 months- 15 years)

Gender (n=17)

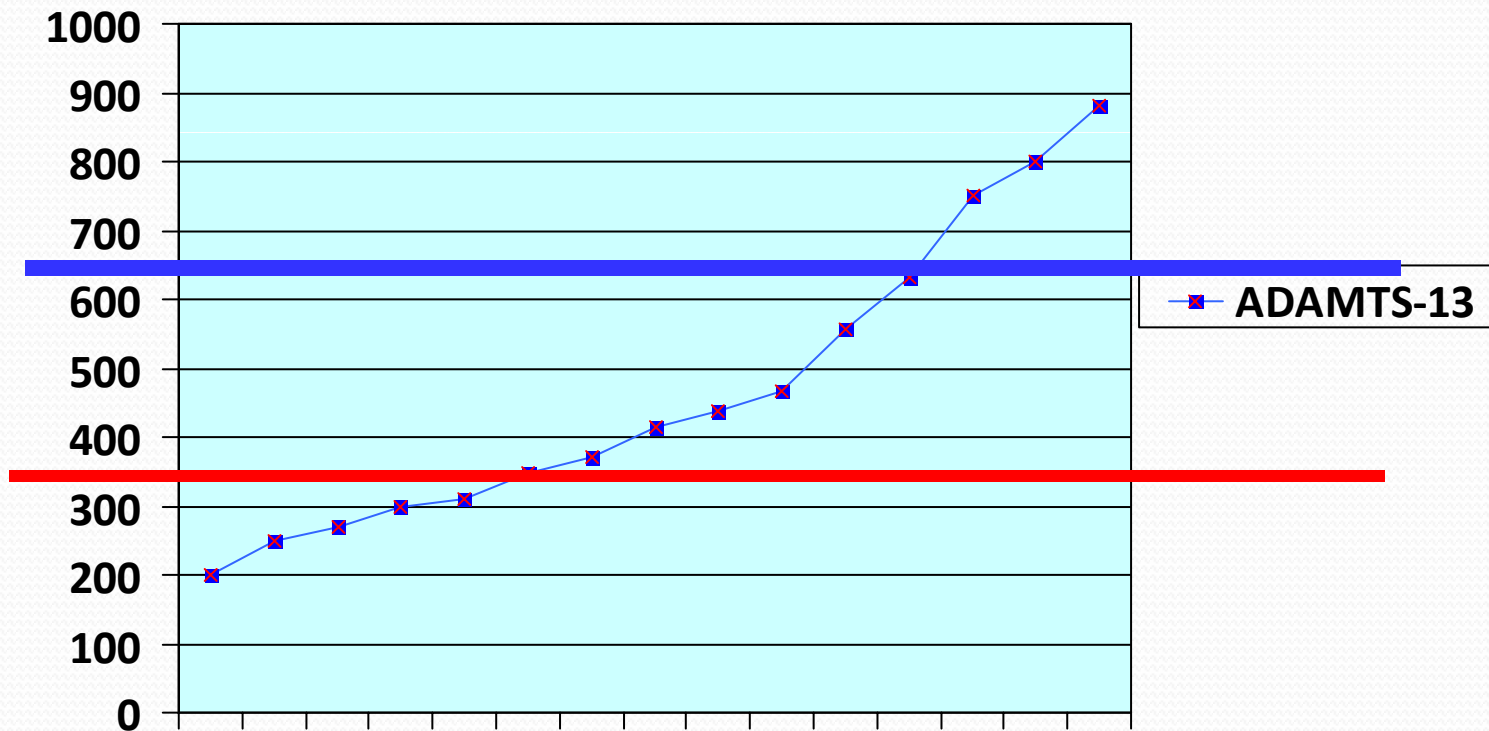




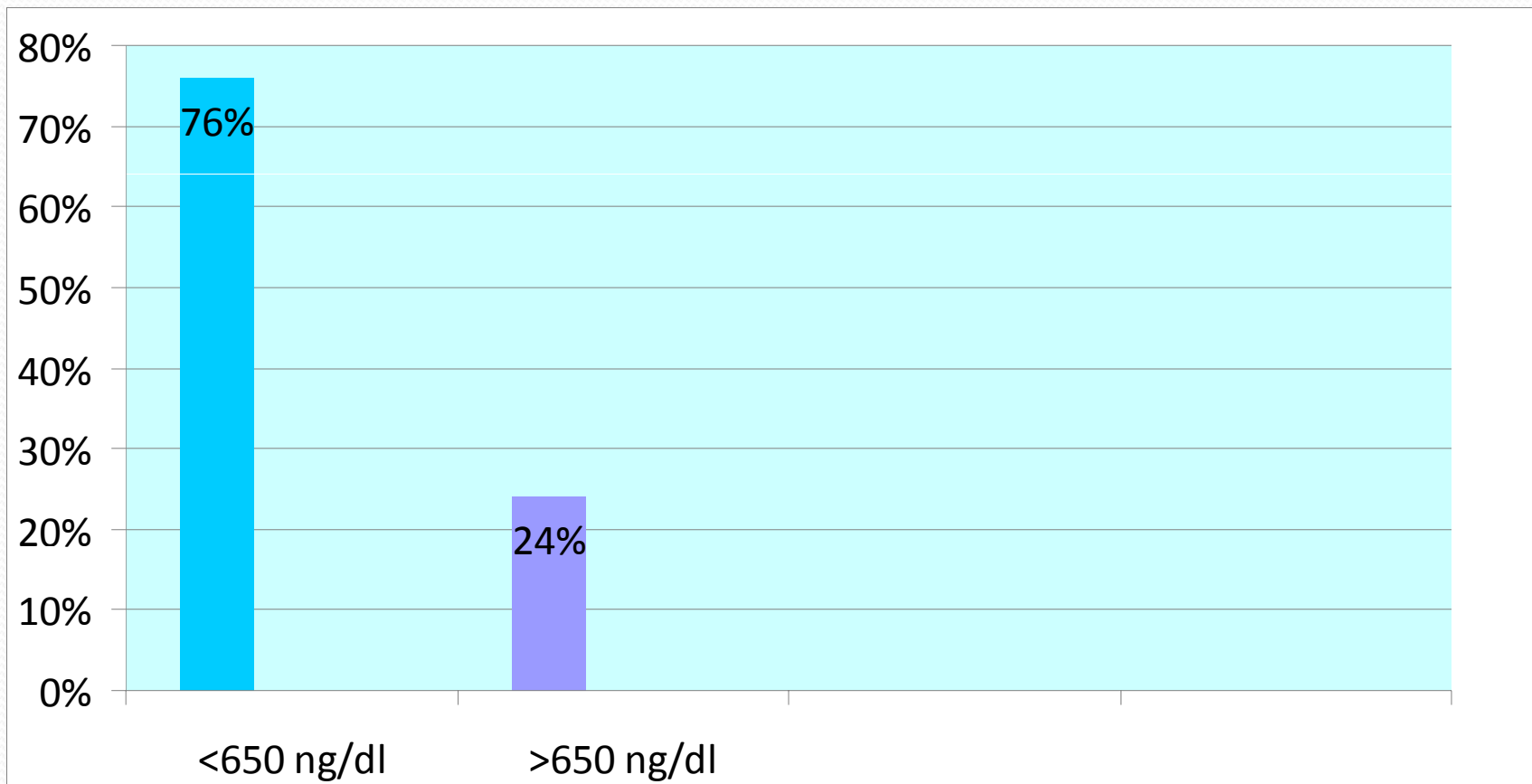
Laboratory parameters of patients (n=17)

	Mean (Range)
Hemoglobin (g/dl)	10.9 (5.4-15.0)
White blood count $\times 10^9/l$	19.7 (4.7-56.1)
Platelets $\times 10^9/l$	269 (15-771)
LDH IU/l	1576 (630-2519)

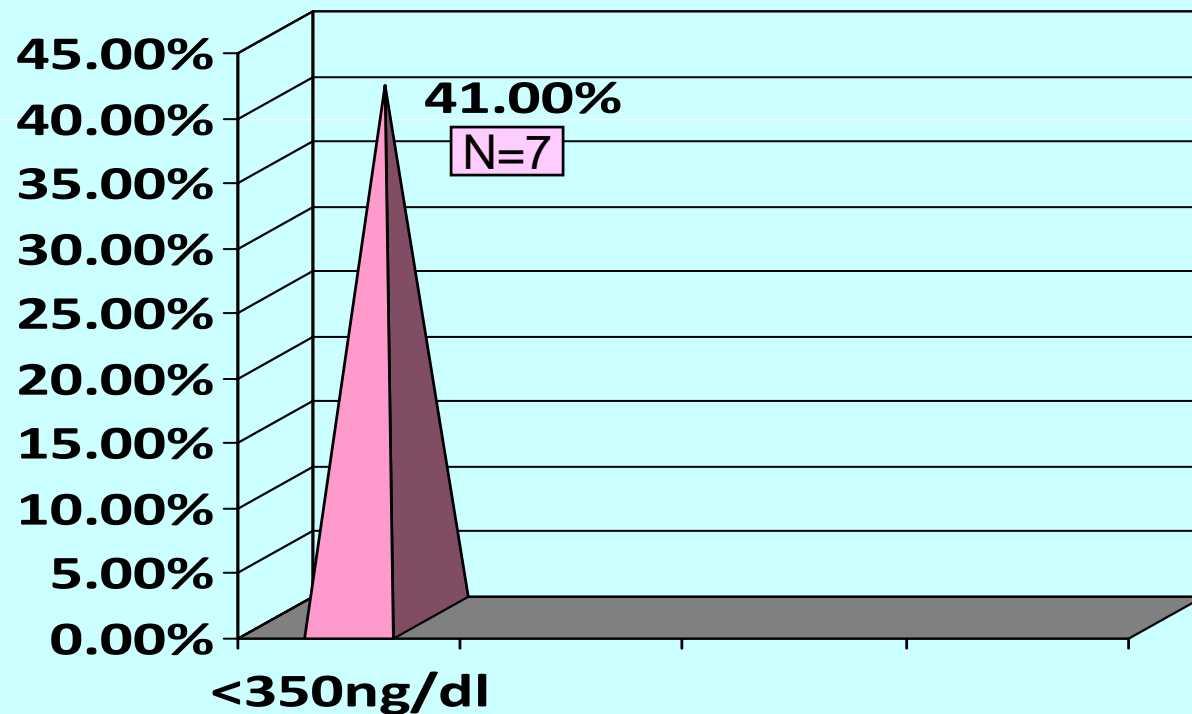
Levels of ADAMTS-13(ng/dl) in Septic Pediatric Patients



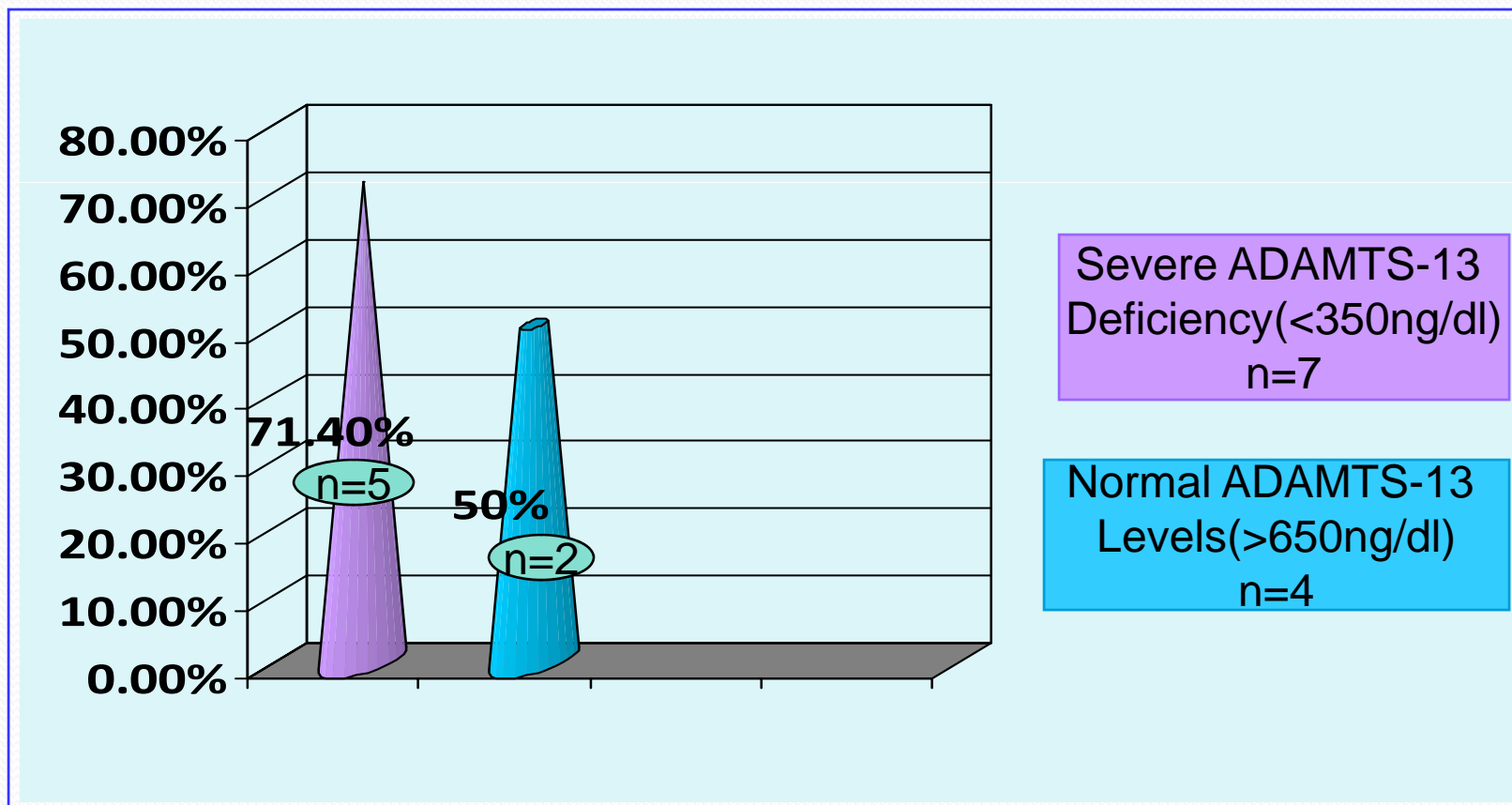
Deficiency of ADAMTS-13 In Septic Patients



Severe Deficiency Of ADAMTS-13



In-Hospital Mortality in Septic Paediatric Patients According To ADAMTS-13 Levels.



COMPARATIVE STUDIES

STUDY	Sample size (n)	ADAMTS-13 Deficiency
Ono T et al Japan, 2007	105 Adults	15.6%
Nguyen TC et al USA, 2006	21 Paediatric	31%
Scully M et al, 2008	48 Paediatric	64%
OUR STUDY, 2009	17 Paediatric	76%

COMPARATIVE STUDIES

STUDY	Sample size (n)	In-hospital mortality in severe ADAMTS-13 Deficient patients (%)
Kim YK et al, Korea, 2009	19 Adults	100%
OUR STUDY, 2009	17 Paediatric	71%



Strengths

- First time being conducted in Pakistan.
- Selected population being studied.



Limitations

- Small number of subjects.
- ADAMTS-13 levels were measured only at the time of presentation and serial monitoring not done.



Conclusion

- It is an ongoing study.
- Increased frequency of ADAMTS-13 deficiency was found in our septic patients.
- Severe ADAMTS-13 deficiency is associated with increased in-hospital mortality in paediatric septic patients.



Recommendations

- More prospective studies with large sample size and serial monitoring of ADAMTS-13 levels are needed to determine the role of ADAMTS-13 in severe septic patients.



Take Home Message

- Determination of ADAMTS-13 levels at the time of hospital admission and serially in severe septic patients would provide better understanding of the extent of disease.