

Perioperative Medicine Summit

Using Evidence to Improve Quality, Safety and Patient Outcomes



Rapid Fire

Answering challenging, common clinical questions

**SuPAR (soluble urokinase plasminogen activator receptor): the risk status marker.
Time to use it perioperatively ?**

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Disclosures

Full Disclosure statement on file with Horizon
CME



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Consultant: Massachusetts General Hospital, Harvard Medical School

Learning Objectives

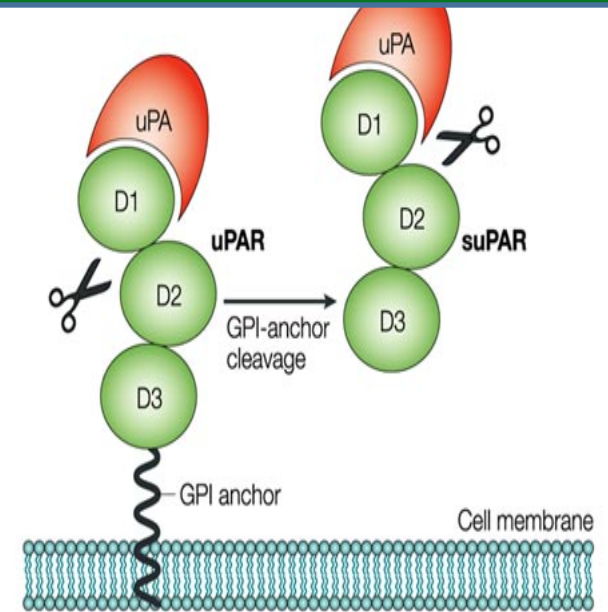
- Objective 1: understand what suPAR is
- Objective 2: suPAR, biomarker versus cause
- Objective 3: suPAR and perioperative setting

ARS Question

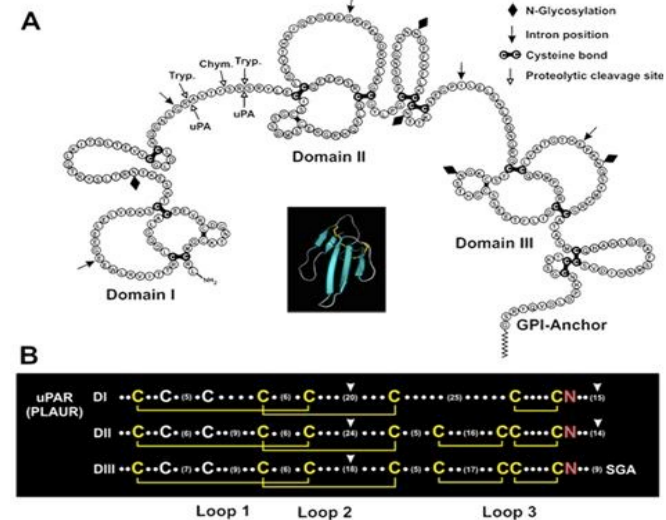
- **Why does suPAR provide a powerful view into immunological risk ?**
- A) suPAR is a product of the CRP pathway
- B) suPAR is rapidly changing levels in the blood and thus a gauge to the acute risk
- C) suPAR originates from immune cells and has cell signaling capacity
- D) the amount of suPAR accumulates over time

(s)uPAR

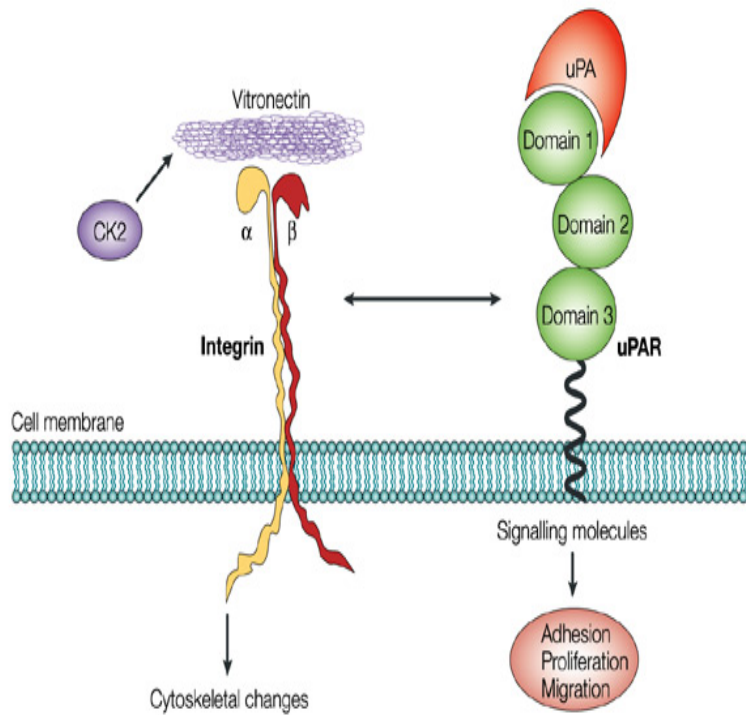
- uPAR (CD87) – rokinase Plasminogen Activator Receptor, cloned in 1989 by Blasi et al.; crystal structure of full length uPAR solved in 2005 by Llinas et al.
- Typically GPI anchored three domain glycoprotein (5 N-glycosylation sites); domains belong to Ly-6/uPAR/alpha-neurotoxin family of signaling proteins
- Cellular receptor for urokinase (uPA) and vitronectin as well as binding partner for integrins (Chapman et al. 1996)
- Expressed on immune cells and others: neutrophils, activated T-cells, macrophages, podocytes
- suPAR is generated by cleavage of GPI anchor or between domains. It has several forms; suPAR(I-III), suPAR(II-III) and suPAR(I), alternative transcript suPAR (I-II)
- In comparison of cDNA sequences, suPAR I differs from suPAR II and suPAR III in its primary and tertiary structure, causing its distinct ligand binding properties
- suPAR- a stable protein: present and measured in various body fluids
- Two commercial ELISA (Virogates and R&D) which capture total suPAR levels



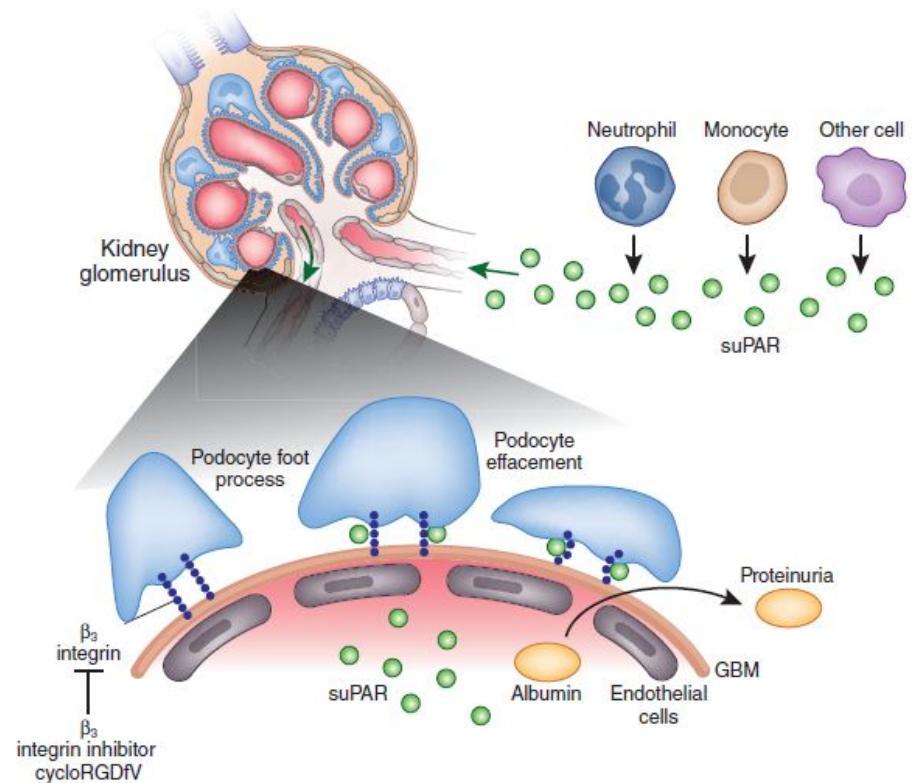
Nature Reviews | Molecular Cell Biology
Blasi and Carmeliet



uPAR and suPAR bind to and regulate podocyte integrin beta 3 activity in FSGS

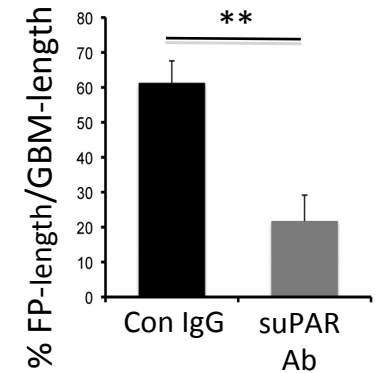
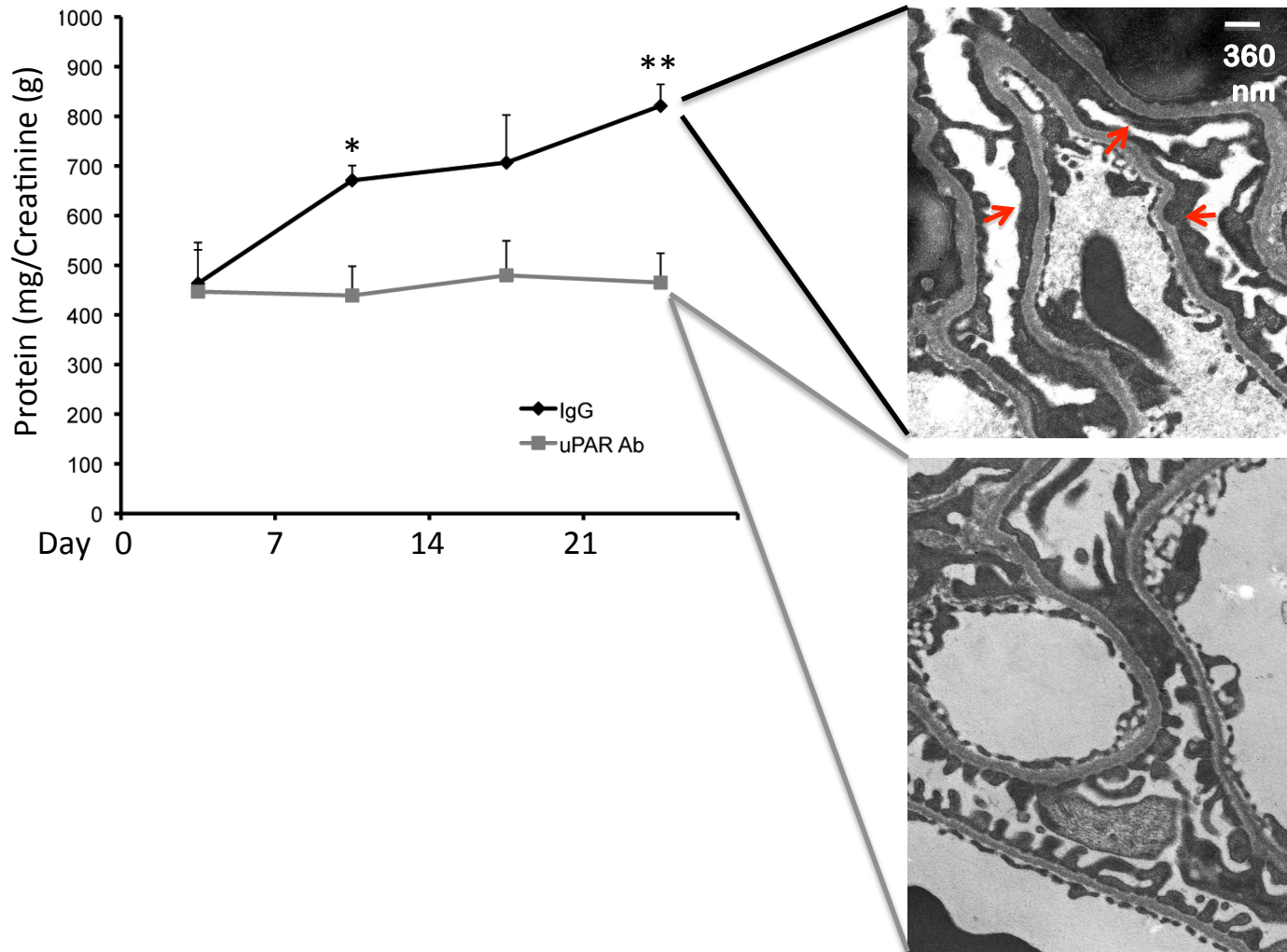


Wei C et al., Nat Med 2007



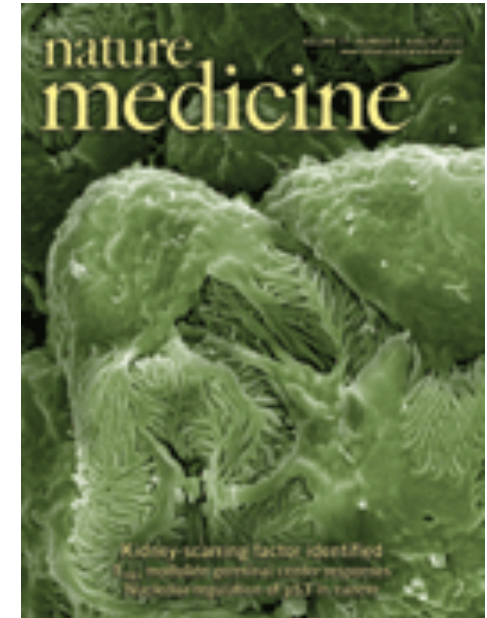
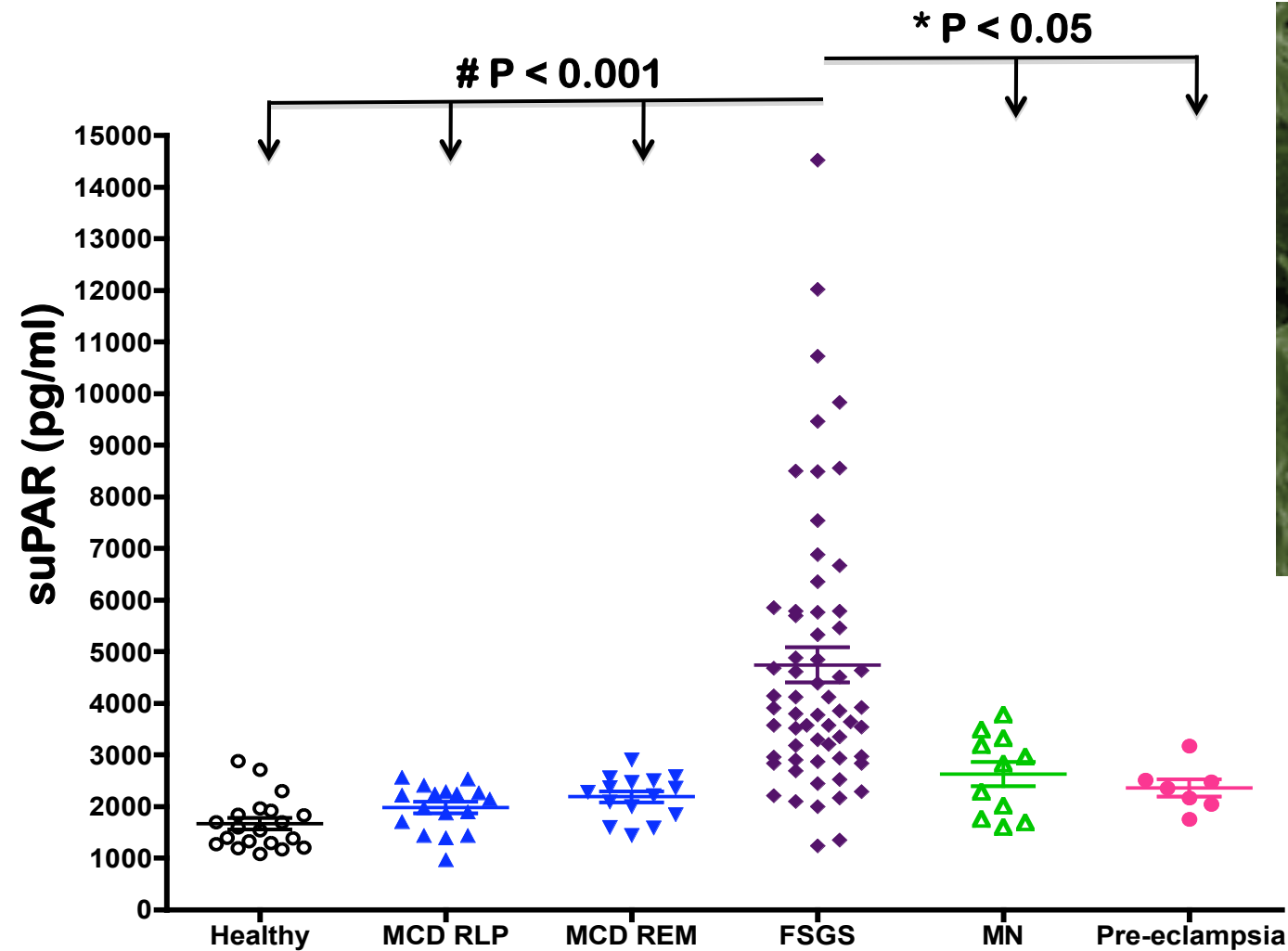
Shankland and Pollak Nat Med 2011
Wei C et al., Nat Med 2011

High suPAR expressing mice develop renal disease and Ab protects from proteinuria



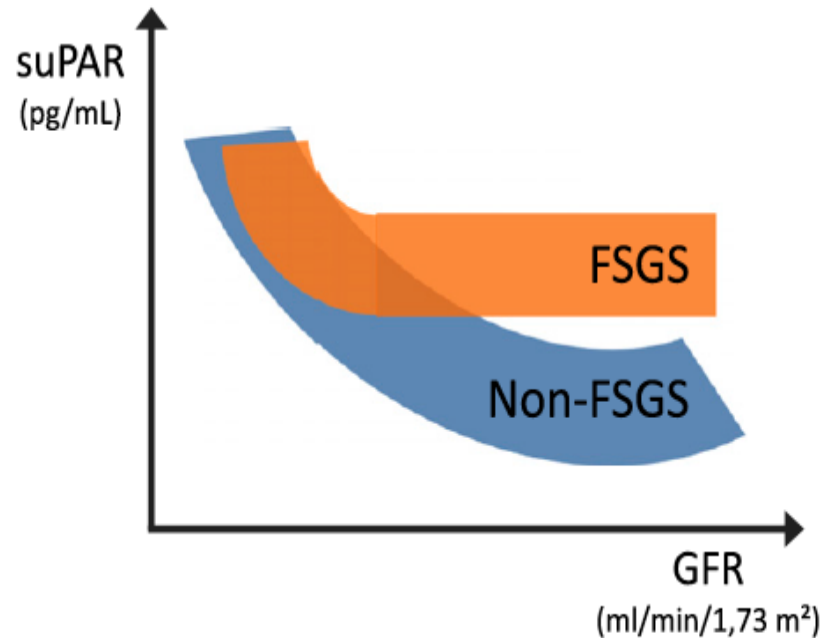
Wei C et al., Nat Med 2011

suPAR is a circulating FSGS factor



Wei C et al., 2011

How do high suPAR levels in FSGS connect to high suPAR from reduced GFR ?



Meijers et al., CJASN 2014



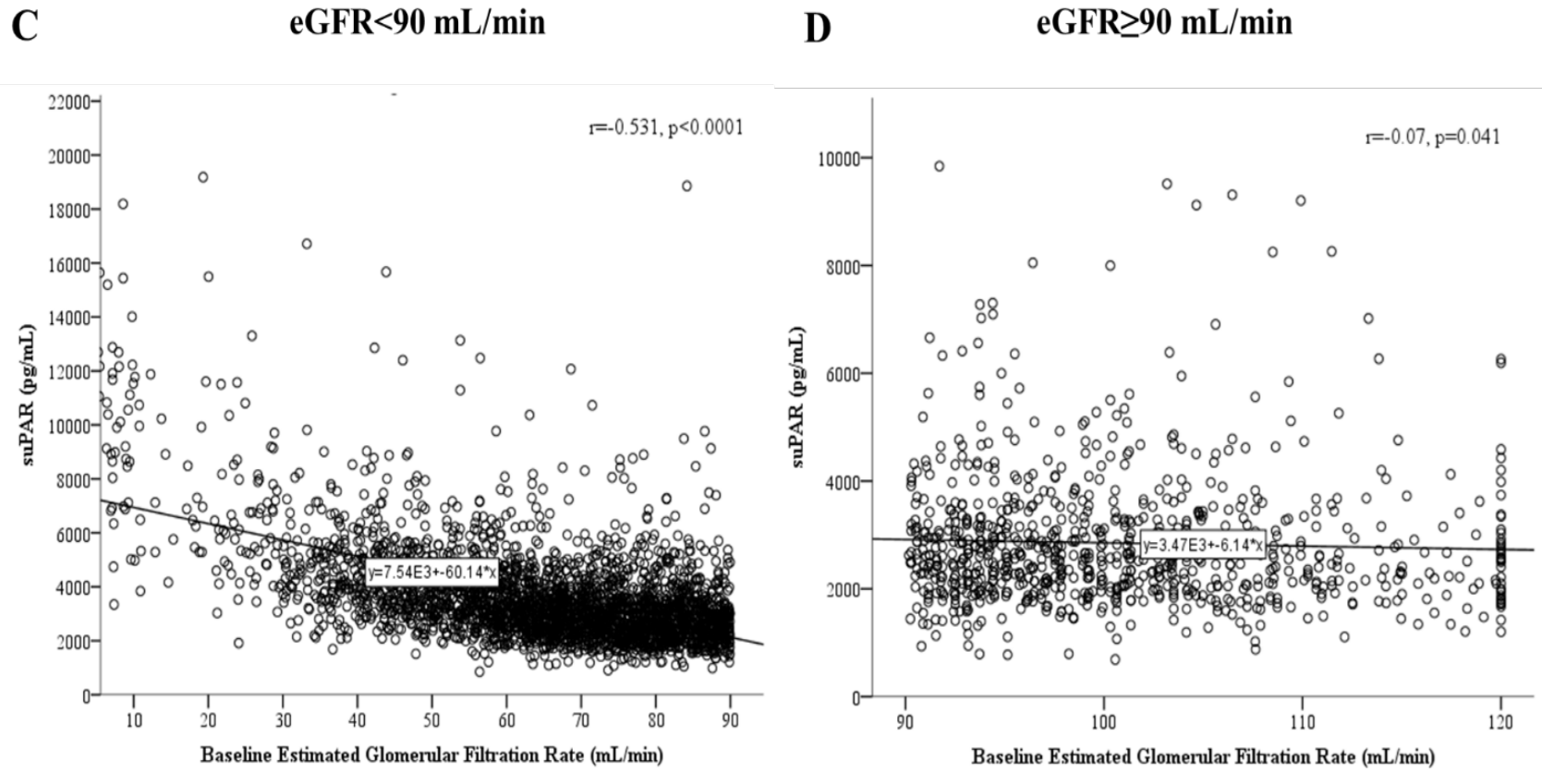
The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Soluble Urokinase Receptor and Chronic Kidney Disease

Salim S. Hayek, M.D., Sanja Sever, Ph.D., Yi-An Ko, Ph.D.,
Howard Trachtman, M.D., Mosaab Awad, M.D., Shikha Wadhvani, M.D.,
Mehmet M. Altintas, Ph.D., Changli Wei, M.D., Ph.D.,
Anna L. Hotton, Ph.D., M.P.H., Audrey L. French, M.D.,
Laurence S. Sperling, M.D., Stamatios Lerakis, M.D., Arshed A. Quyyumi, M.D.,
and Jochen Reiser, M.D., Ph.D.

suPAR levels negatively correlate with GFR up to an eGFR of 90ml/min



Hayek et al., NEJM 2015

Is suPAR a general risk factor for Kidney Disease ?



suPAR[®] level men

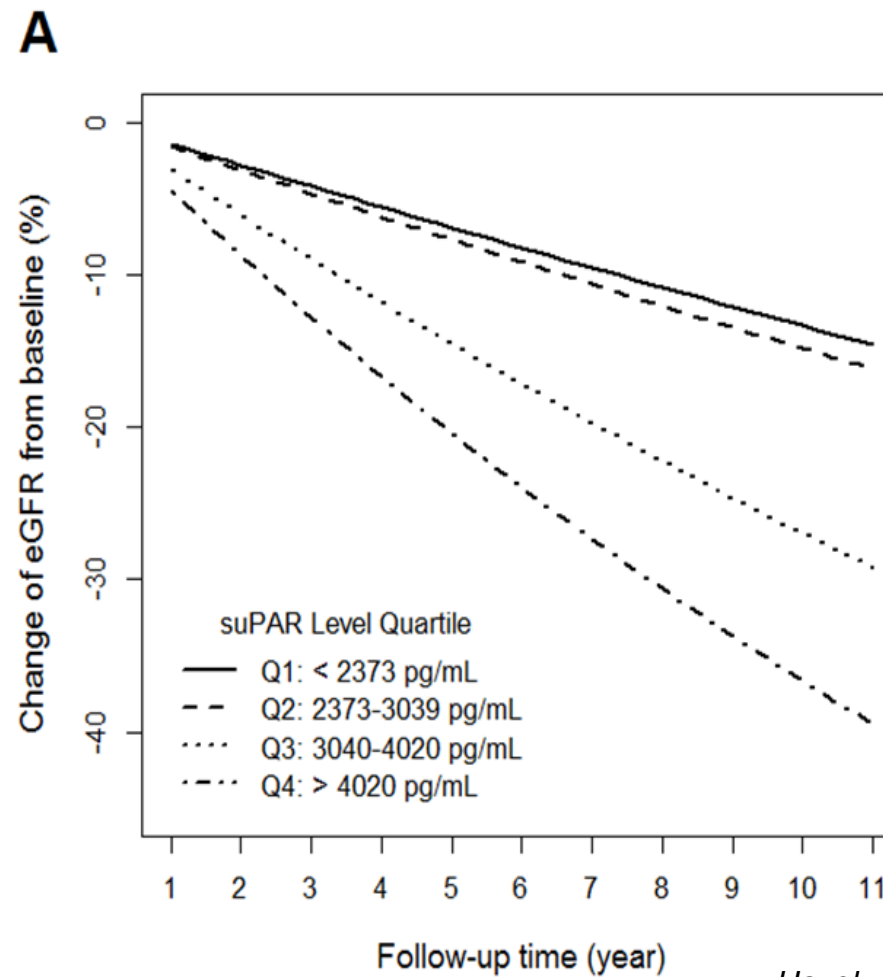
ng/mL	1.5	2.5	3.5	3.7	4.0	4.3
Age	20	30	40	50	60	70+

suPAR[®] level women

ng/mL	2.5	2.9	3.9	4.2	4.3	4.5
Age	20	30	40	50	60	70+

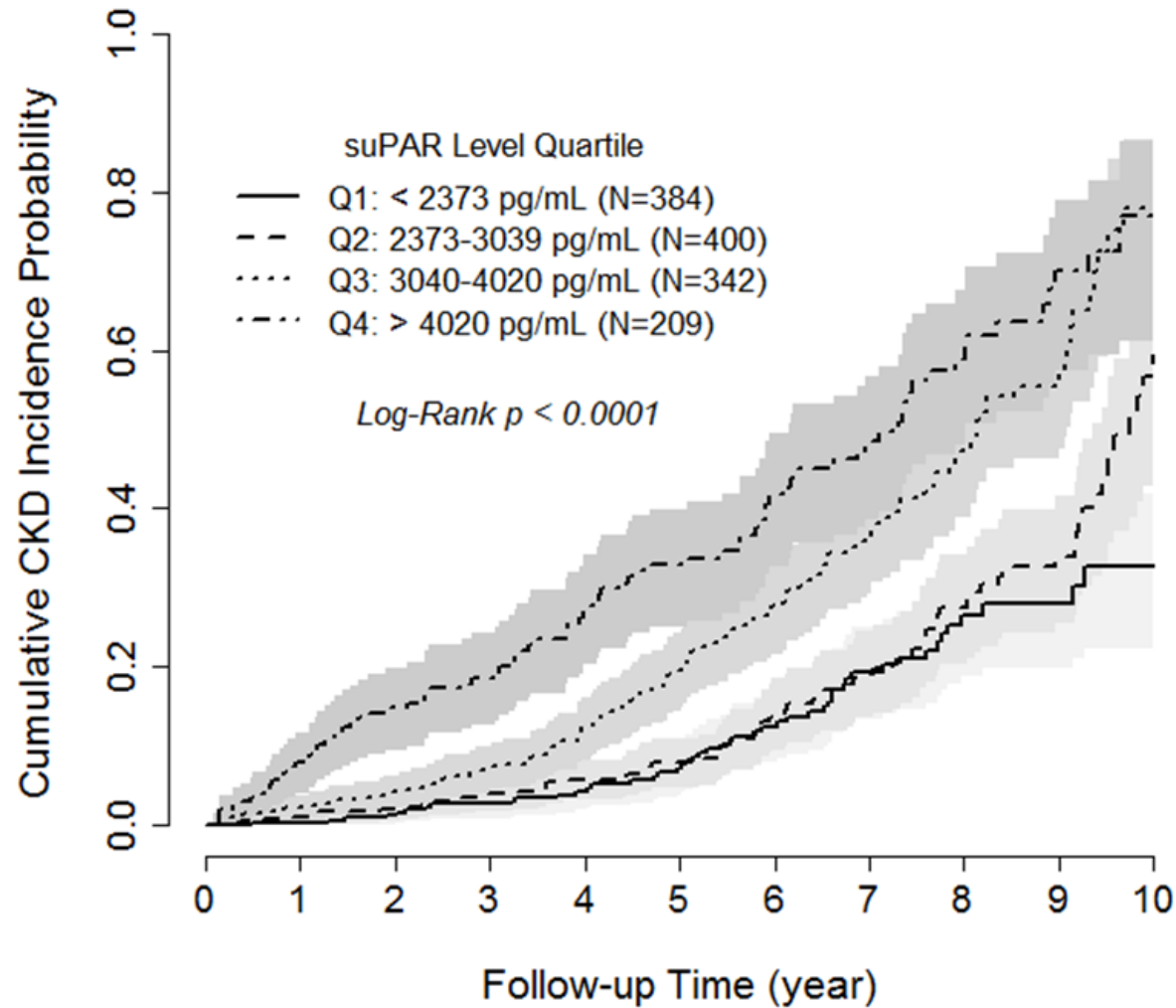


suPAR as risk factor for eGFR decline per year



Hayek et al., NEJM 2015

suPAR predicts incident CKD



Hayek et al., NEJM 2015

suPAR and pneumonia perioperatively

TABLE 4. REGRESSION ANALYSES: ENDPOINT IS POSTOPERATIVE PNEUMONIA

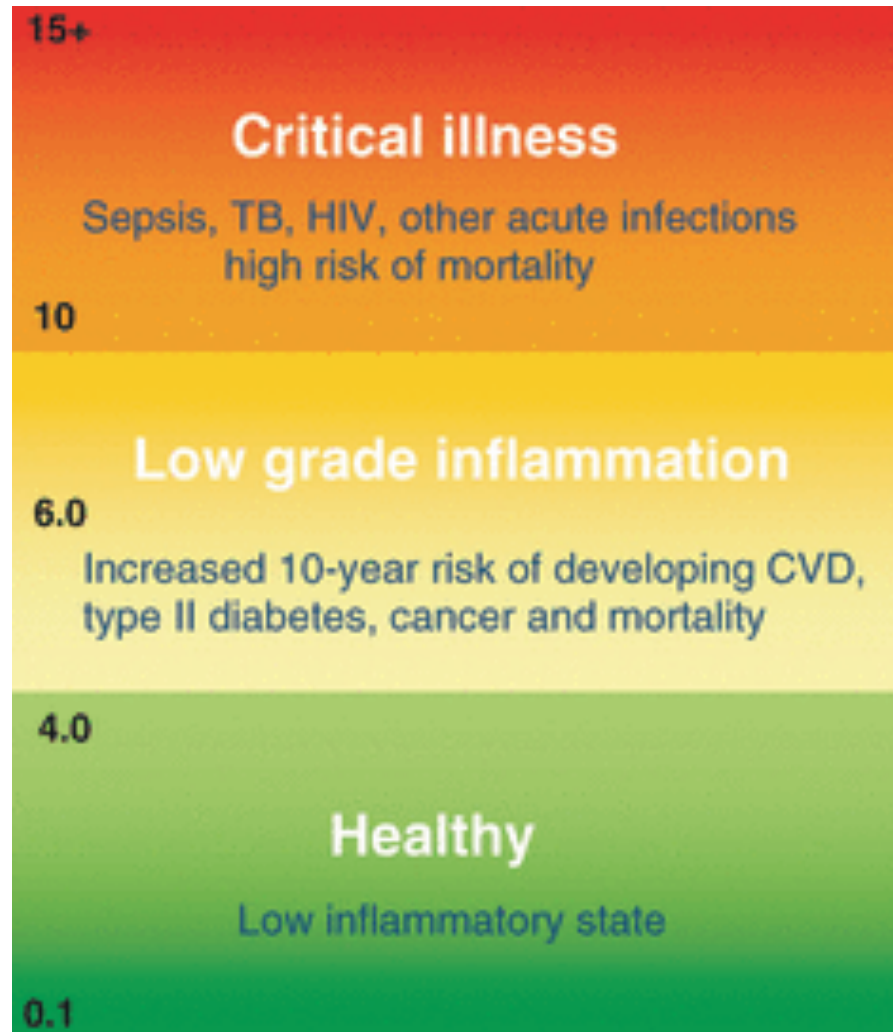
<i>Parameter</i>	<i>P values in univariate analysis (concordance index [%])</i>	<i>P values in multivariate analysis (OR; 95% CI)</i>
Log ^a suPAR	0.01 (59)	0.004 (1.7; 1.2–2.4)
Log ^a MBL	0.02 (59)	0.007 (1.5; 1.1–1.9)
Perioperative blood transfusion	0.003 (60)	0.006 (2.3; 1.3–4.2)
Age	0.65 (52)	0.58
Sex	0.14 (55)	0.12
Location: rectum vs. colon	0.59 (52)	0.63
Dukes B vs. Dukes A	0.20	0.14
Dukes C vs. Dukes A	0.20 (54)	0.14
Dukes D vs. Dukes A	0.38	0.59

^aNatural logarithm.

OR = odds ratio; CI = confidence interval; MBL = mannose-binding lectin; suPAR = soluble urokinase-type plasminogen activator receptor.

Svendsen MN et al. Surgical Infections 2006

suPAR – a future risk marker



Journal of Internal Medicine

[Volume 270, Issue 1](#), pages 29-31, 24 MAR 2011 DOI: 10.1111/j.1365-2796.2011.02372.x



Miltenyi Biotec

Biodevice

SUPAREX™

suPAR
Removal
Device



TRISAQ



- Pilot trial in humans with a first in kind selective suPAR immunadsorbing device
- 4 sites selected in Germany: Hannover, Cologne, Heidelberg and Berlin, 1 site in Netherlands: Neijmegen and 1 site in Belgium (Brussels)
- Specific suPAR immuneadsorption in recurrent FSGS