CLINICAL, LABORATORY AND GENETIC PHENOTYPES OF ADULT SICKLE CELL DISEASE

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ADULT SCD ARE THEY JUST BIG CHILDREN WITH SCD

- **The phenotype of adult SCD patients is poorly defined. Morbidity/etiology data in older patients is limited - sudden death ,mi brain injury?**
- **Sickle cell disease is affected by the primary mutation, severity of hemolysis and anemia, the hemoglobin F, and the cumulative effects of organ injury interacting with the pathophysiology of aging. Genetic modifiers of the pathophysiology of the disease and aging are both likely to be important.**
- **However morbidity of adults is not just cumulative effect of pediatric physiology and different time dependent mechanisms and modifiers maybe active**

Established predictors of phenotype include:

- Beta globin mutation, haplotype
- Age
- Total hemoglobin,Hemoglobin F
- Alpha-thalassemia
- Hemolysis (NO, ARG/ornithine, LDH, PHT, BNP)

Definitions of the Phenotypic Manifestations of Sickle Cell Disease

S. Ballas, et al. (2009)

HEMATOLOGIC COMPLICATIONS

Acute Anemia

- hyperhemolysis
- splenic sequestration
- aplastic episode

Transfusion Complications

- hyperviscosity
- immune hemolysis
- hemosiderosis

SICKLE CELL PAIN SYNDROME

Pain Syndromes

- pain episodes
- acute organ failure
- iatrogenic pain
- neuropathic pain

PULMONARY

- Acute Chest Syndrome
- Pulmonary Hypertension

CARDIAC COMPLICATIONS

- cardiomyopathy
- heart failure
- hypertension

NEUROLOGIC

CVA

- hemorrhagic
- infarct
- aneurysm
- Moya Moya
- silent infarct
- TIA
- seizure

OPHTHALMOLOGIC

Retinopathy

- proliferative
- retinal detachment

Vitreous Hemorrhage

- glaucoma

GASTROINTESTINAL

Hepatic/Biliary

- gallstones/cholecystitis
- hepatic Squestration
- intrahepatic cholestasis

GROWTH AND DEVELOPMENT

- growth failure

RENAL/G.U.

Renal

- acute renal failure
- chronic renal failure
- hematuria
- proteinuria/nephrotic

Penal

- priapism

SPLENIC

- acute splenic infarct
- functional asplenia
- hypersplenism
- sequestration

MUSCULOSKELETAL/SKIN

Skeletal

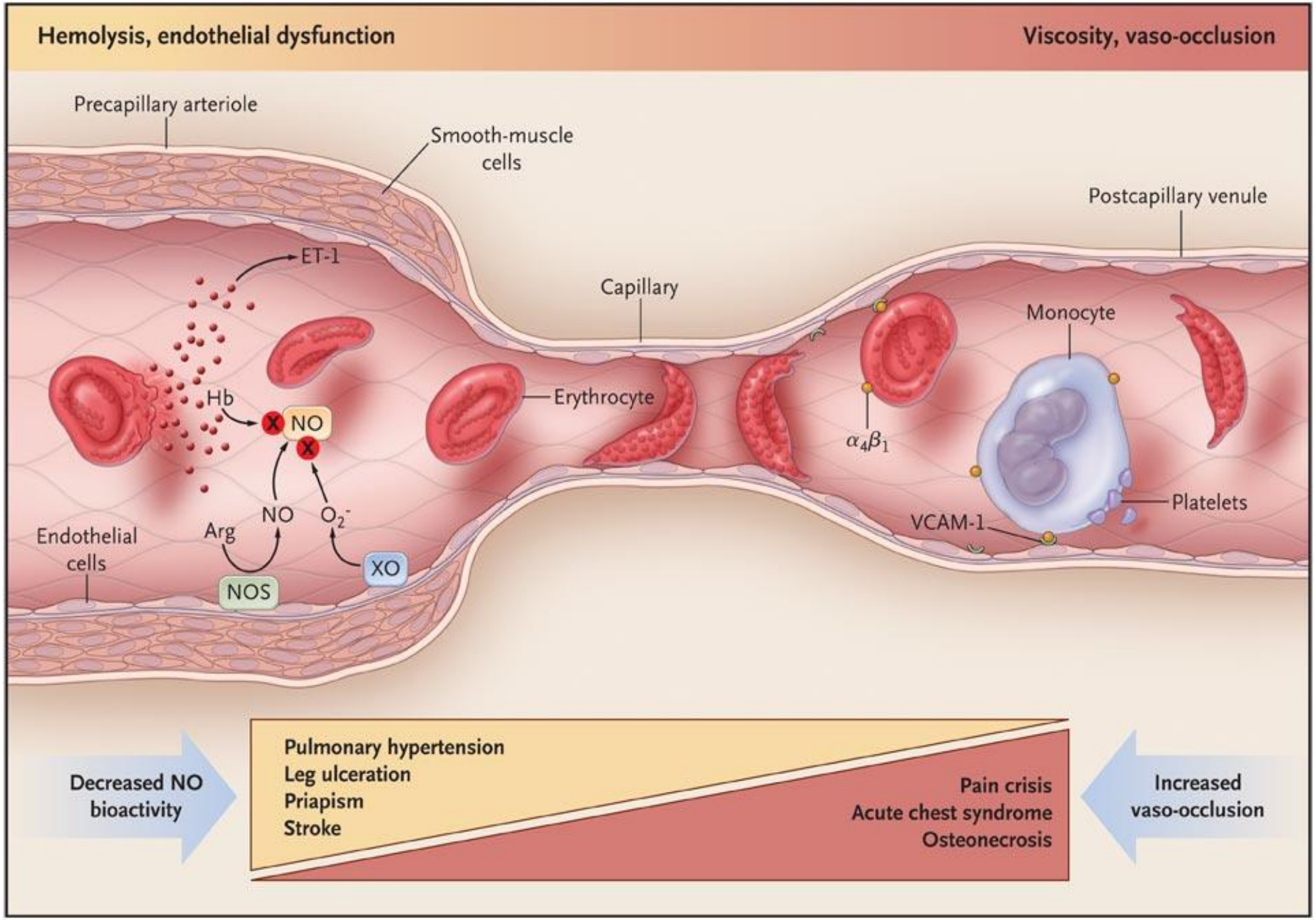
- avascular necrosis
- dactylitis
- osteomyelitis

Muscle

- myonecrosis

Skin

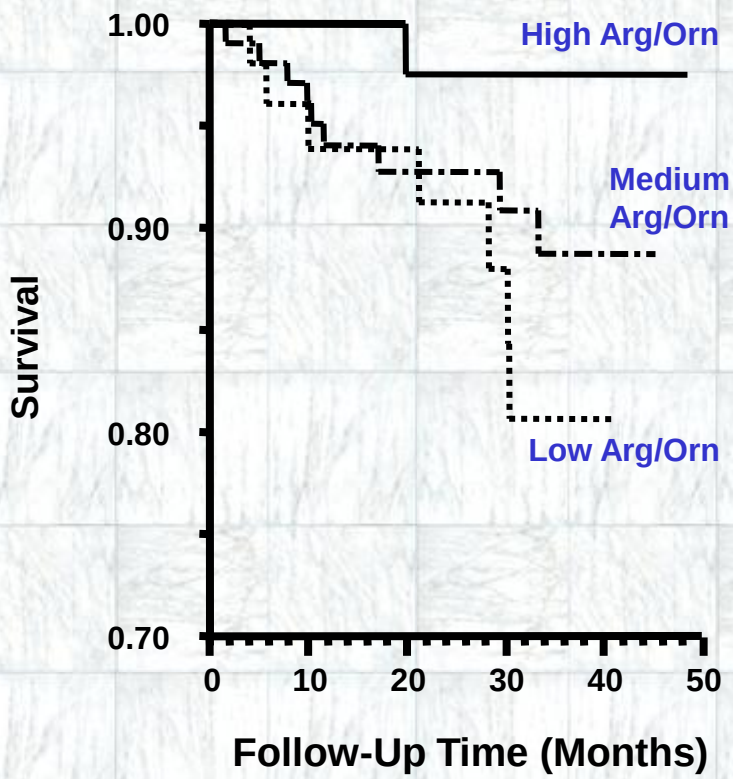
- leg ulcers


Hemolysis, endothelial dysfunction
Viscosity, vaso-occlusion
Precapillary arteriole
Smooth-muscle cells
Postcapillary venule
ET-1
Capillary
Monocyte
Hb
NO
Erythrocyte
$\alpha_4\beta_1$
Platelets
VCAM-1
Endothelial cells
Arg
NO
O_2^-
NOS
XO
Decreased NO bioactivity
Pulmonary hypertension
Leg ulceration
Priapism
Stroke
Pain crisis
Acute chest syndrome
Osteonecrosis
Increased vaso-occlusion

Survival Proportions

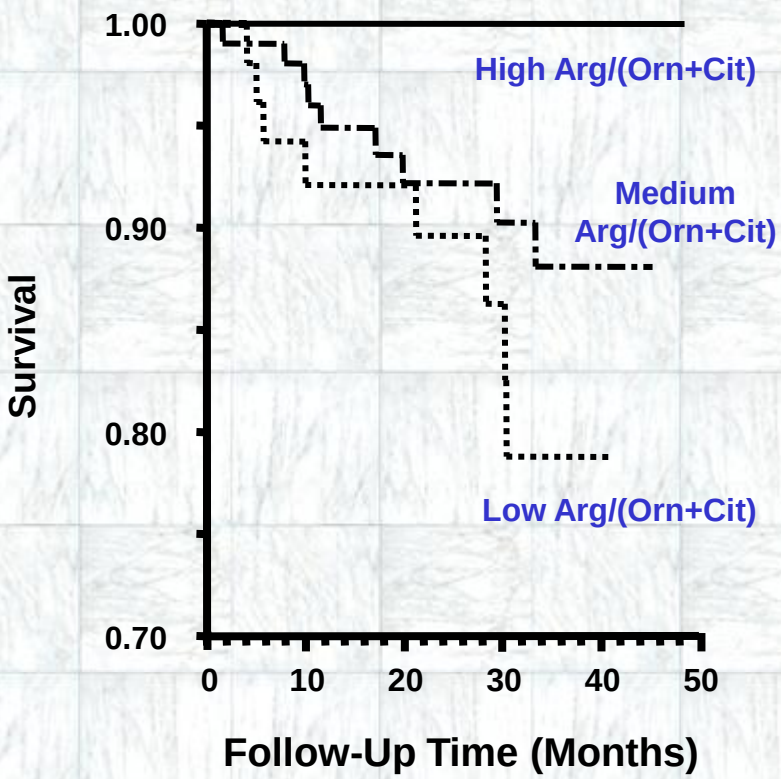
Low Global Arg Bioavailability ↑Risk of Death

Arg/Orn



RR: 2.2 [1.0,4.9], *p=0.02*

Arg/[Orn+Cit]

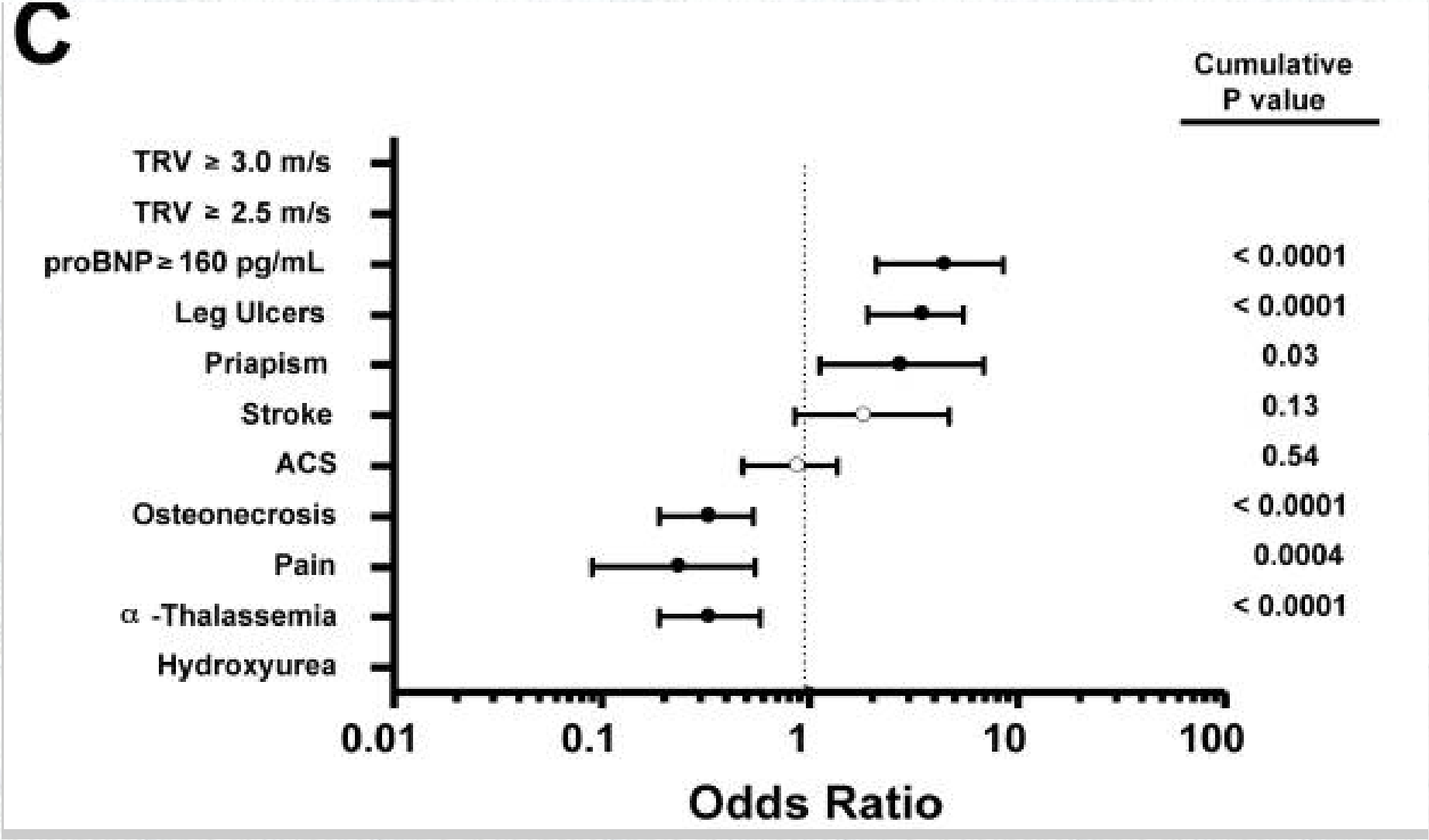


RR: 3.6 [1.5,8.3], *p<0.001*

(Morris et al, JAMA 2005)

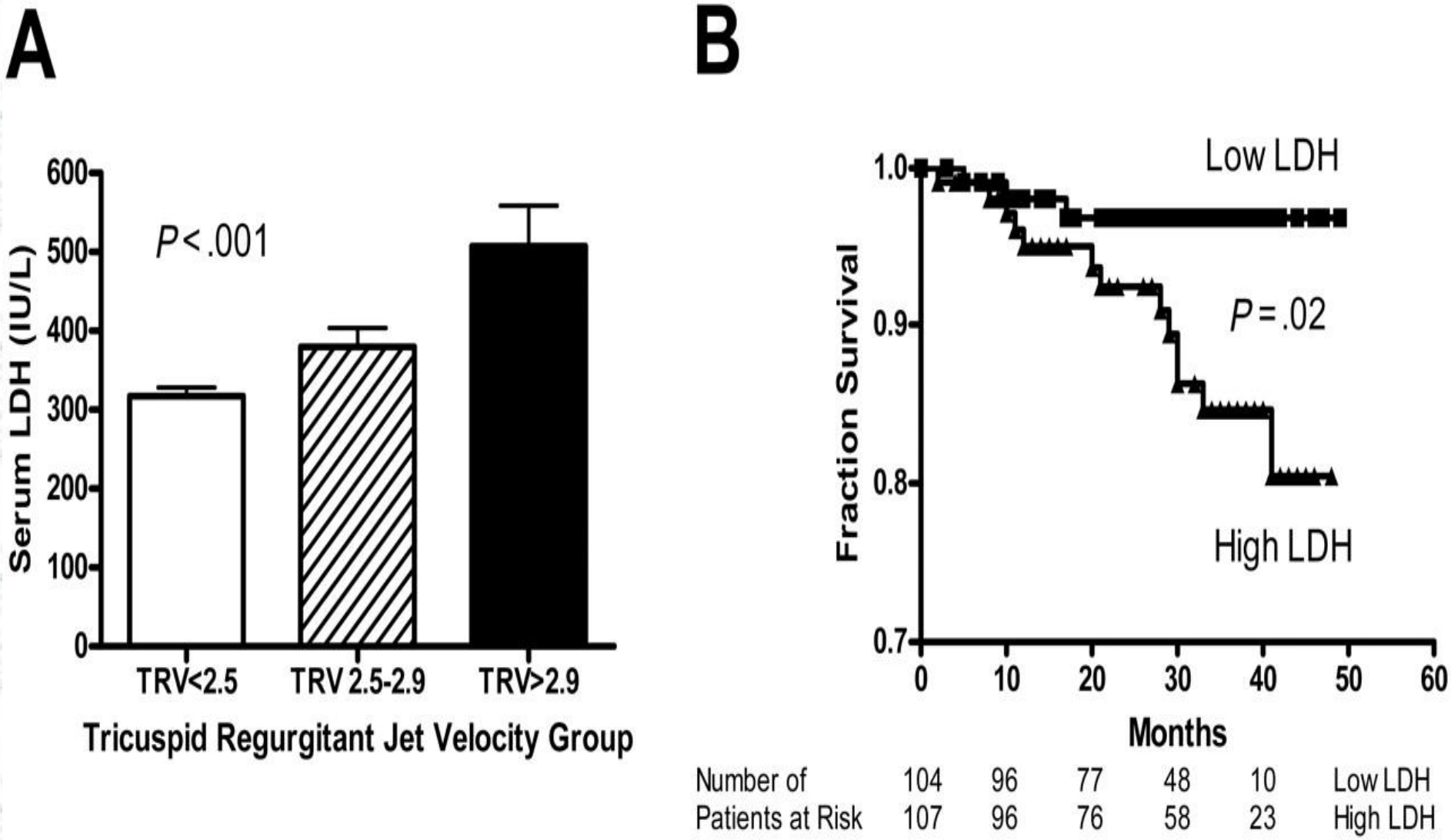
Chronic Hyper-Hemolysis in Hb SS: Association of Vascular Complications and Mortality with Less Frequent Vasoocclusive Pain

LDH Measurement



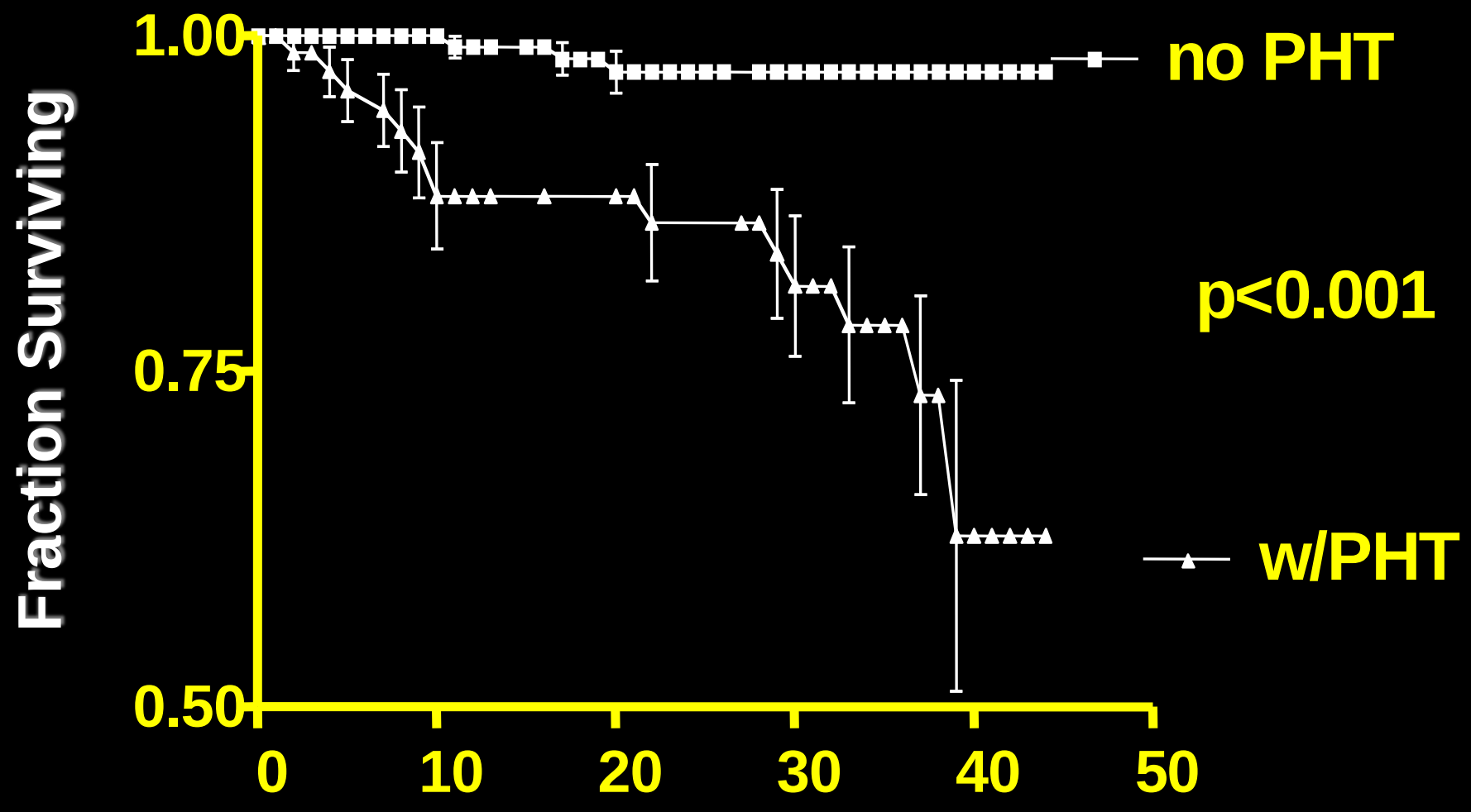
PLoS ONE. 2008; 3(5): e2095. Chronic Hyper-Hemolysis in Sickle Cell Anemia: Association of Vascular Complications and Mortality with Less Frequent Vasoocclusive Pain. **James G. Taylor et al.**

Serum LDH are associated with PHT and early mortality



Kato, G. J. et al. 2006

Survival Proportions



RR:10.1[2.2,47], *p<0.001*

NT-pro brain natriuretic peptide levels and the risk of death in the cooperative study of sickle cell disease

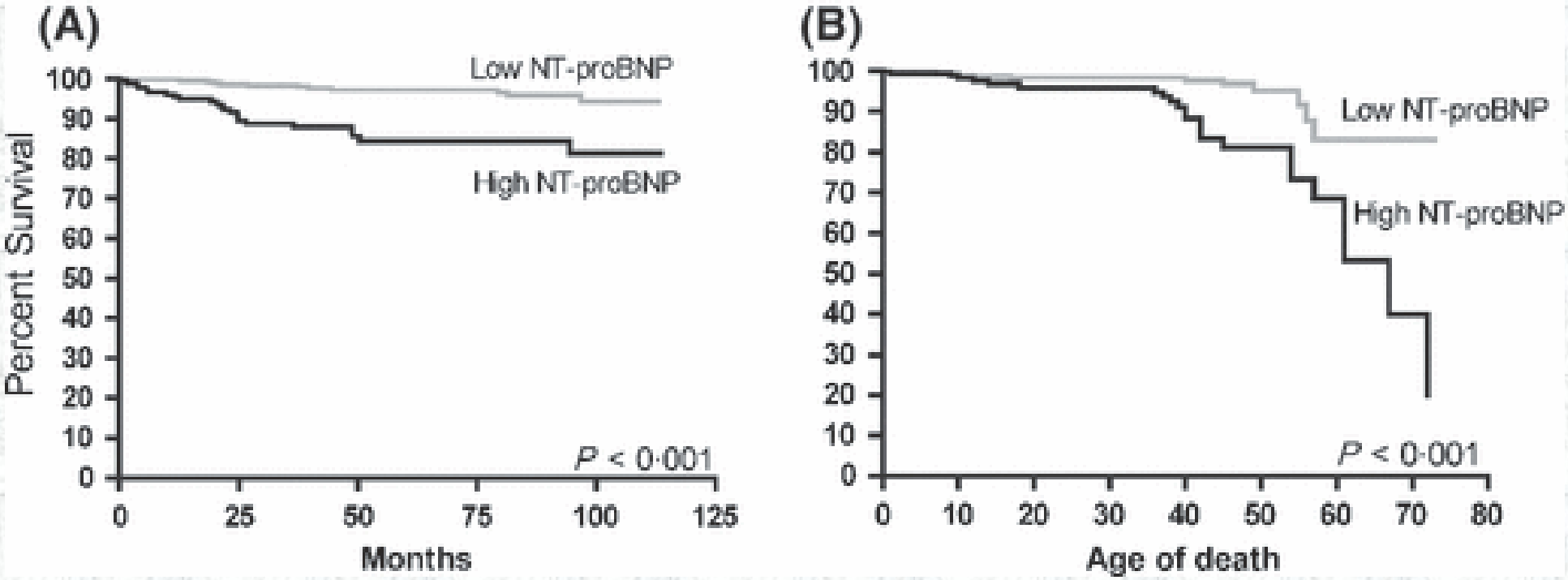


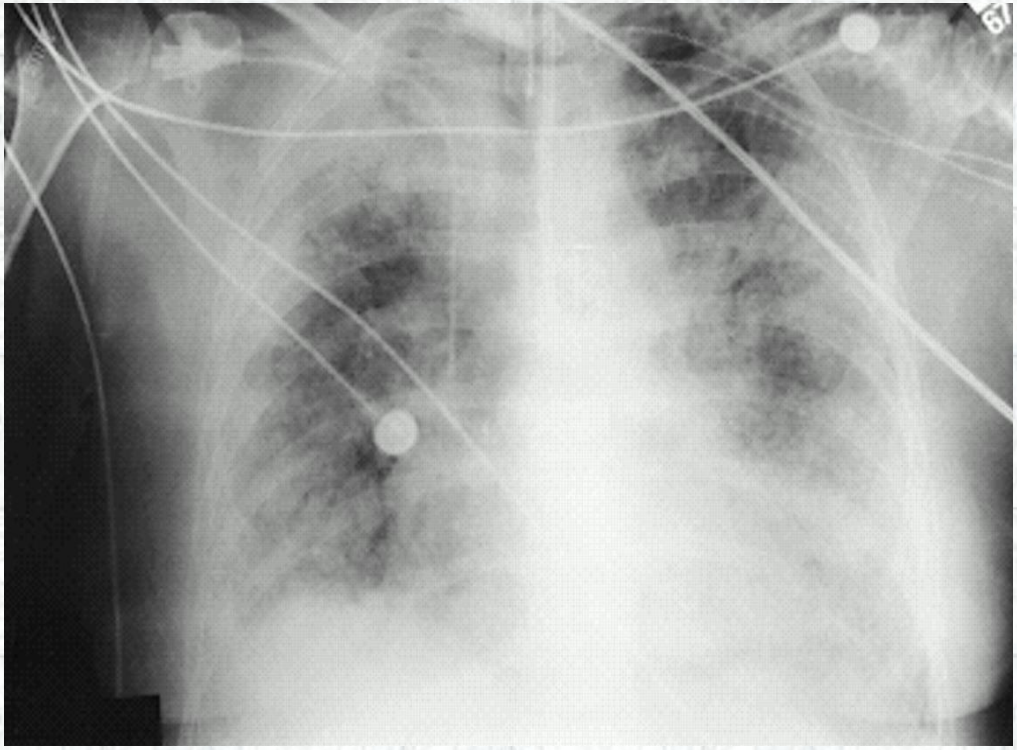
Table III. **Logistic regression analysis of NT-proBNP* by cohort.**

Independent variable	OR† (95% CI)	P‡	P§
Adult			
Age (years)	1·37 (1·0–1·9)	0·05	0·0007
Haemoglobin (g/l)	0·35 (0·2–0·6)	<0·0001	<0·0001
Blood urea nitrogen (μmol/l)	1·53 (1·1–2·1)	0·006	<0·0001
Lactate dehydrogenase (u/l)	1·52 (1·0–2·2)	0·03	0·02

R. Machado, et al. British Journal of Haematology 154:4, p. 512-520.

Lung Disease in Adult Sickle Cell

- **Sickle lung injury is the most common cause of death and morbidity in SCD.**
- **↓Age, ↑Hb, ↓Hb F, ↑WBC and asthma increase the risk.**
- **The clinical course between adult and pediatric patients is markedly different and suggests different pathophysiology.**
- **SNPs affecting NO and *EDN1* gene, *TGFBR3.* Other SNPs involving cell adhesion or NOS were age-dependent.**



- **PHT is a major risk factor for death in adults. It appears to be modulated by genes that control NO, hemolysis oxidative injury, cell-cell interaction, vascular genesis and vaso-reactivity.**
- **Genes associated with TGF-BNP super family have been found in SCD patients and others with PHT.**

Fatal vs. Non-Fatal Cases of ACS: History and Symptoms

HISTORY	Fatal %	Non-Fatal %	P value
Age	24 yrs	13 yrs	< 0.001
Renal disease	15	9	
Cardiac disease	14	4	
CNS disease	13	13	< .001
SYMPTOMS			
Pain	100	78	= .05
Fever	47	79	< .01
CNS dysfunction	33	4	
Cough	20	64	< .001

Cardiopulmonary complications cause 40% of deaths in adults with sickle cell disease

	DECEASED (43 patients)	LIVING (197 patients)	P value
Hemoglobin (gm/dl)	8.3	9.2	< 0.05
TRV (m/s)	3.1	2.6	< 0.001
TRV (m/s) > 2.5	18 (56%)	34 (26%)	< 0.001
Pre-morbid conditions			
* *Congestive heart failure*	11 (26%)	16 (8%)	< 0.003
* *Myocardial infarct*	9 (21%)	3 (1.5%)	< 0.0001
* *Arrhythmia*	6 (14%)	1 (0.5%)	< 0.004

Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. **Courtney D. Fitzhugh, et al. American Journal of Hematology 85:1:36-40 2010**

CNS Disease in Adults

- CNS disease in pediatrics has been aggressively studied, including risk factors and genetic modifiers Every study excluded adults. Middle east pediatric studies found CNS abnormalities rare; on followup, this adult population demonstrated a large increase.
- The pre-imaging CSSCD study found that at least 25% of older adults have had an overt stroke. Stroke was bimodal in distribution, with a peak of hemorrhagic and infarct strokes in older adults.
- The pilot data with modern imaging and neurocognitive testing suggest that adults have progressive, premature cerebral atrophy, silent infarcts, and neurocognitive decline Matched controls are critical
- Pediatric and adult patients may differ in the involvement of small vs. large vessel disease, in biologic markers, and in genetic modifiers. For example, TNF-alpha polymorphism appears to be a major risk in pediatric CNS disease but not in adults.
- In adults without sickle cell disease, blood pressure, renal dysfunction, inflammation (CRP, IL-6) and chronic anemia are risk factors.
- In non sickling hemoglobin disorders cns disease common in, anemic splenectomized adult thalassemia patients 20- 50% had significant CNS infarct including Moya Moya. Anemia, hemolysis .PS exposure, hypercoagulable states, and other factors have been implicated.

CNS Disease in Adults

AGE (years)	Total SCD
Total N	2,436
< 2	.013 (1)
2 - 5	1.02 (20)
6 - 9	0.79 (15)
10 - 19	0.41 (15)
20 - 29	0.52 (14)
30 - 39	0.59 (8)
40 - 49	0.74 (3)
≥ 50	1.28 (2)

The # of CVAs per 100 patient-years, by age group at occurrence and hemoglobin genotype, is shown. The # in parentheses represents the # of events.

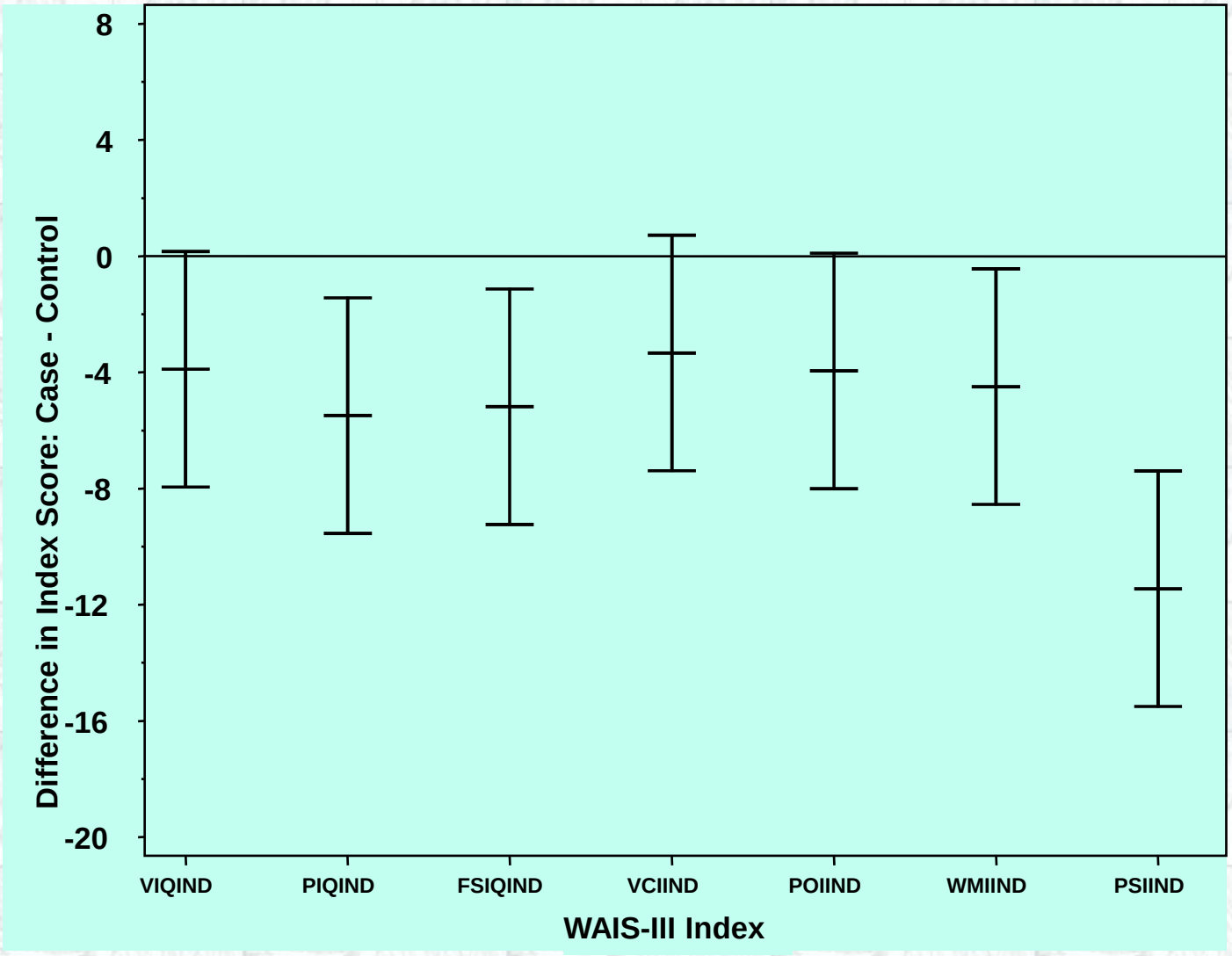
CNS Disease

Table 5. Results of Analyses of Risk of First Stroke in SS Patients

Predictor	Relative Risk	95% CI	*P* Value
A. Infarctive stroke (final multivariate model: five predictors significant at $P < .05$)			
Prior TIA	56.0	12.0, 285	<.001
Steady-state Hb	1.85 per 1 g/dL* decrease	1.32, 2.59	<.001
Acute chest syndrome within 2 weeks prior	7.03	1.85, 26.7	.001
Acute chest syndrome rate	2.39 per event/yr	1.27, 4.48	.005
Systolic blood pressure	1.31 per 10 mm Hg increase	1.03, 1.67	.033
B. Hemorrhagic stroke (final multivariate model: two predictors significant at $P < .05$)			
Steady-state Hb	1.61 per 1 g/dL* decrease	1.11, 2.35	.013
Steady-state leukocyte count	1.94 per 5×10^9/L increase	1.73, 2.18	.026

Hemolysis-associated priapism in sickle cell disease.
G. Nolan, et al. BLOOD 2005: 106

Primary Analysis Results (WAIS-III)



VIQIND = Verbal IQ Index

PIQIND = Performance IQ Index

FSIQIND = Full IQ Index

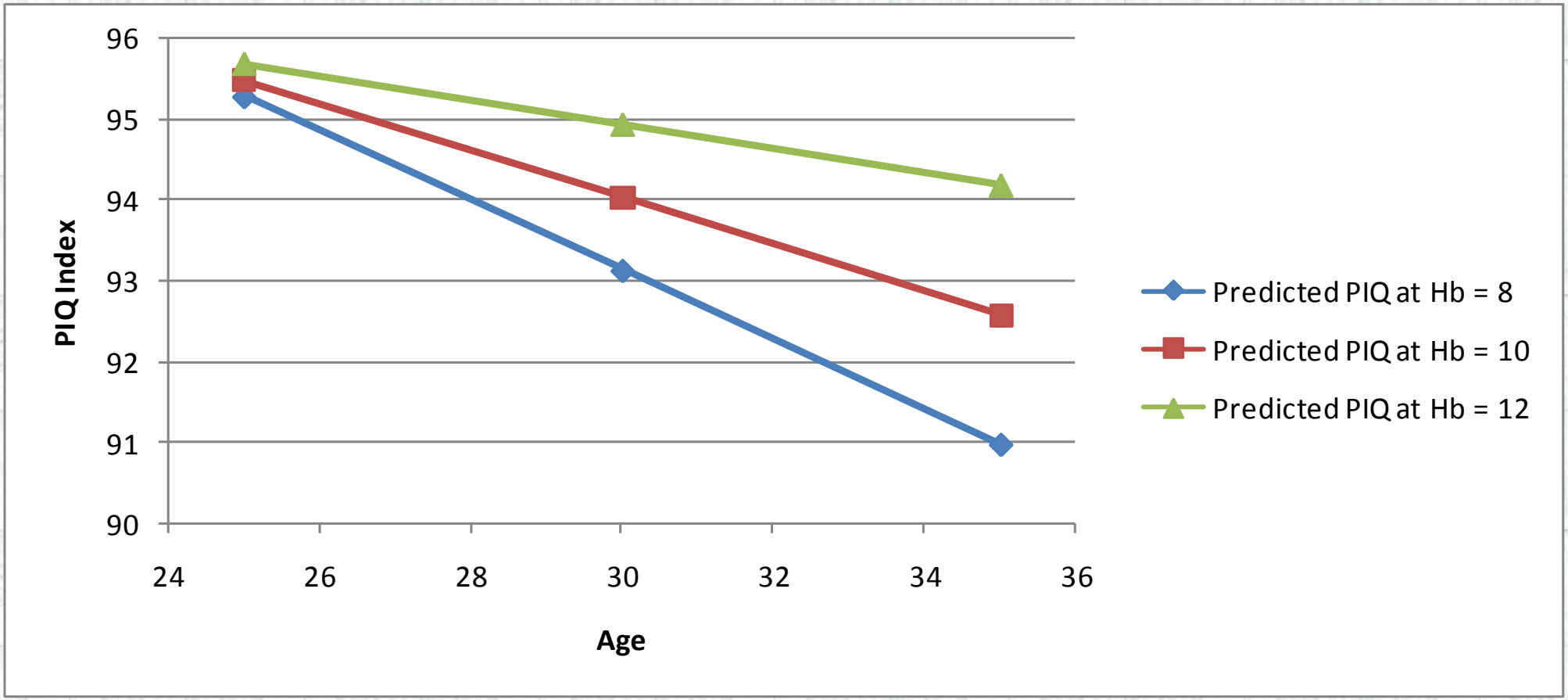
VCIIND = Verbal Comprehension Index

POIIND = Perceptional Organization Index

WMIIND = Working Memory Index

PSIIND = Processing Speed Index

WAIS PIQ Index vs Age At Different Hb Levels



For patients with >12 years of education. For patients with ≤ 12 years of education reduce values by 8.

Predictors of WAIS III PIQ Multivariable Model

	Estimate	Standard Error	P*
Education (< 12 years)	-8.22	1.727	<0.001
Age	-0.993	0.322	0.002
Age by Hemoglobin	**0.074**	**0.031**	**0.02**

***p values are two-sided**

**** estimates are not adjusted for lacune presence**

Risk Factors for Priapism

40 – 90% of patients experience priapism based on definition and data collection.

Problems in Predicting Risk Factors:

- **Age-dependent with limited analysis of older patients**
- **Definition variable: stuttering vs. prolonged**
- **High flow states vs. low flow states**

Risk Factors:

- **Strong association with severity of hemolysis (~ NO)**
- **Hemoglobin, Bilirubin, LDH, Retic count**
- **Platelet count**
- **Increased Age**

Associations with Genetic Modifiers:

- **KL is a glycosal hydrolase in NO metabolism, vascular function**
- **Associations with TGFBR3 (inflammatory modulator transforming growth factor ß receptor, type III), AQP1 (water channel of erythrocytes in endothelial cells), ITGAV (integrin of endothelial cells, a major receptor in sickle cell adhesion), F13A1 (coagulation factor XIII)**

Laboratory Characteristics of Priapism Vs. Controls Significant associations

	Case subjects; n = 273	Control subjects; n = 979	*P*
Age at last follow-up, y ± SD	**26.2 ± 12.28**	**22.8 ± 12.72**	**.001**
Hemoglobin, g/dL	**8.64 ± 0.13**	**9.51 ± 0.07**	**< .001**
HbF, g/dL	**0.44 ± 0.04**	**0.50 ± 0.02**	**.309**
% of HbF	**5.19 ± 0.46**	**5.44 ± 0.24**	**.619**
Bilirubin, mg/dL	**3.52 ± 0.13**	**2.92 ± 0.07**	**< .001**
Packed cell volume	**25.38 ± 0.36**	**28.03 ± 0.19**	**< .001**
LDH, units/L	**526.19 ± 13.08**	**459.23 ± 6.92**	**< .001**
Platelet count, per mL	**425.66 ± 7.61**	**385.16 ± 4.04**	**< .001**
RBC count, million/mm^3	**2.86 ± 0.05**	**3.26 ± 0.03**	**< .001**
WBC count, × 10^9/L	**11.62 ± 0.20**	**10.18 ± 0.10**	**< .0001**

Hemolysis-associated priapism in sickle cell disease. G. Nolan, et al. BLOOD 2005: 106

Risk Factors for Avascular Necrosis of the Hip

Problems in Predicting Risk Factors:

- Age-dependent with limited analysis of older patients
- Definition variable: imaging use varies, clinical diagnosis varies

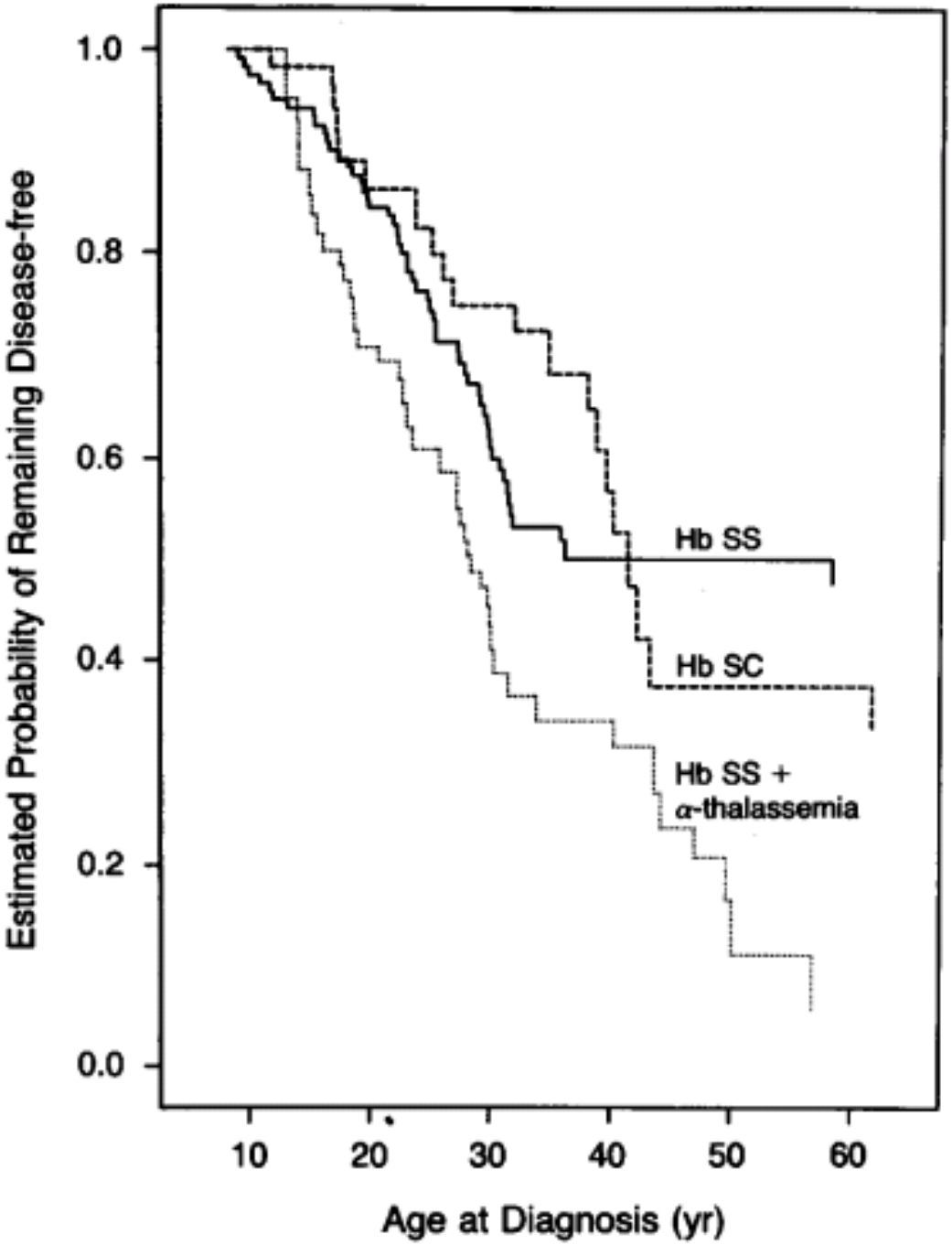
Risk Factors:

- Increased hemoglobin
- Alpha thalassemia
- Increased age
- Hemoglobin F ?

Associations with Genetic Modifiers:

- BMP6 (bone morphogenic protein) → ~ TGF-B (pleotropic-secreted proteins involved in bone formation and modeling)
- ANXA2 (Annexin A2) → Calcium-dependent phospholipid-binding protein in cell growth signal transduction osteoblast activity
- KL is a glycosal hydrolase in NO metabolism and Vitamin D regulation.

Probability of AVN of the Hip



Sickle Cell Disease as a Cause of Osteonecrosis of the Femoral Head. P. Milner et al. New Eng J Med 1991: 325

Risk Factors for Skin Ulcers

From 20 to 70% of US, Jamaican patients develop skin ulcers, vs. 5% or less of African-mediterranean patients. May be a predictor of mortality.

Problems in Predicting Risk Factors:

- **Very Age-dependent with limited analysis of older patients ccscd incidence rises from 3% in 10-20 yr to 19% in 50 yr olds**
- Definition variables: by history, exam, size, scarring

Risk Factors:

- **Strong association with severity of hemolysis (~ NO)**
- **Hemoglobin, Bilirubin, LDH, Retic count**
- **NT-proBNP**
- **Elevated TRV**
- **Increased Age**

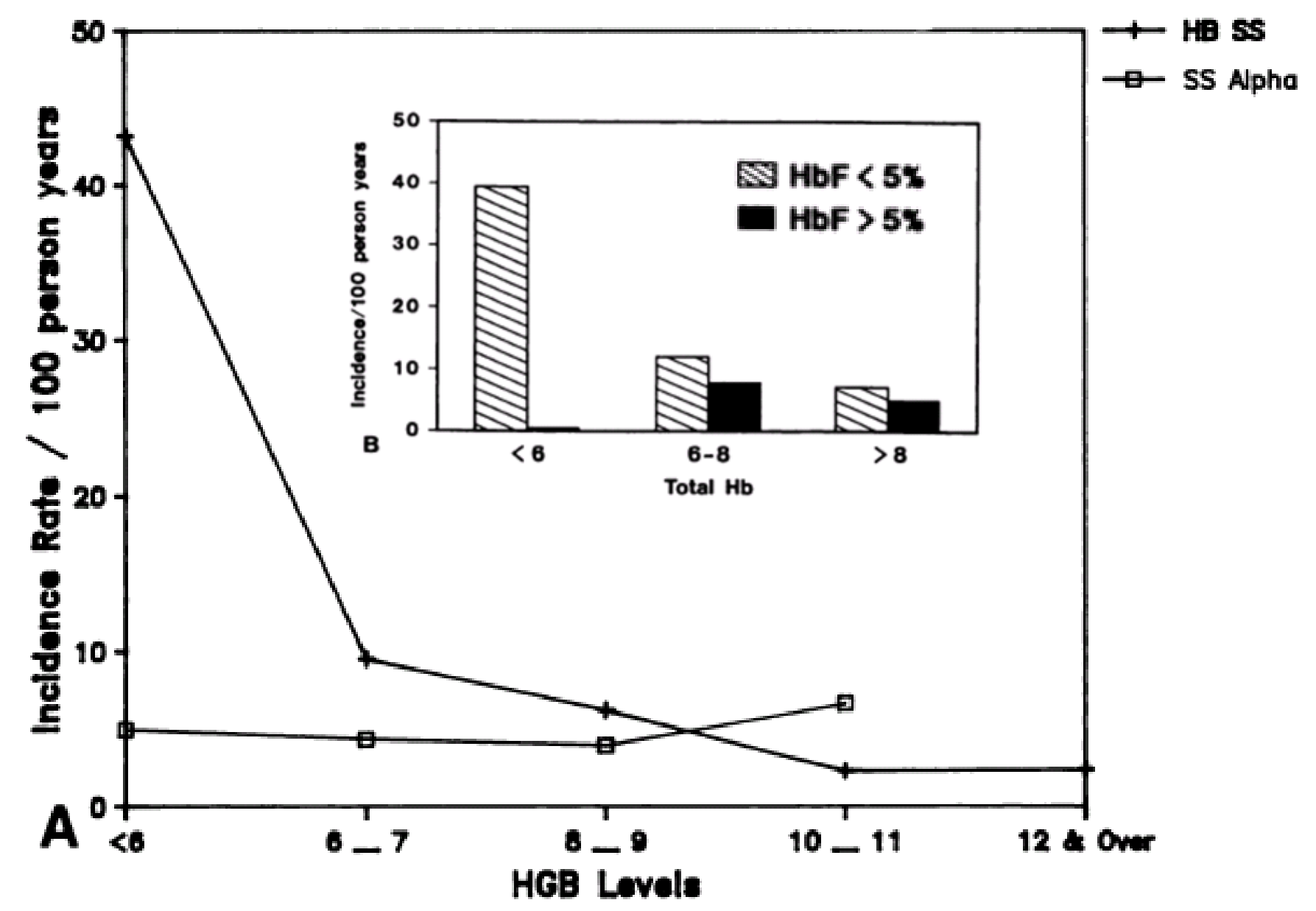
Associations with Genetic Modifiers:

- **KL is a glycosal hydrolase in NO metabolism, vascular function**
- **TGF-BMP (wound healing and angiogenesis)**
- **TEK receptor tyrosine kinase, angiogenesis**
- **HLA B35 and CW14 alleles**

Genome-wide Associations:

- **ALCAM (endothelial regulation)10%**

Hemoglobin Predicts Incidence of Leg Ulcers



Leg ulcers in patients with sickle cell disease. M. Koshy et al. BLOOD 1989 74

Risk Factors for Renal Failure

Common in older adults (18 to 20%); rapidly increases after 40 years of age. Strong predictor of mortality.

Problems in Predicting Risk Factors:

- **Very Age-dependent with limited analysis of older patients**
- **Definitions vary**

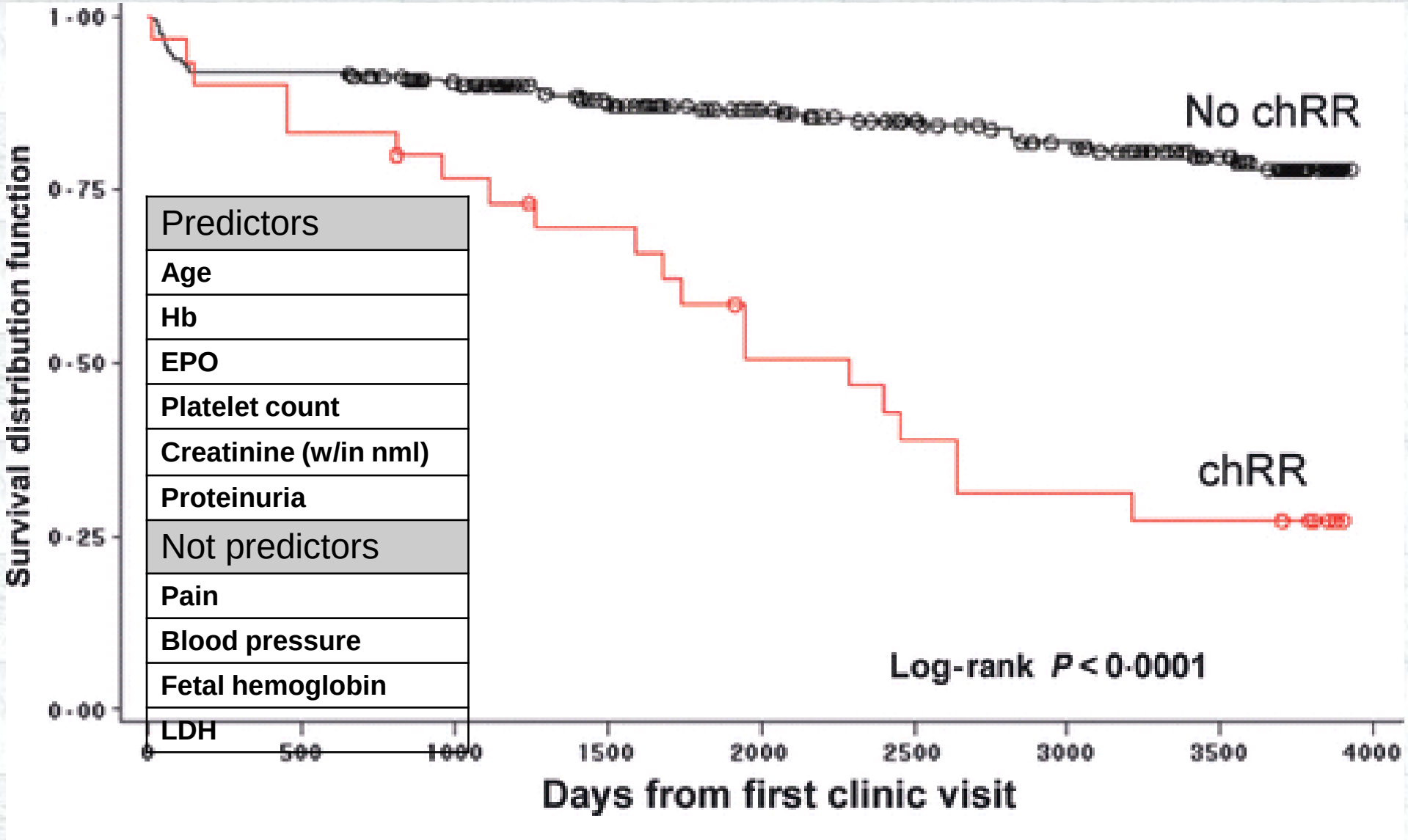
Risk Factors:

- **Age**
- **Microalbumin urinary excretion, Macroalbumuria**
- **Creatinine (even within normal range)**
- **Hypertension**
- **Association with CNS, leg ulcers, multi-organ failure**

Associations with Genetic Modifiers:

- MYH9 **(myosin, heavy chain, non-muscle) and** APOL1 **(apolipoprotein-1) both associated with glomerulosclerosis and renal failure in African Americans**
- **BMPRIB (receptor 1B gene) ~ with GFR**

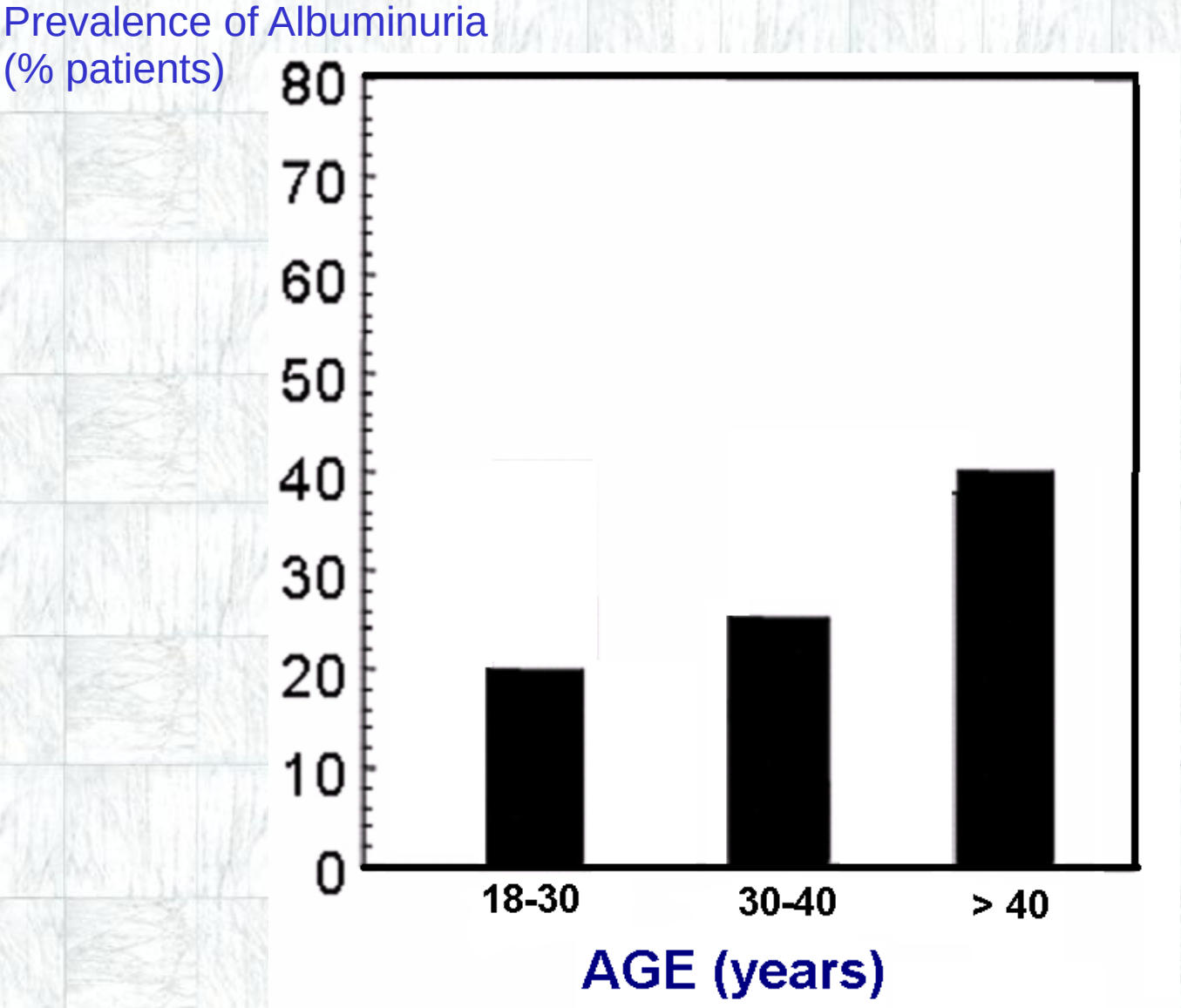
EPO Reticulocytopenia Anemia Progresses with Age & Predicts Death in Adults



Predictors
Age
Hb
EPO
Platelet count
Creatinine (w/in nml)
Proteinuria
Not predictors
Pain
Blood pressure
Fetal hemoglobin
LDH

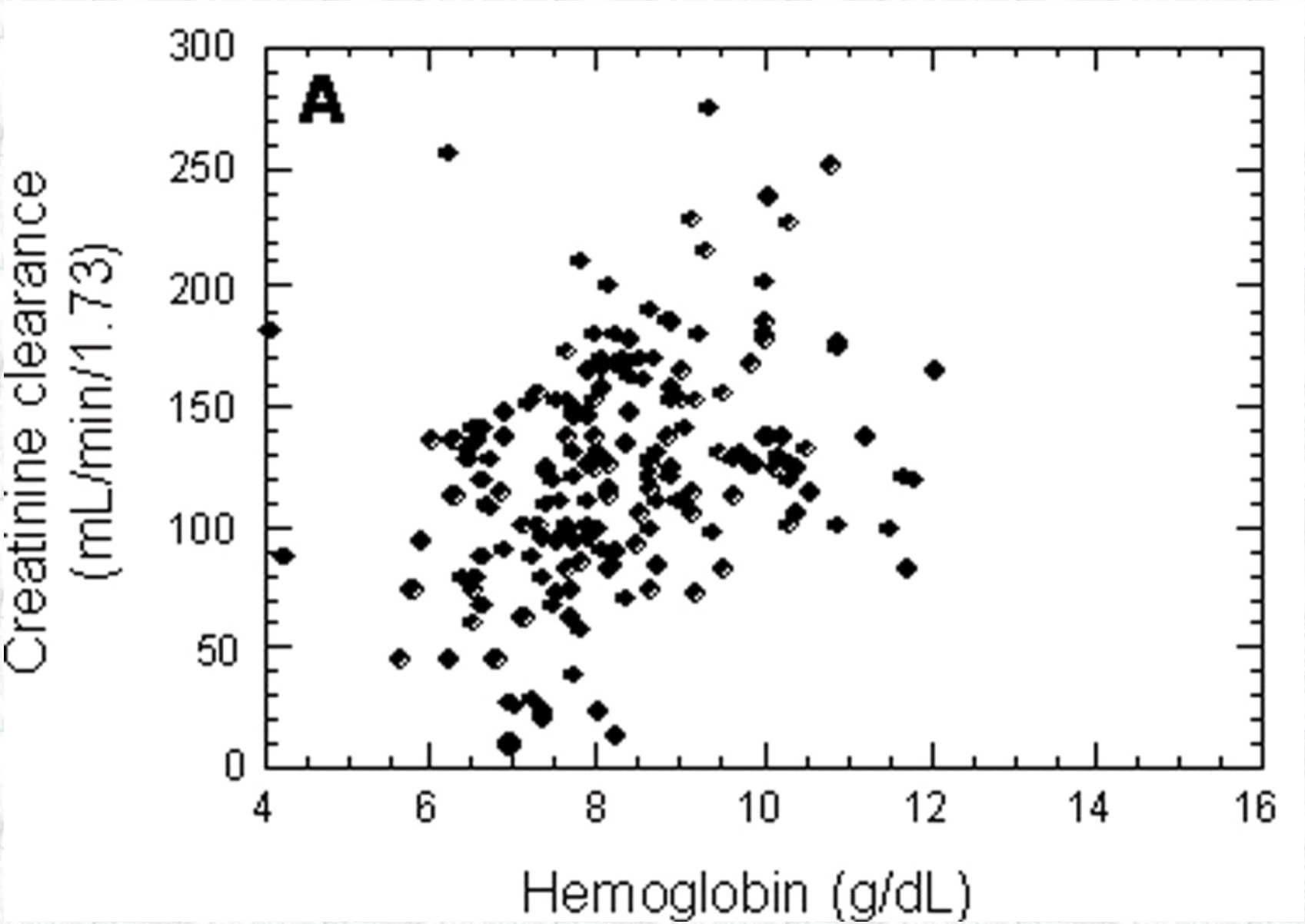
Standard clinical practice underestimates the role and significance of erythropoietin deficiency in sickle cell disease. S. Saraf et al. BJH Mar 2011

The Age and Prevalence of Severe Albuminuria in Adults



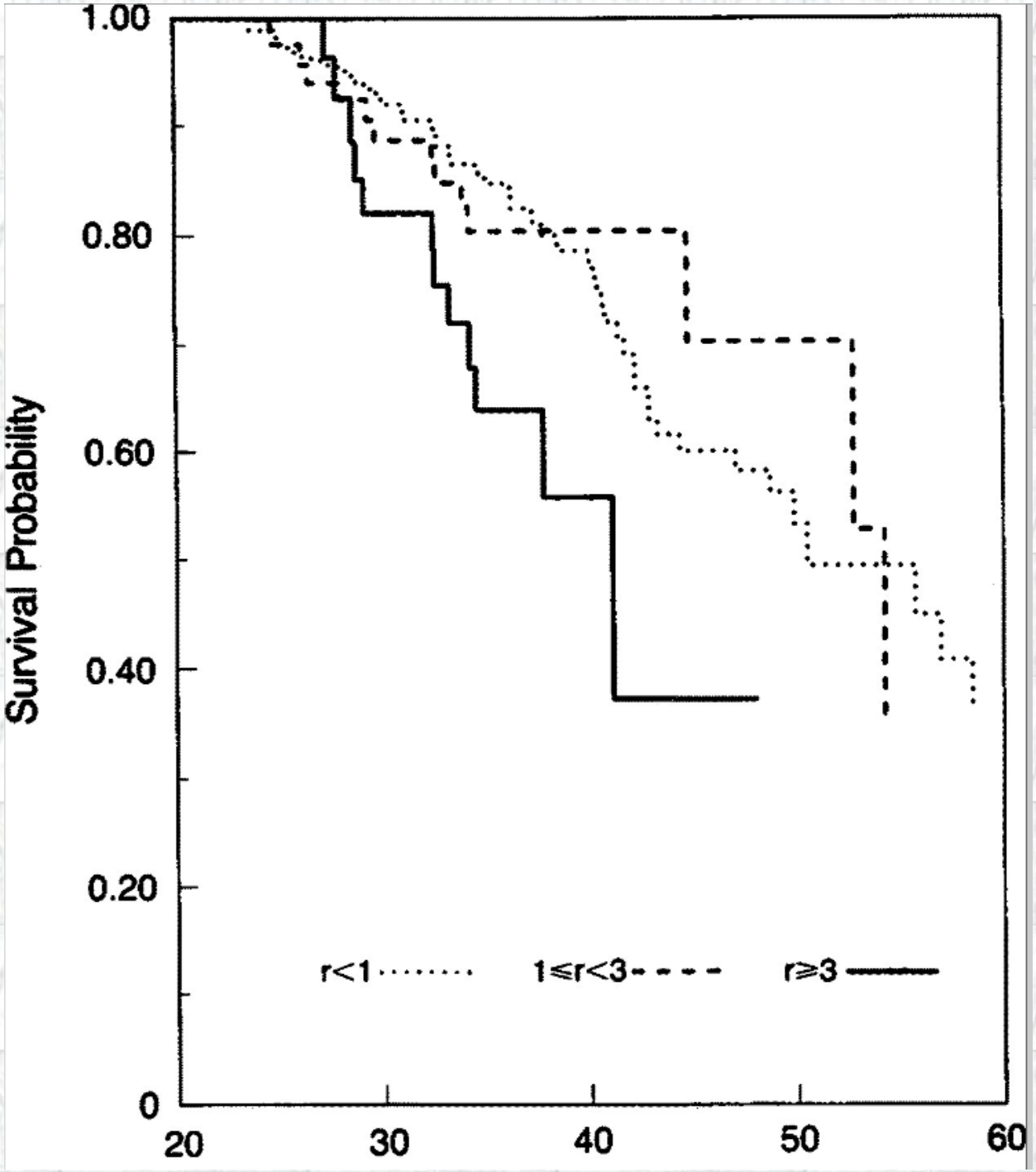
Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical corrrelates of progressive renal failure.
A. Guasch, J Am Soc Nephrol 2006

The Correlation between Hemoglobin and Creatinine Clearance



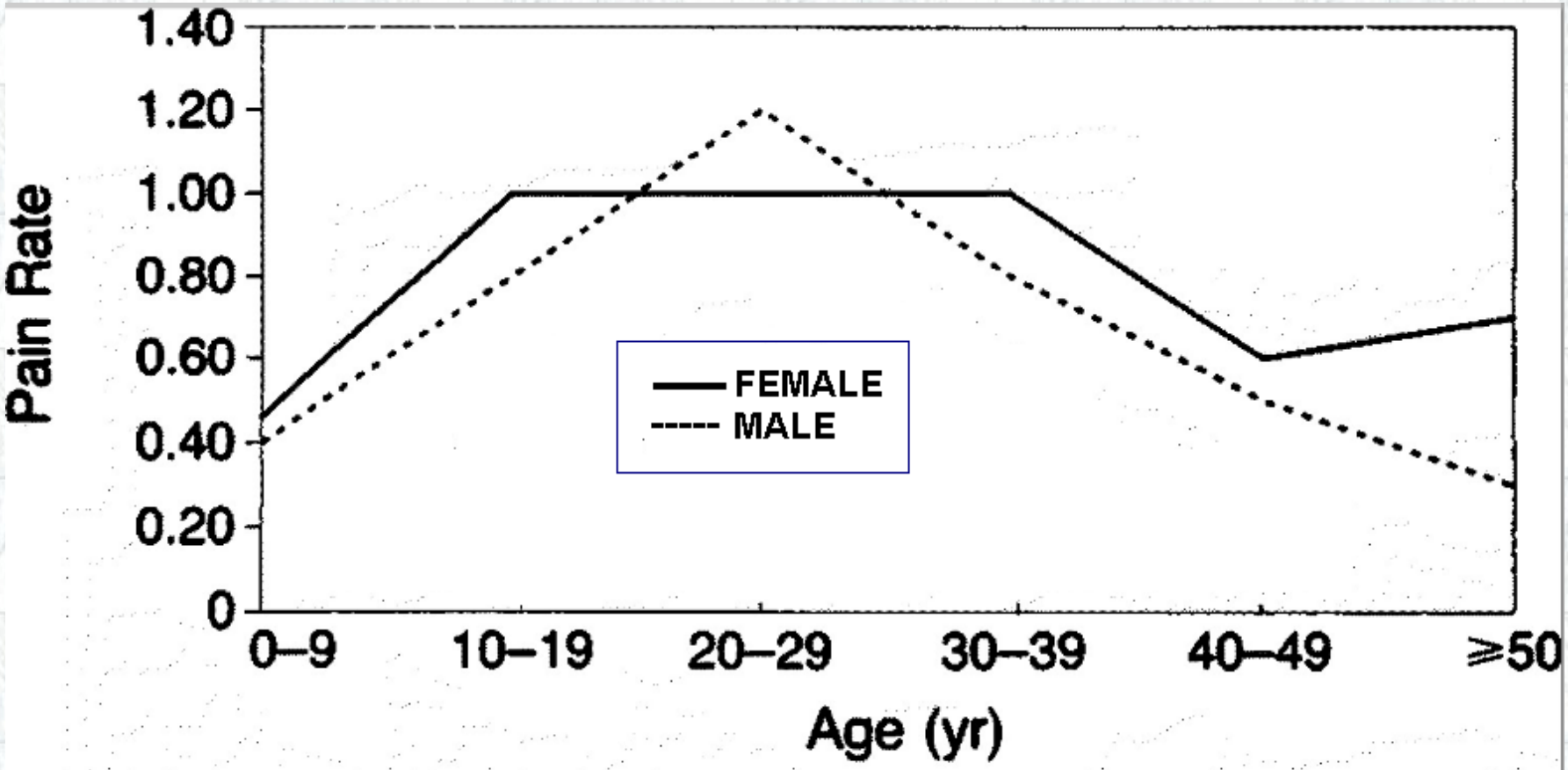
Guasch A et al. JASN 2006;17:2228-2235

Survival of Patients with Sickle Cell Anemia (>= 20 years old at entry) who had different pain rates



Pain in Sickle Cell Disease — Rates and Risk Factors. O. Platt, B. Thorington, D. Brambilla, P. Milner, W. Rosse, E. Vichinsky, T. Kinney. N Engl J Med 1991.

Age-specific Pain Rates (episodes per patient-year) among male and female patients with sickle cell anemia



	0–9	10–19	20–29	30–39	40–49	≥50
Females	527	336	242	97	38	16
Males	566	299	182	76	23	10

Pain in Sickle Cell Disease — Rates and Risk Factors. Orah S. Platt, M.D., Bruce D. Thorington, M.S., Donald J. Brambilla, Ph.D., Paul F. Milner, M.D., Wendell F. Rosse, M.D., Elliott Vichinsky, M.D., and Thomas R. Kinney, M.D. N Engl J Med 1991; 325:11-16July 4, 1991

Summary of Poisson Model for Pain Rate in Sickle Cell Anemia

Variable	Parameter Estimate*	Standard Error	Chi-Square (df)	P Value
Intercept	−2.3190	0.8378		
Age (yr)				
5–9	0	—	16.47 (5)	0.006
10–19	0.3631	0.1399		
20–29	0.5729	0.1703		
30–39	0.3785	0.2109		
40–49	−0.0973	0.2994		
≥50	−0.1641	0.5142		
Fetal hemoglobin level, squared	−0.0032	0.0008	16.57 (1)	<0.001
Hematocrit	0.0860	0.0158	29.59 (1)	<0.001
Sex				
Female	0	—		
Male	−0.3044	0.1036	8.70 (1)	0.003

Pain in Sickle Cell Disease — Rates and Risk Factors. Orah S. Platt, M.D., Bruce D. Thorington, M.S., Donald J. Brambilla, Ph.D., Paul F. Milner, M.D., Wendell F. Rosse, M.D., Elliott Vichinsky, M.D., and Thomas R. Kinney, M.D. N Engl J Med 1991; 325:11-16July 4, 1991

Summary

- The phenotype of adult sickle cell disease is affected by the primary mutation, severity of hemolysis and anemia, the modulatory effects of hemoglobin F, and the cumulative effects of organ injury interacting with the pathophysiology of aging. Environmental factors including access to care, are important variables.
- It is likely that polymorphisms in genes play a central role in altering the pathophysiology and phenotypic heterogeneity that characterizes sickle cell disease. In addition, genetic modifiers that affect the pathophysiology of aging and further modulate the sickle phenotype in adults.
- Understanding of the adult phenotype is limited by the lack of hospitalized and non-hospitalized morbidity data in older adults.
- Based on the differences in clinical manifestations of sickle cell complications between adults and pediatric patients, one cannot assume the same genetic modifiers are responsible for the phenotypic heterogenicity or even pathophysiology