Pregnancy-associated plasma protein-A (PAPP-A) as a mortality predictor of long-term hemodialysis patients

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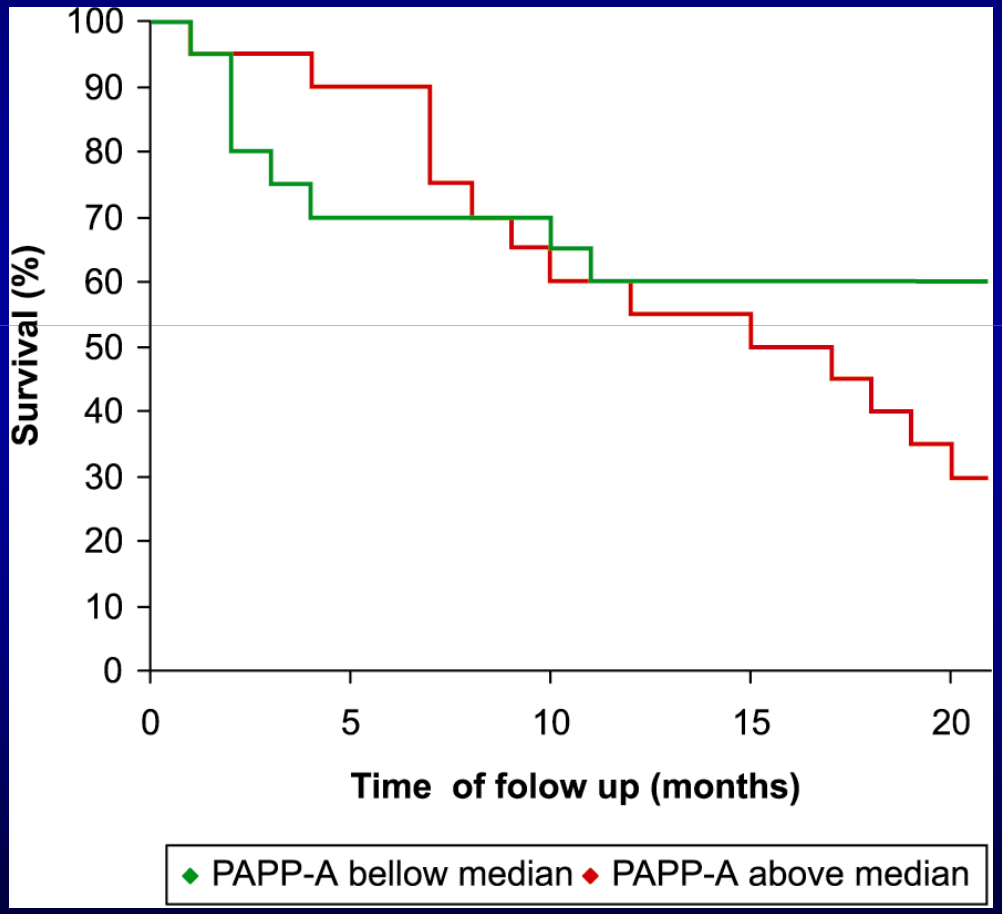
PAPP-A
pregnancy-associated plasma protein A

- metalloproteinase, cleaves IGFBP-4→IGF-1 increase
- screening of Down syndrome in the 1st trimester
- present in ruptured atherosclerotic plaques
- biomarker of acute coronary syndrome
- increased in HD patients, related to renal function

PAPP-A and survival of HD patients – a pilot study

40 patients, 20 months follow-up, 22 patients+

dead vs. living patients 26.8 (21.6-36.8) vs. 20 (14.9-26.6), p=0.034



Kalousová et al., Blood Purif 2004

Aim of the study

PAPP-A and related parameters

- other pregnancy protein – placental growth factor - **PlGF**
- matrix metalloproteinases – **MMP-2** and **MMP-9**
- molecules linked to PAPP-A action – **IGFBP-4** and **IGF-1**
- established cardiac markers – **cTnI, BNP**
- inflammatory markers – **CRP**; **retinol**

→ relationship of their serum levels
to prognosis of long term hemodialysis patients
in 5-years follow-up

Prospective observational study

261 long-term hemodialysis patients

- **follow-up for 5 years (11/2003-11/2008)**
- patients from 6 HD centres in the Czech Republic
- 141 men and 120 women, mean age 64±13 years
- clinical and laboratory characteristics collected at the beginning of the study

66 healthy controls

- 25 men and 41 women, mean age 59±9 years

Clinical characteristics of hemodialysis patients

- duration of HD treatment – median 2 years
- diabetes mellitus - 33%
- dyslipidemia - 41%
- hypertension - 84%
- cardiovascular disease - 61%
- cerebrovascular disease - 24%
- peripheral vascular disease - 25%

Basic laboratory parameters

Parameter	HD patients	Controls	p HD vs. controls
Hemoglobin (g/L)	106±13.2	141±10.1	<0.001
Creatinine (μmol/L)	753±198	88±13	<0.001
Albumin (g/L)	37.8±3.8	44.4±2.6	<0.001
CRP (mg/L)	10.0±16.5	3.3±2.4	0.002
Leukocytes ($x10^9$/L)	6.92±1.95	6.41±1.70	0.1
BMI (kg/m^2)	25.4±4.52	25.5±3.42	0.9

Follow up of HD patients - 5 years

- **+ 146 patients (56%)**
  - 71 – cardiovascular cause
  - 42 – infection
  - 14 – tumour
  - 15 – other cause

- 52 patients – transplantation, 8 of them +
- 2 patients censored to due other reason

Laboratory methods

- **PAPP-A** – TRACE (KRYPTOR, Brahms)
- **PlGF, IGFBP-4, MMP-2 and MMP-9** – ELISA (RD Systems)
- **IGF-1** – IRMA
- **BNP and cTnI** – CLIA
- **Retinol** – HPLC
- Basic nutritional and inflammatory parameters - standard methods, automated analyzers

Statistical analysis

- software **SPSS v.16.0**
- **Survival analysis**
  - **Kaplan-Meier analysis**
  - **Cox regression** – univariate and multivariate analysis (forward and backward methods)
- overall mortality, cardiovascular mortality, mortality due to infection
- transplantation taken as time dependent covariate
- BCH parameters treated as continuous variables
- HR (95%CI) expressed per SD, for age per year

PAPP-A

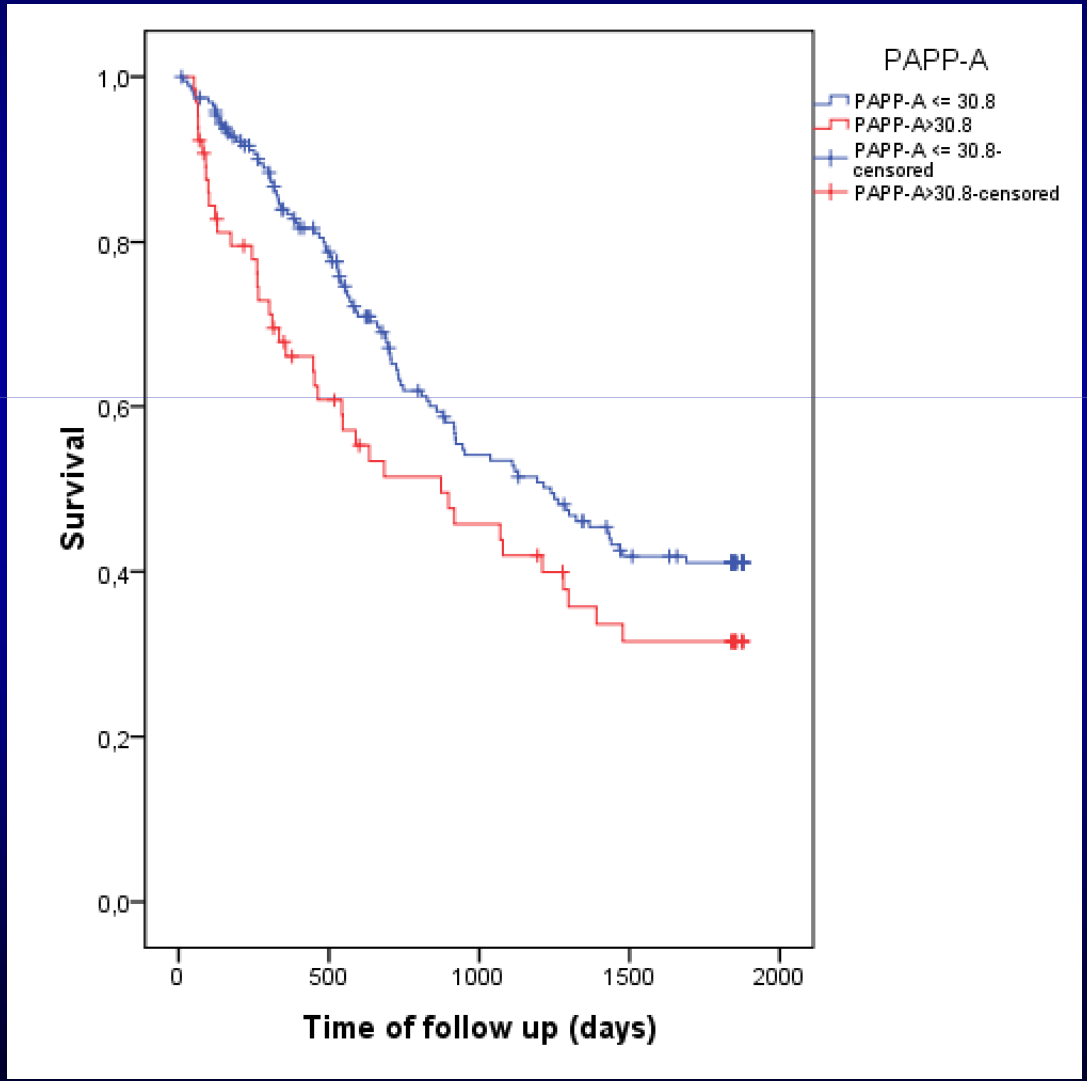
- **27.6±15.5 mIU/L in HD vs. 9.4±2.5 mIU/L in controls, p<0.001**
- **Significant independent predictor**
  - **for overall mortality**

    HR/SD (95%CI) 1.237 (1.060-1.444), p=0.007
  - **for mortality due to infection**

    HR/SD (95%CI) 1.416 (1.115-1.798), p=0.004
  - not for cardiovascular mortality

Overall mortality

PAPP-A below and over 30.8 mIU/L (upper quartile), p=0.03



Other markers and mortality

all increased in HD except for MMP-9

- **PlGF** – n.s. (p=0.08-0.1)
- **MMP-2 and MMP-9** – n.s.
- **IGFBP-4** – n.s.
- **IGF-1** – significant in uni-variate analysis
- **cTnI** – significant in both uni-variate and multi-variate analysis for overall and cardiovascular mortality
- **BNP** - significant only in uni-variate analysis for overall and cardiovascular mortality
- **Retinol** - significant in both uni-variate and multi-variate analysis for overall and cardiovascular mortality

(Kalousová et al. Am J Kidney Dis 2010)

Significant independent mortality predictors

Overall
PAPP-A
cTnI
Albumin
Creatinine
Retinol
Age
Diabetes mellitus
Cardiovascular disease
in the personal history

Cardiovascular
cTnI
Albumin
Retinol
Cardiovascular disease
in the personal history
Transplantation

Due to infection
PAPP-A
Creatinine
Diabetes mellitus

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