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

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Patients with chronic kidney disease

- High mortality rate mainly due to cardiovascular complications
- They differ from the general population
- Classical risk factors as well as non-traditional/ uremia-related ones are involved

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

Aim of the study

PAPP-A and related parameters

- other pregnancy protein – placental growth factor - **PIGF**
- 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

Study design:
Prospective observational cohort 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)
- P**IGF, 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

Conclusion

This study demonstrates PAPP-A as an independent predictor of overall mortality and mortality due to infection in hemodialysis patients. Our results suggest superior relationship of PAPP-A to infection-inflammation than to cardiovascular risk in HD patients.

Acknowledgement

- *physicians and nurses from co-operating dialysis centres*
  Dr. Kratochvilová and Dr. Hodková (Prague)
  Dr. Gorun (Ústí nad Orlicí)
  Dr. Hobzek and Mrs. Žďánská (Písek)
  Dr. Suchanová and Dr. Křížová (Tábor)
  Dr. Nýdlová (Strakonice)
- *laboratory staff*
  Dr. Soukupová and Mrs. Hudcová
- *patients and controls*

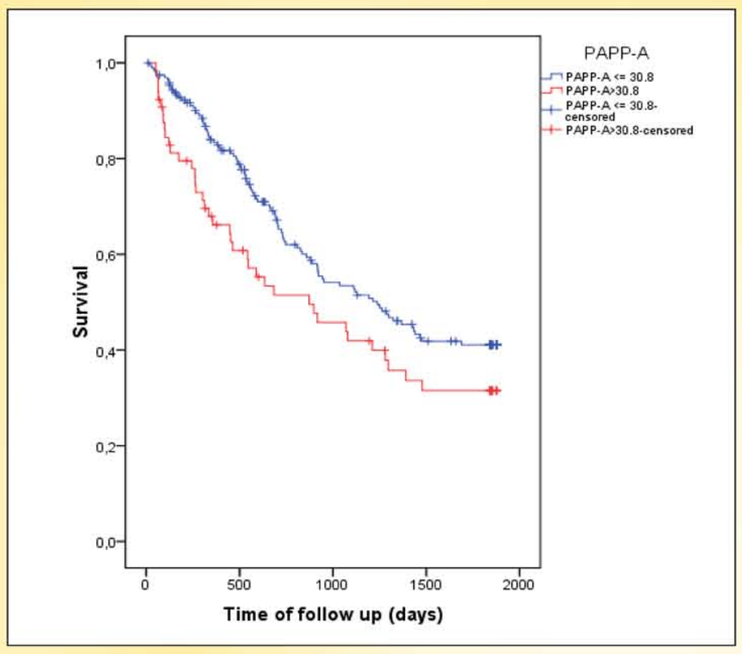
The study was supported by grant IGA MH CZ NS/10043-4/2008 and by the research project MSM 0021620807.

Results: 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

- **PIGF** – 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 for Overall, Cardiovascular and due to Infection Mortality

	Overall mortality HR (95% CI)	p	Cardiovascular mortality HR (95% CI)	p	Mortality due to infection HR (95% CI)	p
PAPP-A	1.237 (1.060-1.444)	0.007			1.416 (1.115-1.798)	0.004
cTnI	1.411 (1.200-1.658)	<0.001	1.470 (1.208-1.790)	<0.001		
Albumin	0.722 (0.595-0.876)	<0.001	0.588 (0.447-0.774)	<0.001		
Creatinine	0.789 (0.637-0.978)	0.03			0.672 (0.487-0.926)	0.02
Retinol	0.775 (0.632-0.950)	0.01	0.671 (0.500-0.902)	0.008		
Parathromone					*0.621 (0.364-1.058)*	*0.08*
Age	1.030 (1.011-1.048)	0.001				
Diabetes mellitus	1.625 (1.128-2.340)	0.009			2.966 (1.474-5.966)	0.002
CVD	1.638 (1.039-2.582)	0.03	3.753 (1.699-8.289)	0.001		
Transplantation			0.121 (0.016-0.893)	0.04		