

Prognostic Impact Of Progastrin Levels In Blood Compared To MSKCC
Based Clinical Prognosis In Metastatic Renal Cell Cancer Patients

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Abstract

Background and Aims: Progastrin is a tumor promoting peptide which is detectable in the blood of patients with different cancers (*Prieur et al. AACR 2017, Prieur et al. ASCO 2017*). Progastrin gene is a direct target of the WNT/ β -catenin oncogenic pathway involved in tumorigenesis of many organs, but it is unknown if it has any prognostic significance in metastatic renal cell cancer (mRCC) patients. We evaluated progastrin as a prognosis marker along with known markers of prognosis in mRCC.

Methods: 144 patients with mRCC were enrolled in this study and blood samples were drawn after consent. Progastrin was measured using the ELISA cancerREAD®. Progastrin concentrations in the 144 mRCC patients (*test set*) was assessed against 213 samples from asymptomatic volunteers from the French blood establishment (*control set*). The prognostic impact of progastrin levels was determined with overall survival (OS) using Cox proportional hazards and also compared to MSKCC based clinical prognosis (good; intermediate; poor). Statistical significance was considered at $P \leq 0.05$.

Results: The median follow-up of the cohort was 5.45 years (IQR: 1.87-9.95) and at the time of analysis 98/144 patients had died from disease progression. Plasma progastrin was detected in 95% of the patients (cut-off value 1 pM, range 0 to 272 pM, median value of 7.2 pM; IQR 3.20-19.71) compared to the control set (median value=0.43 pM; IQR 0.00-1.51). The Receiver Operating Characteristic analysis indicated an area under the curve of 0.91 ($p < 0.0001$; 95% CI 0.88 to 0.94). At the univariate level, MSKCC scores (good; intermediate; poor categories) in this cohort was associated with OS and was prognostic ($p < 0.0001$). We detected progastrin levels were higher with MSKCC score poor prognostic ($p < 0.0002$) (median 30.39 pM; IQR 9.31-57.20). Elevated progastrin was also independently associated with poor survival ($p < 0.0001$) and a multivariate model of MSKCC taken with progastrin levels remained significantly associated with poor survival ($p < 0.0001$).

Conclusion: Elevated progastrin levels in mRCC is correlated with poor survival and further refines clinically used MSKCC prognostic scores. Progastrin assay is a simple and inexpensive blood test that might define subsets of mRCC patients with poor survival who need to be identified for aggressive treatments.

Methods

Patient Methods

A large tertiary level, clinically annotated hospital registry with prospective blood/plasma collection from advanced kidney cancer patients between 5/2011 and 9/2013 and uniform sampling was used. Advanced kidney cancer patients were followed until death.

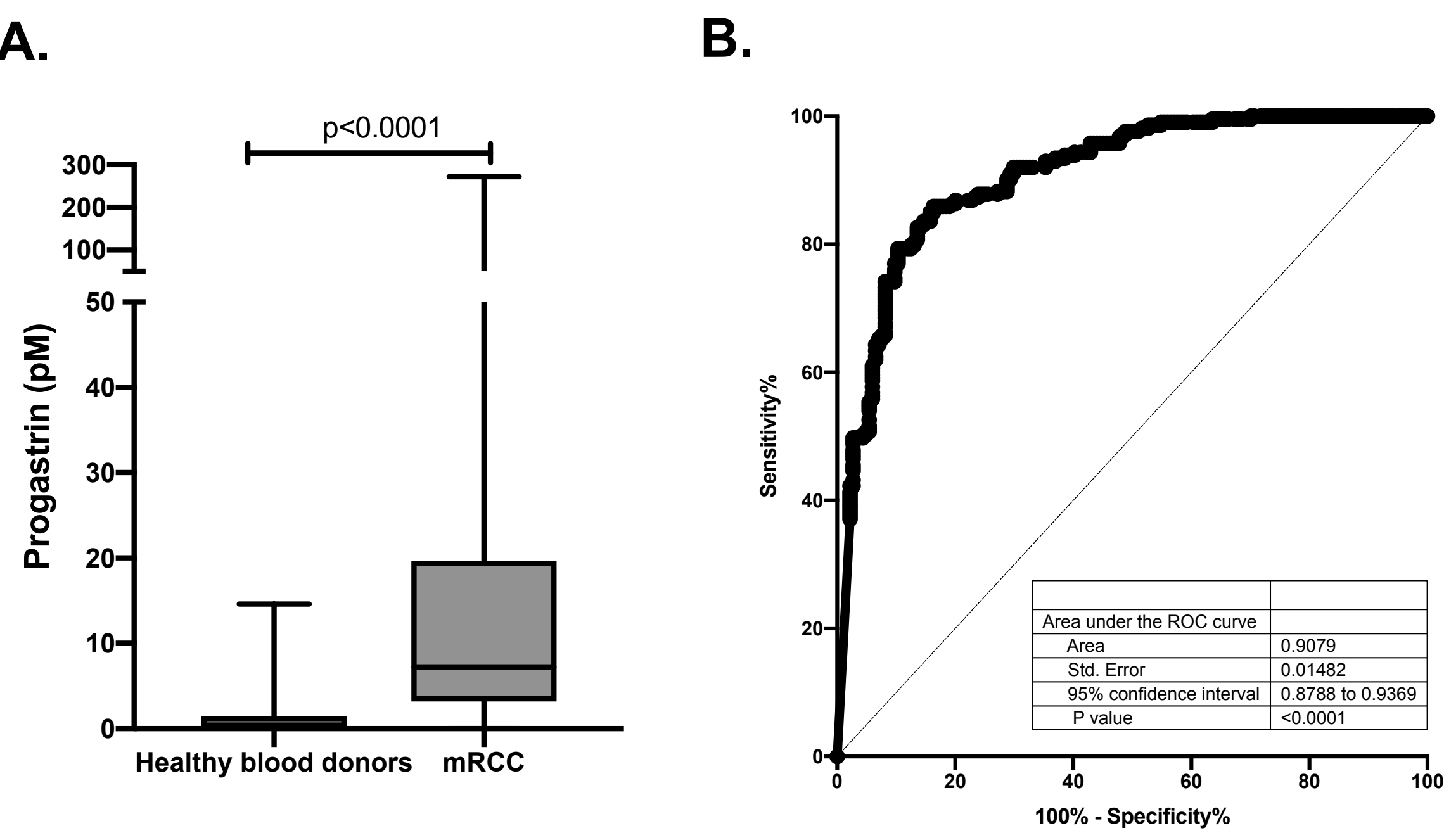
Analytical Methods

Each plasma EDTA sample was tested in duplicate using 50 μ l of plasma using cancerREAD lab test (ECS-Progastrin) following manufacturer’s instructions.

Statistical Methods

Comparisons between groups were performed using the t-test. The statistics were performed with two-sided 5% alfa risks. The Bonferroni–Holm correction was used for multiple comparisons. The Kaplan Meier curves were been compared with the logrank test. The following programs were used to perform the statistical analyses: Prism software (GraphPad, La Jolla, CA, USA); SAS version 9.4 @ software. Graphics were performed using R software version 3.4.4.

Elevated Progastrin Levels in mRCC Patients



A. Plasma progastrin levels in mRCC patients compared to healthy blood donors. Plasma progastrin levels is detected in 95% of the patients (threshold = 1pM). Median and IQR value for control set and mRCC are 0.43 pM (IQR 0.00-1.51) and 7.20 pM (IQR 3.22-19.71) respectively.

B. ROC curve of progastrin for the diagnosis of mRCC compared to healthy blood donors.

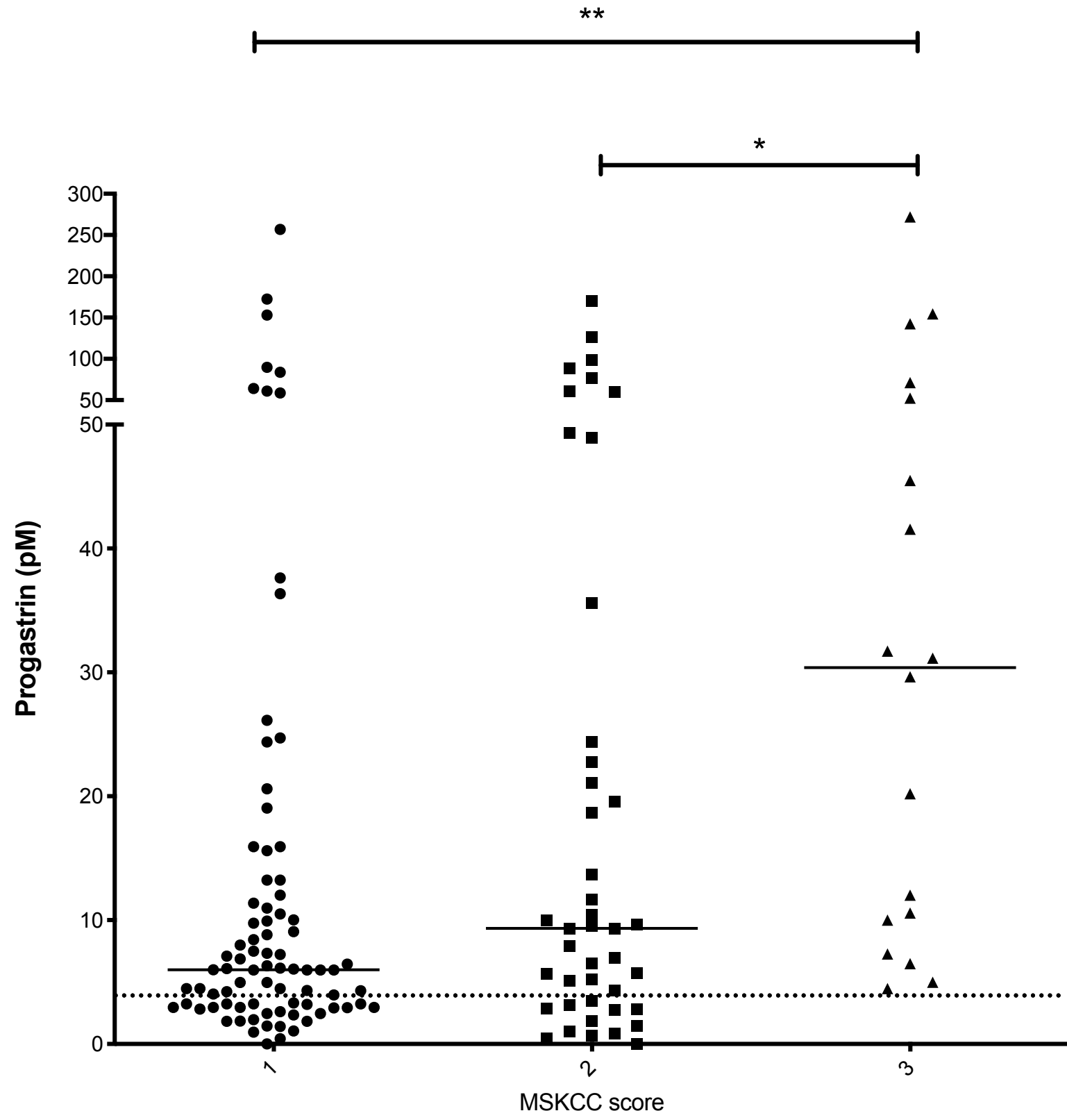
RESULTS: Study Demographics

No. of Patients	Gender		Median Age, Years (range)	Median follow-up, Years (IQR)
	Male	Female		
144	110	34	63 (41-85)	5.45 years (IQR: 1.87-9.95)
	76,4%	23,6%		

AJCC Stage (at diagnosis)					dead	alive	missing
I	II	III	IV	missing			
20	23	41	55	7	46	98	2
13,9%	16,0%	28,5%	38,2%	4,9%	31,9%	68,1%	1,4%

Progastrin Levels Are Higher in MSKCC Poor Prognostic Group

A. Progastrin levels per MSKCC groups (Good; Intermediate; Poor).



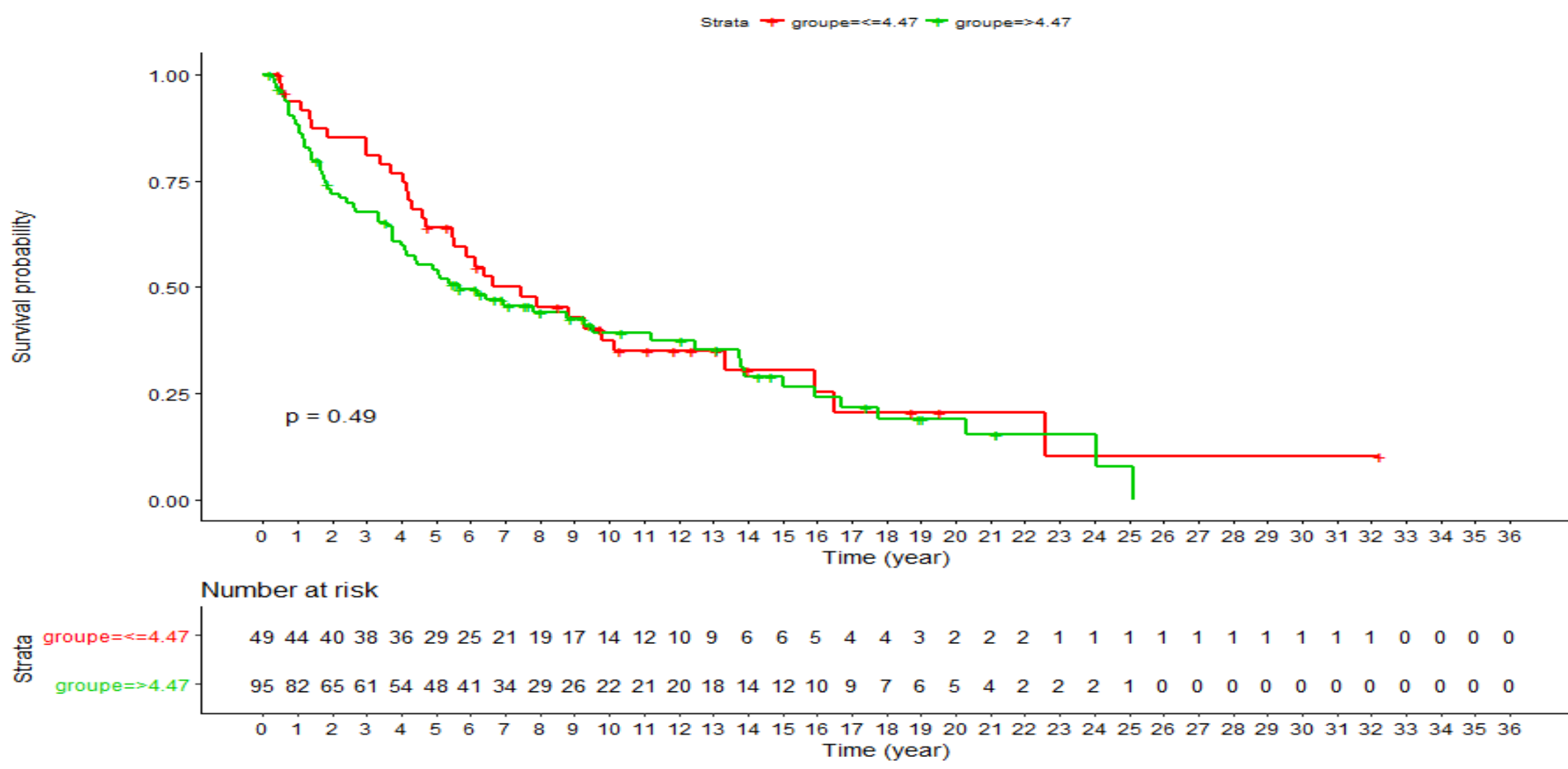
Progastrin levels were higher with MSKCC score poor prognostic ($p < 0.0002$) (median 30.39 pM; IQR 9.31-57.20).

B. Descriptive analysis according MSKCC score.

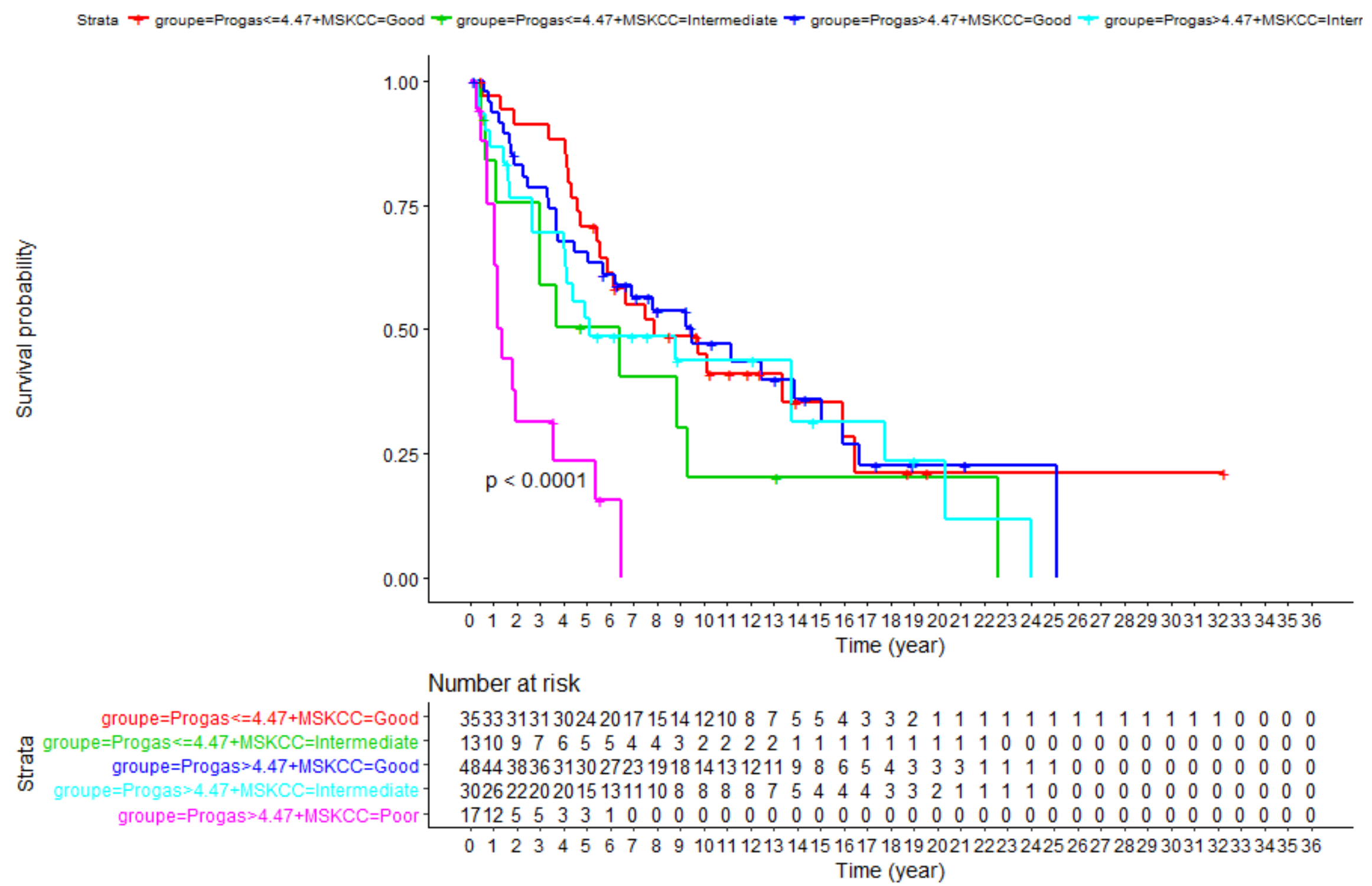
		Score MSKCC		
		Good	Intermedi ate	Poor
Progastrine	N	83	43	18
	NMiss	0	0	0
	Min	0.00	0.00	4.47
	Q1	2.96	3.12	10.00
	Median	6.00	9.34	30.39
	Q3	12.01	24.41	52.56
	Max	256.80	170.17	271.88
	Mean	18.25	24.94	52.67
	Std	39.25	37.28	70.09

Higher Progastrin Levels Are Associated With Poor Survival

A. Progastrin levels (threshold = 4.47pM according to min value of the poor score group from MSKCC score) and their association with OS in mRCC patients.



B. Progastrin levels (threshold = 4.47pM according to min value of the poor score group from MSKCC score) and MSKCC scores and their association with OS in mRCC patients.



Conclusions

- Progastrin was detected in majority (95%) of the kidney cancer patients.
- Elevated progastrin levels in mRCC is correlated with poor survival and further refines clinically used MSKCC prognostic scores.
- Progastrin assay might be useful for defining subsets of mRCC patients with poor survival who need to be treated aggressively.