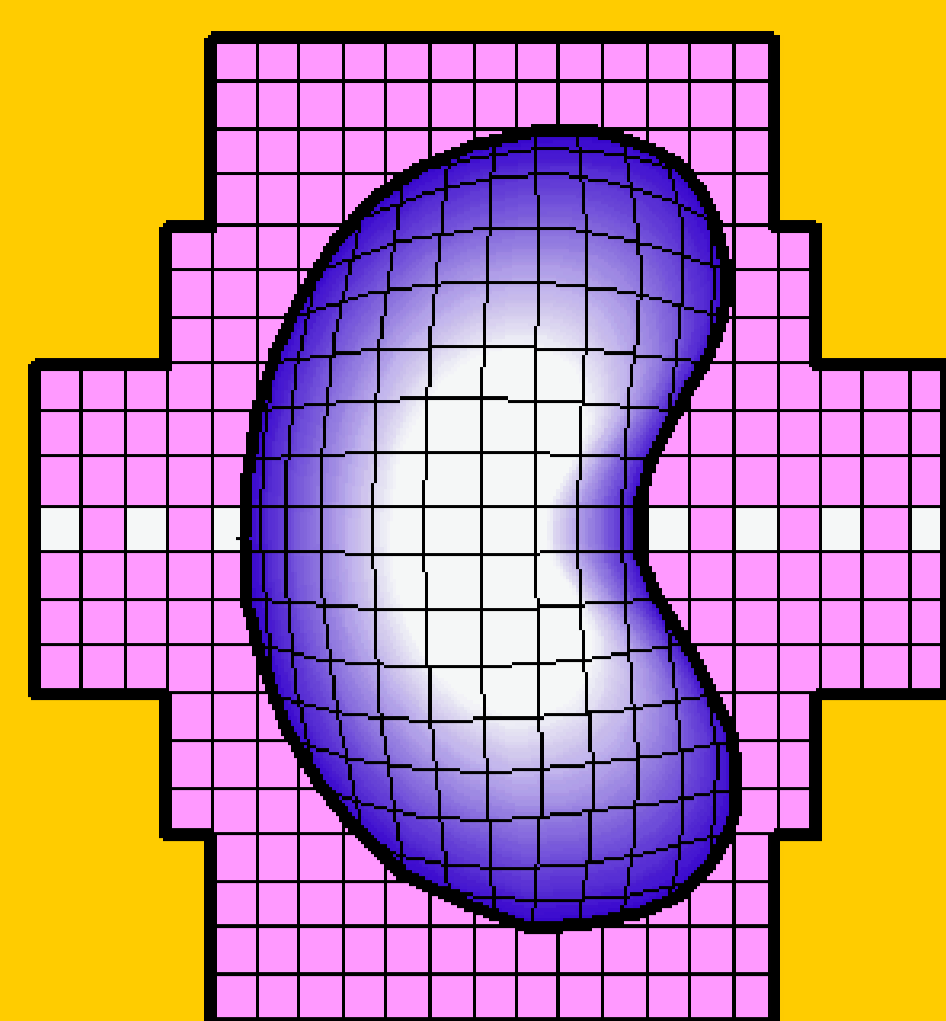


# Predictors of response to therapy in idiopathic membranous nephropathy

Simona Stancu<sup>1,2</sup>, Eugen Mandache<sup>2</sup>, Adrian Zugravu<sup>1, 2</sup>, Ligia Petrescu<sup>1, 2</sup>, Andreea Avram<sup>2</sup>, Gabriel Mircescu<sup>1, 2</sup>

<sup>1</sup>Nephrology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania and

<sup>2</sup>"Dr Carol Davila" Teaching Hospital of Nephrology, Bucharest, Romania



## INTRODUCTION AND AIMS

Idiopathic membranous nephropathy (IMN) is the most common cause of nephrotic syndrome in Caucasians. Auto-antibodies against phospholipase A2 receptors are thought to induce podocyte lesions, resulting in heavy proteinuria. The intensity of proteinuria and its tubular consequences are recognized prognostic markers in IMN. However, about a half of IMN patients have microscopic hematuria. The cause of hematuria in IMN is poorly understood and its prognostic significance was not investigated. Recent data support that the cross-talk between podocytes and the endothelial cells is essential for the integrity of the glomerular filtration barrier, suggesting that the intensity of hematuria, not only of proteinuria, could be a prognostic marker in IMN.

## OBJECTIVES

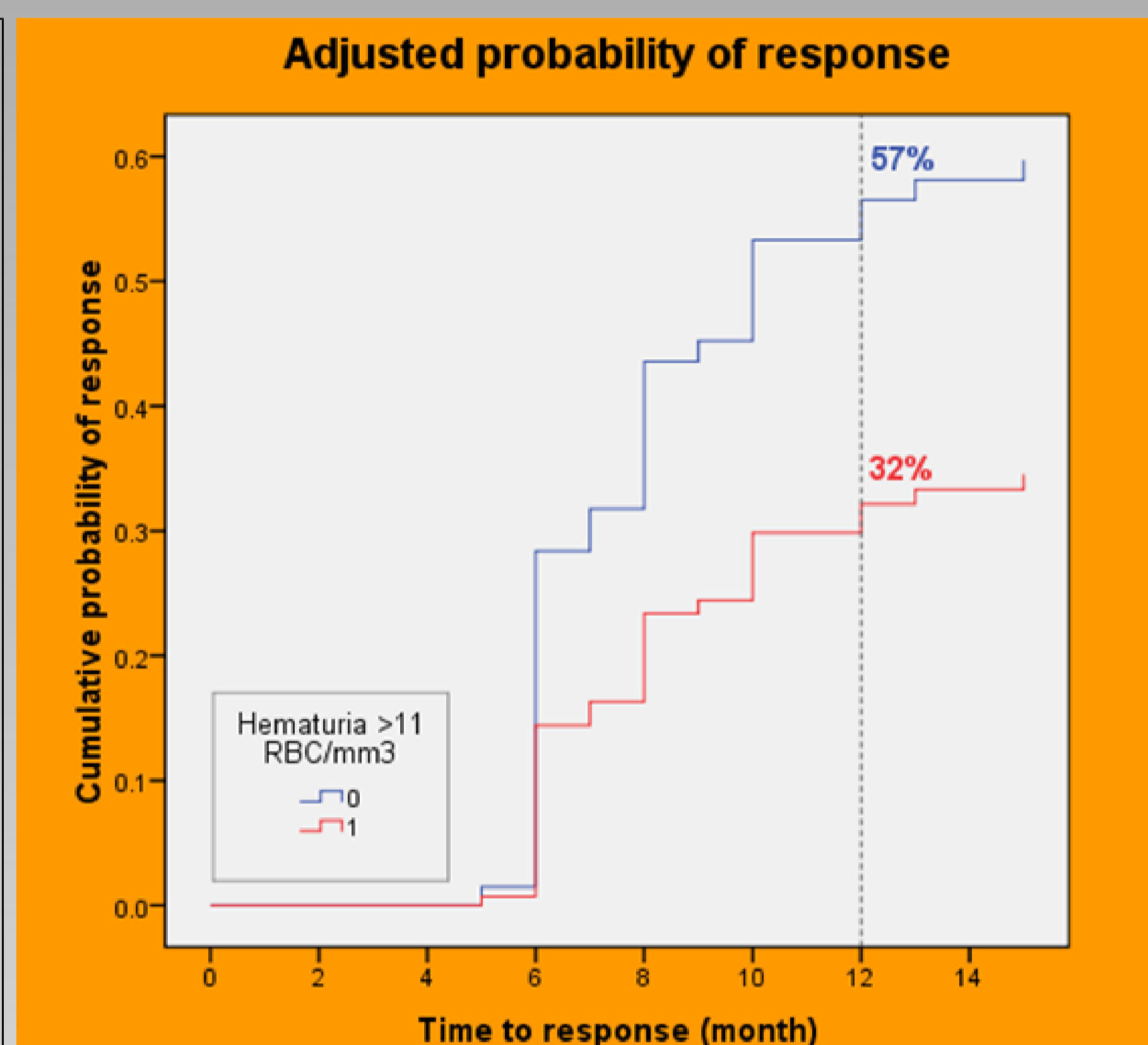
To evaluate the factors associated with the response to therapy in IMN, focusing on hematuria.

## METHODS

Retrospective, single center study including clinical, laboratory and histopathology data on patients with idiopathic membranous nephropathy.

## RESULTS

- From the 206 patients diagnosed with idiopathic membranous nephropathy (kidney biopsy, negative clinical and serology data for a secondary condition), outcome data were available in 118 (64% male, median age 50 [39-60] years); median follow-up period 14 [4-57] months.
- Features at presentation: hypertension 47%, full nephrotic syndrome 66%, abnormal renal function (creatinine >1.2mg/dL) 24%, hematuria 58%. On renal biopsy: 40% had stage III, 27% stage II, 25% stage IV and 8% stage I; 14% had vascular hyaline deposits, 12% glomerulosclerosis and 25% tubular atrophy and/or interstitial inflammation.



In a model of Cox regression analysis, non-responsiveness was independently predicted by therapy with another protocol than Ponticelli's one and by higher hematuria. Although kept in the model, proteinuria had not a significant contribution (Table II).

Moreover, when hematuria and proteinuria were introduced in the model as categorical variables using median values as cut-offs (11 RBC/mm<sup>3</sup> and 6 g/g creatinine), only lower age, other protocols than Ponticelli's one and hematuria >11 RBC/mm<sup>3</sup> but not proteinuria >6g/g creatinine independently predicted the lack of response.

Figure 2. Adjusted probability of response to therapy according to hematuria

- ACEIs or ARBs were prescribed in 68% of patients. 80% received immunosuppression: 60% according to Ponticelli's protocol, and various other protocols in the rest of cases.
- Response was achieved by 53% (complete in 43%) with a median time to response of 8 months. Relapses were seen in 12 patients (10%) (median time to relapse 70.5 [44-98] months), 8 achieving thereafter complete or partial response.

Table II. Factors associated with non-responsiveness to therapy (Cox regression analysis)

Variables	B	SE	Exp. (B)	95% CI	Sig.*
Ponticelli's protocol (Yes)	-0.78	0.35	0.46	0.23 0.90	0.02
Hematuria (RBC/mm <sup>3</sup> )	-0.01	0.00	0.99	0.99 1.00	0.03
Proteinuria	-0.11	0.06	0.89	0.79 1.01	0.06

\* -2 Log Likelihood 292; Chi-square 12; df 3; p=0.006

The non-responders were older, had higher blood creatinine at presentation, higher percent of glomerular sclerosis and hematuria, and were treated in a lower proportion by Ponticelli protocol. Proteinuria was similar in both groups (Table I).

Table I. Patients' characteristics according to the response to therapy

Parameter	Non-responders (n=62)	Responders (n=56)	p†
Age (years)*	53	46.2	0.03
Serum creatinine (mg/dL) #	1.4	1	0.008
Hypertension (%)	60	46	0.05
Hematuria (%)	74	42	0.001
Glomerular sclerosis (%)	24	8	0.002
Ponticelli's protocol (%)	45	64	0.003
Proteinuria (g/g creatinine)*	9.0	7.4	0.06

\* median; # mean; † non-responders vs. responders

The adjusted probabilities of response at 12 months were 32 and 57% in patients with and without hematuria. The adjusted mean time to response was 9 months (Table III, Figure 1).

Table III. Factors associated with non-responsiveness to therapy (Cox regression analysis)

Variables	B	SE	Exp. (B)	95% CI	Sig.*
Age	-0.02	0.01	0.98	0.96 1.00	0.05
Ponticelli's protocol (Yes)	-0.73	0.35	0.48	0.24 0.95	0.03
Hematuria (>5 RBC/mm <sup>3</sup> ) (Yes)	0.76	0.35	2.15	1.09 4.24	0.03
Proteinuria (>6g/g) (Yes)	0.63	0.35	1.97	0.95 3.68	0.06

\* -2 Log Likelihood 290; Chi-square 14; df 3; p=0.003

## CONCLUSIONS

- More than a half of patients responded to treatment, and the probability of response was highest in the first 9 months.
- Hematuria and the Ponticelli's protocol, but not proteinuria, were the independent predictors of the response to therapy. Therefore, it could be speculated that the non-responsiveness to therapy is better described by hematuria because the autoimmune induced podocytes lesions is more severe in non-responders, and the resultant capillary wall damage is better described by hematuria than by proteinuria, which points to a new way of understanding the pathogenesis of membranous nephropathy. However, but further research is necessary.

"Dr. Carol Davila" Teaching Hospital of Nephrology

