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ORIGINALS

Arterial hypertension in primary chronic biopsied glomerulonephritis: prevalence and its influence on renal prognosis

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SUMMARY

Nowadays, glomerulonephritis are one of the most common causes of End-stage Renal Disease and starting point of dialysis in Spain. Several factors may influence negatively in this prognosis; among them, we may show up the systemic arterial hypertension. Though its prevalence in the glomerulonephritis is considered higher than in other nephropathies, with variations among series, probably due to difference in ages, in geographical areas, in histological types, in time on evolution of the nephritis… and because it is difficult to distinguish if the hypertension is a consequence of the nephritis or a consequence of the renal failure that can be present in several cases. In the same way, its negative influence in the renal prognosis may be influenced more by this renal failure, which can be its cause when it is quite severe, than by the hypertension itself. Our aims were to analyse, on the one hand the prevalence of hypertension in the 394 patients diagnosed of primary glomurolonephritis by means of a renal biopsy during two decades in the Bay of Cadiz, as well as its influence in the renal prognosis since the moment of the diagnosis, even with the absence of severe renal failure. We gathered demographic, clinical, analytical and histological data, as well as the situation of the renal function and the survival period of it at the end of each patient study. For the analysis prognosis and renal survival, Kaplan-Meier curves and the long-rank test were used.

Of the 394 patients, 247 are men and 147 are women, with an average age of 36.7 ± 17.7 years old. The global prevalence of hypertension was 39%, with a higher frequency in older patients. The gathered rate of renal survival for hypertensive patients was 54%, 28%, 20% and 4% at 5, 10, 15 and 20 years respectively; while for non-hypertensive patients, it was 83%, 75%, 66% and 62% for the same periods of time ($p < 0,001$). This worse tendency for hypertensive patients is observed too in each particular histological type, especially in the IgA nephropathy and membranous nephropathy. These results were the same for the patients who did not have severe renal failure in the moment of the biopsy.

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Conclusions: *Hypertension is a common fact in the primary glomerulonephritis, which also conditions, in an important way, the renal prognosis itself in a long term, from the moment of diagnosis and even before the existence of a significant renal failure.*

Key words: ***Hypertension. Glomerulonephritis. Renal survival. Renal failure.***

HIPERTENSIÓN ARTERIAL EN LAS GLOMERULONEFRITIS PRIMARIAS CRÓNICAS BIOPSIADAS: PREVALENCIA E INFLUENCIA EN EL PRONÓSTICO RENAL

RESUMEN

Las glomerulonefritis constituyen una causa importante de insuficiencia renal crónica terminal. Varios factores pueden influir negativamente en su pronóstico; de entre ellos destaca la hipertensión arterial. Su prevalencia en las glomerulonefritis es variable según las series, probablemente debido a diferencias demográficas, de tipos histológicos, de tiempo de evolución en el momento del análisis o a que es difícil diferenciar si es secundaria a la propia nefropatía o a la insuficiencia renal que puede producir ésta. Su influencia negativa en el pronóstico renal puede estar mediada más por la propia insuficiencia renal, de la que puede ser a su vez consecuencia cuando es lo suficientemente severa, que por la propia hipertensión.

Nuestros objetivos fueron analizar la prevalencia de hipertensión en el momento de la biopsia renal de los 394 pacientes diagnosticados de glomerulonefritis primaria en dos décadas en la Bahía de Cádiz y su influencia en el pronóstico desde entonces y aún en ausencia de insuficiencia renal severa.

La prevalencia global de hipertensión fue del 39%, siendo más frecuente en los pacientes de mayor edad. La tasa acumulada de supervivencia renal para los hipertensos fue del 54%, 28%, 20% y 4% a los 5, 10, 15 y 20 años respectivamente; mientras que para los normotensos fue del 83%, 75%, 66% y 62% para los mismos períodos ($p < 0,001$). Esta peor tendencia para los hipertensos se observa en cada tipo histológico, con especial significación en las nefropatías IgA y membranosa. Esta influencia negativa de la hipertensión se mantuvo igualmente cuando no coexistía insuficiencia renal severa en el momento de la biopsia.

Conclusiones: *La hipertensión es frecuente en las glomerulonefritis primarias, condicionando el pronóstico renal a largo plazo, desde el momento del diagnóstico e incluso antes de la existencia de insuficiencia renal severa.*

Palabras claves: ***Hipertensión arterial. Glomerulonefritis. Supervivencia renal. Insuficiencia renal.***

INTRODUCTION

Glomerulonephritis (GN) represents currently in Spain the third known cause of end-stage chronic renal failure (ESCRF) and for entry into a dialysis program, behind diabetic nephropathy and renal vascular disease (ischemic and hypertensive).[1] This renal prognosis may be also negatively influenced by several factors present at the time of patient's diagnosis. Among them, we outline arterial hypertension (AHT) as one of the most important ones, not only for GN but also in any type of renal disease[2-10].

Although AHT prevalence in GN is estimated to be higher than the prevalence of other nephropathies, it varies according to series[6,11,12], and that may be due several factors such as population differences, age, geographical areas, histological types, or time course of GN at the time of analysis of different studies, as well as to the difficulty in differentiating whether AHT is secondary to the nephropathy itself or nephropathy is secondary to AHT.

Because of that reason, we must stress that, in the same way, the negative influence of AHT on GN renal prognosis may be mediated preferentially by renal failure itself, (the former being possibly a result of the latter when this one is severe enough) than by hypertension itself.

From what have been said are derived the main goals of the present study, which are, on the one hand, to analyze AHT prevalence in chronic primary GN (PGN) at the time of performance of renal biopsy, and on the other hand, its prognostic value as a progression factor to ESCRF from then on and even in the absence of severe renal failure.

MATERIAL, PATIENTS AND METHODS

Patients: 394 adult patients have been retrospectively studied (age equal to or greater than 15 years; mean age 36.7 years), diagnosed with PGN by means of renal biopsy at Puerto Real and Puerta del Mar University Hospitals, from the Cadiz province ("Cadiz Bay Area"), between January 1st 1982 and June 30th 2003, excluding biopsies from renal grafts and glomerular pathologies related to renal transplantation.

Demographical data have been gathered, such as patients' particulars, date of renal biopsy, age and gender. As basal clinical data at the time of biopsy, the existence or absence of AHT (we considered hypertensive those patients with arterial blood pressure figures higher than 140/90 mmHg[13], or those treated with antihypertensive drugs), and renal failure (measured as glomerular filtration rate [GFR: by means of creatinine clearance in mL/min]). Also, pathological diagnosis from biopsies was recorded and, as the final study outcome, renal function survival, computed as the time elapsed from the date of renal biopsy to definitive loss of renal function, defined as first dialysis session. For that, each patient situation at the end of the study period has been recorded, with regards to their inclusion or not into a dialysis program.

According to the definition and classification of chronic renal disease[14,15], the limit between moderate and severe CRF (NKF-DOQI stages 3 and 4) is defined by a creatinine clearance (GFR) of 30 mL/min. Thus, for the analysis of AHT influence on PGN renal survival (RSV) we have considered 4 groups: Group A, all patients were normotensive independently of renal function; Group B, normotensive patients with GFR < 30 mL/min; Group C, all patients were hypertensive, independently of renal function; Group D, hypertensive patients with GFR < 30 mL/min.

Statistical methods: means, standard deviations (SD), medians, percentiles, and frequency distributions. Kaplan-Meier actuarial survival curves and log-rank test for curves comparison.

A p value < 0.05 was considered as significant. For statistical analyses RSIGMA from HORUS software has been used.

RESULTS

Of the 394 PGN-diagnosed patients, 247 were men (62.7%) and 147 were women (37.3%). Mean age of patients was 36.7 ± 17.7 years. 17.2% of patients were younger than 20 years (15-20 years), 38.1% were between 20 and 40 years, 31.3% between 40 and 60 years, and 13.4% were older than 60 years.

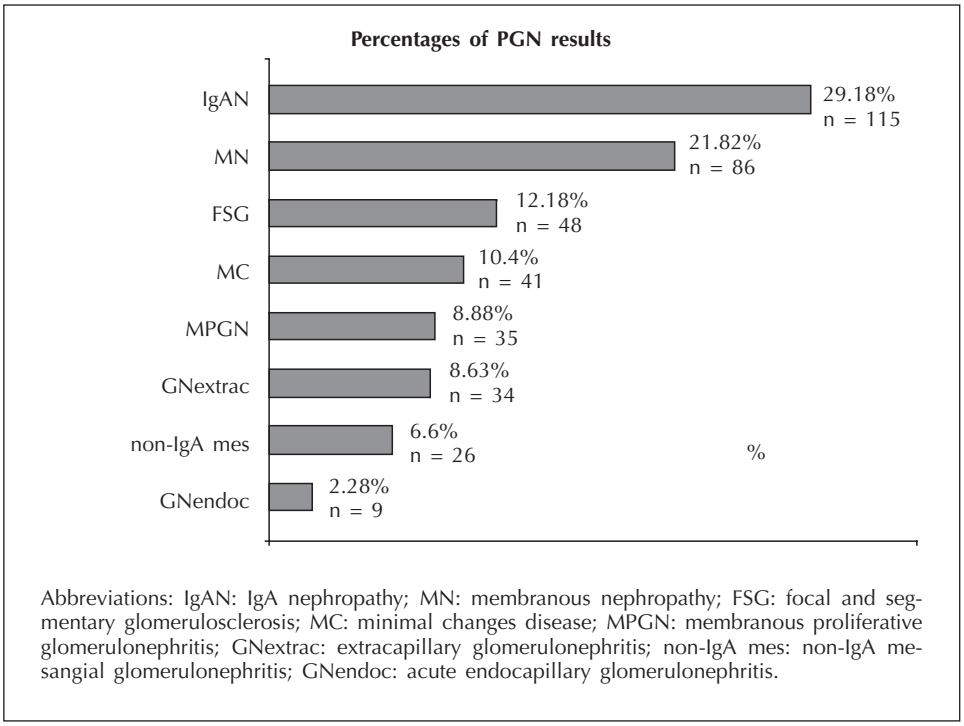
Percentage distribution of biopsied PGN in our setting is shown in Figure 1, predominating IgAN, followed in frequency order by MN, FSG, MPGN, GNExtrac, Mes Non IgA and GNEndoc (abbreviations definitions are shown at figure 1 bottom).

Globally, 39% of patients with biopsied PGN in our area presented AHT. Percentage of hypertensive patients significantly increases ($p < 0.001$) with patient's age, being 14% for those younger than 20, 38% for patients aged 20-40 years, 48% for patients aged 40-60 years, and 71.7% for those older than 60 years.

Global and chronic PGN specific means for plasma creatinine, proportion of patients according to renal function (GFR lower or higher than 30 mL/min), AHT general prevalence, and prevalence in PGN with GFR < 30 ml/min are shown in Table I.

Presence of AHT at the time of renal biopsy significantly determines ($p < 0.001$) a worse renal function prognosis for the whole group of patients diagnosed with PGN (fig. 2). Thus, the RSV cumulative rate for the whole group of non-hypertensive patients (Group A) was 83%, 75%, 66%, and 62% at 5, 10, 15, and 20 years, respectively; whereas for all hypertensive patients (Group C) it was 54%, 28%, 20%, and 4% for the same time periods. If we compare RSV curves between hypertensive and normotensive patients without significant renal failure at the time of diagnosis (GFR _ 30 mL/min), we observe similar results (Figure 2): RSV cumulative rates of 86%, 78%, and 72% at 5, 10, and 15 years for normotensive (Group B) and 67%, 22%, and 6% for hypertensive patients (Group D), respectively ($p < 0.001$).

These RSV differences between hypertensive and normotensive patients are virtually maintained for all particular types of chronic PGN, both



Abbreviations: IgAN: IgA nephropathy; MN: membranous nephropathy; FSG: focal and segmentary glomerulosclerosis; MC: minimal changes disease; MPGN: membranous proliferative glomerulonephritis; GNextrac: extracapillary glomerulonephritis; non-IgA mes: non-IgA mesangial glomerulonephritis; GNendoc: acute endocapillary glomerulonephritis.

Fig. 1.—Percentage distribution of results from biopsied PGN in the Cadiz Bay Area.

Table I. Renal function and AHT prevalence in PGN

	Mean P_{cr} (mg/dL) ± SD	Global AHT % in PGN	% of patients with GFR ≥ 30 mL/min*	% of patients with GFR < 30 mL/min	AHT % in PGN with GFR ≥ 30 mL/min
All PGN	1.9 ± 1.8	39%	62.18%	37.82%	29%
IgAN	1.54 ± 1.09	33.7%	72.17%	27.83%	25%
MN	1.29 ± 0.87	43.7%	69.77%	30.23%	38%
FGS	1.77 ± 1.29	33.3%	60.42%	39.58%	21%
MPGN	1.62 ± 0.97	41.7%	65.7%	34.3%	40%

(*) Limit GFR between 3 (moderate) and 4 (severe) NFK-DOQI stages of chronic renal disease.

with global comparison, without paying attention to baseline renal function, and when comparing RSV between hypertensive and normotensive patients without significant renal failure at the time of biopsy (Group B vs Group D) (fig. 3), being as follows:

Group A vs Group C: significant RSV differences in IgAN ($p < 0.001$), MN ($p < 0.01$), and FSG ($p < 0.05$). In MPGN we still observe this trend to a worse clinical course in hypertensive patients, although it does not reach statistical significance ($p < 0.1$).

Group B vs Group D: significant RSV differences in IgAN ($p < 0.001$), MN ($p < 0.001$), and with a lesser significance in FSG ($p < 0.05$).

DISCUSSION

AHT in the general population is variable depending on geographical distribution and age. For example, Wolf-Maier *et al.*[16] in a study that comprised 6 European countries (including Spain [Banegas JR]) report an AHT global prevalence for patients aged 35-64 years that varies among countries: USA 27.8%, Canada 27.4%, Italy 37.7%, Switzerland 38.4%, United Kingdom 41.7%, Finland 48.7%, Germany 55.3%, and Spain 46.8%. In other publications, this general population prevalence varies with an interval of 20-30%[17]. However, in GN, although it varies in the different studies, it is said to be 30 to 50%,

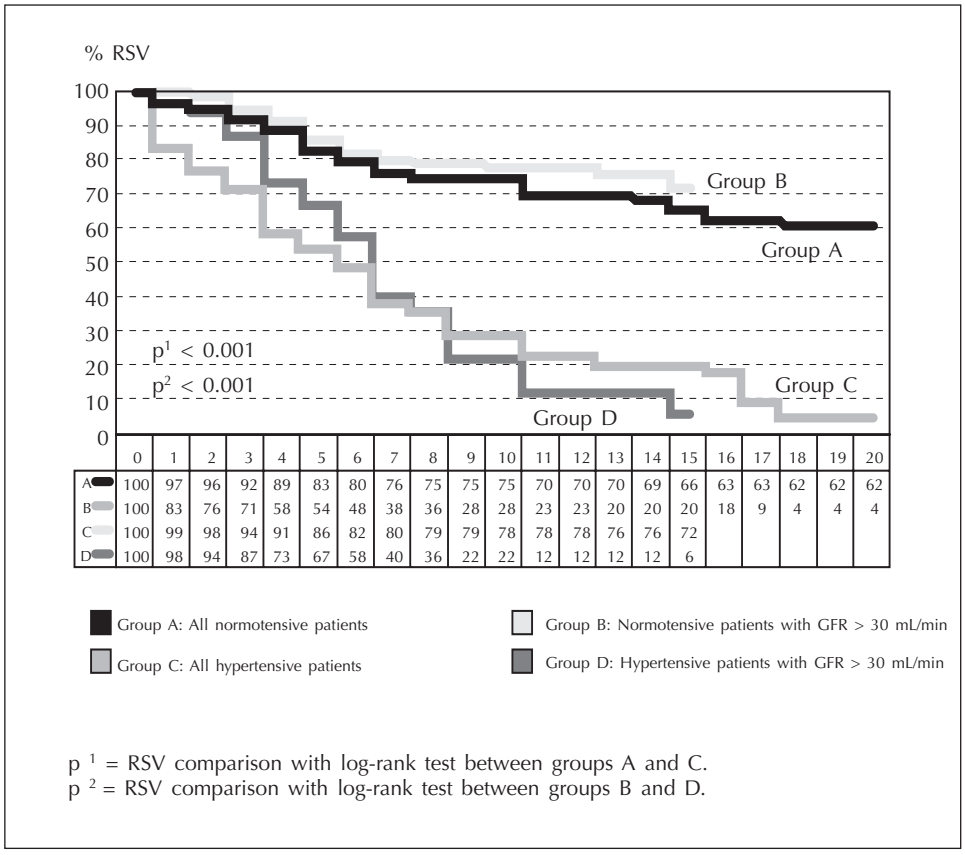


Fig. 2.—Influence of AHT on RSV of the whole PGN group.

or even higher, depending on the particular histological types and published series[6,11,12].

Following this line, we have observed that AHT is a fact that occurs very frequently in primary glomerular pathology in our area at the time of biopsy, reaching 39% of all of our patients. Although this percentage may no be higher than those reported in the cited series, we must consider three issues: on the one hand, that AHT prevalence is only detected in biopsied GN; on the other hand, AHT presence is recorded at the time of biopsy and not throughout the clinical course where its prevalence in GN would be seriously increased and paralleling renal function worsening; and finally, that patients diagnosed with GN tend to be young, especially in our study in which we have included patients 15 years and older and in which mean age is 36.7 ± 17.7 years, an age at which AHT prevalence in the general population is quite lower (14% in the USA and 27% in Europe for patients between 35 and 44 years of age, according to Wolf-Maier *et al.*[16]). AHT prevalence in PGN in our series increases very significantly ($p < 0.001$) with patient's age.

By histological types, MN and MPGN are the ones with the highest AHT rates at the time of biopsy. By contrast, the lowest AHT rate corresponds to patients diagnosed with MC.

Chronic GN are one of the most common etiologies for ESCRF, being such that in the latest national and autonomic dialysis and transplantation registries they still are, in Spain, one of the main causes of entry into a replacement renal therapy program in adults[1,18]. Progression to renal failure varies in some types of GN, so that it is essential to determine which factors may predict a poor course, independently of the histological type itself. Among them, AHT has been classically considered one of the most important ones because, with time, it induces an irreversible damage to preglomerular vessels, glomerular ischemia, gradual loss of renal mass, subsequent hyperfiltration and glomerular hypertension that favor mesangial expansion and global glomerular sclerosis, with long-term severe worsening of renal function[4,19,20].

In this line, we have been able to observe how AHT presence from time of diagnosis is already an important predictor factor for a worse renal course in PGN, since it denotes worse RSV cumulative rates in Kaplan-Meier curves as compared to non-hyper-

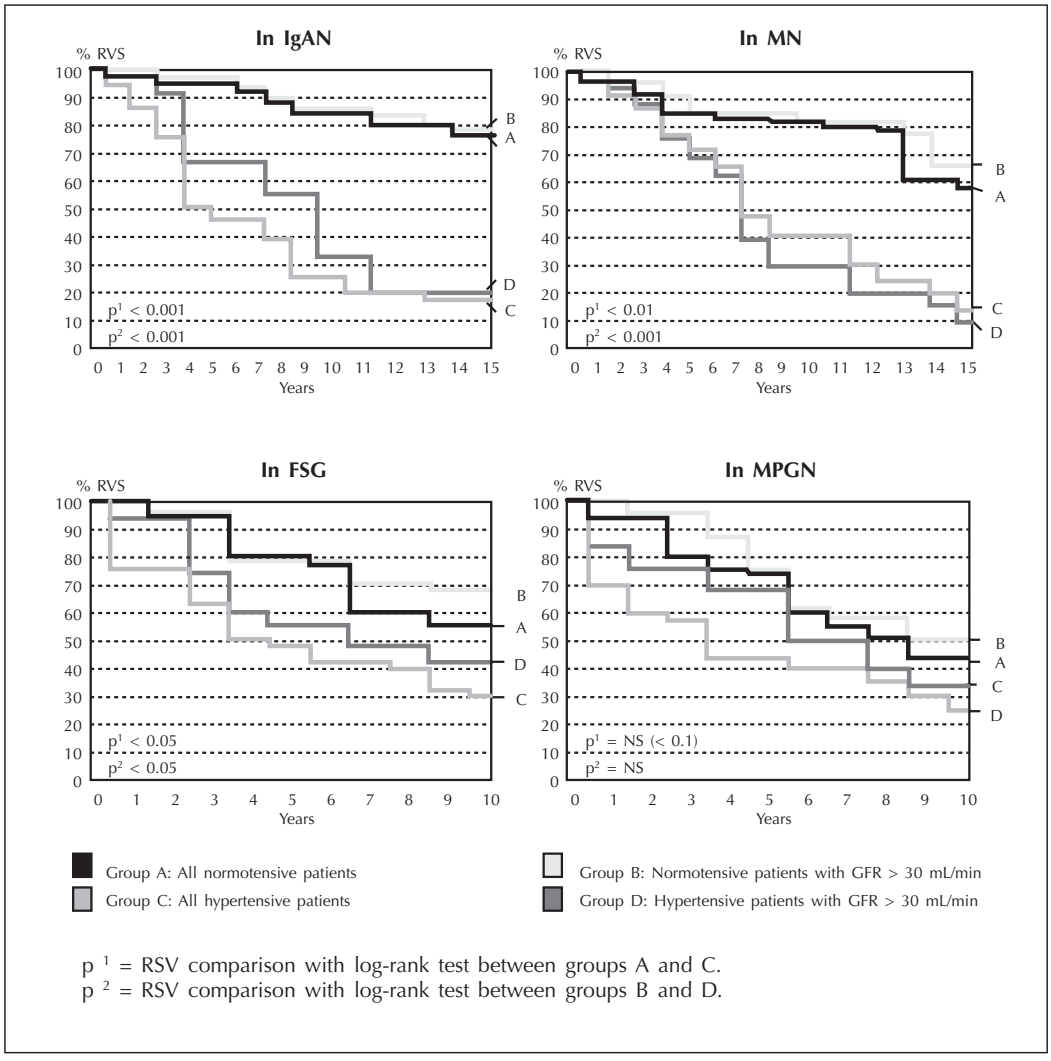


Fig. 3.—nfluence of AHT on RSV in the main types of chronic PGN.

tensive patients. This was also observed in all particular analyzed histological types, reaching a statistical significant difference, especially in IgAN ($p < 0.001$) and in MN ($p < 0.01$), and less in FSG ($p < 0.05$).

But AHT not only plays a role as a cause of renal function worsening but, at the same time, it is a result of the latter since renal disease *per se* induces AHT, completing this pathogenic loop, resulting in further damage besides the originating cause. In this way, as it is difficult to differentiate whether AHT is due to the nephropathy itself or to the resulting renal failure, we may also think that before a renal failure severe enough to influence on long-term prognosis, the latter would be preferentially conditioned by renal failure worsening than by hypertension itself. So that, we have studied its influence on renal survival of patients with a GFR equal to or higher than 30 mL/min at the time of biopsy (the limit between NFK-DOQI stages 3 and 4 of chronic renal failure), observing that AHT determines a worse renal survival as compared to normotensive patients, and it is especially significant, again, in IgAN and MN, and less in FSG.

IgAN and MN are the PGN with the most uncertain and variable progression and, thus, the most difficult to predict at the time of diagnosis, differing from others, such as GFS[21,22] and GNMP[23,24], in which their ominous course is well known. In the case of IgAN, because it is not a benign disease since a variable percentage of patients, varying between 20 and 40% in different series[25,26], progress to ESCRF and must be included into a dialysis program, although renal function survival lasts longer; in the case

of MN, because of its variable course since it may present complete or partial remissions, or progression to ESCRF[27,28]. Then, how can we inform patients of their progression at the time of diagnosis? Although offering an answer to this question may be difficult and it depends on many factors, we do are able to state, however, that in both nephropathies AHT is a very significant parameter for a worse evolution from then on, which may help us to establish a prognosis depending on whether patients present with arterial hypertension or not, and more importantly, it forces us to its management from then on, as with any other hypertensive patient.

Although it has not been a study issue in this work, we must comment that current guidelines recommend angiotensin II converting enzyme inhibitors (ACE inhibitors) as the first treatment option of these patients, except if formally contraindicated[8,10,29-32]. Although ARA-II drugs have an evident anti-proteinuric and anti-proliferative effect[33,34], to date there is not sufficient evidence that has demonstrated their capability to slow progression of non-diabetic renal disease as compared to other anti-hypertensive drugs.

In conclusion, and being aware of our retrospective study limitations, we would like to highlight that our work shows, on the one hand, the high AHT prevalence in primary biopsied GN, considering that we deal with young patients, with a lower AHT prevalence in the general population of the same age, and on the other hand, that AHT presence at the time of biopsy diagnosis is already a negative clinical prognostic marker, even before the occurrence of severe renal failure, being especially significant in IgAN and MN, which are primary glomerulonephritis with a more uncertain and variable clinical course than others. Although, according to our analysis, we cannot demonstrate that blood pressure management modifies renal prognosis in chronic GN, it may be, however, an essential therapeutic goal from the time of diagnosis, as in any other nephropathy.

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