Original article

Correlates of Renal Dysfunction in Hypertensive Chronic Biopsied non Diabetic Glomerulonephritis

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Summary

Background: Hypertension is a chronic disease that is increasing in prevalence worldwide and spans race and gender lines. The worldwide prevalence of hypertension was estimated from 2005 systematic review of published literature to be 26%with a projected 60% increase by the year 2025.Arterial hypertension is (with age, sex, race, proteinuria, hyperlipidaemia, smoking, etc.) also one of the main causes of the progression of diabetic and non-diabetic chronic kidney failure. This progressive kidney failure develops especially in patients with glomerular kidney disease who clinically manifest proteinuria. This process is slow in general, but sometimes the damage to the kidneys can develop very rapidly, with an immediate need for dialysis. The effects of glomerulonephritis onrenal prognosis may be also negatively influenced by several factors present at the time of patient's diagnosis. Among them, arterial hypertension is one of the most important factor, the negative influence of arterial hypertension on glomerulonephritis kidney prognosis may be mediated preferentially by kidney failure itself, the former being possibly a result of the latter when this one is severe enough, than by hypertension itself.

Aims: The aims of this study are to analyze arterial hypertension prevalence in chronic non diabetic glomerulonephritis at the time of performance of kidney biopsy and for the following 36 months after the biopsy. The prognostic value of arterial hypertension as a progression factor to end stage kidney disease is to be analyzed.

Patients and methods: Sixty one patients have been studied. The inclusion criteria for kidney biopsy were: nephrotic syndrome, persistent sub-nephrotic proteinuria, and unexplained abnormal kidney function test when kidney sizes in ultrasound were within normal range, acute kidney injury, acute nephritic presentation, hematuria after excluding urological causes. Demographical data have been gathered, such as patients' particulars, date of kidney biopsy, age and gender. We considered hypertensive those patients with arterial blood pressure figures higher than 140/90 mm-Hg, or those treated with antihypertensive drugs, and kidney failure measured as glomerular filtration rate by means of creatinine clearance less than 60ml/minute. Kidney function survival, computed as the time elapsed from the date of kidney biopsy to definitive loss of kidney function, defined as creatinine clearance <60 ml/minute. For the analysis of the prognosis and kidney survival, Kaplan-Meier curves and the Log-Rank test were used.

Results & Discussion: Of the 58 patients,30 (51.7%) are men and 28 (48.3%) are women and men: women ratio was 1.07:1.The patients' ages range from 2-55 years with an average mean age of 25.38 ± 14.65 years. The global prevalence of hypertension was 44.8%.

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When we compare the kidney log survival function curves between overall hypertensive and normotensive patients, we observe a significant effects with a trend toward a worse clinical course regarding kidney failure in over all hypertensive patients with a P value of 0.018 and a DF of 1 and in focal segmental glomerulosclerosisa P value of 0.024.

Conclusions: We conclude that high arterial hypertension prevalence in primary biopsied non diabetic glomerulonephritis, considering that we deal with young patients, with lowerarterial hypertension prevalence in the general population of the same age. Arterial hypertension presence at the time of biopsy is already a negative clinical prognostic marker, even before the occurrence of end stage kidney disease, being especially significant in focal segmental glomerulosclerosis.

Key words: Hypertension. Glomerulonephritis. End stage kidney disease.

Introduction

Hypertension is a chronic disease that is increasing in prevalence worldwide and spans race and gender lines.The worldwide prevalence of hypertension was estimated from 2005 systematic review of published literature to be 26%with a projected 60% increase by 2025.In countries with established market economies, the prevalence of hypertension ranges between 22% and 55%[1].

Arterial hypertension (ATH) per se is, together with diabetes mellitus, the most important cause of kidney failure and of the introduction of dialysis treatment. It is also a well-known consequence of end stage kidney disease (ESKD).ATH is (with age, sex, race, proteinuria, hyperlipidaemia, smoking, etc.) also one of the main causes of the progression of diabetic and non-diabetic chronic kidney failure. This progressive kidney failure develops especially in patients with glomerular kidney disease and clinically manifest proteinuria[2].This process is slow in general, but sometimes the damage to the kidneys can develop very rapidly, with an immediate need for dialysis[4].The Multiple Risk Factor Intervention Trial (MRFIT) has shown that the increasing risk of development of ESKD correlates significantly with the rise in blood pressure. If systolic blood pressure was >200 mmHg, the risk of ESKD was 48.2 times higher than if it was <120 mmHg. If diastolic blood pressure was >120mmHg, the risk was 30.9 times higher than when it was <70 mmHg. The same data have been obtained in other larger studies, e.g. in the 'Maryland' study, The hypertension detection and follow-up program (HDFP)[3,4].The authors of the study of 'Modification of Diet in Kidney Disease[5] has found that 83% of the investigated patients had ATHmand in those whose glomerular filtration were <10 ml/min, ATH was observed in 95% of them. Glomerulonephritis (GN) represents the third known cause of end-stage kidney disease(ESKD) and for entry into a dialysis program, behind diabetic nephropathy and kidney vascular disease (ischemic and hypertensive)[2].This effects of GN on renal prognosis may be also negatively influenced by several factors present at the time of patient's diagnosis. Among them, AHT is one of the most important factors. The negative influence of AHT on GN kidney prognosis may be mediated preferentially by kidney failure itself, the former being possibly a result of the latter when this one is severe enough, than by hypertension itself[2].

Although AHT prevalence in GN is estimated to be higher than the prevalence of other nephropathies, it varies according to

series[6],and that may be due to several factors such as population differences, age, geographical areas, histological types, 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[2,4,5,6].

The aims of the present study are to analyze AHT prevalence in chronic non diabetic GN (NDGN) at the time of performance of kidney biopsy and for the following 36 months after the biopsy. The prognostic value of ATH as a progression factor to ESKD is to be analyzed.

Patients and methods

Sixty one patients have been studied. They were diagnosed as NDGN by means of kidney biopsy at Iraqi Medical Center in Karbala Holy, between November 1st,2009 and November 30th,2013,excluding 3 biopsies from kidney grafts and glomerular pathologies secondary to systemic disease. The inclusion criteria for kidney biopsy were: nephrotic syndrome, persistent sub-nephrotic proteinuria, and unexplained abnormal kidney function test when kidney sizes in ultrasound were within normal range,acute kidney injury, acute nephritic presentation, and hematuria after excluding urological causes[7].Demographical data have been gathered, such as patients' particulars, date of kidney biopsy, age and gender. As basal clinical data at the time of biopsy, the existence or absence of AHT was determined. We considered hypertensive those patients with arterial blood pressure figures higher than 140/90 mmHg, or those treated with antihypertensive drugs[8], andkidney failure measured as glom erular filtration rate by means of creatinine clearance in mill/minute less than 60ml/minute. Kidney function survival was computed as the time elapsed from the date of kidney biopsy to definitive loss of kidney function, defined as creatinine clearance <60 ml/min. For that, each patient situation at the end of the study period has been recorded with regards their creatinine clearances reached 60ml/min or less. According to the definition and classification function of chronic kidney disease by NKF-KDIGO2012 guidelines[9]. Pathological diagnosis from biopsies was recorded by 2 nephropahologist[8].For all of our NDGN patients ,we compared the impacts of ATH on progression of ESKD by following up both hypertensive and normotensive patients for 36 months from time of biopsies. The same was applied for different types of GN. Statistical methods used in this study were: means, standard deviations (SD),medians, percentiles, and frequency distributions. For the analysis prognosis and kidney survival, Kaplan-Meier actuarial survival curves and the long-rank test were used. A p value < 0.05 was considered as significant. For statistical analyses IBM-SPSS version 20 has been used[10].

Results

Of the 58 NDGN-diagnosed patients,30 were men (51.7%) and 28 were women (48.3%).Mean age of patients was 25.38 ± 14.65 years.44.8% of patients were younger than 20 years,34.8 % were between 20-40 years, and 20.6% were > 40 years, see figure 1.

Percentage distribution of biopsied NDGN in our setting is shown in Figure 2, predominating FSGS, followed in frequency order by MCD, MGN.

Globally,44.8% of patients with biopsied NDGN in our area presented with AHT. Patient's age has no effect on the percentage of overall hypertension prevalence, $p>0.05$, It was 25.9% for those younger than

20,13.8% for patients aged 20-40 years, 6.9% for patients aged 40-60 years, see figure 3.

The presence of AHT at the time of kidney biopsy was significantly determines (P value:0.03)a worse kidney function prognosis for only age group <20 years,but it was not significant for other age groups 20-40 and >40,neither significant for the whole age groups of patients diagnosed with NDGN (figure 3).

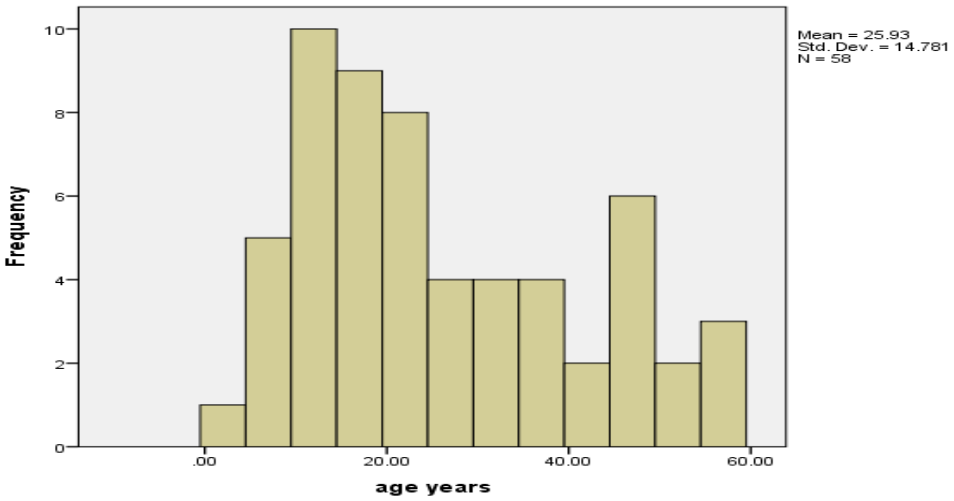

Figure 1:frequency distribution of NDGN according to age groups.

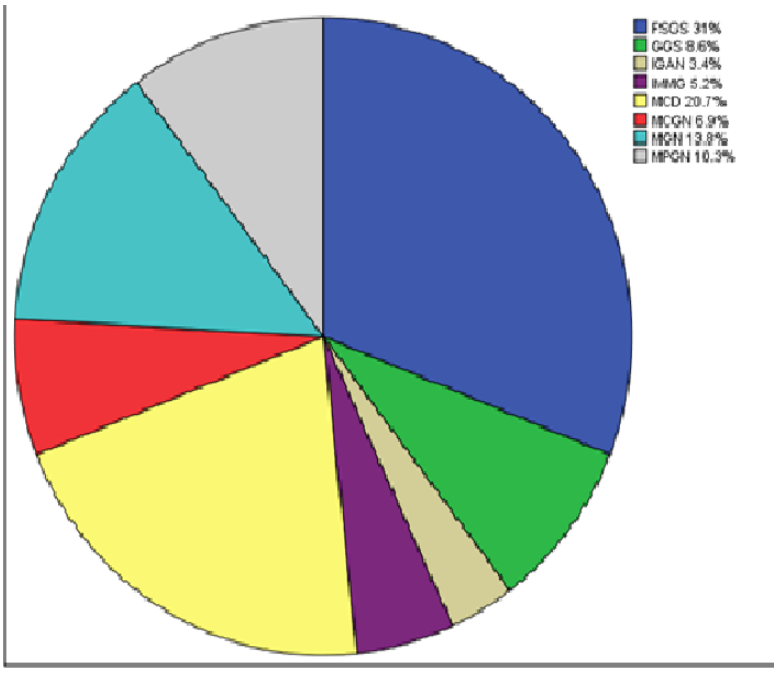

Figure2: Percentage distribution of NDGN according to results of histopathology.

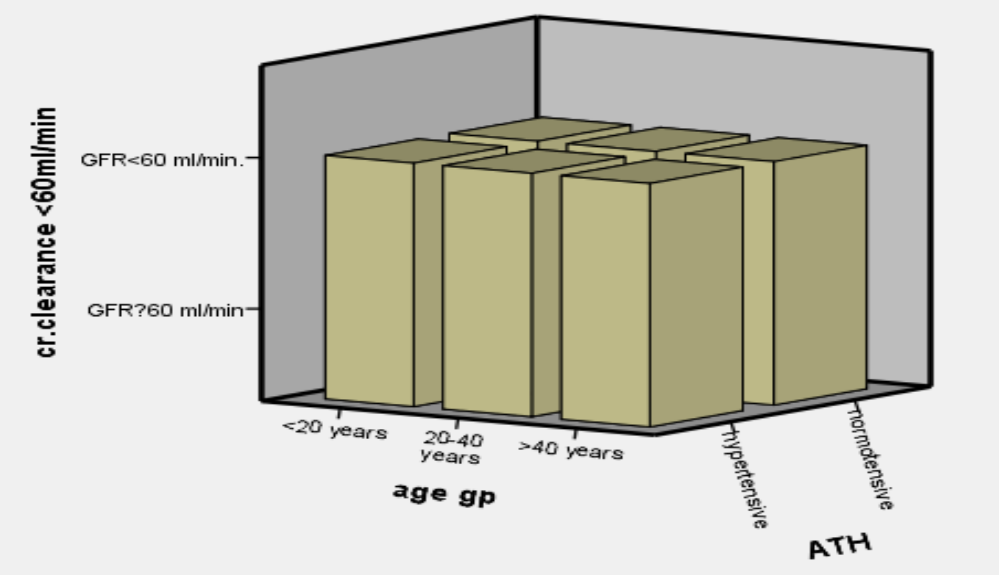

Figure 3: the causal relationship of kidney function and ATH in different age groups. values for age groups <20,20-40,<40 years and all ages were respectivly:X^2:4.594,0.175,1.040,2.019,df:1,1,1,1.P value:0.03S,0.67NS,0.3NS,0.15NS.

Table 1 showed global and chronic NDGN specific means for plasma creatinine, AHT global prevalence, proportion of patients according to kidney function (eGFR higher or lower than 60mill/min),and prevalence of ATH in NDGN with eGFRlower than or equal60 ml/min.

Table I. Kidney function and AHT prevalence in NDGN:

NDGN	**Mean Pcr* (mg/dL) ± SD**	**Global AHT % in NDGN**	**% of patients with eGFR≥60ml/min.****	**% of patients with eGFR<60ml/min****	**AHT % in NDGN with eGFR≤60ml/min****
All PGN*	1.26±0.84	28/58(48%)	36/58(62%)	22/58(38%)	11/28(19%)
IgAN*	0.8±0.28	0(0%)	0(0%)	2/2(100%)	0/0(0%)
MGN*	1.1±0.47	5/8(63%)	3/8(37%)	5/8(63%)	2/8(25%)
FSGS*	1.3±1.0	8/17(47%)	10/1(59%)	7/17(41%)	5/17(29%)
MCGN*	1.6±1.2	3/3(100%)	2/3(66%)	1/3(34%)	1/3(34%)
MCD*	0.78±0.74	3/12(25%)	11/12(92%)	1/12(08%)* MCD+FSGS	1/12(8%)
GGS*	1.7±1.0	3/3(100%)	2/3(66%)	1/3(34%)	1/3(34%)
Immune GN*	1.1±0.0	½(50%)	0(0%)	2/2(100%)	0/2(0%)
MPGN*	1.5±0.0	5/5(100%)	2/5(40%)	3/5(60%)	3/5(60%)

*Pcr: plasmacreatinine. PGN: primary GN, IgAN: IgAnephropathy, MGN: membranous GN, FSGS: focal segmental GN, MCGN: mesangiocapillary GN, MCD: minimal changed disease, GGS: global glomeruloseclerosis, MPGN: membraneoproliferative GN.

When we compare the kidneylog survival function curves between overall hypertensive and normotensive patients, we observe a significant effect with a trend toward a worse clinical course regarding kidney failure in over all hypertensive patients with a P value of 0.018 and a DF of 1 and in FSGS a P value of 0.024 . (Figures 4, 5).However there was no similar significant effect for ATH in any of the

following;MGN :P value 0 .362 ,GGS :P value 0.754,and MPGN :P value 0.319.No statistical values for MCD since all cases were censored.(Figures6,7,8).

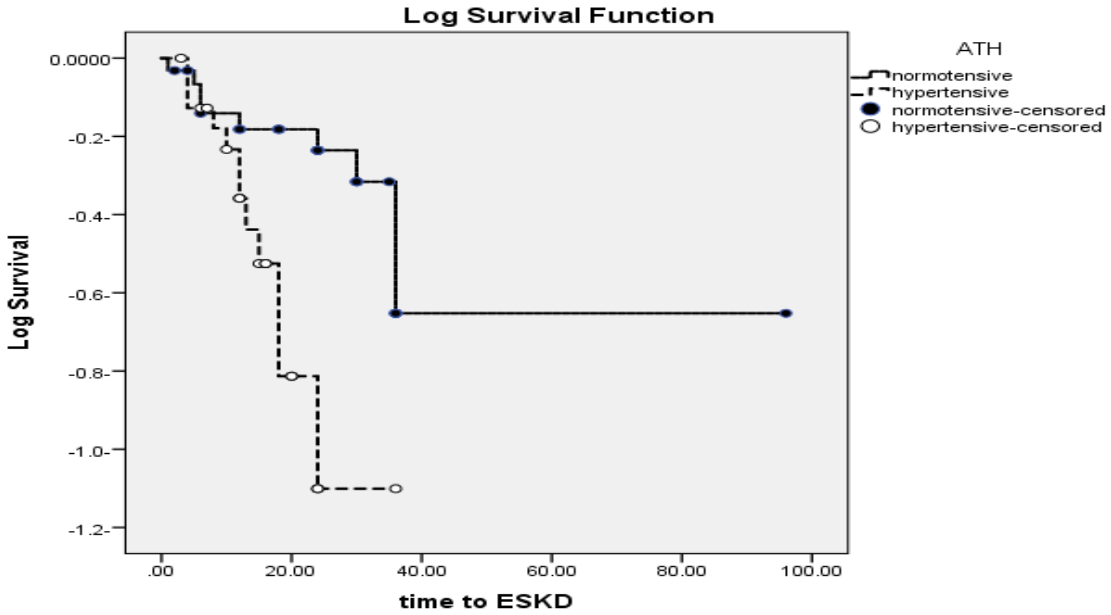

Figure 4: Overall Comparisons between normotensive and hypertensive patients by Log Rank (Mantel-Cox),Chi-Square 5.570, DF 1,andP value 0.018.Test of equality of survival distributions for the different levels of ATH.

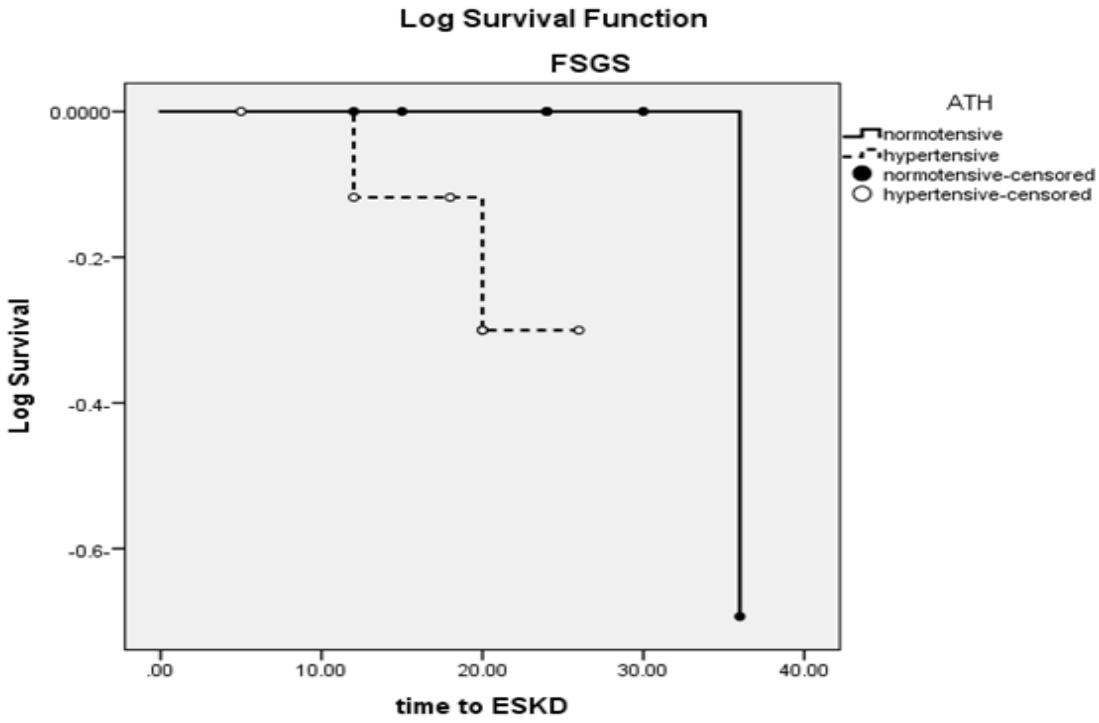

Figure 5, a: Comparisons between normotensive and hypertensive patients with FSGS. Log Rank (Mantel-Cox).Chi-Square5.125df 1,P value 0 .024,Test of equality of survival distributions for the different levels of ATH.

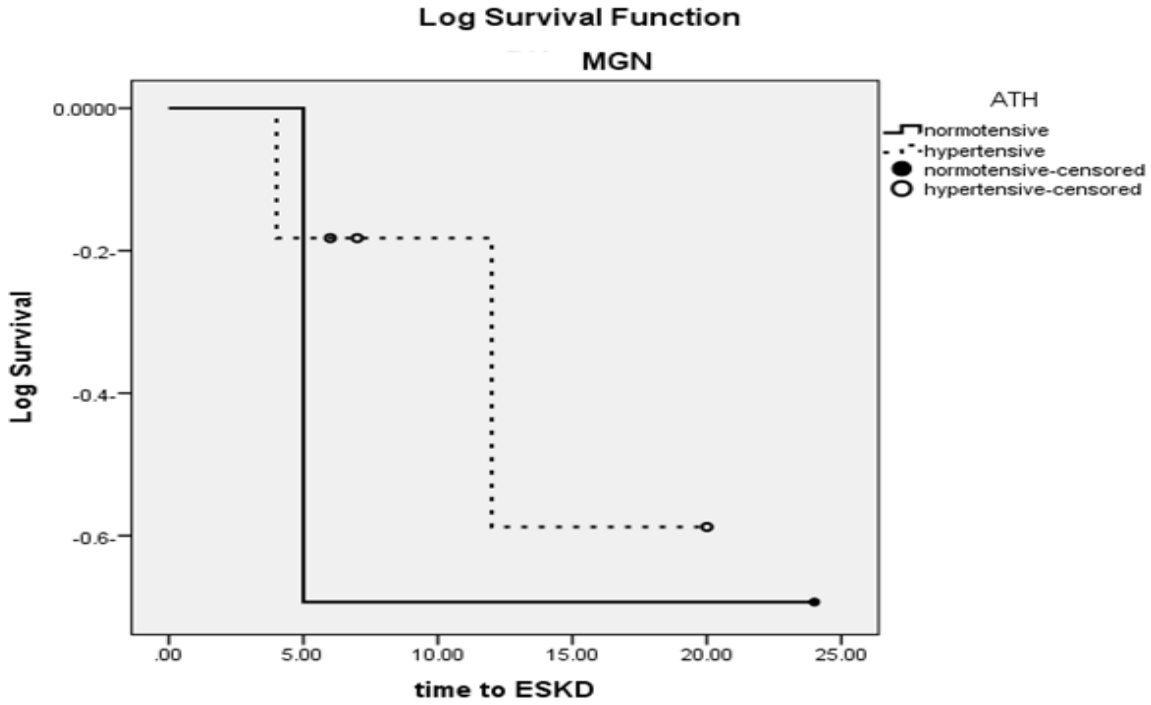

Figure 6:Comparisons between normotensive and hypertensive patients with MGN.Log Rank(Mantel-Cox),chisquare0.098, DF1,P value 0.754.

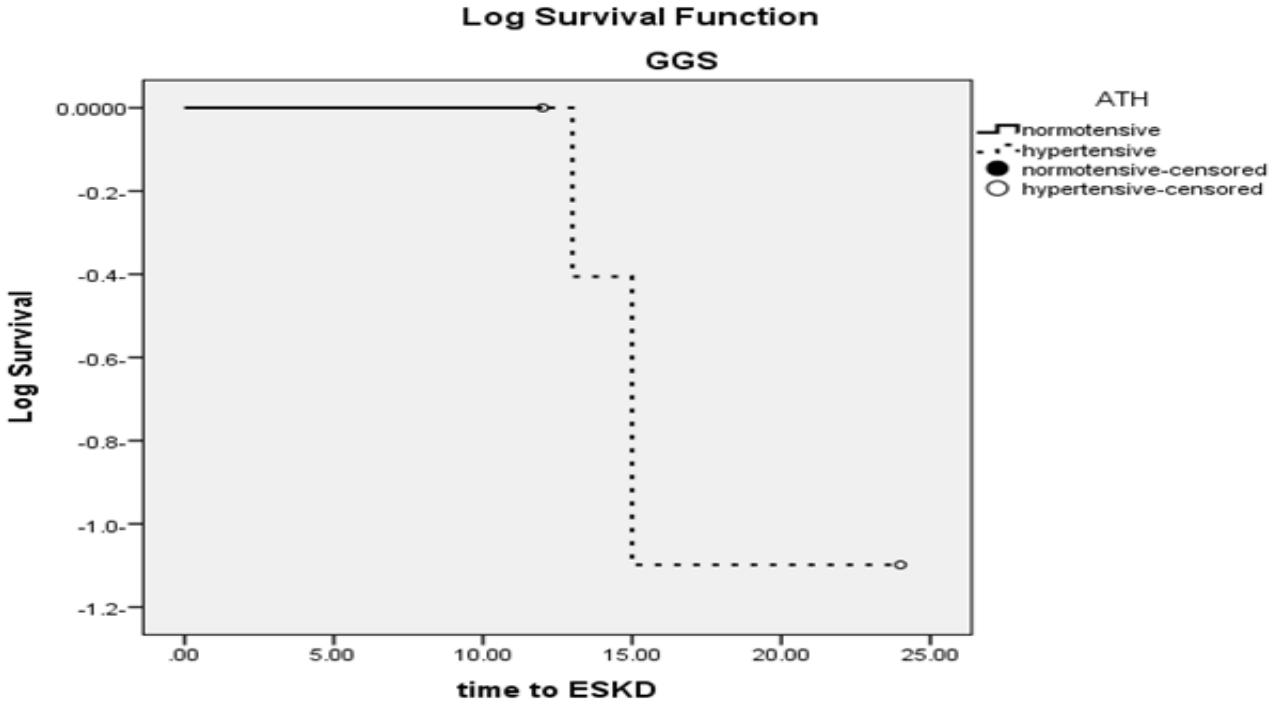

Figure7:Comparisons between normotensive and hypertensive patients with GGS by Log Rank (Mantel-Cox),Chi-Square.0.831,DF 1,P value 0.362. .

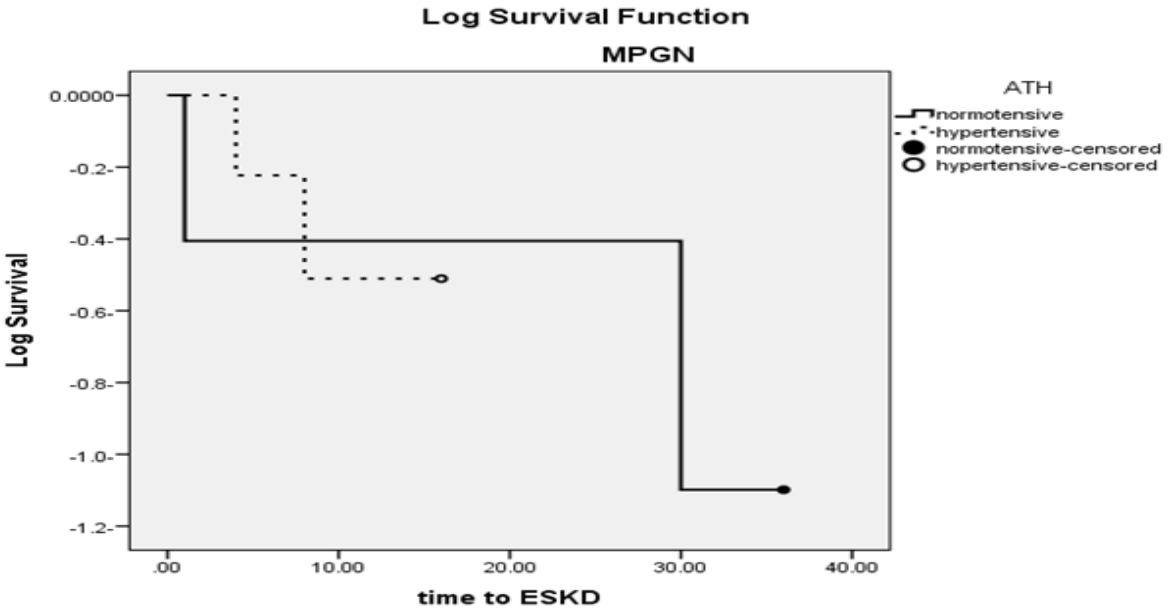

Figure8: Comparisons between normotensive and hypertensive patients of patients with MPGN (we include 3 patients with MCGN under the title of MPGN) by Log Rank (Mantel-Cox), Chi-Square 0.994, DF1, P value 0.319.

Discussion

AHT in the general population is variable depending on geographical distribution and age. In our study about half of our patients with NDGN have ATH (48.4%) and this is the consistent with the rate of prevalence in Finland 48.7%,Germany 55.3%,and Spain 46.8%.Our result of prevalence is higher than USA 27.8%, Canada 27.4%,Italy 37.7%,Switzerland 38.4%,United Kingdom 41.7%,[2,6,11]. The difference in the particular histological types and published series is the reason behind this finding [6]. In addition, we must consider that AHT prevalence is detected in only biopsied GN in our study, and its presence is recorded at the time of biopsy and throughout the clinical course where its prevalence in GN would be seriously increased and paralleling kidney function worsening. Finally, patients diagnosed with GN tend to be younger, especially in our study in which we have included patients 2 years and older and in which mean age ±standard deviation was 26.11 ± 14.65 years[11,12].The significant association between AHT prevalence in NDGN in our series and young ages(<20 years)P value 0.03,can be explained by that patients with glomerular diseases have a younger ages of disease onset, and are more likely to have received blood pressure measurements that potentially leading to a diagnosis of ATH. This idea is supported by our finding of a greater proportion of ESKD among those with diagnosed hypertension than among normotensive group.

The greatest burden of ESKD in the setting of undiagnosed ATH is among those with very low income, again suggesting that healthcare resources may be very limited in this population. Also, ESKD awareness was extremely low in this population, as has been shown in the general population, underscoring the need for improved education both in the community and among healthcare providers. This is especially

because awareness of ATH has also been shown to besuboptimal but improving[4].

By histological types, FSGS is the one with the highest AHT rates at the time of biopsy with significant P value of 0.024.In one hand this may be due to kidney biopsies in patients with clinically diagnosed hypertensive nephrosclerosis often reveal FSGS, but this entity has been relatively overlooked as a common contributor to hypertensive nephrosclerosis[13].On the other hand, the lowest AHT rate corresponds to patients diagnosed with MCD. The difference in the prevalence of ATH in patients suffering from GN is striking in our study 48.4%,compared with that found in older studies. This may be because, in recent years, the incidence of these types of GN associated with a higher frequency of ATH such as MPGN, MCGN, GGS, has decreased, while that of those types of GN producing ATH less frequently, such as FSGS,MGN has increased[12].

We have been able to observe how AHT presence from time of diagnosis is already an important predicting factor for a worse kidney course in NDGN, since it denotes worse kidney survival cumulative rates in Kaplan-Meier curves as compared to non-hypertensive patients. This was also observed a particular analyzed histological types, reaching a statistical significant difference, especially in all NDGN (P 0.018)and in FSGS(P 0.024).This is due to AHT induces an irreversible damage to preglomerularvessels, glomerular ischemia, gradual loss of kidney mass, subsequent hyperfiltration and glomerular hypertension that favor mesangial expansion and global glomerular sclerosis, with long-term severe worsening of kidney function[4,13- 16].AHT not only plays a role as a cause of kidney function worsening, butat the same time,it is a result of the latter since kidney 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 kidney failure, we may also think that before a kidney failure severe enough to influence on long-term prognosis, the latter would be preferentially conditioned by kidney failure worsening than by ATH itself. So that, we have studied its influence on kidney survival of patients with an eGFR equal to or higher than 60 mill/minute at the time of biopsy which is the limit of NKF-DOQI stage 3a of chronic kidney failure [9].MGN,GGS,MPGN and MCD are the NDGN with the most uncertain and variable progression and, thus, the most difficult to predict at the time of diagnosis, differing from others, such as FSGS[19-22],in which their ominous course is well known. Regarding MGN, the current evidence does not support that pathology plays much of a role other than diagnosis: It is not helpful in establishing prognosis[23].In the case of FSGS, because it is not a benign disease since a variable percentage of patients, progress to ESKD and must be included into a dialysis program, although kidney function survival lasts longer[24, 25].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 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 ATH or not, and more importantly, it forces us to its management from then on, as with any other hypertensive patient[26, 27].

Conclusions

In conclusion, and being aware of our study limitations, we would like to highlight that our work shows, on the one hand, the high AHT prevalence in primary biopsied NDGN, 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 ESKD, being especially significant in FSGS, which are primary NDGN with a more uncertain and variable clinical course than others. Although, according to our analysis, we cannot demonstrate that blood pressure management modifies kidney 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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