Original Paper

IgA Nephropathy in Czech Patients – Are We Able Reliably Predict the Outcome?

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Key Words

IgA nephropathy • Risk factors • ESRD • Prognosis

Abstract

Background/Aims: The aim of our study was to retrospectively analyse data of 520 Czech patients with IgA nephropathy (IgAN) and to specify the risk factors affecting renal survival of IgAN patients. **Methods:** Cox proportional hazards regression model was used to evaluate the effects of different variables on renal survival during a median follow up of six years. McNemar's test was used to analyse the progression of renal function according to Bartosik's formula. **Results:** In our retrospective analysis of 520 Czech IgAN patients Cox proportional hazards regression model with five variables [hypertension, sex, GFR, proteinuria, age] was used. Significant regression coefficient was found for GFR, hypertension and proteinuria. Using stepwise algorithm GFR (OR = 3.09), hypertension (OR = 2.09) and proteinuria (OR = 1.97) were found as the most important factors for renal survival in our group of IgAN patients. Among patients with CKD 3 we found significantly better renal survival in patients with proteinuria < 1g/day compared to patients with higher proteinuria. We did not find the significant difference between predicted progression of renal function due to Bartosik's formula and real progression of renal parameters assessed by GFR at the end of the follow up in our group of IgAN patients. **Conclusion:** Our retrospective study of 520 Czech IgAN patients confirmed GFR, hypertension and proteinuria as the most important factors affecting the prognosis of IgAN patients. We validated Toronto Bartosik's formula to predict prognosis of IgAN patients.

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Introduction

IgA nephropathy (IgAN) is one of the most common primary glomerulonephritides in young adults, leading to end stage renal disease in about 50 % of patients within 30 years with the necessity of renal replacement therapy [1].

Around 40 % of renal biopsies from native kidneys in the Czech Republic are performed in our Department of Nephrology (it is about 200 renal biopsies per year) and we have already published our experience with IgAN patients [2]. In this paper we present the retrospective analysis of IgAN patients extended to other nephrology centers in the Czech Republic. In total, we assessed 520 IgAN patients with a median follow up of 6 years. We compared clinical data, risk factors affecting the prognosis of IgAN patients among Czech centers and all around the world.

We also evaluated the progression of renal function according to the Bartosik's formula [3] and we compared it with the real progression of renal function assessed by glomerular filtration rate (GFR) at the end of the follow up in our group of IgAN patients.

Materials and Methods

We retrospectively analysed the findings of 520 patients with histologically proven IgAN diagnosed in the Department of Nephrology of the First Faculty of Medicine, Charles University in Prague (192 patients) and in other Czech nephrology centers (328 patients) from January 2000 to December 2010. Due to apparent limitations of our previous study (relatively short median follow-up of four years, frequent selection of patients with more serious clinical manifestations such as proteinuria or renal insufficiency) [2] we focused on IgAN patients biopsied and followed in our center for longer period (the total median follow up of 6 years). We also addressed other Czech nephrology centers to achieve comprehensive knowledge of patients with IgAN in the Czech Republic. Written informed consent for participation in the study was obtained from all adult participants. We assessed clinical, demographic data, and the medical treatment of IgAN patients. The patients with the diagnosis of Henoch-Schonlein purpura, liver cirrhosis and other secondary etiologies of IgAN were not included in this study. Diagnosis of IgAN was established by renal biopsy. The details about histological diagnoses of renal biopsies have already been published [2, 4]. Written informed consent for renal biopsy and for use of clinical data in this analysis was obtained from all patients and the study was approved by the ethics committee of the General University Hospital in Prague (1443/11 S-IV).

The following clinical data and medical treatment were analysed (initial data at the time of renal biopsy and the data at the end of the follow-up): serum creatinine ($\mu\text{mol/L}$), GFR [$\text{mL/s}/1.73 \text{ m}^2$, measured as creatinine clearance, we used 2 values (initial and final) to calculate slope of CrCl], proteinuria ($\text{g}/24 \text{ h}$), microscopic haematuria (positive or negative according to the urine sediment), arterial hypertension [according to the World Health Organization (WHO) criteria], antihypertensive therapy, immunosuppressive treatment (corticosteroids, cyclophosphamide, azathioprine, cyclosporine in Prague center and „yes“ or „no“ immunosuppression in other nephrology centers).

Definition of arterial hypertension (according to WHO criteria): defined as a repeatedly elevated blood pressure, a systolic pressure $\geq 140 \text{ mmHg}$ with a diastolic pressure $\geq 90 \text{ mmHg}$; or patients with normal blood pressure $< 130 \text{ mmHg}$ (systolic)/ 85 mmHg (diastolic) and taking antihypertensive drugs.

All data were statistically analysed. The influence of different variables on renal survival was analysed by Kaplan-Meier survival curves and comparison was made by the log rank test. The variables affecting renal survival were done by Cox proportional hazards regression model. Multivariate analysis of renal survival with choosed variables was created by stepwise algorithm in Cox proportional model.

To compare clinical parameters among different centers two-sample t-test or chi-square test were used. The comparison with the prediction of the progression of renal function assessed according to Bartosik's formula [3] was evaluated using the analysis of the dependence in accordance with McNemar's test. All tests were two-sided ones with a $P < 0.05$ considered statistically significant. Statistical analyses were performed using BMDP Statistical Software, Release 8.1.

Table 1. Variables at baseline, mean $\pm$ SD or number of patients (%)

	General Teaching Hospital in Prague	Other centers	Czech centers in total	P value
Presenting proteinuria - mean (g/d)	2.48 $\pm$ 3.01	2.54 $\pm$ 2.59	2.51 $\pm$ 2.86	P = 0.82 NS
Gender-males, number of patients (%)	222 (67.7)	136 (70.8)	358 (68.8)	P = 0.45 NS
Presenting hypertension, number of patients (%)	192 (58.7)	113 (59.2)	305 (58.9)	P = 0.92 NS
Age - mean (years)	40.44 $\pm$ 14.19	35.79 $\pm$ 14.39	38.73 $\pm$ 14.43	P < 0.001
Presenting GFR (ml/s)	1.20 $\pm$ 0.68	1.40 $\pm$ 0.59	1.28 $\pm$ 0.66	P < 0.001
S-Creatinine-mean (μ mol/L)	161.95 $\pm$ 116.91	123.90 $\pm$ 63.28	147.90 $\pm$ 102.09	P < 0.001
Immunosuppression, number of patients (%)	112 (21.5)	103 (19.8)	215 (41.3)	
Total patients (number)	192	328	520	

Table 2. Cox proportional hazards regression model.

* P < 0,05; *** P < 0,001

Variable	Coefficient	Standard deviation	Coefficient/ S.E.
Hypertension	0.7415	0.3262	2.2734 *
Sex	0.1404	0.2749	0.5107 NS
Age	-0.2122	0.2999	-0.7075 NS
Proteinuria	0.6781	0.1757	3.8590 ***
GFR	-1.1306	0.2025	- 5.5839 ***

Table 3. Cox proportional model – stepwise algorithm

Variable	Coefficient	Standard deviation	Coefficient/ S.E.	Exp(Coefficient) = OR
Hypertension	0.7050	0.3232	2.1816	2.09
Proteinuria	0.6764	0.1726	3.9193	1.97
GFR	-1.1315	0.2020	-5.6014	3.09

Results

We retrospectively analysed data of 520 patients with IgAN diagnosed between the years 2000 and 2010 with the median follow up of 6 years (children below 15 years were excluded from the study). The clinical data from first clinical presentation are depicted in Table 1. We found significant differences in mean age, mean level of serum creatinine and mean GFR among General Teaching Hospital in Prague and other Czech nephrology centers. Other significant differences in gender, presenting hypertension and proteinuria among Czech nephrology centers were not noticed.

In our retrospective analysis of 520 Czech IgAN patients, we used Cox proportional hazards regression model (Table 2) with five variables (hypertension, sex, age, proteinuria, GFR) to study their effect on renal survival (time to end stage renal disease) in IgAN patients.

Significant regression coefficient was found for GFR, hypertension and proteinuria. Using stepwise algorithm (Table 3), GFR (OR = 3.09), hypertension (OR = 2.09) and proteinuria (OR = 1.97) were found as the most important factors for renal survival in our group of IgAN patients. Patients with hypertension had 2.1 times higher risk of end stage renal disease compared to normotensive patients. Patients with proteinuria > 1g/24 hours had 1.97 times higher risk of end stage renal disease compared to patients with proteinuria $\leq$ 1g/24. The group of patients with renal insufficiency (CKD 2; GFR 1.49 – 1 ml/s) had 3.1 higher risk of end stage renal disease compared to patients with CKD 1 and patients with normal renal parameters. The influence of sex and age was not confirmed.

The total 10-year actuarial renal survival was 77.1 %. We ascertained significant variability in renal survival among centers with 10-year actuarial survival of 64.5 % in General Teaching Hospital in Prague and 88.3 % in other Czech nephrology centers (P < 0.001) (Figure 1).

We confirmed reduced renal survival in patients with renal insufficiency, arterial hypertension and proteinuria > 1g/day (Figure 2, 3 and 4). Among patients with CKD 3 we

Fig. 1. The overall Kaplan-Meier actuarial renal survival in Czech patients with IgAN (red line, the 10-year renal survival was 77.1 %). Renal survival of General Teaching Hospital in Prague (green line, the 10-year renal survival was 64.5 %) vs other nephrological Czech centers (blue line, the 10-year renal survival was 88.3 %; Log rank test: $P < 0.001$).

Fig. 2. Kaplan-Meier curves showing the survival probability according to input GFR. Patients with $GFR \geq 1.5$ ml/s (blue line, the 10-year renal survival was 89 %), patients with $GFR 1-1.49$ ml/s (red line, the 10-year renal survival was 85 %), patients with $GFR 0.5 - 0.99$ ml/s (green line, the 10-year renal survival was 50 %). $P < 0.001$.

Fig. 3. Kaplan-Meier curves showing the survival probability according to arterial hypertension at presentation. Patients with arterial hypertension (red line, the 10-year renal survival was 71 %), patients without arterial hypertension (blue line, the 10-year renal survival was 88 %); $P < 0.001$.

Fig. 4. Kaplan-Meier curves of survival according to the input proteinuria: < 1 g/day (green line, the 10-year renal survival was 92 %), < 2 g/day (blue line, the 10-year renal survival was 81 %) and > 2 g/day (red line, the 10-year renal survival was 65 %); $P < 0.001$.

found significantly better renal survival in patients with proteinuria < 1 g/day compared to patients with higher proteinuria (Figure 5).

Patients with normal renal function and proteinuria < 1 g/day showed significantly better renal survival compared to patients with normal renal parameters and proteinuria ≥ 1 g/day (Figure 6).

In our study of IgAN patients we evaluated the progression of renal function according to the Bartosik's formula [3] and we compared it with real progression of renal function assessed by GFR at the end of the follow up. The Toronto (Bartosik's) formula uses average mean arterial blood pressure and proteinuria during the first 2 years of follow-up to predict the subsequent slope of estimated GFR [3]. The analysis of the progression of renal function

Fig. 5. Kaplan-Meier curves of survival according to GFR < 1 ml/s and different levels of the input proteinuria: < 1 g/day (green line, the 10-year renal survival was 77 %), ≥ 1 g/day and < 2 g/day (blue line, the 10-year renal survival was 59 %) and > 2 g/day (red line, the 10-year renal survival was 35 %); P < 0.001.

Fig. 6. Kaplan-Meier curves of survival according to GFR > 1.5 ml/s and different levels of the input proteinuria: < 1 g/day (red line, the 10-year renal survival was 98 %), ≥ 1 g/day and < 2 g/day (blue line, the 10-year renal survival was 95 %) and > 2 g/day (green line, the 10-year renal survival was 91 %); P < 0.001.

according to Bartosik's formula was performed in 516 patients with IgAN at the end of the follow up (due to missing some data in 4 patients).

In our group of IgAN patients, the progression of renal function was assessed due to GFR (with the range 1,14 ml/s for men and 0,9 ml/s for women). Subsequently, the comparison with the prediction of the progression of renal function assessed according to Bartosik's formula was evaluated using the analysis of the dependence in accordance with McNemar's test with these results: progression of renal function due to Bartosik's formula at the end of the follow up vs. progression of renal function appraised due to GFR at the end of the follow up (with the range 1,14 ml/s for men and 0,9 ml/s for women): p-value: McNemar: 0,072.

In conclusion, we did not find the significant difference between predicted progression of renal function due to Bartosik's formula and real progression of renal parameters assessed by above mentioned GFR at the end of the follow up in our group of IgAN patients.

In our extensive study of 520 Czech IgAN patients with median follow up of six years we assessed not only the risk factors affecting the progression of IgAN and differences among Czech nephrology centers but also the 10-year actuarial renal survival of Czech IgAN patients, KM curves of renal survival according the different risk factors, assessment of median slope of GFR in the Czech Republic and comparison with other countries. In addition, we validated Toronto Bartosik's formula to predict the prognosis of IgAN patients.

Discussion

Our study shows the long-term assessment of the largest cohort of IgAN patients in the Czech Republic (population 10.3 million). The group of 520 IgAN patients with median follow up of six years enables to assess and compare the most important risk factors at presentation affecting long-standing prognosis of the disease.

We ascertained the worldwide known risk factors for the progression of renal function of nephropathies, such as proteinuria, hypertension and the lower GFR at the time of the diagnosis [1, 2, 5-10].

In our group of IgAN patients, the overall 10-year renal survival was 77.1 % which is comparable to previous published evidence (77.8 % [6], 79.8 % [8], 83 % [7], 84 % [11], 84.3 % [1], 85 % [12]). The geographic variability in the long-standing outcome of IgAN is

well known with 10-year renal survival ranging from 93.3 % in Helsinki to 61.4 % in Toronto [6]. The geographic variability might be influenced by genetic factors [13], additional environmental factors, eating habits or by different local medical guidelines for screening and treatment of the disease [13].

In our study of IgAN patients median slope of CrCl was - 1 ml/min/1.73m²/year which is comparable to median slope of CrCl in Helsinki, in Finland (- 1.24 ml/min/1.73m²/year) [6]. On the contrary other countries showed unfavourable median slope of CrCl (- 2.95 ml/min/1.73m²/year in Sydney, in Australia; - 3.46 ml/min/1.73m²/year in Glasgow, UK; - 3.99 ml/min/1.73m²/year in Toronto, in Canada) [6].

In above mentioned study [6] patients from Helsinki and Sydney presented with milder forms of disease with preserved renal function (CrCl > 75 ml/min) and lower proteinuria (< 0.5 g/day) compared to patients from Glasgow and Toronto. Finnish patients originated mostly from large army, employment and driving licence screening programmes. Liberal biopsy practice in subjects with suspected nephropathies was noted in Finland and also in Sydney while patients in Toronto and Glasgow undergo renal biopsy in case of heavy proteinuria (> 1g/24 h) or renal failure [6]. These results correspond with higher biopsy rate in Finland (176 p.m.p./year) [14] and in Australia (215 p.m.p./year) [15] and lower biopsy rate in Scotland (126.3 p.m.p./year) [16, 17]. The biopsy rate in the Czech Republic increased significantly from 44.1 p.m.p./year in 1994 to 58.2 p.m.p./year in 2001 and to 61.6 p.m.p./year in 2011 [4]. We realize that we used two values of CrCl (initial and final) to calculate slope of CrCl compared to minimal 3 mean values in above mentioned publication [6].

In the Czech Republic, we also noticed different renal survival of IgAN patients (the overall 10-year renal survival in the General Teaching Hospital in Prague was 64.5 % compared to the overall 10-year renal survival in other Czech nephrology centers with 88.3 %) which might be influenced by significant differences in the distribution of age (P < 0.01) and GFR (P < 0.01) among Prague center and other Czech nephrology centers. We did not find other significant differences in the distribution of gender, hypertension or proteinuria. We noted significantly more patients > 50 years old in the General Teaching Hospital in Prague (P < 0.01) with significantly more patients with progressive renal insufficiency (55 % of patients with CrCl < 0.99 ml/s, 17 % of patients in the group with CrCl > 1.5 ml/s; significant differences in mean CrCl : 0.99 ml/s in patients above 50 years compared to mean CrCl 1,36 ml/s in patients below 50 years).

We detected higher number of patients (130 patients) from Prague center in the group with CrCl < 0,99 ml/s compared to patients from other Czech nephrology centers (49 patients) and in this group with CrCl < 0,99 ml/s also mean level of CrCl in Prague center 0.58 ml/s was significantly worse compared to other Czech nephrology centers with CrCl 0.7 ml/s (P < 0.01). The distribution of hypertension and proteinuria was not significantly different in the group with CrCl < 0,99 ml/s and differences in renal survival are supposed to be caused by worse GFR in older patients. However, higher risk patients with more serious clinical and laboratory findings are concentrated in our Department of Nephrology in Prague where most of the renal biopsies from native kidneys are performed in the Czech Republic (approximately 200 renal biopsies from native kidneys in a year). The higher number of risk patients is supposed to be the cause of faster progression of renal function decline with worse renal survival.

In our study of 520 Czech IgAN patients, 215 patients (41.3 %) were treated by immunosuppressive regimen. Unfortunately, we know the specific type of immunosuppression only in Prague center (with 192 patients in total), 112 patients (58.3 %) used corticosteroids (34 patients received corticosteroids alone and 85 patients corticosteroids with immunosuppression), 69 patients cyclophosphamide (35.9 %), 11 patients azathioprine (5.7 %), 5 patients cyclosporine (2.6 %). We did not assess the influence of immunosuppressive treatment on the prognosis of IgAN patients.

Recent published reports did not ascertain the impact of gender on the progression of IgAN [18]. Geddes CC et al. [6] showed a higher male : female ratio for IgAN patients in Glasgow (4.6) compared to other centers (1.8 in Toronto; 1.7 in Helsinki and 1.5 in Sydney)

but they did not demonstrate the differences in renal survival or slope CrCl between males and females and suggested the same outcome for males and females. In Czech IgAN patients we found out male : female ratio 2.2 and we also excluded the significant effect of gender on renal survival of IgAN patients. Contrary to these results, in Japan and other Asian countries [1, 7-9, 19-21] women overwhelmed to men which indicated that genetic and ethnic factors might be related to gender distribution of IgAN.

Previous published studies did not show the influence of age on renal survival. In our study, Cox hazards proportional model did not confirm the impact of age on renal survival. We found out the 10- year actuarial renal survival in patients younger than 50 years 78 % in comparison with 74 % in patients $\geq$ 50 years, however the result is non-significant (P 0.514). As well as the dependence of delta GFR (GFR at the end minus GFR at presentation) on age was not ascertained. By way of contrast, Geddes CC et al. [6] and Radford et al. [22] demonstrated protective effect of advancing age on the slope of CrCl and the risk of ESRD.

Due to usually asymptomatic clinical course of IgAN presented frequently by miscellaneous urinalysis, the most common primary glomerulonephritis is often diagnosed in progressive level of renal insufficiency with hypertension and severe prognosis. In our study, the highest number of patients with ESRD (75 %, 48 patients of the whole group) was assessed in the group of patients with input GFR < 0.99 ml/s. Our previous study showed that patients with macroscopic hematuria and earlier onset of the disease showed favourable prognosis [2]. Other study indicated [1] that more recently diagnosed patients with milder disease at the time of renal biopsy showed a better overall prognosis.

Conclusion

We assessed long term renal survival and risk factors associated with prognosis in Czech IgAN patients. We found the overall 10-year renal survival 77.1 % in our group of IgAN patients. Hypertension, higher proteinuria (>1g/d), lower GFR at the time of the diagnosis were independent risk factors affecting renal survival in Czech IgAN patients. We validated Toronto (Bartosik's) formula in our cohort of Czech IgAN patients.

Disclosure Statement

None declared.

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