Prognostic factors in mesangioproliferative glomerulonephritis

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Abstract

Background. The aim of our study was to examine patients with mesangioproliferative glomerulonephritis (MPGN), with or without glomerular IgA deposits, and to analyse the effect of different clinical and histopathological variables at the time of biopsy on progression to end-stage renal failure (ESRF) and death.

Methods. We retrospectively examined 273 patients who got this diagnosis in Norway from April 1988 to December 1990 after a renal biopsy. All patients were followed for a median duration of 34.8 months (0.8–68 months).

Results. The mean age at the time of biopsy was 40±17 years (range 1.1–79 years). Glomerular IgA deposits were present in 45% of the patients; IgA deposits did not affect prognosis. Three years after the time of biopsy, 7% had developed ESRF (chronic dialysis treatment or kidney transplantation) and 8% had died. By Kaplan–Meier analyses, the following clinical variables indicated progression to ESRF: increased serum creatinine, proteinuria >1 g/24 h, systolic blood pressure (BP) >160 mmHg, diastolic BP >90 mmHg, serum albumin <35 g/l, presence of urinary granular casts and age >60 years. Morphological variables indicating progression to ESRF were presence of focal mesangial sclerosis, focal glomerular crescents or necroses, benign nephrosclerosis and increased interstitial score. In the multivariable analysis, the following variables indicated progression to ESRF: increased serum creatinine (P<0.001), decreased serum albumin (P<0.05), increased diastolic BP (P<0.05), low age (P<0.05) and increased interstitial score (P<0.001).

Conclusions. It is possible from clinical and histopathological variables to identify low-risk and high-risk patients at the time of biopsy. There is, however, considerable convergence. A major new observation is the finding of young age, decreased serum albumin and the presence of urinary granular casts as important clinical risk factors. Interstitial damage was the most important histopathological predictor of ESRF.

Keywords: clinical risk factors; end-stage renal failure; histopathological risk factors; IgA nephropathy; mesangioproliferative glomerulonephritis

Introduction

Mesangioproliferative glomerulonephritis (MPGN) is the most commonly made diagnosis in the Norwegian Kidney Register (personal data). This database contains clinical and histopathological data for all patients in Norway with a kidney biopsy from the year 1988. Mesangioproliferative glomerulonephritis is characterized by a highly variable clinical course and common clinical signs are haematuria and proteinuria, with or without hypertension or renal failure. The characteristic biopsy findings in MPGN are diffuse or focal increase of glomerular mesangial cells and matrix with or without mesangial deposits of immunoglobulins and/or complement. Most cases of MPGN where IgA deposits are identified in the glomeruli belong to the entity usually referred to as IgA nephropathy. IgA nephropathy is considered to be the most frequent type of glomerulonephritis in most countries [1,2], representing 15–45% of all cases of glomerulonephritides [3–6], giving a population based incidence level of 10–25 cases per million population per year [3].

The number of clinical studies on the clinical course of MPGN is limited in contrast to a large number of clinical investigations in IgA nephropathy. Patients diagnosed with IgA nephropathy develop end-stage renal failure (ESRF) in approximately 15% of the cases after 10 years and 20% after 20 years, while another 20% have impaired glomerular filtration rate [1,3, 4,6–8]. Clinical factors that have been shown to indicate a worse prognosis are elevated serum creatinine, hypertension, proteinuria >1 g/24 h, age >30 years, serum albumin <40 g/l, absence...
of gross haematuria, hypercholesterolaemia, hypertriglyceridaemia, hyperuricaemia and male sex [1,3–5,7,9–13]. Histopathological features indicating a worse prognosis are glomerulosclerosis, tubulo-interstitial lesions, glomerular crescents, focal or diffuse mesangial proliferation, glomerular tuft adhesions, arteriolar hyalinosis, extension of IgA deposits into the walls of peripheral capillary loops and glomerular and interstitial cellular proliferation [1,3,4,13–15]. The clinical and histopathological risk factors described above are of course important, but they might not have the same validity for MPGN.

The purpose of the present study was to retrospectively analyse and compare clinical and histopathological prognostic factors in MPGN after renal biopsy in Norway in the years 1988–90. We chose a follow-up period of about 3 years to study the early progression to ESRF and studied different clinical and histopathological variables at the time of biopsy in order to investigate predictors of progression to ESRF. In addition, comparisons between patients with and without glomerular IgA deposits were made.

**Subjects and methods**

**Patients**

The patients were selected from the Norwegian Kidney Register, a database containing both clinical and histopathological data at the time of biopsy. The database covers all patients with a renal biopsy in Norway (4.5 million inhabitants). We studied patients biopsied from April 1988 to December 1990. In this period, the register received a total of 1176 biopsies, including 273 with the diagnosis of MPGN. Patients with MPGN associated with systemic diseases such as systemic lupus erythematosus, hepatitis, Wegener’s granulomatosis, polyarteritis nodosa and Goodpasture’s disease were excluded from the study. Five centres of pathology made the initial diagnoses of MPGN, which were later reviewed by one nephropathologist at the Norwegian Kidney Register. Consequently, consistent diagnoses were made in all patients. The patients were treated and followed in 19 hospitals in Norway. The follow-up was done by review of the individual patients’ records by a local physician or by an investigator for 78% of the patients. For the remaining 22%, accurate follow-up data of patient survival and ESRF was retrieved from the Norwegian Population Register and the Norwegian ESRF Register.

**Pathological anatomical diagnosis**

Mesangioproliferative glomerulonephritis was diagnosed in accordance with the criteria given in the WHO monograph of renal disease [16]. Characteristic light microscopic findings are expansion of the mesangium with little or no involvement of the capillary lumina. The expanded mesangium contains clusters of four or more mononuclear cells per mesangial area. This cell increase may be uniform, involving all or nearly all glomeruli, or it may be more focal and segmentally accentuated. Cell proliferation may be accompanied by an increase in mesangial matrix and in advanced cases by mesangial sclerosis [16]. Immunohistochemistry studies were performed in 262 of the 273 biopsies, examining for deposits of IgA, IgG, IgM, C3 and C1q in the glomerular capillary wall or mesangium (abbreviated to glomerular). The presence of deposits was recorded, but was not an obligate finding to make the diagnosis of MPGN. Cases with crescentic glomerulonephritis were not a part of this study of MPGN, but we included cases with focal crescents and/or necroses not related to a systemic disease.

**Clinical and laboratory investigations**

Baseline was defined as the time of biopsy where standard clinical and laboratory tests were performed. In this paper, we have focused on the following baseline clinical variables: age, sex, serum creatinine, urinary protein, blood pressure, serum albumin and urinary granular casts. Urinary stix tests and hypertensive and immunomodulating medication at the time of biopsy also were recorded. Unfortunately, all baseline variables have not been recorded for all patients; especially, urinary protein and serum albumin were missing in some patients.

Continuous variables at baseline of serum creatinine, systolic blood pressure, diastolic blood pressure, urinary protein and age were converted to ordinal values for use in Kaplan–Meier analyses. Urinary granular casts and hypoalbuminaemia (<35 g/l) at baseline were converted into dichotomous values as either present or not present. For use in this paper, values of serum creatinine were set to normal when <110 µmol/l (1.24 mg/dl) for women and <125 µmol/l (1.41 mg/dl) for men (guidelines at Haukeland University Hospital). They were regarded as moderately increased if they were higher than normal but less than 200 µmol/l (2.26 mg/dl) and largely increased if higher than 200 µmol/l.

**Histopathological variables**

We examined the prognostic importance of the following variables, all of which are recorded in the database of the Norwegian Kidney Register: glomerular focal crescents or necroses, focal mesangial sclerosis, benign nephrosclerosis, acute tubular damage, chronic interstitial nephritis, interstitial fibrosis and glomerular immunodeposits of IgA, IgG, IgM, C3 and C1q.

Glomerular focal crescents or necroses were recorded as present when glomerular crescents or necroses were found in one or more glomeruli. Focal mesangial sclerosis, observed as small areas of focal and segmental mesangial scarring in one or more glomeruli, was recorded as present or absent. Characteristic of benign nephrosclerosis is arteriolar sclerosis, especially seen in pre-glomerular vessels, with narrowing of the vascular wall associated with glomerular and tubulointerstitial scarring. Benign nephrosclerosis was recorded as present or absent. Signs of acute tubular damage, often accompanied by interstitial inflammation and/or oedema, were recorded as present or absent. An interstitial score (0–6 points) was calculated by adding the scores separately for interstitial fibrosis and chronic interstitial nephritis. Interstitial nephritis was scored as present (3 points) or absent (0). Fibrosis was scored as none (0), mild focal (1), extensive focal (2) or diffuse (3). For use in statistical analyses, the patients were divided into three groups based on the interstitial scores, as follows: 0–1, 2–4 and 5–6.
Study endpoint

The primary endpoint in the present study was ESRF, defined as chronic renal failure necessitating chronic dialysis treatment or renal transplantation. The secondary endpoint was death. Patients not reaching endpoint were followed for about three years after their renal biopsy and laboratory values and blood pressure were recorded. Endpoints reached after 1 July 1993 were not included in this study and patients were censored in the statistical analyses.

Statistical analysis

The SPSS package was used for statistical analysis. Data are presented as mean ± SD for normally distributed continuous variables and as median (range) for continuous variables not having a normal distribution. Significance testing was done by Student’s t-test and Mann–Whitney test, respectively. Differences of proportions between patient groups and correlations between dichotomous variables were tested by the chi-square test. Correlation testing was performed using Pearson’s coefficient for continuous variables distributed normally and Kendall’s τb coefficient for ordinal variables. A P-value of <0.05 was considered statistically significant, and all tests were two-tailed.

Renal survival for subgroups of patients was described with the Kaplan–Meier method, and the log-rank test was used to estimate P-values of differences between groups. In Kaplan–Meier analyses, the cumulative renal and clinical patient survival for subgroups of patients are given after three years of follow. The Cox proportional hazard regression model was used to evaluate the effects of the individual baseline variables on progression to ESRF or death. The analysis yields estimated relative risks (Hazards ratio) for each change in the included variables. This model controls for differences in other included variables possibly affecting the progression, generating independent risk factors of progression [17]. The following variables were entered into the Cox model: continuous values of age, proteinuria, serum albumin, systolic blood pressure, diastolic blood pressure and a logarithmically transformed serum creatinine, the dichotomous variables urinary granular casts, glomerular crescents or necroses, focal mesangial sclerosis, presence of glomerular IgA deposits and benign nephrosclerosis, and interstitial score divided into three groups. The analyses were done in a backward stepwise manner. The assumption of time-independent covariates was tested with covariate adjusted log-log plots, and the assumption was found to be met. We chose to use logarithmically transformed values of serum creatinine to let the relative increase of serum creatinine gain importance at the cost of the absolute increase. The maximum number of patients was included in each step, and at the last step all variables were significant (P<0.05).

Results

A total of 273 patients was diagnosed with MPGN, 190 men and 83 women. This constituted 24% of the total number of biopsies received at the Norwegian Kidney Register in this period. Mean age at the time of biopsy was 40 ± 17 years (range 1.1–79 years). Median serum creatinine at the time of biopsy was 100 μmol/l (34–1800 μmol/l) and median proteinuria was 0.65 g/24 h (0–67 g/24 h). At the time of biopsy, 180 patients (66%) had normal values of serum creatinine, 53 patients (19%) had moderately elevated values (110–125–200 μmol/l) and 38 patients (14%) had serum creatinine ≥200 μmol/l. Mean systolic blood pressure was 136 ± 23 mmHg, mean diastolic blood pressure was 84 ± 13 mmHg and mean serum albumin was 38.5 ± 8.2 g/l. Median duration of signs of renal disease before biopsy was 24 months (0–550 months), as calculated from the duration of clinical findings such as proteinuria, haematuria, renal failure or nephrotic syndrome. At baseline, 197 patients (76%) had haematuria, 192 (72%) had proteinuria, 148 (55%) had both proteinuria and haematuria and 7 (3%) had glucosuria. Thirty-five patients (13%) had an interstitial score ≥5. 18 (6.6%) had focal mesangial sclerosis, 36 (13%) had focal glomerular crescents or necroses, 78 (29%) had benign nephrosclerosis and 14 (5.1%) had acute tubular damage.

Follow-up data were obtained by questionnaire for 214 patients (78%) and were obtained from registries for 59 patients (22%). Median duration of follow-up was 34.8 months (0.8–68.5 months).

During follow-up, 21 patients (7.7%) developed ESRF after a median of 9.8 months (0.1–52.4 months). Six of these patients died later during the follow-up period. Another 14 patients, who did not develop ESRF, died during the follow-up period, giving a total of 20 deaths (7.3%) in the observation period. Causes of death were renal failure in three patients, renal failure and other organ failure in seven patients, cardiovascular disease in three patients, cancer in one patient and unknown in six patients. Values of serum creatinine at the end of follow-up were recorded in 199 patients (72.8%); 16 (8.0%) of these had values exceeding 200 μmol/l, but had not received renal replacement therapy. In 10 patients (5.0%), serum creatinine normalized during follow-up. As calculated by the Kaplan–Meier method, one- and three-year renal survival was 96% and 93%, respectively. One- and three-year patient survival was 97% and 92%, respectively.

Thirty-three patients (12.1%) received antihypertensive treatment at the time of biopsy. Angiotensin converting enzyme inhibitors were used in 44% of patients, calcium channel blockers in 33%, beta-blockers in 33%, alpha-blockers in 3% and the medication was unknown in 6%. Patients receiving antihypertensive treatment at the time of biopsy had significantly higher systolic and diastolic blood pressure than patients not receiving antihypertensive treatment. At the time of biopsy, 18 patients received corticosteroid treatment and seven of these patients received other immunomodulating treatment.

Glomerular immunofluorescence studies were done on 262 of the 273 biopsies. Of these, 120 (45%) had glomerular IgA deposits in the glomerular capillary wall or mesangium whereas 142 (55%) had no glomerular IgA deposits. In patients who did not have glomerular IgA deposits, glomerular IgM deposits were present in 54%, glomerular IgG deposits...
in 22%, glomerular C1q deposits in 53% and glomerular C3 deposits in 34%. Mean age for patients with glomerular IgA deposits was 6.8 years less than for patients without glomerular IgA deposits ($P<0.005$) (Table 1). Seventy-eight per cent of the patients with glomerular IgA deposits were male compared with 62% without glomerular IgA deposits ($P<0.005$). Eighty-seven per cent of the patients with glomerular IgA deposits tested positive for blood compared with 70% without glomerular IgA deposits ($P<0.005$).

Duration of signs of renal disease before biopsy was similar in patients with and without glomerular IgA deposits. Even though patients with deposits of IgA had higher values of serum creatinine and more often had an interstitial score $\geq 5$ at the time of biopsy, there was no difference in the renal survival for these two groups (Figure 1).

Predictors of progression to ESRF

Patients with normal values of serum creatinine at baseline had a cumulative probability (as calculated by the Kaplan–Meier method) of developing ESRF of 0.015 in three years, those who had moderately increased values had a probability of 0.10, whereas patients with serum creatinine $\geq 200$ μmol/l had a probability of 0.32 (Figure 2) for developing ESRF. The differences between all three groups were highly significant ($P<0.001$).

For patients with a systolic blood pressure (sBP) of $<140$ mmHg at baseline, the cumulative probability of progression to ESRF in three years was 0.04, for patients with sBP of 140–160 mmHg the probability was 0.08 and for patients with sBP of $\geq 160$ mmHg the probability was 0.21 (Figure 3). The group with sBP $\geq 160$ mmHg had a significantly worse prognosis than the two other groups ($P<0.005$). Patients who had a diastolic blood pressure (dBP) of $<90$ mmHg had a cumulative probability of developing ESRF of 0.04 in three years, patients who had a dBP of 90–105 mmHg had a probability of 0.11, whereas the patients who had a dBP of $\geq 105$ mmHg had a probability of 0.27 (Figure 3). The group with the lowest dBP had a significantly better prognosis than the group with dBP of 90–105 mmHg ($P<0.05$) and the group with dBP $\geq 105$ mmHg ($P<0.001$).

The cumulative probability of progression to ESRF in three years for patients with proteinuria $<1$ g/24 h

### Table 1. Comparison of baseline variable-values

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>MPGN with glomerular IgA</th>
<th>MPGN without glomerular IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.9 ± 15.9</td>
<td>42.7 ± 18.1 $^2$</td>
</tr>
<tr>
<td>Gender (% men)</td>
<td>78.3</td>
<td>62.0 $^2$</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>106 (50–892)</td>
<td>94.5 (34–1800) $^3$</td>
</tr>
<tr>
<td>Proteinuria (g/24 h)</td>
<td>1.0 (0–67)</td>
<td>0.5 (0–40.2)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.7 ± 20.5</td>
<td>135.0 ± 24.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84.8 ± 12.4</td>
<td>82.3 ± 12.5</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>38.5 ± 8.0</td>
<td>38.4 ± 8.4</td>
</tr>
<tr>
<td>Duration of renal disease before biopsy (months)</td>
<td>26 (0–360)</td>
<td>22 (0–550)</td>
</tr>
<tr>
<td>Granular casts (%)</td>
<td>45.0</td>
<td>40.8</td>
</tr>
<tr>
<td>Protein on stix (%)</td>
<td>75.4</td>
<td>71.1</td>
</tr>
<tr>
<td>Blood on stix (%)</td>
<td>86.7</td>
<td>70.0 $^2$</td>
</tr>
<tr>
<td>Protein and blood on stix (%)</td>
<td>69.0</td>
<td>48.5 $^2$</td>
</tr>
<tr>
<td>Interstitial score $\geq 5$ (%)</td>
<td>18.3</td>
<td>8.5 $^3$</td>
</tr>
<tr>
<td>Focal mesangial sclerosis (%)</td>
<td>10.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Glomerular focal crescents or necroses (%)</td>
<td>10.0</td>
<td>15.5</td>
</tr>
<tr>
<td>Benign nephrosclerosis (%)</td>
<td>29.2</td>
<td>29.6</td>
</tr>
<tr>
<td>Acute tubular damage (%)</td>
<td>4.2</td>
<td>5.6</td>
</tr>
</tbody>
</table>

MPGN with and without glomerular IgA deposits has been compared. Significant $P$-values are shown as $^1P<0.05$ and $^2P<0.005$.  

![Fig. 1. Kaplan–Meier survival plot illustrating the effect of glomerular IgA deposits ($P>0.6$) on cumulative renal survival for patients with MPGN. The numbers of patients in the different subgroups of patients are given in parentheses.](image)
at baseline was 0.009, those with proteinuria of 1–3 g/24 h had a probability of 0.10, whereas the patients with proteinuria exceeding 3 g/24 h had a probability of 0.19 (Figure 4). The patients with proteinuria of <1 g/24 h developed ESRF significantly less often than patients with 1–3 g/24 h ($P < 0.05$) and patients with $\geq$ 3 g/24 h ($P < 0.001$). The cumulative probability of progression to ESRF in three years for hypoalbuminaemic (<35 g/l) patients was 0.18 in contrast to normoalbuminaemic patients who had a probability of 0.03 (Figure 4). This difference was highly significant ($P < 0.001$). Patients with granular casts by urine-microscopy at baseline (116 patients) had a probability of progression to ESRF of 0.14 at three years whereas patients without granular casts (157 patients) had a probability of 0.03 ($P < 0.01$). Patients with findings of urinary granular casts had significantly higher proteinuria ($P < 0.001$) than patients without this finding.

The patients had a mean age of 40 ± 17 years. For patients younger than 30 years the probability of progression to ESRF in three years was 0.06, for patients aged 30–60 years it was 0.04, whereas for patients older than 60 years the probability was 0.20. The patients older than 60 years had a significantly worse prognosis than those aged < 30 years ($P < 0.05$) and those aged 30–60 years ($P < 0.005$). Gender had no significant impact on progression to ESRF. Duration of signs of renal disease before biopsy did not affect progression to ESRF.

The cumulative probability of progression to ESRF for patients with focal glomerular crescents or necroses in three years after the time of biopsy was 0.23.
whereas patients without this finding had a probability of 0.05 ($P < 0.001$) (Figure 5). For patients with focal mesangial sclerosis, the probability of progression to ESRF in three years was 0.25 and for patients without this finding the probability was 0.06 ($P < 0.05$) (Figure 5). Ten patients with focal mesangial sclerosis and an interstitial score of 2–6 had a probability of progression to ESRF of 0.49, whereas none of the eight patients with focal mesangial sclerosis and an interstitial score of 0–1 progressed to ESRF ($P < 0.05$). Patients with findings of benign nephrosclerosis had a risk of developing ESRF in three years of 0.13 and patients without these findings had a risk of 0.05 ($P < 0.01$) (Figure 6). In patients with
an interstitial score of 0–1 the cumulative probability of progression to ESRF in three years was 0.015, in patients with an interstitial score of 2–4 the probability was 0.16, whereas in patients with a score of 5–6 the probability was 0.28 (Figure 7). The group with a score of 0–1 was significantly different from the two others (\( P < 0.001 \)). For the 14 patients with acute tubular damage the probability of progression to ESRF in three years was 0.34 and for the 263 patients without this finding the probability was 0.06 (\( P < 0.001 \)). Glomerular immunodeposits of IgA (Figure 1), IgG, IgM, C3 or C1q did not affect progression to ESRF.

Baseline variables showed high degrees of covariation (Table 2). Multivariable analysis (Cox regression) was performed with 179 (65.6%) patients in the first step, with 219 (80.2%) in the second step and with 230 (84.5%) patients in the third to the eighth steps because of missing baseline variable-values for the followed-up patients (Table 3). The patients who did not enter this analysis had significantly lower values of urinary protein than the patients who did. At the seventh step, all variables contributed significantly to the analysis. The analysis yielded the following estimated relative risks (with 95% confidence intervals (CI)) for each change in the remaining variables. A doubling of

![Fig. 6. Kaplan–Meier survival plot illustrating the effect of benign nephrosclerosis at baseline on kidney survival. The numbers of patients in the different subgroups of patients are given in parentheses.](image1)

![Fig. 7. Kaplan–Meier survival plot illustrating the effect of interstitial score at baseline on kidney survival. The group with a score of 0–1 highly significantly differs from the other groups (\( P < 0.0001 \)). The numbers of patients in the different subgroups of patients are given in parentheses.](image2)

### Table 2. \( P \)-values of correlation between baseline variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Log S-creat</th>
<th>U-prot</th>
<th>Syst BP</th>
<th>Diast BP</th>
<th>S-alb</th>
<th>Gran casts</th>
<th>Age</th>
<th>Mes scler</th>
<th>Cresc/necr</th>
<th>BN</th>
<th>Tub dam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial score</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
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<tr>
<td>Tub dam</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>BN</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Cresc/necr</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>&lt;0.001</td>
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<td>Mes scler</td>
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<td>Age</td>
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<td>Gran casts</td>
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<td>&lt;0.05</td>
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<td>Diast BP</td>
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<td>Syst BP</td>
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Log S-creat, logarithmically transformed serum creatinine; u-prot, urinary protein; syst BP, systolic blood pressure; diast BP, diastolic blood pressure; s-alb, serum albumin; gran casts, granular casts; mes scler, focal mesangial sclerosis; cresc/necr, glomerular focal crescents or necroses; BN, benign nephrosclerosis; tub dam, acute tubular damage. All correlations were positive, except serum albumin that correlated inversely with other variables.
the serum creatinine concentration increased the risk 3.3 times (CI 1.8–6.0 times, \( P < 0.0001 \)) and each step decrease of 5 g/l in serum albumin increased the risk by 1.7 (CI 1.12–2.7, \( P < 0.05 \)). Each 10 year decrease in age increased the risk by 1.4 (CI 1.01–2.0, \( P < 0.05 \)) and each 10 mmHg increase in diastolic blood pressure increased the risk by 1.8 (CI 1.2–2.8, \( P < 0.005 \)). Compared with an interstitial score of 0–1, a score of 2–4 increased the risk by 10.5 (CI 1.6–70, \( P < 0.05 \)) and a score of 5–6 increased the risk by 16.0 (CI 2.9–88, \( P < 0.001 \)).

**Predictors of death**

Using Kaplan–Meier analyses, baseline predictors of death during follow-up were age \( \geq 60 \) years (\( P < 0.001 \)), elevated serum creatinine (\( \geq 110/125 \) \( \mu \)mol/l) (\( P < 0.05 \)), serum creatinine \( \geq 200 \) \( \mu \)mol/l (\( P < 0.001 \)), systolic blood pressure \( \geq 160 \) mmHg (\( P < 0.05 \)), serum albumin <35 g/l (\( P < 0.001 \)), presence of glomerular crescents or necroses (\( P < 0.001 \)), presence of benign nephrosclerosis (\( P < 0.05 \)) and an interstitial score \( \geq 2 \) (\( P < 0.001 \)). Cox regression analysis for death was performed the same way as for ESRF. The analysis yielded the following estimated relative risks (with 95% CI) for each change in the three remaining variables. Each doubling of the serum creatinine concentration increased the risk 2.1 times (CI 1.5–3.0 times) (\( P < 0.001 \)). Each 10 years increase in age increased the risk by 2.3 (CI 1.4–3.6, \( P < 0.001 \)). Each 10 g/l decrease in serum albumin increased the risk by 1.4 (CI 1.03–1.9, \( P < 0.05 \)).
advanced renal disease at the time of biopsy than patients without IgA deposits. Considering the fact that these two groups of patients progressed equally fast to ESRF, one might conclude that patients without IgA deposits would progress faster towards ESRF from the same level of renal function. However, IgA deposits showed to be of no importance in the Cox analysis and we, therefore, conclude that the presence of IgA deposits does not affect progression to ESRF in MPGN. The number of clinical studies on MPGN is limited in contrast to the high number of studies on IgA nephropathy; we, therefore, made a choice to compare our findings for MPGN with other studies on IgA nephropathy.

As mentioned, MPGN is a commonly occurring renal biopsy diagnosis in Norway, representing 24% of all patients who had a renal biopsy in 1988–90, giving a yearly incidence of 22 per million population. In a Danish study, the corresponding number was 10.8 [18]. The incidence of IgA nephropathy shows great variation [6] and some European studies have shown a yearly incidence of 10–25 per million population [3]. The incidence in Norway seems to be similar to the rest of Europe. The true incidence, however, may be substantially higher and is mainly dependent on the frequency of renal biopsies in the different countries.

Our study represents a rather large group of patients. However, we were not able to obtain follow-up data for more than 78% of the patients by questionnaire. The rest of the patients were followed by accurate registry data. We, therefore, managed to follow up all patients for a median period of 34.8 months. Two methods were used to obtain follow-up data, but both these methods are accurate and allowed us to get information from all patients in the present study. Missing baseline variable-values decreased the number of patients available for the analyses, but the effect of this is probably of minor importance.

Increased serum creatinine at baseline appeared as a strong predictor of progression to ESRF in the multivariable model. This is widely accepted and has also been shown in studies of IgA nephropathy [9,14,19]. The clinical course in MPGN is dominated by chronic progression towards ESRF, with or without acute exacerbations; our findings support this. Serum creatinine correlated closely with the interstitial score. Increased serum creatinine was also a strong and independent predictor of death, as suggested by experience from clinical practice.

Increased proteinuria was a risk factor of progression to ESRF by univariate analyses, but not by multivariable analysis. Urinary protein correlated inversely with serum albumin, which was a significant risk factor both by univariate and multivariable analyses. A likely model of explanation would be that the ability of increased proteinuria to predict ESRF depended on an accompanying low serum albumin and that serum albumin was the important predictive variable. Proteinuria is considered to be a risk factor of progression to ESRF in IgA nephropathy [1,9,13,19]. The effect of hypoalbuminaemia on renal survival has received little attention in the literature, although earlier shown by Johnston et al. [4] for IgA nephropathy. Serum albumin may be decreased from at least two reasons, increased proteinuria as well as by reduced liver-synthesis of albumin. The latter may be due to reduced ability to substitute the lost proteins in the urine or decreased liver function. Our results suggest that reduced liver synthesis or malnutrition is of greater prognostic value than increased proteinuria. However, when liver synthesis of albumin fails, the proteinuria will be reduced also, as protein excretion is dependent on the level of protein in the blood. Consequently, the renal damage may be higher than predicted by proteinuria per se. Many studies are published on the damaging effect of protein being filtered and results are supported by clinical studies where a decrease in urinary protein has been associated with a slowing of progression towards ESRF [20–22].

We suggest that although increased proteinuria may be important, its effect may be due to the accompanying decreased serum albumin in the malnourished patient.

Both increased systolic and diastolic blood pressure were risk factors of progression in the univariate analyses. Increased diastolic blood pressure was the only independent risk factor by multivariable analysis. As diastolic and systolic blood pressure are approximately parallel covariates, the Cox analysis will choose the one that gives the greatest contribution to the analysis, whereas the other will lose its importance. It is, thus, reasonable to doubt that systolic blood pressure is that much less important than diastolic blood pressure. However, diastolic blood pressure may seem to be the most important predictor of ESRF. Hypertension at the time of biopsy is recognized as a risk factor for progression of IgA nephropathy [1,9,13,19]. Our study indicates that this may also be true for MPGN.

The presence of urinary granular casts was a risk factor for progression to ESRF in univariate analysis. This has been shown for IgA nephropathy previously [19], but has received little attention. We suggest that the presence of urinary granular casts, in addition to being a marker of increased proteinuria, is also a predictor of progression in MPGN. Urinary granular casts were associated with mesangial sclerosis, glomerular crescents or necroses and acute tubular damage, all processes that decrease renal survival. These lesions probably may cause further renal damage by increased proteinuria and glomerular and interstitial inflammation and urinary granular casts may be a clinical marker of this process. Interestingly, urinary granular casts were not correlated to interstitial score, suggesting that urinary granular casts may signalize future interstitial fibrosis.

Decreased age was an independent risk factor of progression to ESRF in the multivariable analysis, whereas patients >60 years had a significantly worse prognosis by Kaplan–Meier analysis. Radford et al. [14] found younger age to be an independent risk
factor of progression to ESRF in IgA nephropathy. Older age has been shown to be a risk factor of progression to ESRF in IgA nephropathy in univariate analyses, but not in multivariable analyses [4,12,13]. Our results suggest that younger age is an independent risk factor of progression in MPGN. These findings may suggest a more active renal disease in younger patients even though they did not have significantly shorter duration of renal disease or more severe clinical and morphological variables tested for in Table 2.

We studied involvement of four major compartments of the kidney and their contribution in the development of renal failure: the interstitium, the glomeruli, the vascular system and the tubules. Some of the histopathological variables that were included are signs of chronic renal damage whereas others clearly are signs of acute renal damage (glomerular crescents or necroses and acute tubular damage). The latter were highly significant in Kaplan–Meier analyses, which showed us that when a chronic progressive disease as MPGN develops histopathological findings of an acute exacerbation, patients progress faster to ESRF. This is a well-known fact for IgA nephropathy [13]. Chronic processes, such as interstitial fibrosis, chronic interstitial nephritis, mesangial sclerosis and benign nephroscerosis, were also important predictors of ESRF in the Kaplan–Meier analyses. Hence, when understanding the progression towards ESRF, both chronic and acute processes need to be taken into consideration. The only independent histopathological predictor of ESRF was interstitial score. This has been shown earlier for IgA nephropathy [10,13,23], although many authors have found glomerulosclerosis to be the most important predictor of ESRF [11,13–15]. It is well known that glomerulosclerosis and interstitial fibrosis are strongly associated and a theory has been postulated that glomerulosclerosis may be self-limiting in the absence of tubulointerstitial lesions [24]. We also made this finding, which supports the theory that progression of renal failure is the equivalent of interstitial scarring and all processes in the kidney lead to renal failure through this pathway. By far the best predictor of interstitial score was serum creatinine.

Our study supports many of the well-known risk factors for progression of IgA nephropathy, such as increased serum creatinine, increased blood pressure, advanced tubulointerstitial lesions, glomerular crescents, etc. However, we have identified three additional risk factors that earlier have received little attention: young age, hypoalbuminaemia and the presence of urinary granular casts. When we compared MPGN with IgA deposits to MPGN without IgA deposits, we found differences in baseline variables, but no difference in prognosis. Glomerular deposits of IgG, IgM, C3 or C1q also did not affect prognosis. The division of MPGN into several different entities based on glomerular immunodeposits may be rational on the basis of baseline variables, but seem to be of minor importance when making decisions about prognosis.

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