Improved prognosis in Norwegian patients with glomerulonephritis associated with anti-neutrophil cytoplasmic antibodies

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ABSTRACT

Background. Glomerulonephritis associated with anti-neutrophil cytoplasmic antibodies (ANCA) is associated with increased mortality and a high risk of end-stage renal disease (ESRD). Here, we investigated whether the prognosis has improved over the last 25 years.

Methods. Patients were identified in the Norwegian Kidney Biopsy Registry. We included all patients with pauci-immune crescentic glomerulonephritis and a positive ANCA test from 1988 to 2012. Deaths and ESRD in the cohort were identified through record linkage with the Norwegian Population Registry (deaths) and the Norwegian Renal Registry (ESRD). Outcomes of patients diagnosed in 1988–2002 were compared with outcomes of patients diagnosed in 2003–12.

Results. A cohort of 455 patients with ANCA-associated glomerulonephritis was identified. The mean follow-up was 6.0 years (range, 0.0–23.4). During the study period, 165 (36%) patients died and 124 (27%) progressed to ESRD. Compared with patients diagnosed in 1988–2002, those diagnosed in 2003–12 had higher mean initial estimated glomerular filtration rates (37 versus 27 mL/min/1.73 m²) and lower risk of ESRD (1-year risk: 13 versus 19%; 10-year risk: 26 versus 37%). The composite endpoint, ESRD or death within 0–1 year after diagnosis, was reduced from 34 to 25%. In patients over 60 years old, 1-year mortality fell from 33 to 20%.

Conclusions. In Norwegian patients with ANCA-associated glomerulonephritis, prognosis was significantly better in 2003–12 compared with 1988–2002. This improvement was probably partly due to a shorter diagnostic delay, and better therapeutic management in older patients.

Keywords: ANCA-associated glomerulonephritis, diagnostic delay, end-stage renal disease, mortality, prognosis

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (AAGN) is the most frequent form of the rapidly progressive glomerulonephritis syndrome. AAGN is an important cause of end-stage renal disease (ESRD) [1, 2]. Prior to the introduction of modern therapy, the prognosis of AAGN was very poor, and most patients died within 1–2 years after disease onset [3]. Cyclophosphamide (CYC) combined with corticosteroids (CS) was introduced as a treatment for AAGN more than 4 decades ago. This advent significantly improved prognosis, but morbidity and mortality remained high for several reasons [4–9]. First, treatment was often initiated after severe irreversible organ damage had occurred. Second, some patients had CYC-intolerance or resistance and, until recently, there were no effective
alternative drugs for treatment. Third, both CYC and CS are associated with severe toxicity, which can be fatal. Fourth, AAGN often recurred after long periods of remission and, unless recurrent episodes were treated promptly, they could cause severe organ dysfunction, including ESRD [10–12]. Currently, rituximab has been proven as effective, but not superior, to CYC for inducing remission in patients with ANCA-associated vasculitis [13–15]. However, in Norway, CYC remains the first-line treatment for inducing remission in most patients with AAGN.

Despite the lack of new, safe pharmacological substances that are more effective than CYC, a number of measures have been taken that could improve the prognosis of patients with AAGN. The diagnostic delay has probably been reduced by an increased clinical awareness about AAGN and the availability of an ANCA analysis that provides an answer within 1–2 days. The more recent introduction of rituximab has increased the therapeutic possibilities, particularly for patients with AAGN that are resistant or intolerant to CYC treatment. Also, optimization of CYC usage in maintenance treatments for AAGN may have reduced treatment-related morbidity and mortality. For example, CYC usage may be optimized by reducing doses for older patients and patients with advanced renal failure; by transitioning patients from oral to intravenous CYC; and by substituting CYC with other, presumably safer agents, like azathioprine (AZA) after achieved remission. Finally, the diagnostic delay, and thus, the risk of ESRD may have been reduced by the increased awareness that life-long surveillance is necessary to detect recurrence in patients with AAGN [16–19].

A few recent reports have shown an improved prognosis in patients with ANCA-associated vasculitis over time, but specific data are limited for patients with biopsy-proven AAGN [20–22]. In Norway, since 1988, all patients with kidney biopsies that showed AAGN have been registered in the Norwegian Kidney Biopsy Registry (NKBR). Here, we studied the prognosis in patients with AAGN and compared outcomes between patients diagnosed in 1988–2002 versus those diagnosed in 2003–12. We hypothesized that Norwegian patients with AAGN have experienced improved survival and reduced risk of ESRD over time.

### MATERIALS AND METHODS

This study was approved by the Regional Committees for Medical and Health Research Ethics (REC south-east).

### Registries used in the study

The NKBR was established in 1988. Clinical and histopathological data from patients that underwent a diagnostic kidney biopsy in Norway (current population, 5 million) were registered starting in 1988, and the completeness of registration was estimated to be ~90%.

The Norwegian Renal Registry is located at Oslo University Hospital, Rikshospitalet, Norway. Starting in 1980, all patients that started maintenance dialysis or received a kidney transplant were registered in the Norwegian Renal Registry. The tax office currently administers the Norwegian Population Registry, and all deaths are registered on a weekly basis. Information regarding the causes of death is recorded on the compulsory Norwegian death certificate, and this information is registered in the Cause of Death Registry, administered by Statistics Norway. The unique, 11-digit, Norwegian social security number made linking the different registries simple and reliable.

### Identification of the study population

All patients were included when they had a first time kidney biopsy that showed a crescentic pauci-immune pattern and a documented positive ANCA test.

### Observation period, identification and definition of study endpoints

The total follow-up (TFU) period of this study started on the date of the diagnostic kidney biopsy and ended on the date of death or on 31 December 2012. The observation period was further stratified into short (SFU = 0–1 years) and long (LFU > 1 years) follow-up periods. In the TFU period, the primary endpoints were progression to ESRD [commencement of chronic renal replacement therapy (RRT)] and standardized mortality ratio (SMR). In the SFU period, the study endpoints were all-cause deaths, SMR and ESRD. In the LFU period, the primary endpoints were SMR and ESRD. ESRD and deaths in the cohort were identified by linking the records of the study cohort to the Norwegian Renal Registry (ESRD) and the Norwegian Population Registry (deaths). Causes of death were identified by linking the study cohort to the Norwegian Cause of Death Registry; all deaths were categorized by cause, which included active vasculitis, infection, cardiovascular disease, malignancies and other causes.

### Identification and definition of predicting factors in the study

Predicting factors were identified in the NKBR, and comparison groups were defined as follows:

(i) Early versus late study cohorts: patients with diagnostic biopsies performed before 31 December 2002 (early) were compared with those with biopsies performed after 31 December 2002 (late).

(ii) Age groups at time of biopsy: patients were compared in age groups of <60 years; 60–74.9 years and ≥75 years.

(iii) Renal function groups: pre-biopsy serum creatinine levels were converted to the estimated glomerular filtration rate (eGFR; modified modification of diet in renal disease formula, Caucasians). Patients with mean eGFR ≥15 were compared with patients with eGFR <15 mL/min/1.73 m².

(iv) ANCA specificity groups: patients with cytoplasmic (C)-ANCA (immunofluorescence, IF) or anti-proteinase 3 (PR3) (enzyme-linked immunosorbent assay, ELISA) were compared with those with perinuclear (P)-ANCA (IF) or anti-myeloperoxidase (MPO) (ELISA).

(v) Proteinuria groups: groups comprised patients with proteinuria ≥3 and those with <3 g/24 h.

(vi) Blood pressure: groups comprised patients with blood pressures ≥ or <140/90 mmHg.
Mortality analyses

We compared the mortality rate of patients with AAGN to that of the general population by calculating SMR. The SMR was defined as the ratio between the observed and expected number of deaths in the cohort. The expected number of deaths was calculated based on mortality data for the Norwegian population, stratified by age (20–24, 25–29 years, and so forth), time-period (1990–94, 1995–99 and so forth) and gender (Statistics Norway). Each participant had an expected risk of death that varied depending on age, gender, time-period and duration of follow-up. Thus, the expected number of deaths in the study cohort was the sum of all of these risks. A Poisson distribution for death incidence in the general population was assumed in calculating the 95% confidence interval (95% CI).

First, SMR was calculated for the TFU, SFU and LFU periods. Second, the LFU was stratified into not-RRT and RRT periods, and the SMR was calculated separately for these periods. Finally, the above calculations were repeated after the TFU period, and the SMR was calculated separately for these periods. Second, the LFU was stratified into early (1988–1990), mid (1991–1992), and late (1993–1994) periods. Finally, the above calculations were repeated after the TFU period, and the SMR was calculated separately for these periods.

Availability of ANCA test and treatment protocols for 1988–2012

A questionnaire was sent to hospitals that treated patients with AAGN to determine the availability and response time of the ANCA test. The questionnaire also asked whether the institution practiced substitution of CYC with AZA in maintenance treatment for AAGN, and when they started this practice.

Statistical methods

Continuous variables are expressed as the mean ± SD and categorical variables are expressed as the number (%). The χ²-test was used to compare categorical variables, and the independent sample t-test was used to compare continuous variables. A P-value ≤ 0.05 was considered significant. Kaplan–Meier statistics were used to compare risks of ESRD and death. The log-rank test was used to test statistical significance. Cox regression statistics were used to analyse unadjusted and adjusted hazard ratios (HRs) for ESRD and/or death. Two adjusted HRs were calculated: the first was adjusted for age, gender and ANCA specificity; the second was adjusted for the same factors plus the eGFR.

RESULTS

A cohort of 455 patients with AAGN was identified. The TFU duration was 2720 patient-years, with a mean follow-up of 6.0 years (range, 0.0–23.4). The mean age was 59.6 years (SD 17), and 55% of patients were males. Number of patients with proteinuria ≥3 g/24 h was 94 (21%) and with hypertension 262 (58%). Other baseline characteristics are shown in Table 1. The outcomes of patients in the total study cohort are shown in Figure 1A. During the TFU period, 124/455 (27%) patients progressed to ESRD, and of those, 55/124 (44%) later died. Among the patients who did not progress to ESRD, 492/131 (36%) died. Thus, during the TFU, 165/455 (36%) deaths occurred. The cumulative risk of ESRD was 16% at 1 year, 25% at 5 years, 32% at 10 years and 42% at 15 years after the AAGN diagnosis.

In the SFU period (<1 years after diagnosis), 69/455 patients (15%) progressed to ESRD, and 75/455 (16%) patients died (Figure 1B). Thirteen patients (3%) died after commencement of RRT. Thus, at the end of the SFU period, 324/455 (71%) patients without ESRD were alive, and 56/455 (12%) patients were alive, but were RRT-dependent.

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At start of the LFU period (>1 year), 324 patients were alive without RRT (Figure 1C). Progression to ESRD occurred in 55/324 (17%) patients. The cumulative risk of ESRD was 13% at 5 years, 22% at 10 years and 37% at 15 years. During the LFU period, 90 patients died; of these, 48 patients had not progressed to ESRD, and 42 patients were established in RRT before death. At the end of the LFU period, 221 patients were alive without ESRD and 69 patients were alive with RRT.

Among the 165 deaths during the TFU, the causes of death were acute vasculitis (n = 31; 19%), infection (n = 43; 26%), cardiovascular disease (n = 58; 35%), malignancies (n = 15; 9%) and other causes (n = 18; 11%). The causes of death in the different observation periods and in patients with or without RRT are shown in Figure 1A–C.

In the TFU period, the SMR was 2.8 (95% CI: 2.4–3.3). In the SFU period, the SMR was 10.8 (95% CI: 8.6–13.5), and in the LFU period it was 1.7 (95% CI: 1.4–2.1). In the not-RRT part of the LFU period, the SMR was 1.1 (95% CI: 0.8–1.5), and in the RRT part, the SMR was 4.3 (95% CI: 3.2–5.8).

Table 1. Baseline characteristics of patients diagnosed with AAGN in the early (1988–2002) and late (2003–12) study periods

<table>
<thead>
<tr>
<th></th>
<th>All (n = 455)</th>
<th>1988–2002 (n = 218)</th>
<th>2003–12 (n = 237)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>59.6 (17)</td>
<td>57.6 (19)</td>
<td>61.5 (18)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>94 (21)</td>
<td>31 (14)</td>
<td>63 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>248 (55)</td>
<td>137 (63)</td>
<td>111 (47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-ANCA</td>
<td>258 (57)</td>
<td>142 (65)</td>
<td>116 (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-ANCA</td>
<td>197 (43)</td>
<td>76 (35)</td>
<td>121 (51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean eGFR, mL/min/1.73 m² (SD)</td>
<td>32 (29)</td>
<td>27 (26)</td>
<td>37 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt;15 mL/min/1.73 m²</td>
<td>153 (34)</td>
<td>95 (44)</td>
<td>58 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-albumin, g/L (SD)</td>
<td>31 (7)</td>
<td>31 (6)</td>
<td>32 (7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Proteinuria, g/24 h (SD)</td>
<td>1.8 (1.9)</td>
<td>2.1 (2.2)</td>
<td>1.6 (1.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic BP, mmHg (SD)</td>
<td>143 (22)</td>
<td>144 (21)</td>
<td>142 (22)</td>
<td>0.33</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (SD)</td>
<td>81 (11)</td>
<td>82 (11)</td>
<td>80 (12)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

ANCA, anti-neutrophil cytoplasmic antibodies; C-ANCA, cytoplasmic/proteinase3 ANCA; P-ANCA, perinuclear/myeloperoxidase ANCA; eGFR, estimated glomerular filtration rate; S-albumin, serum albumin; BP, blood pressure.

Values represent the number (%), unless otherwise indicated.
eGFR <15 mL/min/1.73 m² (adjusted HR = 5.1), male gender (adjusted HR = 2.1), P/MPO-ANCA (adjusted HR = 1.8) and age bracket 60–74.9 years (adjusted HR = 0.7). Furthermore, other risk factors for ESRD identified for the TFU period were proteinuria ≥3.0 g/24 h (adjusted HR = 1.7, 95% CI: 1.1–2.4, $P = 0.001$) and blood pressure ≥140/90 mmHg (adjusted HR = 1.9, 95% CI: 1.2–2.9, $P = 0.003$), but not serum albumin <30 g/L (adjusted HR = 0.9, 95% CI: 0.6–1.3, $P = 0.54$).

Risk factors for death in the SFU period

Also shown in Table 2, several significant, independent risk factors for 1-year mortality were identified for the SFU period. These included an initial eGFR <15 mL/min/1.73 m² (adjusted HR = 2.2), age bracket of 60–74.9 years (adjusted HR = 4.0) and age ≥75 years (adjusted HR = 8.4). Moreover, an increased 1-year mortality rate was significantly associated with serum albumin <30 g/L (adjusted HR, 95% CI: 1.1.1–3.1, $P = 0.01$). Proteinuria ≥3.0 g/24 h and blood pressure ≥140/90 mmHg were not significantly associated with increased 1-year mortality.

Comparison of early (1988–2002) and late (2003–12) study cohorts

Compared with the early study cohort, the late study cohort had significantly higher initial renal function, measured as the mean eGFR (37 versus 27 mL/min/1.73 m²), and significantly fewer patients with eGFRs <15 mL/min/1.73 m² (25 versus 45%) (Table 3). As shown in Table 1, there were some important differences in the baseline characteristics of these cohorts. The late study cohort had a higher mean age (62 versus 58 years), a larger fraction of patients ≥75 years (27 versus 14%), a larger fraction of female patients (53 versus 37%) and a higher frequency of type P/MPO-ANCA (51 versus 35%) than the early study cohort.

In comparing the two cohorts, we found that, over time, the 1-year cumulative risk of ESRD decreased from 19 to 13%,
In comparing the two cohorts, we found that the 1-year mortality rate decreased over time from 18 to 15% and it decreased from 33 to 20% in those ≥60 years old (Figure 3). In multivariate analyses, the unadjusted HR for 1-year mortality (1.3) was not significantly different in the early compared with the late study period (Table 4). When this was adjusted for age, gender and ANCA, it was significantly higher than that of the late study period. Then, when it was adjusted also for the initial eGFR (HR = 1.6), it was only borderline significant compared with the late study period. In a sub-group analysis of patients ≥60 years old, the HR for 1-year mortality was 2.4 after adjusting for age, gender and ANCA, and 2.0 after also adjusting for the initial eGFR (Table 4).

In comparing the early and late study groups, we found that, over time, the risk of the composite endpoint of ESRD or death <1 year after the AAGN diagnosis (Figure 4) was reduced from 34 to 25% (all patients), from 21 to 13% (patients aged <60 years), from 38 to 25% (patients aged 60–74.9 years) and from 65 to 38% (patients aged ≥75 years). In the Cox regression analysis, the HR for ESRD or death <1 year after diagnosis was 1.8 after adjusting for age, gender and ANCA, but it decreased to 1.3 (not significantly different from the late study group) after also adjusting for the initial eGFR (Table 4).

During the SFU period, the difference in SMR between study groups was only borderline significant. The SMR was 14.8 (10.9–20.2) in the early cohort and 8.1 (5.8–11.3) in the late cohort. Otherwise, we found no significant differences in SMR between the early and late study cohorts (data not shown).

**Availability of ANCA test and treatment protocols in 1988–2012**

Most hospitals that treated patients with AAGN responded to our questionnaire. All reported good availability of the ANCA analysis, and the response time was one to two working days at most. Historically, all hospitals used CYC to treat AAGN, but in the last few years, some have used rituximab for induction and maintenance treatments. All respondents also practiced the substitution of CYC with AZA for maintenance treatments; this change in practice was introduced between 2003 and 2008 in most hospitals.
The main finding in this study was that the prognosis of patients with AAGN in Norway improved significantly from the early (1988–2002) to late (2003–12) study periods. A similar trend has been described in several other studies in patients with ANCA-associated vasculitis. However, to our knowledge, this was the first, nationwide, unselected, population-based cohort with AAGN confirmed by kidney biopsies [10, 20–22].

A major complication of AAGN is progression to ESRD [23, 24]. We found that this risk decreased substantially over time; for the 1-year follow-up, it decreased from 19 to 13%, and for the 10-year follow-up, it decreased from 37 to 26%.
This was an improvement of great clinical significance, because RRT is associated with reduced quality of life, increased mortality and high costs [25, 26]. The major mechanism of ESRD risk reduction over time seemed to be a shorter diagnostic delay. The mean eGFR at AAGN diagnosis increased significantly over time, from 27 to 37 mL/min/1.73 m², and the fraction of patients with eGFR <15 mL/min/1.73 m² decreased from 44 to 25%. In the Cox regression model, the unadjusted HR for ESRD in the early period (1.5) was significantly higher than that in the late period. Moreover, the HR was basically unchanged after adjusting for age, gender and ANCA sub-type. However, when we also adjusted for the initial eGFR, the HR dropped to 1.2. We interpreted this to indicate that the improvement in eGFR was a mechanistic factor, rather than a confounder.

A primary objective when treating patients with AAGN is to avoid fatal disease courses. In our study cohort, the mortality rate was significantly higher than expected for the Norwegian population (SMR 2.8). However, high mortality rates were only observed in the SFU period (SMR 10.8) and in patients dependent on RRT during the LFU period (SMR 4.3). In patients that survived the first year and did not develop ESRD, the mortality rate was equivalent to that of the general population, after adjusting for age and gender (SMR 1.1). The increased mortality rate observed in patients dependent on RRT was probably not specific to patients with AAGN. We previously showed similar data for patients with IgA nephropathy [27]. Nevertheless, it underscored the clinical importance of avoiding progression to ESRD in patients with AAGN.

The main concern regarding survival in patients with AAGN is the high 1-year mortality rate [10]. We did not observe significantly different short-term mortality rates in the early (18%) versus late (15%) study periods. However, among patients with AAGN aged ≥60 years, the 1-year mortality rate was significantly reduced from 33% (early cohort) to 20% (late cohort). Of interest, in this age group, the unadjusted HR for death at 0–1 year after AAGN diagnosis was 2.0 (P = 0.01), and this HR remained unchanged after adjusting for age, gender, ANCA type and eGFR. Thus, a shorter diagnostic delay did not appear to be a major explanatory factor for the improvement in short-term survival among older patients. We speculated that the improvement in short-term survival might be due to greater care taken in treating the older patients in the later compared with the earlier study period. For example, they may have received more frequent use of prophylactic measures, reduced doses of CYC and more rigorous surveillance, particularly during the induction phase of the treatment.

**FIGURE 3:** Kaplan–Meier plots show 1-year survival in 455 patients with AAGN stratified by study period (1988–2002 versus 2003–12). (A) All patients. (B) Patients aged <60 years. (C) Patients aged ≥60 years. AAGN, anti-neutrophil cytoplasmic antibodies associated glomerulonephritis; ESRD, end-stage renal disease.
The risk of the composite endpoint, ESRD or death, in the SFU period decreased from 34% (early cohort) to 25% (late cohort), which clearly indicated a clinically relevant improvement. In death-censored analyses, a reduced mortality rate could result in an increased risk of ESRD, because death and ESRD frequently occur concurrently, and they may compete as endpoints in the clinical setting of AAGN in older patients. Theoretically, a less toxic, but also less effective, treatment regimen could result in both decreasing the mortality rate and increasing the risk of ESRD. However, it was reassuring that, in our study cohort, the observed improvement in short-term survival-rate was not linked to an increased risk of ESRD; the 1-year risk of ESRD decreased from 18% (early cohort) to 15% (late cohort) among patients aged ≥60 years.

The prognosis of patients with AAGN was better in the LFU than in the SFU period. The mortality risk was, except in patients with RRT, similar to the age- and gender-adjusted general population. The annual risk of ESRD was 2–3% per year of follow-up. Because the death rate did not increase, we did not investigate the composite ESRD or death endpoint in the LFU period. In fact, the prognosis of AAGN in the LFU period was similar to our previous finding in patients with IgA nephropathy [27]. There were no significant differences in prognosis between the early as compared with late cohort in the LFU period.

The overall prognosis in our study cohort was quite similar to that of previous study cohorts from other countries. A substantial improvement in renal function at the time of AAGN diagnosis was also found in a recent study from the Netherlands. In that study, serum creatinine fell from ∼450 µmol/L (in 1979–2000) to 282 µmol/L (in 2001–09) [21]. Most studies reported that the long-term risk of ESRD was 20–40%, similar to our findings [9, 20, 28, 29]. Our finding that the 1-year overall mortality rate was 17% was consistent with previous reports from unselected study cohorts [21]. Finally, our SMR of 2.8 closely resembled the 2.7 SMR found in a study on patients recruited from four clinical European Vasculitis Study Group (EUVAS) trials [10].

This study showed that the prognosis of AAGN significantly improved from the 1988–2002 period to the 2003–12 period. However, even in the late study period, the 1-year mortality rate was 15%, the 1-year risk of ESRD or death was 25% and the 10-year cumulative risk of ESRD was 26%. Thus, there remains room for improvement. Further reduction in diagnostic delay may reduce the risk of ESRD. Optimization of treatment protocols, particularly for older patients, may reduce the short-term mortality from AAGN [28, 30]. More research is needed to find new solutions to these challenges.

The major strengths of this study were the large, nationwide, population-based, unselected nature of the study cohort.
and the very long observation period with many clinically important (ESRD/death), reliably identified endpoints. This study also had some weaknesses. Because the NKBR had a purely renal focus, we could not categorize patients according to non-renal vasculitis activity. For example, we could not use the Birmingham vasculitis activity score. Furthermore, the histological data in the NKBR were, unfortunately, not sufficiently specific to apply to the recently published histopathological classification system for AAGN (focal/crescentic/mixed/sclerotic). Furthermore, we did not have detailed data on individual treatments; thus, we could not analyse the effects of different treatment protocols. Another limitation was that patients with AAGN without kidney-biopsy were not included in the study cohort, and such patients are not registered in the NKBR.

In summary, we have demonstrated that the prognosis of AAGN has improved significantly from 1988–2002 to 2003–12. Nevertheless, morbidity and mortality remain major concerns. More research is needed to identify strategies that can reduce diagnostic delay. Development of safer therapeutic strategies is also needed, specifically for older patients with AAGN.

**REFERENCES**


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