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Predictors of renal and patient outcomes in anti-GBM disease: clinicopathologic analysis of a two-centre cohort

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ABSTRACT

Background. Patients with anti-glomerular basement membrane (GBM) disease are at increased risk of morbidity and mortality from renal failure, pulmonary haemorrhage or complications of treatment. One-third also have circulating anti-neutrophil cytoplasmic antibodies (ANCA). The aim of this study was to determine the clinicopathologic predictors of patient and renal outcomes in anti-GBM disease with or without ANCA.

Methods. Retrospective review of 43 patients diagnosed with anti-GBM disease over 20 years in two centres, including nine with dual anti-GBM and ANCA positivity. Renal biopsies from 27 patients were scored for the presence of active and chronic lesions.

Results. Dual-positive patients were almost 20 years older than those with anti-GBM positivity alone ($P = 0.003$). The overall 1-year patient and renal survivals were 88 and 16%,

respectively. Oligoanuria at diagnosis was the strongest predictor of mortality; none of the 16 patients without oligoanuria died. In a Cox regression model excluding oligoanuria, age was the only other independent predictor of survival. Pulmonary haemorrhage and dialysis dependence did not influence mortality. Thirty-five of the forty-three (81%) patients required dialysis at presentation, including all nine dual-positive patients. Of them, only two (5.7%) regained renal function at 1 year. By logistic regression, oligoanuria at diagnosis and percentage of crescents were independent predictors of dialysis independence at 3 months. However, in biopsied patients, the presence of crescents (>75%) added little to the presence of oligoanuria in predicting dialysis independence. Histological activity and chronicity indices did not predict renal outcome. Two of the nine (22%) dual-positive patients relapsed compared with none of the anti-GBM alone patients. Seven patients received kidney transplants without disease recurrence.

Conclusions. Oligoanuria is the strongest predictor of patient and renal survival while percentage of glomerular crescents

is the only pathologic parameter associated with poor renal outcome in anti-GBM disease. Kidney biopsy may not be necessary in oligoanuric patients without pulmonary haemorrhage.

Keywords: anti-glomerular basement membrane, anti-neutrophil cytoplasmic antibodies, crescentic glomerulonephritis, oligoanuria, survival

INTRODUCTION

Anti-glomerular basement membrane (GBM) disease is a rare but potentially lethal autoimmune disorder characterized by rapidly progressive glomerulonephritis; when accompanied by pulmonary haemorrhage, the condition is often referred to as Goodpasture's syndrome [1–3]. Tissue injury is mediated directly by pathogenic anti-GBM antibodies that bind the $\alpha 3$ chain of type IV collagen found in specialized basement membranes in the kidney, lung, choroid plexus, retina and cochlea [4, 5].

Historically, untreated patients did not recover renal function and had substantial mortality. The use of plasma exchange in association with corticosteroids and cyclophosphamide has dramatically improved outcome [6, 7]. The decline in smoking and lower rates of lung haemorrhage, a major cause of early death, may have impacted on survival rates. Nonetheless, patient and renal survival depend on the degree of renal failure at presentation [7–11]. The disease can progress quickly to end-stage renal disease; as a result, many patients present at a late stage. Therefore, early diagnosis is crucial to improving outcome.

Anti-GBM disease is rarely associated with other autoimmune diseases, although up to a third may also have circulating anti-neutrophil cytoplasmic antibodies (ANCA), most commonly in a perinuclear fluorescent pattern (P-ANCA) with anti-myeloperoxidase reactivity [12–14]. It is not clear whether the ANCA-associated glomerulonephritis predisposes to the development of anti-GBM disease or whether ANCA positivity occurs in the course of anti-GBM disease [15]. Anti-GBM antibodies in the double-positive patients have been shown to have a broader spectrum of target antigens and lower levels of auto-antibodies against $\alpha 3$ (IV) NC1, compared with those without ANCA [16]. There have been conflicting data on the prognostic significance of ANCA positivity [13, 14, 17–19]. Clinically, dual-positive patients behave initially more like those with anti-GBM alone, but they are more likely to have multisystem involvement, and their increased tendency to relapse is more in keeping with ANCA-associated vasculitis [13, 14].

The diagnosis of anti-GBM disease is made by the demonstration of circulating anti-GBM antibodies in the patient serum and/or by kidney biopsy confirming linear deposition of IgG, or rarely IgA, along the glomerular capillary walls [1]. The prognostic value of kidney biopsy in anti-GBM disease has not been well established. Previous studies [8, 19, 20] have focused on the extent of glomerular crescents as the sole pathologic predictor of renal survival.

The aim of this study was to determine the clinicopathologic predictors of patient and renal outcomes in patients with anti-GBM disease, including those with dual antibody positivity. We

also aimed to address the question of whether or not a kidney biopsy should be performed in oligoanuric patients who present late but without pulmonary haemorrhage, since these patients are unlikely to recover independent kidney function.

MATERIALS AND METHODS

Study population

From 1991 to 2011, 43 patients with anti-GBM antibody-associated renal disease were treated at two neighbouring hospitals in the east of England. Nine (21%) also had positive ANCA serology. Anti-GBM antibodies were detected by standard assays against either purified human GBM (radioimmunoassay) or, more recently, sheep non-collagenous domain of the $\alpha 3$ chain of type IV collagen (enzyme-linked immunosorbent assay). Patients were classified according to their urine output on the day the diagnosis was made into either oligoanuric (<500 mL/day) or non-oligoanuric. Dialysis-dependent renal failure was defined as the need for dialysis within 72 h of hospital admission. Pulmonary haemorrhage was diagnosed by the presence of overt haemoptysis, diffuse alveolar infiltrate on chest imaging and confirmed by bronchoscopy and/or an increased carbon monoxide transfer factor.

Thirty-two patients received a standard immunosuppressive regimen of plasma exchange, tapering doses of oral prednisolone plus oral or intravenous cyclophosphamide, depending on discretion of the treating physician. Plasma exchange was performed either daily or every other day for at least five sessions or until anti-GBM antibody was undetectable. Eleven had either minimal immunosuppressive therapy with low-dose oral prednisolone or no treatment. As maintenance therapy, mycophenolate mofetil was given in eight patients and azathioprine in five.

Patients were stratified according to pre-existing co-morbidities into two risk groups: high risk, if they had diabetes, cardiovascular disease or active cancer; low risk, if they had no significant medical illness.

Histological scoring

Twenty-seven patients had a kidney biopsy, including seven with dual anti-GBM and ANCA positivity. A single pathologist reviewed and scored the slides blinded to clinical outcomes. To investigate the prognostic value of kidney biopsy in anti-GBM disease, we developed a scoring system for activity and chronicity taking into consideration the characteristic lesions in necrotizing and crescentic glomerulonephritis (Table 1). Briefly, the glomeruli, tubules and interstitium were assessed separately for inflammatory lesions and sclerotic/fibrotic lesions. Biopsy specimens containing six or more glomeruli per section qualified for evaluation. Each glomerulus was scored for the presence of fibrinoid necrosis and glomerular sclerosis, and the percentage of the glomeruli affected by each of these changes was calculated. Points were given as follows: 1 point for 1–30% affected, 2 points for 31–60% and 3 points for >60%. The percentage of glomerular crescents was noted separately. All crescents were separated into cellular, fibrocellular and fibrous, and scored as indicated in Table 1. Interstitial lesions, such as interstitial inflammation, interstitial

Table 1. Activity and chronicity indices

Activity index	Score (max 12)
Crescent type	
Cellular	3
Predominately cellular	2
Predominately fibrous	1
Fibrous	0
Fibrinoid necrosis (% glomeruli)	
>60%	3
31–60%	2
1–30%	1
None	0
Acute tubular necrosis (% area)	
>60%	3
31–60%	2
1–30%	1
None	0
Interstitial inflammation (% area)	
>60%	3
31–60%	2
1–30%	1
None	0
Chronicity index	Score (max 12)
Crescent type	
Fibrous	3
Predominately fibrous	2
Predominately cellular	1
Cellular	0
Glomerular sclerosis (% glomeruli)	
>60%	3
31–60%	2
1–30%	1
None	0
Tubular atrophy (% area)	
>60%	3
31–60%	2
1–30%	1
None	0
Interstitial fibrosis (% area)	
>60%	3
31–60%	2
1–30%	1
None	0

fibrosis, tubular necrosis and tubular atrophy, were quantitatively graded on a scale of 0–3: absent (0 point), 1–30% of tubular or interstitial area affected (1 point), 31–60% (2 points) and >60% (3 points). The results were used to derive the activity and chronicity indices (AI and CI). Data are shown as total AI (maximum score 12) and total CI (maximum score 12) and percentage crescents.

Outcome measures

Follow-up data were obtained from patients' medical records. All patients had follow-up data for at least 3 months from time of presentation or until death. The primary outcomes were patient and renal survival. For calculations of renal survival, the time of renal death was defined as the start of renal replacement therapy or the time of death.

Statistical analysis

Categorical variables were compared with Fisher's exact test, whereas analysis of variance was performed for

Table 2. Clinicopathologic characteristics of patients with anti-GBM disease by ANCA positivity

	Anti-GBM alone (N = 34) ^a	Double positive (N = 9) ^b	P-value
Age (years)	51.7 ± 19.5	69.0 ± 11.8	0.003
Male (%)	15 (44)	4 (44)	NS
Organ involvement kidney/lung/both	21/4/9	5/0/4	NS
Dialysis at diagnosis (%)	26 (76)	9 (100)	NS
Glomerular crescents >75% (%)	14 (70)	4 (57)	NS
Activity index	8 (2–12)	6 (4–11)	NS
Chronicity index	3 (3–10)	3 (0–10)	NS
Months of follow-up	27 (1–187)	54 (1–97)	NS
Relapse (%)	0 (0)	2 (22)	0.04

Values are expressed as mean ± SD, median (range) or number (percent).

^a(N = 20).

^b(N = 7) had kidney biopsy.

continuous variables. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Cox regression was used to assess the variables that were significantly associated with patient survival in univariate analysis. A logistic regression model was constructed using a stepwise procedure to identify variables significantly associated with dialysis independence. For all analyses, we used SPSS version 13.0 and considered a P-value of <0.05 to be statistically significant.

RESULTS

Patient characteristics

Of 43 patients, 9 had positive ANCA, with anti-myeloperoxidase specificity in 7 and anti-proteinase-3 in 2 (Table 2). ANCA-positive patients were almost 20 years older ($P = 0.003$), and all required dialysis at presentation. Pulmonary haemorrhage occurred in 13/34 (38%) ANCA-negative and 4/9 (44%) ANCA-positive patients. There were no differences in the pathological characteristics between patients with and without ANCA, and no granulomata or extraglomerular vasculitis was present in the dual-positive group.

Survival

Overall, 1-year patient survival was 88% (95% CI, 78–98%). Five patients died within the first year with a median time from diagnosis of 2 months (range, 1–10); two from pneumonia, one from line sepsis, one from multi-organ failure and one from an unknown cause. Age ≥ 60 years ($P = 0.001$), high co-morbidity ($P = 0.015$), oligoanuria ($P = 0.009$) and ANCA positivity ($P = 0.027$) were associated with patient survival (Figure 1A–D). There were no deaths among patients with a urine output of >500 mL/day at diagnosis. Among the 27 patients with oligoanuria, 1-year patient survival rate was 81% (95% CI, 66–96%). In a Cox regression model excluding oligoanuria, age was the sole independent predictor of mortality. Dialysis dependence, the presence of pulmonary haemorrhage and the type of immunosuppressive therapy did not predict patient survival.

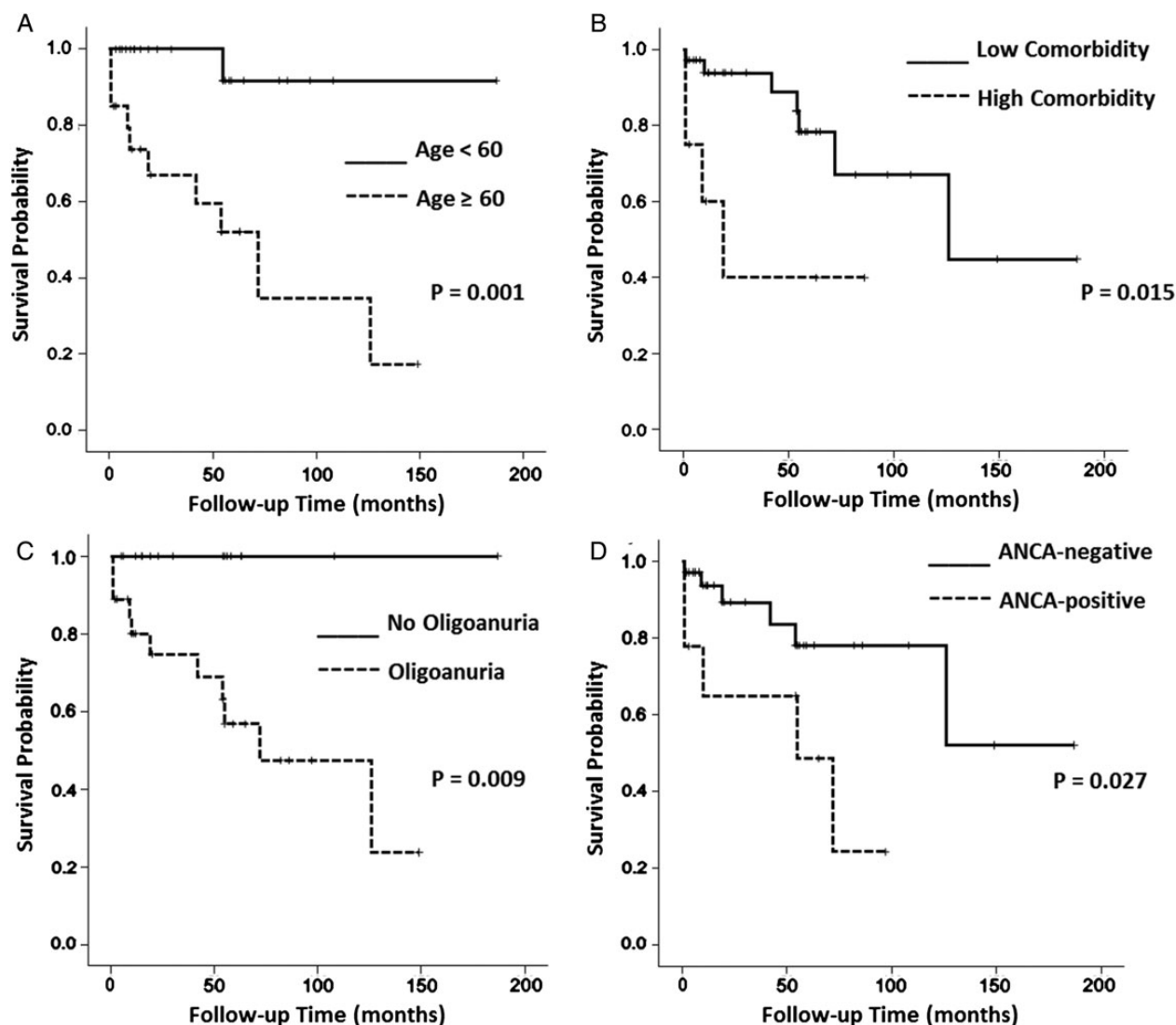


FIGURE 1: Kaplan–Meier patient survival curves for anti-GBM disease according to (A) age group (≥ 60 versus < 60), (B) co-morbidity group: high (diabetes mellitus, cardiovascular disease or cancer) versus low (no significant medical illness), (C) presence of oligoanuria at presentation and (D) ANCA positivity.

Renal survival

Overall, 1-year renal survival was 16% (95% CI, 5–27%). Only 2 of 35 (5.7%) patients who needed dialysis at diagnosis and none who had oligoanuria had recovered renal function 1 year after diagnosis. All nine ANCA-positive patients remained on dialysis.

We compared renal survival at 3 months according to initial clinical and pathologic data (Table 3). Age ($P = 0.013$), serum creatinine $> 500 \mu\text{mol/L}$ at diagnosis ($P = 0.003$) and oligoanuria ($P = 0.0003$) were associated with dialysis dependence. In all studied patients, the best logistic regression model showed oligoanuria at diagnosis to be the only independent predictor of dialysis dependence at 3 months ($P = 0.02$). When the analysis was confined to patients who underwent renal biopsy ($N = 27$), the best model showed the percentage of crescents as the only independent predictor of dialysis dependence at 3 months ($P = 0.03$). In biopsied patients, the presence of crescents ($> 75\%$) added little to the presence of oligoanuria in predicting dialysis independence. None of the 15 patients

Table 3. Renal survival at 3 months according to initial clinical and pathologic data

	On dialysis ($N = 30$) ^a	Not on dialysis ($N = 10$) ^b	P-value
Age (years)	59 \pm 15	37 \pm 22	0.013
Male (%)	11 (37)	7 (70)	NS
Initial creatinine $> 500 \mu\text{mol/L}$ (%)	25 (83)	3 (30)	0.003
Oligoanuria (%)	23 (77)	1 (10)	0.0003
Glomerular crescent $> 75\%$ (%)	15 (68)	0 (0)	0.01
Activity score	9 (2–12)	6 (4–10)	NS
Chronicity score	2 (0–10)	3 (0–5)	NS

Values are expressed as mean \pm SD, median (range) or number (percent).

^a $N = 22$.

^b $N = 5$ had kidney biopsy.

with 75% crescents or more achieved dialysis independence at 3 months compared with 5 of 12 (42%) in those with $< 75\%$ ($P = 0.01$). In comparison, dialysis independence was achieved

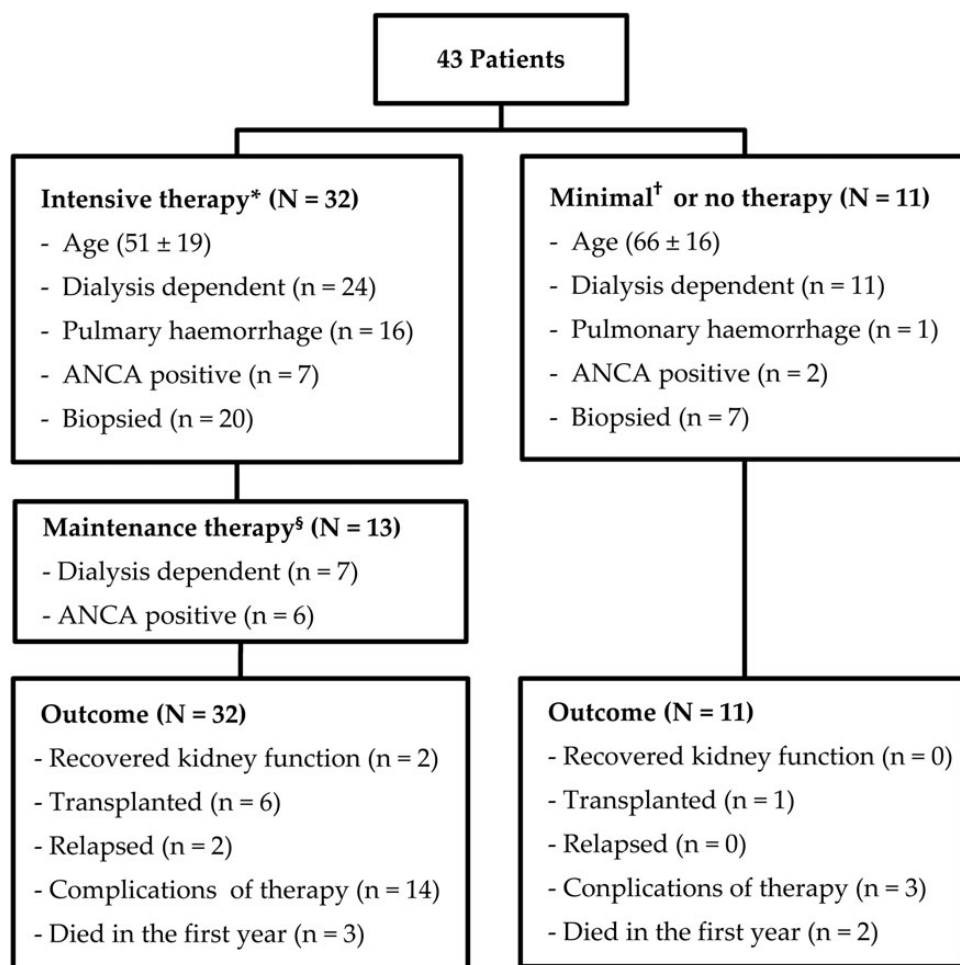


FIGURE 2: Flowchart showing patients' characteristics and outcomes according to the treatment modality. *Intensive therapy with plasma exchange plus cyclophosphamide and corticosteroids; †minimal therapy with low-dose prednisolone; §maintenance therapy with mycophenolate mofetil in eight patients and azathioprine in five.

in 1 of 17 biopsied patients (5.9%) with oligoanuria compared with 4 of 10 (40%) without oligoanuria ($P = 0.05$). Neither AI nor CI predicted renal survival.

Management and outcome

Patients' characteristics and outcomes according to the treatment modality are shown in Figure 2. Among the 32 patients who received intensive immunosuppressive therapy, 19 had their treatment discontinued either because of sepsis or lack of renal recovery. The other 13 received maintenance therapy with either mycophenolate or azathioprine; of these, six were ANCA positive. Two double-positive patients relapsed more than a year after initial presentation; one had pulmonary haemorrhage and a positive MPO-ANCA, and the other had expanding pulmonary lesions and a positive PR3-ANCA, without anti-GBM antibodies. Both were not on maintenance therapy at the time of relapse. Patients who did not receive specific treatment ($N = 11$) were older ($P = 0.03$). None of these patients regained independent kidney function, but one was subsequently transplanted. Almost all (94%) patients with pulmonary renal syndrome received intensive therapy including plasma exchange. There was no

difference in renal and patient survival between the intensively treated and untreated patient groups. Infections and bone marrow suppression were the two major complications of immunosuppressive treatment. Seven patients underwent renal transplantation (48 ± 23 ; range, 14–82) months after initial diagnosis. None of these had circulating anti-GBM antibodies at the time of operation, and none had recurrence of disease. One patient died 41 months post-transplantation with a functioning graft.

DISCUSSION

We report the clinical outcomes of 43 patients with anti-GBM disease with and without ANCA positivity, treated in two UK hospitals. We found that oligoanuria was the strongest predictor of both patient and renal outcomes. Oligoanuric patients typically have severe necrotizing glomerulonephritis involving almost all glomeruli, together with tubulointerstitial damage, resulting in a rapidly progressive, often irreversible, renal failure [21]. No patients with oligoanuria recovered renal

function in this study, whether treated with immunosuppressive therapy or not.

There is consensus in the literature about the importance of early diagnosis and treatment before the onset of oligoanuria or the need to start dialysis [7, 8, 10, 11, 19]. Levy *et al.* [8] reported a retrospective cohort of 71 patients treated with plasma exchange and identical immunosuppressive regimens. Patients presenting with a serum creatinine $<500 \mu\text{mol/L}$ had 100% patient survival and 95% renal survival at 1 year. In those presenting dialysis dependent, these values were 65% and 8%, respectively. This confirms the benefits of intensive treatment in those presenting before the onset of very advanced kidney failure, likewise, patients with pulmonary haemorrhage also benefit from immediate intensive treatment irrespective of renal function at presentation [8, 19].

Whether patients with very advanced kidney failure should be offered intensive treatment, even in the absence of pulmonary haemorrhage, remains controversial. In general, patients with renal-limited disease with a serum creatinine $\geq 600 \mu\text{mol/L}$ or with $\geq 80\%$ crescent formation, rarely benefit from such therapy [8–11]. Flores *et al.* [21] reviewed eight patients with oligoanuric anti-GBM disease without lung haemorrhage, none of whom received plasma exchange or intensive immunosuppression (though two were briefly immunosuppressed). None recovered renal function, though circulating anti-GBM antibodies fell and eventually disappeared in all and two were successfully transplanted. We found similar patient and renal survival in those who received intensive therapy and those who had minimal or no treatment. One small prospective randomized controlled study [22] compared plasma exchange with drug treatment alone and demonstrated a more rapid fall in anti-GBM antibodies and a trend towards better outcomes in the plasma exchange group though patients with $<30\%$ crescents and well-preserved kidney function did well with either treatment. A recent Chinese study [19] compared the effect of different therapeutic regimens in 96 patients with renal limited anti-GBM nephritis. There was an overall beneficial effect of combined therapy (plasma exchange, corticosteroids and cyclophosphamide) on renal survival [Hazard ratio (HR) for renal failure, 0.41; $P=0.002$]. Those with initial serum creatinine $\geq 600 \mu\text{mol/L}$ also benefitted from plasma exchange (HR for renal failure, 0.52; $P=0.014$). They concluded that combination therapy was preferred in patients with severe renal damage, even if in the absence of pulmonary haemorrhage. Overall, the value of intensive treatment, in patients with anti-GBM disease and advanced kidney disease and without lung haemorrhage, especially in the context of oligoanuria, seems very limited, though there is a need for more controlled data.

How long immunosuppressive therapy should be continued is also a contentious issue. Anti-GBM disease is generally considered a monophasic non-relapsing condition, with only a handful of cases of recurrent disease reported [23]. Spontaneous cessation of anti-GBM antibody formation can take 3–6 months or longer [21]. This has led to the suggestion that maintenance therapy may be required for a few months following the initial intensive therapy [24]. Most patients in large series [7, 8, 19], including ours, were successfully treated with

2–3 weeks of plasma exchange, ~ 3 months of cyclophosphamide and prednisolone and prednisolone alone for the subsequent 6–9 months; some also received azathioprine as maintenance [7, 8]. None of our patients with anti-GBM alone relapsed though only 20% (those with well-preserved renal function and/or detectible anti-GBM titres after induction) received maintenance therapy with mycophenolate or azathioprine. Given the low risk of relapse, we suggest that maintenance therapy is not required after anti-GBM antibodies have disappeared. This may not be so in patients with dual positivity in whom the long-term course is less predictable [25, 26]. Lindic *et al.* [26] reported that two dialysis-dependant patients with double positivity developed pulmonary relapse associated with MPO positivity despite the lack of anti-GBM antibodies. In the series of dual-positive patients reported by De Zoysa *et al.* [27], one patient had a renal relapse 6 years after the initial diagnosis and progressed to end-stage renal failure in the absence of anti-GBM antibodies. Two of our double-positive patients had late pulmonary relapse associated with increased ANCA activity. Because of the relapsing nature of the ANCA component of the double-positive disease, continuing management should be along the same lines of that for ANCA-positive systemic vasculitis, even though double-positive patients are less likely to regain independent kidney function [2].

Double-positive patients seem to have a poorer overall prognosis? In early reports, double positivity was linked to a better renal prognosis. None of the dialysis-dependent patients with pure anti-GBM disease recovered independent renal function, compared with 45% of double positives [17]. A more recent Swedish study of 29 patients also reported a better overall survival and more chance of recovering renal function in double-positive patients, even those presenting with severe renal failure [18]. In contrast, other studies [13, 14, 19] showed renal survival of double-positive patients to be poor and similar to those with anti-GBM positivity alone. None of 18 double-positive patients who presented with a creatinine $>500 \mu\text{mol/L}$ or dialysis dependency recovered renal function despite immunosuppression [13]. Rutgers *et al.* [14] reported no significant difference in the 1-year patient survival in those with anti-GBM (100%), double positive (79%) and MPO-ANCA vasculitis (75%). Double-positive patients with crescentic glomerulonephritis had severe renal involvement at diagnosis, similar to patients with anti-GBM, and more severe than in patients with ANCA positivity alone. In the Chinese study [19], patient survival rate at 1 year (48.7%), in the double-positive patients, was much worse than in those with anti-GBM alone (79.6%; $P<0.001$). In the same study, immunosuppression was found to have a beneficial effect on renal survival but not on patient survival. In our study, ANCA positivity was not assessed as an independent predictor of mortality, because patients with dual positivity were almost 20 years older and apart from oliguria age was the only independent predictor of death. Previous publications [13, 14, 19] have similarly shown that double-positive patients were older than those with pure anti-GBM disease. Another recent Chinese series [20] focusing on older patients (age $65 \geq$ years) with anti-GBM disease found that 46% (23 of 50) of these older patients had a positive ANCA, compared with 15% (25

of 171) of dual positives in the younger cohort ($P < 0.001$). ANCA positivity, unlike age, was found to be an independent risk factor for death (HR 2.5, $P = 0.01$) [13]. All of our double-positive patients were dialysis dependent at presentation and none recovered renal function. The numbers are small, but this may suggest that double-positive patients present late. Their worse overall prognosis may be due to a combination of older age and more extensive glomerular injury mediated by both ANCA and anti-GBM antibodies.

The diagnosis of anti-GBM disease requires the demonstration of anti-GBM antibodies in either the serum or the kidney. Circulating anti-GBM antibodies are detected in clinical practice by a number of commercially available ELISA assays that are highly sensitive (>95%) and specific (91%) [28]. Because two different assays were used in our series, we could not examine whether anti-GBM antibody titres correlated with prognosis. There is no doubt that anti-GBM antibodies are pathogenic; nonetheless, a kidney biopsy is usually recommended as cases in which antibodies are not detected by conventional means have been described [29]. The demonstration of a linear immunoglobulin deposition along the GBM in the context of crescentic glomerulonephritis is diagnostic. Kidney biopsy can also provide important information regarding the activity and chronicity of renal involvement that may help guide therapy [30]. Our study, as well as others, showed that the percentage of glomerular crescents predicted the eventual need for dialysis. Previous series [8, 19, 20] focused on the extent of crescent formation as a prognostic marker in anti-GBM disease. We evaluated whether other active or chronic pathologic characteristics grouped together would help predict prognosis but found that neither AI nor CI predicted renal survival. This could be due to the small sample size. Alternatively, it may be because the majority of our patients presented late and were dialysis dependent at diagnosis, with only few recovering renal function. In contrast to ANCA-associated pauci-immune glomerulonephritis where crescentic lesions tend to vary in a range of activity versus chronicity, crescents in anti-GBM disease are usually at the same stage of evolution highlighting its explosive nature. Thus, renal survival is poor when the majority of glomeruli are affected, no matter what stage of activity or chronicity.

In conclusion, oligoanuria is the strongest predictor of patient and renal survival while percentage of glomerular crescents is the only pathologic parameter associated with poor renal outcome. Nonetheless, the percentage of crescents added little to the presence of oligoanuria in predicting renal survival. In addition, neither AI nor CI predicted renal outcome, suggesting that a kidney biopsy may not be essential in oligoanuric patients in whom the diagnosis is made clinically and serologically. Double-positive patients had poor prognosis possibly due to a combination of older age and more extensive kidney injury. Early diagnosis and treatment before the onset of oliguria is crucial to improving outcome.

CONFLICT OF INTEREST STATEMENT

None declared.

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Diagnostic validation and prognostic significance of the Malnutrition-Inflammation Score in nondialyzed chronic kidney disease patients

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ABSTRACT

Background. Malnutrition and inflammation are highly prevalent and intimately linked conditions in chronic kidney disease (CKD) patients that lead to a state of protein-energy wasting (PEW), the severity of which can be assessed by the Malnutrition-Inflammation Score (MIS). Here, we applied MIS and validated, for the first time, its ability to grade PEW and predict mortality in nondialyzed CKD patients.

Methods. We cross-sectionally evaluated 300 CKD stages 3–5 patients [median age 61 (53–68) years; estimated glomerular filtration rate 18 (12–27) mL/min/1.73 m²; 63% men] referred for the first time to our center. Patients were followed during a median 30 (18–37) months for all-cause mortality.

Results. A worsening in MIS scale was associated with inflammatory biomarkers increase (i.e. alpha-1 acid

glycoprotein, fibrinogen, ferritin and C-reactive protein) as well as a progressive deterioration in various MIS-independent indicators of nutritional status based on anthropometrics, dynamometry, urea kinetics and bioelectric impedance analysis. A structural equation model with two latent variables (assessing simultaneously malnutrition and inflammation factors) demonstrated good fit to the observed data. During a follow-up, 71 deaths were recorded; patients with higher MIS were at increased mortality risk in both crude and adjusted Cox models.

Conclusions. MIS appears to be a useful tool to assess PEW in nondialyzed CKD patients. In addition, MIS identified patients at increased mortality risk.

Keywords: acute phase response, outcomes, renal disease, undernutrition, uremia