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CLINICAL RESEARCH

Effect of Immunosuppressive Treatments on Kidney Outcomes After Gross Hematuria-Related Acute Kidney Injury in Older Patients With IgA Nephropathy

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Introduction: Macroscopic hematuria (MH) bouts, frequently accompanied by acute kidney injury (AKI-MH) are one of the most common presentations of IgA nephropathy (IgAN) in the elderly. Immunosuppressive therapies are used in clinical practice; however, no studies have analyzed their efficacy on kidney outcomes.

Methods: This is a retrospective, multicenter study of a cohort of patients aged ≥50 years with biopsy-proven IgAN presenting with AKI-MH. Outcomes were complete, partial, or no recovery of kidney function at 1 year after AKI-MH, and kidney survival at 1, 2, and 5 years. Propensity score matching (PSM) analysis was applied to balance baseline differences between patients treated with immunosuppression and those not treated with immunosuppression.

Results: The study group consisted of 91 patients with a mean age of 65 ± 15 years, with a mean follow-up of 59 ± 36 months. Intratubular red blood cell (RBC) casts and acute tubular necrosis were found in all kidney biopsies. The frequency of endocapillary hypercellularity and crescents were low. Immunosuppressive therapies (corticosteroids alone or combined with mycophenolate mofetil or cyclophosphamide) were prescribed in 52 (57%) patients, whereas 39 (43%) received conservative treatment. There were no significant differences in the proportion of patients with complete, partial, or no recovery of kidney function at 1 year between patients treated with immunosuppression and those not treated with immunosuppression (29% vs. 36%, 30.8% vs. 20.5% and 40.4 % vs. 43.6%, respectively). Kidney survival at 1, 3, and 5 years was similar among treated and untreated patients (85% vs. 81%, 77% vs. 76% and 72% vs. 66%, respectively). Despite the PSM analysis, no significant differences were observed in kidney survival

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between the two groups. Fourteen patients (27%) treated with immunosuppression had serious adverse events.

Conclusions: Immunosuppressive treatments do not modify the unfavorable prognosis of patients with IgAN who are aged ≥50 years presenting with AKI-MH, and are frequently associated with severe complications.

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MH bouts, frequently associated with respiratory tract infections, represent one of the most characteristic clinical presentations of IgAN.[1] For many years, it has been known that some of these episodes are accompanied by AKI of variable severity.[2,3] Occlusion of the tubular lumen by RBC casts and subsequent acute tubular necrosis are the predominant lesions found in kidney biopsies performed during an episode of AKI-MH.[4] On the contrary, glomerular structure is relatively well preserved. Based on these findings, the pathogenesis of AKI-MH has been attributed to a direct injury on the tubular epithelium caused by hemoglobin, or iron released by intratubular erythrocytes.[5]

The first descriptions of AKI-MH reported a complete recovery of kidney function after disappearance of MH in majority of patients. It should be noted, however, that in these series, young patients were mostly included.[6] More recent studies show that a substantial number of patients (25% in one of these studies) did not completely recover their baseline kidney function after the disappearance of MH.[7] Age greater than 50 years, duration of the MH episode >10 days, decreased baseline kidney function, and the severity of tubular necrosis were predictors of worse outcomes after AKI-MH.[7]

Interestingly, recent reports have shown that MH bouts (frequently accompanied by AKI-MH) are one of the most common presentations of IgAN in the elderly.[8,9] Factors associated with this increased trend in the diagnosis of IgAN in elderly patients are unknown, although it has been speculated that the frequent use of anticoagulants in this population could be a potential precipitating factor.[10]

Information about optimal treatments and outcomes of patients with AKI-MH, particularly in the elderly, is scarce. Kidney Disease: Improving Global Outcomes guidelines recommend a conservative approach, based on the general measures indicated in any type of AKI.[11] Nevertheless, different immunosuppressive regimens are commonly used in clinical practice, based on the autoimmune pathogenesis of IgAN and the poor prognosis of these episodes in elderly patients.[7-9]

Therefore, the aim of this study was to analyze the influence of immunosuppression on kidney outcomes after AKI-MH, compared to conservative non-immunosuppressive management, in a multicenter observational cohort of patients with IgAN who were aged >50 years.

METHODS

Patients

Patients aged ≥50 years presenting with AKI-MH between January 1985 and August 2018 and whose kidney biopsy showed an IgAN were recruited from 17 nephrology departments belonging to the Spanish Group for the Study of Glomerular Diseases. Kidney biopsies were performed during AKI-MH in all cases. No patient had previously received the diagnosis of IgAN. Patients with a histologic diagnosis of IgA vasculitis, those with acute or chronic liver diseases, alcoholism, systemic lupus erythematosus, or any other systemic disease were excluded.

The study was approved by the institutional review board of Hospital Universitario 12 de Octubre (Madrid, Spain), and was conducted in accordance with the Declaration of Helsinki.

Baseline and follow-up data were collected from medical records following a uniform protocol. All patients had been admitted to the hospital during AKI-MH and were followed-up with at regular intervals after the resolution of MH. The following clinical and biochemical data were recorded: demographics, comorbidities at the time of kidney biopsy, the need for acute dialysis, serum creatinine (Scr), estimated glomerular filtration rate (eGFR), serum albumin, 24-hour proteinuria, and urinary sediment. The evolution of these analytical parameters during admission and thereafter during follow-up also was recorded. All patients had at least 1 Scr record before the episode of AKI-MH. Information about the medications prescribed was obtained from medical records at baseline and throughout the follow-up period, with particular attention to immunosuppressive drugs.

Kidney Biopsy

Kidney biopsy specimens were reevaluated at every participating hospital and lesions were scored according to the Oxford classification[12]: mesangial score <0.5 (M0) or >0.5 (M1); segmental glomerulosclerosis absent (S0) or present (S1); endocapillary hypercellularity absent (E0) or present (E1); tubular atrophy/interstitial fibrosis <25% (T0), 26%–50% (T1) and >50% (T2); and glomerular crescents: no crescents (C0), crescents in <25% of glomeruli (C1) and crescents in >25% of the glomeruli (C2).

Definitions

AKI was defined according to the Kidney Disease: Improving Global Outcomes guidelines criteria.[13] AKI-MH was defined as an AKI accompanied by gross hematuria or very intense nonvisible hematuria, and the finding of tubular necrosis associated with RBC casts as the most important lesion in kidney biopsy. The diagnosis of IgAN was based on the finding of mesangial glomerulonephritis with predominant mesangial deposits of IgA on immunofluorescence staining.

The baseline was established at the time of kidney biopsy. Peak Scr was defined as the highest Scr value during AKI. In those patients who needed acute dialysis, the highest Scr value before the initiation of dialysis was recorded as peak Scr. Slopes of eGFR were calculated from baseline to 12 months after AKI-MH.

Recovery of kidney function after AKI was established by the ratio between the Scr value at 6 and 12 months and the last determination of Scr before AKI-MH. No recovery of kidney function was defined by a Scr value higher than at least 75% of the last Scr value before AKI-MH or the need of kidney replacement therapy (KRT); partial recovery was defined by a Scr value that was lower than 75% and higher than 25% of the last Scr value before AKI-MH; and complete recovery by a Scr value lower than 25% of the Scr value before AKI-MH.

Chronic kidney disease (CKD) before the episode of AKI-MH was defined by an eGFR <60 ml/min/1.73 m^2. Kidney failure (KF) was defined by an eGFR <15 ml/min/1.73 m^2 or the need for kidney replacement therapy. eGFR was calculated using the CKD-Epidemiology Collaboration equation.[14] Follow-up was defined as the interval between kidney biopsy and last outpatient visit, death, or KF. Definitions of the study, as well as inclusion and exclusion criteria are shown in Supplementary Table S1.

Outcomes

The main outcome was the proportion of patients with complete, partial, or no recovery of kidney function at 1 year after AKI-MH. Secondary outcomes included the proportion of patients with complete, partial, or no recovery of kidney function at 6 months, and kidney survival (defined as a status free of KF) at 1, 2, and 5 years, and global survival (status free of KF or death).

Statistical Analyses

This is a retrospective, multicenter, observational cohort study. Descriptive statistics are presented as mean and standard deviation, or median and interquartile ranges for continuous variables, and absolute values and percentages for categorical variables.

Comparisons of continuous variables between 2 groups were assessed by using the unpaired t-test or the Mann-Whitney U-test, where appropriate. Chi-squared test, or Fisher exact test were used for categorical variables.

Cox proportional hazards regression models were used to analyze the main determinants of KF, using a backward progressive conditional elimination process. The proportional hazard assumption was checked graphically (log–log survival curves) for all covariates, and with the scaled Schoenfeld residuals. Distributions of time to KF or death were depicted by survival curves using the Kaplan-Meier method.

Because there were baseline differences between patients treated with immunosuppression and those not treated with immunosuppression, a PSM analysis was further applied for comparisons between groups. The following confounding variables were used for adjustment between groups: age, eGFR at kidney biopsy, need for acute dialysis, MEST score, history of hypertension and proteinuria. A 1:1 nearest neighbor matching algorithm was applied with a caliper of 0.2 without replacement. To evaluate the quality of the different PSM models, we assessed the balance before and after matching between the groups.

A P value <0.05 was considered significant. All P-values are reported 2-sided. Analyses were performed using IBM SPSS Statistics 24.0 (IBM Corp. Armonk, NY).

RESULTS

Baseline Characteristics

The study group consisted of 91 patients with a mean age of 65 ± 15 years, and 72 patients (79%) were males. Baseline clinical and histologic characteristics are shown in Table 1. Mean Scr and eGFR before AKI-MH were 1.2 ± 0.47 mg/dl and 65 ± 24.9 ml/min per 1.73 m^2, respectively. Thirty-seven patients (41%) had some degree of CKD before admission. Twenty-seven patients (30%) were under anticoagulant therapies when MH appeared.

Table 1. Baseline clinical and histologic characteristics[a]

	All patients ($N = 91$)
Clinical findings	
Age, yrs	65.3 ± 15.7
Gender (males), n (%)	72 (79.1)
HTN, n (%)	60 (65.9)
SBP, mm Hg	136.6 ± 21.6
DBP, mm Hg	78.2 ± 16.9
Diabetes mellitus, n (%)	19 (20.7)
Anticoagulant treatment, n (%)	27 (29.7)
CKD before admission, n (%)	37 (40.7)
Scr, mg/dl	4.3 ± 2.8
eGFR, ml/min per 1.73 m^2	19.3 ± 13.4
Proteinuria, g/d[b]	1.1 (0.5–2.4)
KRT required at presentation, n (%)	32 (35.2)
Histologic findings	
M_1, n (%)	59 (64.8)
E_1, n (%)	23 (25.3)
S_1, n (%)	38 (41.8)
$T_{1–2}$, n (%)	30 (33)
Crescents (C1), n (%)	5 (5%)

CKD, chronic kidney disease; DBP, diastolic blood pressure; E_1, endocapillary hypercellularity; eGFR, estimated glomerular filtration rate; HTN, hypertension; KRT, kidney replacement therapy; M_1, mesangial hypercellularity; S_1, segmental glomerulosclerosis; SBP, systolic blood pressure; Scr, serum creatinine; $T_{1–2}$, tubular atrophy/interstitial fibrosis >25%.
[a]Data are presented as mean (SD), and number (%), unless otherwise stated.
[b]Median (interquartile range).

Table 2. Clinical characteristics of patients treated or not with immunosuppressive therapies

	Immunosuppression ($N = 52$)	No immunosuppression ($N = 39$)	*P* value
Clinical findings			
Age, yrs	69.4 ± 9.9	59.9 ± 9.1	0.01
Gender (males), n (%)	38 (73)	34 (87)	0.10
HTN, n (%)	40 (77)	20 (51)	0.01
SBP, mm Hg	140.2 ± 19.6	131.9 ± 23.6	0.09
DBP, mm Hg	80.2 ± 15.04	75.5 ± 19.02	0.22
Diabetes mellitus, n (%)	10 (19)	9 (23)	0.65
CKD before admission n (%)	24 (47.1)	13 (36.1)	0.31
Scr, mg/dl	4.6 ± 2.7	4.1 ± 2.7	0.38
eGFR, ml/min per 1.73 m^2	17.1 ± 10.6	22.2 ± 16.1	0.07
Proteinuria, g/d[a]	1.3 (0.7–3.2)	1 (0.4–1.5)	0.23
KRT required at presentation, n (%)	24 (46.2)	8 (20.5)	0.01
Histologic findings			
M_1, n (%)	38 (73.1)	21 (53.8)	0.06
E_1, n (%)	13 (25)	10 (25.6)	0.94
S_1, n (%)	27 (51.9)	11 (28.2)	0.02
$T_{1–2}$, n (%)	17 (32.7)	13 (33.3)	0.95
Crescents (C1), n (%)	2 (3.8)	3 (7.7)	0.42

CKD, chronic kidney disease; DBP, diastolic blood pressure; E_1, endocapillary hypercellularity; eGFR, estimated glomerular filtration rate; HTN, hypertension; KRT, kidney replacement therapy; M_1, mesangial hypercellularity; S_1, segmental glomerulosclerosis; SBP, systolic blood pressure, Scr, serum creatinine; $T_{1–2}$, tubular atrophy/interstitial fibrosis >25%.
[a]Median (interquartile range).
Data are presented as mean (SD), and number (%), unless otherwise stated.

Mean Scr at presentation was 4.3 ± 2.8 mg/dl and mean eGFR was 19.3 ± 13.4 ml/min per 1.73 m^2. Thirty-two patients (35%) required acute dialysis at presentation.

All patients showed intratubular RBC casts and acute tubular necrosis features in kidney biopsies. Most of them (59 patients, 64%) presented with mesangial proliferation (M1), whereas endocapillary hypercellularity (E1) was found in 23 patients (25%). Segmental glomerulosclerosis was observed in 38 patients (41%), and T1-T2 degrees of tubular atrophy/interstitial fibrosis (T1–2) were observed in 30 patients (33%). Crescents (C1) were found in only 5 patients (5%). Mean follow-up was 59 ± 36 months.

Treatment

Sixty-nine patients (76%) were treated with renin-angiotensin-aldosterone system blockade. Different immunosuppressive therapies were prescribed in 52 (57%) patients as follows: 32 patients (62%) received corticosteroids alone; 12 patients (23%) received corticosteroids plus mycophenolate mofetil; and 8 cases (15%) received corticosteroids plus cyclophosphamide. The rest of the patients (39, 43%) were treated conservatively.

Clinical characteristics of patients who received immunosuppressive treatments and those who did not are shown in Table 2. Treated patients were significantly older (69.4 ± 9.9 vs. 59.9 ± 9.1 years), presented a higher rate of hypertension (76% vs. 51%) and a greater requirement of acute dialysis (46% vs. 20%), compared to those who only received conservative treatment. Treated patients presented a nonsignificant worse kidney function at presentation. The proportion of patients with segmental glomerulosclerosis was significantly higher among treated patients (51% vs. 28%) and there was a nonsignificant trend for a higher proportion of patients with mesangial hypercellularity (73% vs. 53%) among treated patients. No differences were found in the proportion of patients with endocapillary hypercellularity or severe tubulointerstitial lesions.

Outcomes

Overall, at 1 year, 29 patients (32%) achieved complete recovery of kidney function, 24 (26%) achieved partial recovery, whereas 38 cases (42%) had no recovery of kidney function (Table 3).

No significant differences were observed in the proportion of patients with complete, partial or no recovery of kidney function at 1 year among patients treated with immunosuppression and those not treated (29% vs. 36%, 30.8% vs. 20.5%, and 40.4% vs. 43.6%, respectively). Likewise, no differences were found in the proportion of patients with complete, partial, or no recovery of kidney function at 6 months

Table 3. Outcomes of all patients, according to immunosuppression

	All patients ($N = 91$)		Immunosuppression ($N = 52$)		No immunosuppression ($N = 39$)	
Kidney function recovery	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo
Complete recovery, n (%)	23 (25.3)	29 (32)	13 (25)	15 (29)	10 (25.6)	14 (36)
Partial recovery, n (%)	25 (27.5)	24 (26)	17 (32.7)	16 (30.8)	8 (20.5)	8 (20.5)
No recovery, n (%)	43 (47.3)	38 (42)	22 (42.3)	21 (40.4)	21 (53.8)	17 (43.6)

among treated and untreated patients (25% vs. 26%, 32.7% vs. 20%, and 42.3 % vs. 54%, respectively; Table 3).

The decrease in Scr after AKI-MH at 6 and 12 months is shown in Figure 1. No significant differences were found between patients treated with immunosuppressive agents and those not treated with immunosuppressive agents. Likewise, no significant differences were found in eGFR slopes: +19 ± 17 ml/min per 1.73 m^2/yr in treated patients and +24 ± 27 ml/min per 1.73 m^2/yr in not treated patients. ($P = 0.62$).

Kidney survival at 1, 3, and 5 years was similar between treated and untreated patients (85% vs. 81%, 77% vs. 76%, and 72% vs. 66%, respectively) (Figure 2a). Likewise, no significant differences were observed in global survival (Figure 2b). The proportion of patients with different degrees of CKD before and after AKI-MH is shown in Figure 3.

By multivariable Cox regression analysis (Table 4), the main determinants of KF were peak Scr during AKI (hazard ratio [HR]: 1.19; 95% confidence interval [CI]: 1.05–1.34; $P = 0.005$), and the degree of tubulointerstitial fibrosis as assessed by T1–T2 score (HR: 1.88; 95% CI: 1.08–3.29; $P = 0.03$).

Four deaths occurred during the first year of follow-up, 3 among patients who received immunosuppressive treatments and 1 among untreated patients. At 5 years, 14 patients had died, 9 (17%) among treated patients and 5 (13%) among untreated ones ($P = 0.45$).

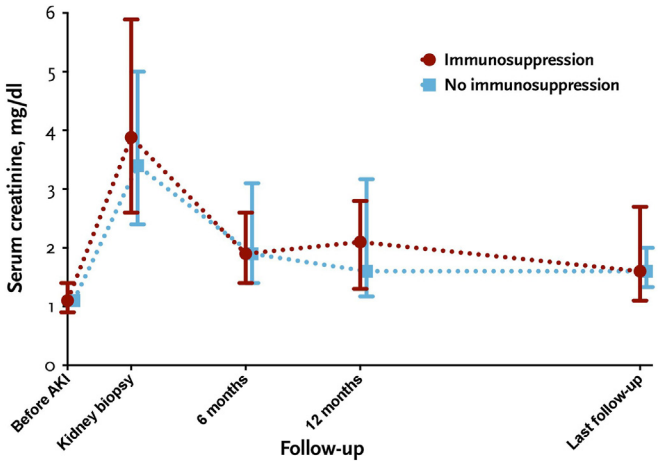

Figure 1. Evolution of serum creatinine in patients treated and not treated with immunosuppressive therapies. AKI, acute kidney injury.

PSM

To investigate whether baseline characteristics between groups could influence outcomes, a PSM analysis was applied to compare kidney survival of patients treated with immunosuppression with those who were not treated with immunosuppression, after adjusting for baseline differences (age, previous comorbidities, eGFR at presentation, and histologic MEST score). These prognostic covariables were properly balanced between subgroups after PSM analysis, and no significant differences were observed (Supplementary Table S2 and Supplementary Figure S1).

Kaplan-Meier curves for kidney survival according to treatment with immunosuppression in this matched cohort are presented in Figure 4. No significant differences were observed in kidney survival between the groups despite adjusting for baseline characteristics.

Immunosuppression-Related Adverse Events

Fourteen out of the 52 patients (27%) treated with immunosuppression had some adverse event. Infectious complications were the most common adverse events (7 patients, 13%), followed by the development of diabetes mellitus (2 patients, 4%), cytopenia (2 patients, 4%), and vertebral collapse (1 patient, 2%).

DISCUSSION

Age has a crucial influence on the prognosis of patients with IgAN presenting with AKI-MH.[7-9] Whereas complete recovery of kidney function is commonly observed in young patients, a substantial number of adult or elderly patients show an incomplete kidney function recovery after suffering one of these episodes, and many of them develop KF in the long-term.[7-9]

This impact of age on the risk of poor outcomes after AKI-MH is important considering that age at the time of IgAN diagnosis seems to be increasing in recent years.[8,9] Furthermore, AKI-MH is reported to be a frequent clinical presentation of IgAN in older patients.[8] In a previous study of our group, we found that 53 patients from a cohort of 151 patients with IgAN who are aged 65 years or older at diagnosis presented with AKI-MH; at the end of follow-up, 23 of them had died or developed KF.[9]

Despite this poor prognosis, no studies have analyzed therapeutic possibilities for this variant form

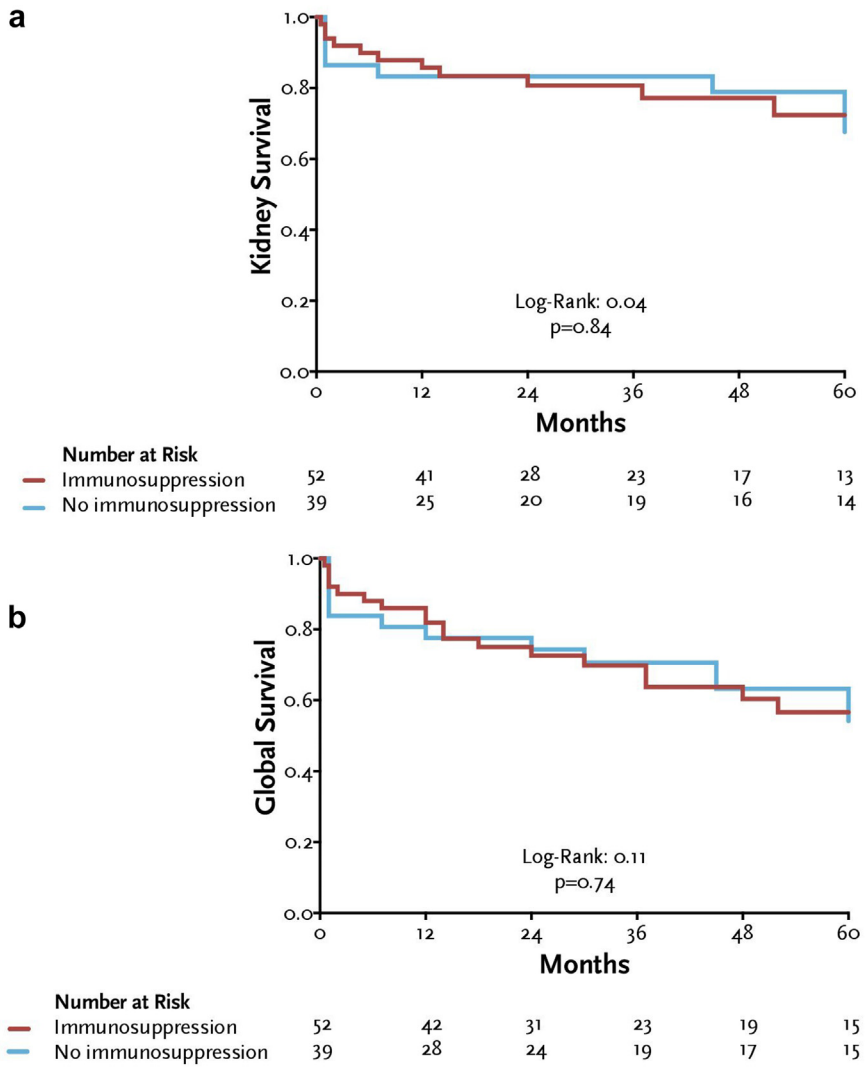

Figure 2. (a) Kidney survival of patients treated and not treated with immunosuppressive therapies; (b) Global survival of patients treated or not with immunosuppression.

of IgAN in adult and elderly patients. In general, conservative and supportive treatment, including KRT for the most aggressive cases, is recommended while waiting for a spontaneous recovery of kidney function after the cessation of gross hematuria.[11] This attitude seems reasonable in AKI-MH occurring in young

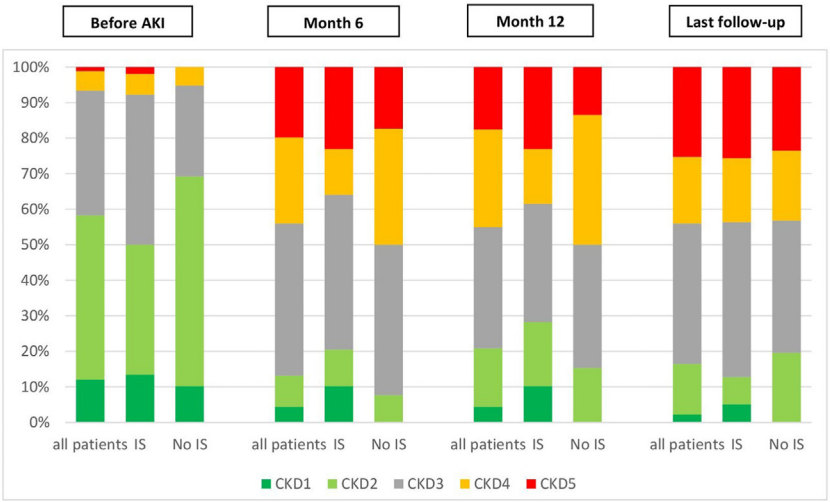

Figure 3. Chronic kidney disease stages before AKI-MH, at 6 and 12 months after AKI-MH, and at last follow-up. AKI, acute kidney injury.

Table 4. Cox proportional hazard regression analysis for association between covariables and kidney failure

	Univariable		Multivariable	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age, yrs	0.99 (0.95–1.04)	0.89		
Gender, male	2.68 (0.84–8.56)	0.10		
Peak serum creatinine	1.23 (1.06–1.43)	0.007	1.19 (1.05–1.34)	0.005
Proteinuria	1.12 (0.94–1.34)	0.22		
M1	1.15 (0.39–3.42)	0.79		
E1	2.46 (0.87–6.99)	0.09		
S1	0.69 (0.25–1.93)	0.48		
T_{1-2}	2.03 (1.01–4.08)	0.04	1.88 (1.08–3.29)	0.03
RAAS blockade	0.44 (0.16–1.20)	0.11		
Immunosuppression	0.73 (0.28–1.91)	0.52		

CI, confidence interval; M1, mesangial hypercellularity; E1, endocapillary hypercellularity; RAAS, renin-angiotensin-aldosterone system; S1, segmental glomerulosclerosis; T_{1-2}, tubular atrophy/interstitial fibrosis >25%.

patients, given their reported good prognosis.[6,15,16] However, although the use of immunosuppression is controversial for the treatment of IgAN, different immunosuppressive regimens are prescribed in real life for elderly patients presenting with AKI-MH, considering the high risk of incomplete kidney function recovery and KF.[7,17]

In our study, immunosuppressive treatment did not influence kidney outcomes of adult and elderly patients with IgAN presenting with AKI-MH. It should be stressed that our patients cannot be considered as rapidly progressive forms of IgAN, characterized by a rapid decline in kidney function and the finding of crescents in >30% to 50% of the glomeruli. The number of our patients with crescents as well as the percentage of glomeruli occupied by crescents was very low. Likewise, the frequency of endocapillary hypercellularity was low and no active inflammatory lesions were found.

The most commonly reported lesions in kidney biopsies performed during AKI-MH are RBC casts filling

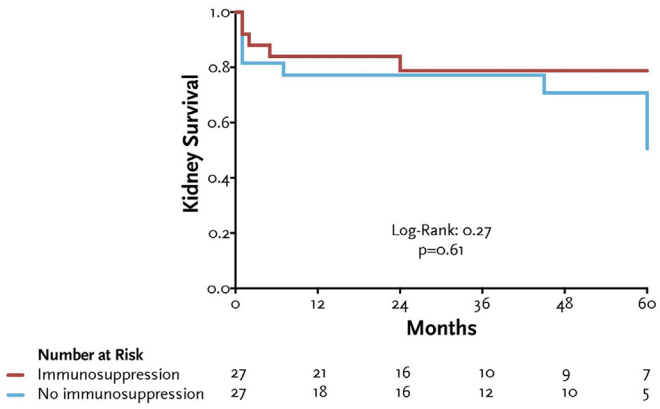

Figure 4. Kidney survival of patients treated or not with immunosuppressive therapies after propensity score matching analysis.

numerous renal tubules and tubular necrosis in areas close to the casts. In contrast, glomerular lesions are usually mild.[18] Crescents have been reported in several studies, although the percentage of glomeruli occupied by crescents is usually low.[15] The revision of kidney biopsies of our patients agrees with these previous reports; intratubular erythrocyte casts and lesions of tubular necrosis were the most prominent lesions in all the cases. As might be expected from the high prevalence of CKD before AKI-MH, chronic lesions were frequently observed.

Patients who received immunosuppression had more aggressive characteristics than those treated conservatively; they were significantly older and required KRT in a significantly higher number of cases. These imbalances might have influenced our results, leaving the question as to whether immunosuppressive treatments could have a more beneficial influence in patients who are not so old or in those with less aggressive AKI-MH. However, after performing a PSM analysis that properly balanced baseline characteristics, no significant differences were observed in kidney survival between the groups. Moreover, as might be expected, immunosuppressive treatment was accompanied or followed by serious complications (infections, diabetes, cytopenia, and vertebral collapse) in more than a quarter of treated patients. Previous studies have reported a high toxicity of immunosuppressive drugs in patients with reduced kidney function.[19]

Our study also confirms the poor prognosis of adult or elderly patients with IgAN who present with AKI-MH. One-fourth of patients had developed KF and almost one-fifth had died during follow-up, with no differences between treated and untreated cases.

The pathogenesis of AKI-MH is not completely understood. Hemoglobin and its heme-derivatives released by the erythrocytes occluding renal tubules can generate reactive oxygen species and decrease nitric oxide levels, thus inducing renal vasoconstriction and tubular ischemia.[5,6] On the other hand, tubular cells can internalize these heme-derivatives, increasing intracellular iron-derived hydroxyl radicals, promoting mitochondrial damage and finally apoptosis.[15] These mechanisms of intracellular damage mediated by hemoglobin and its derivatives can also affect podocytes.[20]

The reduced enzymatic defense against oxidative damage associated with aging, and the frequent occurrence of baseline CKD and chronic histologic lesions, as observed in many of our patients, would explain the poor prognosis of AKI-MH in older patients in contrast to the general good recovery reported in the young.

Several experimental studies suggest that the mechanisms of tubulointerstitial damage induced by

gross hematuria could be shared by other types of pigment-induced AKI, like rhabdomyolysis or paroxysmal nocturnal hemoglobinuria.[21,22] In these conditions, myoglobin and hemoglobin freely filtered by the glomerulus cause a direct tubular damage by mechanisms similar to those described above for hemoglobin and heme-derivatives. Interestingly, activation of nuclear factor erythroid-2-related factor 2, a transcription factor that plays a key role in the defense against oxidative damage, significantly improved heme-associated kidney damage.[23] However, whether nuclear factor erythroid-2-related factor 2 may protect from AKI-MH in older patients is unknown.

Our study has important limitations, derived mainly from its retrospective and uncontrolled design. Immunosuppressive treatments were administered to patients with more aggressive presentations, which resulted in an imbalance between the baseline characteristics of treated and untreated patients. However, our study has evident strengths. To our knowledge, it is the largest case series of AKI-MH in adult and elderly patients with IgAN reported to date; complete clinical and histologic data set were available in all included cases; and a regular long follow-up was performed in all the cases, which allowed to analyze the influence of baseline characteristics and the treatment received on the kidney outcomes.

In conclusion, patients with IgAN who are older than 50 years who present with AKI-MH have a poor prognosis, with almost half of the cases reaching KF or death. Immunosuppressive treatments do not provide benefits in the absence of active glomerular inflammation or crescentic lesions and are accompanied by severe adverse effects related to reduced kidney function and age. Newer therapeutic alternatives are urgently needed in this type of patients.

APPENDIX

List of Members of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Dot plot and histogram of standardized mean differences in propensity-matched cohort.

Table S1. Inclusion and exclusion criteria, definitions and outcomes.

Table S2. Clinical characteristics of patients treated or not with immunosuppressive therapies after the propensity score matching.

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