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Clinical Practice Patterns in IgA Nephropathy: A Global Questionnaire-Based Survey

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Introduction: IgA nephropathy (IgAN) displays ethnic differences in disease phenotype. We aimed to examine how this common disease is managed worldwide.

Methods: An online 2-step questionnaire-based survey was conducted among nephrologists globally focusing on various management strategies used in IgAN.

Results: A total of 422 nephrologists responded to the initial survey and 339 to the follow-up survey. Of the nephrologists, 13.7% do not get MEST-C scores in biopsy reports; 97.2% of nephrologists use renin-angiotensin-aldosterone system (RAAS) blockade with angiotensin-converting-enzyme inhibitors (ACEi) / angiotensin receptor blockers (ARB) as initial treatment. Other supportive treatments commonly employed are fish oil (43.6%) and sodium-glucose co-transporter-2 (SGLT2) inhibitors (48.6%) with regional differences. Immunosuppression is generally (92.4%) initiated when proteinuria >1 g/d persists for ≥ 3 months.Main considerations for initiating immunosuppression are level of proteinuria (87.9%), estimated glomerular filtration rate (eGFR) decline (78.7%), lack of response to RAAS blockade (57.6%) and MEST-C score (64.9%). Corticosteroids (89.1%) are universally used as first-line immunosuppression; mycophenolate mofetil is commonly used in resistant patients (49.3%). Only 30.4% nephrologist enroll patients with persistent proteinuria >1 g/d in clinical trials. Nephrologists in Europe (63.6%), North America (56.5%), and Australia (63.6%) are more likely to do so compared to South America (31.3%) and Asia (17.2%). Only 8.1% nephrologists in lower-middle income countries (LMICs) enroll patients in clinical trials, though 40% of them are aware of such trials in their nations.

Conclusion: Although most nephrologists agree on common parameters to assess clinical severity of IgAN, use of RAAS blockade, and blood pressure control, there is heterogeneity in use of other supportive therapies and initiation of immunosuppression. There is reluctance to enroll patients in clinical trials with novel treatments, principally in LMICs.

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IgAN is a common primary glomerular disease. The clinical trajectory varies from an asymptomatic, nonprogressive course to an aggressive one, with a 20% to 40% risk of progressing to end-stage kidney disease within 10 years with significant ethnic variability.[1,2] IgAN is reported to manifest an aggressive disease phenotype in Asian countries,[2,3] which may influence how the disease is managed in this region.

Since 2003, the Kidney Diseases Improving Global Outcomes (KDIGO) Clinical Practice Guidelines have been a reference for the management of glomerular diseases, including IgAN. The update to the KDIGO guidelines[4] in 2021 mainly emphasizes on optimized supportive nephroprotective therapy in patients with IgAN. Some recommendations in the KDIGO guidelines have been region-specific, due to a few regional trials

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[9]HT and SB have contributed equally to this work. Both the authors participated in the inception of the paper, the design of the 2 questionnaires, the objectives of the study, supervised the study, drafted and edited the manuscript and the response to reviewers.

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showing efficacy.[5-8] With little evidence supporting most prescribed therapies, it is critical to assess how IgAN is managed in the "real world." In this respect, we decided to globally distribute an *ad hoc* questionnaire to address the different approaches of nephrologists to the many clinical phenotypes of IgAN.

METHODS

A questionnaire-based survey was developed, focusing on both supportive therapy and immunosuppression use in IgAN in accordance with the KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases,[4] 1 year after publication. It was piloted among 10 nephrologists from different nations with expertise in the management of patients with IgAN. The final questionnaire was distributed using mailing lists of various nephrology societies across the world and by scoping the literature for practitioners in nephrology. All participants gave their electronic consent before proceeding with the survey.

The survey questionnaire consisted of 2 steps. The first step was divided into 2 parts as follows: (i) demographic data and (ii) practice patterns in IgAN. Considering that the KDIGO guidelines[4] suggest enrolling patients at high risk of disease progression (defined as persistent proteinuria >1g/d despite optimized supportive care for at least 3 months) in clinical trials, the second step was designed as a short survey to assess the attitude of nephrologists to randomized clinical trials (RCTs) that evaluate newly developed drugs in IgAN and was circulated among those who had responded to the initial survey. However, some nephrologists who did not have the chance to take part in the first step of this questionnaire, participated in the second step because their colleagues shared the survey. The study was approved by the Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi.

Statistical Analysis

All data were tabulated in Microsoft Excel and analyzed through the statistical software Stata 14.0 (College Station, TX). Descriptive statistics of percentages, medians (interquartile ranges), and means (SD) were reported where appropriate. Standard statistical tests were performed to assess whether regional and demographic parameters influenced responses. A *P*-value of ≤0.05 was considered significant.

RESULTS

The initial questionnaire was answered by 422 nephrologists across the world and their demographic details are shown in Figure 1.

Initial Supportive Therapy

Details of approach to supportive treatment are described in Tables 1 and 2. ACEi/ ARB therapy (410/422, 97.2%) for proteinuria reduction and blood pressure control (386/422, 91.5%) are the most common initial supportive treatment strategies used across geographies. The majority of the respondents (251/422, 59.5%) target blood pressure of ≤130/80 mm Hg. Dual RAAS blockade with ACEi and ARB is used by only 110 of 422 (26.1%) nephrologists, most commonly in South America (43/73, 58.9%) and Europe (14/30, 46.7%) ($P < 0.001$). Overall, about half (224/422, 53.1%) prescribe mineralocorticoid receptor antagonists (MRA) for persistent proteinuria despite maximal doses of ACEi or ARB; and this was more common in South America (48/73, 65.8%) and North America (26/42, 61.9%). Only 10 of 422 (2.4%) reported using MRAs in all patients. When the survey was undertaken, spironolactone and eplerenone were the only MRAs available for clinical use in Latin America and India.

As shown in Table 3, SGLT2 inhibitors (205/422, 48.6%) and fish oil (184/422, 43.6%) are the most frequently used nonimmunosuppressive therapies beyond RAAS blockade. Fish oil is used primarily in Asia (131/258, 50.8%) and South America (30/73, 41.1%) ($P = 0.001$).

Initiating Immunosuppression

The initial survey did not allow the respondents to choose 'no immunosuppression' or 'recruitment to a clinical trial' as options in patients with persistent proteinuria. Most respondents (390/422, 92.4%) reported waiting at least 3 months before labeling the disease as unresponsive to supportive therapy and starting immunosuppression (Figure 2). While planning immunosuppression, considerations (Figure 3, Table 4) included proteinuria (371/422, 87.9%), renal function (332/422, 78.7%), and kidney histology (274/422, 64.9%). However, 58 of 422 (13.7%) nephrologists said they do not have access to the MEST-C scores and this was more common in Australia and Africa (Figure 4).

Majority of respondents (260/422, 61.6%) start immunosuppression if there is persistent proteinuria >1 g/d. In newly diagnosed patients with stable eGFR, 166 of 422 (39.3%) will start immunosuppression directly at proteinuria >3.5 g/d especially in Asia (118/258, 45.7%) and South America (27/73, 37.0%). Many nephrologists (250/422, 59.2%) start immunosuppression immediately after diagnosis for patients with proteinuria >1 g/d if eGFR is <60 ml/min per 1.73 m^2, 57 of 422(13.5%) would do so if eGFR <45 ml/min per 1.73 m^2 and 20 of 422 (4.7%) if eGFR is <30 ml/min per 1.73 m^2. Many nephrologists reported starting immunosuppression directly in patients with active, proliferative histological

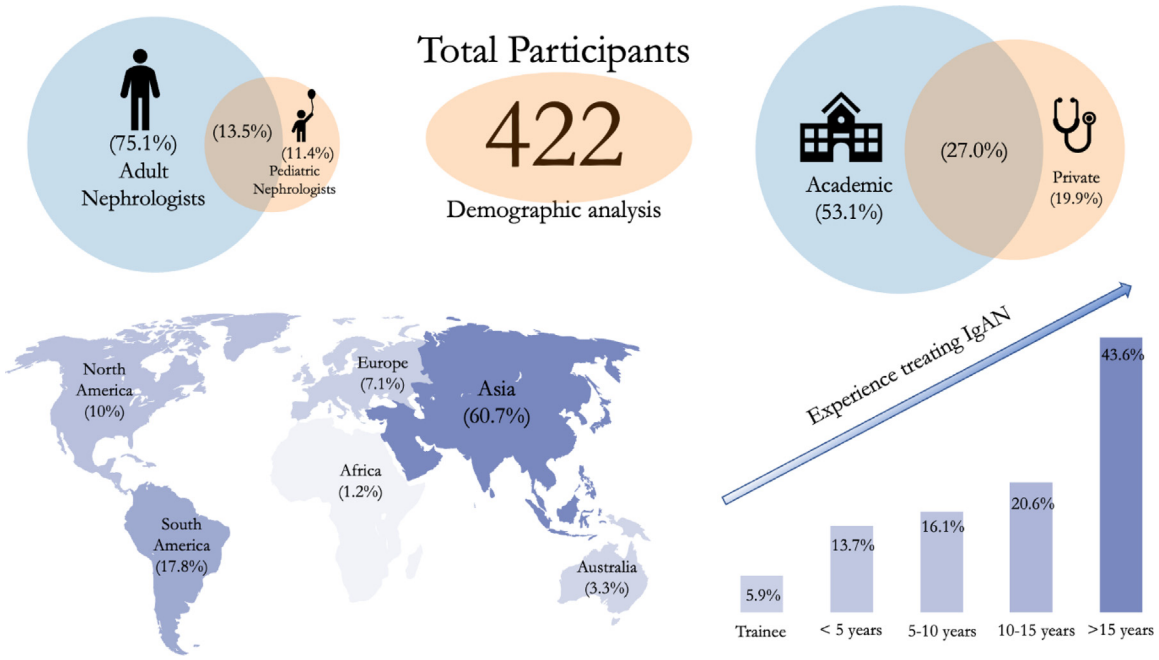

Figure 1. Demography of nephrologists who participated in the initial survey. IgAN, IgA nephropathy.

signs on biopsy, including E1 (162/422, 38.4%), C1 (108/422, 25.6%), C2 (214/422, 50.7%) lesions, and thrombotic microangiopathy (178/422, 42.2%). This practice is more commonly encountered in Asian countries compared to the rest of the world. A quarter (106/422, 25.1%) of our respondents use immunosuppression in patients diagnosed with secondary IgAN.

Over half (221/422, 52.4%) of the nephrologists, particularly in South America (48/73, 65.8%) and Australia (10/14, 71.4%), would prescribe concomitant cotrimoxazole prophylaxis for infection prevention while using immunosuppression ($P = 0.007$). Of the nephrologists, 175 of 422 (41.5%) routinely vaccinate patients for influenza virus and Pneumococcus before starting immunosuppression, and 107/422 (25.4%) do so only in high-risk populations.

Type of Immunosuppression

Details of immunosuppression use are depicted in Table 5. Corticosteroids are commonly used as first-line immunosuppression (376/422, 89.1%). Mycophenolate mofetil (208/422, 49.3%) and cyclophosphamide (76/422, 18.0%) are the 2 most frequently used second-line drugs in resistant patients, particularly in Asia and South America ($P = 0.04$). Cyclophosphamide (271/422, 64.2%) is most commonly combined with corticosteroids for patients with crescentic (with C2 lesions) IgAN. Asians and South American nephrologists are more likely to use immunosuppression in patients with C1 crescentic lesions, differing from nephrologists in other regions ($P = 0.005$).

When we examined the practice patterns of nephrologists in academic institutes (224), private centers (84), or having a combined academic and private practice (114), we did not observe any significant difference except for less frequent counseling about protein restriction by academic nephrologists compared to the others (65/224, 29.0% vs. 41/84, 48.8% vs. 52/114, 45.6% respectively, $P < 0.001$) and more widespread use of fish oil by those in private practice compared to those in academic or combined practice (58/84, 69.0% vs. 81/224, 36.2% vs. 45/114, 39.5%, respectively, $P < 0.001$).

Table 1. Initial supportive treatment

Question	Asia ($n = 258$)	South America ($n = 73$)	Europe ($n = 30$)	North America ($n = 42$)	Australia ($n = 14$)	Africa ($n = 5$)	Total ($N = 422$)	*P*-value
Initial supportive treatment strategy								
Salt restriction	195 (75.6%)	61 (83.6%)	23 (76.7%)	25 (59.5%)	7 (50.0%)	2 (40.0%)	313 (74.2%)	0.008
Protein restriction	97 (37.6%)	41 (56.2%)	7 (23.3%)	9 (21.4%)	2 (14.3%)	2 (40.0%)	158 (37.4%)	0.001
Blood pressure control	237 (91.9%)	67 (91.8%)	27 (90.0%)	38 (90.5%)	13 (92.9%)	4 (80.0%)	386 (91.5%)	0.956
Renin-angiotensin-aldosterone system blockade with ACEi/ARB therapy	252 (97.7%)	68 (93.2%)	29 (96.7%)	42 (100.0%)	14 (100.0%)	5 (100.0%)	410 (97.2%)	0.278

ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers

Table 2. Approach to blood pressure control and renin-angiotensin-aldosterone system (RAAS) blockade

Question	Asia (n = 258)	South America (n = 73)	Europe (n = 30)	North America (n = 42)	Australia (n = 14)	Africa (n = 5)	Total (N = 422)	P-value
Target blood pressure?								<0.001
<120/80 mm Hg	76 (29.5%)	41 (56.2%)	15 (50.0%)	21 (50.0%)	4 (28.6%)	0 (0%)	157 (37.2%)	
<130/80 mm Hg	172 (66.7%)	31 (42.5%)	14 (46.7%)	21 (50.0%)	8 (57.1%)	5 (100.0%)	251 (59.5%)	
<140/90 mm Hg	10 (3.9%)	1 (1.4%)	1 (3.33%)	0 (0%)	2 (14.3%)	0 (0%)	14 (3.3%)	
Preference of ACEi vs. ARB in patients prescribed RAAS blockers								<0.001
No preference	94 (36.4%)	30 (41.1%)	12 (40.0%)	17 (40.5%)	7 (50%)	4 (80%)	164 (38.9%)	
ACEi first with ARB used only if intolerant to ACEi	65 (25.2%)	29 (39.7%)	16 (53.3%)	20 (47.6%)	4 (28.6%)	1 (20%)	135 (32.0%)	
ARB first with ACEi used only if intolerant to ARB	99 (38.4%)	14 (19.2%)	2 (6.7%)	5 (11.9%)	3 (21.4%)	0 (0%)	123 (29.1%)	
Feel that ACEi and ARBs have the same effect on proteinuria	181 (70.2%)	48 (65.8%)	19 (63.3%)	33 (78.6%)	12 (85.7%)	5 (100%)	298 (70.6%)	0.26
Usage of dual RAAS blockers	46 (17.8%)	43 (58.9%)	14 (46.7%)	4 (9.5%)	3 (21.4%)	0 (0%)	110 (26.1%)	<0.001
Use of mineralocorticoid receptor antagonists								<0.001
No	128 (49.6%)	18 (24.7%)	17 (56.7%)	16 (38.1%)	7 (50%)	2 (40.0%)	188 (44.5%)	
In all patients	2 (0.8%)	7 (9.6%)	0 (0%)	0 (0%)	1 (7.1%)	0 (0%)	10 (2.4%)	
Persistent proteinuria despite maximal doses of ACEi/ARB	128 (49.6%)	48 (65.8%)	13 (43.3%)	26 (61.9%)	6 (42.9%)	3 (60%)	224 (53.1%)	

ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers. RAAS, renin-angiotensin-aldosterone system.

Nephrologists' attitude to clinical trials in IgAN

We received 339 responses to the follow-up survey about clinical trials in IgAN (Table 6). Only 103 of 339 (30.4%) enroll patients in clinical trials; and this practice is less common in Asia (27/157, 17.2%) and South America (35/112, 31.3%) compared to North America, Europe, and Australia (>50%).

Nephrologists in high and upper-middle income countries[9] were significantly more likely to enroll patients in clinical trials compared to those in LMICs (Figure 5, $P < 0.001$). In addition, 81 of 105 (77.1%) nephrologists from high-income countries, 81 of 135 (60%) from upper-middle income countries, and only 40 of 99 (40.4%) from LMICs were aware of clinical trials with novel drugs being conducted in their respective countries (Figure 6, $P < 0.001$).

DISCUSSION

IgAN is pathologically, genetically, and clinically, a heterogeneous disease process. Therefore, a "single treatment option for all" strategy has not been effective in its management. Treatment decisions take into consideration the clinical presentation, histology, demographics, geography, and even ethnicities within the same geographic region.

The KGIDO 2021 guidelines[4] primarily focus on a nephroprotective approach, including strict blood pressure control, salt restriction, smoking cessation, and weight control, taking into consideration that by the time of the latest publication, no labeled therapy for IgAN was available or approved. RAAS blockade to the highest tolerable limits is recommended in patients with proteinuria (>0.5 g/d), even in the absence of hypertension. The employment of corticosteroids or enrolling into an RCT are the recommended measures in high-risk patients with persistent proteinuria >0.75 to 1 g/d despite at least 3 months of supportive treatment. If corticosteroids are chosen, this decision must be balanced against their toxicity and potential side effects, especially when eGFR <50 ml/min per 1.73 m^2.

We found that RAAS blockade with ACEi/ARB is almost universally used for initial management of IgAN along with blood pressure control. More than half of the respondents reported using MRAs in patients with persistent proteinuria despite maximal tolerated doses of ACEi/ARBs. This practice is slightly more common in South America and North America

Table 3. Adjunct non-immunosuppressive therapies

Question	Asia (n = 258)	South America (n = 73)	Europe (n = 30)	North America (n = 42)	Australia (n = 14)	Africa (n = 5)	Total (N = 422)	P-value
Adjunct therapies used for supportive management								
Tonsillectomy	16 (6.2%)	9 (12.3%)	1 (3.3%)	1 (2.4%)	0 (0%)	0 (0%)	27 (6.4%)	0.206
Antiplatelet agents	25 (9.7%)	11 (15.1%)	1 (3.3%)	0 (0%)	0 (0%)	1 (20.0%)	38 (9.0%)	0.054
Fish oil	131 (50.8%)	30 (41.1%)	7 (23.3%)	14 (33.3%)	1 (7.1%)	1 (20.0%)	184 (43.6%)	0.001
Hydroxychloroquine	36 (14%)	12 (16.4%)	2 (6.7%)	5 (11.9%)	1 (7.1%)	0 (0%)	56 (13.3%)	0.674
SGLT2 inhibitors	130 (50.4%)	28 (38.4%)	14 (46.7%)	24 (57.1%)	8 (57.1%)	1 (20.0%)	205 (48.6%)	0.243

SGLT2, sodium-glucose co-transporter-2.

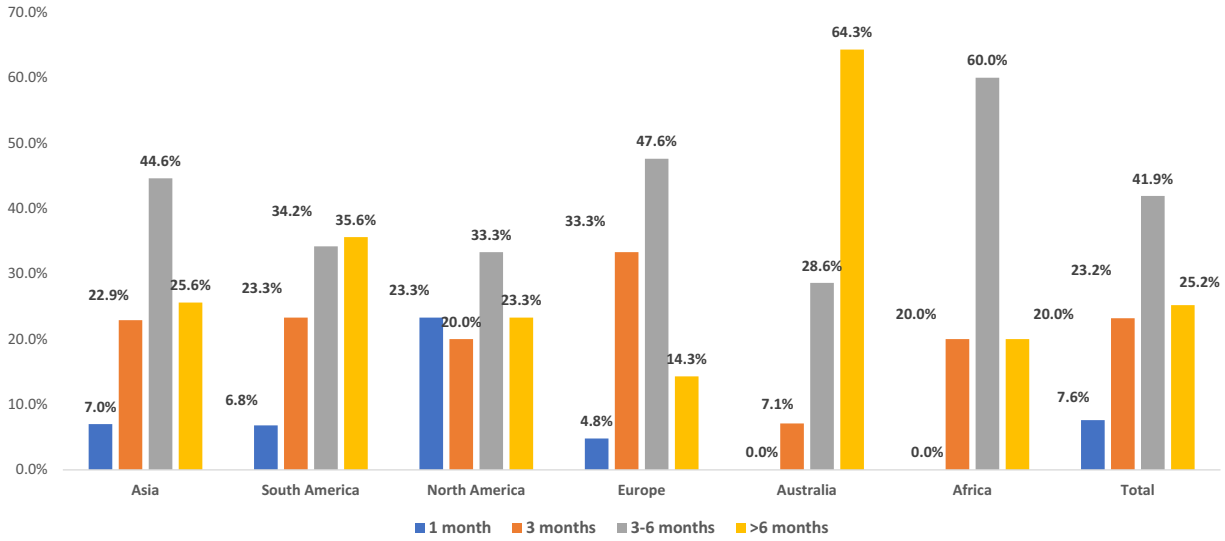

Figure 2. Time threshold for initiating immunosuppression in patients with persistent proteinuria >1 g/d with stable eGFR with supportive treatment.

compared to other regions. Though not evaluated specifically for IgAN, MRAs have been found to be effective in controlling hypertension and reducing proteinuria in kidney disease[10] and their use in this disease is likely to increase, especially with the recent availability of finerenone.

Other adjunctive therapies are frequently prescribed despite the lack of definite guidelines. Fish oil and SGLT2 inhibitors are the most commonly used agents. Fish oil is commonly prescribed despite inconsistent evidence of its efficacy.[11,12] It is more commonly used in Asia and South America compared to the other regions probably due to the lack of serious side effects of this compound as well as easy accessibility and low cost of this compound in these regions.

The employment of SGLT2 inhibitors in glomerular diseases started with the first published study, the Dapagliflozin and Prevention of Adverse Outcomes in CKD trial,[13] which included patients with IgAN followed by the Empagliflozin in Patients with Chronic Kidney Disease study,[14] which also included patients with glomerular diseases. A prespecified analysis of a cohort of 270 patients with IgAN who participated in the Dapagliflozin and Prevention of Adverse Outcomes in CKD trial found that dapagliflozin reduced the risk of progression of disease.[13] This prospective study was not designed specifically for IgAN and 16 (6%) patients did not have biopsy-proven IgAN. In our study, 48.6% of nephrologists reported using SGLT2 inhibitors despite the higher cost and lack of any RCT specifically evaluating its efficacy in IgAN. The efficacy of other therapies as hydroxychloroquine, tonsillectomy, and antiplatelet agents (aspirin) have been reported only by a few local studies predominantly in Asia.[5-8] With unclear

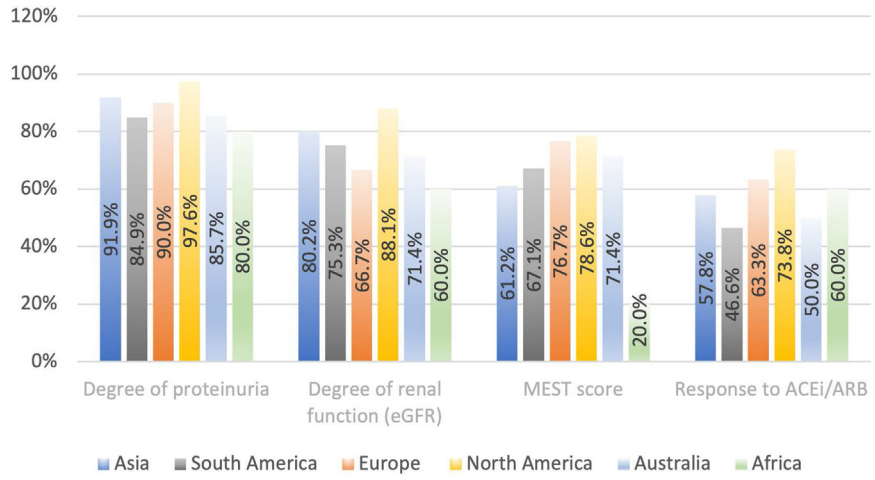

Figure 3. Parameters considered by nephrologists for initiating immunosuppression. ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate.

Table 4. Thresholds for initiating immunosuppression

Parameters considered for initiating immunosuppression	Asia (n = 258)	South America (n = 73)	Europe (n = 30)	North America (n = 42)	Australia (n = 14)	Africa (n = 5)	Total (N = 422)	P-value
Proteinuria	237 (91.9%)	62 (84.9%)	27 (90%)	41 (97.6%)	12 (85.7%)	4 (80%)	371 (87.9%)	0.234
Renal function (eGFR)	207 (80.2%)	55 (75.3%)	20 (66.7%)	37 (88.1%)	10 (71.4%)	3 (60%)	332 (78.7%)	0.211
MEST-C score	158 (61.2%)	49 (67.1%)	23 (76.7%)	33 (78.6%)	10 (71.4%)	1 (20%)	274 (64.9%)	0.04
Response to ACEi or ARB	149 (57.8%)	34 (46.6%)	19 (63.3%)	31 (73.8%)	7 (50%)	3 (60%)	243 (57.6%)	0.113
Proteinuria thresholds at which immunosuppression is started (stable eGFR) for patients on optimal supportive treatment								0.013
Any amount of proteinuria	9 (3.5%)	0 (0%)	2 (6.7%)	0 (0%)	0 (0%)	0 (0%)	11 (2.6%)	
Proteinuria >0.5 g/d	14 (5.4%)	6 (8.2%)	5 (16.7%)	2 (4.8%)	1 (7.1%)	1 (20%)	29 (6.9%)	
Proteinuria >1 g/d	156 (60.5%)	52 (71.2%)	18 (60%)	29 (69.0%)	4 (28.6%)	1 (20%)	260 (61.6%)	
Proteinuria >3.5 g/d	79 (30.6%)	15 (20.6%)	5 (16.7%)	11 (26.2%)	9 (64.3%)	3 (60%)	122 (28.9%)	
Proteinuria thresholds at which immunosuppression is started (stable eGFR) immediately after diagnosis								<0.001
Never	52 (20.2%)	15 (20.6%)	13 (43.3%)	20 (47.6%)	11 (78.6%)	2 (40%)	113 (26.8%)	
All patients	3 (1.2%)	0 (0%)	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)	4 (0.9%)	
Proteinuria >0.5 g/d	6 (2.3%)	6 (8.2%)	3 (10%)	1 (2.4%)	0 (0%)	1 (20%)	17 (4.0%)	
Proteinuria >1 g/d	62 (24.0%)	20 (27.4%)	5 (16.7%)	2 (4.8%)	0 (0%)	0 (0%)	89 (21.1%)	
Proteinuria >2 g/d	17 (6.6%)	5 (6.8%)	5 (16.7%)	6 (14.3%)	0 (0%)	0 (0%)	33 (7.8%)	
Proteinuria >3.5 g/d	118 (45.7%)	27 (37.0%)	3 (10%)	13 (31.0%)	3 (21.4%)	2 (40%)	166 (39.3%)	
eGFR at which immunosuppression is started (if proteinuria > 1 g/d) immediately after diagnosis								0.038
Never	54 (20.93%)	14 (19.18%)	6 (20%)	13 (30.95%)	7 (50%)	1 (20%)	95 (22.5%)	
eGFR <60 ml/min/1.73 m^2	153 (59.3%)	45 (61.64%)	20 (66.67%)	24 (57.14%)	4 (28.57%)	4 (80%)	250 (59.2%)	
eGFR <45 ml/min/1.73 m^2	43 (16.67%)	6 (8.22%)	3 (10%)	4 (9.52%)	1 (7.14%)	0 (0%)	57 (13.5%)	
eGFR <30 ml/min/1.73 m^2	8 (3.1%)	8 (10.96%)	1 (3.33%)	1 (2.38%)	2 (14.29%)	0 (0%)	20 (4.7%)	
Histological features triggering immunosuppression immediately after diagnosis of proteinuria								
M1	60 (23.3%)	13 (17.8%)	10 (33.3%)	9 (21.4%)	0 (0%)	0 (0%)	92 (21.8%)	0.124
E1	109 (42.3%)	25 (34.3%)	14 (46.7%)	11 (26.19%)	3 (21.43%)	0 (0%)	162 (38.4%)	0.063
S1	29 (11.2%)	10 (13.7%)	5 (16.7%)	5 (11.9%)	0 (0%)	0 (0%)	49 (11.6%)	0.61
T1	14 (5.4%)	6 (8.2%)	2 (6.7%)	1 (2.4%)	0 (0%)	0 (0%)	23 (5.5%)	0.695
T2	17 (6.6%)	5 (6.8%)	1 (3.3%)	2 (4.8%)	1 (7.1%)	0 (0%)	26 (6.2%)	0.958
C1	79 (30.6%)	18 (24.7%)	5 (16.7%)	6 (14.3%)	0 (0%)	0 (0%)	108 (25.6%)	0.015
C2	147 (57.0%)	26 (35.6%)	16 (53.3%)	20 (47.6%)	4 (28.6%)	1 (20%)	214 (50.7%)	0.008
Thrombotic microangiopathy	116 (45.0%)	36 (49.3%)	12 (40%)	11 (26.2%)	2 (14.3%)	1 (20%)	178 (42.2%)	0.031
Use immunosuppression in patients with non-crescentic IgA nephropathy with eGFR <30 ml/min/1.73 m^2	71 (27.5%)	29 (39.7%)	10 (33.3%)	17 (40.5%)	5 (35.7%)	3 (60%)	135 (32.0%)	0.174
Use of immunosuppression in patients with secondary IgA nephropathy	52 (20.2%)	22 (30.1%)	14 (46.7%)	13 (31.0%)	2 (14.3%)	3 (60%)	106 (25.1%)	0.005

eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers.

guidelines based on minimal data and lower levels of evidence, majority of clinical practice approaches beyond RAAS blockade seem to be governed by the local anecdotal experience of the facility or the nephrologist.

The Oxford MEST-C score is the standard classification system for reporting histology of IgAN[15]; however, a fraction of nephrologists around the world may not get MEST-C scoring in the kidney biopsy reports. A large number of nephrologists (64.9%) worldwide consider the MEST-C score when initiating immunosuppression, although this is not recommended by the KDIGO 2021 guidelines and despite the Oxford score not being designed for that purpose. Noteworthy, this practice is more common in North America, Europe, and Australia.

The use of immunosuppression in IgAN has been controversial with lack of consensus and distinct regional variations. Most nephrologists (92.4%) would wait at least 3 months after starting supportive treatment before considering immunosuppression as recommended by the KDIGO guidelines in all patients with IgAN, irrespective of their MEST-C profile (the only exception being patients with C2 lesions). Whether patients with proliferative lesions such as E1 and C1 should be initiated on immunosuppression immediately after diagnosis irrespective of their proteinuria levels to prevent fibrosis or one should wait to assess response to RAAS blockade for 3 months, which may actually increase the risk of progressive chronic disease remains debatable.[16,17] Again, whether patients with persistent proteinuria >1 g/d due to secondary glomerulosclerosis and hyperfiltration should receive immunosuppression as per KDIGO guidelines or continued on optimized nephroprotective supportive therapy also remains controversial and needs to be investigated.

There is a propensity for immunosuppression even in advanced disease with about one-third nephrologists doing so in noncrescentic IgAN with advanced renal

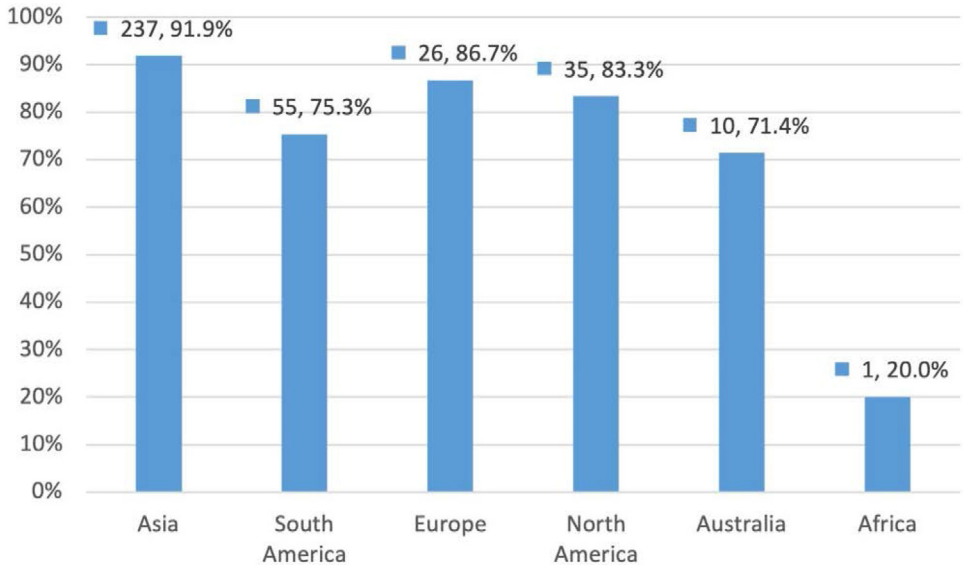

Figure 4. Frequency of MEST-C score reporting in kidney biopsies.

dysfunction (eGFR <30 ml/min) though the guidelines explicitly recommend not to do so.[4]

Many nephrologists employ immunosuppression in secondary IgAN though the KDIGO guidelines emphasize that the therapeutic approach in these patients should be treatment of the primary disease instead of immunosuppression. In our opinion, this finding is worrisome and indicates that medical education is required worldwide to prevent the unnecessary use of immunosuppression and the attendant adverse effects in these patients.

Corticosteroid is the most commonly prescribed first-line immunosuppression worldwide. The STOP-IgAN[18] and TESTING[19] were landmark trials investigating the use of corticosteroid immunosuppression in IgAN with conflicting results, which may be attributed to the

Table 5. Type of immunosuppressive agents used

	Asia (n = 258)	South America (n = 73)	Europe (n = 30)	North America (n = 42)	Australia (n = 14)	Africa (n = 5)	Total (N = 422)	P-value
First-line of immunosuppression used in patients with IgA nephropathy without crescents								0.023
Corticosteroids	232 (89.9%)	59 (80.8%)	28 (93.3%)	40 (95.2%)	13 (92.9%)	4 (80%)	376 (89.1%)	
Mycophenolate mofetil	19 (7.4%)	5 (6.8%)	2 (6.7%)	0 (0%)	0 (0%)	1 (20%)	27 (6.4%)	
Cyclophosphamide	2 (0.8%)	7 (9.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (2.0%)	
Azathioprine	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1(0.2%)	
Immunosuppression used in patients with crescentic (with C2 lesions) IgA nephropathy								<0.001
Corticosteroids + Cyclophosphamide	161 (62.4%)	52 (71.2%)	18 (60%)	29 (69.0%)	7 (50%)	4 (80%)	271 (64.2%)	
Corticosteroids + Mycophenolate Mofetil	82 (31.8%)	16 (21.9%)	9 (30%)	12 (28.6%)	4 (28.6%)	1 (20%)	124 (29.4%)	
Rituximab	1 (0.4%)	2 (2.7%)	3 (10%)	0 (0%)	0 (0%)	0 (0%)	6 (1.4%)	
Corticosteroids + Azathioprine	9 (3.5%)	2 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (2.6%)	
Corticosteroid only	5 (1.9%)	1 (1.4%)	0 (0%)	1 (2.4%)	2 (14.3%)	0 (0%)	9 (2.1%)	
Is immunosuppression always used in patients with C1 crescentic lesions IgA nephropathy								0.005
No	16 (6.2%)	6 (8.2%)	6 (20%)	8 (19.0%)	4 (28.6%)	0 (0%)	40 (9.5%)	
Yes	115 (44.6%)	38 (52.0%)	11 (36.7%)	16 (38.1%)	1 (7.1%)	2 (40%)	183 (43.4%)	
Selected cases based on eGFR and proteinuria	127 (49.2%)	29 (39.7%)	13 (43.3%)	18 (42.9%)	9 (64.3%)	3 (60%)	256 (60.7%)	
Second-line immunosuppression used in patients with steroid resistant IgA nephropathy								
Do not use	31 (12.0%)	5 (6.8%)	7 (23.3%)	11 (26.2%)	5 (35.7%)	0 (0%)	59 (14.0%)	0.003
Corticosteroids	4 (1.6%)	2 (2.7%)	0 (0%)	1 (2.4%)	0 (0%)	0 (0%)	7 (1.7%)	0.913
Mycophenolate mofetil	139 (53.9%)	28 (38.4%)	14 (46.7%)	18 (42.9%)	5 (35.7%)	4 (80%)	208 (49.3%)	0.096
Cyclophosphamide	44 (17.0%)	22 (30.1%)	4 (13.3%)	3 (7.1%)	2 (14.3%)	1 (20%)	76 (18.0%)	0.044
Azathioprine	13 (5.0%)	5 (6.8%)	1 (3.3%)	3 (7.1%)	0 (0%)	0 (0%)	22 (5.2%)	0.851
M-TOR Inhibitors	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1(0.2%)	0.986
Calcineurin Inhibitors	36 (14.0%)	8 (11.0%)	3 (10%)	4 (9.5%)	1 (7.1%)	0 (0%)	52 (12.3%)	0.811
Rituximab	5 (1.9%)	2 (2.7%)	1 (3.3%)	1 (2.4%)	1 (7.1%)	0 (0%)	10(2.4%)	0.867

M-TOR, mammalian target of rapamycin.

Table 6. Nephrologists' attitude toward clinical trials in IgA nephropathy

Africa (n = 3)	Asia (n = 157)	Australia (n = 11)	Europe (n = 33)	North America (n = 23)	South America (n = 112)	Total (N = 339)	P-value	
For a patient with persistent proteinuria >1g/d despite optimum supportive therapy for 3–6 months, what is your next step?								<0.001
Continue with supportive treatment only	0	17(10.8%)	1(9.1%)	2(6.1%)	1(4.3%)	4(3.6%)	25(7.4%)	
Initiate immunosuppression	3(100%)	113(72.0%)	3(27.3%)	10(30.3%)	9(39.1%)	73(65.2%)	211(62.2%)	
Enroll in a randomized control trial	0	27 (17.2%)	7 (63.6%)	21 (63.6%)	13 (56.5%)	35 (31.3%)	103 (30.4%)	
Do you enroll difficult to manage IgA nephropathy in clinical trials at your center?								<0.001
Do not have access	1 (33.3%)	52 (33.1%)	1 (9.1%)	5 (15.2%)	3 (13.0%)	27 (24.1%)	89 (26.3%)	
No	1 (33.3%)	41 (26.1%)	0	4 (12.1%)	2 (8.7%)	29 (25.9%)	77 (22.7%)	
Sometimes	0	27 (17.2%)	0	6 (18.2%)	7 (30.4%)	15 (13.9%)	55 (16.2%)	
Yes	0	37 (23.6%)	10 (90.91%)	18 (54.6%)	11 (47.8%)	41 (36.6%)	118 (34.8%)	
Would you refer such cases to other centers for enrollment in clinical trials?								0.134
No	3 (100.0%)	109 (69.4%)	7 (63.6%)	25 (75.8%)	9 (39.1%)	55 (49.1%)	208 (61.4%)	
Sometimes	0	28 (17.8%)	2 (18.2%)	2 (6.1%)	11 (47.8%)	26 (23.2%)	69 (20.4%)	
Yes	0	20 (12.7%)	2 (18.2%)	6 (18.2%)	3 (13.0%)	31 (27.7%)	62 (18.3%)	
Do you know of any clinical trials with new drugs are being conducted for IgA nephropathy in your country?								<0.001
No	3 (100.0%)	72 (45.86%)	1 (9.09%)	3 (9.09%)	1 (4.35%)	57 (50.89%)	137 (40.41%)	
Yes		85 (54.14%)	10 (90.91%)	30 (90.91%)	22 (95.65%)	55 (49.11%)	202 (59.59%)	

difference in ethnicity of the study populations. Although the extended TESTING study using lower doses of corticosteroids concluded that it was beneficial, they also observed a high prevalence of adverse effects in those with advanced renal dysfunction.

Although the employment of mycophenolate mofetil is believed to be of benefit mainly in Chinese patients based on the available evidence,[3,17,20] it is quite frequently used in other regions. Despite not being indicated by guidelines, some nephrologists continue to use cyclophosphamide or calcineurin inhibitors in IgAN.

The respondents to both steps of the survey were mainly from Asia and South America where supportive therapy seems to be prescribed as per the KDIGO guidelines. However, there were some interesting observations in these regions: The prescription of immunosuppression is more widespread with shorter time thresholds for early initiation; its employment in patients with advanced kidney disease (eGFR <30 ml/min per 1.73 m^2) is common and there is more frequent use of second-line drugs in these circumstances contrary to KDIGO guidelines. The potential implications of overtreatment with immunosuppression in these regions where the infectious disease burden is high needs to be taken into consideration and evaluated in prospective studies. This aggressive use of immunosuppression in Asia and South America, which besides Africa account for a large number of LMICs, may be attributed to the perceived high risk of progression to end-stage kidney disease in these populations which has a significant long-term economic impact worsening poverty and causing malnutrition vis-a-vis the low cost of corticosteroids and other generic immunosuppressive drugs.

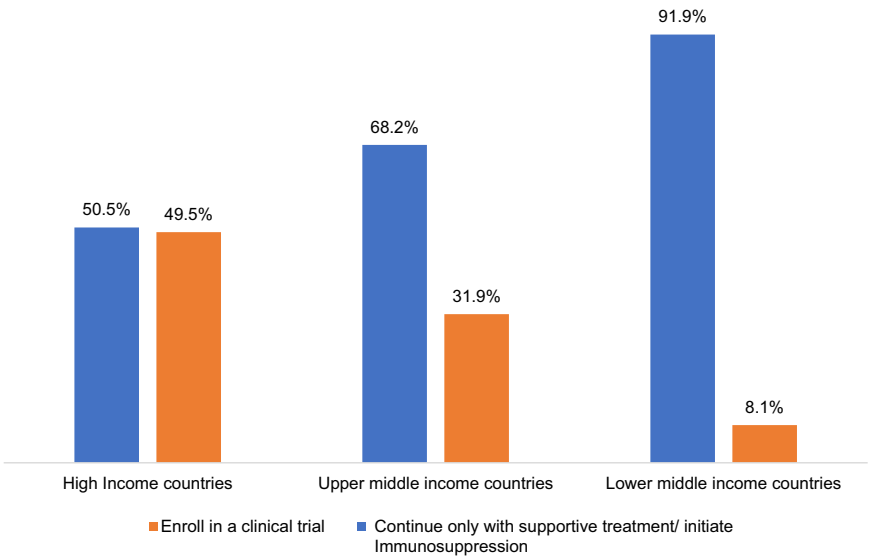

Figure 5. Enrolling patients of IgAN with persistent proteinuria >1g/d despite optimized supportive therapy for 3 to 6 months in clinical trials.

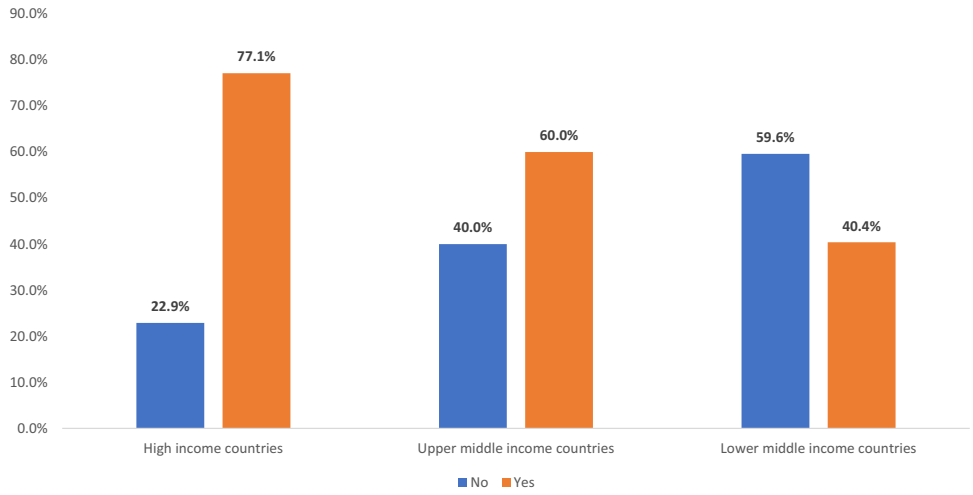

Figure 6. Awareness about ongoing clinical trials with new drugs in their country.

As per KDIGO guidelines, enrolling into clinical trials should be discussed if patients present with proteinuria above 1 g/d despite at least a 3-month course of nephroprotective measures. In this respect, enrollment of patients with IgAN in clinical trials (30.4%) is still infrequent and immunosuppression is still the most common treatment modality worldwide in patients with persistent proteinuria. This is especially true in LMICs, which are all mainly situated in Asia, South America, and Africa; and are home to >80% of the world's population. Therefore, interpretation and generalizability of trials may be limited by underrepresentation of the population from LMICs, in some of which IgAN may progress rapidly. The awareness and access to clinical trials is particularly low in these regions. In addition, there exists a marked reluctance to refer patients to other centers. Other key barriers to trial enrollment[21] may be time constraints, shortage of trained staff and infrastructure, skepticism about trials, and administrative and regulatory issues which need to be examined further. We feel that these factors should be considered when framing treatment guidelines so that they may be practiced in the real world. Even if we consider that the KDIGO guidelines were based on availability of "ideal and optimum treatment facilities" as seen in high-income countries, only about 50% to 60% of nephrologists in these countries refer patients to clinical trials and about one-third continue to use immunosuppression.

It is difficult to follow KDIGO guidelines for enrolling patients in clinical trials in most LMICs. For instance, in Latin America and the Caribbean, only 5 of 33 nations (15%) participate in RCTs related to IgAN, underscoring the low representation of this large region in IgAN clinical trials. When IgAN is discussed in the Asian context, it is often restricted to Chinese and Japanese populations without considering the wide ethnic and genetic diversity in this region. Traditionally, only China, Japan, Hong Kong, South Korea, Taiwan, and certain Southeast Asian countries have been invited to participate in clinical trials with poor representation of Middle East and South Asia, particularly India, the most populated country in the world, where IgAN appears to behave differently compared to other Asian populations.[22] Access to RCTs is limited in India, now the world's most populous country, with few trial sites mostly restricted to large centers in big cities, with poor awareness and reluctance among nephrologists impeding patient recruitment. Countries located in Middle-East Asia are consistently not represented in trials. The situation is worse in Africa, where the underrepresentation is virtually absolute. It is believed that IgAN is rare in this continent, but scientific published evidence is lacking: Is it a matter of nondiagnosis due to resource or infrastructure constraints and lack of access to kidney biopsies, or due to other ethnic or environmental factors? Biomedical data from Africa is sparse[23] with Africans often perceived as a single homogenous population despite the wide ethnic, genetic, environmental, and economic diversity impacting health on this continent. A recent systematic review[24] examined 3 studies reporting race specific incidence of IgAN in the US with conflicting results and failed to establish the relationship between Black race and IgAN. Extrapolating these findings in African Americans to Africa *per se* remains controversial and may be erroneous, especially considering that we know that environmental exposures, infections, and other epigenetic factors play key roles in the pathogenesis of IgAN. In addition, not all Africans are Black, and even the Black race is a misleading word, as many different ethnicities constitute it.

To date, 2 new drugs have been recently approved for treating IgAN at high risk of progression (i.e., urine protein-to-creatinine ratio >1.5 mg/g), a targeted

release formulation of budesonide, and sparsentan, an endothelin-1 receptor A inhibitor plus angiotensin II receptor antagonist.[25] The extent to which these new therapies will actually change how IgAN is managed will depend largely on their availability and affordability especially in economically disadvantaged populations. Also, any updated guidelines should focus on step-wise inclusion of these drugs only when absolutely required as their long-term use in this smoldering disease may pose a significant financial burden on patients especially in LMICs which do not provide universal health care.

A 2-round Delphi survey (DEFINE) examined the opinion of 158 nephrologists from 7 countries in Europe and North America regarding various aspects of IgAN.[26] Most of these nations represent the high-income countries group. In addition to management, they also deliberated on pathophysiology, diagnosis, and monitoring, which were not addressed in our survey. The views of nephrologists in these regions were mostly aligned with KDIGO guidelines. There was high level of agreement about proteinuria determining prognosis and management and ACEi/ARBs being the cornerstone of supportive treatment, which is also observed in our survey. There was also a high level of agreement for using steroid with cyclophosphamide in selected patients with severe or rapidly progressive disease. About half of our respondents also reported that they would use cyclophosphamide with steroids immediately after diagnosis of crescentic (C2) IgAN. There was only a moderate level of agreement among nephrologists about corticosteroid use in adults, which is the most controversial aspect of managing this disease. There was moderate level of consensus about avoiding long-term maintenance (duration not defined) corticosteroid use, which was not deliberated in our survey. More than 20% of nephrologists who participated in the first round did not return for the second round which may have led to attrition bias and overestimation of the level of consensus. They did not examine details of nonimmunosuppressive nephroprotective therapy beyond RAAS blockade and other aspects of immunosuppression use.

Our study had certain limitations. Despite the survey including many nations, the number of respondents is low in relation to the global population of nephrologists; therefore, the conclusions may not be fully representative and must be taken with caution. There is a possibility of bias because participants may attempt to answer according to existing guidelines. The use of long-term immunosuppression (low dose, maintenance) to prevent relapsing proteinuria and progression of disease was not investigated, which is also a gap not addressed by the KDIGO guidelines. The use of the International IgAN network tool[16] to prognosticate patients was not assessed in our survey. Most of the respondents were mainly from Asia and South America, and other regions were underrepresented. We conducted the survey in 2 stages: in the initial step of the survey, we did not include an option for clinical trial referral because we were considering a more "real world" scenario especially in LMICs. According to these obtained results, we proceeded with the second step where we focused on the nephrologists' attitude to trials and immunosuppression in a follow up questionnaire which we e-mailed to all those who had responded to the initial survey. Three hundred thirty-nine of the nephrologists answered the follow-up survey; the vast majority of them were from the initial group of respondents though there were some additional respondents who had not participated in the first part. Moreover, in one question about immunosuppression, there was no option to choose "no immunosuppression use" or "recruitment in RCT" because the initial survey when designed was focused on LMICs where clinical trials may not be a practical option. This was then addressed in the second step of the survey; however, not all nephrologists who took part in the first step did it in the second step.

The awareness of KDIGO guidelines among practicing nephrologists may vary but it should be noted that the survey was performed a year after the latest KDIGO guidelines were published and it is freely available online and widely discussed in various nephrology platforms. As compared to nephrologists at large, we obtained a larger sample of answers from academic nephrologists, who are more likely to be informed about and aware of KDIGO. Though we did not observe many differences between the practice patterns of academic and nonacademic nephrologists, our data may probably represent a low degree of disagreement with KDIGO guidelines, and the problem of nonadherence to guidelines and variation in clinical practice may be starker than it appears.

In conclusion, this survey indicates how nephrologists routinely manage IgAN globally, which to some extent is more pragmatic and deviates from the existing guidelines. These findings also question the feasibility of following published guidelines in LMICs highlighting the need for better representation of stakeholders from disparate regions and economies when framing such guidelines.

Overtreatment and early initiation of immunosuppressive drugs and certain supportive therapies must be analyzed in the context of cost and broader outcome measures such as disability-adjusted life years or all-cause mortality to account for the varied side effect profiles of such drugs. Although the field of IgAN is

growing rapidly with a large number of clinical trials with promising and emerging potential novel and safer therapies, access, awareness, and referrals to clinical trials are limited in economically disadvantaged countries where the majority of the global population lives.

DISCLOSURE

BWT reports receiving honoraria, fees for speaking and consultations, and advisory board meetings from AstraZeneca, Bayer, Boehringer Ingelheim, and Servier. He is the site principal investigator of IgAN trials from sponsors Visterra, Otsuka, Takeda, Omeros, and Novartis. HT reports receiving honoraria for scientific work from Alexion-AstraZeneca, Bayer, BioCryst, Calliditas, Chinook, Dimerix, GSK, Novartis, Omeros, Roche, Travere Therapeutics, Vera and Visterra Otsuka; and reports that The George Clinical Institute for Global Health holds research contracts for trials in kidney disease. SB is the site principal investigator for IgAN and C3 glomerulopathy trials of Novartis (all funding is received by All Institute of Medical Sciences, New Delhi with no personal financial involvement)

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Data Availability Statement

All the required data is available in the study. The corresponding author may be contacted if any further information is required.

AUTHOR CONTRIBUTIONS

BB and AG designed the survey; collected and analyzed the data; and wrote the initial draft of the manuscript. TBW collected the data and edited the manuscript. YS, MS, HH, AKS, and DB helped in collecting the data, SA collected the data and edited the manuscript. HT designed the survey, collected data and edited the manuscript. SB conceptualized the study, designed the survey, collected and analyzed data, and wrote the manuscript.

A part of this study was presented by BB at the American Society of Nephrology Renal Week 2022 and he also received the ASN kidney STARS award.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Checklist.

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