

Systematic Review on Health-Related Quality of Life and Utilities in Immunoglobulin A Nephropathy (IgAN)

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Introduction

- Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide and is characterized by the presence of predominant IgA1 deposits in the glomerular mesangium.¹
- The incidence of IgAN is estimated to be 2.5 per 100,000 population per year worldwide,² with the peak incidence observed in young adults aged 20-30 years.³
- Approximately 50% of IgAN patients with proteinuria ≥ 1 g/day progress to kidney failure in 15 years, irrespective of being on current standard of care like renin-angiotensin aldosterone system inhibitors and corticosteroids or other immunosuppressive agents.⁴
- Common signs and symptoms in IgAN include proteinuria, hematuria, hypertension, fatigue, pain and deteriorating kidney function (estimated glomerular filtration rate; eGFR),^{5,6} which could have an impact on health-related quality of life (HRQoL).

Objective

- The aim of this systematic literature review (SLR) was to identify, collate and assess evidence related to HRQoL and utilities associated with IgAN.

Methods

- The SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analysis guidelines.⁷
- The following databases were searched to identify relevant publications. Inclusion criteria are provided in Table 1.
 - Embase and Pubmed not MEDLINE: from inception to 06th June 2021 (through embase.com)
 - Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily: from 1946 to 06th June 2021 (through OVIDSP.com)
 - Cochrane database: from inception to 06th June 2021 (through cochranelibrary.com)
- Additionally, key conferences, health technology assessment websites and bibliographies of included publications were hand-searched for relevant publications.
- The quality of included publications was assessed using criteria for the quality assessment of health state utility value (HSUV) studies defined in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 9.⁸

Table 1: Inclusion Criteria

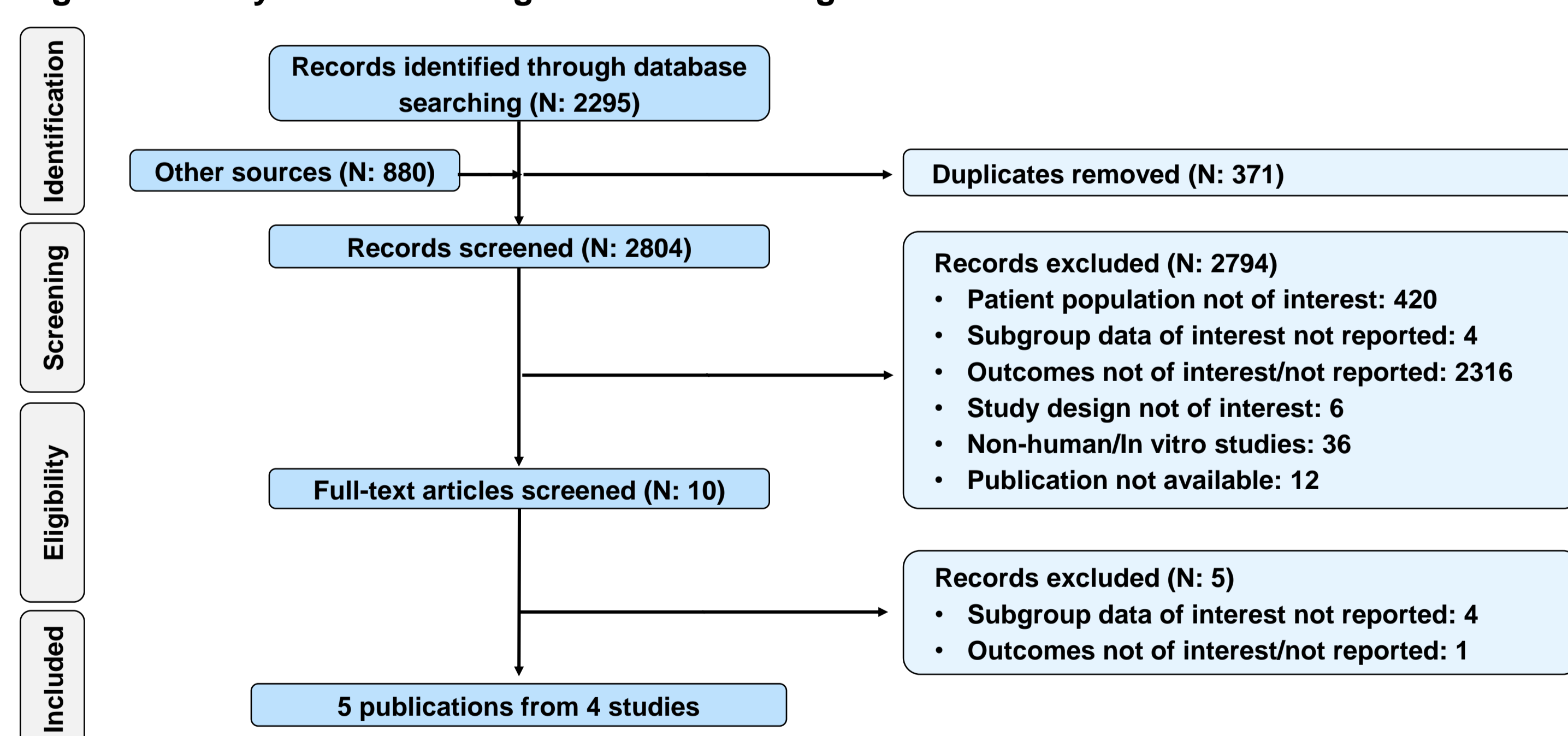
Criterion	Inclusion
Patience population	Patients diagnosed with IgAN
Interventions	Any intervention/no intervention for IgAN patients
Comparator	Any other intervention/no intervention for IgAN patients; placebo, standard of care
Outcomes	Utilities and HRQoL
Study designs	Any study reporting HRQoL using relevant instruments Studies reporting utilities/mapping algorithms from HRQoL to utilities using relevant instrument Studies reporting caregiver burden using relevant instrument
Language	No language restriction
Publication timeframe	No date restriction
Country	No country restriction

Abbreviations: HRQoL: Health-related Quality of Life; IgAN: Immunoglobulin A Nephropathy.

Results

- Out of 3,175 citations identified, five publications^{9,10,11,12,13} from four studies met the inclusion criteria (Table 1) and were included in this review (Figure 1).

Figure 1: Study selection using PRISMA flow diagram



Study characteristics:

- Sample size:** The number of IgAN patients in the included studies ranged from 51 to 470.^{9,10}
- Country and study setting:** One study each was conducted in China,¹¹ Japan,¹² and Poland;⁹ the fourth (CureGN) study was conducted in three countries (Canada, Italy and US).^{10,13} Three studies were multi-center^{9,10,12} and one was a single-center study.¹¹
- Study design:** All four included studies used an observational study design.^{9,10,11,12}

Patient characteristics:

- Age group and gender:** Two studies included both pediatric (aged 11 to 18 years) and adult patients,^{10,12} one study exclusively included pediatric patients (aged 8 to 18 years)⁹ and another included adult patients.¹¹ The proportion of female patients ranged from 37.3% to 60.2% in the included studies.^{9,11}
- eGFR:** Mean/median eGFR was only reported in three studies and ranged from 34.9 to 107.2 mL/min/1.73 m².^{11,9}

HRQoL:

- All four included studies reported data on HRQoL.^{9,10,11,12}
- Various instruments were used to report HRQoL outcomes across studies.
- Well-being:** A lower physical, psychological, and social well-being score was reported in Polish children and adolescents with IgAN (n=51) compared to their healthy peers, using the Kidscreen-52 questionnaire (Table 2). Reasons for lower physical well-being score were reported to be disease symptoms (i.e. edema), recurrent hematuria episodes and adverse effects of pharmacotherapy (i.e. overweight, weakness, and susceptibility to infections).⁹
 - Boys:** Boys with IgAN reported significantly (p < 0.05) worse scores of physical well-being, psychological well-being, self-perception and social support and peers compared to their healthy peers. This was possibly due to decreased participation in competitions, peer and sport activities and increased school absence.⁹
 - Girls:** Girls with IgAN reported significantly (p < 0.05) worse psychological well-being compared to their healthy peers. In contrast, social acceptance was rated significantly (p < 0.05) higher compared to their healthy peers, but the reason was not reported.⁹

Table 2: Kidscreen-52 questionnaire findings in Polish children and adolescents with IgAN⁹

Component	Study Value* (n=51)	Reference Value*	P-value (study vs. reference)
Physical well-being	62.84 (20.25)	70.21 (17.35)	0.055
Psychological well-being	66.83 (18.86)	68.02 (18.78)	NR
Overall mood	77.31 (17.07)	71.55 (16.67)	NR
Self-perception	69.71 (21.71)	69.67 (20.65)	NR
Leisure time – autonomy	67.84 (19.86)	66.05 (19.80)	NR
Relations with parents	78.27 (19.14)	73.27 (19.71)	NR
Financial resources	69.44 (28.41)	56.11 (27.68)	< 0.05
Social support and peers	62.91 (23.17)	64.62 (21.40)	NR
School environment	62.99 (20.88)	56.78 (20.02)	NR
Social acceptance	91.67 (16.67)	86.34 (18.83)	NR

*Values represent mean (SD); study value indicates the score provided by study patients with IgAN; reference value indicates the standard score provided by Polish population of healthy children and adolescents

- Symptoms:** The CureGN cohort study in children and adults^{10,13} and a cross-sectional study in children and adolescents⁹ reported the impact of various IgAN symptoms on HRQoL of IgAN patients:
 - Physical symptoms such as increasing severity of edema were associated with worsening of HRQoL in both children and adults; fatigue negatively impacted HRQoL of children.¹⁰ Furthermore, IgAN negatively impacted sleep and mental health in adults.¹³
 - However, it was reported that hypertension had no impact on HRQoL of children and adolescents with IgAN.⁹
- Adverse events:** Adverse events associated with steroid therapy such as body weight increase, and short stature were reported to have contributed to lower HRQoL in children and adolescents with IgAN.⁹
- Proteinuria:** Presence of proteinuria in children and adolescents with IgAN was reported to be associated with a significantly worse physical well-being compared to IgAN patients without proteinuria (p < 0.05), as assessed using the Kidscreen-52 questionnaire.⁹
- Pain due to tonsillectomy:** Tonsillectomy, a common intervention for treating IgAN patients in Japan, resulted in postoperative pain irrespective of the method used. However, a significantly lower level of postoperative pain was reported in IgAN patients (aged >16 years) who had undergone bipolar scissors tonsillectomy followed by pharyngeal mucosa cooling compared with traditional cold dissection tonsillectomy (p < 0.0001).¹²
- Depression:** Being part of a personalized physical activity (PA) training program for six months significantly improved HRQoL compared to treatment as usual (TAU) in Chinese adult IgAN patients with depression, as measured by various questionnaires. The improvement in IgAN patients' HRQoL may be due to the significant (p < 0.001) improvement in depression (as shown by the Beck Depression Inventory-II scale) as well as psychoticism, neuroticism, extroversion and lies (as assessed by Eysenck Personality Questionnaire) (Table 3).¹¹

Table 3: Comparison of variables between the PA and TAU groups in patients with IgAN¹¹

	At enrolment			After 6-months of treatment		
	PA group (n=108)	TAU group (n=108)	P-value (PA vs TAU)	PA group (n=108)	TAU group (n=108)	P-value (PA vs TAU)
HRQoL scores						
QLI	7.2 (1.6)	7.3 (1.8)	0.67	9.6 (1.5)	8.9 (1.8)	0.002
LSI	40.6 (8.5)	41.1 (9.7)	0.69	56.1 (9.7)	47.1 (8.7)	0.001
SF-36 PCS	41.6 (7.2)	39.9 (6.8)	0.08	47.5 (8.7)	44.6 (7.1)	0.007
SF-36 MCS	45.1 (9.1)	44.7 (7.9)	0.73	49.6 (9.8)	43.7 (7.7)	<0.001
BDI-II Scores						
Mildly depressed	16.6 (2.1)	16.4 (1.9)	0.46	14.1 (1.2)	16.3 (1.7)	<0.001
Moderately depressed	25.2 (2.6)	24.9 (2.3)	0.37	21.0 (1.6)	25.1 (2.5)	<0.001
Severely depressed	48.2 (11.3)	49.1 (9.8)	0.53	33.4 (9.6)	46.1 (10.1)	<0.001
EPQ scores						
Psychoticism	7.2 (1.6)	6.9 (1.5)	0.16	5.6 (0.8)	7.2 (0.9)	<0.001
Neuroticism	12.1 (2.4)	12.3 (1.9)	0.50	9.1 (1.8)	11.9 (1.2)	<0.001
Extroversion	9.8 (1.7)	10.1 (1.6)	0.18	7.8 (1.5)	9.7 (0.9)	<0.001
Lies	11.7 (1.3)	11.5 (1.2)	0.24	8.2 (1.0)	11.7 (1.2)	<0.001

Abbreviations: BDI-II: Beck Depression Inventory-II; EPQ: Eysenck Personality Questionnaire; LSI: Life Satisfaction Index; MCS: Mental Component Scale; PA: Physical Activity; PCS: Physical Component Scale; QLI: Quality of Life Index; SD: Standard Deviation; SF: Short Form; TAU: Treatment As Usual; Note: Values are in median (SD)

- Rural and urban areas:** No significant difference was reported in HRQoL (measured using Kidscreen-52 questionnaire) of children and adolescents with IgAN who were living in rural compared to those living in urban areas. This was reported to be possibly explained by the similar living conditions, advances in communication and adequate access to health care.⁹
- Anger intensity:** A majority of children and adolescents with IgAN reported a significantly lower intensity of expressed anger (p < 0.001) and higher intensity of suppressed anger (p < 0.001) compared to healthy peers, as measured using anger expression scale.⁹
- Other factors:** No impact on HRQoL in children and adolescents with IgAN was reported with regard to mode of education, erythrocyturia, or azathioprine or cyclophosphamide treatment (within the last three months).⁹ No association between HRQoL and patients' age⁹ or disease duration^{9,10} was reported in children and adults with IgAN.

Utility: No study reported utility data among IgAN patients.

Quality assessment: Included studies reported information for most of the parameters of the assessment criteria, which implies high-quality evidence in the published studies.

Conclusions

- This review did not identify health state utility values for IgAN, and evidence on HRQoL was sparse.
- Children and adolescents with IgAN reported lower well-being scores compared to their healthy peers.
- Steroid-associated adverse events contributed to lower HRQoL in children and adolescents with IgAN. Tonsillectomy procedure in patients with IgAN (aged >16 years) caused postoperative pain irrespective of the method used.
- Physical activity training in adults with IgAN led to a small but significant improvement in depression and thereby improved HRQoL compared to treatment as usual.
- Existing HRQoL evidence suggests that both IgAN as a disease and currently used treatments such as immunosuppressants and tonsillectomy impact patients' HRQoL. This warrants the need for improved targeted therapy in IgAN to improve quality of life.

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