



## Renal biopsy reports in nephritic syndrome: Update

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### Abstract

#### BACKGROUND

Nephritic syndrome (NiS) is a major indicator of serious renal diseases necessitating kidney biopsies for histopathological evaluations, but due to the lack of comprehensive reviews in the literature, the current understanding of the syndrome and its significance is limited.

#### AIM

To collect all the evidence retrievable from the literature on the diagnoses made on the renal biopsies performed for NiS as the indication to the procedure.

#### METHODS

A literature search was conducted to find studies reporting final diagnoses on renal biopsies in NiS patients. Data were pooled and analyzed with stratifications on age and regions. Meta-analyses were performed using Stata v.9.

#### RESULTS

Overall, 26414 NiS patients from the total number of 96738 kidney biopsy diagnoses reported by 47 studies from 23 countries from all continents (except sub-Saharan Africa) were found and analyzed. NiS was the indication for renal biopsy in 21% of the patient populations across the reviewed studies. Immunoglobulin A (IgA) nephropathy was the single most frequent diagnosis in these patients (approximately 38%) followed by lupus nephritis (approximately 8%) and Henoch Schönlein purpura (approximately 7%). IgA nephropathy was the most frequent diagnosis reported for the NiS patients from the East Asia, comprising half of all the cases, and least prevalent in South Asia. Considering the age subgroups, adult (*vs* pediatric or elderly) patients were by far the most likely age group to be diagnosed with the IgA nephropathy. A myriad of such regional and age disparities have been found and reported.

#### CONCLUSION

As the indication for renal biopsy, NiS represents a very distinctive epidemiology of final renal disease diagnoses compared to the other major syndromes.

**Key Words:** Renal biopsy; Nephritic syndrome; Immunoglobulin A nephropathy;

Diagnosis; Histopathology; Epidemiology

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**Core Tip:** Despite the extreme relevance of the renal biopsies in patients with different clinical syndromes and the final diagnoses that are being assigned to them, the current knowledge on the epidemiology of such diagnoses for nephritic syndrome is limited. This lack of understanding becomes more prominent when it comes to specific subpopulations, for example subgroups regarding age, ethnicity and global regions. This study tried to answer these questions, finding quite unprecedented, interesting, and clinically relevant findings.

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## INTRODUCTION

Renal disease is a major public health concern and a subject for considerable financial and mortality burden. However, different kidney diseases generally emerge with a limited spectrum of presentations most notably proteinuria and hematuria, different constellations of which comprise specific renal syndromes. These syndromes are not considered the final diagnosis of a specific renal disease, but rather they allude to specific renal diseases of different epidemiological magnitudes. In the approach to diagnose the culprit disorders, panels of experts have introduced definite indications for renal biopsies to be performed based on the presence or absence of these clinical syndromes.

Characterized by hematuria, elevated blood pressure, edema, and decrease in urine output, nephritic syndrome (NiS) is a major indicator of serious renal diseases necessitating kidney biopsies for histopathological evaluations. According to the published statistics for the year 2017, along with the nephrotic syndrome, NiS was reportedly the 9<sup>th</sup> leading cause of death in the United States[1], and extensive data from all around the world suggests consistent risk pattern for other global regions as well. Despite the invaluable data in the literature on the subject in general, scarcity of information exists on the estimated rates of the renal disease entities diagnosed upon analysis of renal biopsies for each renal syndrome. In two previous publications, the current author addressed the abovementioned issues for nephrotic syndrome, as well as subnephrotic proteinuria[2,3]. In the current study, NiS is the subject of the systematic review.

## MATERIALS AND METHODS

### Searching and selecting reports for review

**Figure 1** summarizes the study search and selection processes. This study aims to review the literature on the epidemiology of renal disease diagnoses made through investigating renal biopsy specimens from patients with NiS. One hundred and sixty-two reports were originally identified. After a preliminary review on the renal biopsy diagnoses (irrespective of their clinical syndromes), for studies whose data for NiS could be retrieved, 47 reports[4-50] were fully reviewed for this report. More detailed information on the methodology of this series of systematic reviews are published elsewhere, including two other reports on the epidemiology of nephrotic syndrome and subnephrotic proteinuria [2,3].

### Definitions and event classifications

NiS was diagnosed when criteria for the NiS (hematuria, elevated blood pressure, decreased urine output, and edema) were fulfilled or the reports were clearly reporting either acute or chronic NiS, NiS (not otherwise specified), or NiS with nephrotic-range proteinuria (NiS-NS). Only definitive cases of NiS were included in the analysis while those with vague or equivocal data were excluded.

**Renal disease diagnoses:** Renal disease diagnoses included immunoglobulin A (IgA) nephropathy (Berger's Disease), Henoch Schönlein purpura (HSP), Membranous glomerulonephritis (MGN), focal & segmental glomerulosclerosis (FSGS), lupus nephritis, mesangioproliferative glomerulonephritis (MesPGN), membranoproliferative glomerulonephritis (MPGN), amyloidosis, diabetic nephropathy, crescentic glomerulonephritis (CresGN), minimal change disease (MCD), tubulointerstitial diseases

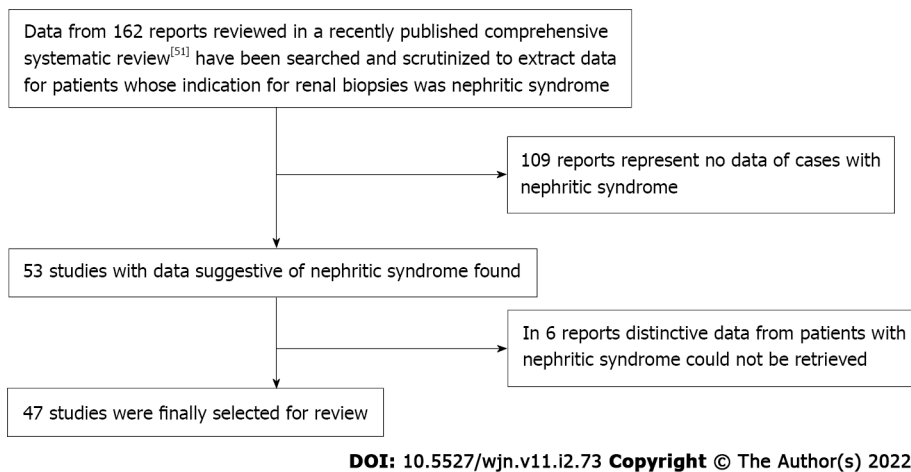


Figure 1 Flowchart of the study selection protocol in the current review report.

(TID), vascular nephropathy, nephroangiosclerosis (NAS), hereditary nephropathy, uspecific paraproteinemias (PPEs), and uspecific proliferative glomerulonephritis (PGN). Further specifications of the diagnoses have been published previously.

**World regions:** World regions were defined as follows: Middle East (including Egypt, Iran, Iraq, Jordan, Kingdom of Saudi Arabia, and Kuwait), Europe (including Belgium, Croatia, Cyprus, Czech R, Poland, Portugal, Romania, Serbia, and Turkey), Latin America (including Brazil and Colombia), East Asia (including China and Japan), South Asia (including India and Pakistan), and United States-Canada-Australia (USCA) (including United States & Australia).

**Age groups:** Age groups were defined as '*pediatrics*', '*adults*', '*elderly*', and '*general*'. *Pediatric* group included patients 18 years of age or younger. Adults were classified for study populations older than 18 and younger than 65 years. However, some studies had inconsistent age categorizations. For example, in some studies, the lower limits of the range of patients' ages was lower than 18 years; in such cases, if the age cut was 14 years, those above the cut-off were considered as adults, but if the cut-off was less the 14, the respective study population was classified as general age. Moreover, if a study population's age range surpassed 65, the group was classified as adults. This means that in certain situations, the adult population could include elderly patients. However, if any study group contained both elderly and pediatric patients (*i.e.* less than 14 years), or the age specific epidemiology could not be definitely derived, the report was considered as a general age group. Additionally, in general, the cut-off age for defining elderly patients was 65 years; however, the subclass still included studies where the cut-off point was as low as 60 years. If the age range was less than 60 in its lower boundary, the population was classified as adults.

**Trial selections for inclusion into the meta-analyses:** Any study with a report of renal syndromes including definitive cases of NiS patients undergoing renal biopsies with a final diagnosis report, discretely or individually, defined for patients with each clinical syndrome (particularly NiS) were considered eligible for inclusion. No quality control criteria more than the abovementioned was used to include or exclude the studies identified.

#### Data extraction and quality assessment

Data extraction, data set preparations, and accuracy check (twice) were done by the author. The information extracted from each study were as follows: author, publication year, time and duration of the study, country, region/province/town, nephrology center(s), range (or mean  $\pm$  SD) of age, incidence of NiS in all renal biopsy population, cases of NiS-NS, and final diagnoses of renal biopsies due to NiS. All studies that had been representing their epidemiological data for NiS and associated diagnosis without significant skewed selection in their series reports were considered eligible for entering the meta-analysis without more scrutiny in the study quality assessment.

#### Data synthesis and analysis

More detailed methodology of data synthesis and meta-analyses has been published previously. Final renal diagnoses have been extracted as dichotomous data (*e.g.*, MGN yes/no) and analyses have been reported as proportions with 95% confidence intervals (CIs, truncated at 0 and 1) from the extracted data. The study results were then stratified by the reports' age subgroups (*i.e.* pediatric, adult, elderly, general), and global regions of the reviewed studies (*i.e.* East Asia, Europe, Latin America, Middle East,

South Asia, United States-Australia; no report from sub-Saharan Africa). A random effect model was employed in order to pool outcome event rates using Stata v.9.0 software (StataCorp LP). Statistical heterogeneity between summary data was assessed using the Cochrane  $I^2$  statistic. SPSS software for Windows 15.0 (SPSS Inc.) and Microsoft Excel 2013 were used wherever needed.

## RESULTS

### *NiS as the indication for renal biopsy*

**Table 1** summarizes characteristics of the reviewed reports. Overall, 26414 patients with NiS have been identified from a total of 96738 patients undergoing a renal biopsy procedure reported by 47 studies from 23 countries, and their data have been reviewed and analyzed. China with 13581 NiS patients (out of a total number of 35523 cases undergone renal biopsy for any reason) contributed the largest share (51.4%) of the pooled NiS cases in this review, followed by Japan and The Czech Republic [4629 (17.5%) and 2728 (10.3%), respectively]. The frequency (95%CI) of NiS as the indication for renal biopsy was 21% (20.7-21.2) for the reviewed studies, ranging from 8% (7.5-8.5) in South Asia to as high as 36.3% (35.9-36.8) in East Asia (**Figure 2A**). Pediatric patients represented the lowest frequency (95%CI) of NiS as the indication for renal biopsy [7% (5.8-8.2)] while the general age group represented the highest [25.1% (24.6-25.5)] (**Figure 2B**). The single highest prevalence of NiS as the indication for renal biopsy in an age-region subgroup was for East Asian patients in the general-age group (**Supplementary Figure 1**).

### *Global disparity in the epidemiology of the final diagnoses made on NiS patients*

**Table 2** summarizes meta-analyses results of the final diagnosis epidemiology in NiS patients regarding the reports' global continental regions (**Supplementary Figures 2-19** represent the forest plots). As is evident from the table and figures, the single most likely renal diagnosis to be made in NiS patients is IgA nephropathy (38.3%), followed by the lupus nephritis (8.2%) and HSP (7.1%).

There were profound disparities in the epidemiology of diagnoses regarding the reports' global regions. For example, the possibility of diagnosing unspecific PPEs in NiS patients from South Asia is about 20 times more than that for the East Asia (**Table 2**). MGN and FSGS were more frequently diagnosed in NiS patients from the Middle East, while in the South Asia, unspecific PPEs, as well as PGN, were by far the most likely diagnoses compared to the other world regions. In East Asia, as expected, IgA nephropathy, and MesPGN were the most likely diagnoses, together comprising over 60% of all the diagnoses made for NiS patients; whereas both entities were the least likely ones to be reported in the South Asia. Hereditary nephropathy, diabetic nephropathy, amyloidosis, and HSP were relatively more frequent in the European NiS patients, while in the USCA region, MPGN and CresGN were the relatively predominant diagnoses (**Table 2**).

### *Age disparity in the epidemiology of diagnoses*

As mentioned for the world regions, there has also been disparity in the epidemiology of renal disease diagnoses in NiS patients regarding their age subgroups (**Table 2** summarizes results of the respective meta-analyses, and **Supplementary Figures 20-35** illustrate the forest plots). Relative to the pediatric and elderly patient groups presenting with NiS, adults were significantly more likely to be diagnosed with IgA nephropathy, HSP, and MGN. Among these, the disparity was most prominent for IgA nephropathy (only 11% and 6% of pediatric and elderly patients with NiS, respectively, were finally diagnosed with IgA nephropathy *vs* about 43% for the adults). On the other hand, pediatric NiS patients were more frequently diagnosed with lupus nephritis, MCD, hereditary nephropathy, MesPGN, and unspecific PGN, with the relatively largest disparity found with MCD. Finally, elderly patients were more likely to get diagnoses with CresGN, MPGN, T1D, unspecific PPEs, diabetic nephropathy, and vascular nephropathy (including NAS), among which CresGN, unspecific PPEs and NAS were by far more frequent in this age group (*vs* the younger ones).

Another interesting observation in the study of the age-groups was that there was a trend towards higher or lower frequencies in the rates of diagnoses based on the subgroups' ages. For example, while lupus nephritis, MCD and MesPGN were decreasing in the frequency of diagnosis by advances in age (pediatrics > adults > elderly), CresGN, diabetic nephropathy, vascular nephropathy (and NAS), and unspecific PPEs were increasing by age. This observation might more strongly recommend the age effect on the occurrence of the respective renal diseases.

### *Final NiS diagnoses regarding age and region-double characterized subclasses*

To further subclassify the patients according to their epidemiological characteristics in order to find the ones at the highest risks for each renal entity, the reports have been categorized simultaneously upon their age and world region. **Supplementary Figures 36-42** summarize the results. As is depicted in **Supplementary Figure 36**, among all the other age and region subgroups, MGN was most frequently diagnosed in adults with NiS from the East Asia, comprising 13% of all the diagnoses. Likewise, IgA nephropathy was also most prevalently diagnosed among the East Asian adults, which together with

Table 1 Characteristics of the reviewed studies and their patient populations

Ref.	Country	Region/town	Nephrology centers	Study duration	Publication year	Age, range/mean $\pm$ SD	Total, <i>n</i>
Ossareh <i>et al</i> [4]	Iran	Tehran	Hasheminejad Kidney Center	1998-2007	2010	12-84	1407
Saberafsharian <i>et al</i> [5]	Iran	Mashhad	Ghaem and Emam Reza hospitals	2016-2018	2020	41.40 $\pm$ 16.02	860
Pakfetrat <i>et al</i> [6]	Iran	Shiraz	Shiraz University of Medical Sciences	January 2011-December 2017	2020	1- 60	1355
AlFaadhel <i>et al</i> [7]	Kingdom of Saudi Arabia	Riyadh and Jeddah	Hospital, Jeddah; Security Forces Hospital, Riyadh; College of Medicine, King Saud University, Riyadh	1998-2017	2019	18-65	1070
Al-Saegh <i>et al</i> [8]	Iraq	Kerbala	University Hospital of Kerbala	June 2010-June 2012	2013	6-50	58
Ismail <i>et al</i> [9]	Egypt	Zagazig	Zagazig University	June 2012- November 2014	2016	16-70	150
Al-Qaise <i>et al</i> [10]	Jordan	Amman	Princess Iman Research and Laboratory Center, King Hussein Medical Center	January 2005- December 2008	2010	14-75	273
Turkmen <i>et al</i> [11]	Turkey	Nation-wide data	47 centers across Turkey	May 2009-May 2019	2020	41.5 $\pm$ 14.9	4399
Sahinturk <i>et al</i> [12]	Turkey	Antalya	Antalya Training and Research Hospital	2006-2016	2019	> 65 yr	136
Hu <i>et al</i> [13]	China	Henan	The First Affiliated Hospital of Zhengzhou University	January 2009- December 2018	2020	$\leq$ 14-60+	34,630
Su <i>et al</i> [14]	China	Changchun	First Hospital of Jilin University	January 2007- December 2016	2019	> 14 yr	2725
Wang <i>et al</i> [15]	China	Xinxiang	The First Affiliated Hospital, Xinxiang Medical University	January 1996-December 2010	2013	16-72 yr	919
Chiu <i>et al</i> [16]	Taiwan of China	Taichung	Taichung Veterans General Hospital	January 2014- September 2016	2018	48.4 $\pm$ 16.6	1445
Nair <i>et al</i> [17]	United States	Nationwide	Multiple referral centers	March 2001- December 2003	2004	60-91	533
Harmankaya <i>et al</i> [18]	Turkey	Istanbul	Bakirkoy Dr. Sadi Konuk Education and Research Hospital	2006 and 2014	2015	$\geq$ 65	103
Sarwal <i>et al</i> [19]	India (North)	Chandigarh	Post Graduate Institute of Medical Education and Research	2007 to 2016	2019	2-94	359
Devadass <i>et al</i> [20]	India (South)	Bangalore	M.S. Ramaiah Medical College and Hospitals	2008 to 2013	2014	8 mo-78 yr	680
Das <i>et al</i> [21]	India (South)	Hyderabad	M.S. Ramaiah Medical College and Hospitals	January 1990- December 2008	2011	10-80	1849
Gupta <i>et al</i> [22]	India	New Delhi	Sir Ganga Ram Hospital	January 2011- December 2014	2018	60-85	109
Mohapatra <i>et al</i> [23]	India	Vellore	Christian Medical College and Hospital	January 1996- December 2015	2018	12.8 $\pm$ 4.9	1740
Modugumudi <i>et al</i> [24]	India	Tirupati	Sri Venkateswara Institute of Medical Sciences	May 2010- August 2012	2016	15-74	137
Khetan <i>et al</i> [25]	India	Hyderabad	Apollo Hospitals, Jubilee Hills	N/A	2018	0-15	799/958
Beniwal <i>et al</i> [26]	India	Jaipur, Rajasthan	SMS Medical College and Hospital	January 2012- December 2017	2020	60-87	230
Koshy <i>et al</i> [27]	India	Chennai, Tamil Nadu	Madras Medical Institute	January 2010- August 2016	2018	60-82	231
Maixnerova <i>et al</i>	Czech	National report	31 centers	1994-2011	2014	0-75+	10472



[28]							
Horvatic <i>et al</i> [29]	Croatia	Zagreb	Dubrava University Hospital	1996 till February 2012	2013	16-84	922
Oygar <i>et al</i> [30]	Cyprus	North Cyprus	Burhan Nalbantoglu General Hospital	January 2006-2015	2017	18-78	153
Perkowska-Ptasinska <i>et al</i> [31]	Poland	National	The Polish Registry of Renal Biopsies	2009-2014	2017	19-88	8443-951 = 7492
Pio <i>et al</i> [32]	Portugal	Porto	Hospital Geral de Santo António	January 1997-December 2008	2010	1 mo-18 yr	142
Naumovic <i>et al</i> [33]	Serbia	Belgrade	University of Belgrade	1987 to 2006	2009	16-79	1733
Volovät <i>et al</i> [34]	Romania	Iasi	“Dr. C. I. Parhon” Hospital	2005-2010	2013	41.9 ± 2.8	514/559
Covic <i>et al</i> [35]	Romania	Timisoara	C.I. Parhon’ Hospital, Iasi and 2 Dialysis and Transplantation Centers	1995–2004	2006	18–80	635
Costa <i>et al</i> [36]	Brazil (NorthEast)	Pernambuco	2 centers: Hospital das Clinicas da Universidade Federal de Pernambuco (HC-UFPE) and Instituto de Medicina Integral Professor Fernando Figueira (IMIP)	February 1998-January 2016	2017	0-60+	677/1151
Özkayin <i>et al</i> [37]	Turkey	Edirne	Trakya University School of Medicine	2005-2015	2016	1-17	100
Sugiyama <i>et al</i> [38]	Japan	National registry report	94 centers	January 2009-December 2010	2013	0-80+	7034
Sugiyama <i>et al</i> [39]	Japan	Nationwide	23 centers	1979 and 2008	2011	0–80+	2404
Malik <i>et al</i> [40]	Pakistan	Bahawalpur	Bahawal Victoria Hospital	January 2012-April 2018	2019	14-68	195
Imtiaz <i>et al</i> [41]	Pakistan	Karachi	The Kidney Center Post Graduate Training Institute	January 1996-December 2013	2017	18–88	1521
Hashmi <i>et al</i> [42]	Pakistan	Karachi	Liaquat National Hospital	January 2009-December 2013	2016	20-75	140
Mubarak <i>et al</i> [43]	Pakistan	Karachi	Sindh Institute of Urology and Transplantation	July 1995-December 2008	2011	19–85	1793
Imtiaz <i>et al</i> [44]	Pakistan	Karachi	The Kidney Center Post Graduate Training Institute	1997 to 2013	2016	0.1-17	423
Lanewala <i>et al</i> [45]	Pakistan	Karachi	Sindh Institute of Urology and Transplantation	July 1995 and June 2008	2009	4 mo-18 yr	801
AlYousef <i>et al</i> [46]	Kuwait	Sabah Al Nasser	Farwaniya Hospital	January 2013-December 2018	2020	12-90	545
Mesquita <i>et al</i> [47]	Belgium	Brussels	Brugmann University Hospital	January 1991-December 2006	2011	Adult (47 ± 19)	326
Jegatheesan <i>et al</i> [48]	Australia	Queensland	11 hospitals	January 2002-December 2011	2016	48 ± 17 (18+)	2048/3697
Prada Rico <i>et al</i> [49]	Colombia	Bogotá, Cundinamarca	Fundación Cardioinfantil, Bogotá	2007-2017	2013	11 ± 4.3	241

MGN, comprise about 60% of all the diagnoses in this subgroup of NiS patients (Supplementary Figure 37). On the other hand, FSGS was the predominant diagnosis among the European elderly (14%), followed by adults from the Middle East (13%), Supplementary Figure 38. But the single most frequent diagnosis for the Middle Eastern adults was lupus nephritis, comprising as high as 68% of all the diagnoses in these patients (Supplementary Figure 39).

Elderly Americans (54%) and elderly Europeans (34%) presenting with NiS were most likely to be finally diagnosed with the crescentic nephropathy, followed by the adult Australians and adult Europeans (17% each, Supplementary Figure 40). MPGN was the predominant diagnosis among the South Asian elderly (27%), followed by the European pediatrics (23%) and South Asian pediatrics and adults (14% each). This suggests that patients in South Asia presenting with NiS are at a substantial risk of MPGN diagnosis, irrespective of their age. But MPGN was not the only renal diagnosis frequently

**Table 2 Meta-analysis of the estimated incidence (95% confidence interval) of nephropathy diagnoses for patients with nephritic syndrome**

Nephropathy	Highest rate (%)	Lowest rate (%)	Pediatric (%)	Adults (%)	Elderly (%)	General (%)	NiS-NS (%)	Total (%)
MGN	M.E. 10.2 (8.1-12.3)	Eu. 2.4 (1.9-2.8)	2.5 (0.4-4.6)	7.3 (6.9-7.7) <sup>1</sup>	2.3 (0-5.7)	4.4 (3.9-4.8)	11.7 (6.8-16.6)	5.9 (5.6-6.2)
IgA nephropathy	E.A. 50.1 (49.3-50.8)	S.A. 9.8 (7.6-11.2)	11 (8.2-13.7)	42.6 (41.9-43.4) <sup>1</sup>	5.9 (2.8-8.9)	37.4 (36.4-38.3)	3.7 (0-7.8)	38.3 (37.7-38.9)
Henoch Schönlein purpura <sup>2</sup>	Eu. 10.7 (2.8-18.6)	S.A. 1.9 (0.5-3.2)	6.3 (3-9.6)	7.6 (7.2-8.1) <sup>1</sup>	-	1.2 (0-2.6)	-	7.1 (6.6-7.5)
FSGS	M.E. 11.4 (9.3-13.4)	E.A. 1.6 (1.4-1.8)	3.4 (1.7-5.1)	1.6 (1.4-1.8)	3.9 (0.9-6.8)	4.3 (3.9-4.7) <sup>1</sup>	19.4 (13-25.8)	2.1 (1.9-2.2)
Lupus nephropathy	L.A. 44.6 (33.7-55.5)	Eu. 4.6 (4-5.3)	12.9 (9.8-15.9) <sup>1</sup>	9.3 (8.9-9.8)	5.3 (1.6-8.9)	5.4 (4.7-6.1)	10.4 (6.1-14.7)	8.2 (7.8-8.6)
MCD	S.A. 4.4 (1.8-6.9)	E.A. 0.7 (0.5-0.8)	5.7 (0-12.6) <sup>1</sup>	0.7 (0.6-0.8)	-	1.6 (1.2-1.9)	-	0.8 (0.7-0.9)
Crescentic GN	USCA 18.9 (16.6-21.3)	E.A. 0.6 (0.2-1)	3.4 (1.7-5)	1.7 (1.3-2.2)	45.7 (36.6-54.8) <sup>1</sup>	6.4 (5-7.9)	-	2.3 (1.9-2.7)
MPGN	USCA 12.9 (4.8-20.9)	E.A. 0.9 (0.7-1.1)	14.2 (11.4-17)	1 (0.9-1.2)	17.5 (12.1-22.9) <sup>1</sup>	4.1 (3.5-4.8)	9.2 (4.2-13.5)	1.3 (1.1-1.4)
Amyloidosis	Eu. 1.2 (0.5-1.9)	E.A. 0.8 (0.6-1.1)	0.6 (0-1.4)	0.4 (0.1-0.7)	-	2 (1.6-2.4) <sup>1</sup>	-	0.9 (0.7-1.1)
Diabetic nephropathy	Eu. 3.9 (3.3-4.5)	S.A. 0.8 (0-1.6)	-	1.5 (1.3-1.7)	3.1 (0-6.2) <sup>1</sup>	2.7 (2.2-3.2)	-	1.7 (1.5-1.9)
TID	L.A. 27.8 (4.9-50.7)	E.A. 0.6 (0.5-0.7)	3.5 (1.1-5.8)	0.6 (0.5-0.8)	6.7 (1.8-11.7) <sup>1</sup>	2.3 (1.3-3.3)	-	0.7 (0.5-0.8)
Vascular nephropathy	L.A. 19.3 (10.6-27.9)	M.E. 0.8 (0.1-1.5)	2.9 (0.4-5.4)	2.2 (1.9-2.4)	4.3 (1.4-7.2) <sup>1</sup>	3 (2.5-3.5)	-	2.3 (2.1-2.5)
Nephroangiosclerosis <sup>2</sup>	M.E. 20 (0-57.8)	S.A. 0.7 (0-1.6)	-	1.7 (1.5-1.9)	22.7 (9.8-35.6) <sup>1</sup>	3.3 (2.7-3.9)	-	1.8 (1.6-2)
Hereditary nephropathy	Eu. 3.4 (0.9-5.9)	E.A. 0.7 (0.6-0.9)	2.9 (0.8-5) <sup>1</sup>	0.7 (0.6-0.9)	-	-	-	0.8 (0.6-0.9)
Unspecific Proliferative GN	S.A. 34.2 (31.5-37)	E.A. 1.4 (1.2-1.6)	23.4 (20-26.9) <sup>1</sup>	1.6 (1.4-1.8)	20.4 (9.7-31)	11.7 (9.8-13.6)	14.1 (9-19.2)	1.7 (1.6-1.9)
MesPGN <sup>2</sup>	E.A. 10 (8.2-11.8)	S.A. 4.5 (3.1-5.9)	7.5 (5.2-9.7) <sup>1</sup>	5.3 (4.5-6.2)	-	6.2 (4.5-8)	9.2 (4.2-13.5)	5.7 (5-6.5)
Unspecific Paraproteinemia	S.A. 11.8 (1.6-22)	E.A. 0.6 (0.4-0.7)	-	0.6 (0.4-0.7)	11.8 (1.6-22) <sup>1</sup>	-	-	0.6 (0.4-0.7)

<sup>1</sup>Zero incidence rates have been omitted to report; the frequency (95% confidence interval) are those representing the highest for each diagnosis.

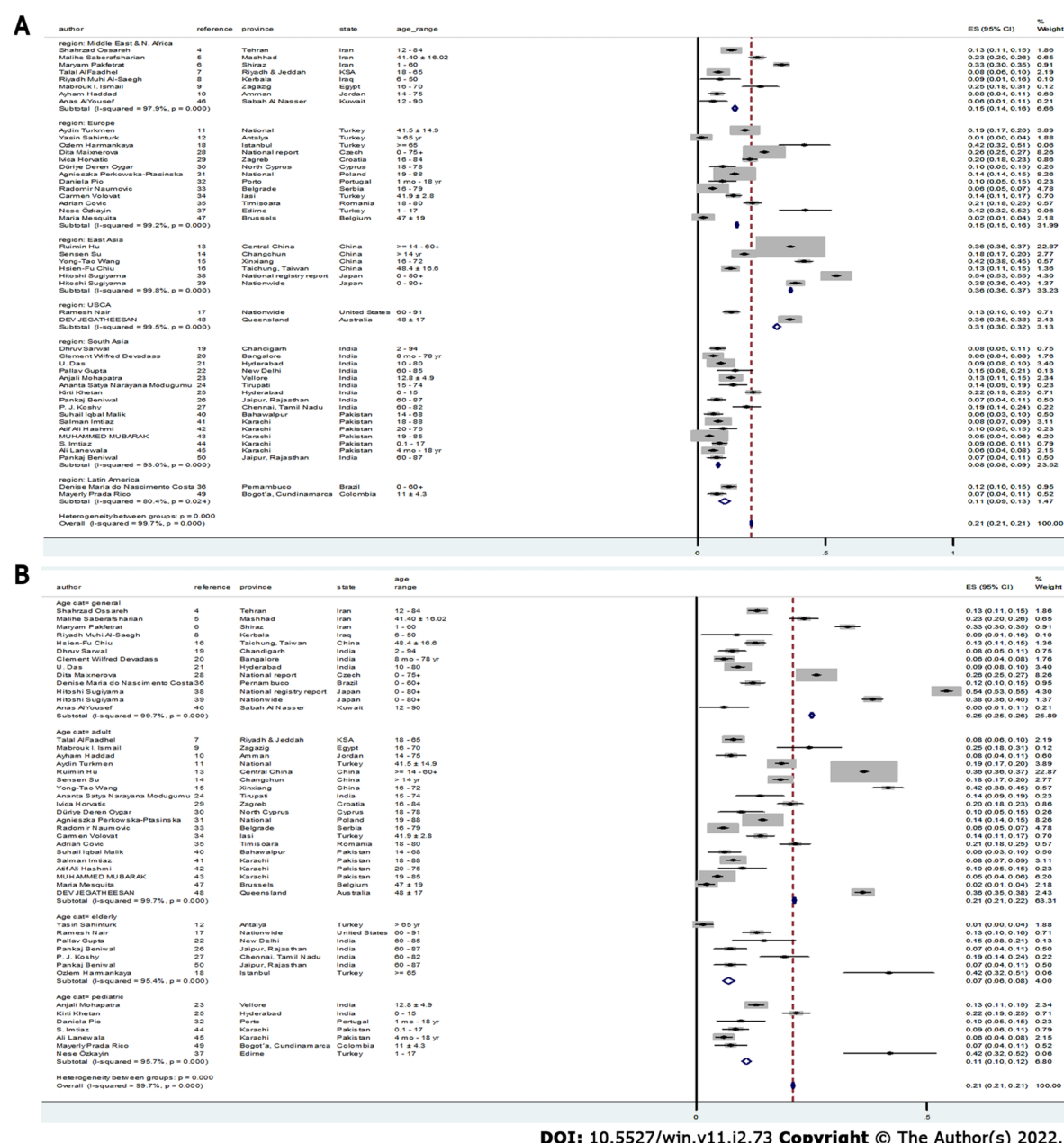
<sup>2</sup>Subsections of their abovementioned entity as described previously[2].

E.A.: East Asia; Eu.: Europe; FSGS: Focal and segmental glomerulosclerosis; L.A.: Latin America; MCD: Minimal change disease; M.E.: Middle East; MesPGN: Mesangial proliferative glomerulonephritis; MGN: Membranous glomerulonephritis; MPGN: Membranoproliferative glomerulonephritis; NiS-NS: Patients simultaneously presenting with nephritic- & nephrotic syndromes; S.A.: South Asia; TID: Tubulointerstitial diseases; USCA: United States-Canada-Australia.

found in the South Asia (Supplementary Figure 41). Unspecific PGN was most frequently found in the general age South Asians (47%, Supplementary Figure 42), which together with MPGN, it suggests South Asia as a main source of diagnosing PGN among NiS patients.

### **NiS-NS: NiS with nephrotic-range proteinuria**

Three of the reviewed studies had discriminately reported their series with patients representing NiS-NS, and the epidemiology of their final diagnosis has been compared to that of the NiS-alone patients. As summarized in Table 2 and illustrated in the Supplementary Figures 43-50, NiS-NS patients represented higher diagnosis rates for MGN, FSGS, MPGN, MesPGN, and unspecific PGN than NiS-alone patients, while representing a lower frequency of IgA nephropathy. Lupus nephritis was comparably observed between the two groups.



**Figure 2 Frequency of nephritic syndrome.** A: Frequency of nephritic syndrome as indication for renal biopsy divided by the global region; B: Frequency of nephritic syndrome as indication for renal biopsy regarding the study subjects' age.

## DISCUSSION

This study in all probability represents the literature with the single most comprehensive overview of NiS as the indication for renal biopsy procedure, the expected diagnoses, and predictive factors. The overall frequency of NiS as the indication for renal biopsies was about 21% of the total reports, with the highest rates in East Asia comprising over one third of all the cases (Japan represented the single highest frequency) and lowest in the South Asia (8%, Figure 2A). Patients of the general and adult age groups were the most likely age subgroups receiving kidney biopsies due to NiS, while pediatrics represented the lowest frequency of NiS as the indication for renal biopsies (Figure 2B).

Compared to the other renal syndromes, this study showed that NiS is associated with significant bias in the frequency of different final diagnoses. Some of the renal diagnoses (including proliferative endocapillary glomerulonephritis, hepatitis B virus nephropathy, IgM nephropathy, and minor glomerular abnormalities) were in such scarcity in NiS patients that this led to their exclusion from the final report, while some of which were quite frequent diagnoses in patients with other renal syndromes [2,3,50]. MGN was a dominant diagnosis in nephrotic syndrome patients comprising about 20% of the total population[2], however, this rates in the sub-nephrotic proteinuria[3] and NiS (current report), were much lower (7.5% and 6%, respectively). On the other hand, IgA nephropathy was the most likely diagnosis in NiS patients comprising over one third of all the diagnoses, while these rates for the sub-



nephrotic proteinuria and nephrotic syndrome were much less (17% and 4.5%, respectively)[2,3].

The global disparities in the epidemiology of the final diagnoses being made on renal biopsies of patients representing with any renal syndrome is also of extreme interest. For example, a previous systematic review has demonstrated that IgA nephropathy is most prevalent in the East Asia, comprising more than one third of all the diagnoses made for patients undergoing renal biopsies for any indication. However, this will be of limited practical relevance due to the profound disparity in diagnoses expected for different renal syndromes. For instance, the incidence of IgA nephropathy in the East Asia as reported by the current study was roughly 50% for NiS patients, far more than its overall frequency reported for the same region when estimated irrespective of the clinical syndrome (approximately 35%); similar observations have been made for nephrotic syndrome and sub-nephrotic proteinuria in the previous systematic reviews[2,3].

The next region representing a highly skewed frequency for a specific diagnosis was Latin America for lupus nephritis (approximately 44%); interestingly, considering the same concept for nephrotic syndrome and sub-nephrotic proteinuria, Sub-Saharan Africa and the Middle East were, respectively, the predominant regions of high frequency (approximately 12% and approximately 14%), with the former having no representative patients in the current review study on NiS.

A profound discrepancy has also been detected in the frequency of renal diagnoses regarding the reports' age groups. While MCD, lupus nephritis, hereditary nephropathy, MesPGN, and unspecific PGN made the predominant diagnoses in the pediatric NiS patients, about 43% of adults were finally diagnosed with IgA nephropathy. A similar observation was observed for the elderly population with over 45% of them being diagnosed with crescentic nephropathy. Predictably, the elderly population was the predominant age subgroup for the diagnosis of vascular nephropathies (including NAS), T1D, diabetic nephropathy, and PPEs. Here again, a profound bias has been detected in the epidemiology of renal diagnoses regarding the clinical syndromes. For example, for nephrotic syndrome[2], about half of the pediatric patients were ultimately diagnosed with MCD, while this percentage was about 8% for sub-nephrotic proteinuria[3], and 6% for NiS patients (current study). Detection of MCD such a high percentage of pediatric patients with NiS is a considerable finding and changes presumptions. The next substantial disparity was detected for MGN in the elderly, with 35%, approximately 19% and 2.3% rates of diagnosis, respectively, for nephrotic, sub-nephrotic, and NiS (2, 3 and current study).

Meta-analyses from the current study have also revealed age-dependent disparities in the frequencies of final diagnoses. For example, the frequency of IgA nephropathy in NiS patients was by far highest among adults, while in the contexts of nephrotic syndrome or sub-nephritic proteinuria, pediatric patients were the age subclass most likely to be diagnosed with the entity, with a decreasing trend being detected with increases in the age subclasses (lower for adults and then the lowest in the elderly)[2,3].

Subcategorization of the reports simultaneously for their age and the global regions also revealed some very interesting and unprecedented observations. Two of the most interesting findings were the high rates of diagnosing crescentic nephropathy in various age subclasses from regions with the majority white ethnicity (Europe, United States, and Australia), as well as South Asia being the leading source of MPGN diagnosis in all their age subgroups; both the abovementioned suggest high levels of ethnic liability, environmental predispositions, and life-style effects on the epidemiology of renal diseases even within the same clinical syndromes.

Another subject of analysis in this study was the NiS-NS subgroup whose clinical syndrome included NiS with nephrotic range proteinuria that had been reported in a subgroup of patient populations by some of the reviewed studies. A comparison of NiS-NS epidemiological findings with the respective results from subnephrotic proteinuria, NiS-(alone) and nephrotic syndromes suggests that NiS-NS patients exhibit considerable disparities in the frequencies of renal diagnoses, proposing NiS-NS as a new syndrome entity. Although the limited sample size, as well as the disparities in other potential intervening factors, could confound the conclusion.

The findings of the current study are associated with limitations. The limited number of reports from specific regions of the world, the small sample sizes for each study and occasionally selection deviations in some of the studies (*e.g.*, age specific reports) were the most important limitations. For example, a finding of this study was the preponderance of crescentic nephropathy as the final diagnosis of NiS patients for both the elderly patients among the age subgroups and United States-Australia regarding the regional analyses. Together, it is conceivable that the observed high frequency of crescentic nephropathy diagnosis reported for the latter might in part be due to the potential inclusion of relatively older patients compared to the reports from the other global regions. Finally, sub-Saharan Africa had no representative in this review, and therefore the results of this study might not be well applied to patients from this region/ethnicity.

## CONCLUSION

In conclusion, NiS, as the indication for renal biopsy, represents a very distinctive epidemiology of renal diagnoses than those of other major syndromes. Within the NiS group, there is a wide spectrum of epidemiological variations regarding the age subclasses as well as the regions of studies. Understanding

of these disparities helps the researchers, clinicians, and the health care systems in the management of their patients, and helps societies plan the best way to assign available resources to the areas that might promise more health advantages. It also provides motivations for future research to find the reasons behind the reported disparities and to intervene accordingly.

## ARTICLE HIGHLIGHTS

### **Research background**

Nephritic syndrome (NiS) is a major indicator of severe kidney disease requiring renal biopsy for histopathological evaluation, but limited understanding of the syndrome and its significance is currently lacking due to the lack of a comprehensive review in the literature.

### **Research motivation**

The current understanding on the epidemiology of renal diseases finally diagnosed in patients representing various clinical syndromes as indications for the renal biopsy is inaccurate and skewed.

### **Research objectives**

This systematic review aims at collecting the available data in the literature to give the most possible comprehensive overview on the epidemiology of diagnoses that we may expect from the evaluations of renal biopsies in patients with nephritic syndrome.

### **Research methods**

A systematic review of the literature has been conducted, with 47 studies identified for meta-analyses.

### **Research results**

A myriad of results have been made through this systematic review, the most important of them is the high prevalence of immunoglobulin A nephropathy (about 38%) as the final diagnosis of nephritic syndrome, and diagnosing minimal change disease in a proportion of pediatric patients representing with NiS.

### **Research conclusions**

The diagnostic spectrum of nephritic syndrome is quite wide, and clinicians should have a better overview on all the possibilities.

### **Research perspectives**

It has clinical, research and health care perspectives to the society.

## FOOTNOTES

**Author contributions:** Taheri S performed the literature review, meta-analyses, and report preparation.

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