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# Factors affecting the distribution of glomerulonephropathies among adult Saudi patients : A single-center, biopsy-based clinico-pathological study

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ABSTRACT

**Introduction:** Glomerulonephropathies (GNs) have high burden of morbidity and mortality worldwide. The distribution GNs varies significantly due to several factors.
**Materials and Methods:** This retrospective clinico-pathological study estimates the biopsy-proven distribution of primary and secondary GNs and detects the predominant patterns among adult patients who underwent renal biopsy at Nephrology Centre, King Abdul-Aziz Specialist Hospital, Taif City, Kingdom of Saudi Arabia (KSA) from 2008 to 2013 with comparing data to other KSA studies and to other countries. Analysis of possible contributing factors for variation is provided. Relevant patients' data were collected from hospital records. Renal biopsies stained with H&E, Periodic Acid Schiff (PAS), Gomori Methenamine Silver (GMS), Masson Trichrome (MT) and immunofluorescence (IF) were examined and categorized according to the World Health Organization (WHO) classification of glomerular diseases. Comparisons to other studies were set.
**Results:** Primary and secondary GNs comprised 59.4% and 40.6%. Focal segmental glomerulosclerosis (FSGS) was the commonest primary GN (29.3%), followed by minimal change disease (MCD, 22%) then membranous glomerulonephropathy (MGN, 19.5%). IgA nephropathy was the least frequent (IgAN, 2.4%). Lupus nephritis (LN) was the commonest secondary GN (75%), followed by diabetic and vascular nephropathies (DN, 17.9% ; VN, 7.1%). Spatial and temporal variations in GNs distribution existed locally and worldwide.
**Conclusion:**Factors including selection criteria; biopsy rate and indications; local facilities; demographic distribution; racial, ethnic and genetic differences; and prevalence of etiological factors contribute to the variations of GNs distribution. National renal biopsy registry is recommended for obtaining correct distribution of GNs leading to proper prevention and treatment.

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## 1. Introduction

Glomerulonephropathies (GNs) represent the third most common cause of end-stage renal disease,[1] with an increasing worldwide incidence up to a rate of 2.5 cases per 100 000 person/year.[2] The distribution of GNs has changed in the past two decades, as the incidence of focal segmental glomeruosclerosis (FSGS) has increased while that of membranoproliferative GN (MPGN) has declined.[2–4]

Clinically, GNs can present with proteinuria, hematuria, hypertension, impaired renal function, nephrotic syndrome, nephritic syndrome, rapidly progressive renal failure, acute kidney injury, chronic kidney disease or end-stage renal disease.[5] Although, the clinical presentation of glomerular disease may not essentially conform to a given morphological pattern of GN, the renal outcomes are greatly dependent on the etiology and the histopathological

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diagnosis.[5,6] Therefore, renal biopsies are important not only for making appropriate diagnosis but also for guiding treatment and prognosis.[7] On histopathological basis, the distribution of GNs varies widely from country to country. It differs with time within the same country as well as from region to region within.[8,9] This variation has been attributed to a myriad of factors in different studies.[10,11]

For this reason, the World Health Organization (WHO) has led the current classification of glomerular diseases in 1982 relying on renal biopsy from West Europe, USA and Japan. Biopsies were classified based on light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM).[7] However, a series of published biopsy- based studies performed in different countries within different periods of time has shown geographical and temporal variations in such distribution among different populations.[2,12,13] In Kingdom of Saudi Arabia (KSA), the distribution of GNs is not well documented. Some retrospective and few prospective studies have been conducted in different KSA regions and the results showed variable distribution. Moreover, an epidemiological study at the national scale is still lacking.[8] Therefore, there is a need for epidemiological data to manage GNs and their long-term consequences in our locality.[14]

This study detects the histopathological distribution of GNs, estimates the frequency of primary and secondary GNs and identifies the predominant pattern of each category among adult Saudi patients who underwent renal biopsy for diagnosis of glomerular disease in a tertiary care center in Taif area, KSA during the period from 2008 to 2013. Data are compared to other studies in different time periods and regions of KSA and with similar population studies in some other countries of the world with the aim of analyzing the factors affecting the distribution of GNs reflecting the possible effects of spatial, temporal, socio-economic, environmental factors as well as nephrology practice and facilities available in that locality.

## 2. Materials and Methods

This retrospective clinico-pathological cohort study was performed at Nephrology Centre, King Abdul-Aziz Specialist Hospital, Taif City, KSA. This center is the only nephrology center in Taif area. King Abdul-Aziz Specialist Hospital represents a tertiary referral hospital in Taif area, playing a major role in health care management. Percutaneous renal biopsies performed at this center and submitted for histopathology during a period of 6 years from January 2008 to December 2013 were enrolled in the study.

### 2.1. Inclusion and exclusion criteria

During the study period, a total of 104 adult patients' renal biopsies were retrieved from files. Biopsies for patients younger than 16 years were ruled out. Repeated biopsies from same patient were handled as a single case. Out of the collected 104 biopsies, 35 biopsies (33.7%) were excluded. Exclusion criteria were: unrecorded clinico-patological data, unavailable microscopic slides and/or paraffin tissue blocks (14 biopsies; 40%), diagnosis of interstitial (6 biopsies; 17.1%) or tubular renal diseases (2 biopsies; 5.7%) and biopsied transplanted kidney (13 biopsies; 37.2%). Finally, a sum of 69 cases (66.3% of biopsies) was enrolled in the study.

### 2.2. Clinical definitions and biopsy indications

Decision to carry out biopsy has been taken by a nephrologist after clinical examination. Indications of renal biopsy included nephrotic syndrome (proteinuria$>$3.5g/day/1.72m$^2$ and serum albumin$<$2.5g/dL), nephritic syndrome (gross hematuria and urine sediment showing red cells$>$5/high-power field), chronic renal failure (serum creatinine $>$4mg/dL with persistent glomerular filtration rate (GFR) less than 60 mL/minute/1.72m$^2$), impaired renal function (elevated serum creatinine below the renal failure limit; 2.5-4mg/dL) and systemic diseases with renal involvement.[4,8,15] An interventional radiologist performed an ultrasound guided biopsy under local anesthesia using Tru -Cut biopsy needles. Two to 3 cores of renal tissue were obtained to en sure sample adequacy.[9,16]

### 2.3. Data collection and tissue preparation

Relevant patients' data were collected from hospital records including: biopsy date, age, sex, clinical presentation, biopsy indication and any underlying condition associated with renal disease.[4,8,11] For all studied biopsies, the following materials were retrieved from pathology lab archives: (1) routinely prepared, formalin-fixed, paraffin-embedded tissue slides cut at 2-4$\mu$m and stained with routine hematoxylin and eosin stain (H&E), Periodic Acid Schiff (PAS), Gomori Methenamine Silver (GMS) and Masson Trichrome (MT); (2) cryopreservation medium-embedded, immunofluorescence (IF)-stained slides performed on frozen sections labeled with direct fluorescein isothiocyanate (FITC)-conjugated antibodies against IgG, IgA, IgM, C3 and C1q. Electron microscopy (EM) was performed for few selected cases in which definitive diagnosis was not possible with light and IF microscopy. For EM, tissues were fixed in Trump's fixative (combination of Sodium Cacodylate buffer, formalin and 1% glutaraldehyde), routinely processed into resin-embedded blocks, cut into ultrathin sections, stained with uranyl acetate /lead citrate and examined with transmission electron microscope Philips CM100.

### 2.4. Slide examination and analysis of data

Retrieved materials were independently revised by two pathologists who were blinded of the previous diagnosis. A sample was considered representative when contained at least 3 glomeruli and optimal when contained 6 glomeruli.[11] Biopsies were re-categorized according to the WHO classification. Primary GNs were classified into the following patterns: focal segmental glomerulosclerosis (FSGS); minimal change disease (MCD); membranoproliferative glomerulonephritis (MPGN); membranous glomerulonephropathy (MN); diffuse proliferative glomerulonephritis (DPGN); crescentic glomerulonephritis (CGN) and IgA nephropathy (IgAN). Secondary GNs were classified into: lupus nephritis (LN); diabetic nephropathy (DN); and hypertensive and vascular nephropathies (VN).[4,15] Data were expressed as absolute numbers and percent ages. Information on the frequency of GNs were presented in sufficient detail to allow comparisons with other series presented in the literature.

### 2.5. Ethical considerations

Conduction of this study was retrospect and had not influenced the biopsy decision.[11] Prior the biopsy procedure, all participants were oriented about the renal biopsy purpose and technique. Informed consents were obtained. All procedures were followed in accordance with the current revision of Helsinki Declaration.

## 3. Results

The current study included renal biopsies from 69 adult patients ranging in age from 17 to 75 years (mean age of 45.9 years). Thirty-four (49%) patients were females and 35 patients (51%) were males. Biopsies with histopathologically- proven GNs represented 66.4% of all biopsies registered during the study period.

Regarding the clinical presentation (Table 1), most of patients were presented with nephrotic syndrome (73.9%), followed by impaired renal function (15.9%) then by chronic renal failure (5.8%). The least frequent clinical presentation was nephritic syndrome that comprised 4.4% of cases.

As confirmed by renal biopsy, the distribution of GNs by histopathological pattern is shown in Table 2. Primary GNs were detected in 59.4% of biopsies, whilst secondary GNs encompassed 40.6%. Among primary GNs, FSGS was the most predominant histopathological pattern (29.3%; Figure 1), followed by MCD (22%) and MGN (19.5%). The least frequent type in this group was IgAN being diagnosed in one case (2.4%). The commonest cause of secondary GNs was lupus nephritis (LN) that comprised 75% of biopsies in this group (Figure 2). All of patients diagnosed with LN were females and the most frequent histological pattern among these cases was diffuse proliferative glomerulonephritis (WHO class IV). Secondary GNs due to diabetes mellitus (DN) or vascular and hypertensive diseases (VN) were diagnosed in 17.9% and 7.1% of biopsies in this group respectively.

Table 3 demonstrates our results as compared to related researches performed on Saudi patients in different regions of KSA and different time periods. We also included comparable studies performed on other populations in different countries. Emphasis is provided in discussion section.

## 4. Discussion

Renal biopsy is the most important diagnostic procedure in nephrology to estimate disease activity and direct treatment decisions. Likewise, the improved histological diagnostics have expanded the indications for renal biopsy.[4,17] Through many renal biopsy-based studies, the distribution of GNs has shown geographical, racial, ethnic and temporal variations.[4,13] However, most published studies are difficult to compare due to unstandardized procedures.[7,13] In our center, glomerular diseases comprised 66.4% of renal biopsy indications which is quite close to the reported indication rate in other researches.[3] The mean age of our patients was matching with some other studies involving cases with the same age range,[7,13] but the comparison seems difficult to other series that include d children or different age ranges.[8,16,17] Almost half of our patients were males and the remainder was females, which is the case in most compared studies.[7,9,17]

The clinical presentation of GNs appeared to vary widely among different studies. For example most of our patients were presented with nephrotic syndrome and most studies performed in KSA reported nephrotic syndrome to be the most frequent clinical presentation of GNs as well.[8,16]This also applies to the data of comparable studies worldwide.[9,18,19] Nevertheless, we reported impaired renal function as the next common clinical presentation in accordance with Jeganathan et al.[20] On the contrary, Polito et al.[19] reported urinary abnormalities as the second common clinical indication to perform renal biopsy after nephrotic syndrome. Moreover, other studies reported higher rates of nephritic syndrome and chronic kidney disease than ours, in addition to different clinical presentations such as acute renal failure, rapidly progressive GN, isolated proteinuria and/or hematuria.[9] This is almost related to different local biopsy rate and biopsy indications. Besides, it was noted that clinical diagnosis and biopsy diagnosis might be discordant in about one third of renal biopsies.[20]

Among this cohort, primary GNs comprised 59.4% of biopsies for glomerular diseases. This comes in accordance with another two recent studies performed in KSA in which primary GNs comprised 55.1% and 61.4% of cases.[8,16] Overall, primary GNs represent approximately half of all

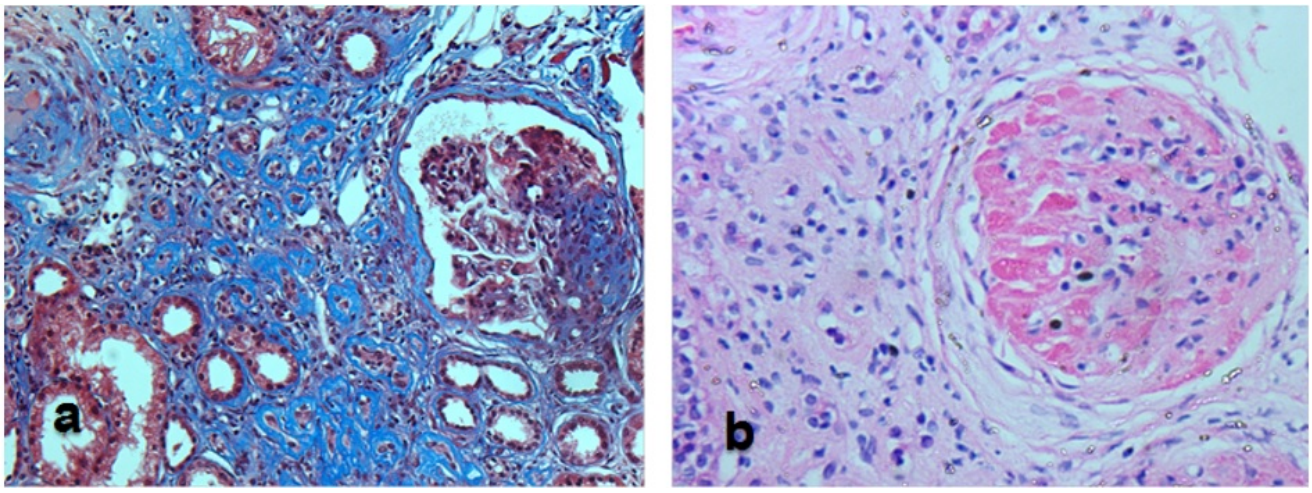


**Fig. 1:** Focal segmental glomerulosclerosis (FSGS). (a)Collagenous sclerosis affecting some (focal) glomeruli and just part of the affected glomerulus (segmental) (Masson trichrome, 200x), (b) Segmental hyaline deposits (PAS, 250x).

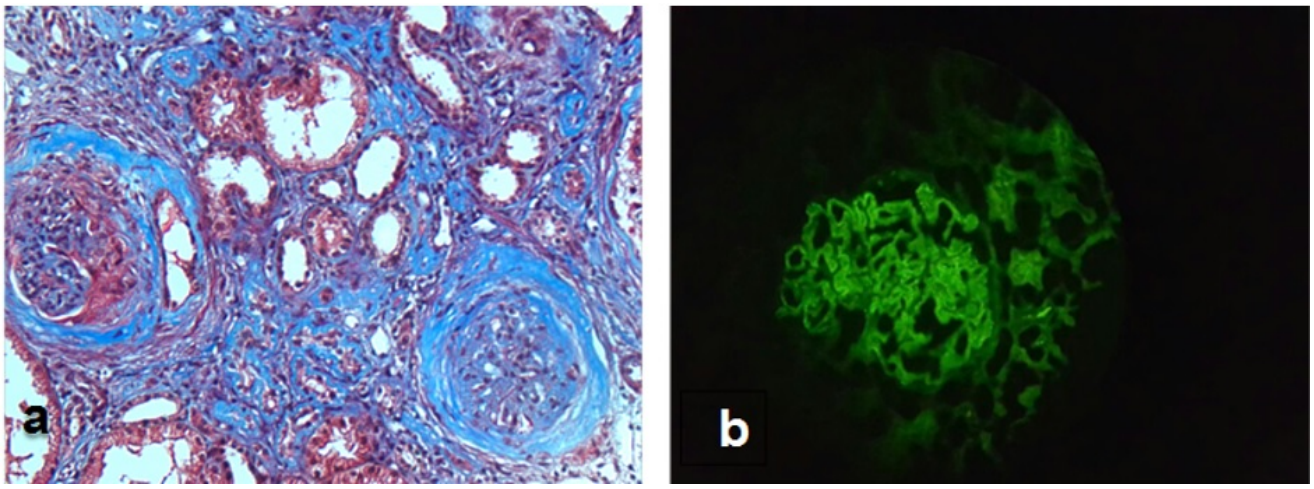


**Fig. 2:** Diffuse proliferative lupus nephritis (LN); WHO class IV (a) Global proliferative lesions, crescents, sclerosis and prominent inflammatory interstitial infiltrate (Masson trichrome, 100x). (b) Immunofluorescence micrograph showing glomerular IgG localization with wire-loop lesions in thickened capillary walls (IF, 200x)

**Table 1:** Distribution of clinical presentations among the included 69 cases of glomerulonephropathy

| ***Clinical presentation*** | ***Cases* (N, %)** |
|---|---|
| Nephrotic syndrome | 51 (73.9%) |
| Nephritic syndrome | 3 (4.4%) |
| Impaired renal function | 11 (15.9%) |
| Chronic renal failure | 4 (5.8%) |
| Total (N, %) | 69 (100%) |

N, number of patients

**Table 2:** Distribution of primary and secondary glomerulonephropathies by histopathological diagnosis among the included 69 cases.

| *Histopathological Pattern* | *Cases* (N, %) |
|---|---|
| **Primary glomerulonephropathie**s | **41 (59.4%)** |
| Focal segmental glomerulosclerosis (FSGS) | 12 (29.3%) |
| Minimal change disease (MCD) | 9 (22%) |
| Membranous glomerulonephropathy (MPG) | 8 (19.5%) |
| Membranoproliferative glomerulonephritis (MPGN) | 5 (12.2%) |
| Diffuse proliferative glomerulonephritis (DPGN) | 3 (7.3%) |
| Crescentic glomerulonephritis (CGN) | 3 (7.3%) |
| IgA nephropathy (IgAN) | 1 (2.4%) |
| **Secondary glomerulonephropathie**s | **28 (40.6%)** |
| Lupus nephritis (LN) | 21 (75%) |
| Diabetic nephropathy (DN) | 5 (17.9%) |
| Hypertension, vasculitis (VN) | 2 (7.1%) |
| **Total (N, %)** | **69 (100%)** |

N, number of patients

**Table 3:** Comparison of current study results with different studies in different KSA regions and some other countries of the world

| *Study* | *Present study* | *Jalalah* [22] | *Nawaz* [8] | *Al-Matham* [16] | *Hanko* [13] | *Oygar & Neild* [7] | *dos-Santos* [18] | *Khalid* [14] | *Khakurel* [9] |
|---|---|---|---|---|---|---|---|---|---|
| **Country, region** | KSA, Taif area | KSA, Western region | KSA, Central region | KSA, Riyadh area | United Kingdom | Cyprus | Brazil | Pakistan | Nepal |
| **Year** | 2019 | 2009 | 2013 | 2017 | 2009 | 2017 | 2017 | 2017 | 2015 |
| **Study period** | 2008-2013 | 1989- 2007 | 2005- 2009 | 2007-2016 | 1996-2005 | 2006-2015 | 2003-2015 | 2012-2015 | 2000-2009 |
| **Age** | | | | | | | | | |
| Range | 17-75y | 17-76y | 2-90y | 13-70y | 16-92y | ≥17y | 1-88y | 13/73y | 7-74y |
| Mean | 45.9y | - | 33y | 28.9y | 49y | 45.7y | 27y | 37.5y | 28y |
| **Gender** | | | | | | | | | |
| Male/Female | 51/49% | 46/54% | 50/35% | 59.8/40.2% | 61/39% | 51/49% | 52/48% | 57/43% | 52.8/47.2% |
| **Primary GNs** | **59.4%** | - | - | **61.4%** | - | - | - | - | - |
| FSGS | **29.3%** | 21.3% | **27.6%** | **35.3%** | 4% | **29%** | **23%** | **23%** | 24.1% |
| MCD | 22% | 5.4% | 17.7% | 26.5% | 11% | 5% | 4% | 4.5% | **31.9%** |
| MGN | 19.5% | **25.7%** | 9.9% | 12.7% | 26% | 18% | 11% | 12% | 15.6% |
| MPGN | 12.2% | 11.5% | 13% | 5.9% | 10% | 9% | 7% | 7% | 4.1% |
| DPGN | 7.3% | 4.7 | - | - | - | - | 3% | 6% | - |
| CGN | 7.3% | - | - | - | - | - | 2% | 4% | 3.9% |
| IgAN | 2.4% | 17.6% | 11.5% | 7.8% | **43%** | 24% | 5% | 9% | 13.3% |
| **Secondary GNs** | **40.6%** | - | - | **36.8%** | - | - | - | - | - |
| LN | **75%** | Not studied | **54.5%** | **100%** | **-** | **52%** | **26% of all cases** | **28.6%** | **54.7%** |
| DN | 17.9% | - | 6.8% | - | - | 17% | - | - | - |
| VN | 7.1% | - | 26.5% | - | - | 1% | - | 16.3% | 3.8% |

KSA, Kingdom of Saudi Arabia; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous glomerulonephropathy; MPGN, membranoproliferative glomerulonephritis; DPGN, diffuse proliferative glomerulonephritis; CGN crescentic glomerulonephritis; IgAN, IgA nephropathy; LN, lupus nephritis; DN, diabetic nephropathy; VN, vascular nephropathy; y, year

native renal biopsies in almost all databases.[21] Though, some other studies reported primary GNs in up to 80% of biopsies.[20]

Marked differences in the frequency of FSGS exist worldwide.[4] In the present study, FSGS was the most observed pattern of primary GNs (29.3%). This finding came to support data provided by recent studies in other regions of KSA[8,16] as well as other countries such as Cyprus, Brazil, Pakistan and Nepal[7,9,14,17] that documented FSGS in a range from 27.6% to 35.3% and described FSGS as the commonest glomerular disease as well as commonest cause of nephrotic syndrome in adults despite racial differences. On the contrary, a study in Western KSA by Jalalah[22] described MGN as the commonest primary GNs with a frequency of 2 5.7% and his results were similar to other two studies published in the same y ear in United Kingdom (UK) and Korea.[4,13] This difference may state a temporal and spatial variation s in distribution of GNs during the past few years with trends for raising incidence of FSGS worldwide.[3,9] Although Jalalah[22] attributed this difference to ethnic factors because FSGS is more prevalent in blacks and MGN is more common in white patients. We have to consider that ethnicity is not documented in patient's data in studies arising from KSA. There are also, well-documented causes of secondary FSGS such as human immunodeficiency virus (HIV) infection and obesity, but it is unlikely that the higher frequency of primary FSGS is attributed to failure to diagnose secondary FSGS. It is plausible that there are other unidentified etiological factors for rising frequency of primary FSGS to be further investigated.[13]

MCD is commonly recorded in the Western literature as an important type of primary GN causing nephrotic syndrome.[4] The frequency of MCD was 22% of primary GNs in our study, which is compatible with the values reported in two recent studies in both central and eastern regions of KSA.[8,16] In contradiction, MCD comprised 5.4% of primary GNs in the study by Jalalah,[22] although the later study was performed in western region of KSA similar to our study and the patients had almost the same age and sex distributions of our patients. Similarly, Chang et al.[4] reported a decline in the relative frequency of MCD in Korea. Whether the difference is related to genetic background, environmental factors or frequent infections is uncertain. A recent study had related variation in frequency of MCD to being less prevalent in older patients.[6]

We noticed a wide variation in the frequency of MGN. It constituted the third most common cause of primary GNs comprising 19.5% of our biopsies, while other studies in KSA reported a wide range from 9.9% to 25.7%[8,16,22] and the later study reported MGN as the most common primary GN in KSA. Two factors[7,9,13,14,17] seem to control the prevalence of MGN. First, MGN is known to match with age, so MGN is the most common glomerular disease between the $7^{th}$ and $8^{th}$ decades of life.[17] This is why, Hanko et al.[13] reported MGN to be the second most frequent primary GN (26%) in UK and owed this to the rising age of patients biopsied in their series. Second, the prevalence of MGN is closely paraleled to the geographic distribution of HBsAg-positivity. This is why MGN is most frequently reported in Asian populations.[4]

MPGN is a non-specific glomerular disease associated with immune complex or complement deposition in patients with infectious and autoimmune diseases.[8,17,22] MPGN was identified in biopsies from 5.9% to 13% of patients in KSA including our cohort and in a range of 4.3% to 10% in different counties. Chang et al.[4] observed a decline in the frequency of MPGN, which was previously common in countries with a lower socioeconomic status due to the proposed hygiene hypothesis and the alteration in the immune balance of the TH-1 and 2 cells. The low frequency of MPGN may reflect improved control of infections and prevention of viral infections including hepatitis C virus.[6,17]

In contradiction to this study, compared studies came across small numbers of either DPGN or CGN.[8,9,14,17] Some of the former studies classified their cases as secondary GNs instead of primary. In this work, each of both glomerulonephritides comprised 7.3% of primary GNs. We were unable to identify features of an inciting disease in any of the reported cases. Particularly, Jeganathan et al.[20] had the same percentage of primary CGN among their biopsies. We have to be aware that the etio-pathogenesis of glomerular diseases designates almost about half of DPGN or CGN to be idiopathic in nature.

Our data indicate that IgAN is not a common primary GN in KSA and that there are obvious variations in the occurrence of IgAN in the different regions of KSA and other parts of the world.[22] IgAN was the least frequent primary GN in this study. Our reported frequency is similar, although lower than that reported in recent studies performed in Riyadh, KSA,[16] Brazil and Pakistan.[14,17] However, it is much lower than the frequency observed in earlier studies in western and central regions of KSA[8,22] and by far lower than other countries such as United States of America (USA), Korea, Cyprus and UK.[3,4,7,13] Some of the previous studies confirmed IgAN as the most common primary GN among adults. Racial and genetic differences may account for this geographic variation as IgAN is linked to a gene on chromosome 6q22-23. Additionally, Wirta et al.[11] have confirmed a relation between IgAN and biopsy rate where countries with high biopsy rate always show high IgAN incidences as compared to those with low biopsy rates. Variation also reflects biopsy indications because i n countries where nephrologists biopsy patients with isolated microscopic hematuria, IgAN was the most frequent primary GN.[4,13,23] We have to note that nephritic syndrome, which is a usual presentation of IgAN, was observed in only 4.4% of our biopsied patients. Hence,

studies are required to define if the low IgAN frequency is due to an actual low prevalence of the disease or to the criteria used to indicate kidney biopsy in a particular locality.[17]

There was a consensus that LN is the most common secondary GN in adults[21] in most biopsy-based studies in KSA;[8,16] as well as in other countries such as Cyprus, Brazil, Pakistan, Nepal, India and Australia[7,9,14,17,20,24] in a range from 28.6% to 100%. In agreement with or study, LN dominated in females and the WHO class IV was the most encountered histopathological class. Yet, comparing other causes for secondary GNs may be incorrect as biopsy exclusions in different studies may include DN, controlled hypertension, evident myelomatosis and acute renal failure,[11] in addition to the relative rarity of immune-mediated vasculitis. We reported DN as the next common secondary GN (17.9% of our biopsies) in accordance with Oygar and Neild.[7] Although DN is a common renal disease occurring in many countries, it is usually diagnosed without renal biopsy in the absence of other findings suggesting another disease. A small minority of patients with DN might be referred for renal biopsy.[4] Some researchers reported post-infectious glomerulonephritis as the a common cause for secondary GNs,[8,9], however, the frequency of this type is decreasing in most industrialized countries but remains high in developing communities.[21]We were able to detect nephropathies due to hypertension and vascular diseases in 7.1% of secondary GNs. However, Briganti et al.[24] described VN as a common renal disease in adults with a male predominance and Nawaz et al.[8] reported hypertensive nephropathy as the second most common cause for secondary GNs. This difference is attributed to variation in the incidence of vasculitis and hypertensive diseases across populations.

## 5. Conclusion

Among adult Saudi patients in Taif area, FSGS and LN are the most predominant patterns of primary and secondary GNs, respectively. Comparisons of our findings highlighted the spatial and temporal variations in the distribution of GNs in KSA and also worldwide. Suggested factors for variation included patients' selection criteria, renal biopsy rate and indications, facilities in the study locality, demographic distribution of study population, etiological factors related to racial, ethnic or genetic variation and prevalence of related infectious agents, autoimmune and vascular diseases. In KSA, the recruitment threshold for renal biopsy is low especially for a mild disease. Therefore, the histopathological documentation reflects moderate or severe diseases. Optimization of diagnostic facilities, standardization of reporting and setting up a national renal biopsy registry are recommended for obtaining correct epidemiological description about the distribution of GNs leading to proper prevention and treatment of glomerular diseases.

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## 7. Ethical approval

Conduction of this study was retrospect and had not influenced the biopsy decision. Prior the biopsy, all participants were oriented about the renal biopsy purpose and technique. Informed consents were obtained. All procedures were followed in accordance with the current revision of Helsinki Declaration.

## 8. Conflict of interest

The authors declare that they have no conflict of interest.

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