

# The Spectrum of Biopsy-Proven Glomerular Disease in China: A Systematic Review

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## Abstract

**Background:** Chronic kidney disease has become a leading public health concern in China, as it is associated with increased morbidity, mortality, and costs. However, the overall situation regarding common glomerular diseases in China remains unclear. Hence, the aim of this study was to assess the national profile of the common types of glomerulonephritis in China.

**Methods:** We searched Medline, Embase, Cochrane Library, CNKI, SinoMed, VIP, and Wanfang databases for English and Chinese language articles from inception to September 2017. We also collected potentially relevant studies and reviews using a manual search. The following words in combinations are as keywords: “renal biopsy”, “kidney pathological diagnosis”, and “spectrum of pathological types”.

**Results:** We identified 23 studies involving 176,355 patients from 15 provinces/cities in China. The detection rates of primary glomerulonephritis (PGN) and secondary glomerulonephritis (SGN) were 0.740 and 0.221, respectively. Over the past 30 years, the top five types of PGN were immunoglobulin A nephropathy (IgAN; 24.3%), mesangial proliferative glomerulonephritis (MsPGN; 10.5%), membranous nephropathy (MN; 12.6%), minimal change disease (MCD; 9.8%), and focal segmental glomerulosclerosis (FSGS; 4.6%), and the top four types of SGN were lupus nephritis (LN; 8.6%), Henoch-Schönlein purpura glomerulonephritis (4.1%), hepatitis B virus-associated glomerulonephritis (HBV-GN; 2.6%), and diabetic nephropathy (DN; 1.6%). The proportion of MN, MCD, HBV-GN, and DN tended to increase, while those of IgAN, MsPGN, FSGS, and LN tended to drop.

**Conclusions:** Although the incidence of SGN is increasing gradually, PGN is still the leading form of kidney disease in patients undergoing renal biopsies in China. IgAN and LN are the most common types of PGN and SGN, respectively. Differences between regions are related to various factors such as nationality, environment, and diet. Furthermore, unified standards and norms for evaluating renal biopsies are urgently needed.

**Key words:** Primary Glomerulus Nephritis; Renal Biopsy; Secondary Glomerulus Nephritis

## INTRODUCTION

In recent years, chronic kidney disease (CKD) has become a leading public health concern in China and other countries,<sup>[1]</sup> as it is associated with increased morbidity, mortality, and financial costs. The overall prevalence of CKD in China ranges from 10.8% to 13%.<sup>[2]</sup> Despite numerous studies, there are no early diagnostic markers for CKD.<sup>[3]</sup> The renal biopsy is still the golden diagnostic criterion for nephropathy.

The first renal biopsies in China were performed in the 1980s. Now, they are performed widely in tertiary hospitals.<sup>[4,5]</sup> Some hospitals have reported on the spectrum of pathological types seen in renal biopsies, but the overall situation regarding the common types of glomerular disease in China remains unclear. The distribution of the spectrum of glomerular

disease varies temporally and geographically and in different ethnic groups.<sup>[6]</sup> Few studies have systematically investigated the spectrum of primary glomerulonephritis (PGN) and secondary glomerulonephritis (SGN) in China when stratified by geographic region and time period. Therefore, this study was focused on the detection rate of different types of glomerulonephritis and aimed to assess the national profile of the common types of PGN and SGN in China.

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## METHODS

This systematic review followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,<sup>[7]</sup> and the report complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>[8]</sup> The protocol and registration information are available at [http://www.crd.york.ac.uk/PROSPERO/\(CRD 42017082724\)](http://www.crd.york.ac.uk/PROSPERO/(CRD 42017082724)).

### Search strategy

We performed a systematic electronic search of the PubMed, Embase, Cochrane Library, SinoMed (Chinese Biomedical Literature Database), Chinese National Knowledge Infrastructure (CNKI), VIP, and Wanfang databases from their inception through September 2017.

All articles written in either Chinese or English containing any word regarding pathological types of renal biopsy were identified; the following words in combinations are as keywords: “renal biopsy,” “kidney pathological diagnosis,” and “spectrum of pathological types.” After completing the electronic database search, we performed a manual search of professional journals and thesis.

### Inclusion and exclusion criteria

Studies that met the following inclusion criteria were included in the review: (1) renal biopsy performed in a hospital located in China; (2) more than 1000 cases were reported in the study; (3) the total cases of renal biopsy, PGN, and SGN were reported or could be calculated; and (4) detection rates of various types of glomerular diseases were reported or could be calculated.

Studies were rejected for the following reasons: (1) inclusion of data from other countries or regions and (2) limits placed on age or gender.

### Record selection and data extraction

Two authors (Yang Y and Zhang Z) performed the initial search independently, deleted duplicate records, screened the titles and abstracts for relevance, and identified records as included, excluded, or uncertain. In the case of uncertainty, a third researcher (Zhuo L) was responsible for examining the data and discussing the findings with the other two. Studies were included only when all three researchers reached a consensus.

Data were extracted by Yang Y and confirmed independently by two other authors (Zhang Z and Zhuo L). We also sought supplementary appendices of the included studies or contacted the corresponding authors to verify the extracted data and request any missing data. Discrepancies were resolved by discussion with the coauthors. The predefined outcomes were the detection rates of the top five types of PGN and top four types of SGN and their proportion trends.

## RESULTS

### Basic information regarding the studies included

The electronic and manual searches identified 2027 potentially relevant papers. After browsing the titles and

abstracts, we selected 421 papers. After reading the entire texts of these 421 papers, we excluded 398 papers and included 23 papers,<sup>[4,9-30]</sup> with a total of 176,355 patients from 15 different provinces/cities in China. According to the geographical and administrative divisions, we divide our country into five regions: north, east, south, west, and central China, at least two studies were included in each region. In east and south China, the economically developed regions, more than 130,000 cases were enrolled, and even in west China, there are still more than 10,000 cases. The process of paper inclusion is shown in Supplementary Figure 1, and the detailed information on the studies is summarized in Table 1.

### Detection rate of the main primary glomerulonephritis in China

The detection rate of PGN to renal biopsy patients in China was based on 22 studies<sup>[4,9-29]</sup> involving 170,420 cases. The detection rate of PGN was 0.740 (126,031 cases).

IgA nephropathy (IgAN, 24.3%), mesangial proliferative glomerulonephritis (MsPGN, 10.5%), membranous nephropathy (MN, 12.6%), minimal change disease (MCD, 9.8%), and focal segmental glomerulosclerosis (FSGS, 4.6%) were the most common pathological types. Pathological data were also analyzed with different regions of China [Table 2].

### Detection rate of the main secondary glomerulonephritis in China

The detection rate of SGN to renal biopsy patients in China was based on 23 studies<sup>[4,9-30]</sup> involving 176,355 cases. The detection rate of SGN was 0.221 (38,979 cases).

Lupus nephritis (LN, 8.6%), Henoch-Schönlein purpura glomerulonephritis (HSP-GN, 4.1%), hepatitis B virus-associated nephritis (HBV-GN, 2.6%), and diabetic nephropathy (DN, 1.6%) were the most common pathological types. Pathological data were also analyzed with different regions of China [Table 3].

### Trends in frequency of the most common glomerulopathies in China

To observe the changing trend of disease spectrum of renal biopsy, we set three periods: before 2000 (period 1), 2001–2010 (period 2), and after 2010 (period 3).

The trends of PGN proportion were based on 16 studies<sup>[4,5,9,12,14-19,21-23,25,26,28]</sup> involving 55,014 cases. The proportion of IgAN, MsPGN, and FSGS tended to drop, that is, 36.7% versus 28.3%, 33.7% versus 14.1%, and 7.0% versus 2.1% during period 1 and period 3, respectively [Figure 1]. The proportion of MN and MCD tended to rise, that is, 8.2% versus 16.3% and 1.4% versus 16.4% during period 1 and period 3, respectively [Figure 1].

The trends of SGN proportion were based on 16 studies<sup>[4,5,9,12,14-19,22,23,25,26,28,30]</sup> involving 10,243 cases. The proportion of LN tended to drop, that is, 53.1% versus 23.9% during period 1 and period 3 [Figure 2]. The proportion of HBV-GN and DN tended to rise, that is, 2.7% versus

**Table 1: Characteristics of studies included in the systematic review**

Study	Year	Region	Province	Biopsies (N)	PGN (N)	SGN (N)	Patients' gender (male/female)	Patients' age (years)
Chen <i>et al.</i> <sup>[5]*</sup>	2000	East China	Jiangsu	10,594	7059	2283	5654/4348†	31.4 ± 13.0†
Li and Ye <sup>[9]</sup>	2003	East China	Zhejiang	1171	1009	124	539/632	8–79
Li and Liu <sup>[10]*</sup>	2004	East China	Jiangsu	13,519	9278	3359	7752/5767	32.7 ± 12.2
Wang <i>et al.</i> <sup>[11]</sup>	2005	East China	Jiangxi	1602	1205	320	952/650	29.6 (6–68)
Du <i>et al.</i> <sup>[12]</sup>	2006	West China	Shanxi	1542	1070	414	937/604	43.54 ± 15.3
Li <i>et al.</i> <sup>[13]</sup>	2006	North China	Liaoning	1295	990	246	730/565	33.62 ± 8.53
Liu <i>et al.</i> <sup>[14]</sup>	2009	South China	Guangdong	1245	1031	170	506/739	9–73
Xu <i>et al.</i> <sup>[15]</sup>	2009	South China	Guangdong	1627	1214	103	811/816	30.7 ± 15.1
Liao <sup>[16]</sup>	2010	South China	Guangxi	3035	2194	760	1539/1496	34.10 ± 14.78
Zhang <i>et al.</i> <sup>[17]</sup>	2010	Central China	Henan	1200	870	273	690/510	35.5 ± 15.3
Li <i>et al.</i> <sup>[18]</sup>	2011	North China	Liaoning	1042	840	185	485/557	35.83 ± 15.03
Du <sup>[19]</sup>	2011	West China	Xinjiang	1148	874	149	602/546	34.06 ± 11.84
Shang and Yin <sup>[20]</sup>	2011	West China	Shanxi	5000	3870	972	3306/1694	35.5 ± 11.4
Shi <sup>[21]</sup>	2012	East China	Fujian	36,379	13,825	6953	18,553/17,826	30.53 ± 15.07
Wu <i>et al.</i> <sup>[22]</sup>	2013	Central China	Henan	6995	4638	2191	3636/3359	Male: 33.64 ± 17.75 Female: 35.36 ± 15.46
Luo <sup>[23]</sup>	2013	West China	Xinjiang	1224	1000	149	661/563	4–82
Wei <i>et al.</i> <sup>[24]</sup>	2013	East China	Shandong	1071	795	258	538/533	7–81
Liu and Zhang <sup>[25]</sup>	2014	West China	Yunnan	1594	893	550	894/700	45.54 ± 10.44
Zhang <i>et al.</i> <sup>[4]</sup>	2014	North China	Beijing	11,608	8209	2406	6646/4972	35 (3–85)
Sun <i>et al.</i> <sup>[26]</sup>	2014	West China	Shanxi	1363	1119	209	712/651	37.0 ± 7.8
Yang <i>et al.</i> <sup>[27]</sup>	2015	North China	Jilin	4382	2781	1341	2434/1948	6–82
Li <i>et al.</i> <sup>[28]</sup>	2016	East China	Anhui	1217	1022	186	666/551	34.5 ± 15.8
Xu <i>et al.</i> <sup>[29]</sup>	2016	South China	Guangdong	71,151	54,743	15,883	35,641/35,510	37.3 ± 15.9
Wang <i>et al.</i> <sup>[30]</sup>	2017	East China	Shandong	5935	–	1038	525/513‡	38.05 ± 17.05‡

\*Two articles were performed with the same team at different periods. In our study, Chen's article was only used to analyze the trend of primary glomerulus nephritis; †Data from 10,002 nontransplant patients; ‡Data from 1038 secondary glomerulus nephritis patients; PGN: Primary glomerulonephritis; SGN: Secondary glomerulonephritis; –: Not applicable.

**Table 2: Detection rate of PGN in China, n (%)**

Region	N	IgAN	MsPGN	MN	MCD	FSGS
North China	18,337	5820 (31.7)	2446 (13.3)	2055 (11.2)	975 (5.3)	836 (4.6)
East China	54,959	10,326 (18.8)	7527 (13.7)	2657 (4.8)	1376 (2.5)	1721 (3.1)
South China	77,058	20,898 (27.1)	4271 (5.5)	15,143 (19.7)	12,288 (15.9)	4287 (5.6)
Central China	8195	2048 (25.0)	396 (4.8)	744 (9.1)	1580 (19.3)	414 (5.1)
West China	11,871	2256 (19.0)	3185 (26.8)	951 (8.0)	531 (4.5)	519 (4.4)
Total in China	170,420	41,348 (24.3)	17,825 (10.5)	21,550 (12.6)	16,750 (9.8)	7777 (4.6)

IgAN: IgA nephropathy; MsPGN: Mesangial proliferative glomerulonephritis; MN: Membranous nephropathy; MCD: Minimal change disease; FSGS: Focal segmental glomerulosclerosis; PGN: Primary glomerulonephritis.

12.4% and 6.2% versus 18.8% during period 1 and period 3, respectively [Figure 2].

## DISCUSSION

This systematic review identified 23 studies involving more than 170,000 patients from 15 provinces/cities in China. The detection rates of PGN and SGN in all renal biopsies were 0.740 and 0.221, respectively. PGN is still the leading kidney disease in patients undergoing renal biopsies in China, although the detection rate of PGN has decreased gradually, while the incidence of SGN has increased. The top five types of PGN were IgAN, MsPGN, MN, MCD, and FSGS and the top four types of SGN were LN, HSP-GN, HBV-GN, and DN.

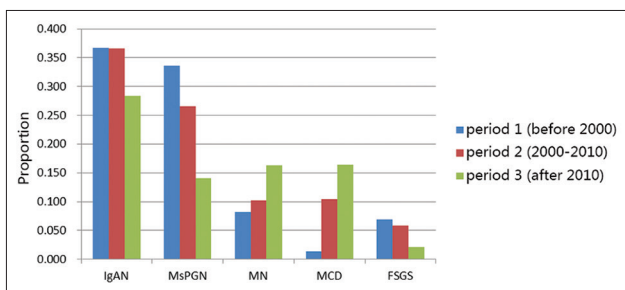
IgAN may be the most common type of PGN worldwide. While the detection rate in Africa was <5%,<sup>[31]</sup> it was 17.8–22.0% in America,<sup>[32,33]</sup> 26–37% in Europe,<sup>[34,35]</sup> and up to 30–40% in Asia.<sup>[36,37]</sup> In countries in East Asia, the detection rate of MsPGN in a broad sense (IgAN and non-IgA MsPGN) can exceed 50%.<sup>[36,37]</sup> Obviously, ethnic and genetic factors play important roles. The prevalence of IgAN and MsPGN has decreased in the recent decades. The main reasons for this may be that other types of PGN, such as MN, have increased and PGN is being diagnosed more accurately, while MsPGN tended to be misdiagnosed in the past.

MN was the leading cause of nephrotic syndrome in middle age, whereas MCD was the most common histological

**Table 3: Detection rate of SGN in China, *n* (%)**

Region	<i>N</i>	LN	HSP-GN	HBV-GN	DN
North China	18,337	1188 (6.5)	1025 (5.6)	631 (3.4)	449 (2.4)
East China	60,894	5397 (8.9)	2668 (4.4)	2216 (3.6)	731 (1.2)
South China	77,058	6674 (8.7)	2377 (3.1)	1108 (1.4)	1283 (1.7)
Central China	8195	868 (10.6)	508 (6.2)	326 (4.0)	113 (1.4)
West China	11,871	967 (8.1)	604 (5.1)	245 (2.1)	211 (1.8)
Total in China	176,355	15,094 (8.6)	7182 (4.1)	4526 (2.6)	2787 (1.6)

LN: Lupus nephritis; HSP-GN: Henoch–Schönlein purpura glomerulonephritis; HBV-GN: Hepatitis B virus-associated glomerulonephritis; DN: Diabetic nephropathy; SGN: Secondary glomerulonephritis.



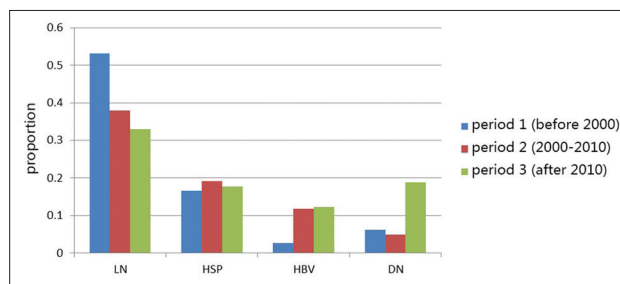
**Figure 1:** Trend of PGN in China. Trends of proportion (%) of PGN in China. PGN: Proliferative glomerulonephritis; IgAN: IgA nephropathy; MsPGN: Mesangial PGN; MN: Membranous nephropathy; MCD: Minimal change disease; FSGS: Focal segmental glomerulosclerosis.

diagnosis among younger patients. The detection rate of MN was about 20% in Brazil<sup>[38]</sup> and Italy<sup>[35]</sup> and 10% in the USA.<sup>[32]</sup> In Asia, MN was not as common in the past, but its incidence is increasing.<sup>[6,29,36]</sup> The presence of unidentified environmental factors, such as PM2.5, may increase the risk of MN.<sup>[29]</sup>

In recent years, the incidence of FSGS has tended to increase in the USA<sup>[39]</sup> and Brazil,<sup>[40]</sup> but it dropped in our study. The area-varying distribution of FSGS might be related to race and environmental factors.<sup>[39]</sup>

LN is the most common SGN worldwide, comprising 45.5–66.2% of all SGN.<sup>[31,32,34,38]</sup> Our data showed a nonsignificant tendency for a decrease in the detection rate by decade. With advances in clinical medicine and technology, more autoimmune diseases are being identified and diagnosed, which may explain the trend in LN.

The prevalence of DN increased significantly after 2010. It is SGN caused by diabetes mellitus and is one of the most common diabetic complications. The prevalence of type 2 diabetes mellitus has increased rapidly in recent decades, and it has become a global public health problem. Diabetes is the leading cause of CKD in developed countries, whereas glomerulonephritis has been identified as the predominant cause of CKD in developing countries. Zhang *et al*<sup>[41]</sup> was the first to report that CKD was more frequently associated with diabetes than glomerulonephritis in China, in both the general population and a hospitalized urban population. DN will likely play a more important role in the spectrum of SGN in China in the coming decades.



**Figure 2:** Trend of SGN in China. Trends of proportion (%) of SGN in China. SGN: Secondary glomerulonephritis; LN: Lupus nephritis; HSP-GN: Henoch–Schönlein purpura glomerulonephritis; HBV-GN: Hepatitis B virus-associated nephritis; DN: Diabetic nephropathy.

This present study also had limitations. Due to the high heterogeneity, the existing data are not suitable for meta-analysis. The inter-regional and regional differences and heterogeneity may be related to many factors. The reasons for the differences between regions are complex and may involve nationality, population mobility, economic conditions, education, environment, diet, and other factors. Second, there are significant differences in renal biopsy indications between regions; in some areas, it is considered only in patients with nephrotic syndrome and normal renal function. This will undoubtedly lead to heterogeneity in the spectrum of renal biopsy between hospitals. Third, the production and staining process of kidney sections and the diagnostic accuracy of pathologist differ across regions. In some underdeveloped areas, this is still a long way to go. Clinicians and pathologists in different provinces and cities require standardized training and the uniform guidelines are needed urgently.

In summary, although decreasing gradually, IgAN and MsPGN are still the most common types of PGN in patients undergoing renal biopsies in China, whereas LN is still the top SGN. The detection rates of MN, MCD, and DN are tending to increase, while that of FSGS is dropping. Differences between regions are related to various factors. Unified standards for assessing renal biopsies are urgently needed.

*Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.*

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## Conflicts of interest

There are no conflicts of interest.

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# 中国患者肾穿刺肾小球疾病谱的系统评价

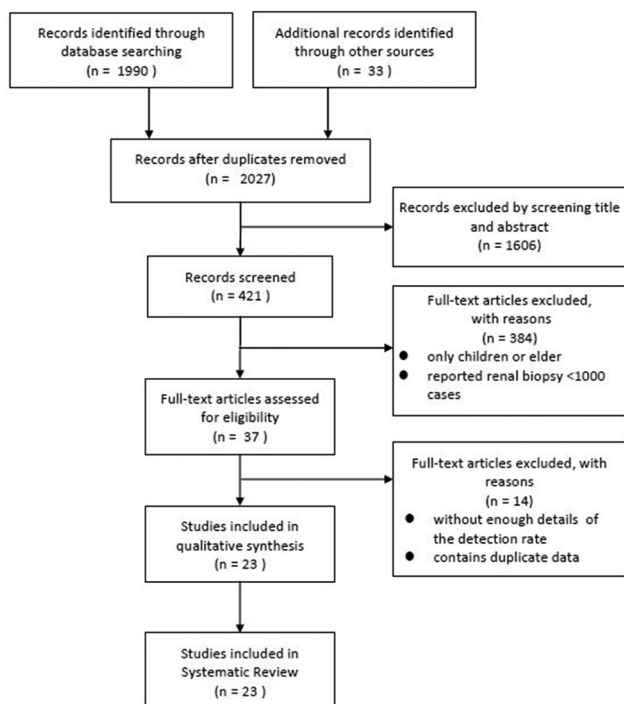
## 摘要

**背景：**慢性肾脏病发病率高，导致死亡风险高，医疗花费巨大，已成为中国一个令人瞩目的公共卫生问题。然而，中国各地各种不同病理类型肾小球疾病的分布情况目前仍不清楚。

**方法：**我们检索了MEDLINE, EMBASE, Cochrane图书馆, CNKI, SinoMed, VIP和万方数据库，语言限定为英文或中文，时间截止2017年9月。此外，我们也对会议论文，学位论文等灰色文献相关进行了人工搜索。检索词为下列组合：“肾活检”，“肾脏病理诊断”和“病理类型谱”。

**结果：**我们最终纳入了23项研究，涉及中国15个省市的176,355名患者。原发性和继发性肾小球肾炎的检出率分别为0.740和0.221。在过去30年中，肾穿刺最常见的5种原发性肾小球疾病分别是：IgA肾病（IgAN; 24.3%），系膜增生性肾小球肾炎（MsPGN; 10.5%），膜性肾病（MN; 12.6%），微小病变（MCD; 9.8%）和局灶节段性肾小球硬化（FSGS; 4.6%）。最常见的继发性肾小球疾病依次为：狼疮性肾炎（LN; 8.6%），过敏性紫癜性肾炎（HSP-GN; 4.1%），乙型肝炎病毒相关性肾小球肾炎（HBV-GN; 2.6%）和糖尿病肾病（DN; 1.6%）。其中MN, MCD, HBV-GN和DN呈增加趋势，IgAN, MsPGN, FSGS和LN呈下降趋势。

**结论：**尽管继发性肾小球疾病检出率逐渐增高，临床最常见的仍是原发性肾小球疾病。IgAN和LN分别是最常见的原发和继发性肾脏病理类型。不同地区之间疾病检出率存在明显差异，可能与基因、环境、饮食等多种因素有关。另外，肾活检病理诊断的规范化也是一个亟待解决的问题。



Supplementary Figure 1: Flow diagram.