Nephrology in China

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Area	9,597,000 km^2
Population	1.428 billion (2018)
Capital	Beijing
Three most populated cities	1. Guangzhou 2. Shanghai 3. Chongqing
Official language	Chinese[‡‡]
Gross Domestic Product (GDP)	99,086.5 billion RMB (2019); represent 21.95% of the world economy[‡]
GDP per capita	70,892 RMB (2019)
Human Development Index	0.758 (2018)
Official currency	Renminbi (RMB)
Total number of nephrologists	~15,000
National Society of Nephrology	Chinese Society of Nephrology www.csnchina.org
Incidence of kidney failure[1]	2015 – 122.19 pmp (age-adjusted)
Prevalence of kidney failure[1] (on dialysis)	2015 – 402.18 pmp on HD, 39.95 pmp on PD (data in 2015)
Total number of patients on dialysis[2] (all modalities)	2017 – 610,811
Number of patients on hemodialysis[2]	2017 – 524,467
Number of patients on peritoneal dialysis[2]	2017 – 86,344 2018 – 99,145 (20% of total dialysis population)
Number of renal transplantations per year	7087 per year (between 2008 and 2018)

[1]Wang F, Yang C, Long J, Zhao X, Tang W, Zhang D, et al. Executive summary for the 2015 Annual Data Report of the China Kidney Disease Network (CK-NET). Kidney Int. 2019;95(3):501–5

[2]Data from Chinese National Renal Data Registry

[‡]Sources: National Bureau of Statistics of People's Republic of China. http://www.stats.gov.cn/tjsj/zxfb/202002/t20200228_1728913.html

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Introduction

People's Republic of China (PRC) is a big country with an area of 9.6 million km^2 and over 1.4 billion population. It has 34 provincial-level administrative units: 23 provinces, 4 municipalities (Beijing, Tianjin, Shanghai, Chongqing), 5 autonomous regions (Guangxi, Inner Mongolia, Tibet, Ningxia, Xinjiang), and 2 special administrative regions (Hong Kong, Macau) with a total of 686 cities (Fig. 20.1). To the Han Chinese population, the territory of the country is defined by the regions of Tibet, Inner Mongolia, and Manchuria and the Xinjiang Province which is the most western land of China. China is the fourth largest country in the world after the United States of America, Russia, and Canada. China has great physical diversity. The eastern plains and southern coasts of the country consist of fertile lowlands and foothills and represent most of China's agricultural output and human population. The southern areas of the country (South of the Yangtze River) consist of hilly and mountainous terrain. The west and north of the country are dominated by sunken basins, rolling plateaus, and towering massifs and contain part of the highest tableland on earth, the Tibetan Plateau, and have much lower agricultural potential and population.

The people of China have gradually moved from rural farming areas to business-centered cities. The annual rate of increase in urbanization from 2015 to 2018 was 2.42%. Currently, China has an urban population of 59.3%. The most populated urban areas are Shanghai 25.582 million, Tianjin 13.215 million, Guangdong 12.683 million, Beijing (capital) 19.618 million, Shenzhen 11.908 million, and Chongqing 14.838 million. The life expectancy for the total population stands at 75.7 years in 2016 with men averaged out at 73.6 years and women 78 years [1].

The Chinese Mainland has a three-tiered system for healthcare delivery that remains today, consisting of large hospitals (first tier), intermediary hospitals (second tier), and community-based services/facilities (third tier). The public health sector is the main healthcare provider. In 2017, 82% of inpatient care was provided by public hospitals [2].

The central government is responsible for overall national health legislation, policy, and administration and is guided by the working principle of universal health coverage. However, benefits remain low, and quality and extent of care and coverage vary widely. Co-pays are often very high, certain drugs are excluded from coverage, and out-of-pocket expenses are insufficiently reimbursed. The out-of-pocket cost issue is the most pressing, especially in rural areas. In 2013, out-of-pocket spending per capita accounted approximately 34% of total healthcare expenditures [3].

The 2009 reform (the 12th 5-year plan) of the Chinese government was set out to establish a more affordable system to supply essential drugs for all levels of medical facilities and achieve national comprehensive universal health insurance coverage by 2020, by shifting resources into primary care. It included measures to strengthen a nationwide network of community health clinics and also train primary care physicians in order to divert resources away from the expensive acute hospital system. A key initiative involved the development of "medical alliances" which consists of group of hospitals including a tertiary hospital and primary care facilities that work together in a more coordinated fashion. It was hoped that this type of care coordination would meet the demand for chronic disease care and help to better contain rising costs and improve healthcare quality [4, 5].

In 2014, the Chinese Mainland spent approximately 5.6% of its gross domestic product (GDP) (3531 billion Renminbi) on healthcare, lower than most developed nations in the Organization for Economic Cooperation and Development (OECD), with 30% funded by central government and local government and 38% by publicly financed health insurance, private health insurance, or social health donations [4]. In 2018, the total healthcare expenditure was around 6.39% of its GDP (data from Bloomberg 2019 Nov). Trends in total healthcare expenditure by the government and social health insurance system showed bigger increases than out-of-pocket payments between 2000 and 2017 [5]. The Chinese Mainland has three main basic health insurance schemes – rural and urban resident-based health insurance, which are funded mainly by government subsidies (about 70% of the total funds), and employee-based health insurance funded by employer and employee contributions. Publicly financed insurance consisted of urban employment-based basic medical insurance launched in 1988, urban resident basic medical insurance launched in 2009 (which provides coverage for urban residents without formal employment), and the new cooperative medical scheme for rural residents launched in 2003 which covered more than 90% of all rural residents in 2010. A brief overview of the three main insurance schemes is outlined in Table 20.1 [6].

The health system reform in the Chinese Mainland in the past decade covered five main areas: social health security, essential medicines, primary healthcare, basic public health service package, and public hospitals. The reform policies were designed to tackle access to healthcare and financial protection. Some key progress made in health reform policies included the following: (a) 95% of the population covered by the social health insurance schemes by the end of 2017; (b) catastrophic illness insurance systems were established in all provinces; (c) the Chinese government has invested ¥ 965 billion in primary

Provinces (省)					***Claimed Province***
• Anhui (安徽省) • Fujian (福建省) • Gansu (甘肃省) • Guangdong (广东省) • Guizhou (贵州省)	• Hainan (海南省) • Hebei (河北省) • Heilongjiang (黑龙江省) • Henan (河南省) • Hubei (湖北省)	• Hunan (湖南省) • Jiangsu (江苏省) • Jiangxi (江西省) • Jilin (吉林省) • Liaoning (辽宁省)	• Qinghai (青海省) • Shaanxi (陕西省) • Shandong (山东省) • Shanxi (山西省) • Sichuan (四川省)	• Yunnan (云南省) • Zhejiang (浙江省)	• *Taiwan* (台湾省) *governed by R.O.China*

Autonomous regions (自治区)	Municipalities (直辖市)	Special administrative regions (特别行政区)
• Guangxi (广西壮族自治区) • Inner Mongolia / *Nei Menggu* (内蒙古自治区) • Ningxia (宁夏回族自治区) • Xinjiang (新疆维吾尔自治区) • Tibet / *Xizang* (西藏自治区)	• Beijing (北京市) • Chongqing (重庆市) • Shanghai (上海市) • Tianjin (天津市)	• Hong Kong / *Xianggang* (香港特别行政区) • Macau / *Aomen* (澳门特别行政区)

Fig. 20.1 Map of China, provinces, municipalities, special administrative regions, and autonomous regions

Table 20.1 An overview of major health insurance schemes in the Chinese Mainland

	Urban employee basic medical insurance (UEBMI)	Urban resident basic medical insurance	New rural cooperative medical insurance
Year introduced	1998	2007	2003
Insured population	Urban employees	Urban residents who are not covered by UEBMI	Rural residents
Number of insured by 2010 year-end (million)	237	195	836
General outpatient services	Covered	Limited and vary by location	Limited and vary by location
Outpatient services for catastrophic illnesses	Covered	Covered	Covered
Inpatient services	Covered	Covered	Covered
Premium paid by	Employer and employee	Government and insured individual	Government and insured individual

Reference source: Nofri [6]

healthcare; government budgets for community and township health centers have increased by 20%; (d) tiered healthcare system providers (tertiary, secondary, and primary) were started in 95% of municipalities by the end of 2017; (e) clinical pathways for 442 diseases were developed by the end of 2015 and 65% of secondary and tertiary hospitals implemented case-based payment reform by the end of 2017; (f) pricing policies also improved with removal of price mark-ups of drugs as a source of finance for public hospitals or primary healthcare providers; and (g) integration of rural and urban basic health insurance systems is also currently underway [5].

In 2016, Mr. Xi released the country's first long-term blueprint to improve healthcare since the nation's founding in 1949, called Healthy China 2030, which pledged to bolster health innovation and make access to medical care more equal and achieve health targets aligned with the United Nation's sustainable development goals. Healthy China 2030 was built on four core principles, namely, health priority, innovation, scientific development, and justice and equity (Fig. 20.2). The blueprint emphasized the importance of both prevention and cure, focusing on prevention and control, Chinese and Western medicine, and changes in service mode to reduce gaps in basic health services. The rural areas of the country are given special attention to promote equal access to basic public health services and to maintain public welfare. Furthermore, healthcare is prioritized and placed in a strategic position in public policy implementation [7].

Brief History of Nephrology: How Nephrology Began in the Country

In 1977, the "Nephritis Symposium" held in Beidaihe City served as a landmark for the official founding of the Chinese Society of Nephrology (CSN) in 1980, under the auspices of Chinese Medical Association. During the symposium, Chinese nephrologist experts reached a consensus on the classification, clinical diagnosis, and treatment of primary glomerular diseases. After nearly 40 years' efforts, Chinese nephrologists established a comprehensive guide on the diagnosis and treatment of glomerular diseases.

Renal replacement therapy (RRT) was first available in the Chinese Mainland between the 1960s and 1970s. Peritoneal dialysis (PD) was first used to treat patient with acute renal failure (AKI) in 1963, and continuous ambulatory peritoneal dialysis (CAPD) in 1978, as a RRT modality for patients with chronic renal failure at the First Affiliated Hospital of Sun Yat-sen University in Guangzhou. Since the 1970s, hemodialysis (HD) has been widely adopted as a RRT modality. The first kidney transplantation operation was successfully conducted in 1960 at the Peking University First Hospital by Dr. Jieping Wu, and the first kidney transplantation with long-term patient survival was done by Dr. Huamei of the First Affiliated Hospital of Sun Yat-sen University and Dr. Huijuan Yu of Beijing Friendship Hospital in 1972 in Guangzhou.

Over the years, CSN working in close partnerships with the Chinese government has made significant progress in improving the standard and quality of the healthcare system and care delivery models for patients with kidney disease in the Chinese Mainland. At the same time, CSN has provided continuous medical education for health professionals and nephrology specialist training. CSN launched the National Dialysis Registry in 1999 with the first electronic registry established in 2009. A total of 14,000 HD patients and 6000 PD patients' data has been captured in the registry since 2009. CSN has been working closely with the Chinese government to update the Dialysis Registry. In 2010, the Chinese National Renal Data System (CNRDS) was launched [8]. There is also significant development and progress made in

13 Core Indicators under 5 health themes				
Health level	Healthy life	Health services and security	Environmental health	Health industry
1. Average life expectancy	1. Number of people doing physical exercise	1. Proportion of personal health spending in the total health expenditure	1. Rate of good air quality of all cities at prefecture level or above	1. Total investment scale of health services
2. Mortality rate of infants	2. Level of health literacy among residents	2. Number of registered doctors and registered nurses per 1000 residents	2. Rate of surface water quality better than III	
3. Mortality rate of children <5years age		3. Premature mortality as a result of major non-communicable diseases		
4. Mortality rate of pregnant women				
5. Proportion of those meeting the national physical determination standard among urban and rural residents				

Fig. 20.2 Framework of Healthy China 2030 vision with 4 key principles, namely, health priority, reform and innovation, scientific development, and justice and equity, and 13 core indicators under 5 main themes in health

kidney research from basic science to epidemiology and clinical trials in the Chinese Mainland in the last 40 years. Professional nephrology associations were established at both provincial and city level across the entire country. The number of participants at the CSN annual meeting has increased dramatically in the last 40 years from having only a dozen of participants in the initial years to now over 10,000 participants in 2018.

To tackle the growing burden of chronic kidney disease (CKD), CSN has continued to advocate efforts on CKD prevention, screening, early detection, and treatment with an aim to delay the progression of CKD, reduce the need for RRT, improve patients' quality of life and survival, reduce complications and hospitalizations, and reduce healthcare expenditure. CSN has partnered with several other key international nephrology societies and organizations to facilitate further development of kidney care and research and to reduce the burden of kidney diseases in the Chinese Mainland.

Highlights of Nephrology in the Chinese Mainland

Nephrologists in the Chinese Mainland have conducted nationally representative studies to examine the burden of different kidney diseases. These data form an important basis to guide the government's decision-making on healthcare policies and financing on kidney disease care in the Chinese Mainland. CKD is a public health issue. A cross-sectional survey conducted in a nationally representative sample of adults in China in 2012 showed that the overall prevalence of CKD was 10.8% (95% CI [confidence intervals] 10.2–11.3) and was higher in the northern (16.9% [95%CI 15.1–18.7]) and southwestern (18.3% [95% CI 16.4–20.4]) regions compared with other regions. The degree of kidney damage was associated with the socioeconomic status of each region, in that patients from regions with lower socioeconomic status had more kidney damage [9]. Subsequent to this national cross-sectional survey, the prevalence of CKD in China was reported from two other sources. First is the Hospital Quality Monitoring System (HQMS), a mandatory national, hospitalized patients' database set up by the National Health Commission of China that tracks all hospitalized patients' discharge records from tertiary hospitals in the Chinese Mainland between 2010 and 2015. In contrast to tertiary hospitals in developed countries, tertiary hospitals in the Chinese Mainland provide primary, secondary, and tertiary care and have a nationwide catchment of a nonselective patient population. The database contains data of 35.3 million patients hospitalized between 2010 and 2015. Second, there was a general population-based study with a nationally representative sample of 47,204 subjects recruited between 2009 and 2010. Data from these two additional sources have shown that CKD related to diabetic kidney disease (DKD) is now more common than CKD related to glomerular disease (GD) in both the general population cohort and in the hospitalized patients' database since 2011 [10].

A nationwide, cross-sectional survey of adult hospitalized patients in 2013 showed that AKI also incurred enormous financial burden to the healthcare system in the Chinese Mainland. In addition, AKI was substantially underdiagnosed and undertreated, reflecting a huge service gap and unmet need in early detection and early initiation of treatment for hospitalized patients with AKI and lack of accessibility to acute dialysis support for AKI in rural parts of China. Many other developing countries in the world also face similar problems. The findings urged nephrologists in China to take up the lead and responsibility to improve AKI detection and improve accessibility to acute dialysis support for AKI [11].

The CNRDS, a nationwide kidney failure (ESRD) data collection system, is a landmark development of nephrology for the Chinese Mainland in 2010. It contains the largest and most comprehensive national ESRD patients' registration. By the end of 2017, the CNRDS included data of 524,467 HD patients and 86,344 PD patients from 5479 HD centers and 981 PD centers, respectively, covering 31 provinces, autonomous regions, and municipalities. The registry provides information on the national burden of ESRD as well as the prevalence, incidence, and severity of CKD in the Chinese Mainland and helps to raise the government's awareness of the importance and burden of ESRD. Most important of all, it prompts national coverage of ESRD in the country's Critical Illness Insurance Program. The CNRDS Annual Data Report (ADR) provides the annual number of prevalent and incident dialysis patients and their mortality rates, enabling quality assurance of kidney care delivered. The CNRDS also enables monitoring of various ESRD-related complications including anemia and mineral and bone disorder so to assure quality of care for various ESRD-related complications.

Academic nephrologists in the Chinese Mainland also play an increasingly important role in conducting global clinical trials that made an impact to the global clinical practice guidelines (CPGs) development. Some examples are the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study [12], the Study of Diabetic Nephropathy with Atrasentan (SONAR) [13], and the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) [14].

Chinese nephrologists also contributed to the development of many international CPGs, including those of Kidney Disease: Improving Global Outcomes (KDIGO), International Society for Peritoneal Dialysis (ISPD), International IgA Nephropathy Network (IIgANN), and Renal Pathology Society (RPS). Chinese nephrologists also involved in steering clinical trials on roxadustat treatment for anemia in patients with kidney disease undergoing long-term dialysis and in non-dialysis CKD patients [15, 16]. Based on the results of these trials, roxadustat was recently approved as a new drug treatment for renal anemia in patients with kidney disease in the Chinese Mainland. These landmark trials marked the emerging role of Chinese nephrologists in leading global clinical trials in kidney diseases.

Chinese nephrologists also performed significant groundbreaking work in basic research in kidney diseases. Mutations in two genes, polycystic kidney disease-1 (PKD1) and PKD2, accounted for most cases of autosomal dominant polycystic kidney disease (ADPKD). A research group from China reported the 3.6-angstrom cryo-electron microscopic structure of truncated human PKD1-PKD2 complex assembled in a 1:3 ratio and established a framework for dissecting the function and disease mechanisms of the PKD proteins [17]. The study, for the first time, identified the structure of transient receptor potential channel family hetero-complex for further study to understand the pathogenesis of PKD.

A two-stage genome-wide association study (GWAS) of IgAN in the Han Chinese showed that IgAN was associated with variants near genes involved in innate immunity and inflammation [18]. This work from China contributed significantly to the understanding of genetic factors in the pathogenesis of complex kidney diseases and provided important evidence that genetic factors play an important role in the pathogenesis of IgAN.

Prevalence and Awareness of CKD

The Chinese Mainland has not had a national surveillance system for kidney disease until recently. This constitutes an important barrier to understand the exact scope of the problem and develop effective preventive and therapeutic strategies. In a cross-sectional nationwide survey of a representative adult population in the Chinese Mainland between 2009 and 2010, the overall prevalence of CKD was estimated around 10.8% [9], being comparable to that of developed countries such as the United States (US) (13.0%) [19] and Norway (10.2%) [20]. It also implies that the Chinese Mainland has nearly 119.5 million adults with kidney disease. However, the prevalence and severity of CKD vary according to the economic development of the region, defined by the National Bureau of Statistics

Table 20.2 Prevalence of CKD (%) in the Chinese Mainland stratified by geographical region and urban or rural residency (%)

	eGFR <60 mL/min/1.73 m^2	Albuminuria	CKD
Region			
East	1.1	7.5	8.4
South	1.3	6.0	6.7
Middle	1.4	13.1	14.2
North	2.5	15.4	16.9
Northwest	1.5	5.6	6.7
Southwest	3.8	15.1	18.3
Residency			
Urban	2.3	7.0	8.9
Rural	1.6	10.1	11.3
Total	1.7	9.4	10.8

Note: Data were age- and gender-adjusted prevalence (%). Albuminuria was defined as a urinary albumin-to-creatinine ratio > 30 mg/g creatinine. CKD was defined as eGFR <60 mL/min/1.73 m^2 or albuminuria
Abbreviations: *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate

(Table 20.2). As an example, the prevalence of CKD was higher in the north (16.9%) and southwest (18.3%) regions compared to other regions (Table 20.2) [9]. Rural areas showed lower prevalence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, but higher prevalence of albuminuria, compared with urban areas [1]. Furthermore, the prevalence of albuminuria was positively associated with economic status (evaluated by GDP) in rural areas but negatively associated with economic status in urban areas [1].

Most subjects (84%) presented in early stages of CKD with albuminuria and well-preserved kidney function [9]. This indicates the potential to institute early CKD screening, detection, and prevention programs as well as education campaigns to raise more awareness of the importance of kidney health. In a more recent comparative study between China and the USA, the prevalence of eGFR <60 mL/min/1.73 m^2 was higher in the USA than in China (6.5% vs. 2.7%) [21]. Nearly two-thirds of this difference was accounted for by the higher prevalence of various CKD risk factors, including increasing age, male gender, diabetes, hypertension, central obesity, cardiovascular disease (CVD), and hyperuricemia in the USA [21].

The Chinese Center for Disease Control and Prevention included both eGFR and urine albumin-creatinine ratio, in the China Chronic Disease and Nutrition Surveillance in 2018, a nationally representative adult population from 302 monitoring sites, in order to estimate the latest prevalence of CKD in the Chinese Mainland. Despite a high prevalence of CKD, the awareness of CKD diagnosis was low (10.04%) [22]. Subjects with advanced CKD were more aware of their diagnosis (15.6% for normoalbuminuria and 61.8% for albuminuria group) than those with early CKD or with normoalbuminuria (7.7–16.7%) [22]. The National Health and Nutrition Examination Survey (NHANES) 1999–2004 showed that 6.0% of CKD subjects in the USA were aware of their diagnosis [23], an awareness rate lower than that reported in China. Compared with those unaware of their CKD diagnosis, subjects aware of their CKD diagnosis were more likely to be educated, have free medical insurance, received health examination during the previous 2 years, and have hypertension, family history of kidney disease, and self-report concern about kidney disease [22].

Burden of Kidney Failure

The growing burden of CKD in China implies an increasing population requiring RRT [24]. The China Kidney Disease Network (CK-NET) developed a national surveillance system for kidney diseases by integrating national administrative and claims data that covers millions of CKD subjects from all regions of China. According to the CK-NET 2015 ADR, the estimated prevalence of HD and PD was 402.18 and 39.95 per million population (pmp), respectively, and the age-adjusted incidence rate for dialysis was 122.19 pmp [25]. The prevalence rates of dialysis population were higher than that reported previously for the Chinese Mainland [26]. Although HD and PD patients in total constituted only a small percentage (0.16% and 0.02%, respectively) of the entire insured population in the Chinese Mainland, they incurred a disproportionately high percentage of healthcare expenditures (2.08% and 0.34%, respectively) [25].

The Beijing Regional HD Registry and Shanghai Renal Registry reported that the prevalence and incidence of maintenance HD in 2011 were 524.6 pmp and 107.3 pmp in Beijing [27] and 544.7 pmp and 82.9 pmp in Shanghai [28], respectively. The prevalence of ESRD was still lower in the Chinese Mainland than in most other parts of Asia such as Taiwan (2285 pmp in 2007) and Japan (2233 pmp in 2007) [29]. Factors contributing to the very different prevalence rates of ESRD in the Chinese Mainland versus other Asian countries may be related to limited affordability and poor accessibility to RRT in less developed regions [30]. With government support, the number of HD centers has grown to more than 4000 in 2015 [31]. New HD facilities were set up at both county level and township level to improve accessibility and provision of HD service in less developed regions of the Chinese Mainland.

Evolving Spectrum of Causes of CKD/ESRD

The relative proportion of various causes of ESRD varies according to the race and geographical regions of China [32]. Diabetes is a leading cause, accounting for one-third of all incident ESRD patients worldwide [33]. However, this differs from the Chinese Mainland, where GD is the predominant cause of ESRD. Data from the CNRDS 2015 showed that GD was the most common cause of ESRD (54.2%), followed by diabetes (17.0%) and hypertension (9.9%) [31].

The rapid urbanization of the Chinese Mainland in the last three decades with dramatic changes in lifestyle and dietary habits of native Chinese resulted in a very considerable increase in the burden of various metabolic and noncommunicable diseases such as obesity, diabetes, and hypertension [34]. The prevalence of obesity has increased from 0.6% in 1982 to 2.9% in 2002 [35], and that of diabetes has increased from 0.7% in 1980 [36] to 10.9% in 2013 [37]. The substantial burden of noncommunicable diseases has increased the incidence and prevalence of CKD and changed the relative proportion of causes of CKD/ESRD in the Chinese Mainland over the years.

Data from HQMS showed that CKD patients constituted 4.8% of all hospitalized patients in the Chinese Mainland. The most common causes of CKD in hospitalized patients were DKD (27.0%), hypertensive nephropathy (HTN) (20.8%), obstructive nephropathy (ON) (15.6%), and GD (15.1%) (Fig. 20.3). An increasing number of hospitalizations were observed in patients with CKD due to diabetes [10]. The relative proportion of different causes of CKD varies according to the socioeconomic status and geographic areas (Fig. 20.4). For example, DKD (32.7%) and HTN (23.0%) were the leading causes of CKD in hospitalized patients in urban areas. However, in rural areas, the top 3 leading causes of CKD were ON (21.4%), GD (18.5%), and DKD (17.4%) in hospitalized patients (Fig. 20.2) [38]. In North China, the percentage of hospitalized patients with CKD due to diabetes was higher among residents from urban than rural areas, while more hospitalized CKD patients in rural areas had GD than urban areas [38]. On the other hand, South China had higher prevalence of CKD due to ON than North China [38] (Fig. 20.3) [10]. In 2017, 1.14% of all hospitalized patients had CKD due to DKD and 0.68% of all hospitalized patients had CKD due to GD (unpublished data). The HQMS also showed an increasing proportion of hypertensive kidney disease and ON (mostly associated with kidney stones) as causes of CKD between 2010 and 2015 [38].

In the last decade, GD was a principal cause of CKD in the Chinese Mainland [10, 39], accounting for nearly half of the causes of ESRD in dialysis patients in 1999 [40]. However, its prevalence has decreased since 2013 [10]. The percentage of hospitalized patients with CKD due to IgAN decreased from 19.0% in 2010 to 10.6% in 2015 [41]. In a nationwide survey conducted in 938 hospitals (both tertiary and community hospitals) between 2004 and 2014 [42] including 71,151 biopsy-proven GD, IgAN (36.3%) was the most common primary GD, followed by

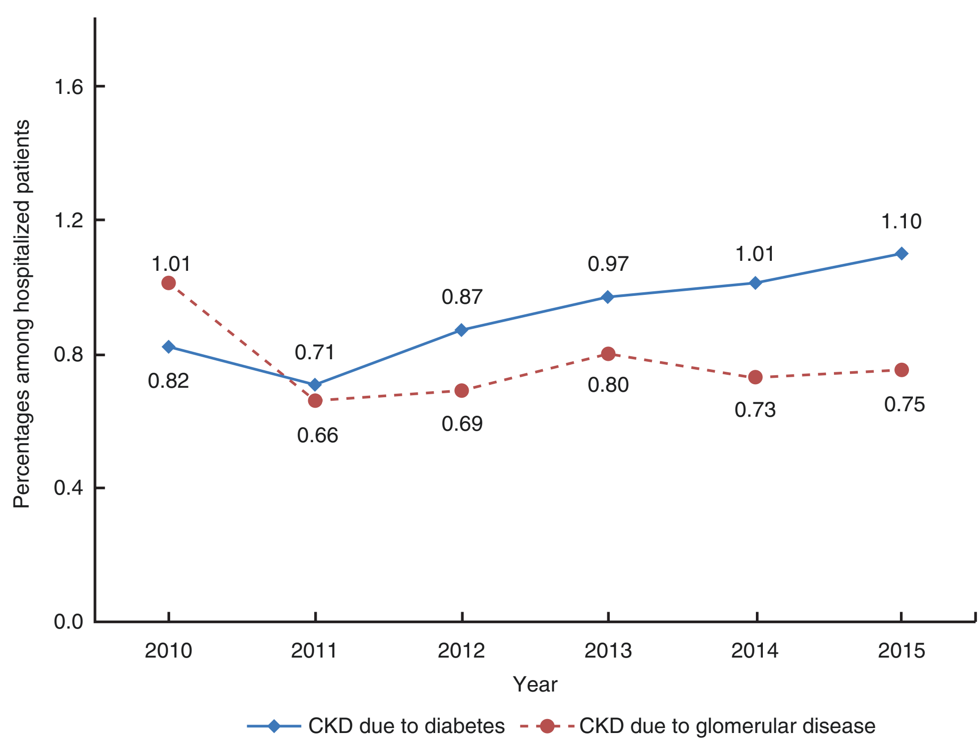


Fig. 20.3 Trends in CKD due to diabetes or GD among hospitalized patients in the Chinese Mainland from 2010 to 2015. Percentages were calculated based on the overall numbers of hospitalized patients for each year, obtained from the Hospital Quality Monitoring System. Abbreviations: CKD, chronic kidney disease; GD, glomerular disease

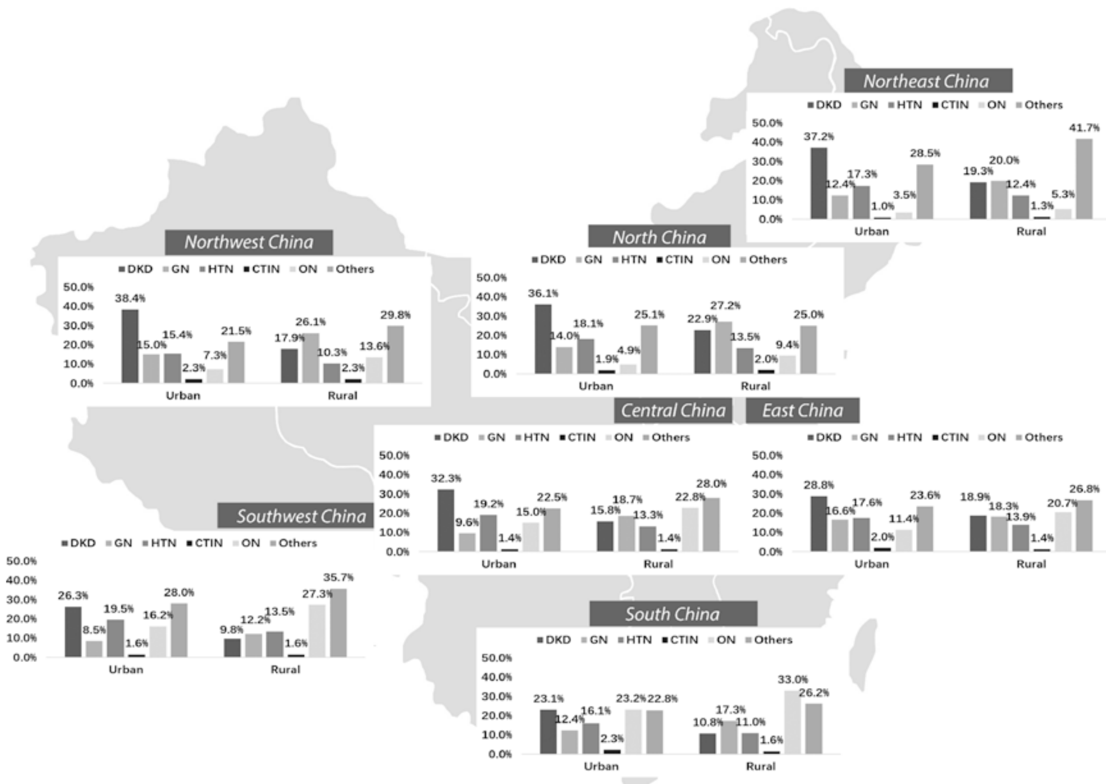
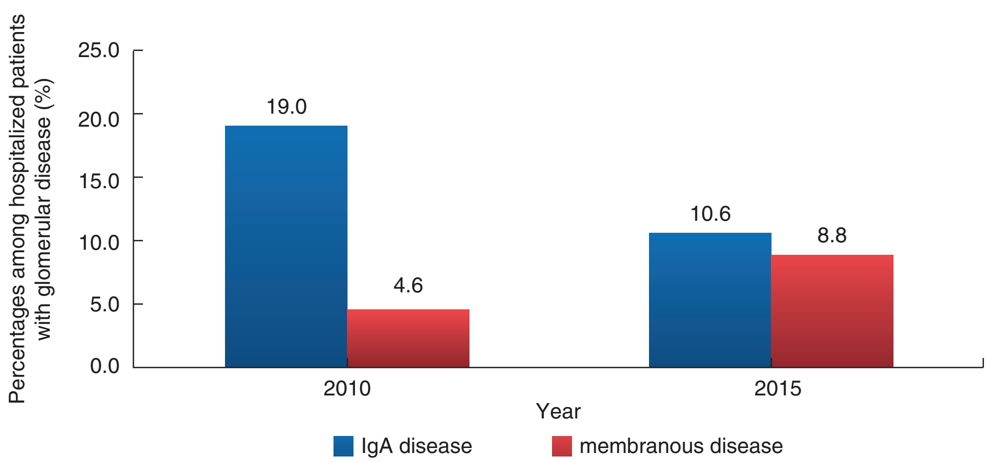


Fig. 20.4 Proportion of various causes of CKD stratified by geographic regions among hospitalized population with CKD in 2015. Note: numbers represented percentages among patients with CKD. Reproduced from Huang et al. [38]. (With permission from John Wiley and Sons, Inc). Abbreviations: DKD diabetic kidney disease, GN glomerulonephritis, HTN hypertensive nephropathy, CTIN chronic tubulointerstitial nephritis, ON obstructive nephropathy

Fig. 20.5 Proportion of IgA disease and membranous disease among hospitalized patients with primary glomerular nephropathy in 2010 and 2015. Note: numbers represented percentages among hospitalized patients with primary glomerular nephropathy



membranous nephropathy (MN) (30.2%) with age and region standardization. In adults aged <45 years, IgAN was a leading cause of primary GD. However, in adults aged >45 years, MN was the most frequent primary GD. Lupus nephritis and vasculitis-related nephritis were the most common secondary GD [41]. The proportion of hospitalized patients with CKD due to MN almost doubled, from 4.6% in 2010 to 8.8% in 2015 (Fig. 20.5), possibly partly attributed to long-term exposure to air particulate matter (PM) that posed a serious environmental hazard in some parts, especially in the northern region. Each 10 μg/m^3 increase in $PM_{2.5}$ was associated with a 14% higher odds of MN in regions with $PM_{2.5} > 70$ μg/m^3 compared to regions with $PM_{2.5} < 70$ μg/m^3 [42].

IgA Nephropathy (IgAN)

Three genome-wide association studies (GWAS) in the Chinese population [18, 43, 44] identified five genetic loci associated with IgAN [43]. Besides three independent loci in human leukocyte antigen (HLA) regions, variants in the complement factor H (CFH) and the related CFHR3 and CFHR1 genes on chromosome 1q32 that affected complement activation through their influence on CFH levels and genetic variants of oncostatin M (OSM) and interleukin 6 family (LIF) on chromosome 22q12 may predispose individuals to develop IgAN [45]. A subsequent GWAS in the Chinese population identified two additional loci: 17p13 containing TNF superfamily member 13 (TNFSF13) and 8p23 containing defensin alpha (DEFA) [18]. Polymorphisms within the DEFA genes were involved in gene transcription regulation, and associated with clinical phenotype of gross hematuria, suggesting mucosal immunity may involve in the pathogenesis of IgAN [46, 47]. Another GWAS [44] in 20,612 individuals of European and East Asian origin identified six new loci that increased susceptibility to IgAN, namely, four in integrin subunit alpha M-X (ITGAM-ITGAX), vav guanine nucleotide exchange factor 3 (VAV3), and caspase recruitment domain family member 9 (CARD9) and two at HLA-DQB1 and DEFA. This suggests interaction between the host and intestinal pathogens may play a possible role in shaping genetic predisposition to IgAN [44].

Glycosyltransferases are involved in the synthesis of the O-glycan of IgA1 molecules, and abnormal O-glycosylation of IgA1 molecules is involved in the pathogenesis of IgAN [48, 49]. One protective (YATIG) and two risk (YAGDA, YATDG) regulatory haplotypes in key glycosyltransferase genes for IgA1 O-glycosylation (C1GALT1) gene were associated with IgAN [50]. ADG haplotype in the promoter region of ST6GALNAC2, a key glycosyltransferase gene, has functional significance in increasing predisposition to IgAN [51]. Association has been demonstrated between C1GALT1 and ST6GALNAC2 gene with IgA1 glycosylation, as well as with the severity of IgAN [52].

The TESTING study [12] was a multicenter, double-blind, randomized controlled trial (RCT) that evaluated the efficacy and safety of corticosteroids in IgAN patients with proteinuria >1 g/day and eGFR between 20 and 120 mL/min/1.73 m^2, after at least 3 months of blood pressure control with renin-angiotensin-aldosterone system (RAAS) blockade. Study recruitment was discontinued after 262 subjects entered study and followed for a median of 2.1 years, because of significantly more serious adverse events in the methylprednisolone group (14.7%) than placebo group (3.2%) (p = 0.001; risk difference 11.5%), mostly due to serious infections (8.1% vs. 0; risk difference 8.1%; p < 0.001), including two deaths. However, methylprednisolone group showed significant benefits in reducing the incidence of primary renal endpoint (5.9%) than placebo (15.9%) with a risk reduction of 63% (p = 0.02). The study protocol was amended using a reduced dose of methylprednisolone with septrin as prophylaxis and is currently ongoing.

Another recent multicenter RCT from the Chinese Mainland [53], comparing mycophenolate mofetil (MMF) plus prednisone versus full-dose prednisone in IgAN with active proliferative lesions, failed to show renal benefits with MMF, but combining MMF with prednisolone showed fewer adverse events compared to full-dose prednisolone.

In a prospective follow-up study of IgAN in the Chinese Mainland (mean follow-up, 45 months) of which subjects received mainly RAS inhibitors and steroids added, if persistent proteinuria (n = 703) [54], the mean eGFR decline was −3.1 ml/min/1.73 m^2 per year, and annual rate of ESRD was 2.3%. Baseline eGFR (hazard ratio, 0.76 per 10 ml/min/1.73 m^2), proteinuria at 6 months (hazard ratio, 1.53 per 1 g/day), and systolic blood pressure at 6 months (hazard ratio, 1.36 per 10 mmHg) were associated with an increased risk of composite kidney failure events using multivariable Cox regression analysis. Baseline eGFR (regression coefficient, 20.1), time-averaged proteinuria (regression coefficient, 20.2), and time-averaged mean arterial pressure (regression coefficient, 20.15) were independent predictors of eGFR slope by linear regression.

Membranous Nephropathy (MN)

The prevalence of MN has increased quite substantially in the Chinese Mainland in the last 10 years. A nationwide survey of biopsy-proven GD showed that MN accounted for 12.2% of all GD in 2004 but doubled to 24.9% in 2014 (24.9%). The proportion of other major GD has remained similar [42]. This meant that the percentage of MN has increased by an average of 13% per year. Among hospitalized patients with primary GD, MN increased from 4.5% in 2010 to 8.8% in 2015 [55] (Fig. 20.5). Notably, the proportion of MN exceeded that of IgAN in the northern and northeastern China since 2014 and is now the leading cause of GD in these regions.

Air pollution has become a serious public health problem in some cities in the Chinese Mainland and may account for the rising prevalence of MN. Between 2004 and 2014 [56], the 3-year average levels of aerosol optical depth (AOD)-derived $PM_{2.5}$ have increased and plateaued in 2008, with a mean ambient level of 55.6 μg/m^3 (range, 8.1–110.5 μg/m^3). The aerosol level of $PM_{2.5}$ was much higher than that reported in many developed countries. Indeed, a nationwide survey [42] showed that long-term exposure to high levels of $PM_{2.5}$ was associated with an increased risk of MN. Every 10 μg/

m^3 increase in $PM_{2.5}$ concentration was associated with a 14% higher odds of MN in the regions with a $PM_{2.5} > 70$ μg/m^3. Assuming a causal relationship, 15.2% of MN in the Chinese Mainland may be attributed to $PM_{2.5}$ exposure. HQMS data showed that these patients were clustered in the Hebei Province and Guangxi Province [55]. The association between $PM_{2.5}$ exposure and an increased risk of MN was confirmed in the Northern region demarcated by the Yangtze River. On the other hand, in Southern China, the Zhuang population, the largest minority population in China, showed a high preponderance of MN, but MN in this population was not associated with $PM_{2.5}$ exposure [55]. These data showed how genes and environmental factors may both contribute to an increased risk of MN in the Chinese Mainland.

In a cross-sectional study (n = 578) in the Chinese Mainland [57], 89% of patients with MN were phospholipase A2 receptor (PLA2R)-associated, including 68% with circulating anti-PLA2R antibodies and 21% negative for the antibody but showing granular expression of PLA2R in glomeruli. Eleven percent had no detectable anti-PLA2R antibody or PLA2R antigen in immune deposits. Two percent had thrombospondin type I domain-containing 7A (THSD7A)-associated MN, which accounted for 16% of the PLA2R-negative patients. These percentages were similar to those reported in the Western population.

A GWAS of primary MN identified two significant genetic loci: chromosome 2q24 containing the PLA2R1 gene (SNP rs4664308) and chromosome 6p21 containing the HLA complex class II HLA-DQα1 chain (HLA-DQA1) (SNP rs2187668), with strong gene-gene interactions between the two risk alleles [58]. Validation studies in China showed that individuals carrying these risk alleles were strongly associated with positive serum anti-PLA2R antibodies (73%) and glomerular expression of PLA2R (75%) [59]. In contrast, among individuals who did not carry these genotypes, none had anti-PLA2R antibodies and glomerular expression of PLA2R was weak or absent. This suggested that individuals carrying these risk alleles were predisposed to the generation of circulating anti-PLA2R autoantibodies that contribute to the pathogenesis of MN.

Three other studies from the Chinese Mainland also provided novel insights into the contribution of specific HLA alleles in primary MN [60–62]. A case-control association analysis identified DRB1*1501 and DRB1*0301 as increasing the risk of primary MN among Han Chinese. Both HLA alleles exhibited interactions with PLA2R1 variant rs4664308 and were associated with circulating anti-PLA2R antibodies [60]. Another study demonstrated the association of DRB1*1501 with anti-PLA2R-positive MN and suggested DRB3*0202 as the second independent risk factor for MN. DRB3*0202 resides on the same haplotype as DRB1*0301 [61]. Extending these findings, another study showed that DRB1*0301 was associated with higher level of anti-PLA2R antibodies and DRB1*1502 was associated with lower eGFR at baseline, a worse renal outcome, and a higher risk of ESRD [62].

In a follow-up study (n = 371) in the Chinese Mainland [63], 68.5% of patients were treated with immunosuppressive agents with or without corticosteroids, and the others by RAS blockade alone. During a median follow-up of 27 months, 87.6% achieved remission (of which 45.3% had complete remission and 42.3% had partial remission). Relapse occurred in 27.7% and 2.2% progressed to ESRD, while 18.1% experienced worsening kidney function with eGFR decline over 50%. Multivariable Cox regression analysis identified the positivity of anti-PLA2R antibodies (HR = 2.5, p = 0.009) and failure to remit (HR = 3.2, p = 0.004) as independent risk factors for worsening kidney function in the Chinese population. The severity of chronic tubule-interstitial injury (HR = 25.8, p = 0.035) and failure to remit (HR = 10.2, p = 0.010) were independent risk factors for ESRD in Chinese.

As in the western population, rituximab induced remission in 41.7% of primary MN not responding to other immunosuppressive therapy (with 36.1% being partial and 5.6% being complete remission) [64]. Those who responded to rituximab had lower baseline levels of anti-PLA2R antibodies and all subjects had antibody depletion or reduction with rituximab.

Minimal Change Disease (MCD)

A nationwide survey of kidney biopsies done in 7962 children <18 years in the Chinese Mainland [65] showed that nephrotic syndrome was the most frequent (50%) presentation and MCD was the most common primary GD (29%) followed by IgAN (17%). Henoch-Schönlein purpura nephritis (13%) and lupus nephritis (9%) were the most common secondary GD. The proportion of MCD was significantly higher in boys (38%) than in girls (13%), whereas lupus nephritis was more prevalent in girls (20%) than in boys (3%). Purpura nephritis (23%) was the major pathological diagnosis in younger children (0–12 years old). MCD (33%) was the most common glomerular disease in adolescents (13–18 years old). The proportions of MCD, purpura nephritis, and MN increased between 2004 and 2014, while the proportion of FSGS declined.

A RCT was conducted in 8 kidney centers in the Chinese Mainland, of which 119 adults with nephrotic syndrome due to MCD (n = 119) were randomized to receive either glucocorticoid or tacrolimus after 10-day treatment of intravenous methylprednisolone (0.8 mg/kg/day). The study showed non-inferiority of tacrolimus monotherapy to glucocorticoid. Remission occurred in 96.2% of glucocorticoid-treated subjects and 98.3% of tacrolimus-treated subjects with no significant difference between them. Relapse rate was similar (49.0% and 45.5%, respectively) for glucocorticoid- and tacrolimus-treated subjects. However, adverse events occurred more frequently in glucocorticoid group [66].

Focal Segmental Glomerulosclerosis (FSGS)

FSGS accounts for 3–4% of primary GD in the Chinese Mainland. Mutations of type IV collagen α3–5 (COL4A3–5) [67], inverted formin 2 (INF2) [68], transient receptor potential cation channel 6 (TRPC6) [69], and α-actinin-4 (ACTN4) [69] may contribute to FSGS development under dominant forms. NPHS1 gene mutations were quite common in sporadic Chinese FSGS patients [70]. Mutations in nuclear pore complex nucleoporin160 kD (NUP160) were implicated in steroid-resistant nephrotic syndrome [71].

Chronic tubulointerstitial injury predicted a worse prognosis of FSGS. Han et al. found that C3a and suPAR drive versican V1 expression in tubular cells by promoting transcription and splicing, respectively, and increases in tubular cell-derived versican V1 induced interstitial fibrosis by activating fibroblasts in FSGS [72].

The efficacy of glucocorticoids in ameliorating FSGS depends on the capacity to expand myeloid-derived suppressor cells (MDSCs). Rapid elevation of MDSCs in peripheral blood may predict the efficacy of glucocorticoids in FSGS [73]. miR-30s protected podocytes by targeting Notch1 and p53 and loss of miR-30s may facilitate podocyte injury. Sustained miR-30 expression may be a novel mechanism underlying the therapeutic effectiveness of corticosteroids in treating podocytopathy [74].

Adult-onset FSGS is often associated with poor response to corticosteroid and immunosuppressive treatment and poor kidney survival. In a cohort ($n = 98$) of Chinese patients with biopsy-proven primary FSGS using treatment recommended by KDIGO guidelines 2012, 84.7% achieved remission during a median follow-up of 58.9 months, 60.2% had relapse, 11.2% progressed to ESRD, and 19.4% had worsening kidney function with serum creatinine increased >30% from baseline or >1.5 mg/dL. Multivariable Cox regression analysis showed that baseline eGFR, combined IgM and C3 deposition, and IgM deposition alone were independent factors predicting worsening kidney function [75].

Lupus Nephritis (LN)

Lupus nephritis is the most common secondary GD in Chinese. Chinese lupus patients showed a higher incidence of kidney involvement (50–60%) compared with Caucasians (30–40%) and had more severe kidney disease with worse long-term outcomes [76, 77]. A large number of genetic variants were associated with systemic lupus erythematosus (SLE) in Chinese. One GWAS in a Chinese Han population identified nine new susceptibility loci (ETS1, IKZF1, RASGRP3, SLC15A4, TNIP1, 7q11.23, 10q11.22, 11q23.3, and 16p11.2) and confirmed seven previously reported susceptibility loci (BLK, IRF5, STAT4, TNFAIP3, TNFSF4, 6q21, and 22q11.21) for SLE [78]. Another GWAS involving a total of 3300 Asian SLE patients from Hong Kong, Mainland China, and Thailand [79] found genetic variants in ETS1 (rs1128334) and WDFY4 (rs7097397) associated with SLE. In a meta-analysis of GWAS in the Chinese Han population with replication in four additional Asian cohorts in a total of 5365 SLE subjects and 10,054 controls [80], genetic variants in or near CDKN1B, TET3, CD80, DRAM1, and ARID5B were associated with SLE. These findings suggest potential roles of cell-cycle regulation, autophagy, and DNA demethylation in the pathogenesis of SLE. Genetic biomarkers that correlated with LN are however limited and require further exploration [81–86].

The first RCT using mycophenolate mofetil (MMF) was conducted in Chinese patients with diffuse proliferative LN [87] and showed a renal remission rate of >80% with 12-month treatment of corticosteroids and MMF, comparable to a sequential regimen of 6-month oral cyclophosphamide induction followed by 6-month maintenance azathioprine. MMF was associated with fewer adverse events including infections as compared with cyclophosphamide. The subsequent Aspreva Lupus Management Study (ALMS) confirmed that Chinese LN patients had similar renal response rates to MMF or intravenous cyclophosphamide induction therapy [88]. Low-dose corticosteroids combined with azathioprine or MMF are now two commonly used maintenance immunosuppressive regimens for LN in China.

In Chinese patients with class IV LN, corticosteroids and cyclosporine also led to significant reduction in proteinuria after 1 month and histological improvement at 1 year with no significant deterioration in serum creatinine or creatinine clearance after a follow-up of 48 months [89]. Dual immunosuppressive treatment with corticosteroids and tacrolimus achieved a response rate similar to that with corticosteroids plus either cyclophosphamide or MMF in the treatment of class III/IV LN [90, 91].

Previous study from the Chinese Mainland showed that triple immunosuppression comprising corticosteroids, tacrolimus, and reduced-dose of MMF was more effective than corticosteroids plus cyclophosphamide in patients with class IV+V LN [92]. More recently [93], this "multi-targeted therapy" was shown to achieve a higher complete remission rate (45.9 vs. 25.6%; $p < 0.001$) and overall response rate (83.5 vs. 63.0%; $p < 0.001$) at 6 months with similar adverse events when compared with corticosteroids and intravenous cyclophosphamide in patients with class III/IV +/− V LN. This multi-targeted therapy, when used as a maintenance treatment in patients who initially responded, showed similar cumulative renal relapse rates and similar eGFR but with fewer adverse events and lower withdrawal rate than maintenance azathioprine [94]. Another study comparing leflunomide with intravenous cyclophosphamide in treating type IV LN in the Chinese Mainland showed comparable complete remission and partial remission rates with the two treatments [95].

Anti-neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV)

AAV nephritis is a common form of secondary GD in elderly Chinese. Data from the HQMS between 2010 and 2015 showed that 0.25% of the hospitalized patients had AAV. The prevalence of AAV was stable throughout the 5-year period, and increased with latitude, and was associated with exposure to carbon monoxide. In Yunnan Province, the prevalence of AAV increased by 1.37-fold after the Zhaotong earthquake in 2014. The Dong population, an ethnic minority of Chinese, showed the highest prevalence of AAV (0.67%). The mean age of diagnosis of AAV was 60.0 ± 15.6 years and 46.4% were men [96].

In Chinese, microscopic polyarteritis (MPA) constituted about 80% of AAV [97, 98]. Even among patients with granulomatosis polyangiitis (GPA), 60% had ANCA specificity for MPO [98]. DQA1*0302 and DQB1*0303 are risk alleles, predisposing to the development of MPO-ANCA AAV in Chinese. HLA-DPB1 variant rs3117242 was also associated with GPA in Han Chinese population [99, 100]. Positive ANCA was also reported in 15–64% of patients receiving propylthiouracil but only a quarter developed clinical vasculitis [101, 102]. Their ANCA was against multiple antigens. Patients with propylthiouracil-induced AAV had less organ involvement and milder kidney lesions, compared to those with primary AAV.

Rituximab is a recent adopted induction and maintenance treatment regimen for AAV. Recent data showed the importance of alternative complement pathway activation in the pathogenesis of human AAV [103–105]. In particular, C5a plays a critical role in ANCA-mediated neutrophil activation. Inhibition of C5a has emerged as a potential therapeutic approach for AAV. Treatment resistance however occurred in 10.7% of patients and around one-third relapsed [106]. Relapses were likely to develop in the same organ as with the disease onset [107].

One center from the Chinese Mainland reported that 33.9% of AAV patients died during follow-up, including 20.9% within the first 12 months after diagnosis. This was before the availability of rituximab [108]. Secondary infection was the leading cause of death in the first year. Other independent predictors included older age, pulmonary involvement of AAV, and initial kidney function. Cardiovascular events became the leading cause of death for those who survived the first year.

Hepatitis B Virus (HBV)-Associated GD

China's HBV prevention program that targeted toward interrupting perinatal transmission has been highly effective. Compared with the survey done before vaccination was available in 1992, the prevalence of HBV surface antigen (HBsAg) positivity has declined 46% in 2006 and 52% in 2014. Among children aged less than 5 years, HBsAg positivity has declined by 97% [109]. Work is ongoing to completely eradicate hepatitis B infection in the Chinese Mainland by 2030.

The China Kadoorie Biobank followed 469,459 participants for a median of 9.1 years (4.2 million person-years) of which 4555 were incident CKD cases. HBsAg-positive subjects showed a 1.37 higher adjusted hazard for incident CKD compared with HBsAg-negative subjects [110].

A single-center review of 11,618 kidney biopsies showed that among the biopsies with a diagnosis of secondary GD, LN accounted for 26.5%, Henoch-Schönlein purpura GD accounted for 25.8%, HBV-associated GD accounted for 14.6%, and DKD accounted for 10.7%. The detection rate of HBV-related GD between 2008 and 2012 (with age adjustment) has declined significantly compared to the period between 1987 and 1992 ($p < 0.001$) [111].

Diabetic Kidney Disease and Obesity-Related Kidney Disease

Prevalence of Diabetes and Obesity in China

China faces a huge burden of diabetes with rapid societal modernization and adoption of a "westernized diet" by many local Chinese. The International Diabetes Federation (IDF) estimated that the burden of diabetes will increase from 90 million population in 2011 to nearly 130 million by 2030 in China [112]. According to the most recent national survey, the overall estimated prevalence of diabetes and prediabetes were 10.9% and 35.7%, respectively, indicating that an estimated 110 million people currently suffer from diabetes in China. Of this population, only 36.5% were aware of the diagnosis of diabetes and 32.2% received antidiabetic medications [37]. The increase in the prevalence of diabetes is attributed mostly to an increase in type II diabetes, which accounts for approximately 95% of

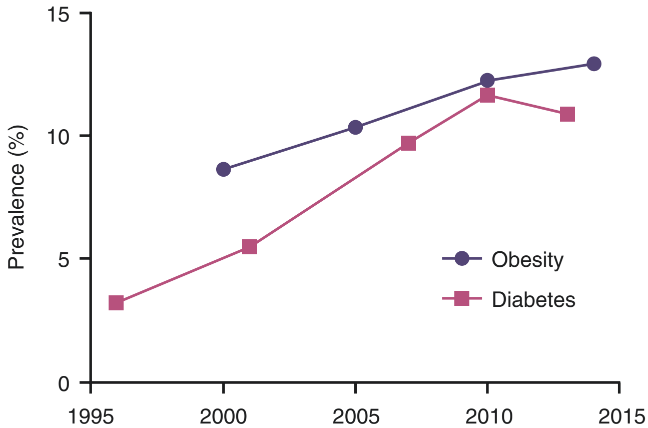


Fig. 20.6 Prevalence of diabetes and obesity in the Chinese Mainland in the last decades. (Date referred to Ma et al. [114] and Tian et al. [115])

all diabetes in the Chinese Mainland. Chinese patients generally have type II diabetes diagnosed at a relatively younger age and with a lower body mass index than the Western population [113].

Similarly, the prevalence of obesity (defined as having a body mass index ≥27.5 kg/m^2 in Chinese) showed a significant increase from 8.6% in 2000 to 10.3% in 2005 and 12.9% in 2014 (Fig. 20.6). The prevalence of central obesity (defined as a waist circumference greater than 90 cm in men and greater than 85 cm in women) has dramatically increased from 13.9% in 2000 to 18.3% in 2005, and 24.9% in 2014, reflecting an enormous public health issue for the Chinese Mainland [115].

Prevalence of Diabetic Kidney Disease (DKD) and Obesity-Related Kidney Disease in China

The dramatic increase in the prevalence of diabetes and obesity in recent years changed the epidemiology of CKD in the Chinese Mainland. The CRDS 2011 showed that DKD accounted for 16.4% of the ESRD, second to GD (57.4%) [30]. In the CRDS 2015, GD was still the leading cause of ESRD in HD patients (45.8%) but the proportion of DKD had increased to 21.2% [116]. The prevalence of diabetes in the overall dialysis population was 27.1% with no significant difference between HD (26.7%) and PD (28.5%) [25].

DKD has become more prevalent than GD in hospitalized patients in the Chinese Mainland since 2011. The percentage of hospitalized patients with CKD due to diabetes was lower than that due to GD in 2010 (0.82% vs. 1.01%). However, in 2015, more hospitalized CKD patients had diabetes than GD as their causes of CKD (1.10% and 0.75%, respectively) [10]. According to the ADR of the CK-NET in 2015, DKD was the most common cause of CKD among hospitalized patients in the Chinese Mainland (27.0%), followed by hypertensive nephropathy (HTN) (20.8%) and GD (15.1%) [25]. Notably, the prevalence of DKD was higher in developed areas than in rural areas. Among CKD population in developed areas, 32.7% had DKD. In rural areas, DKD accounted for 17.4% of all hospitalized patients with CKD [25].

Cross-sectional surveys from Shanghai and Hong Kong estimated the frequency of DKD ranged between 10% and ~ 40% in patients with diabetes [114]. A new national CPG of DKD was recently published to standardize the screening, diagnosis, and treatment of DKD in China [117]. In keeping with the guidelines from the American Diabetes Association, the Chinese CPG recommended annual screening of urinary albumin-to-creatinine ratio (UACR) and eGFR in patients with type I diabetes with disease duration of ≥5 years and in those with type II diabetes immediately after diagnosis. DKD is diagnosed based on the presence of diabetes with increased UACR (≥30 mg/g) and/or eGFR (<60 ml/min/1.73 m^2) after excluding other CKD due to nondiabetic kidney disease [117, 118]. Renal biopsy may be considered if the diagnosis is uncertain, for example, in patients with sudden onset of overt proteinuria, obvious or microscopic hematuria, or rapid progressive decline in kidney function.

Although kidney biopsy is not routinely performed in all patients with DKD, there is a rising trend of biopsy-proven kidney damage due to diabetes in the past two decades [119]. Based on the Renal Biopsy Registry of the National Clinical Research Center of Kidney Disease that included 40,749 renal biopsies, the frequency of DKD nearly doubled from 2003 to 2014. DKD accounted for 13% of all secondary GD between 2003 and 2006 but increased to 24% between 2011 and 2014. Among patients with age between 45 and 70 years, DKD was the predominant cause of secondary GD, accounting nearly 40% [119]. Reports from other centers in the Chinese Mainland indicated that the prevalence of DKD ranged between 25% and 74% among patients with type II diabetes [120].

Obesity contributed significantly to CKD across all age groups and in both gender. A cross-sectional survey from the Chinese Mainland showed that among men aged ≥45 years, the prevalence of impaired kidney function in nonobese, peripherally obese, and centrally obese subjects was 5.1%, 5.1%, and 10.1%, respectively. Among women aged 45 years or older, the prevalence of impaired kidney function was 4.9%, 7.9%, and 20.3%, respectively [121]. The incidence of biopsy-proven obesity-related glomerulopathy (histologically manifested as obesity-associated FSGS with glomerulomegaly or obesity-associated glomerulomegaly alone) showed progressive increase over the years, from 0.63% of all secondary GD in 1992–2002 to 4.94% in 2003–2014 [119, 122].

Current Treatment and Prognosis of DKD in the Chinese Mainland

The Chinese CPG of DKD recommends lifestyle interventions, glycosylated hemoglobin target <7% and blood pressure <130/80 mmHg as well as low-density lipoprotein cholesterol <2.6 mmol/l for the general DKD population and <1.8 mmol/l for those with previous history of atherosclerotic cardiovascular disease or eGFR <60 ml/min/1.73 m^2. Less stringent glycosylated hemoglobin targets are recommended for patients with impaired kidney function (≤8%) and older adults (8.5%). Sodium-glucose cotransporter-2 (SGLT2) inhibitors are currently recommended for DKD patients who fail to meet their glycemic target after metformin in the Chinese Mainland. Glucagon-like peptide-1 receptor agonists are recommended when SGLT2 inhibitors are not tolerated or contraindicated [117]. Referral to nephrologists is recommended for subjects with an eGFR <30 ml/min/1.73 m^2, or eGFR <60 ml/min/1.73 m^2 and accompanied by metabolic disorders, or uncertainty about the etiology of kidney disease [117].

Recent prospective study including 8811 subjects with DKD in Tangshan, China, followed for a median of 6.9 years [123] showed that the incidence of cardiovascular events, ESRD requiring dialysis, and all-cause mortality were 1227.3, 93.7, and 1626.4 per 100,000 person-years in subjects with DKD having isolated kidney function decline. The incidence of cardiovascular events, ESRD requiring dialysis, and all-cause mortality increased to 1976.6, 602.2, and 3886.5 per 100,000 person-years, respectively, in subjects with DKD having overt proteinuria combined with kidney function decline compared with 951.8, 2.4, and 354 per 100,000 person-years, respectively, for diabetic subjects without DKD [123].

The huge growing burden of DKD has prompted Chinese government and clinicians to focus on early screening, prevention, and evidence-based intervention for diabetes and DKD in China. Since the late 1980s, a series of primary prevention programs for diabetes and obesity were implemented in different parts of the Chinese Mainland. For example, the Da Qing Diabetes Prevention Study demonstrated positive benefits of lifestyle intervention in reducing the risk of cardiovascular and all-cause mortality among subjects with impaired glucose tolerance during a 23-year follow-up [124].

Reimbursement Policies for DKD

In 2009, the Chinese government announced a healthcare reform plan to provide affordable and equitable basic universal healthcare by 2020. The basic national medical insurance scheme now covers over 95% of the residents in both developed and rural areas [125]. As CKD and diabetes are major chronic diseases, the basic medical insurance scheme provides insurance cover, most of which are partial cover, for all patients with DKD, including those with ESRD receiving HD or PD treatment. However, the reimbursement rates may vary from 70% to 90% of the expenses across regions with different socioeconomic status. New antidiabetic drugs such as SGLT-2 inhibitors and GLP-1 agonists are reimbursed by the national medical insurance scheme and available for use in DKD.

Hypertension and Hypertension-Related Kidney Disease

The 2012–2015 national hypertension survey showed that the overall crude prevalence of hypertension was 27.9% (weighted rate 23.2%) in Chinese residents aged 18 and over and has increased compared to previously [126]. The prevalence of CKD in hypertensive subjects was 10.9–11.29% in the Chinese Mainland [127, 128]. On the other hand, CKD subjects showed a very high prevalence of hypertension. In one of the largest cross-sectional surveys that enrolled 6079 CKD participants (mean age, 51.0 ± 16.37 years) with or without hypertension from 22 centers across the Chinese Mainland, the prevalence, awareness, and treatment rates of hypertension were 71.2%, 95.4%, and 93.7%, respectively. However, blood pressure control rates (<140/90 and <130/80 mmHg) were only 41.1% and 15.0%, respectively. The prevalence of hypertension increased with increasing age, smoking, body mass index, low physical exercise, family history of hypertension, hyperuricemia, and increasing CKD severity.

Among patients with stage 1–5 CKD, 31% had hypertension. In patients with stage 3–5 CKD, 68–71% had hypertension. Blood pressure control rate was associated with CKD stage, blood pressure monitoring at home, and use of drug combinations [129]. Among patients receiving dialysis treatment, hypertension-related kidney disease (17%) was second to GD as the most common causes of ESRD [130].

Given the poor control rates of high blood pressure in the Chinese Mainland, the Intelligent Hypertension Center (IHEC) was set up by the China High Blood Pressure Alliance and Shanghai Hypertension Research Institute in recent years (http://www.ihec.org.cn), with the aim to standardize blood pressure management and improve blood pressure control rates in China using Internet platform and mobile technology. The China National Health and Food Safety Standard recommended that salt intake for healthy adult do not exceed 6 g salt (with 1 g salt equals to 400 mg sodium). However, it was noted that the daily salt intake for healthy adult in China averaged about 10.5 g (Chinese reference source).

The 2018 Chinese Guidelines for Prevention and Treatment of Hypertension recommended that the blood pressure goal for general hypertensive patients should be <140/90 mmHg (I, A) and further lower to <130/80 mmHg as tolerated or if patients belong to high-risk category (I, A).

In patients with CKD and urine albumin excretion <30 mg/24 h (or equivalence), blood pressure goal should be <140/90 mmHg (I, A), and with albuminuria ≥30 mg/24 h (or equivalence) <130/80 mmHg (IIA, B).

The initial antihypertensive therapy in CKD patients should include one ACEI (IIa) or ARB (IIb) alone or in combination with other antihypertensive drugs. Combination of ACEI and ARB is not recommended (A).

The recommended target blood pressure in patients with diabetes mellitus should be <130/80 mmHg (II a, B).

In the general elderly population aged 65–79 years with BPs ≥150 mmHg systolic and 90 mmHg diastolic, drug therapy is recommended (IA), and when BPs are ≥140 mmHg systolic and 90 mmHg diastolic, pharmacologic treatment should be considered (IIa, B); for elderly aged ≥80 years, pharmacologic treatment should be initiated if SBP ≥160 mmHg (IIa, B).

In elderly aged 65–79 years, pharmacologic treatment should be initiated if SBP ≥150 mmHg and DBP ≥90 mmHg. If the treatment is well tolerated, BP can be lowered to <140 mmHg systolic and 90 mmHg diastolic (IIa, B), and for elderly aged ≥80 years, BP should be lowered to <150 mmHg systolic and <90 mmHg diastolic (IIa, B) [131].

Aging and Kidney Disease Burden

The Chinese Mainland has been an aging society since 1999 [132]. China's one-child policy, together with improvement in healthcare, has contributed to increased life expectancy and decreased China's birth rate. This demographic shift presents considerable social and economic challenges. According to the 6th China National Census, populations over the age of 60 years accounted for 13.26% of the total population in the Chinese Mainland [133].

An aging kidney is vulnerable to various stressors due to its structural and functional alterations. Aging is one of the major risk factors for the development of CKD [134]. Acute injury in aged kidney tends not to recover, leading to a higher risk of CKD and greater progression to ESRD in elderly [135]. The incidence and prevalence of CKD increased with increasing age. According to a population study from Beijing, the prevalence of CKD in the elderly aged between 60–69 years, 70–79 years, and older than 80 years was 20.8%, 30.5%, and 37.8%, respectively, and was much higher than that reported in the general population in the Chinese Mainland (10.8%) [9, 136] (Fig. 20.7).

The CK-NET ADR 2015 reported that 4.8% of the 18.5 million hospitalized patients had CKD [25]. The prevalence of CKD increased with age, reaching 6.2% and 9.69% for those patients aged 60 years and 85 years or older, respectively. Nearly half of the CKD patients were aged 60 years or older. Diabetes and hypertension were common among these patients (13.9% and 11.3%, respectively) and were common causes of CKD in the Chinese Mainland (27.0% for DKD and 20.8% for HTN).

The in-hospital mortality rate of CKD patients also increased with increasing age. The in-hospital mortality rate was 2.47% for subjects aged between 65 and 69 years but increased to 7.63% for those aged 80 years or over and was much higher than subjects with diabetes and non-CKD in the same age group (Table 20.3) [137]. Data from the CNRDS also observed an increase in the mean age of prevalent dialysis patients, from 53.1 years in 2011 to 55.7 years in 2015. Patients' aged ≥60 years accounted for 33.42% of incident dialysis population in 2011 and rose to 39.87% in 2015. In economically developed areas of China, nearly half of the incident dialysis patients had age ≥60 years [138].

Death was a more likely event than progression to ESRD in CKD subjects aged ≥60 years due to complications and comorbidities. CK-NET data showed that the mortality rates among Chinese CKD subjects aged 18–44 years, 45–64 years, and > 65 years were 11.80, 31.57, and 91.69 per 1000 patient-years, respectively. The all-cause mortality risk was nearly sevenfold higher in CKD subjects aged ≥65 years than in

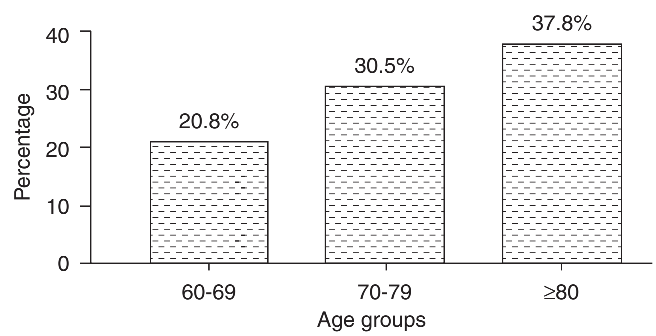


Fig. 20.7 The prevalence of CKD in elderly

Table 20.3 In-hospital mortality rate (%). Mortality rate is in % stratified by age group

Age group	CKD	DM	Non-CKD
65–69	2.47	1.27	0.95
70–74	3.43	1.83	1.30
75–79	5.12	2.79	1.96
80–84	7.63	4.32	2.94

Note: *CKD* chronic kidney disease, *DM* diabetes mellitus subjects aged 18–44 years [138]. However, mortality rate from CK-NET registry may be underestimated because patients covered by commercial insurance scheme in the CK-NET registry may generally have higher socioeconomic status and better health awareness than those without insurance coverage.

Elderly CKD subjects also suffered more depression, cognitive impairment, and protein-energy wasting [139]. The C-OPTION was a prospective observational study in 1079 elderly CKD subjects recruited from 32 clinic centers from 24 provinces in the Chinese Mainland [140]. The estimated prevalence of depression was around 23.0% in elderly Chinese CKD subjects and the severity of depression correlated with the degree of kidney dysfunction. Furthermore, depression had a major negative impact on health-related quality of life (HRQOL) [141]. Further studies will need to examine risk factors for CKD progression among elderly population and develop models to identify elderly who are at high risk for CKD progression.

Renal Replacement Therapy

In keeping with a global increase in the incidence and prevalence of ESRD [142], the burden of ESRD is on the rise in the Chinese Mainland. According to the CNRDS, the number of ESRD patients receiving dialysis treatment has increased from 261,877 in 2011 to 610,811 by the end of 2017 (Fig. 20.8) [143]. This poses a huge burden on healthcare resources and manpower need. Among the registered dialysis population, HD accounted for 86%, while PD accounted for 14% (Fig. 20.8).

The reasons for limited access to PD in the Chinese Mainland include geographical variations in socioeconomic status, differences in access to healthcare between rural and urban areas, lack of training and education for healthcare professionals, and quality control in most parts of China. To facilitate and increase PD utilization, the Chinese government adjusted the reimbursement policies, introduced new insurance systems (especially in rural areas), and initiated and supported the local production of PD solutions. Currently, 90% of the PD solutions consumed in the Chinese Mainland were imported, and international trade agreements were in place to reduce overall costs.

Kidney transplantation program began in the 1960s and the number of kidney transplants showed steady increase since 1985, with 1-year transplant graft survival above 80% between 1985 and 1993. There were two landmark developments for kidney transplantation policy in the Chinese Mainland in the last 10 years. First, it has become mandatory to allocate kidney organs for kidney transplantation through the China Organ Transplant Response System (COTRS) which is a national, open, and transparent computerized organ allocation system set up since September 1, 2013 [137]. Second, since January 1, 2015, organs from death row prisoners were banned and civil donation has become the only legal source of organ donation. The number of kidney transplantations has grown from 1009 cases in 2010 to

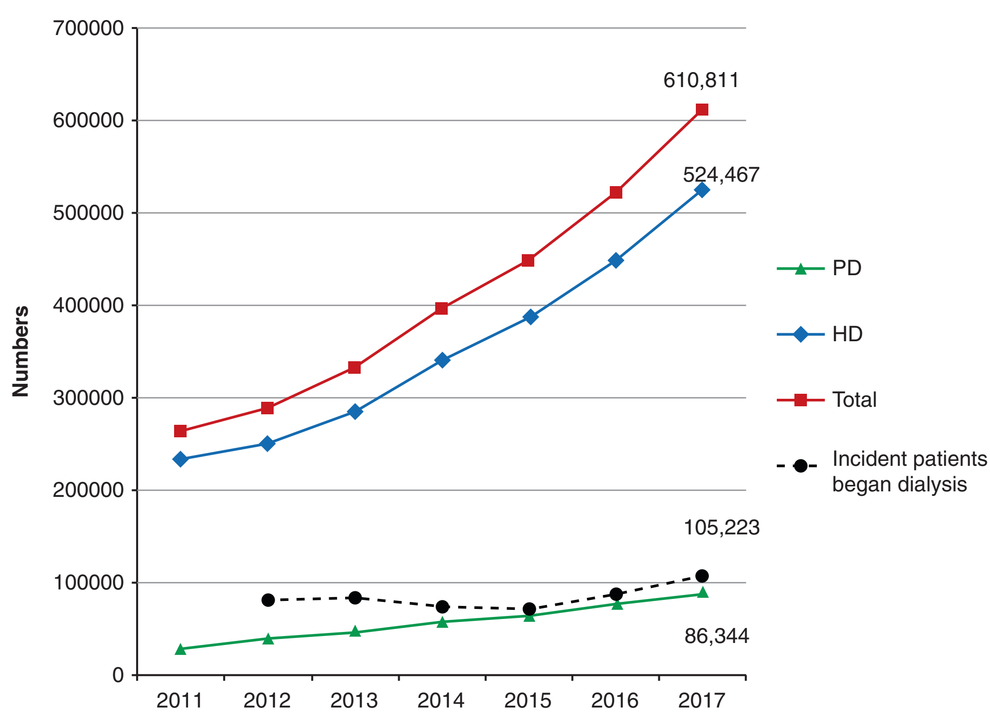


Fig. 20.8 The increasing number of hemodialysis, peritoneal dialysis, and total dialysis patients in the Chinese Mainland between 2011 and 2017. Data was from the Chinese National Renal Data System. Solid line indicated prevalent dialysis patients at each year and dashed line indicated incident patients began dialysis at each year

13,029 cases in 2018 [144] (Fig. 20.9). The estimated 1-year and 5-year kidney graft survival rate ranged between 91% and 98.3% and 73.2% and 88.6% in different centers, respectively [144].

Hemodialysis

Prevalence of HD

HD is the predominant dialysis modality, accounting for 90.96% of all dialysis in the Chinese Mainland [127]. According to a nationwide registration in 1999, the prevalence of dialysis was 33.2 pmp [145] and increased rapidly to 237.3 pmp in 2012 [26] and 442.13 pmp in 2015 [127]. The 2018 National Report on the Services, Quality and Safety in Medical Care System issued by the National Health Commission of the PRC showed that HD patients have continued to grow from 174.1 pmp in 2011 to 379.1 pmp in 2017 in the Chinese Mainland (Fig. 20.10). The prevalence of HD showed a significant increase in the last 10 years as government-operated medical insurance scheme reimburses a large proportion of the RRT since 2010. Patients only need to contribute a small amount for their RRT. However, the prevalence of RRT in the Chinese Mainland remains much lower compared with other developed regions/countries including Hong Kong Special Administrative Region (HKSAR) [146], Taiwan Province [147], Singapore, Japan, and the USA.

It is anticipated that the prevalence of RRT will continue to increase in the Chinese Mainland and there will be a rapid growth in the number of dialysis centers in the near future. The physician- and nurse-to-patient ratios in HD centers are currently much lower when compared with other countries.

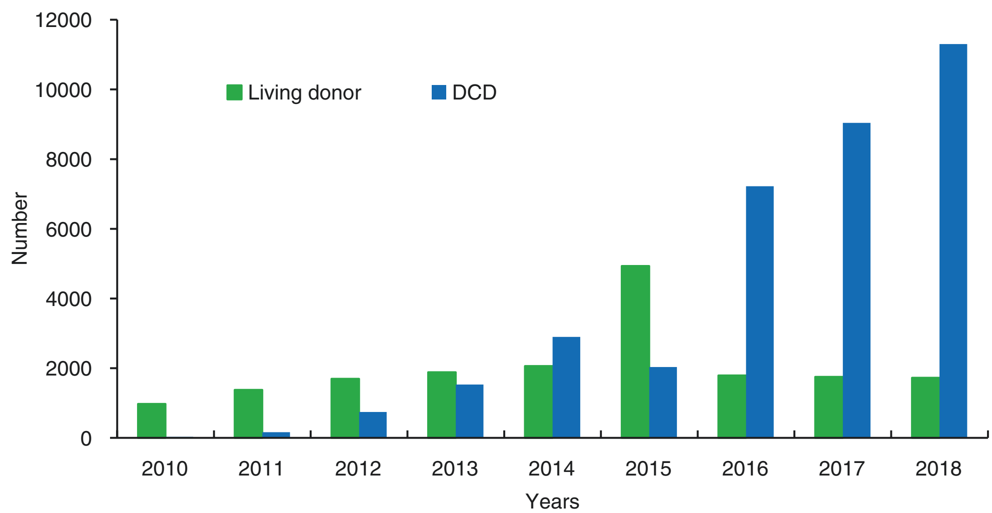


Fig. 20.9 Number of kidney transplantations in the Chinese Mainland between 2009 and 2018. Abbreviation: DCD, donation after circulatory death

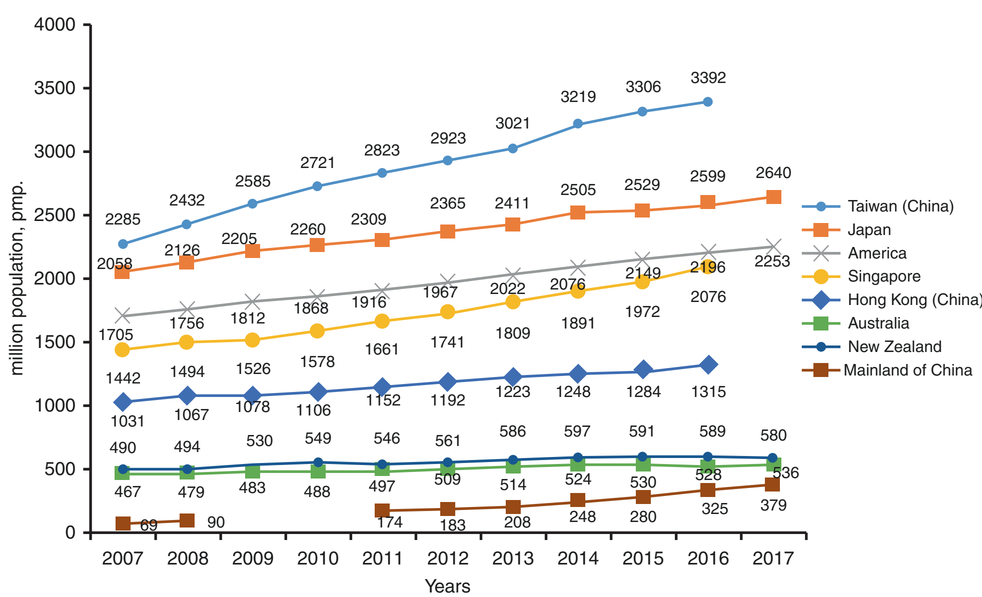


Fig. 20.10 Number of prevalent dialysis patients per million population by year in different countries and cities

In Chinese Mainland, the average number of dialysis stations in each dialysis center is around 25–30, but larger ones may have more than 100 stations. The average number of patients per center is around 100. As an example, in Beijing and Shanghai, the smallest center has only 4 dialysis stations with 12 patients, but the largest HD center has 150 dialysis stations with 600 patients (unpublished data). The standard operating procedures (SOP) formulated by the Chinese National Health Commission require that there should be at least two physicians in each HD center and one nurse taking care of no more than five patients during one HD session. Meanwhile, each HD center should have one dialysis technician taking care of machines and water and dialysate quality. For PD centers, there should be one physician and one nurse taking care of 20–30 PD patients. Every 50 or 80 PD patients increase in the center should be accompanied by one nurse and one physician increase. On average, each nurse takes care of around 100 PD patients in most PD centers. Currently there are around 2000 PD physicians and 900 PD nurses in the Chinese Mainland. The number of patients per PD center may range between 20 and 1000. Most centers in the Chinese Mainland do not have psychologist, social worker, or renal dietitian.

Current Status of HD

From the CK-NET 2015 ADR, arteriovenous fistula (AVF) and arteriovenous graft (AVG) were the predominant vascular access used, accounting for 80.48% of all vascular accesses used in prevalent HD patients [127]. Fewer diabetics used AVF and/or AVG than nondiabetics (57.73% versus 84.80%). On the other hand, incident HD patients used more catheters as vascular access than prevalent patients. From the Shanghai 2015 ADR, 31.38% of incident HD patients used short-term catheter, and 13.67% used long-term catheter (Fig. 20.11). The mean HD session length adopted in HD facilities was 243 min, and the mean blood flow rate was 235 mL/min [148]. Nearly a quarter of the HD population receives twice-weekly HD [148, 149]. According to observational data from the China Dialysis Outcomes and Practice Patterns Study (DOPPS), 19% of patients received twice-weekly HD, and 78% received thrice-weekly HD. Patients who received twice-weekly HD had similar survival and hospitalization rates compared with patients who received thrice-weekly HD [150].

Hemodiafiltration (HDF) use increased from 7% in 2007 to 42% in 2014 [151] and majority of patients received HDF once a week**.** Usually online HDF is done. Most centers use post-dilution method and the convective volume commonly used is around 15 L per session. According to China DOPPS5 (2012–2015), 15.6% of HD patients had hepatitis B and 8.5% had hepatitis C (unpublished data). Dialyzer reuse is allowed but no centers in China currently reuse dialyzers.

Survival Rate of Patients Receiving Hemodialysis

A study from Beijing that followed 11,175 HD patients for 8 years showed that patients who initiated dialysis with an eGFR ≥15 ml/min per 1.73 m^2 and between 10 and 15 ml/min per 1.73 m^2 had higher mortality rate than those that started dialysis with eGFR between 5 and 10 or <5 ml/min per 1.73 m^2 (unpublished data). In Beijing, patients who initiated dialysis “early” (eGFR>10 ml/min per 1.73 m^2) accounted for 15% of new dialysis start [152], and thus, there is a potential to delay the start of dialysis in the ESRD population in the Chinese Mainland.

Notably, the mortality rate in the first 2 months after dialysis initiation was high in the Chinese Mainland; thereafter mortality rate reduced to a lower level and stabilized at 90 days after dialysis initiation [152]. The mortality rate was nearly 30 per 100 patient-years for diabetic patients in the first month after dialysis initiation but was much higher in nondiabetic patients (50 per 100 patient-years) [152]. The

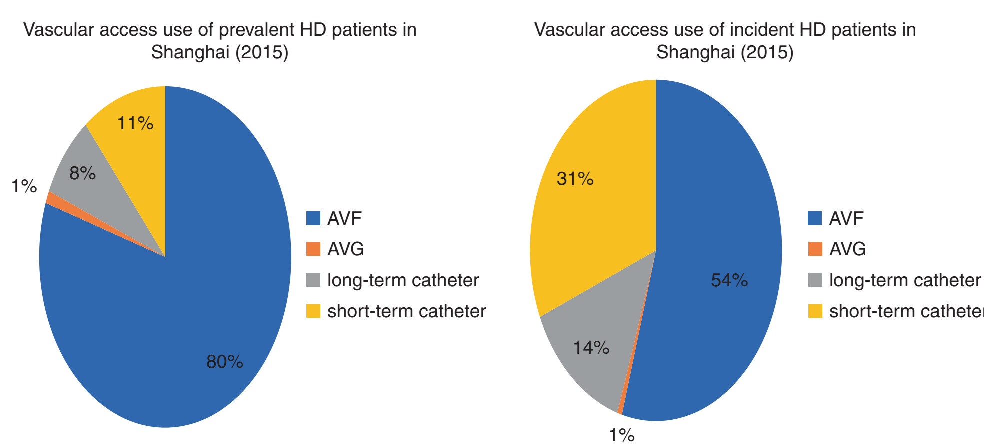


Fig. 20.11 Vascular access use of prevalent/incident HD patients in Shanghai, China (2015)

exact explanation for this finding is uncertain. One speculation may be that better pre-dialysis care in diabetic patients may contribute to survival benefits 90 days after dialysis initiation than nondiabetics.

The raw annual maintenance HD (MHD) mortality in Beijing has increased from 47.8 per 1000 patient-years in 2007 to 76.8 in 2010 [153] but was still lower when compared with the US Renal Data System (USRDS) results (236.3 in 2009). In Shanghai, the annual MHD patients mortality rate was 7.5% in 2005 [154] and was lower than the mortality reported in Europe (15.6%) and the USA (21.7%) in 2003 but similar to that reported in Japan (6.6%). The observed survival advantage for HD patients in China/Asia compared to the western counterparts could be in part explained by differences in race and practice patterns among different countries.

Management of Anemia and Mineral and Bone Disorder

Anemia management in dialysis patients is a challenge in the Chinese Mainland. Data from China DOPPS4 showed that 21% of MHD patients had hemoglobin (Hgb) level <9 g/dl, compared with ≤10% in Japan and the USA [155]. Possible reasons for more anemia in Chinese HD patients could be the following: First, more patients from China received twice-weekly HD than other DOPPS countries. Second, erythropoietin-stimulating agent (ESA) dose used in China was lower than in the USA. Third, there was low insurance coverage for ESA treatment in China. In 2018, roxadustat, an oral hypoxia-inducible factor stabilizer and propyl hydroxylase inhibitor, was approved for treatment of anemia in dialysis patients in the Chinese Mainland. A 26-week, phase 3 trial showed that oral roxadustat was non-inferior to parenteral epoetin alfa in treating anemia in Chinese dialysis patients [15], providing a novel treatment for renal anemia.

According to the questionnaires distributed to the dialysis facility director in DOPPS5, the Chinese translated KDIGO guideline was the reference guide for mineral and bone disorder (BMD) management in the Chinese Mainland. However, serum calcium, phosphorus, and parathyroid hormone (PTH) control were not optimal. DOPPS5 showed that more HD patients in the Chinese Mainland had hypocalcemia than in the USA and Europe, and the percentage of subjects with hypercalcemia was higher than other countries (*Chinese Medical Journal*, in press). Phosphate control was also worse in the Chinese Mainland than other DOPPS countries (26% of HD patients in the Chinese Mainland had serum phosphate >7.0 mg/dL compared with 7–10% in other DOPPS countries). Twenty-seven percent had serum PTH <150 pg/ml, and 21% had PTH >600 pg/ml.

HD Quality Control

In 1998, Shanghai took the lead to set up the Hemodialysis Quality Control Center. The Beijing Health Bureau also established the Hemodialysis Quality Control and Improvement Center (BJHDQCIC) in 2002. Since then, dialysis quality control centers were established in various provinces and regions to promote the standardization of HD and strengthen the quality control of HD service.

This coincided with the setup of CNRDS in 2010, of which comprehensive epidemiological data of all dialysis patients were collected nationwide. It enables the government to work out healthcare financing and formulate health policies. The CNRDS also published the Blood Purification SOP in 2010 that provided detailed guidelines recommendations on safe and quality HD service delivery.

In 2017, China national standardization management committee published a consortium on standard management regulations. Some organizations published their consortium standard for HD facility configuration (to be published by ZGC Nephrology Blood Purification Innovation Alliance) and service (published by Chinese Hospital Association) [156] to assure safe and quality HD service provision by all HD facilities.

Peritoneal Dialysis

Similar to some developing countries in Asia [157], the Chinese Mainland is home to a large number of low-income people who live in rural and remote areas where HD facility may not be available or not accessible [158]. PD serves as a more feasible and cost-effective alternative dialysis modality than HD and has been in use in the Chinese Mainland for over 30 years [158]. Most patients do CAPD with four bags (2L/bag) per day, while only 0.9% of patients receive automated peritoneal dialysis (APD) [158]. Primary GD accounted for about 50% of background kidney disease in PD patients, while DKD accounted only for 15%~16% [143]. Table 20.4 shows the background causes of kidney disease in incident PD patients. Observational studies showed that patients receiving PD had comparable clinical outcomes and quality of life as those receiving HD [159]. Since PD is done by patients/caregivers at home and incurs lower cost, the Chinese government has been actively promoting more PD utilization nationwide. This explains the rapid growth in PD utilization in the Chinese Mainland in the last 10 years [158]. The provision of PD education programs for health professionals by high-quality PD centers and nephrologists and health professionals trained in PD also contribute to increased PD utilization in the Chinese Mainland [160]. A representative model is the satellite center

Table 20.4 The composition of primary kidney diseases for incident PD patients at each year

Year	Primary glomerular disease (%)	Diabetic kidney disease (%)	Hypertensive nephropathy (%)	Polycystic kidney disease (%)	Tubulointerstitial disease (%)	Others (%)
2013	52.6	15.6	14.9	1.5	1.4	14.0
2014	54.1	16.2	14.4	1.5	1.5	12.3
2015	50.8	16.1	15.1	1.4	1.7	14.9
2016	50.0	16.2	16.6	1.4	1.6	14.2
2017	51.1	13.0	14.3	1.3	1.6	18.8

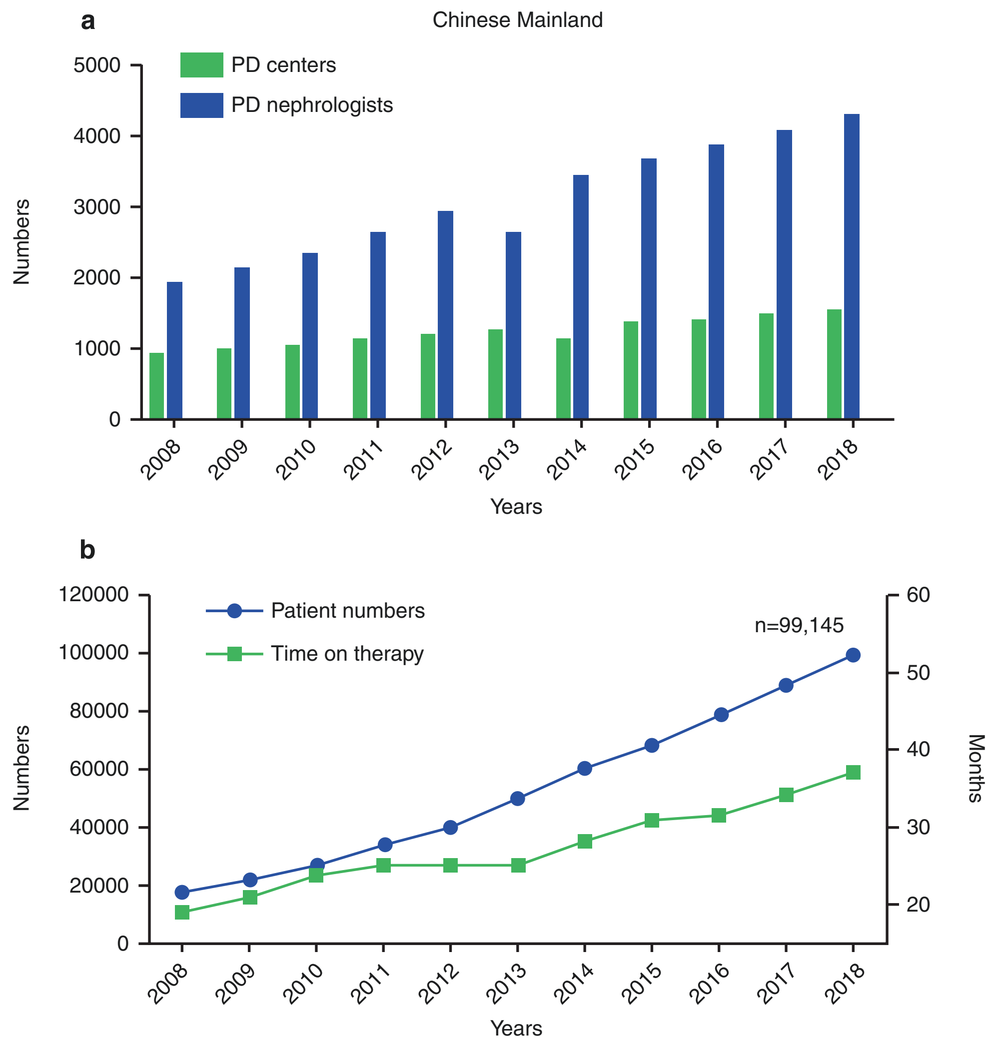


Fig. 20.12 (**a**) An increasing number of PD centers and nephrologists working in PD treatment in the Chinese Mainland in the last 10 years. (**b**) An increasing number of PD patients along with increasing duration of PD therapy over in the Chinese Mainland the last 10 years

program established at the Sun Yat-sen University PD center in Guangzhou, China. The center has trained dozens of centers, and over hundreds of nephrologists and nurses have become very experienced with PD practices and procedures across the Guangdong Province [161]. As depicted in Fig. 20.10, PD centers have increased from 930 in 2008 to 1560 in 2018 in the Chinese Mainland, reflecting an average increase of 63 new PD centers per annum [143]. Accordingly, the number of nephrologists who practice PD has more than doubled in 10 years' time (Fig. 20.12a) [143]. The number of ESRD patients receiving PD treatment has also grown remarkably from 17,897 in 2008 to the latest 99,145 in 2018, and the number is still on the rise (Fig. 20.12b) [143]. Figure 20.13 shows the distribution of PD utilization on a provincial level by 2018, the top ranked provinces being Guangdong and Zhejiang, with over 9000 PD patients in total [143]. Government's active promotion, national medical insurance coverage, improvement in PD technology, PD being a home-based therapy, and lower overall cost than HD are all important elements that drive the growth in PD utilization [162]. Currently, PD accounts for only about 20% of the dialysis modality in ESRD [158]. Since less developed cities and more remote areas have resource constraints in expanding HD facility and service, it adds incentives for

Fig. 20.13 The distribution of PD utilization in a provincial level in the Chinese Mainland. Note: PD, peritoneal dialysis. Data calculated from CNRDS [1], while Hong Kong, Macao, and Taiwan were not included in the statistical map

more PD utilization as the therapy is home-based and overall less costly than HD. Furthermore, patients are more engaged and empowered in managing their own dialysis treatment [160], and the average time on PD therapy (technique survival) has increased from a mean of 19.2 to 37.1 months in the last decade [144] (Table 20.5).

Nephrologists in the Chinese Mainland have put tremendous efforts in developing high-quality PD programs in the last 10 years [158, 160, 170]. Table 20.5 listed the published reports of clinical outcomes of PD patients from large university-affiliated PD centers in the Chinese Mainland between 2008 and 2018, showing high patient survival rates and technique survival rates as well as low peritonitis rates [163–165, 168, 171, 172] compared to international reports. A recent observational study from the Chinese Mainland reported that patients who initiated PD during 2011–2015 had better survival than those that initiated PD between 2005 and 2010 [163]. Cardiovascular disease and infection are the two leading causes of death in PD patients. The key elements of a successful PD program include a multidisciplinary, collaborative team with nephrologists, nurses, and patients/carers together with a comprehensive social support system [160]. Nephrologists in the Chinese Mainland have dedicated tremendous efforts in developing PD research programs in basic, translational, and clinical science with an aim to identify evidence-based interventions to advance PD care quality. Between 2008 and 2018, the numbers of PD-related publications from the Chinese Mainland in local and international journals have increased substantially [173]. Of note, the number of PD-related publications in internationally indexed journals has increased from 34 in 2008 to 92 in 2016, with an average annual growth rate of 13% [173]. This reflects strong interests and engagement of nephrologists in the Chinese Mainland in PD research, growing impact of Chinese Mainland's PD research on the global PD community, and China gradually taking the lead as one of the major countries that contribute to advances in PD technology and practices.

Table 20.5 A review of the clinical outcomes of PD patients in major PD centers of the Chinese Mainland

District	Reference	Number of cases	Time of review	Peritonitis rate (patients' month per episode)	Technique survival	Patient survival
Guangzhou	Yang et al. [163, 164]	2021	2006–2014	75[170]	1 year: 97% 3 years: 90% 5 years: 83% 10 years: 57%	1 year: 97% 3 years: 87% 5 years: 74%
Beijing	Xu et al. [165]	307	2002–2007	50.1~76.7	–	1 year: 97% 3 years: 71% 5 years: 51%
Beijing	Li et al. [166]	577	1996–2015	77	1 year: 96.5% 3 years:89.1% 5 years: 81.7%	1 year: 91.3% 3 years: 70.9% 5 years: 49.7%
Shanghai	Fang et al. [167]	339	2005–2009	62.5	1 year: 96% 3 years: 92% 5 years: 82%	1 year: 93% 3 years: 82% 5 years: 71%
Zhejiang	Chen et al. [168]	712	2004–2011	75	1 year: 95% 3 years: 88% 5 years: 80%	1 year: 96% 3 years: 85% 5 years: 76%
Nanjing	Liu et al. [169]	619	2005–2011	22.86~77.25	1 year: 90%~96% 2 years: 79%~93% 3 years: 77%~93%	1 year: 93%~97% 2 years: 82%~96% 3 years: 67%~96%

Dialysis Reimbursement Policies

The median annual overall cost for PD was lower than that of HD (73,266 RMB vs. 87,125 RMB per patient per year) [137]. With China Healthcare Reform, basic medical insurance now provides coverage for over 95% of its residents. The National Social Medical Insurance reimburses around 70% of the total medical expenditures with PD. In urban areas, for example, HD and PD patients had, on average, around 70.5% and 68.4% of the medical expenditures reimbursed, respectively [137, 158]. The National Development and Reform Commission has recently increased government insurance coverage for dialysis-related expenses [158]. This will facilitate and improve accessibility to dialysis treatment for ESRD patients in the Chinese Mainland.

Organ Procurement and Transplant Policies

In 2007, the Chinese Mainland promulgated the Regulations on Human Organ Transplantation with a new national program for deceased organ donation, procurement, allocation, and transplantation implemented in 2013 [174]. Organs harvest from executed prisoners has been banned since January 2015 [175]. Three categories of deceased donors issued by the Organ Transplantation Committee under the Ministry of Health in China were summarized as follows: Category I, donation after brain death (DBD); Category II, donation after cardiac death (DCD), the same as the Maastricht categories (started in the Chinese Mainland in 2010) [176]; and Category III, DBCD, organ donation after brain death followed by circulatory death [177].

According to China's Human Organs Acquisition and Distribution Management Regulations, organ donation is to be coordinated and processed by organ procurement organizations (OPOs), which are composed of organ transplant surgeons, neurologists, neurosurgeons, nurses, critical care medicine experts, and transplant coordinators.

The Process of Organ Donation

After a potential deceased donor is identified in a hospital, the doctors will inform patient's relatives of his/her illness status. The transplant coordinator will be involved in offering the potential donor's immediate family the option of being a DCD donor. The potential donor could have his/her organs donated if (1) the deceased has expressed willingness to donate organs in either a living will or other written form; (2) their immediate family provides written consent for organ donation if the deceased has not expressed opposition to donating his/her organs prior to death; or (3) the deceased has verbally expressed a wish to donate while in a conscious state in the presence of two doctors, who are not part of the organ procurement or transplantation team, and the deceased's immediate family does not object [176]. The attending physicians will contact the OPO, and the OPO will be responsible for overall evaluation of the potential organ donor. The neurologists/neurosurgeons need to make sure that the deceased fulfills the Harvard definition of brain death. The transplant surgeons will be involved in organ evaluation but the transplant team is not allowed to contact relatives of the donor. The transplant coordinators are responsible for all the liaisons work. They need to confirm that the deceased individual meets all the abovementioned criteria as an organ donor and all the required written consents have been signed by the deceased donor's immediate family with witness from an independent observer from the Red Cross. In Guangdong Province, the package of clinical and ethical data will be presented to the ethical committee for approval before organ donation. To avoid organ trafficking, direct financial compensation to the deceased donor's family is forbidden. However, medical aid and funeral allowance is permissible.

DBDs will be procured after declaration of brain death according to the diagnostic criteria of brain death [178]. Following declaration of brain death in DBCD or DCDs, written consent for deceased organ donation and withdrawal of life support will be obtained from the donor's immediate family. The obtained consent for organ donation will then be reported to the Organ Donation Committee, who will supervise the DBCD or DCD process. Deceased donors are monitored with invasive blood pressure sensors in the operating room. Following condolences, mechanical ventilation and vasopressors will be withdrawn and vital signs will continue to be monitored. The definition of cardiac death is determined according to the aforementioned criteria, and death is declared after 5 minutes of observation following cardiac arrest and then the organ procurement will initiate. The protocols for DBD, DBCD, and DCD in the Chinese Mainland are detailed in the national guidelines for organ donation [174, 177].

Organ Allocation and Transplant Waitlist Registry

The legal framework for organ donation is in place in accordance with the WHO guidelines on organ transplantation. A third-party nonprofit organization is involved in implementing organ donation policy according to the law [179]. Deceased organ allocation in the Chinese Mainland is now done via China's Organ Transplant Response System (COTRS), an electronic distribution system maintained by the independent China Transplant Response System Research Center that is affiliated with the University of Hong Kong. The principles in the State Council Regulation call for "fairness, justice, and transparency" in assessing the medical need of waitlisted patients. This State Council directive is designed to ensure fairness and public trust in the organ allocation system [174].

Before harvesting the deceased organs, information of the deceased donor will be uploaded to the organ allocation system. Organ allocation takes into consideration medical urgency, waiting time for patients on the waitlist, HLA compatibility, and patients' clinical need. The organ allocation is conducted electronically to ensure transparency and fairness of the process. In principle, the hospital where the OPO is located has the highest priority to receive the organs. If no eligible recipients are identified from that hospital, the donated organs will be allocated to another hospital that is out of region from the primary OPO. After kidney transplant, data of the recipients will be uploaded to the registry system within 72 hours. The China Health Authority will verify the recipients' identity to avoid illegal change of recipients.

A national registry of transplant recipients has been established [174] and is integrated with the COTRS and other regulatory databases. This enables a national surveillance network for organ procurement and transplantation in the Chinese Mainland and prevents possible illegal organ trafficking, procurement, and transplant activities.

Future Perspectives of Organ Donation

The Chinese Mainland needs to set up a national registration for volunteers of organ donation and actively promote both living-related and deceased donor's organ donation. Other issues to be addressed include setting up an independent foundation managed by an independent third party to provide some medical aid and funeral service allowances to donor's immediate family [180].

Kidney Transplantation in the New Era

Organ Transplantation began in the Chinese Mainland in the 1960s and is one of the largest organ transplant programs in the world, reaching over 13,000 transplants per year in 2004. The first living-related kidney transplant was done in 1972. The number of organ donors and organ transplants has steadily increased since the use of DCD in 2010 (Fig. 20.14). According to the Chinese Scientific Registry of Kidney Transplantation (CSRKT), 37,873 kidney transplants from DCD and 15,309 from living donor were performed between 2010 and 2018 [181]. However, this number remained far from meeting the demand for organ transplants in ESRD patients in the Chinese Mainland. It was estimated that 1–1.5 million people in the Chinese Mainland require organ transplantation every year. However, data from the China Organ Donation Administration Center showed that the estimated deceased organ donation rate increased gradually to 3.71 per million Chinese population in 2017 (Fig. 20.15) and only around 10,000 patients received organ transplantation per year.

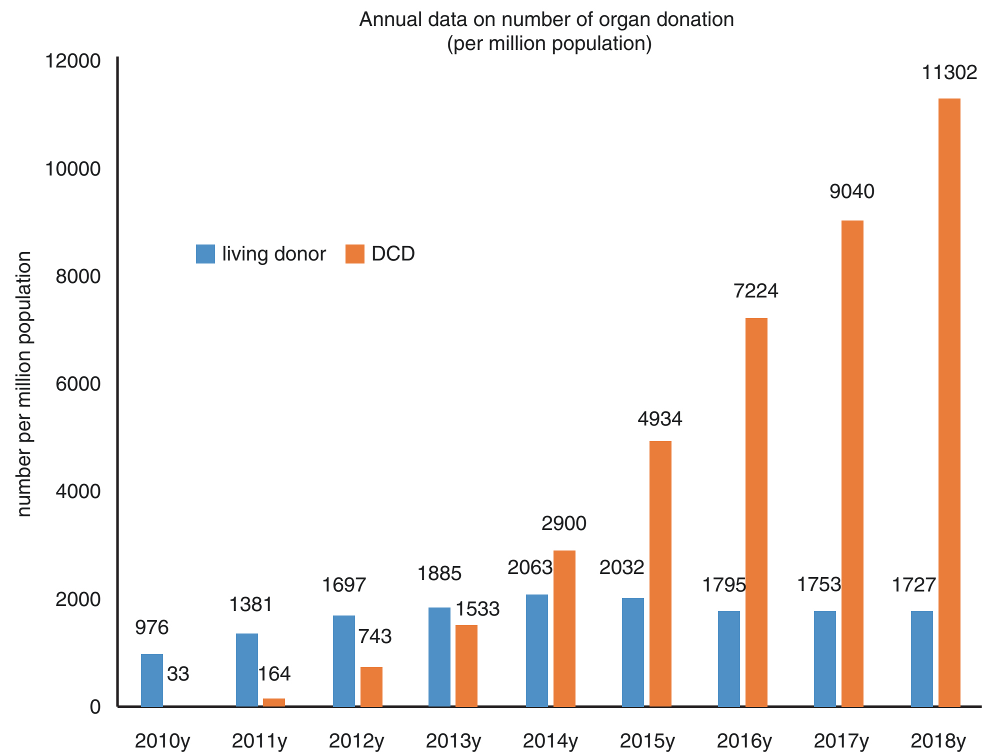


Fig. 20.14 China annual kidney transplantation from different donor sources between 2010 and 2018. (Data from Chinese Scientific Registry of Kidney Transplantation)

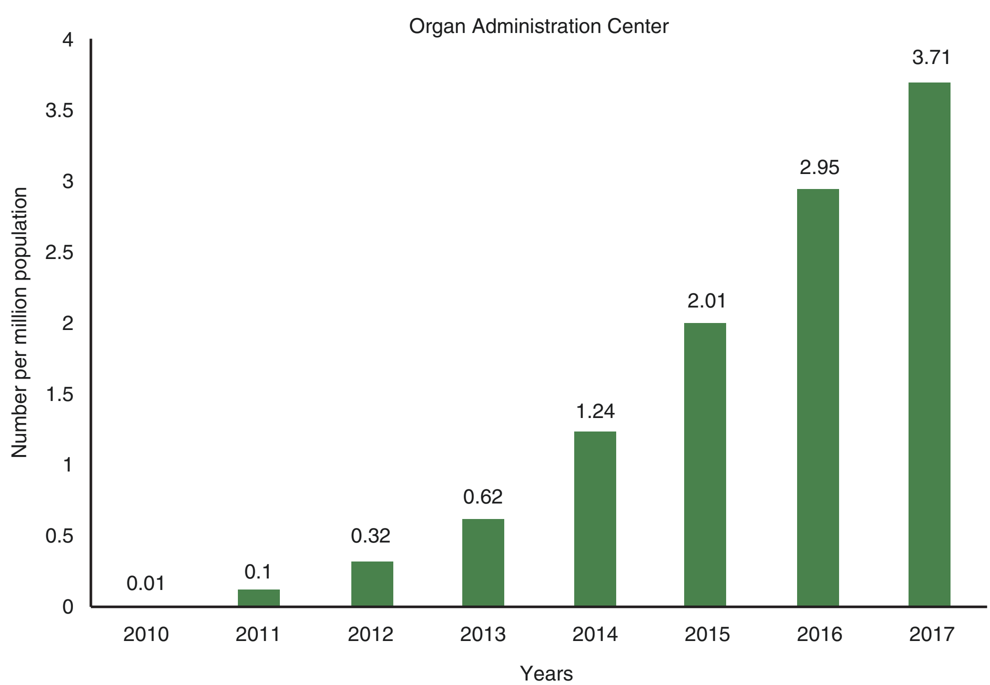


Fig. 20.15 Annual data on organ donation (per million population). (Data from Chinese Organ Administration Center)

A questionnaire survey conducted among holders of driving license in the Chinese Mainland showed that although 74.4% of survey respondents supported voluntary organ donation and 64.0% advocated organ donation after death, only 48.4% expressed willingness to be organ donors themselves [182]. In another recent survey of organ donation among healthcare professionals in eight hospitals in 2013/2014, only 19.6% of the surveyed healthcare professionals knew where organ procurement and donations were conducted, and only 13.7% knew how the procedure of organ donation happens [183]. Thus, more active promotion campaigns and education are required to promote voluntary organ donations among healthcare professionals, other than the public in China.

In 2014, the Chinese Mainland launched its official organ donation registration websites www.savelife.org.cn or www.rcsccod.cn. All Chinese citizens can register as organ donors in the two sites. Since then, organ donation from community-based deceased donor has become one of the two legitimate primary sources of transplantable organs. Allocation of organs from deceased donor are conducted automatically through the China Organ Transplant Response Electronic System (COTRS, http://www.cot.org.cn) since September 1, 2013, as mandated by the Chinese government to ensure fairness and transparency in the donor organ allocation process [184].

The Red Cross Society has played an important role in registering organ donations in the Chinese Mainland in the past two decades since its establishment. From 2008 to 2009, the Red Cross Society received 10,423 registrations of donations [185]. Furthermore, the organization of organ donation and transplantation in the Chinese Mainland was restructured. According to the COTRS and scientific registries (as of February 3, 2016), between January 1, 2015, and December 31, 2015, there were 2766 community-based deceased organ donations, resulting in 2150 liver transplants, 4931 kidney transplants, 279 heart transplants, and 118 lung transplants.

Figure 20.16 presents the annual number of kidney transplants performed between 2010 and 2018 from different donor sources in the Chinese Mainland (data from CSRKT). DCD is now the dominant source of organ donation and transplantation since 2014. The total number of cases has increased from 2900 in 2014 to 11,302 in 2018. Despite some initial fluctuations, there was a steady increase of kidney transplants in the Chinese Mainland since 2015, especially donations after cardiac death, which is anticipated to continue to increase. Some kidney transplant-related data from 2018 are shown in Figs. 20.17, 20.18, and 20.19.

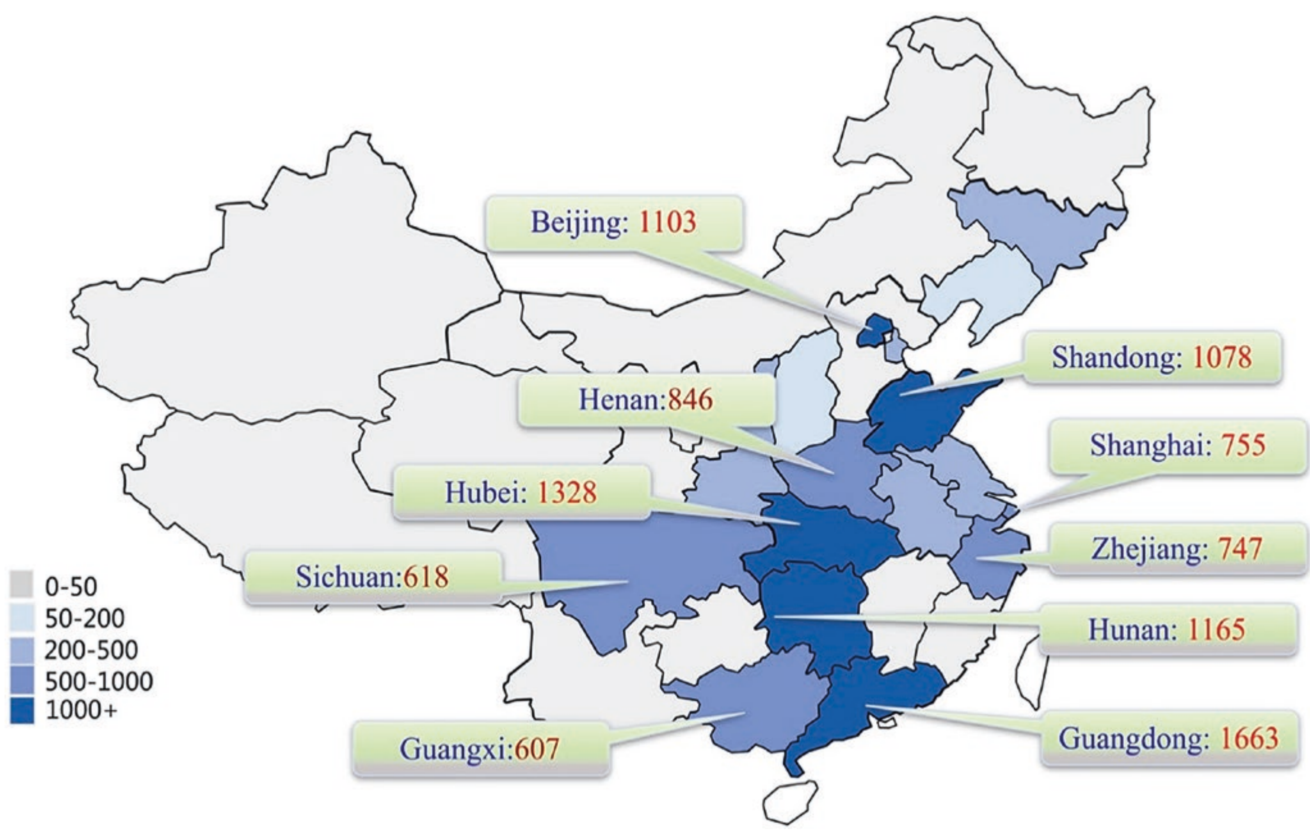


Fig. 20.16 An overview of kidney transplant in 2018. (Data from CSRKT)

Fig. 20.17 Top 20 provinces in the Chinese Mainland with highest number of kidney transplants performed in 2018. (Data from CSRKT)

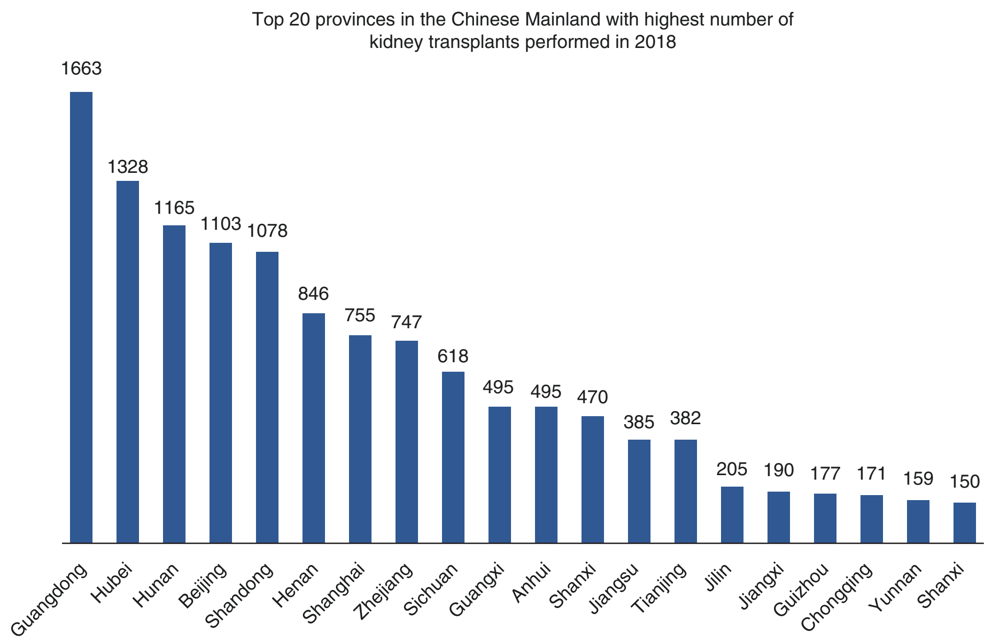


Fig. 20.18 Deceased donor organ donations in the Chinese Mainland in 2018. abbreviations; DBD, donation after brain death; DCD, donation after circulatory death; DBCD donation after brain death followed by circulatory death

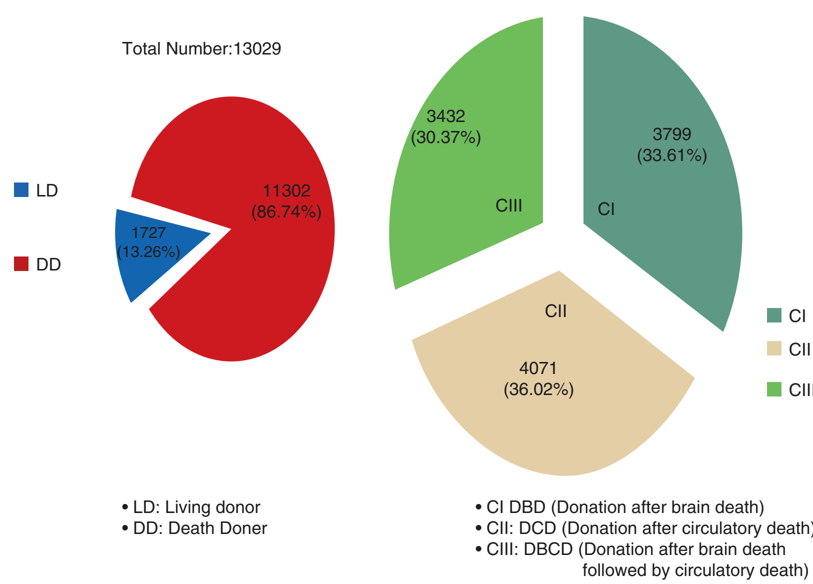
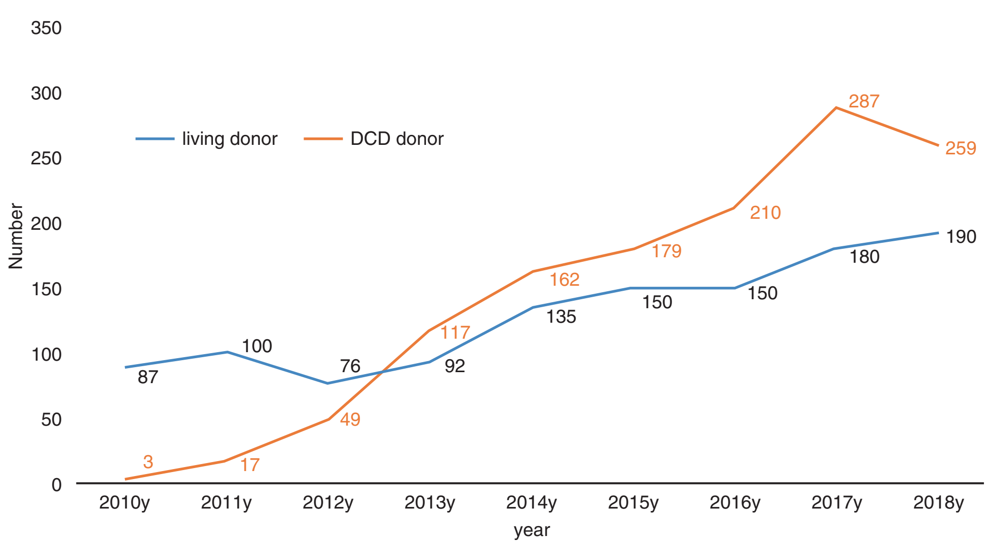


Fig. 20.19 Annual number of kidney transplantation from DCD donor and living donor in the First Affiliated Hospital of Zhejiang University



Kidney transplantation from DCD also increased steadily from near zero case in 2011 to 1283 cases in 2018 in the First Affiliated Hospital of Zhejiang University (Fig. 20.20), one of the major kidney transplant centers in China. This steady increase is expected to continue to the next decade. The number of living donor kidney transplantations in our center has also grown steadily since 2007 (Fig. 20.20). Figure 20.21 presents a snapshot of percentages of eight different donor-recipient relationships in living-related kidney transplantation performed in the First Affiliated Hospital of Zhejiang University. The percentages of donation from mother to son were the highest, reaching 33% among all living-related donations, while donation from mother to daughter and father to son was 21% and 18%, respectively (Fig. 20.21). Kidney transplantation from DCD showed a high rate of delayed graft function (DGF) and infections. Of the 1283 kidney transplantations from DCD performed without machine perfusion up to end of 2018, the rate of delayed graft function (DGF) was 17.2%, but 93.2% recovered from the DGF. Patients with DGF achieved similar eGFR at 1 year posttransplant when compared to patients without DGF (unpublished data).

Infection was an important complication posttransplant, accounting for 70% of all peri-transplantation deaths. Acute rejection is another important complication. According to unpublished data from the First Affiliated Hospital of Zhejiang University, 3.57% of kidney transplants from living donor and 3.99% from DCD had biopsy-proven acute rejection within the first 6 months posttransplant. Biopsy-proven acute rejection was diagnosed in 5.45% and 6.65% of living donor and DCD kidney transplant at 12 months posttransplant; and 9.02% of living donor and 8.11% of DCD until the end of 2018, respectively.

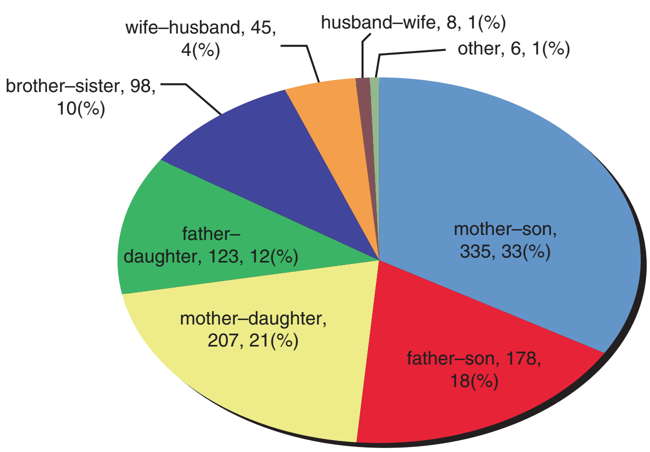


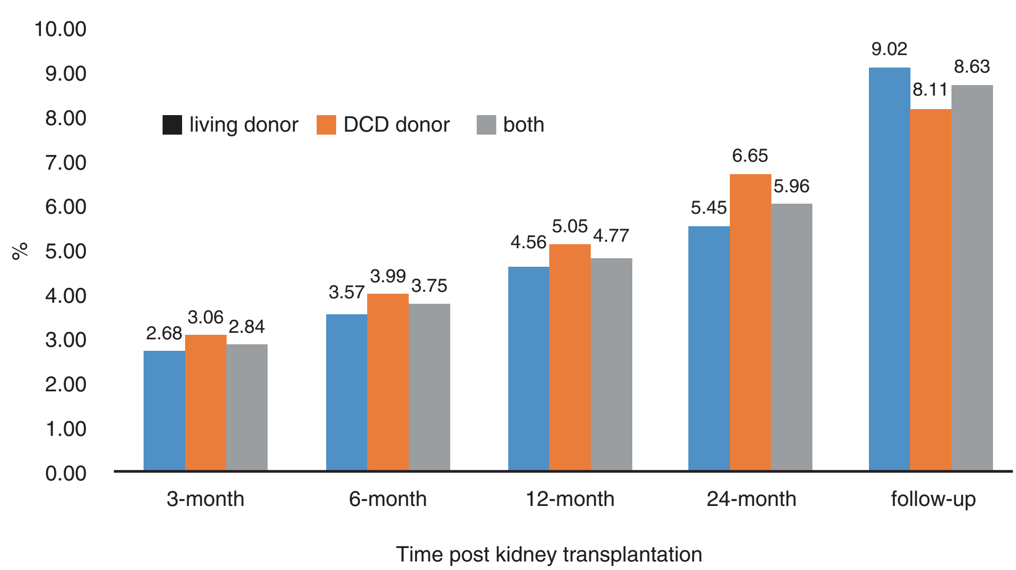
Fig. 20.20 Relationships of living kidney transplantation in the First Affiliated Hospital of Zhejiang University

Acute Kidney Injury (AKI) and Critical Care Nephrology

AKI Disease Burden

A nationwide cross-sectional AKI survey conducted by the *International Society of Nephrology (ISN) 0 by 25 China Consortium* screened 2.2 million adult hospitalized patients from 44 academic or local hospitals in 22 provinces from the Chinese Mainland, based on changes in serum creatinine by the Laboratory Information System [11]. The overall detection rate of AKI was 1.0% by KDIGO criteria (and varied between 0.8% and 1.2% among different geographic regions) and 2.0% by expanded criteria (i.e., ≥50% rise in serum creatinine during hospital stay). The in-hospital mortality rate for AKI was around 12.4% and was lower than that reported from US nationwide inpatient data in 2002 (20.3%) [186]. Over half of the patients with AKI were >60 years old, and

Fig. 20.21 Percentage of biopsy-proven acute rejection in the First Affiliated Hospital of Zhejiang University



half of the AKI were prerenal in nature, with renal hypoperfusion, nephrotoxic drugs, or environmental toxins being the most common causes. A striking feature of AKI in the Chinese Mainland is a high proportion of nephrotoxic drug exposure (71.6%) before or at the time of AKI compared with those reported in other developed countries (average between 20% and 50%) [187–189]. Nearly half of the AKI occurred in patients with severe critical illness and over a quarter of the AKI were of stage 3 or worse. Furthermore, increasing age, presence of cardiovascular disease, delayed AKI recognition, critical illness, higher peak AKI stage, and need for RRT were all independent risk factors predicting mortality from AKI. Notably, around 74.2% of the AKI that developed during hospitalization was not recognized by physicians. Of the 25.8% of AKI that were recognized, diagnosis was delayed in 17.6%. Regions of lower socioeconomic status were independently associated with more under-recognition or delayed diagnosis of AKI. On the other hand, patients with preexisting CKD, more severe AKI, and early referral to nephrologists were less likely to be under-recognized for their AKI. Since only 25% of the hospitalized patients had serum creatinine measurement repeated during hospitalization, the prevalence of AKI was likely vastly underestimated. Having a timely diagnosis of AKI with early referral to nephrologists may be an important strategy to lower mortality rates from AKI in the Chinese Mainland.

In another multicenter retrospective cohort study conducted in 9 regional central hospitals in the Chinese Mainland in 659,945 adults hospitalized with a wide variety of clinical settings, the estimated incidence of community-acquired (CA)-AKI was 2.5%, and hospital-acquired (HA)-AKI was 9.1%, giving rise to an overall incidence of AKI of 11.6%. Preexisting CKD was identified as a major risk factor of AKI, contributing 20% for the risk of CA-AKI and 12% for the risk of HA-AKI. The three most common clinical settings associated with CA-AKI were sepsis (15.2%), urinary tract obstruction (12.3%), and CKD (11.8%). On the other hand, cardiac surgery (43.7%), sepsis (32%), and intensive care (30.3%) were the three most common clinical settings associated with HA-AKI. Nephrotoxic drugs were important causes of AKI, accounting for 39.2% of CA-AKI and 42.9% of HA-AKI. Chinese traditional medicines/remedies were also important causes of AKI, accounting for 15.3% of CA-AKI and 16.2% of HA-AKI, while contrast agents contributed to 9.1% of the HA-AKI [190]. The estimated in-hospital mortality of AKI in this study was 8.8% and increased in a stepwise fashion with increasing severity of AKI. The risk of mortality with AKI further increased among subjects with preexisting CKD and subjects who need intensive care [190].

Treatment of AKI poses significant financial burden to the hospital systems in the Chinese Mainland. According to an analysis by Xu et al., HA-AKI increased healthcare expenditure by more than 66% compared to patients without AKI. Average length of stay for patients complicated with AKI increased by a median of 5 days compared to those with no AKI. According to a report from National Health and Family Planning Commission of PRC, an estimated 1.4 million people with AKI by KDIGO criteria (2.9 million by the expanded criteria) were hospitalized in 2013 and consumed about US$13 billion, accounting for 10% of total healthcare expenditure in the Chinese Mainland. If patients with severe AKI were discharged without further treatment, an estimated 700,000 patients would have died from AKI during 2013. However, only 16.7% of the AKI were presented to the healthcare system. Thus, the real clinical significance and financial impact of AKI may be grossly underestimated in the Chinese Mainland.

CA-AKI accounted for nearly 50% of all AKI in the Chinese Mainland [11]. Patients in Northern China were more likely to develop AKI due to renal hypoperfusion, whereas more AKI in Southern China were due to exposure to nephrotoxins or urinary tract obstructions [191]. Rates of timely diagnosis of AKI and appropriate initiation of RRT were higher in more developed regions of China [191].

Based on a pediatric AKI survey from 25 regional, central, general, and children hospitals in the Chinese Mainland, the estimated incidence of AKI in pediatric population was 20%, of which 7% were community-acquired and 13% were hospital-acquired. The three most common settings with AKI were heart failure (25%), respiratory failure (24%), and congenital heart disease/cardiac surgery (24%) [192]. The incidence of AKI in pediatric intensive care unit (PICU) was very high (46% on admission and 56% during the PICU stay) in one report from HKSAR [193].

Critical Care Nephrology

AKI in the ICU settings was very often more complicated than AKI outside ICU and associated with more postoperative complications, sepsis, advanced invasive procedures such as extracorporeal membrane oxygenation (ECMO), and vasoactive support. According to a nationwide survey, 21.6% and 28.5% of the AKI occurred in surgical departments and ICUs, respectively [11]. ICU had the highest detection rate of AKI (22.46%) and had more severe AKI (nearly a third of the AKI were stage 3) and higher mortality rate (50%) than AKI outside ICU [194]. The most common risk factors for AKI in the ICU settings in the Chinese Mainland were renal hypoperfusion, use of nephrotoxic drugs, sepsis, and other critical illnesses. Data from a prospective, multicenter, observational study conducted in 22 ICUs in the Chinese Mainland showed that around 31.6% of the ICU patients developed AKI, with 30% being stage 3 AKI, and 27% of patients with AKI died during hospitalization [195]. Tables 20.6 and 20.7 summarize the recent epidemiologic studies of AKI in the adult and pediatric intensive care units in the Chinese Mainland, respectively.

Access to RRT for AKI

A nationwide survey in the Chinese Mainland showed that only 59.3% of patients with AKI requiring RRT received the required treatment. This meant nearly 41% of patients with AKI did not receive RRT as required. Extrapolating this data to the whole of China, this meant that an estimated 139,000 patients who should receive RRT for their AKI did not receive the required treatment. Patients who were elderly, men, from lower socioeconomic areas, from local hospitals, and complicated with malignancies or other severe comorbidities were less likely to receive RRT. Subjects who received RRT had lower mortality than those not receiving RRT despite requiring the treatment. In terms of the RRT modality for AKI, continuous renal replacement therapy (CRRT) was used in 53.9% of AKI cases, intermittent HD in 38%, and PD in 1.1% [203]. On the other hand, over a third of the patients who received CRRT did not require the treatment, suggesting that CRRT may be overutilized in some AKIs. The medical costs incurred in providing CRRT for those not requiring this modality [median (interquartile range), USD 7944 [4248, 16,055] vs. 5100 [2948, 9396], $p < 0.001$] and the mortality rate were higher (10.6% vs. 4.4%, $p = 0.047$) compared to those receiving other RRT modalities [203].

Two hundred ICU physicians were surveyed about their clinical practice in sepsis-induced AKI. Forty percent of ICU patients with sepsis had AKI and 25% required extracorporeal therapy. CRRT was the most commonly used modality and the median duration of CRRT was 12 hours per day for 5 days. Heparin-based anticoagulation rather than regional citrate

Table 20.6 Recent epidemiology studies of AKI in the adult intensive care unit in the Chinese Mainland

No.	Study	ICU admissions	Incidence of AKI	Mortality rate	RRT rates	Risk factors	Ref
1	2013 nationwide retrospective survey of AKI	9657	22%	21.8%	17.4%	Renal hypoperfusion, nephrotoxic drugs, other critical illness	[194]
2	Prospective survey of AKI from 30 ICUs at 28 large tertiary hospitals	2526 (1731 postoperative, 917 sepsis)	46.3 (44.8% for postoperative, 11.6% for septic AKI)	25.7% (9.3% and 5.1% for postoperative and sepsis, respectively)	18.9% (35.5% for septic AKI)	Emergency surgery, CKD, nephrotoxic drugs, cardiovascular surgery, APACHE II, SOFA score, fluid overload, use of diuretics, and sepsis	[196–198]
3	Retrospective review of stroke patients from neurology department	647	20.9%	36.3%	–	Higher NIHSS score, lower baseline eGFR, the presence of hypertension, and infectious complications	[199]
4	Prospective cohort study of 3063 patients in 22 tertiary ICUs in 2009	1058 for KDIGO study and 1255 enrolled for RIFLE study	55.4% for KDIGO study and 31.6% for RIFLE study	25.8% for KDIGO study and 35.9% for RIFLE study	26.5% for RIFLE study	A higher burden of comorbidities and higher overall severity of illness scores	[195, 200]

Abbreviation: *ICU* intensive care unit, *CKD* chronic kidney disease, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* sepsis-related organ failure assessment, *NIHSS* National Institute of Health Stroke Scale, *eGFR* estimated glomerular filtration rate, *RIFLE* risk, injury, failure, loss, and end stage, *RRT*, renal replacement therapy

Table 20.7 Recent epidemiology studies of AKI in the pediatric intensive care units in the Chinese Mainland

No.	Study	ICU admissions	Incidence of AKI	Mortality rate	RRT, rates	Risk factors	Ref
1	Observational study from PICU of Children's Hospital of Soochow University	370	6.8%	–	–	Fluid overload	[201]
2	Multicentric retrospective cohort study of 25 medical centers comprising 9 of the 15 children's hospitals and 16 of the 17 general hospitals	14,866	34.6%	–	–	–	[192]
3	Critically ill children admitted to PICU with confirmed influenza A (H1N1) or enterovirus 71 infection (EV71 group) from Oct. 2009 to Oct. 2010	28	25%	71.4%	–	–	[202]
4	A local pediatric intensive care unit in Hong Kong between 2005 and 2007	140	56%	21%	6%	–	[193]

Abbreviation: *PICU* pediatric intensive care unit, *RRT*, Renal Replacement Therapy.

anticoagulation method was preferred. Femoral vein was the predominant vascular access for CRRT. However, there was a lack of evaluation of treatment efficiency and no systematic follow-up. The mismatch between high cost of CRRT and lack of insurance cover and social support created difficulty in deciding the initiation of CRRT [204]. A retrospective study from a tertiary hospital in Ningbo, China, showed that lack of insurance coverage was one of the independent predictors of AKI-associated mortality in the ICU [205]. PD may serve as a useful alternative modality for AKI treatment in neonates. This was supported by a retrospective analysis in children that received PD as the RRT modality for AKI in a teaching hospital in Northwest China between 2003 and 2013 [206]. However, the lack of PD equipment for use in very young infants and neonates may pose a major barrier to adopt PD as the RRT modality in very young patients [207].

In order to improve AKI management and outcomes, an AKI electronic alert based on electronic monitoring of serial changes in serum creatinine levels in the medical laboratory system has been set up in several academic hospitals in China, such as Peking University First Hospital and Guangdong General Hospital. This enabled early detection and diagnosis of AKI [208]. Pilot studies (Chinese Clinical Trial Registry No. ChiCTR900021115, http://www.chictr.org.cn/index.aspx) were initiated to evaluate AKI care bundle which included screening of high-risk subjects, optimizing kidney perfusion in at-risk subjects, adjustment of drug dosages, etc. A multicenter clinical trial is currently underway to evaluate PD as a RRT modality for AKI. Preventive strategies for AKI in high-risk clinical settings such as cardiac surgery and nephrotoxin exposure are also under evaluation. There are also studies examining factors or biomarkers that may be useful for risk stratification in AKI.

In conclusion, AKI poses a huge financial burden to China healthcare and hospital system. There are major challenges in making early AKI diagnosis and initiation of treatment. More collaborative efforts are required not only from the healthcare professionals but also from the Chinese government in order to optimize the social-economic support and management of AKI, thereby improving the outcomes of patients complicated with AKI.

Nephrology Practice and Job Market in the Chinese Mainland

The nephrology workforce is essential in tackling the increasing burden of kidney disease and providing kidney care in the Chinese Mainland. With the growing burden of CKD and an enormous demand of providing RRT for CKD patients approaching ESRD, current kidney care system in the Chinese Mainland faces an unprecedented challenge. However, the exact number of the nephrology workforce and its distribution in the Chinese Mainland are currently not known due to limited studies and lack of a central medical registration office that captures clinical manpower data. In this section, we provide a brief review of nephrology workforce and nephrologists specialist training structure in the Chinese Mainland.

Most nephrology divisions are based in tertiary comprehensive hospitals, while some are in secondary referral hospitals. In 2017, there were 2340 tertiary hospitals in mainland China (with 593 in North China, 538 in East China, 455 in South China, 323 in Southwest China, 269 in Northeast China, and 162 in Northwest China) (Fig. 20.22) [209]. The distribution of tertiary hospitals reflects the distribution of nephrology divisions in the Chinese Mainland. Overall, the density of nephrology divisions in the Chinese Mainland averaged around 1.69 pmp. There are about 8.46–33.84 nephrologists pmp in the Chinese Mainland, assuming that each nephrology division had at least 5–20 nephrologists. The estimated density of nephrologists for the Chinese Mainland was higher than that reported (5.18 pmp) in the Global Kidney Health Atlas (GKHA) project of the ISN and

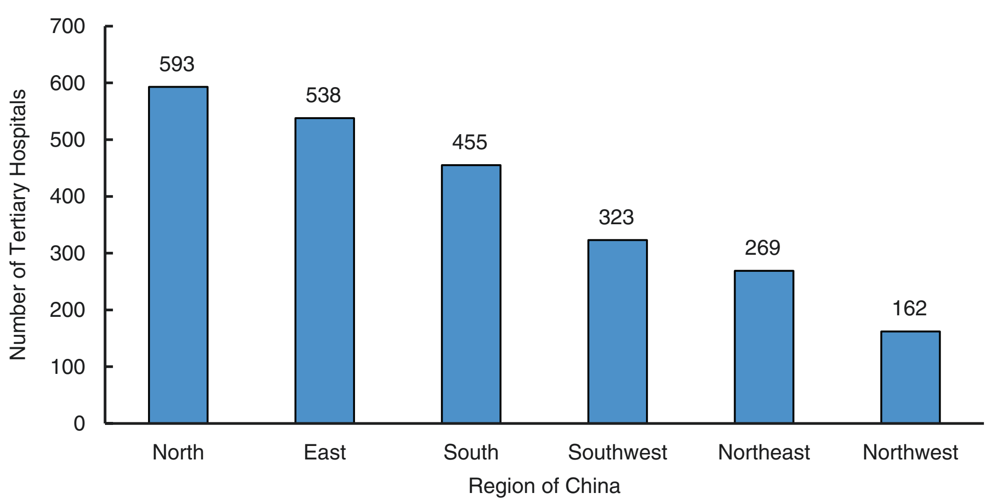


Fig. 20.22 Number of tertiary hospitals in different regions of the Chinese Mainland

surpassed the density of nephrologists in upper-middle-income countries (7.23 pmp) [210]. However, nephrologists' densities vary widely across different regions. The number of nephrologists is much lower in many county hospitals in underdeveloped and rural areas, while in many developed cities such as Beijing, Shanghai, Guangzhou, and Nanjing where large research centers of kidney disease are located, nephrologists' densities are comparable to that reported in high-income countries (28.52 pmp) [210]. The variations in nephrologists' densities across the country may impact the quality of kidney care delivery in different regions. According to the Science and Technology Evaluation Metrics report of China nephrology divisions from the Chinese Academy of Medical Science, more than 30% of the 100 top-tier nephrology divisions in the Chinese Mainland are located in three major cities (14 divisions in Shanghai, 12 in Beijing, and 8 in Guangzhou). However, in the rural or underdeveloped areas, such as Southwest and Northwest Region that accounted for more than 20% of the total population, the number of top-tier nephrology divisions is disproportionately low with only 13 divisions being among the 100 top-tier nephrology divisions in the country [211].

Apart from inpatient department of nephrology, the outpatient dialysis center constitutes another important working area for nephrologists. According to the unpublished data from CNRDS, the numbers of HD centers and PD centers in the Chinese Mainland were 5419 and 1211, respectively, in 2017. Most dialysis centers were based in tertiary and secondary referral hospitals and managed by nephrologists. In recent years, dialysis corporations, such as Fresenius and Wego, have started to set up dialysis chains in the Chinese Mainland. However, the number of these community-based dialysis centers remains very limited and serves no more than 5% of the total dialysis patients. This was different from the situation in developed countries like the USA, where community-based centers are very prevalent and operated by large dialysis organizations such as DaVita and Fresenius. The "tertiary hospital-based" structure has in part resulted in an imbalance distribution of dialysis centers in the Chinese Mainland. The Chinese government currently encourages investment and setting up of private or independent dialysis centers in order to meet the increasing market need and demand for dialysis in the country. It is foreseen that there will be a rapid growth in the number of dialysis centers in the near future. The ratios of physician to patient and nurse to patient in HD or PD centers is currently much lower in the Chinese Mainland compared with other countries.

The training program for nephrologists in the Chinese Mainland is divided into three phases: Phase 1 involves a standardized training program for residents for general internal medicine. Phase 2 involves standardized training program for specialists (nephrologists) and phase 3 involves continuous medical education of specialists (nephrologists) (Fig. 20.23). Unlike the resident training program, specialist training (or fellowship training) program for nephrologists

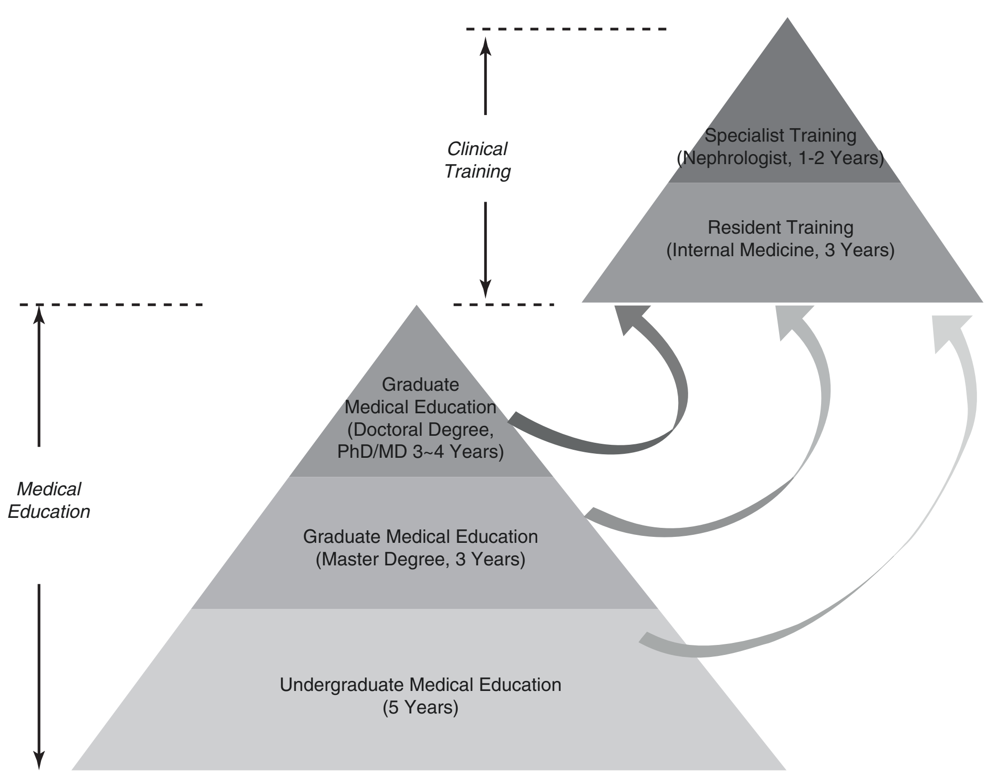


Fig. 20.23 The medical education and clinical training of nephrologists in the Chinese Mainland

(or other specialties) has not been implemented nationwide. Only a small proportion of nephrologists in developed regions of China receive specialist training in tertiary hospitals/medical centers in the country or receive fellowship training abroad. In the GKHA project, the Chinese Mainland reported a nephrology trainee density of 1.46 pmp, a little lower than the global average level of 1.87 pmp and much lower than that of high-income countries (6.03 pmp) [210]. There is great disparity in the highest degree attained by nephrologists working in tertiary and secondary referral hospitals. A master's degree is usually an essential prerequisite for practicing nephrologists in first- or second-tier cities of the Chinese Mainland, and a large proportion of them (specifically for those age below 45 years) also hold a doctoral degree (MD or PhD). However, a bachelor degree is usually the highest degree attained by most nephrologists working in the third- or fourth-tier cities or underdeveloped areas. The salaries of nephrologists vary among different parts of the Chinese Mainland but are comparable to those of other physicians.

Apart from the nephrologists' workforce, the Chinese Mainland faces significant gaps and deficiencies in specialized nephrology nursing manpower, especially nurses with skills and experience in providing dialysis service. The Chinese Mainland is in need of more renal pathologists. There are also significant gaps in other nephrology-related workforce or allied health professionals' manpower such as renal dietitians [210].

Apart from clinical service provision, academic research is an integral part in many teaching hospitals. However, there are very few full-time academic positions in the Chinese Mainland. Research is mostly done by graduate students of Doctor of Philosophy (PhD) or master's degree (MD). In general, research grants in the Chinese Mainland do not include the salary of research staff. This is very different from research grants funded in most other countries. This may possibly explain why the country has very low number of full-time researchers. Nevertheless, many young nephrologists are still interested in and enthusiastic with academic and research work as academic achievement adds merit for their career development and job promotion in most university-affiliated hospitals. Research grants are mostly supported by the National Natural Scientific Foundation, which provides 300–400 grant programs annually with each grant fund around USD 35,000–80,000. Chinese nephrologists have increasing academic contributions and publications in world leading, high impact kidney and medical journals in the recent years. There are also an increasing number of Chinese nephrologists involved in the leadership of global nephrology societies such as ISN, KDIGO, and ISPD. Chinese nephrologists are very open in establishing connections with global or regional nephrology organizations in order to contribute to kidney research and advances in kidney care.

RRT in HK Special Administrative Region (SAR)

The hospital system in HKSAR is independent and entirely different from that in the Chinese Mainland. The Hospital Authority (HA) of HKSAR was set up in Hong Kong in 1990 and is responsible for providing RRT and kidney care in over 80% of the ESRD patients in Hong Kong. The remaining 20% of ESRD patients are managed in private settings/hospitals. The RRT public services in Hong Kong are delivered through 7 clusters with 15 renal units under the HA. There are four kidney transplant centers in Hong Kong, including Princess Margaret Hospital, Prince of Wales Hospital, Queen Elizabeth Hospital, and Queen Mary Hospital. The Hong Kong Renal Registry (HKRR) was set up by the HA in 1995 and is an online computerized registry developed by the Central Renal Committee of HA of Hong Kong to capture data of all patients receiving RRT in the public healthcare system under HA of Hong Kong. Each individual renal center can access patients' data from their own center online, and each center is responsible for inputting data of all patients receiving RRT in their center. The system provides important data for the unit as a whole and for the HA Head Office to produce an up-to-date registry data for the RRT situation in the whole HA. The information is useful for audit and monitoring purpose as well as healthcare financing and planning of future renal service development in Hong Kong. The HKRR also comprises the Organ Registry and Transplant System (ORTS) that includes the Organ Procurement System and Transplant Immunogenetics System. The Organ Procurement System collects demographic details, immunological and virology results of all cadaveric donors. Transplant and Immunogenetics System centralizes all the transplant immunogenetics and tissue typing data of deceased donor and patients on transplant waiting list. The HKRR also serves the function of deceased donor kidney allocation. A scoring system was developed, based on the years on RRT, HLA matching, and age of patients, so to assign the priority of the patients on the transplant waiting list. When a deceased donor is confirmed, tissue typing of the deceased donor will be performed by the Tissue Typing Laboratory centralized in the Queen Mary Hospital, Hong Kong, and inputted in the system so to generate the final scoring for deceased donor kidney allocation [212].

RRT service development in Hong Kong has undergone the following milestones over the years. The first acute HD was done in HK in 1962 followed by the development of chronic HD. In 1969, the first cadaveric kidney transplant was performed and in 1980 the first living-related kidney transplant was performed. In the 1980s, CAPD was introduced in Hong Kong. In 1985, PD-first policy was adopted by the HA of Hong Kong of which PD was reimbursed by the government as a first-line dialysis modality in patients with ESRD. Automated PD (APD) was introduced in 1989. PD patients may face technique failure either due to PD-related complications such as peritonitis, peritoneal sclerosis/adhesions, or inadequate PD due to peritoneal membrane failure, requiring permanent switch to HD. Thus, there is an increasing demand for long-term HD support. HA of Hong Kong introduced the nocturnal home HD program in 2006 and the public-private partnership HD program since 2010 to cope with an increasing demand of HD services [212].

Data first captured by the HKRR in 1996 showed that the number of incident ESRD patients in Hong Kong was 615. This number showed steady increase to 1147 in 2013, equivalent to an incidence rate of 159 pmp. By 2013, there were 8510 patients receiving RRT in Hong Kong with 3501 kidney transplants, 1192 HD, and 3817 PD. The ratio of PD:HD was 76.2:23.8. Over 90% of the HD is provided by hospital HD centers. Eighty-six percent of all PD patients received CAPD, while the remaining 14% received automated PD. The use of APD showed a gradual increase in Hong Kong over the years. In 1997, only 3.14% of PD patients used APD but APD use was slowly increased to 5.52% in 2007 and 13.89% in 2013. Data from the HKRR 2016 showed that the annual mortality rate per 100 patient-years was 1.88 for patients who received a renal transplant, 17.89 for patients on PD, and 18.89 for those on HD in Hong Kong [213].

Data from the HKRR showed a trend of increasing age in incident PD patients over the last 17 years from 1996 to 2013. The median age of incident patients into the RRT program was 59.1 years in 2013 with the biggest increase in the age group 45–64 years and age group over 75 years**.** There was a male preponderance in both incident (male-to-female ratio, 1.54) and prevalent (male-to-female ratio, 1.29) dialysis population. Over the years, the demographics of background causes of kidney disease also changed. In 1995, GD accounted for 29% of the causes of kidney disease in incident dialysis patients but dropped to 17% in 2013. On the other hand, DKD increased from 26.2% in 1996 to 49.6% in 2013 as the cause of incident ESRD cases requiring RRT and is the leading cause of ESRD followed by GD and unknown causes [212].

Hong Kong faces a serious shortage of organ donations that did not seem to improve much over the years. In 2013, there were 1991 ESRD patients on the kidney transplant waiting list. However, only 69 deceased donor kidney transplants and 12 living-related kidney transplants were conducted in Hong Kong. In fact, the number of living-related kidney transplants has not shown much increase in the last 15 years (from 297 cases in 1996 to 415 cases in 2013). However, prevalent kidney transplant patients showed a steady rise from 956 in 1996 to 3498 in 2013, mainly because of an increase in deceased donor kidney transplants (from 659 cases in 1996 to 3085 cases in 2013). Data from the HKRR showed that a living-related kidney transplant had higher 10-year graft survival rate (81%) compared with deceased donor kidney transplant (70%). The 20-year graft survival rate was 44% for deceased donor and 61% for living donor kidney transplant. However, the average waiting time could be approximately 6 years but may also be as long as 28 years [213, 214]. Public education is therefore essential to raise general awareness of the need for deceased organ donation. In the second half of 2018, HA of Hong Kong introduced a pair exchange scheme for kidney transplants that enables two pairs of donor-recipients to exchange kidney donors so that each recipient can receive a better-matched organ.

In terms of anemia treatment, there was a big increase in the proportion of dialysis patients receiving ESA treatment from 29.3% in 1996 to 65% in 2013 as the Hong Kong government has provided additional funding to support ESA treatment in dialysis patients. Currently, HKRR did not include data on patients with CKD or AKI. Thus, representative territory-wide data in these regards were not available.

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