Chronic Kidney Disease Burden in Low-Resource Settings: Regional Perspectives

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Summary: The burden of chronic kidney disease (CKD) has increased exponentially worldwide but more so in low- and middle-income countries. Specific risk factors in these regions expose their populations to an increased risk of CKD, such as genetic risk with *APOL1* among populations of West African heritage or farmers with CKD of unknown etiology that spans various countries across several continents to immigrant/indigenous populations in both low- and high-income countries. Low- and middle-income economies also have the double burden of communicable and noncommunicable diseases, both contributing to the high prevalence of CKD. The economies are characterized by low health expenditure, sparse or nonexistent health insurance and welfare programs, and predominant out-of-pocket spending for medical care. This review highlights the challenges in populations with CKD from low-resource settings globally and explores how health systems can help ameliorate the CKD burden.

Keywords: Burden of chronic kidney disease, low-resource setting, low- and middle-income countries, health systems

Chronic kidney disease (CKD) affects 13.4% (11.7%-15.1%) of the world's population.[1] Between 4.90 and 7.08 million patients with end-stage kidney disease (ESKD) need kidney replacement therapy.[1] In 2020, the World Health Organization (WHO) ranked CKD as the 10th leading cause of death. It is expected to become the fifth leading cause of life lost by 2040.[2] According to the Global Burden of Disease (GBD) study, CKD deaths increased by 41.5% from 1990 to 2017.[3] In recent decades, the incidence and prevalence of CKD has increased exponentially worldwide, reaching epidemic levels in developing and developed countries. Diabetes mellitus, hypertension, obesity, and aging drive the global increase, but infections and herbal and environmental toxins also contribute in low-resource countries.[1] In many low-income countries, communicable diseases such as streptococcal infections, schistosomiasis, leishmaniasis, and HIV as risk factors for kidney disease are common. Because of the concomitant increasing prevalence of noncommunicable disease (NCD) risk factors, many low- and middle-income countries (LMICs) now have a double disease burden that compounds the risk for kidney disease.[4]

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By 2030, more than 70% of ESKD patients will live in low-income countries, including sub-Saharan Africa, where the gross domestic product (GDP) per person averages less than US $1,500.[5] A cross-sectional population study of more than 8,000 persons, ages 40-60, in six centers in four African countries had 10.7% prevalence of CKD (95% confidence interval [CI] 9.9-11.7).[6] A 2022 meta-analysis of 4,760,147 subjects from 110 moderate- to high-quality studies in 14 LMICs in Asia reported an 11.2% prevalence of CKD stages 3-5 (95% CI 9.3-13.2%).[7] CKD prevalence was lowest in eastern Asia at 8.6% (95% CI 7.2-10.2%) and highest in southern Asia at 13.5% (95% CI 9.5-8.0%).[7] Upper middle-income countries had a lower prevalence of CKD 9.8% (8.3-11.5%) versus 13.8% (9.9-18.3%) in LMICs.

Most people in LMICs cannot afford dialysis or kidney transplantation, with less than 10% of patients in these settings receiving kidney replacement therapy,[8] and untreated kidney failure kills over 1 million people annually.[9] Lack of awareness, limited access to health care, late-onset presentation, limited health worker capacity for CKD detection, and lack of prevention strategies in resource-poor countries contribute to the growing CKD burden. In addition, the absence of national kidney registries and poor funding prevent understanding of the true magnitude of the problem.[8] Many factors, therefore, drive the burden of CKD in LMICs (Fig. 1) and require strategies to improve in various aspects of care delivery, funding, and human resources (Table 1). This review highlights the CKD burden in Latin America, Africa, the Middle East, and Southeast Asia (many countries in these regions belong to LIC and LMIC according to World Bank income level classification, Fig. 2).[10]

PERSPECTIVES FROM SOUTH AMERICA

South America covers 19 million square meters and has 638 million people growing at a 1% annual rate. Every country in this region was a colony of the 16th century Iberian empires (Spain and Portugal). The countries are diverse because of their geography (mountains, coasts, deserts, plains, and jungles), indigenous people, immigration patterns, and economic activities. Despite its wealth (GDP: US $5.954 billion), inequity exists in personal and collective development such that 26% to 50% of its population lives in poverty.[11]

Many indigenous communities suffer social isolation and lack health visibility. They have more advanced

Figure 1. Factors that drive CKD burden in low-resource settings.

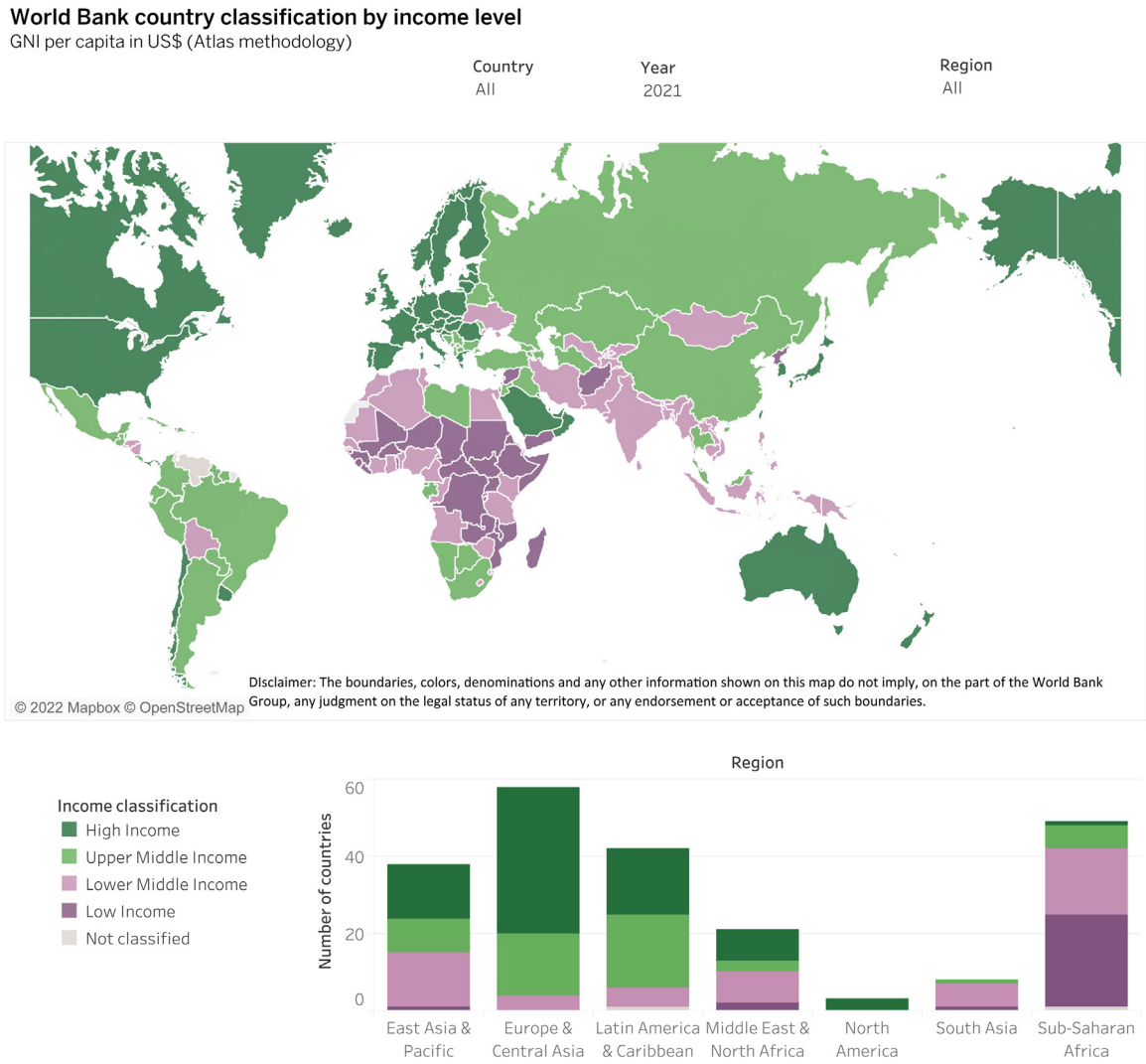

Figure 2. Map of World Bank country classification by income level.[10]

Table 1. Key Challenges Pertinent to Low-Resource Settings in Asia

S/N	Challenges	Probable Mitigation Strategies
1	Scarce data on disease burden	Nationwide registries, population-based screening
2	Population explosion	Mass education and incentivizing couples practicing family planning
3	Low sociodemographic index	Economic growth
4	Delayed presentation of cases	Community-based screening programs and strengthening primary care
5	Inaccessibility to kidney diagnostics	Strengthening public-funded institutions
6	Pregnancy-associated kidney diseases	Institutional delivery and regular training of obstetricians on basic management of AKI
7	Tropical infections	Environmental reforms, strengthening disaster management programs, reducing anthropogenic hazards
8	Endangered population	Organic farming, improving access to safe drinking water, public health education
9	Lack of KRT infrastructure	Promoting CAPD, promoting public-private partnership for establishing in-center HD
10	Wide treatment gaps	Increasing training programs, governmental funding, private-public partnership
11	Lower kidney transplant rate	Public awareness programs, legislative reforms to allow altruistic donation, expand eligible live donation criteria, curb organ trafficking, opt-out system for deceased donation

Abbreviations: AKI, acute kidney injury; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis; KRT, kidney replacement therapy; S/N, serial number.

hypertension, diabetes, and dyslipidemia than urbanites. In remote communities, cultural beliefs and the influence of healers, shamans, and wizards create an additional barrier to accessing health care.[12] Latin America allocates 3.7% of its GDP to population health and has one of the lowest numbers of health workers overall. The region has only 16 nephrologists per million people, compared with the minimum target of 20 as recommended by SLANH (Latin American Society of Nephrology and Hypertension).[13]

CKD Epidemiology in South America

CKD is one of the 10 leading causes of death in Latin America and the second leading cause of disability-adjusted life years.[12,14] Regional CKD prevalence ranges from 9% to 35%, and it is diagnosed in one-third of people with other comorbidities, older adults (age > 60 years), and those in the three lowest sociodemographic quintiles.[12,14] CKD incidence in the region has doubled in 10 years and will affect 1 million people by 2030.[14] These figures are likely underestimated because many in the population cannot access health care, and many health authorities do not keep records.[12]

Lupus nephritis is also common in the Colombian Caribbean,[15] and Mesoamerican nephropathy or CKD of unknown etiology (CKDu) is common in agricultural communities in Central America.[16,17] Maternal-fetal factors, especially low birth weight (LBW), promote incomplete nephrogenesis, which increases the lifetime risk of kidney disease.[18]

PERSPECTIVES FROM AFRICA

Africa has 54 countries with 1.2 billion people. Many African countries have a double burden of communicable diseases and NCDs due to Western lifestyles and rapid urbanization. CKD is a major public health threat in Africa because of increasing risk factors and limited access to kidney care services. As in other low-resource settings, prevention and early detection are crucial in Africa. Pooled prevalence of CKD in general and high-risk populations in Africa is estimated to be between 10.1% and 15.8%.[19] North Africa has the lowest pooled prevalence at 4%, followed by East Africa (11.0%), Southern Africa (12.2%), Central Africa (16%), and West Africa (16.5%). The pooled prevalence of CKD in those with HIV/AIDS is 5.6%, 24.7% in those with diabetes mellitus, and 34.5% in those with hypertension, and, as expected, is higher than in the general population.[19]

Evolving CKD Epidemiology in Africa

The discovery of kidney disease risk variants in the *APOL1* gene for CKD is highest among those of West African ancestry and may shed light on the pathogenesis of this region's susceptibility to kidney diseases. In sub-Saharan Africa, two haplotypes (G1 and G2) with high population frequency are strongly associated with non-diabetic CKD (odds ratio range 3-29).[20] West Africa has the highest population frequency.[20] About 23.3% of Igbo people in southeastern Nigeria have two *APOL1* risk alleles, increasing to 66% in CKD patients.[21] This high population frequency of carrying two *APOL1* risk alleles raises several concerns about acceptable kidney donation risk in Africa, need for genetic testing among specific ethnic communities to screen for kidney disease given the heterogeneity of the prevalence of risk alleles across the continent, and risk of other diseases such as pre-eclampsia. Furthermore, the understanding of genetic and environment interaction also needs to be studied.

PERSPECTIVES FROM ASIA

Asia, spanning the northern and eastern hemispheres, is home to 60% of the world's population. The continent's ethnic groups, cultures, environments, economies, and governments are diverse. Despite surpassing other regions in transitioning from low-income to middle high-income economies,[22] Asia has the highest CKD prevalence.

According to the GBD study in 2017, 434.3 million (95% CI 350.2 to 519.7 million) adults in Asia have CKD, and 65.6 million (95% CI 42.2 to 94.9 million) have advanced CKD, compared with 697.5 million globally.[3] India and China account for 70% of all CKD cases in Asia.[23] South Asia has surpassed others with a 13.5% (9.5%-18.0%) prevalence.[7] South Korea has a 7% CKD prevalence, while Singapore has 34.3%.[22]

Afghanistan, Maldives, Bhutan, and Sri Lanka lack population-based kidney disease screening data. Few multistage cluster screenings from rural India have identified non-proteinuric kidney disease in lean farmers with CKDu.[24] Age, lack of formal education, and rural residence were risk factors for lower estimated glomerular filtration rate.[23]

CKD Epidemiology in Asia

Local etiology, genetics, sociodemographics, and health care access affect CKD incidence and prevalence. The lack of national registries or community-based surveys obscures the burden of CKD in low-resource settings. In most South Asian countries, health authorities neglect NCDs to address infectious diseases and high infant and maternal mortality. COVID-19 has exacerbated the challenges of managing NCDs like CKD. Most South Asian countries have no screening or management policy for kidney disease. Low GDP, low health care funding, and a large low-income population exacerbate the problems. CKD disproportionately affects low-income groups, making risk factor identification and mitigation difficult. It is generally detected early only when kidney function

is evaluated for other health reasons or, less commonly, by routine screening.[25] More than 65% of the population lives in rural areas, where few health care facilities are located. Social and cultural taboos encourage reliance on unproven local remedies that can harm kidney health and delay nephrology care. High out-of-pocket costs, lack of health insurance, low nephrologist-patient ratio, fewer care centers, and lack of universal kidney replacement therapy access hinder quality care. Low income and limited resources make treatment unavailable, unaffordable, or both.

Poverty, poor sanitation, pollution, water contamination, overcrowding, and nephrotoxins (including heavy metals and plant toxins) exacerbate the problem. Inadequate regulatory oversight increases the risk of accidental pesticide exposure and suicide. Agricultural workers, women, children, and the elderly population have limited treatment options. The government has little or no contribution to providing kidney replacement therapy, and because South Asia lacks resources, 90% of patients die within months of diagnosis.[26]

South Asian infants are more likely to be underweight compared with Africans (2.7 kg versus 3.1 kg).[27] Poor nutrition and socioeconomic status are linked to LBW in infants. LBW and early malnutrition increase South Asian children's risk of proteinuria, high blood pressure, metabolic syndrome, and diabetic nephropathy.

PERSPECTIVES FROM INDIGENOUS AND IMMIGRANT COMMUNITIES IN THE UNITED STATES AND CANADA

Global indigenous populations, including those from North America, Australia, native Hawaii, and Asian Americans, as an immigrant group in the United States, are understudied. Neither the burden of CKD nor risk factors leading to CKD progression are well characterized. Studies have demonstrated higher mortality among Blacks and American Indian/Alaska Natives when compared with Hispanics and Whites. Asian/Pacific Islanders and Hispanics had lower odds than Whites for most multiple chronic condition combinations.[28] Similarly, in Canada, indigenous First Nations populations with diabetes but without CKD had disparities in quality indicator assessment such as urine albumin/creatinine ratio, fasting low-density lipoprotein cholesterol, and glycated hemoglobin target achievement.[29]

CKD Epidemiology in Indigenous and Immigrant Populations

Native Hawaiians and Pacific Islanders have the highest ESKD incidence rate among all races, even after multirace reporting. A 2020 analysis found that Native Hawaiians and Pacific Islanders' ESKD incidence rate of 921 (95% CI 904-938) per million population per year was 2.7 times higher than that of Whites and 1.2 times higher than that of Blacks.[30] Using multirace reporting, the report documented 941 (95% CI 895-987) per million population annually. Diabetes was the most frequent primary cause of ESKD for Native Hawaiians/Pacific Islanders and American Indians/Alaska Natives. The Hawaiian and Pacific Island territories provided less pre-ESKD nephrology care than the other 50 states.[29] Additionally, in another 2020 retrospective cohort study using US Renal Data System (USRDS) data that included 1,547,438 adults with no prior transplantation and first dialysis between April 1, 1995, and September 28, 2012, the crude mortality rate (deaths per 100 patient-years) was lower for Whites in the Hawaiian and Pacific Island territories than in the 50 states (14 versus 29), similar for Blacks (18 versus 17), and higher for Hispanics (27 versus 16) and Asians (22 versus 15).[31] Furthermore, in matched analyses, Hispanics (hazard ratio [HR] 1.65, 95% CI 1.60-1.70, $P < .001$) and Asians (HR 2.01, 95% CI 1.78-2.27, $P < .001$) living in the Hawaiian and Pacific Island territories had higher death risks than their 50 state counterparts.[30] Besides, Latinx—people of Latin American ethnic identity—have a 1.3-fold higher incidence of kidney failure than non-Latinx Whites.[32]

Indian Health Service and the Centers for Disease Control and Prevention (CDC) reported a 54% decrease in kidney failure among American Indian/Alaskan Natives with diabetes in 2018.[33] A population health approach to diabetes care in the community and primary care settings reduced ESKD incidence. Better kidney care was integrated into routine diabetes care.[33] This program shows that simple, evidence-based interventions can reduce the burden of ESKD and that population-based approaches to chronic diseases have significant benefits. Large pragmatic trials may be best for testing this hypothesis.[33]

Disparities in the Provision of Kidney Replacement Therapy

Differences in treatment modalities (transplantation, peritoneal dialysis, home hemodialysis, or in-center hemodialysis[34] from 2011 to 2018 as of day 90) were quantified for patient subgroups defined by race, ethnicity, and age.[34] Eighty-one percent of patients received in-center hemodialysis, 3.0% had kidney transplantation (85% preemptive, 57% living donor), 10.5% were on peritoneal dialysis, and 0.7% were on home hemodialysis.[34] Absolute treatment disparities were greatest among patients aged 22 to 44 years. Non-adjusted treatment percentages for non-Hispanic White, Hispanic, and non-Hispanic Black patients were transplantation (10.9%, 4.4%, and 1.8%), peritoneal dialysis (19.0%, 16.9%, and 13.8%), and home hemodialysis (1.2%, 0.5%, and 0.6%), respectively. After adjustment, the largest relative treatment disparities were observed for kidney transplantation: compared with non-Hispanic White

patients, the adjusted risk ratios for non-Hispanic Black and Hispanic patients were 0.21 (0.19-0.23) and 0.47 (0.43-0.51), respectively.[34] This analysis demonstrated that racial and ethnic disparities in kidney transplantation and home dialysis use were greatest among young adults with incident kidney failure even in a high-resource setting.[34]

Comparisons of waitlisting and deceased donor kidney transplantation among 503,090 nonelderly adults of different racial/ethnic groups who began hemodialysis between 1995 and 2006 and were followed through 2008 revealed that fewer racial-ethnic minorities than Whites had deceased donor kidney transplantation.[35] Annual rates were lowest in American Indians/Alaska Natives (2.4%) and Blacks (2.8%), intermediate in Pacific Islanders (3.1%) and Hispanics (3.2%), and highest among Whites (5.9%) and Asians (6.4%). The reduction in kidney transplant rates attributable to measured factors ranged from 14% in Blacks to 43% in American Indians/Alaska Natives compared with Whites.[35]

A recent study examined the experience of 75 undocumented immigrants from Mexico, Central America, or South America who underwent transplantation in Sacramento, California; most had received deceased donor kidneys with 85.9% graft survival for deceased donor recipients at 8 years and 100% for live donor recipients.[36] Clearly, despite the limitations of limited or nonexistent financial coverage, socioeconomic instability, and poor access to social services among undocumented immigrants, kidney transplantation, when possible, is medically and financially a sustainable and better treatment modality for ESKD.[36] The excellent kidney transplant outcomes suggest that the undocumented status did not confer an increased graft loss risk.[36] Such findings make a very strong case to increase access among undocumented immigrants to kidney transplantation.

Reducing Disparities in Kidney Replacement Therapy in the United States

Recently, a scalable metric measures kidney transplantation centers' performance in providing equitable access to minority patients based on ESKD prelisting prevalence. The USRDS and United Network for Organ Sharing (UNOS) data (2013-2018) were combined to calculate the Kidney Transplant Equity Index, which compares the number of minority patients undergoing transplantation at a center with the prevalence of minority patients with ESKD in each center's health service area. High and low Kidney Transplant Equity Index centers compared socioeconomic status and recipient outcomes. About 249 transplant centers performed 111,959 kidney transplants on 475,914 ESKD patients. High Kidney Transplant Equity Index centers performed more kidney transplants on Black (105.5 versus 24, $P < .001$), Hispanic (55.5 versus 7, $P < .001$), and American Indian (1.0 versus 0.0) patients. They performed more kidney transplants on unemployed (52 versus 44, $P < .001$), socially deprived (53 versus 46, $P < .001$), and low-educated (52 versus 43, $P < .001$) patients. High Kidney Transplant Equity Index centers had improved patient survival (HR 0.86, 95% CI 0.77-0.95). This novel metric demonstrates national variation in transplant practices and should be used to ensure best practices for minority and low-income ESKD patients.[37]

PEDIATRIC PERSPECTIVES

The burden of CKD in children is unknown and underreported because many low-resource settings lack renal registries.[38] Because of nonspecific and late-appearing symptoms, CKD is often missed, especially in its early stages. In low-resource settings, CKD in children is often associated with little or no kidney function, late hospitalization, and no health insurance to enable adequate and appropriate kidney care. They die before or soon after initiating dialysis.[38] In Pakistan, many children with CKD seek treatment late, resulting in an age-specific mortality rate 30 to 150 times higher than for healthy children in high-income countries.[39] Countries with low resources spend less than 5% of their GDP on health, which is well below WHO recommendations, with the greatest negative impact on children.

CKD Epidemiology in Children

Data from the United States show that the burden of pediatric CKD increased gradually in the 1980s and marginally until the early 21st century, when treatment improved, leading to better survival.[40] Recent single-center research in Nigeria reports that ESKD affects 4 per million at-risk children.[41] The incidence in many South American countries ranged from 2.8 to 15.8 new cases per million at-risk populations.[42] The prevalence of CKD ranges from 1% to 13% in India,[26] and data from a major tertiary hospital showed that 12% of patients (n = 305) seen by the pediatric nephrology service over 7 years had moderate to severe CKD (CrCl <50 mL/min/1.73 m^2), and 25% of them already had ESKD, highlighting the late diagnosis and referral pattern.[43] International Society of Nephrology Kidney Disease Data Center Study reported a 17% prevalence in Southeast Asia.[44]

Congenital abnormalities of the kidney and urinary tract (CAKUT) (48.0%), nephrotic syndrome (10.4%), glomerulonephritis (8.1%), and renal ciliopathies (5.3%) are the main causes of CKD in children (accounting for >70% of cases) in high-income countries where well-developed registries exist. Chronic glomerulonephritis is the main reported cause from India, Southeast Asia, Latin America, and sub-Saharan Africa, with a prevalence of 30% to 60%.[42] Infection-associated glomerulonephritis is often from the high prevalence of bacterial, viral, and parasitic infections. Reports show variations in

Table 2. Epidemiology and Etiology of CKD in Selected Pediatric Populations

Country, Region	Egypt, North Africa[47]	Nigeria, West Africa[48]	Guatemala[49]	Nepal[46]	Pakistan[39]	Italy[50]
Study Year	2012-2018	2000-2009	2004-2014	2012-2013	2008-2019	1990-2000
Number of Children	1,018	154	1,545	206	229	1197
Mean Age (SD)/Age Range, y	1-19	10 (0.2-15.5)	6.19 (±4.66)	8.3 (±3.70) 0-16	0-16	0-19
Male:Female Ratio	1.3:1	1.3:1	1.1:1.0	1.38:1	1.8: 1	2.04:1
Mean Incidence	—	11(6-20) pmcp/y				12.1/pmcp
Prevalence	—	48 (8-101) pmcp/y		6.98%	NA	74.7/pmarp
Major Etiologies (%)						
Glomerular Diseases	15.3	90.26	11.6	63.8	15.0	5
CAKUT	46	7.79	27.7	4	49.0	58
Hereditary Nephropathy	6.7	1.95	1.4	15	—	15
Urolithiasis	—		2.4	1	17.5	—
Unknown	20.6		0.0	3	5.7	3

The table contains data from selected geographically diverse regions.
Abbreviations: CAKUT, congenital anomalies of the kidneys and urinary tract; NA, not available; pmcp, per million children population; pmarp, per million age-related population

etiology within the low-resource settings according to geographic location. In Sudan, Brazil, Nigeria, and India, higher prevalence of chronic glomerulonephritis predominates, whereas in Cape Town, South Africa and Egypt, CAKUT is the predominant etiology, similar to high-resource settings (Table 2).[39,41,45–50] Observations from studies may appear that in areas with a predominance of non-Black children, CAKUT is the most common cause of CKD. Although ultrasonography is widely available, many children are not diagnosed before birth. High rates of preterm births in low-resource settings, especially in Asia and sub-Saharan Africa, account for 81% of all preterm births, contributing to low nephron numbers in LBW and small-for-gestational age newborns, which are predisposing factors for CKD.[51]

Kidney Replacement Therapy in Children

Between 4% and 10% of ESKD patients in low-resource settings received kidney replacement therapy compared with 60% in Western Europe.[52] Between 2.3 million and 3.2 million people die annually from lack of dialysis.[49] A review of 12 studies from four sub-Saharan African countries found that 61% of children with kidney failure started dialysis, 49% stopped dialysis, 19% received kidney transplants, and within days to months of diagnosis, 62% died.[53] In contrast, in Europe, children with kidney failure have a 5-year mortality rate of 15.8 per 1,000 patient-years. South Africa and Sudan pay for maintenance dialysis. However, in South Africa, it is rationed,[54] and in Sudan, it is offered less frequently, ie, two instead of three times per week.[55] According to the Global Kidney Health Atlas, 68% of African countries have no access to kidney transplantation.[18] In Europe, pediatric kidney transplant rates range from 0 to 13.5 per million children.[56] Data for low-resource settings are sparse, but some report rates as low as 4 per million children population.[56]

CKD in children and the associated comorbidities such as malnutrition, metabolic acidosis, mineral and bone disorders, anemia, and fluid and electrolyte abnormalities can impair growth,[57] reduce the quality of life, neurocognitive ability, and exercise capacity, and lead to early mortality from hypertension and cardiovascular disease. Children with ESKD have a 1,000-fold higher risk of cardiovascular disease than age-matched non-CKD patients.[53] Children in low-resource settings will not have optimal management of each comorbidity to maximize both survival and quality of life. Further, caring for children with kidney failure is difficult, and in some cases, the burden of caring for a child with ESKD may affect the decision to initiate dialysis treatment.[57] Parents may have to perform time-consuming technical procedures, such as peritoneal dialysis exchanges and enteral feeding, and ensure medications are taken.[58] Dialysis caregivers report financial difficulties, social

isolation, poor physical health, depression, family disruption, and lower health-related quality of life. A recently developed Pediatric Renal Caregiver Burden Scale, which quantitatively measures caregiver burden, has been validated in the UK and Egypt but not globally.[58] In many low-resource settings, ESKD treatment is not prioritized because of the high cost of kidney replacement therapy, dwindling financial resources, and insufficient health care funding, which are well beyond the ability of most parents.[53]

EMERGING DISEASES AND CHALLENGES

CKD of Unknown Etiology

CKD of unknown etiology refers to kidney diseases that are not caused by the traditional risk factors, such as diabetes, hypertension, and HIV.[53] It was first described in agricultural communities of South America and Southeast Asia and affects many young and middle-aged agricultural workers in communities in Africa who live around the equator. Among Asian countries, the epicenter is in South Asia: Sri Lanka, India, and Bangladesh.[29] CKDu is the second-most prevalent underlying cause of CKD (16%), after diabetic kidney disease (31.3%), according to data from the Indian CKD Registry.[59] Data from Sri Lanka reveal a doubling of the incidence of CKDu every 4 to 5 years.

COVID-19-Associated Nephropathy

The current COVID-19 pandemic has revealed a rebirth of reports of collapsing glomerulopathy similar to the HIV epidemic. COVID-19-associated nephropathy (COVAN) is a new clinical entity related to SARS-CoV-2 infection.[60] It can present as acute kidney injury (AKI) or acute worsening of pre-existing CKD with marked proteinuria, usually in the nephrotic range.

Although most reports on COVAN emanate from regions outside Africa, practically all documented cases are individuals of African heritage who possess the *APOL1* high-risk allele.[7] The extent of COVAN in Africa is unknown, as reported cases originating from Africa are few.[24]

Climate Change

Climate change affects kidney disease epidemiology and presentation. Its implication for low-resource settings like Southeast Asia and sub-Saharan Africa is crucial. Rising global temperatures have led to an upsurge in heat waves, which increases morbidity and mortality. The kidney shields the host from heat and dehydration and is a key target for heat-related diseases. Extreme heat increases core body temperature, causes dehydration, and raises blood osmolality.[61] Both clinical and subclinical whole-body hyperthermia can lead to AKI/acute kidney disease owing to rhabdomyolysis and heat-induced inflammatory injury.

Social Transformation and Modernization

Social transformation and modernization are common in sub-Saharan Africa, South America, and Asia. In South America, the process of globalization has transformed the identities of the population with positive (trade and demographic improvement) and negative (cross-border and rural-urban migration and infrastructural deficit) effects. Similarly, sub-Saharan Africa is rapidly modernizing. Progress and development have improved the quality of life; however, they also lead to unhealthy lifestyle changes such as increased salt intake, sedentary lifestyle, alcohol consumption, and tobacco use.[62] Modernization increases CKD risk with rising rates of obesity, hypertension, and diabetes, as well as high-risk behaviors leading to HIV and hepatitis B and C infections.

Migration of Workforce

Migration of health care workers, mostly doctors and nurses, to more affluent regions is another major challenge to kidney care throughout Africa, although it is an issue globally.

Regional Kidney-Specific Issues

Acute kidney injury

Low-resource settings are rife with community-acquired AKI (CA-AKI) and pregnancy-related AKI (PRAKI). CA-AKI accounts for 80% of AKI patients in these settings according to the International Society of Nephrology's "0by25" Global Snapshot study.[63] Suboptimal prenatal care, out-of-health care facility delivery, unsafe abortion practices by unqualified personnel, and widespread use of unproven therapies make PRAKI difficult in these settings.[64] These insults can lead to ESKD; thus, it is crucial to treat them early and comprehensively.

Glomerulonephritis

South Asia has the highest age-standardized incidence and prevalence rates of acute glomerulonephritis as documented by the Global Disease Burden Report (1990-2019).[65] However, glomerulonephritis in many low-resource settings, especially in sub-Saharan Africa, is second to hypertension as a cause of CKD because of prevailing subclinical and clinical infections. Globally, lupus nephritis is linked to poverty; therefore, it is not uncommon in low-resource settings and should be considered in the evaluation of glomerular diseases. Glomerulonephritis, including IgA nephropathy and lupus nephritis in Asia, varies by prevalence, severity, treatment response, and adverse outcomes.[66]

Kidney Care and Challenges in Low-Resource Settings

Globally, at least 2.3 million patients die prematurely because of lack of or limited access to kidney replacement.[23] According to a recent systematic analysis of worldwide access to ESKD treatment, the most significant treatment gaps are noted in Asia (1.9 million) and Africa (0.4 million), and they are projected to more than double (to 5.4 million) by 2030, with Asia witnessing the most remarkable increase.[23]

The challenges are protean and may vary depending on the region, but poverty, poor health literacy, ignorance, and lack of awareness of kidney disease, as well as insufficient health workers and health facilities, are major challenges to kidney care across all low-resource settings. Others include lack of health care insurance, out-of-pocket payment for health care by the patient and family, poor health-seeking behavior, late presentation to health facilities, sociocultural practices, and use of herbal medicine and toxins (Table 1).

Some countries and urban centers have more facilities than others. Poor infrastructure, geographic remoteness, lack of brain death legislation, and religious, cultural, and social constraints lower kidney replacement therapy rates in many countries.[23] Late referrals to nephrology care also occur, resulting in delays in access to potential preventive care and earlier access to dialysis. These factors, along with patient poverty, contribute to poor outcomes. Those with ESKD in the region have very poor outcomes, with up to 80% mortality.[53]

Hemodialysis is challenged by exorbitant costs, dearth of facilities, poor accessibility, inadequately trained workforces, and affordability of the service resulting in patients having infrequent dialysis because most pay out of pocket. In Africa, dialysis began in Krugersdorp, South Africa, in 1957, but its growth has been slow.[67] Recent progress has been made with almost all African countries able to provide hemodialysis, but access is limited, and only 1% of incident patients in sub-Saharan Africa sustain hemodialysis for 1 year.[68] Some countries and urban centers have more facilities than others. In South America, hemodialysis use is highest in Chile and lowest in Colombia, Peru, and Paraguay. The average incidence is 162 patients per million population, and the prevalence has been increasing in the last decades at an annual growth rate of 10%.[11] About 68% of hemodialysis patients in South America start with temporary vascular access, 44% are anemic, and 55% are malnourished.[11] Incentives to prescribe cost-effective alternatives to hemodialysis (kidney transplant and peritoneal dialysis) have been proposed. The most popular form of kidney replacement therapy in Asia is in-center hemodialysis, and less than 10% of ESKD patients have access to dialytic therapy.[23]

Although the global prevalence of continuous ambulatory peritoneal dialysis (CAPD) decreased from 23% in 2012 to 11% in 2018, CAPD expansion in Asia is significant, with Hong Kong having the highest CAPD penetration worldwide. Furthermore, Hong Kong and Thailand have implemented "peritoneal dialysis-first" policies to reduce costs. Hong Kong, Vietnam, Taiwan, and Thailand now reimburse for peritoneal dialysis, but not yet for hemodialysis. Despite no significant cost difference (direct + indirect), CAPD use is low in many South Asian countries.[69] In Latin America, peritoneal dialysis is underused.[11] Similarly, in Africa, peritoneal dialysis is limited because of huge costs and infections; however, countries like South Africa, Sudan, and Tunisia have well-established peritoneal dialysis programs because of government commitment.

Transplant programs in low-resource settings face formidable constraints in adapting to the different cultural and societal values and practices. Conservative religious values may also decrease organ donations. The goal should be to bridge the gap between public sentiment and the various barriers to consenting to deceased organ donation in different countries. The commercialization of organ donation deserves special mention.[70] Fortunately, improved legislation and surveillance have addressed various impediments to ethical organ transplantation.

Living donor kidney transplants are more common in South Asia than deceased donor transplants. Singapore's adoption of an opt-out organ donation system is unique in Asia. In South America, Uruguay, Brazil, and Argentina have high kidney transplant rates, whereas Peru has a low rate.[11] Kidney replacement therapy costs in the region are exorbitant, estimated at US $26,000 per patient annually in Argentina.[14] Economic disparities and differences between and within countries, populations, education levels, and health care services also affect kidney replacement therapy availability.[14] In sub-Saharan Africa, many countries offer living donor kidney transplants only, whereas South Africa, Egypt, Morocco, Tunisia, Algeria, and Libya offer deceased donor transplants.[68]

IMPROVING HEALTH CARE SYSTEMS FOR DELIVERY OF KIDNEY CARE IN LOW-RESOURCE SETTINGS

Health systems include organizations, people, and actions that promote, restore, or maintain health. The six building blocks that constitute a health system include leadership and governance; health information systems; health financing; health workforce; medicinal products, vaccines, and technologies; and delivery of health services.[71] In 2000, the World Health Report defined the goal of health systems as improving health and health equity in responsive, financially fair, and

efficient ways.[71] This framework provides the backbone of health services, and if all building blocks are in place and goals are met, all individuals with all health conditions should have their needs met quickly, effectively, and without financial hardship. Almost every country globally struggles to provide truly equitable and appropriate care.[72]

For people at risk of or living with CKD, each building block is crucial, yet CKD as a disease entity is often overlooked by most health systems and governments.[73] Kidney disease is not yet a priority NCD because of a lack of data on the global burden, and kidney replacement therapy is too expensive for many health systems. Global strategies to prevent and treat diabetes, cardiovascular disease, and stroke will likely reduce the global burden of kidney disease. However, without recognizing CKD as a significant contributor to morbidity and mortality, equitable access to timely and appropriate kidney care will remain elusive (Table 3).[73] Equitable care is a benchmark and goal of a robust health system. Gender, extreme age, language, refugee or migrant status, culture, kidney disease type, and socioeconomic status can be barriers to care. Such inequities should be tracked, acknowledged, and addressed, requiring input from each health system component.

Leadership and Governance

These are the overarching health system requirements, where policy decisions direct resource allocation between public health and primary, secondary, and tertiary care (Table 3).[74] Equity—that everyone receives the care they need to reach their best possible (kidney) health—should be a consideration in policymaking.[73] When budgets are limited, policymakers must decide to focus on prevention and early diagnosis and treatment for the majority or ESKD care for the few. Being a life-saving, expensive intervention, dialysis presents many challenges for policymakers, who must weigh dialysis costs against other conditions. If dialysis is to be provided or subsidized, the location of dialysis facilities, financing and procurement strategies for all supplies, health care workforce training, and health system coverage must be decided. Providing limited dialysis services without transparent rationing criteria leads clinicians to moral distress and likely contributes to a brain drain of migrating clinicians.[74]

Health Information Systems

Registries are urgently needed to understand the kidney disease burden in low-resource settings. Robust, reliable, and ethical health information systems are needed to track local risk factors and kidney disease incidence and prevalence (Table 3), monitor care delivery and quality, and facilitate implementation research.[75]

Sustainable Health Financing

Financing is the crucial stumbling block in terms of providing kidney care in low-resource settings and is crucial for health system functioning (Table 3).[76–79] In low-resource settings, kidney disease is the leading cause of catastrophic health expenditures (10% of total household income or 40% of non-food household expenditures).[80] Catastrophic health expenditures are caused by dialysis costs, clinic visits, and medications.[81] CKD increases pill counts and costs. In low-resource settings, high dialysis costs lead to high dropout rates and death among ESKD patients.[53]

Health Workforce

Quality health care requires a motivated, well-resourced, and engaged workforce (Table 3). Low-resource settings have fewer nephrologists and relevant professionals.[13] Therefore, task-shifting may be required. Moral distress among the nephrology workforce is high when resources are limited because care must be denied frequently.

Products, Vaccines, and Technologies

To provide high-quality kidney care at all stages, routine diagnostics like serum creatinine and urine protein (often not available in low-resource settings) are needed (Table 3).[82] Such deficiencies lead to delayed or missed diagnoses and missed opportunities to treat AKI or CKD and potentially save lives. ESKD care requires infrastructure and equipment as well as consistent supplies and trained personnel.

Service Delivery

Kidney care service delivery is complex, and it includes prevention, early detection, and treatment. Poor health systems may cause 8 million avoidable deaths annually in low-resource settings.[83] Many of these deaths are a result of cardiovascular diseases, and more people die from poor health care than from not using it.

Safety, effectiveness, timeliness, patient-centeredness, efficiency, and equity are six quality care dimensions.[83] Patients should trust their health care system to meet their needs. Health systems must be resilient to adapt to shocks and be able to continue to deliver necessary care even under pandemics or emergencies. NCDs and kidney disease service delivery should be more predictable and achievable than a pandemic, but it requires a health system-wide reckoning, transparent policymaking, planning, and accountability. All health care building blocks should strive for quality and effectiveness.[84]

Table 3. Health Systems Building Blocks and Relevance for Kidney Disease

Building Block	Opportunity to Improve Kidney Health

Leadership and Governance	• Resource allocation:
	  • Prevention versus treatment
	  • Primary, secondary, tertiary level care
	  • Dialysis, transplantation yes/no
	• Priority setting—strategies for NCDs, kidney disease
	• Public health (primordial prevention)
	• Intersection between all sustainable development goals and health system
	• Legalize transplantation, brain death
	• Legalize cadres of health care workers, scope of practice
	• Models of care
	• Transparent guidance to allocate scarce resources
	• Reduce monopolies
	• Tackle corruption

Health Financing	• Sustainability • Universal health coverage • Domestic resource mobilization • Transparent procurement strategies and negotiations • Fair remuneration for health care workers
Health Information Systems	• Track risk factors for kidney disease • Disease registries—AKI, CKD, dialysis, transplant, living donors • Track costs—health system and societal • Track quality of care
Health Workforce	• Appropriate training for all cadres • Reduce brain drain • Reduce moral distress • Incorporate, engage traditional health care workers
Medical Products, Vaccines, and Technologies	• Essential medicines • Essential diagnostics • Local manufacture of health products • Extend essential diagnostics and medicine lists • Access to products and technologies for dialysis and transplantation

Service Delivery	• Optimize infrastructure
	• Optimize access to early diagnosis
	• Optimize access to sustainable, affordable, accessible early treatment
	• Optimize access to dialysis and transplantation
	• Ensure quality care
	  • Safe, effective, timely, patient-centered, efficient, equitable
	  • Resilient

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; NCD, noncommunicable disease.

RECOMMENDATIONS

In low-resource settings, CKD awareness is low, and many people go undiagnosed. Population health prevention is crucial and has demonstrated effectiveness in reducing disease burden in populations.[33] Screening, early identification, and prevention of CKD are general recommendations; however, implementation is challenging. Reliable and functional kidney registries will enable health service planning and government policies to combat CKD and CKDu. Governments should improve health expenditures, institute credible health insurance to reduce out-of-pocket spending, improve existing health facilities, and invest in training/retraining of the health care workforce. Providing health insurance and subsidies can also ease patients' and families' financial burdens. ESKD patients need comprehensive kidney replacement therapy centers with multiple treatment modalities. Countries in the regions should develop organ donation and transplantation laws to enable ethical transplantation.

A New Approach to CKD Management

This new approach was proposed in South America and can be replicated in other low-resource settings.

CKD management based on biological risk factors and health policies has been ineffective.[12] To improve outcomes in these regions, achievement of the following goals is required: (1) implementing integrated health care programs; (2) encouraging local and national CKD registries in every country; (3) using informatics to improve patient care and medical team coordination; (4) promoting CKD prevention and early detection to optimize treatment and slow progression, minimizing complications and costs; (5) implementing nephroprotection strategies by family physicians and nephrologists; (6) facilitating patients' transition from predialysis to dialysis; (7) increasing nephrologists and other nephrology workforce numbers to target; (8) increasing peritoneal dialysis programs; (9) enhancing kidney transplant programs; and (10) promoting nephrology research.[12]

Complementary strategies to achieve these goals include early CKD detection, which would require educational, technical, and organizational measures like raising health professionals' and public kidney care awareness.[12,14] Using point-of-care tests to evaluate and monitor CKD patients in low-access areas[85] and promoting the use of validated estimated glomerular filtration rate equations[86] are also needed, as well as adopting a CKD model that promotes kidney health, ie, the new paradigm that controls biomedical and population risk factors.[12] Changing from a reactive (against CKD) to a planned and proactive (person-centered) health care model would enable better protective measures in many low-resource settings.

CONCLUSION

Incidence and prevalence of CKD have surged in the past decade, especially among low-resource settings. Even with the heavy burden of CKD, the disease pattern and challenges in accessing adequate health care are similar throughout these regions. In high-income settings, the priority of equitable distribution of existing services and attention must be paid to historically disadvantaged indigenous and immigrant populations. Certain aspects of kidney disease risk or access to care are unique to regions and require local solutions. Any solutions will require and rely upon robust health systems to provide stewardship of resources to ensure equitable, sustainable, and quality care for all at risk of or living with kidney disease. In low-income settings, the challenges are first and foremost those of population-level prevention, equitable access, early diagnosis, and treatment such that kidney disease progression and the need for unaffordable ESKD care can be reduced. Global inequities in delivering the full range of kidney care must be identified and remedied.

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