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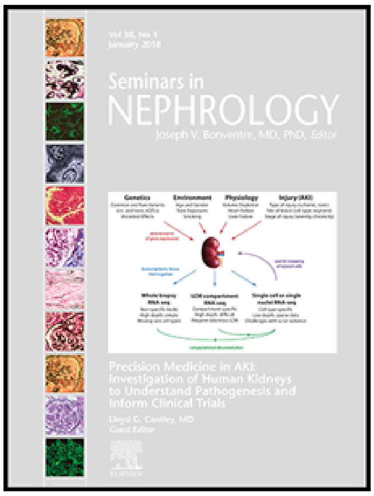

COVID-19 and kidney disease: Progress in health inequity from low income settings

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COVID-19 and kidney disease: Progress in health inequity from low income settings

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Abstract

COVID-19 pandemic has had significant impact on the incidence and prevalence of acute kidney injury (AKI) and chronic kidney disease (CKD) globally and in low-income settings. CKD increases the risk of developing COVID-19 and COVID-19 causes AKI directly or indirectly and its associated with high mortality in severe cases. Outcomes of COVID-19 associated kidney disease were not equitable globally due to lack of health infrastructure, challenges in diagnostic testing and management of COVID-19 in low-income settings. COVID-19 also significantly impacted kidney transplant rates and mortality among kidney transplant recipients. Vaccine availability and uptake remains a significant challenge in low- and lower-middle income countries (LLMICs) as compared to high income countries.

In this review, we explore the inequities in LLMICs and attempt to highlight the progress made in the prevention, diagnosis and management of patients with COVID-19 and kidney disease. We recommend further studies into the challenges, lessons learnt and progress made in the diagnosis, management and treatment of patients with COVID-19 related kidney diseases and suggest ways to improve the care and management of patients with COVID-19 and kidney disease.

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) causing Corona Virus Disease - 2019 (COVID-19) has had significant impact on the burden and management of patients with kidney diseases globally and in low- and lower-middle income countries (LLMICs)[1-5]. COVID-19 increases the risk of proteinuria, haematuria, tubulopathies, acute kidney injury (AKI) and chronic kidney disease (CKD) [5-7] and its associated with severe COVID-19 disease[2, 4, 8]. COVID-19 infection when complicated by AKI or in patients with underlying CKD or kidney failure are associated with increased mortality especially in low-income settings[3, 9-12]. The care and management of patients on kidney replacement therapy (KRT) was also significantly affected by the COVID-19 pandemic leading to missing dialysis sessions. Transplant programs were suspended with uncertainties in immunosuppression dosing among some kidney transplant recipients (KTR) associated with increased morbidity and mortality [13-17].

The diagnosis and management of patients with COVID-19 associated kidney disease has been greatly affected as a result of the COVID-19 pandemic[18, 19]. Inequitable distribution of resources needed for the screening, diagnosis and optimal management of COVID-19 associated kidney disease has been highlighted coupled with the looming vaccine inequity in LLMICs though high vaccine rollout was the most effective remedy for the prevention of COVID-19 transmission and decrease in COVID-19 severity[20-22].

In this review, we set out to describe the impact of COVID-19 on kidney disease and the progress made in the care and management of patients with COVID-19 associated kidney disease and provide suggestions to improve the diagnosis and management of COVID-19 associated kidney disease in LLMICs.

COVID-19 and kidney disease

COVID-19 affects multiple organs including the kidneys. The effect of COVID-19 on the kidneys ranges from asymptomatic proteinuria, haematuria to acute kidney injury (AKI) and progression to chronic kidney disease (CKD) and kidney failure[1-5]. Kidney failure in those with underlying CKD and severe cases of AKI in patients with severe COVID-19 may require KRT [9]. SARS-CoV-2 can have direct or indirect effect on the kidneys. Directly, it can cause AKI by cytokine storm, angiotensin 2 pathway activation, dysregulation of the complement system, hypercoagulability, microangiopathy and collapsing glomerulopathy [5-7]. Indirectly, COVID-19 increases the risk of AKI through hemodynamic instability, hypoxemia, sepsis and exposure to nephrotoxins[5]. COVID-19 may lead to CKD as a consequence of clinical or subclinical AKI or as a result of residual inflammation associated with SARS-CoV-2 infection[5].

The pooled incidence of AKI was reported in a meta-analysis to be 10% (95% CI 7.0-12.0%)[23] and a pooled prevalence of 17% (range 0.5% - 80.5%) among hospitalized patients with COVID-19 [24]. The wide variations result from varying AKI definitions, differences in gender, race, carrier status of *APOL-1* risk alleles, co-morbidities, severity of COVID-19 and changes in the virulence of SARS-CoV-2 with different mutations over time[25].

The consensus report of the 25th Acute Disease Quality Initiative (ADQI) summarized all of these risk factors for COVID-19 into three broad categories - demographic risk factors, AKI risk factors at admission and during hospitalization[5]. We have expanded the list of risk factors to include those relevant to low income settings[Figure 1] [1, 3, 12, 26]. Some medications are such as vancomycin, aminoglycosides and angiotensin converting enzyme inhibitor (ACEi) are also associated with AKI[27, 28]. COVID-associated AKI is associated with increased mortality especially in severe cases[12, 29].

Proteinuria occurs in 24-84% of patients with COVID-19 in the presence or absence of AKI and it is a predictor of mortality with or without AKI and/or microscopic hematuria [30]. Proteinuria may also suggest subclinical kidney pathology or underlying comorbidities such as diabetes mellitus and/or hypertension [31]. The first COVID-19-related glomerular disease were case reports describing collapsing glomerulopathy [6, 32, 33] found mostly in Black patients who were carriers with *APOL1* risk alleles presenting with nephrotic range proteinuria and AKI [25, 32]. Minimal change glomerular injury, anti-glomerular basement membrane glomerulonephritis and membranous glomerulonephritis have all been described in patients with COVID-19 disease. Sub-nephrotic proteinuria is mainly of tubular origin predominantly due to 1-α microglobulin [34, 35]. Proximal tubulopathy with acute Fanconi syndrome has also been described and it is associated with severe disease. Tubulopathy has been shown to precede the onset of AKI and disappeared with kidney recovery [36-38].

Inequity and progress in the screening and diagnosis of COVID-19

Diagnostic polymerase chain reaction test is preferred to antigen testing for diagnosing SARS-CoV-2 infection[39] and intensified polymerase chain reaction testing decreased the rate of transmission during the first wave [40]. The diagnosis and management of kidney disease at the onset of the COVID-19 pandemic was very challenging especially in LLMICs given the inability to carry out rapid polymerase chain reaction testing due to lack of resourced laboratories and technical staff [41]. The International Society of Nephrology and the Dialysis Outcome and Practice Pattern (ISN-DOPPS) survey highlighted gross disparities in the testing for COVID-19 during the pandemic[19]. Diagnostic polymerase chain reaction testing was reportedly unavailable or of limited availability in low income countries (LIC)(72%) and lower-middle income countries (LMIC) (68%) as compared to 20% in high income countries at the peak of the pandemic [41]. Rates declined during the period of the ISN-DOPPS survey in November 2020 - March 2021 from 68% to 21% in LMICs but only marginally from 72% to 62% in LIC as compared to the peak of the pandemic in March 2022. The turnaround time for receiving diagnostic test results was also delayed [42]. Same day results were received in 60% in high income country as compared to 13-21% in LLMICs according to respondents, whereby those infected had delayed diagnosis and possibility of impacting higher transmission rates. The low testing rates supported the hypothesis that rates of COVID-19 and mortality in Africa was low due to under-testing and not from a low infection rate [43-45].

During the peak of the pandemic, a mandatory negative test was required before discharge of patients, this criterion was later revised by the World Health Organization(WHO) on 27th May 2020, where patients were considered to have recovered after 2 weeks without symptoms. This new criterion was useful in LLMICs due to challenges with frequent testing[46] as the previous criteria for discharge from isolation was clinical recovery and two negative reverse transcriptase polymerase chain reaction results on sequential results taken at least 24 hours apart [39]. These changes were recommended by the WHO based on limited laboratory supplies, equipment and personnel in low income settings.

Testing capacity and rapid results of diagnostic tests improved through the pandemic as tests were made readily available for the diagnosis of COVID-19 by some governments. In the Philippines and Kenya, the costs for testing was between $11-55 for diagnostic testing, however, in India, Ghana and Zambia, it was free in public institutions. Even within a country, there was wide variation of costs leading to even more misinformation. Within the same country prices ranged from $0-91 in Kenya, $0-99 in Zambia, $0-104 in the Philippines and $0-14 in India depending whether facility is public or private. Stigmatization and government and/or employer enforced isolation after a positive test, which often discouraged people from availing themselves for testing even when the test was readily available [44].

Rates of COVID-19 in Africa for example were favourable in terms of infection and mortality rates as compared to the rest of the world. At the peak of the pandemic in August 2020, though Africa inhabits 17.2% of the world's population, it accounted for 5% of COVID-19 cases and 3% of COVID-19 related mortalities. Seeding effect, low testing capacity, low population density, more youthful population, exposure to previous infections and environmental conditions postulated as reasons for this phenomenon [43]. LLMICs, however, have unique challenges due to poverty and low infrastructure leading to poor outcomes in severe cases [11, 47]. The gross inequities in the screening and diagnosis of COVID-19 in kidney failure patients on haemodialysis during the COVID-19 pandemic were, however, associated with higher increased mortality [19].

COVID-19 and AKI in low income settings

Generally, LLMICs have challenges in the diagnosis of AKI due to low nephrology workforce, absence of quality laboratory infrastructure and quality histopathology even during non-pandemic times[48]. The pandemic widened the gap in care in LLMICs. Furthermore, the lack of adequate specialized medical/laboratory personnel, significant knowledge gaps among primary healthcare providers, suboptimal diagnostic capacity limited the detection and optimization in management of AKI [49].

AKI occurred in 5-15% of COVID-19 patients and its associated with increased mortality of up to 90% especially in patients admitted into intensive care units (ICU) in China during the onset of the pandemic[50]. A retrospective study in New York, however, showed 87.2% attained full recovery of kidney function in most patients with AKI in the ICU[51]. A recent study in South Africa reported that AKI occurred in 33.9% of patients admitted with COVID-19 and 24.3% were admitted to ICU [12]. The risk of AKI during the pandemic was associated with severity of COVID-19, high comorbidity burden, underlying CKD, decreased vaccination rate, high risk carriers of *APOL1* and decreased access to specialized care[52].

Pre-renal and acute tubular necrosis were the most common causes of AKI indirectly but collapsing glomerulopathy also termed COVID-19 associated Nephropathy (COVAN) were suggested to be caused directly by SARS-CoV-2[6, 53]. There are also reports of pauci-immune crescentic necrotizing glomerulonephritis as a result of COVID-19 vaccination[54]. Such diagnosis requires adequate nephropathology which may be lacking in most low-income settings. Where histopathology is available, most countries in LLMICs use light microscopy without immunofluorescence and electron microscopy[55].

A recent introduction of the Extended Kidney Disease Improving Global Outcome (eKDIGO) AKI criteria was adopted by the International Society of Nephrology (ISN) AKI 0by25 studies for COVID-19. The new definition includes the decrement of serum creatinine of 26.5umol/L in 48 hours or fall by 1.5 times from the baseline in 7 days, which identified twice as many cases of AKI as compared to the traditional criteria (31.7% versus 16.8%)[56]. This classification has significant logistic challenges if implemented in LLMICs as it requires frequent measurement of serum creatinine even in stable cases, which is prohibitive due to cost.

Optimal management of AKI in the light of COVID-19 is impossible without an adequate nephrology workforce. The nephrologists per million population (pmp) in high income countries is 28.5pmp as compared to 2.4pmp in LMIC and 0.31pmp in LICs. This is a direct result of the dearth of training programs to train both physicians and nurses. Africa has 9 of the 10 countries with the lowest nephrology workforce globally [57-59]. There are also challenges in access to KRT in low income settings in Africa leading to increased mortality[60]. There is inequity in the distribution of haemodialysis services in most countries in low income settings even within the same country [61]. Patients pay out of pocket for haemodialysis sessions in some countries and mortality increases in the absence of KRT in some low income settings.

During the COVID-19 pandemic patients with underlying CKD or AKI with COVID-19 were prevented from accessing ICU care when needed due to perceived poor prognosis during triaging [18, 19]. This resulted in were increased mortality from treatable causes of AKI in low income settings[19]. Though the roll-out of vaccination decreased incidence and prevalence of COVID-19 and COVID-19 associated AKI worldwide, there has not been any marked documented improvement in the access to KRT as only 7% of those on KRT live in LLMICs[62].

Some suggested solutions to improve diagnosis of AKI include engaging local and regional stakeholders in healthcare financing, developing educational programs and guidelines, training of healthcare workers, providing adequate health care resources, linking with regional health care projects and improving research opportunities in low income settings[63].

COVID-19 and chronic kidney disease in low-income settings

CKD increases the risk of AKI and AKI can lead to CKD and progression to kidney failure in both hospitalized and non-hospitalized patients with COVID-19[64, 65]. COVID-19 infection could be due to the presence of unknown underlying CKD before hospitalization [66]. There is a high global prevalence of CKD of 11%[67] which is even higher in low income continents such as Africa with a prevalence of 13.9-15.8%[68-70].

COVID-19 survivors may also develop long-term kidney issues [65]. A Chinese study reported a 35% reduction in estimated glomerular filtration rate (eGFR) six months after COVID-19 hospitalization[66]. Even without documented evidence of AKI on admission, 13% of patients showed a reduction in eGFR during follow-up [71]. Although many patients have normalization of creatinine after AKI, the kidneys may not recover completely and increase the risk of CKD over time [64]. Progression of kidney disease in COVID-19 is likely multifactorial and could be driven by continuous inflammation, intrinsic tubular lesions or improper repair[65]. In most patients with CKD in low income countries, progression to kidney failure requiring dialysis increases mortality due to absence of KRT and increased cost associated with poor outcomes[61, 72]. The risk factors associated with worse outcome with CKD include increasing age, diabetes mellitus, hypertension, the unavailability of adequate nephrology workforce and the absence of adequate diagnostic tools[8].

Awareness of CKD in low income settings

There has not been much progress made in raising awareness for the prevention and management of risk factors for COVID-19-associated kidney disease in low income settings. Moreover, incidence and prevalence of the non-communicable diseases such as diabetes and hypertension that can lead to kidney disease are also increasing and account for 80% of global deaths in LLMICs [73]. Governments must invest more in health to decrease burden of NCDs and conditions that impact kidney health. Public health interventions such as education, healthy dietary lifestyle, and exercise should be part of a national agenda to prevent CKD. There has been poor governmental support in this regard with few sustainable programs to decrease the burden of kidney disease. Such public health interventions have been championed by individuals and some non-governmental organizations (NGOs) such as the World Kidney Day activities of the ISN[74-76]. Such initiatives should be encouraged to decrease the kidney disease burden with or without COVID-19. The reduction of the burden of kidney disease in patients with COVID-19 is based on the decrease in the transmission of SARS-CoV-2. This calls for optimization of vaccination across the globe with the early detection and appropriate management of cases to prevent AKI and CKD [77].

Inequity in kidney failure patients on chronic haemodialysis with COVID-19 in low income settings

Patients on chronic dialysis are at increased risk of COVID-19 due to decreased immune status, frequent hospital visits for haemodialysis sessions, difficulty in maintaining social distancing during haemodialysis session especially in constrained spaces among dialysis units from low income settings[9, 17, 78, 79]. The incidence of SARS-CoV-2 infection range from 1-19.9% in dialysis populations and had significant mortality of 10-41%[17, 24, 80-84]. In the peak of the pandemic due to lockdown measures it was reported that patients in low income countries missed their dialysis sessions more frequently than those in high income countries. According to the ISN-DOPPS survey, haemodialysis sessions were reportedly missed in 66-67%

in LLMICs as compared to 20-33% in upper-middle income countries and high income countries [19]. Transportation to and from haemodialysis units were reportedly more affected in patients in those in LLMICs. These, however, improved with easing of lockdown restrictions anecdotally but published evidence is lacking.

There were also major supply chain disruptions of haemodialysis consumables in low income countries during the pandemic. Intensive care admission, mechanical ventilation and dialysis during hospitalization were more restricted or prohibited in patients with kidney failure on chronic dialysis in low income settings as compared to high income settings during the peak of the pandemic (Figure 2)[19].

Patients with kidney failure were at increased risk of infection due to frequent centre visits for haemodialysis sessions. They are also particularly at risk due to the decrease in the immunity as a result of the kidney failure. Close proximity by patients during transportation as well as long durations in close proximity during haemodialysis sessions further increased their risk[79].

Guidelines were instituted by many societies[85-88] to help decrease the spread of infections in haemodialysis units but this could not be strictly adhered to in most low income settings due to poor testing and unavailability of resources for transmission prevention. Some dialysis centres were reportedly turning away dyspneic patients for fear of COVID-19 transmission to other patients as testing was not readily available but this improved when testing was made more readily available. The rollout of vaccinations in patients with kidney failure on dialysis was also filled with challenges with uptake due to various myths about the vaccines but vaccine hesitancy has improved with time based on better education[41, 89].

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COVID-19

Figures

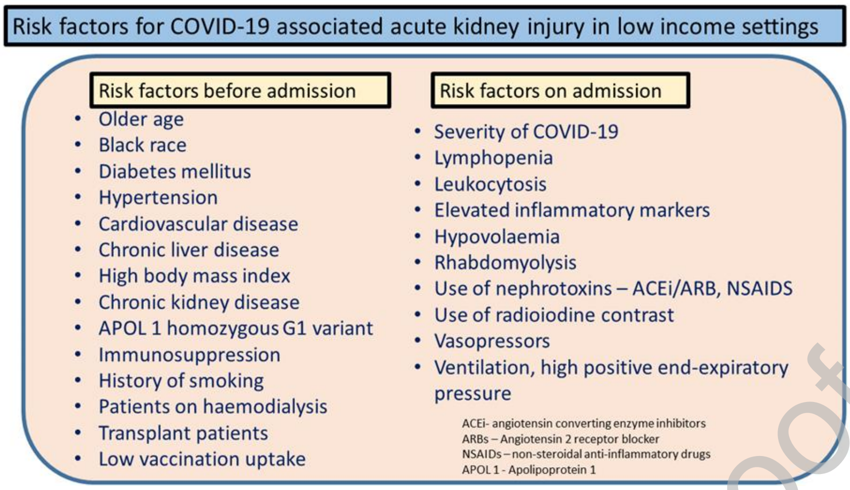


Figure 1: Risk factors for acute kidney injury in patients with COVID-19 in low income settings

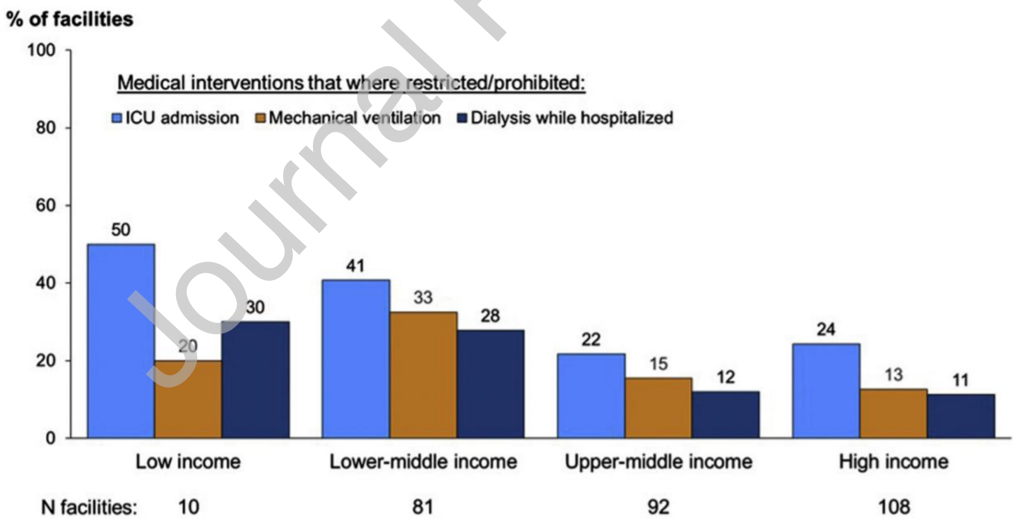


Figure 2 Medical interventions such as ICU admission, mechanical ventilation and dialysis while hospitalized became more restricted or prohibited for chronic dialysis patients admitted to the hospital with COVID-19 by World Bank income [19]

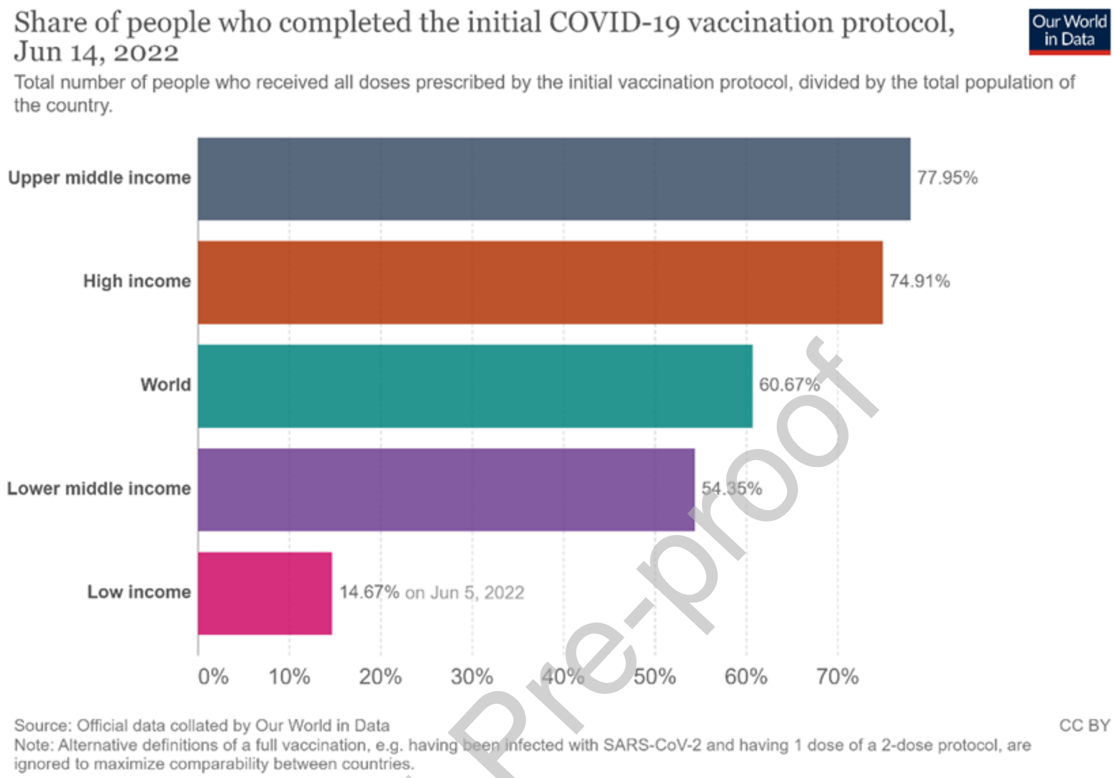
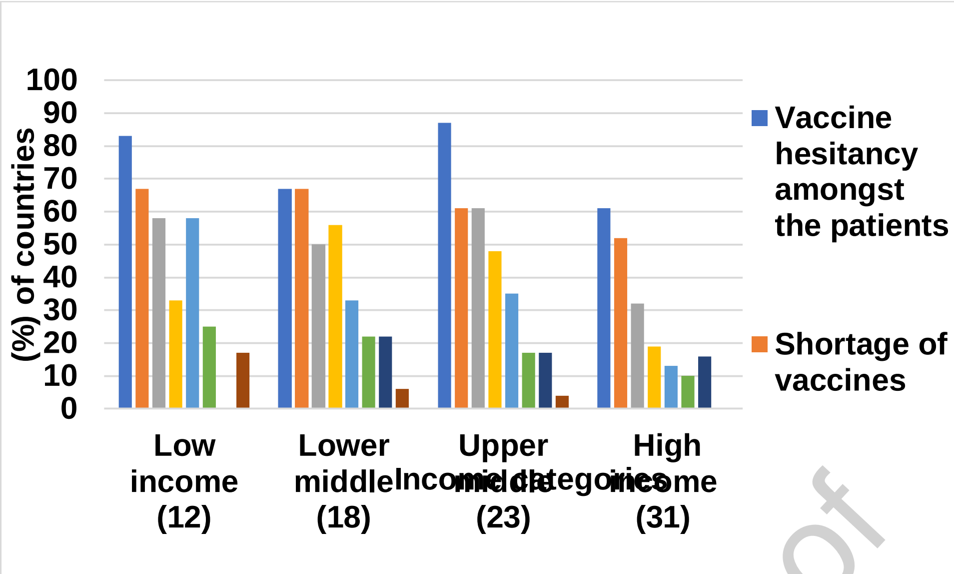


Figure 3 Showing the number of people fully vaccinated per world bank income status [127]


100
90
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(%) of countries
Low income (12)
Lower middle (18)
Upper middle (23)
High income (31)
Income categories
Vaccine hesitancy amongst the patients
Shortage of vaccines