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Identifying Potential Vulnerability to Long COVID Through Global-to-Local Inequalities in Years Lived With Disability Attributed to COVID-19, 2020–2021, Across 920 Locations

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ABSTRACT

The COVID-19 pandemic has reshaped global health; however, the long-term burden of long COVID remains poorly understood, especially in low- and middle-income countries (LMICs), where limited surveillance and data gaps may obscure a substantial and sustained impact. Using the Global Burden of Disease (GBD) 2021 framework, we previously assessed the direct COVID-19 burden—including incidence, prevalence, mortality, and disability-adjusted life-years (DALYs)—across 920 locations during 2020–2021. In this study, we focus on years lived with disability (YLDs), particularly in 2021, as a potential early indicator to identify locations and populations that may be at higher risk of long COVID burden in subsequent years (e.g., 2022–2023). We also examine patterns of inequality to highlight vulnerable groups. Our findings are consistent with multiple large-scale studies on long COVID and suggest that YLDs may serve as a useful early proxy for ongoing burden. Importantly, we identify notably higher age-standardized YLD rates in LMICs—especially in Sub-Saharan Africa and in parts of South Asia and Eastern Europe. These areas, previously underexplored in long COVID research, might be particularly susceptible to its effects. Among the top 10 countries with the highest age-standardized YLD rates in 2021, 80% fell within the low, low-middle, and middle Socio-demographic Index (SDI) categories. These high age-standardized YLD rates may point to systemic vulnerabilities and entrenched structural health disparities, indicating a potential for considerable and enduring long COVID burden that could persist to the present day in the absence of targeted interventions. Furthermore, our inequality analysis underscores that while both advantaged and disadvantaged groups in LMICs require attention, the most disadvantaged groups warrant special focus due to their more severe resource constraints and restricted capacity for resilience-

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building. Overall, this study supports calls for stronger surveillance, expanded access to rehabilitation, and better integration of long COVID care into universal health coverage. Continued GBD updates will be essential for monitoring trends and guiding responsive public health strategies.

1 | Introduction

The COVID-19 pandemic profoundly disrupted global health and health systems, reversing prior improvements in population health [1]. Building on earlier iterations of the Global Burden of Diseases (GBD) study, the GBD 2021 analysis delivered the first comprehensive estimates of COVID-19's direct burden [2]. To address underreporting and ensure comparability across diverse locations, GBD 2021 implemented multiple methodological enhancements within its COVID-19 estimation framework. These included adjusting seroprevalence data for vaccination, waning antibody sensitivity, and reinfection to estimate infection-detection ratios; applying hierarchical Bayesian meta-regression models to estimate infection-fatality ratios and infection-hospitalization ratios; and standardizing case definitions to account for differences in surveillance and reporting systems across locations [1–5]. Leveraging these advances, we previously produced the most comprehensive and granular estimates to date of the direct burden of COVID-19, including incidence, prevalence, mortality, and disability-adjusted life-years (DALYs), across 920 global locations during 2020–2021 [6].

Long COVID is a condition characterized by persistent multi-system symptoms lasting weeks or months beyond the acute infection [7]. A meta-analysis integrating 144 studies published between 2021 and 2024 found that the estimated global pooled prevalence of long COVID among COVID-19 positive individuals was 36% [8]. However, to date, few studies have systematically investigated the direct burden of long COVID at fine-grained geographic scales, largely due to limited availability of robust data, with a particular scarcity of research from low- and middle-income countries (LMICs) [9]. Long COVID's far-reaching consequences for individuals and society make it essential to address this knowledge gap. Notably, the rigorous GBD 2021 framework that adjusted for incomplete data may help estimate potential long COVID burden even in LMIC settings where data remain limited [9]. In LMICs, limited healthcare access puts high-risk individuals at greater risk of developing severe long COVID, potentially leading to widespread chronic disability. Many affected individuals might never return to full-time work or normal daily functioning as a result. Furthermore, the lack of social protection and economic support in many LMICs could exacerbate the health and economic inequalities associated with long COVID [10]. Because long COVID is a chronic condition, analyzing COVID-19 data from 2020 to 2021 may help flag locations and populations that could have been particularly vulnerable to long COVID in subsequent years [11].

Among the six key health burden metrics used in the GBD framework, including incidence, prevalence, mortality, DALYs, years lived with disability (YLDs), and years of life lost (YLLs), YLDs may be more appropriate for assessing the burden of long COVID, as they are specifically designed to capture nonfatal health losses by accounting for both the prevalence and severity of symptoms [11]. To this end, in this study we aimed to quantify the YLDs due to COVID-19 during this period, particularly in 2021, at global, regional, national, subnational, and local levels. Our primary goal was to identify which locations and population groups may be more susceptible to a high long COVID morbidity burden in subsequent years (e.g., 2022–2023). We also aimed to examine inequality patterns, highlighting cross-regional, cross-country, and cross-local disparities.

2 | Methods

2.1 | Overview

We conducted a secondary analysis of direct COVID-19 burden in terms of years lived with disability (YLDs), following the GBD 2021 study framework [12]. Age-standardized YLDs, as well as age-, sex-, and location-specific estimates, were generated for COVID-19 in 2020 and 2021. Our analysis covered 920 distinct locations globally, comprising 1 global level, 77 international regions, 204 countries and territories, 20 subnational regions, and 618 local units. Detailed definitions of these geographic levels are available in our previous report [6].

2.2 | Data Sources and Estimates

Full methodological details on the estimation of COVID-19 burden for 2020–2021, including data sources and processing steps, are provided in Supporting Information S1 (Sections 1–2). Specifically, data on reported COVID-19 cases and deaths were obtained primarily from the Johns Hopkins University COVID-19 repository, supplemented by location-specific datasets obtained from ministries of health, public health departments, or other third parties [2]. Comprehensive information on data sources and validation processes is available via the Global Health Data Exchange (GHDx) platform (http://ghdx.healthdata.org/). We extracted age-standardized YLD estimates, as well as estimates disaggregated by age, sex, and location (with 95% uncertainty intervals [UIs]), for 2020 and 2021 from the GBD 2021 results. However, given the limited data availability at the subnational level, this study restricted local-level evaluations to 618 units across 17 countries [2].

2.3 | Disease Definitions and Burden Categorization

COVID-19 was defined according to the World Health Organization (WHO) as the disease caused by infection with SARS-CoV-2, with clinical manifestations ranging from mild symptoms (e.g., fever and cough) to severe illness such as pneumonia,

acute respiratory distress syndrome, and death [13]. Within GBD 2021, the Institute for Health Metrics and Evaluation (IHME) classified COVID-19 cases into five mutually exclusive severity categories for burden estimation: (i) Asymptomatic cases (individuals with SARS-CoV-2 infection who presented detectable viral loads but exhibited no symptoms); (ii) Community cases (symptomatic infections of mild or moderate severity that did not require hospitalization); (iii) Hospitalized cases (symptomatic cases requiring hospital admission but not intensive care unit (ICU) support, irrespective of healthcare access or utilization); (iv) ICU cases (critically ill cases requiring ICU-level care due to severe acute symptoms, independent of healthcare availability or utilization); (v) Death cases, determined by the causes according to the International Classification of Diseases (ICD-10) guidelines, specifically codes U07-U07.2 for COVID-19 (https://ghdx.healthdata.org/record/ihme-data/gbd-2021-cause-icd-code-mappings). In addition, long COVID (alternatively referred to as post-acute conditions due to COVID-19 in the following descriptions) was defined as the persistence of one or more primary symptom clusters, including fatigue, cognitive impairment, and respiratory difficulties, that lasted for at least three months post-infection [2].

In the GBD 2021 framework, the COVID-19 burden is partitioned into direct (Level 3) and indirect (Level 1) components [2]. The direct burden encompasses the health loss directly resulting from confirmed COVID-19 infection and its acute outcomes (e.g., hospitalizations, critical illness, and deaths) as well as post-acute sequelae (e.g., long COVID). The indirect burden refers to broader health impacts of the pandemic, including disruptions in health services, delayed care for other conditions, and other pandemic-associated effects on population health. Although indirect effects (such as excess non-COVID mortality or care disruptions) are important, our analysis focused exclusively on the direct COVID-19 burden (Level 3), measured in terms of YLDs.

2.4 | YLD Calculations and Long COVID Impact

YLDs were calculated using the standard GBD prevalence-based approach: for each health outcome, the number of affected individuals (prevalence) was multiplied by the disability weight (DW) for that condition (i.e., *YLDs = Prevalence x Disability Weight*) [14]. Disability weights range from 0 (representing full health) to 1 (equivalent to death) and represent the severity of health loss associated with each nonfatal condition. In GBD 2021, IHME incorporated both acute COVID-19 outcomes and post-acute conditions (i.e., long COVID) into the direct YLD calculations. A total of 28 distinct COVID-19 sequelae (acute and post-acute) were defined, each with an assigned DW. These DWs ranged from 0 (asymptomatic infection) to 0.743 (for critical acute COVID-19 requiring ICU care). A detailed description of all 28 post-COVID conditions and their corresponding DWs is provided in Supporting Information S1: Section 3.

Generally, more severe acute illness and more severe post-acute sequelae were associated with higher DWs. The five highest DWs associated with post-COVID conditions were: (i) critical acute COVID-19 (DW = 0.743); (ii) post-acute fatigue syndrome and severe respiratory and severe cognitive symptoms due to COVID-19 (DW = 0.705); (iii) post-acute severe respiratory and severe cognitive symptoms due to COVID-19 (DW = 0.627); (iv) post-acute fatigue syndrome and moderate respiratory and severe cognitive symptoms due to COVID-19 (DW = 0.618); and (v) post-acute fatigue syndrome and severe respiratory and mild cognitive symptoms due to COVID-19 (DW = 0.566). In contrast, asymptomatic COVID-19 (DW = 0), mild acute COVID-19 (DW = 0.006), post-acute mild respiratory symptoms due to COVID-19 (DW = 0.019), and moderate acute COVID-19 (DW = 0.051) had the 4 lowest DWs. The average DW for post-acute mild symptoms (cognitive or respiratory, or both) is 0.058—over 9 times higher than the DW for mild acute COVID-19. The average DW for post-acute moderate symptoms (at least persistent fatigue or moderate respiratory symptoms without severe cognitive or respiratory symptoms) is 0.293—over 5 times higher than the DW for moderate acute COVID-19.

Epidemiologically, a large proportion of COVID-19 cases were asymptomatic or mild in the acute phase, but a notable fraction of infected individuals went on to develop long-term symptoms. In 2021, a pooled estimated 40.50% of confirmed COVID-19 cases were asymptomatic, while mild-to-moderate acute cases comprised 80% of symptomatic cases (around 40% mild, 40% moderate) [15, 16]. On the other hand, the global estimated pooled prevalence of long COVID was 36% among COVID-positive individuals [8], with most long COVID patients experiencing persistent fatigue and/or mild-to-moderate respiratory and/or cognitive symptoms [17–19]. However, a subset could still develop more severe forms of long COVID that severely affect quality of life [20]. Given these factors, it is unlikely that a population or location with a high YLD rate (per 100,000), particularly an age-standardized YLD rate, in 2021 had a low proportion of individuals with mild-to-severe long COVID-related symptoms and/or critical acute COVID-19 [21].

Considering that (i) the prevalence of asymptomatic and mild-to-moderate acute COVID-19 cases, as well as long COVID cases, was substantial; (ii) the DWs associated with mild-to-severe long COVID-related symptoms were notably higher than those of asymptomatic or mild-to-moderate acute COVID-19; (iii) even initially mild acute COVID-19 could increase the risk of developing long COVID in the post-acute phase [22]; (iv) initially critical acute COVID-19 and hospitalization due to COVID-19 could notably elevate the risk of developing long COVID [19]; (v) the second through the fifth highest DW conditions were directly related to long COVID [7, 23]; and (vi) among individuals followed for up to 3 years after the initial infection, the mean duration of long COVID was estimated to exceed 2 years (though the true mean may be underestimated due to censoring in individuals whose symptoms had not resolved by the end of follow-up) [20], it is reasonable to infer that locations or populations with a higher YLD rate for COVID-19 in 2021 were more likely to experience an increased burden of long COVID (particularly in terms of incidence, prevalence, and YLDs) in subsequent years (e.g., 2022–2023). As a result, YLDs emerged as a relatively optimal health measure, compared to other burden metrics (e.g., DALYs and YLLs), for identifying locations and populations more vulnerable to higher burden of long COVID morbidity in more recent years [24–26].

2.5 | Inequality Analysis

To assess the extent of health inequalities in the COVID-19 YLD burden across different locations, we calculated two complementary metrics: the Slope Index of Inequality (SII) and the Concentration Index of Inequality (CII), following established methods for health inequality analysis [27, 28]. These metrics quantify the degree of inequality in the distribution of COVID-19 burden (YLD rates, in this case) across different levels of socio-demographic development.

Slope Index of Inequality (SII): The SII is an absolute measure of inequality that represents the difference in a health outcome between the extremes of a socioeconomic spectrum. We modeled the relationship between each location's COVID-19 YLD rate and its Socio-demographic Index (SDI) using population-weighted robust linear regression. SDI is a composite development indicator (incorporating per capita income, average educational attainment, and fertility rate under age 25) standardized on a scale from 0 (lowest development) to 1 (highest development). Each location was ranked by SDI, and the SII was defined as the regression-predicted absolute difference in YLD rate (per 100,000 population) between the lowest-SDI and highest-SDI ends of the scale. By convention, an SII greater than 0 indicates higher COVID-19 burden in more advantaged (higher SDI) locations, whereas a negative SII indicates higher burden in more disadvantaged (lower SDI) locations [29]. We assumed a linear gradient of YLD rates across the SDI spectrum, consistent with standard SII methodology [27–29]. A larger magnitude of SII (farther from zero) corresponds to greater absolute inequality. We used robust regression to reduce the influence of outlier observations, and the SDI ranking of locations was population-weighted so that larger populations carried proportional influence in the inequality estimates.

Concentration Index (CII): The CII is a relative inequality measure that quantifies the concentration of health outcomes across the socioeconomic spectrum [29]. Locations were again ranked by SDI (with population weighting), and we plotted the cumulative percentage of the population (x-axis) against the cumulative percentage of total COVID-19 YLD burden (y-axis) contributed by locations up to each SDI rank. This yielded a concentration curve, analogous to a Lorenz curve in economics. The CII is defined as twice the area between the concentration curve and the line of equality (45° line); its values range from −1 to +1 [29]. A CII of 0 indicates perfect equality (the outcome is evenly distributed across SDI levels). A negative CII indicates the COVID-19 burden is concentrated in less-advantaged populations (skewed toward lower SDI locations), whereas a positive CII indicates concentration of burden in more-advantaged (higher SDI) locations. Larger absolute values of CII signify greater relative inequality in the distribution of COVID-19 burden.

We computed SII and CII at multiple geographic scales (i.e., global, international regional, national, subnational regional, and local) to examine inequality patterns. For local inequality analyses, we restricted the analysis to countries with robust and available local SDI data. 13 countries met these criteria: Brazil; Ethiopia, Kenya, and South Africa; Indonesia, Iran, Japan, and Pakistan; the United States and Mexico; and Norway, Sweden, and the United Kingdom. All inequality analyses were conducted according to standard WHO health inequality assessment guidelines to ensure consistency and comparability across settings [27].

2.6 | Statistical Analysis

To maintain consistency with the official GBD Results Tool data (https://vizhub.healthdata.org/gbd-results/), no additional statistical modeling was performed on the YLD estimates beyond those provided by the GBD 2021 study. Inequality analyses and all visualizations were conducted using R (version 4.2.0). YLD rates were reported per 100,000 population, accompanied by 95% uncertainty intervals (UIs). Because male and female YLD estimates were generated from separate GBD models, each with their own uncertainty distributions, age-specific female-to-male YLD rate ratios were calculated using point estimates for each sex within each age group. We acknowledge that this approach does not incorporate the full uncertainty surrounding these estimates. Therefore, these ratios should be interpreted with caution.

3 | Results

3.1 | Global Overview of the YLD Burden in 2021

Globally, the YLD number was 14,252,860 (5,138,707–33,727,828) in 2021. Figure 1 presents the global distribution of age-standardized and sex-combined YLD rates in 2021, incorporating detailed subnational visualizations derived from data in 17 countries with robust local-level reporting. Among individuals aged ≥ 20, YLD rates were generally higher in women than in men at the global level, with an estimated female-to-male sex ratio (SR) of 1.77. However, among those under 20, YLD rates were similar between the two sexes (SR = 1.02) (Figure 2). Consequently, across all ages, the overall female-to-male ratio was 1.62. By age group (< 20, 20–54, ≥ 55), the highest YLD rate was in the 20–54 age group at 234.9 (78.8–568.8) per 100,000, followed by ≥ 55 and then < 20 (Figure 3).

3.2 | Regional and SDI-Based Patterns in YLD Burden

Regionally, although the sex ratio followed a similar global pattern (Figure 2), age-specific trends (i.e., < 20, 20–54, ≥ 55) were not always consistent across regions (Figure 3). For example, in the High-SDI region, YLD rates were slightly higher for individuals aged 20–54 at 113.4 (39.4–266.8) per 100,000 than for those aged ≥ 55 at 111.4 (50.1–224.5) per 100,000. In contrast, the High-Middle SDI region exhibited a higher YLD rate in the ≥ 55 age group at 175.2 (77.4–368.0) per 100,000 compared to 145.2 (50.8–338.9) per 100,000 in the 20–54 group. The Low-SDI region had the highest age-standardized YLD rate (285.5 [103.5–689.3] per 100,000) among the five SDI regions (i.e., High-SDI, High-middle SDI, Middle-SDI, Low-middle SDI, and Low-SDI) in 2021, followed by the Low-middle SDI region (258.4 [94.7–609.2] per 100,000) and the Middle-SDI region

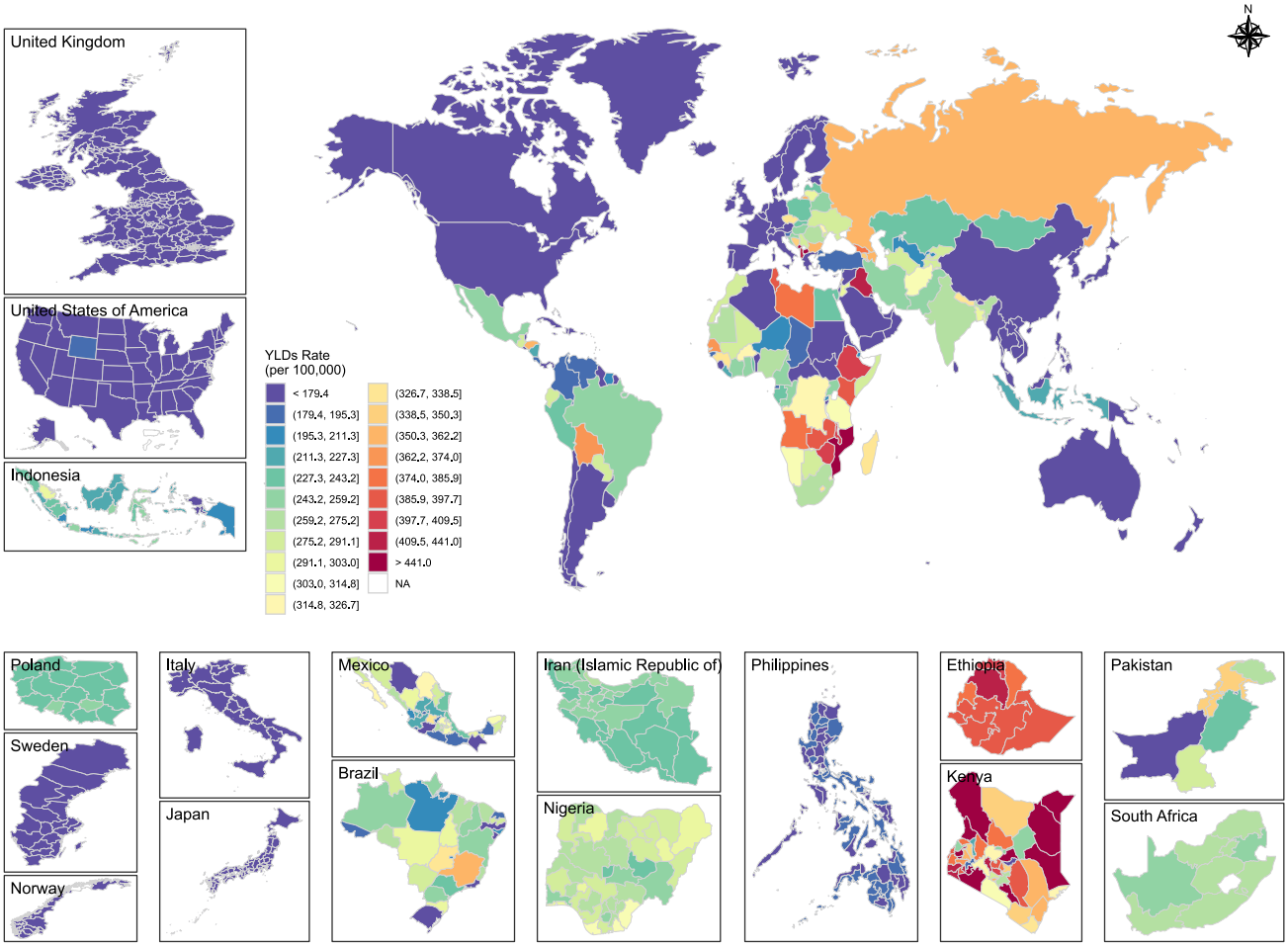

FIGURE 1 | Age-standardized global distribution of YLD rates attributed to COVID-19, 2021. This figure illustrates the global distribution of age-standardized YLD rates in 2021, including detailed subnational visualizations based on data from 17 countries with robust local-level reporting. Rates are presented per 100,000 population and are combined for both sexes. The map indicates relatively higher burden of age-standardized YLD rates in Sub-Saharan Africa, as well as parts of South Asia and Eastern Europe. Many low- and middle-income countries (LMICs), such as Ethiopia and Kenya, experienced a notably higher age-standardized YLD burden in 2021. In contrast, most high-income countries, such as those in North America (e.g., the United States) and Europe (e.g., the United Kingdom, Sweden, and Norway), exhibited substantially lower age-standardized YLD rates, often below 179.4 per 100,000.

(150.3 [54.1–357.3] per 100,000). Unlike the global trend, the highest age-specific YLD rate in the Low-SDI region was observed in the ≥ 55 age group (390.1 [162.9–842.9] per 100,000), surpassing both the 20–54 age group (379.1 [125.3–937.8]) and the < 20 age group (118.7 [37.1–331.4]) (Figure 3). Among the 21 GBD regions, Eastern Sub-Saharan Africa had the highest age-standardized YLD rate at 338.4 (122.0–819.3) per 100,000, slightly exceeding Eastern Europe's rate of 335.4 (127.2–788.9). In Eastern Europe, the YLD rate for the ≥ 55 age group was 532.4 (230.0–1132.1) per 100,000, substantially higher than 418.3 (150.9–984.4) per 100,000 among those aged 20–54.

3.3 | National-Level Disparities: Top Countries by YLD Burden

Figure 4 presents the national trends and variations in age-standardized, sex-combined YLD rates from 2020 to 2021. Table 1 presents the top 10 countries with the highest age-standardized and all-age crude YLD rates in 2021, along with YLD rates for 13 countries included in the inequality analysis. Figure 5a–w illustrates trends in age-standardized and age-specific YLD rates from 2020 to 2021 across these countries, with Figure 5a–j focusing on the top 10 countries with the highest age-standardized YLD rates and Figure 5k–w covering those in the inequality analysis. Figure 6a–z further illustrates the age-standardized and all-age crude YLD rates across local units within the 13 countries during 2020–2021. Specifically, in 2021, the 10 countries with the highest age-standardized YLD rates ranged from 397.2 (138.1–973.0) per 100,000 in Zambia to 466.8 (164.3–1092.7) per 100,000 in Mozambique (Figure 4). Among these, 8 (80%) were low, low-middle, or middle SDI countries, including Mozambique, Albania, Iraq, Malawi, Zimbabwe, Palestine, Ethiopia, and Zambia. The remaining 2 (20%) were classified as high-middle SDI countries, with no high SDI countries represented. In all these 10 countries, crude YLD rates for aged ≥ 20 were consistently higher in women than men. Unlike the global trend, these countries' highest age-specific YLD rates were in the ≥ 55 group (Figure 5a–j). On the other hand, the 10 countries with the highest all-age crude

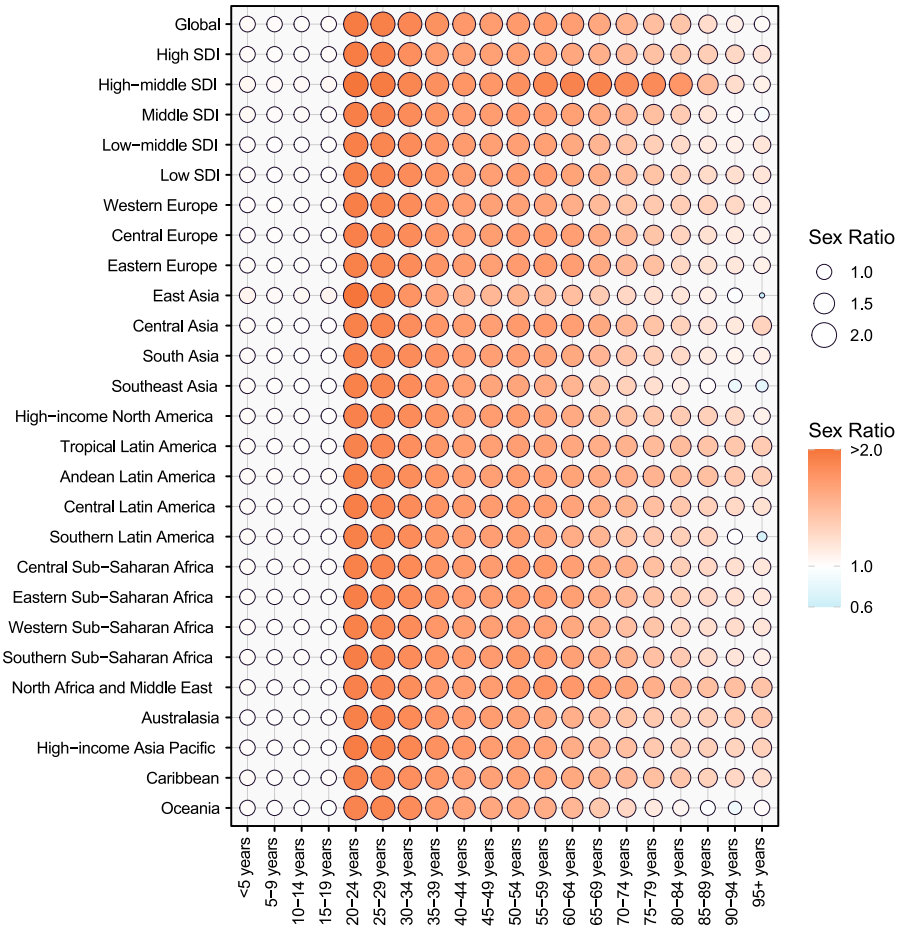

FIGURE 2 | Global and regional age-specific female-to-male sex ratios of YLD rates attributed to COVID-19, 2021. This figure illustrates the global and regional age-specific female-to-male sex ratios (SRs) of YLD rates in 2021.

YLD rates ranged from 393.1 (135.0–934.0) per 100,000 in Libya to 536.2 (189.0–1244.4) per 100,000 in North Macedonia. Of note, 8 (80%) were classified as high-middle or high SDI countries, while the remaining 2 (20%) fell into the middle SDI category. No low SDI countries were represented. In addition, among the 13 countries analyzed for inequality, both age-standardized and all-age crude YLD rates in 2021 generally followed a gradient: lowest in high SDI countries (e.g., Japan, Norway), followed by middle SDI (e.g., Brazil, Indonesia), then low-middle SDI (e.g., Kenya), and highest in low SDI (e.g., Ethiopia). Full details on the YLD burden from global to local levels can be found in Supporting Information S2 and S3 of our previous report [6].

3.4 | YLD Inequality Trends From Global to Local Levels

Table 2 and Figure 7 show the global-to-national absolute and relative inequalities in COVID-19 YLD rates from 2020 to 2021. Global absolute inequality in YLD rates, measured by the SII, increased from −43.0 (−62.1 to −23.9) in 2020 to −66.3 (−117.3 to −15.2) in 2021 (Figure 7). Among the 5 SDI regions, the High-SDI region had the largest negative YLD SII in 2021, with a value of −70.2 (−163.8 to 23.4), signifying disproportionately higher YLD rates in lower SDI countries within that region. In contrast, the Middle-, Low-middle, and Low- SDI regions showed limited within-region inequalities (SII: 7.3, −88.1–102.7; −4.7, −138.4–128.9; 7.8, −107.8–123.3, respectively). Relative inequality (CII) followed a similar pattern: in 2021, lower SDI populations in the High-SDI region faced a disproportionately higher burden (CII = −0.16), while the Low-SDI region had little internal disparity (CII = −0.03). At the subnational level, SII and CII analyses showed varying trends in YLD rate inequalities across local units in 13 countries with different SDI levels from 2020 to 2021 (Figure 8a–m). Notably, the United States had the most negative SII at −68.9 (−94.6 to −43.1) in 2021, while Mexico had the most positive SII at 89.9 (−2.7 to 182.5). The United Kingdom, Japan, and Norway exhibited the smallest negative SII values at −3.7 (−6.1 to −1.2), −2.6 (−3.2 to −1.9), and −2.0 (−4.2 to 0.3), respectively, with the United Kingdom also showing the smallest CII at 0.01.

4 | Discussion

4.1 | YLD Patterns and Vulnerable Populations and Locations

Importantly, to flag which locations and populations might be at higher risk of long COVID morbidity in more recent years (e.g., 2022–2023), we analyzed age-standardized and age-sex-location-

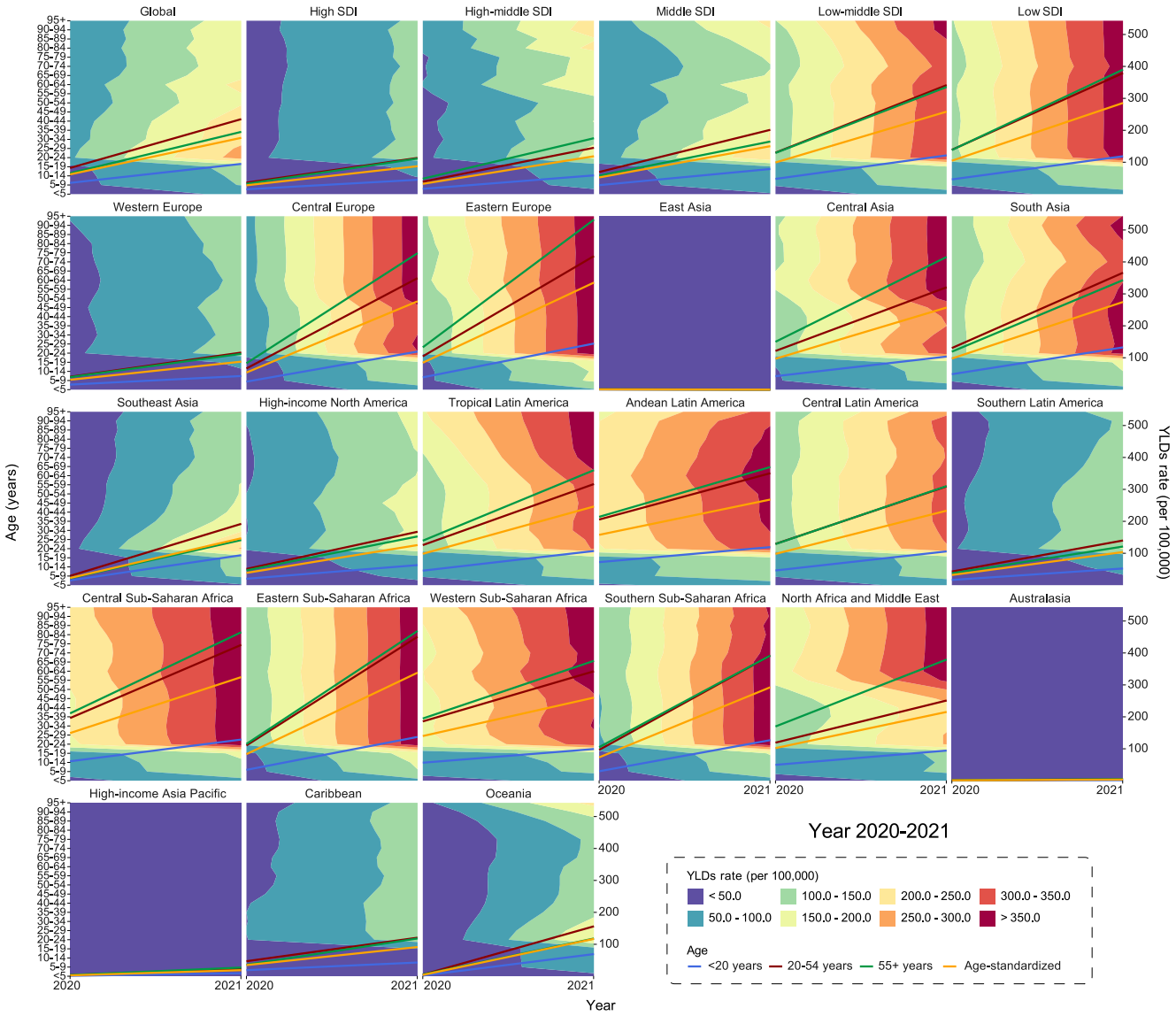

FIGURE 3 | Global and regional variations in YLD rates attributed to COVID-19, 2020–2021. This figure illustrates the global and regional trends in age-standardized, age-specific, and sex-combined YLD rates per 100,000 population from 2020 to 2021. Within the High-SDI region, some countries amplified the global disparity between the 20–54 and ≥ 55 age groups. For instance, in the United States, YLD rates were higher among individuals aged 20–54 (178.8 [62.7–423.6]) than among those aged ≥ 55 (161.9 [72.7–325.9]). Other High-SDI countries, such as Japan, Norway, and Sweden, exhibited an inverse trend, with higher YLD rates in the ≥ 55 age group compared to younger groups.

specific YLD rates from global to local levels across 920 locations for 2020–2021. We also examined YLD inequalities across these spatial scales to better understand potential disparities in the long COVID burden. The results revealed distinct patterns by age, sex, and socio-demographic context, as well as pronounced geographic inequalities, as detailed below.

4.1.1 | Age and Sex Disparities

Globally, in 2021, we found that COVID-19 YLD rates were generally higher in women than in men for individuals aged ≥ 20 (female-to-male ratio = 1.77), whereas rates were similar between sexes for those < 20 (ratio = 1.02), yielding an overall all-age female-to-male ratio of 1.62. These findings align with multiple large-scale studies of long COVID incidence and prevalence conducted in recent years [8, 19, 30]. For example, a Bayesian meta-analysis covering 1.2 million people across 22 countries estimated that women aged ≥ 20 were nearly twice as likely as men to develop long COVID in 2020–2021 (10.6% vs. 5.4% prevalence) [19]. A most recent study using the Pediatric Learning Health System (PEDSnet), which included 727,994 individuals between 2020 and 2024, found that women ≤ 21 years had a slightly higher likelihood of developing long COVID than men in the same age group (adjusted hazard ratio 1.17, 95% CI 1.14–1.22) [30]. Although statistically significant, the hazard ratio's proximity to 1 suggests that the increased risk for young women is limited. Moreover, our observed global YLD sex ratio of 1.62 may provide fundamental supporting evidence for a recent global meta-analysis (incorporating 22 original studies published between mid-2021 to mid-2024), which reported a pooled odds ratio of

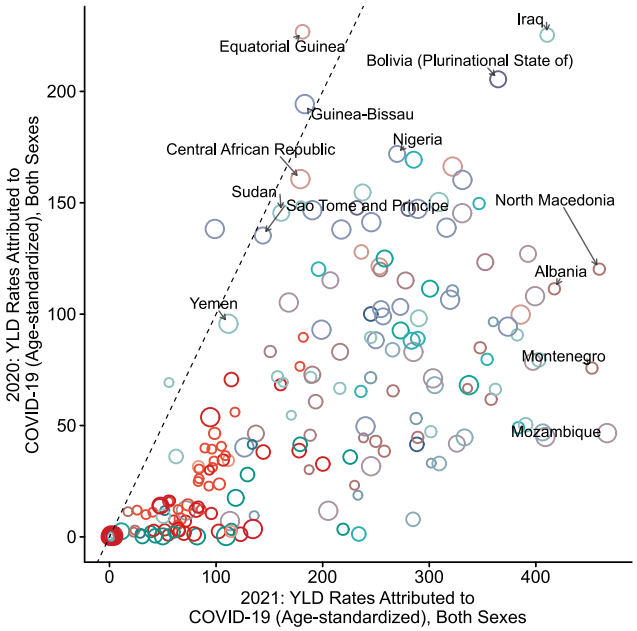

FIGURE 4 | National variations in YLD rates attributed to COVID-19, 2020–2021. This figure illustrates the national trends and variations in age-standardized, sex-combined YLD rates per 100,000 population from 2020 to 2021.

1.55 (95% CI 1.25–1.92) for women developing long COVID compared to men [8].

Age patterns in YLD burden varied. At the national level, for instance, our results showed that in the United States, YLD rates in 2021 were higher among younger and middle-aged adults (aged 20–54 years) than among adults aged ≥ 55. This might contrast with the intuitive expectation that older adults would bear the greater burden, and it matches findings from two recent United States long COVID studies suggesting that younger and middle-aged adults were more severely impacted by long COVID than older adults [31, 32]. Taken together, this combined evidence suggests that YLD rates in 2021 could serve as a useful preliminary measure to indicate age- and sex-specific groups that might be at higher risks of long COVID morbidity in subsequent years. Furthermore, the differing age trends in YLD rates (e.g., < 20, 20–54, and ≥ 55), observed at global and regional levels in our study, highlight the necessity of fine-grained analyses so as not to overlook vulnerable subgroups whose risks might be masked in more aggregated data.

4.1.2 | LMIC Vulnerability

Across socio-demographic development levels, we found that in 2021, the Low-, Low-middle-, and Middle-SDI regions had the

TABLE 1 | Top 10 countries with the highest age-standardized and all-age crude YLD rates in 2021, and YLD rates in 13 countries with available SDI data for inequality analysis.

Category (rank)	Country (SDI level)	Age-standardized YLD rate (per 100,000)	All-age crude YLD rate (per 100,000)
Top 10 countries by age-standardized YLD rates in 2021			
(1)	Mozambique (low SDI)	466.8 (164.3–1092.7)	/
(2)	North Macedonia (high-middle SDI)	459.5 (157.9–1089.3)	/
(3)	Montenegro (high-middle SDI)	452.6 (166.4–1054.2)	/
(4)	Albania (middle SDI)	417.4 (147.5–992.7)	/
(5)	Iraq (middle SDI)	410.6 (134.9–1013.4)	/
(6)	Malawi (low SDI)	409.0 (139.1–973.9)	/
(7)	Zimbabwe (low-middle SDI)	406.5 (111.9–1004.4)	/
(8)	Palestine (middle SDI)	402.8 (125.0–966.7)	/
(9)	Ethiopia (low SDI)	399.3 (145.7–947.7)	/
(10)	Zambia (low-middle SDI)	397.2 (138.1–973.0)	/
Top 10 countries by all-age crude YLD rates in 2021			
(1)	North Macedonia (high-middle SDI)	/	536.2 (189.0–1244.4)
(2)	Montenegro (high-middle SDI)	/	516.0 (195.7–1174.3)
(3)	Albania (middle SDI)	/	482.4 (174.5–1134.8)
(4)	Georgia (high-middle SDI)	/	436.0 (113.3–1081.2)
(5)	Bulgaria (high-middle SDI)	/	430.4 (129.9–1050.5)
(6)	Tunisia (middle SDI)	/	417.2 (133.4–1015.5)
(7)	Russian Federation (high-middle SDI)	/	416.5 (169.9–944.6)
(8)	Bosnia and Herzegovina (high-middle SDI)	/	414.4 (153.5–929.4)
(9)	Czechia (high SDI)	/	397.6 (153.0–882.1)

(Continues)

TABLE 1 | (Continued)

Category (rank)	Country (SDI level)	Age-standardized YLD rate (per 100,000)	All-age crude YLD rate (per 100,000)
(10)	Libya (high-middle SDI)	/	393.1 (135.0–934.0)
Thirteen countries with available SDI data for inequality analysis			
South America	Brazil (middle SDI)	245.1 (88.7–575.4)	263.1 (96.1–612.8)
Africa	Ethiopia (low SDI)	399.3 (145.7–947.7)	338.5 (117.8–828.2)
	Kenya (low-middle SDI)	392.6 (138.8–917.6)	350.2 (116.3–839.8)
	South Africa (middle SDI)	265.5 (96.3–632.9)	271.1 (96.5–652.7)
Asia	Indonesia (middle SDI)	225.8 (81.7–529.3)	233.9 (83.7–554.2)
	Iran (middle SDI)	245.0 (91.3–588.1)	255.4 (94.5–616.5)
	Japan (high SDI)	23.9 (8.6–56.1)	28.6 (11.6–62.8)
	Pakistan (low-middle SDI)	258.1 (88.6–606.1)	237.6 (79.3–576.9)
North America	The U.S. (high SDI)	133.9 (49.6–307.8)	146.3 (57.7–327.5)
	Mexico (middle SDI)	254.1 (96.2–584.2)	263.5 (99.1–609.2)
Europe	Norway (high SDI)	40.7 (16.0–93.1)	45.9 (18.8–99.7)
	Sweden (high SDI)	89.5 (33.6–213.0)	101.7 (40.3–229.1)
	The UK (high SDI)	105.0 (39.3–241.0)	116.2 (47.0–258.1)

three highest age-standardized YLD rates among the 5 SDI regions, with Eastern Sub-Saharan Africa ranking the highest among the 21 GBD regions. Notably, in contrast to the global pattern, the Low-SDI region showed the highest age-specific YLD rates among individuals aged ≥ 55. These observations, taken in the context of the paucity of prior research systematically investigating the long COVID burden in low- and middle-income countries (LMICs) in 2022–2024 [10, 33], provide early evidence that LMIC populations may have been particularly vulnerable to long COVID in recent years.

The underlying vulnerabilities of LMIC populations could be understood from two core perspectives. On the one hand, individuals with long COVID (particularly older adults) in LMICs often receive fragmented care due to constrained health system capacity, under-resourced primary care, and competing healthcare demands arising from a high burden of chronic noncommunicable diseases (e.g., cardiovascular diseases, diabetes, and chronic respiratory diseases) [10, 34–36]. These systemic weaknesses are compounded by relatively limited social protection measures (e.g., income support), which leave patients with long-term post-COVID sequelae with less mitigation of health and economic impacts. On the other hand, conducting long COVID research in many LMICs is extremely challenging: weak referral systems, limited patient follow-up capacity, and lower awareness of the condition all contribute to these challenges. These barriers, combined with restricted access to care in resource-poor settings, contribute to substantial underdiagnosis and underreporting of long COVID [9]. As a result of these barriers, the true magnitude and impact of long COVID in low-resource settings remain nearly impossible to assess directly [10]. Indeed, a recent international study that aimed to estimate long COVID burden using electronic health records drew data from 10 databases in high SDI and high-middle SDI countries—and none from LMICs [37]. This dearth of research from LMICs exacerbates their vulnerability by effectively obscuring the true burden of long COVID in these populations [9, 10].

Utilizing the GBD 2021 modeling adjustments (which considerably account for underreporting), our study is the first to indirectly shed light on potential long COVID vulnerabilities in countries within the Low-, Low-middle-, and Middle-SDI tiers, broadly aligned with LMIC classifications. For example, we found that low, low-middle, and middle SDI countries (including Mozambique, Albania, Iraq, Malawi, Zimbabwe, Palestine, Ethiopia, Zambia) constituted 80% of the top 10 countries with the highest age-standardized YLD rates in 2021 (half of these countries are in Sub-Saharan Africa). The highest age-standardized YLD rate in the Low-SDI region in 2021 may reflect deep-rooted structural health disparities and systematic vulnerabilities in those settings. Moreover, among the 13 countries we analyzed for inequality, both the age-standardized and the all-age (crude) YLD rates in 2021 followed a clear gradient: the highest rates were observed in low SDI countries (e.g., Ethiopia) and the lowest in high SDI countries (e.g., Japan, Norway). This finding aligns with prior research suggesting that long COVID may have a disproportionately severe impact on daily functioning in LMICs, exacerbated by inadequate healthcare infrastructure and a higher prevalence of pre-existing medical conditions [33]. Chronic disability from long COVID could place additional strain on already overstretched healthcare resources, worsening health inequalities and adversely affecting economies [10].

It is noteworthy that in low, low-middle, and middle SDI countries we examined, both the most disadvantaged and the relatively advantaged subpopulations experienced high long COVID risks. We observed only limited regional inequalities (i.e., small cross-national differences in SII and CII) within these SDI groups in 2021, indicating that the long COVID burden was not confined to the very poorest individuals. Nonetheless, the

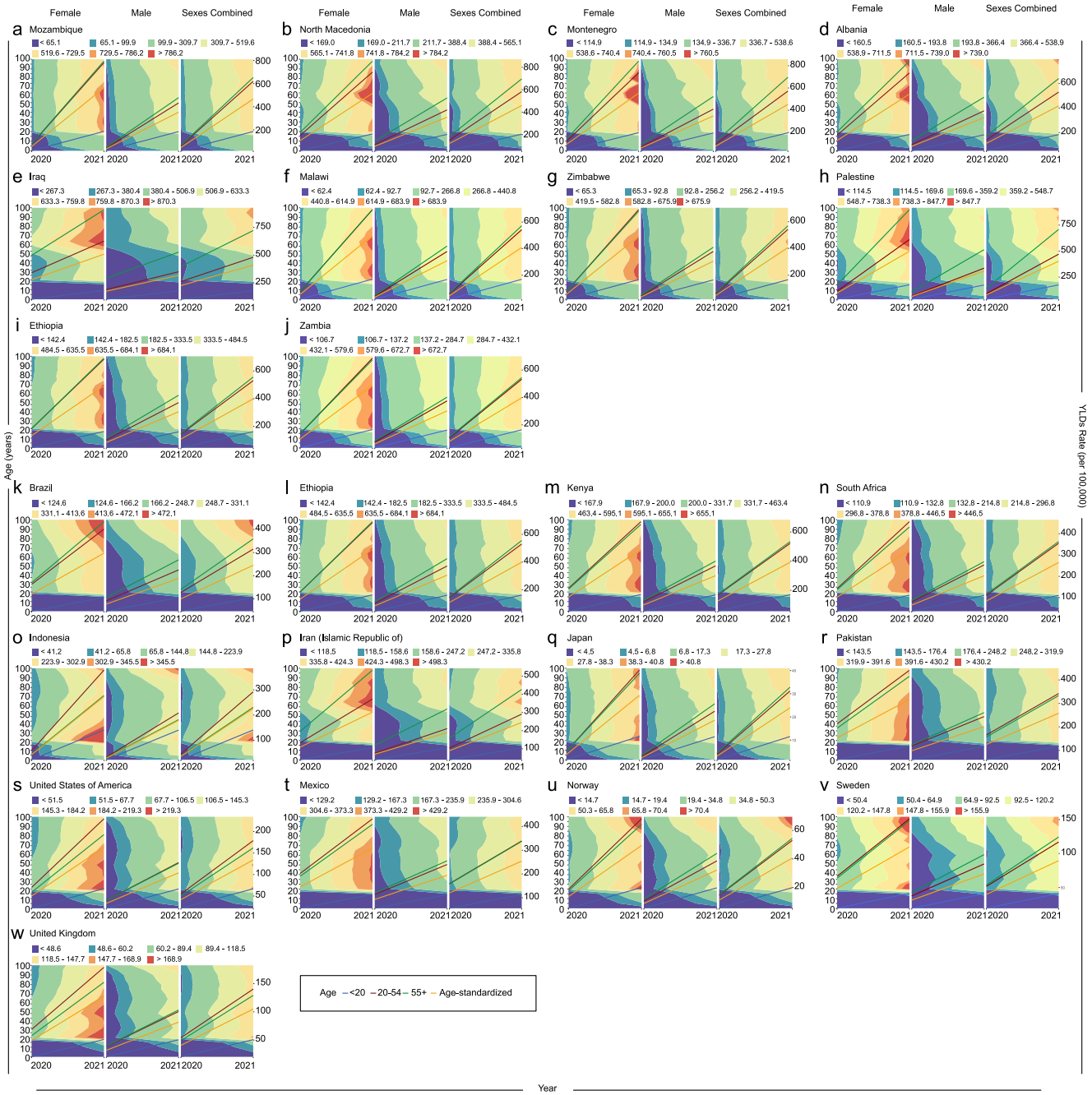

FIGURE 5 | Trends in YLD rates (2020–2021) for the top 10 countries with the highest age-standardized YLD rates in 2021 and 13 countries selected for inequality analysis. Panels (a–w) presents trends in age-standardized and age-specific YLD rates from 2020 to 2021 for the top 10 countries with the highest age-standardized YLD rates in 2021 (a–j) and the 13 countries selected for inequality analysis (k–w). This figure was adapted from Supporting Information of our previous study on global-to-local COVID-19 burden inequalities [6].

most socioeconomically disadvantaged groups in LMIC settings still warrant special attention, as they typically have the fewest resources and least support to build resilience against long-term health shocks. Detailed Supporting Information tables and figures from our previous GBD 2021 COVID-19 study provide additional age-standardized and age-sex-location–specific YLD estimates for low- and middle-income locations [6]. This information may be helpful in understanding the potential burden of long COVID in LMICs in recent years, thus assisting policymakers in establishing adequate access to services that ensure patients in these areas regain a better quality of life [10].

4.1.3 | Elevated YLDs in Certain High SDI Countries

Notably, the potential disproportionate long COVID impact on LMICs discussed above was paralleled by broader COVID-19 health disparities during the acute phase of the pandemic. For example, overall COVID-19 DALY rates in 2020–2021 were markedly higher in LMIC areas, as reflected by the negative global SII and CII values for DALYs [6]. Regions such as Sub-Saharan Africa, characterized by under-resourced health systems, widespread poverty, and high population density, struggled disproportionately during the pandemic [38]. By contrast,

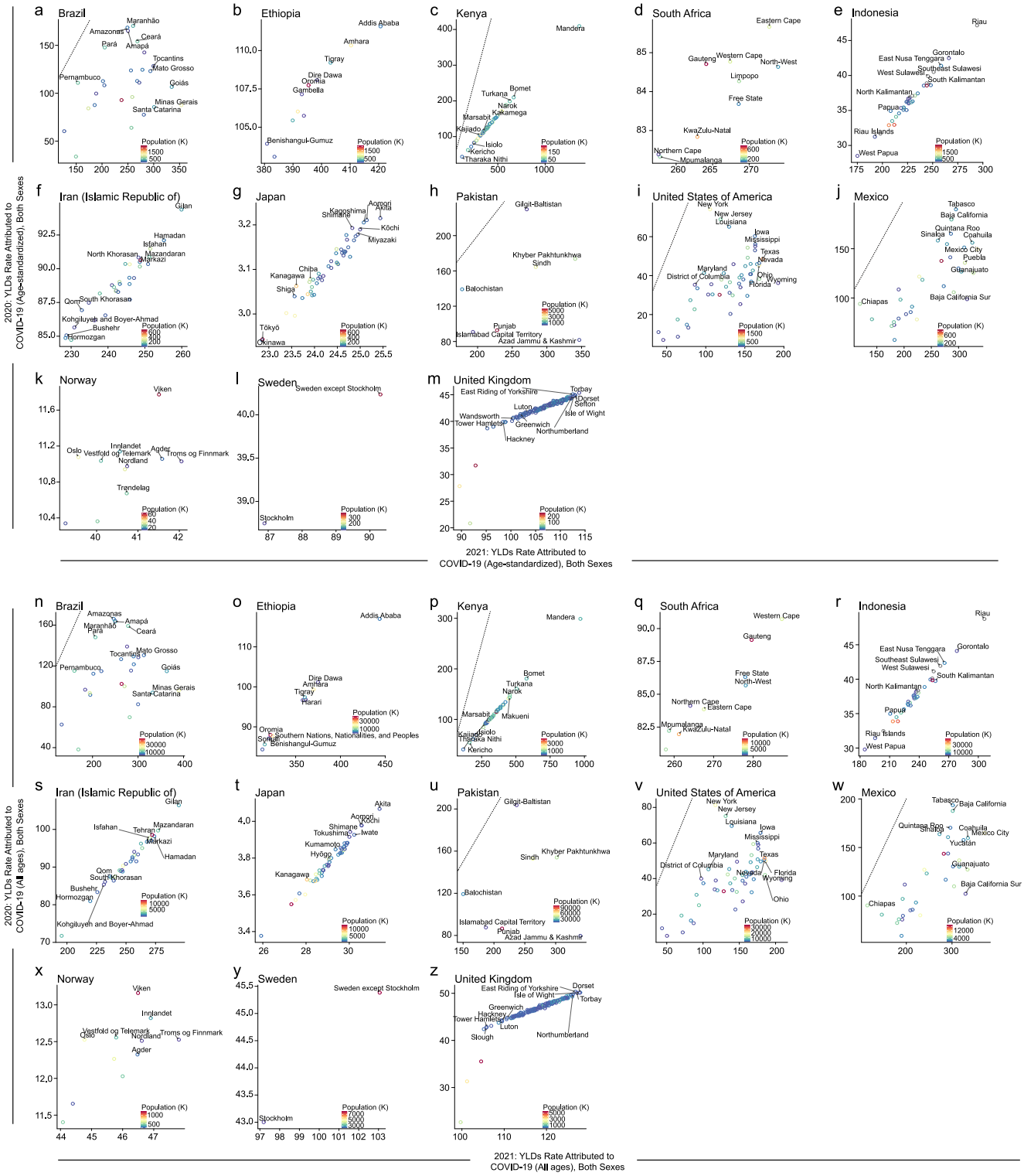

FIGURE 6 | Local variations in COVID-19 YLD rates (2020–2021) across 13 countries selected for inequality analysis. Panels (a–z) illustrates the age-standardized (a–m) and all-age crude YLD rates (n–z) across local units within the 13 countries during 2020–2021.

the High-SDI region generally experienced lower age-standardized COVID-19 burden. In our analysis, the High SDI region had a lower overall age-standardized YLD rate in 2021 than the Middle- and Low-SDI regions. However, we found that the High-SDI region exhibited the largest cross-country inequalities (as measured by SII) in YLD rates in 2021. This may indicate that certain countries within the High-SDI category still faced potentially substantial long COVID burden in subsequent years, even though the group average was lower. Hence, coarse-grained analyses that treat all high SDI countries as homogeneous could overlook critical country-level disparities in long COVID outcomes.

TABLE 2 | Absolute and relative inequalities in YLDs (2020–2021) at global, regional (across 5 SDI regions), and national levels (across 13 countries).

Location	Absolute inequality (SII) across locations 2020–2021 (per 100,000 population) YLD rate	Relative inequality (CII) across locations 2020–2021 YLDs
Global	−43.0 (−62.1 to −23.9) to −66.3 (−117.3 to −15.2)	−0.33 to −0.30
High-SDI region[a]	−70.2 (−163.8 to 23.4)	−0.16
High-middle-SDI region[a]	−21.1 (−145.9 to 103.6)	−0.30
Middle-SDI region[a]	7.3 (−88.1 to 102.7)	−0.04
Low-middle-SDI region[a]	−4.7 (−138.4 to 128.9)	0.28
Low-SDI region[a]	7.8 (−107.8 to 123.3)	−0.03
South America		
Brazil (middle SDI)	−45.6 (−96.4 to 5.1) to 10.8 (−92.9 to 114.6)	0.24 to 0.26
Africa		
Ethiopia (low SDI)	14.4 (7.2–21.7) to 55.5 (31.1–80.0)	0.06 to 0.06
Kenya (low-middle SDI)	0.4 (−24.5 to 25.3) to 2.3 (−84.1 to 88.5)	0.20 to 0.21
South Africa (middle SDI)	10.0 (4.4–15.6) to 27.3 (5.3–49.3)	0.21 to 0.21
Asia		
Indonesia (middle SDI)	−2.5 (−5.6 to 0.5) to −16.9 (−36.9 to 3.0)	−0.02 to −0.04
Iran (middle SDI)	8.2 (0.3–16.1) to 21.7 (−4.3 to 47.7)	0.33 to 0.34
Japan (high SDI)	−0.3 (−0.4 to −0.2) to −2.6 (−3.2 to −1.9)	0.33 to 0.32
Pakistan (low SDI)	−92.3 (−165.6 to −18.9) to −47.5 (−201.6 to 106.6)	0.14 to 0.20
North America		
The U.S. (high SDI)	−7.8 (−21.1 to 5.4) to −68.9 (−94.6 to −43.1)	0.03 to −0.06
Mexico (middle SDI)	38.5 (−10.7 to 87.6) to 89.9 (−2.7 to 182.5)	0.18 to 0.19
Europe		
Norway (high SDI)	−0.3 (−1.3 to 0.7) to −2.0 (−4.2 to 0.3)	0.09 to 0.08
Sweden (high SDI)	−4.8 (N/A) to −11.7 (N/A)	−0.15 to −0.15
The UK (high SDI)	−1.1 (−1.9 to −0.3) to −3.7 (−6.1 to −1.2)	0.03 to 0.01

Abbreviations: CII, Concentration Index of Inequality; DALYs, Disability-adjusted life years; SDI, Socio-demographic Index; SII, Slope Index of Inequality; The U.S., The United States; The UK, The United Kingdom; YLDs, Years lived with disability.
[a]Estimates of regional SII and CII are provided solely for 2021.

In our study, several high SDI countries emerged as clear outliers with notably elevated YLD rates. For instance, the United States, Belgium, and Qatar had notably higher age-standardized (and crude) YLD rates in 2021 compared to other high SDI countries. This suggests that national-level vulnerabilities and inequalities in long COVID burden may persist even in high-resource settings [39]. Indeed, 8 of the 10 countries with the highest all-age YLD rates in 2021 were classified as high SDI or high-middle SDI (including countries like Czechia, the Russian Federation, and Bulgaria), and no low SDI country appeared in this top 10 list. Such findings reinforce the need for granular analysis: remarkable long COVID burden may be "hidden" within affluent regions when one looks only at broad averages.

Several factors may explain why some high and high-middle SDI countries experienced unexpectedly high crude YLD rates. First, an older demographic profile could increase a country's overall long COVID burden: older people are at greater risk than younger people of suffering persistent post-COVID symptoms [40], and COVID-19 could also trigger or exacerbate chronic conditions common in older adults (e.g., cardiovascular, respiratory, or neurodegenerative diseases), leading to additional disability [40]. Second, robust health systems and higher

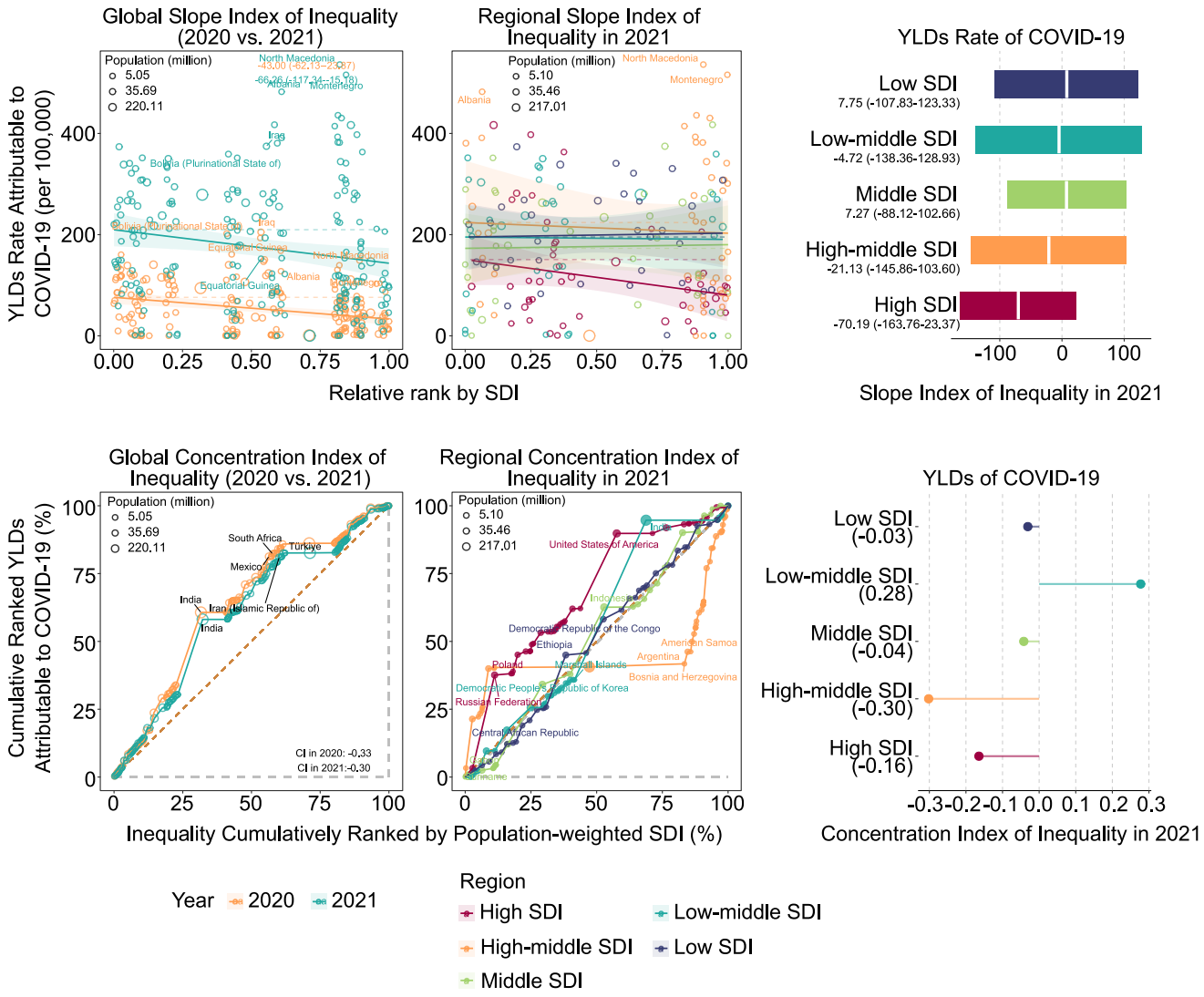

FIGURE 7 | Global and regional inequalities in COVID-19 YLD rates (2020–2021), all ages, both sexes combined. This figure illustrates global inequalities in YLD rates from 2020 to 2021, and regional inequalities in 2021, for all ages and both sexes combined. This figure was adapted from Supporting Information of our previous study on global-to-local COVID-19 burden inequalities [6].

awareness in these countries likely led to more thorough recognition and reporting of long COVID cases—in contrast to LMIC settings, where limited follow-up and lower awareness have led to underdiagnosis. In high SDI populations, individuals may have been more likely to seek post-acute care for lingering symptoms, and providers more likely to diagnose long COVID, thus inflating documented YLD rates relative to places with underreporting. Third, many high SDI and high-middle SDI countries carry a substantial burden of chronic comorbidities (e.g., obesity, diabetes, and cardiovascular disease) which are known risk factors for more severe acute COVID-19 and for post-COVID conditions [8]. A higher prevalence of such comorbidities could amplify the likelihood of prolonged disability after infection. These contributors are consistent with our observed patterns: despite greater resources, certain high SDI or high-middle SDI countries sustained high YLD burden in 2021. Identifying these outliers is important for targeted domestic policy responses, and it underscores that even wealthier nations need to remain vigilant about long COVID as a public health challenge.

4.1.4 | Subnational Disparities

Notable disparities were also evident at the subnational level, even within countries that have strong overall health systems. For example, among the 13 countries included in our inequality analysis, we identified that the United States showed the largest absolute inequality in 2021 YLD rates (reflected by its most negative SII) and a concentrated burden in disadvantaged groups (reflected by its negative CII) across its states. This is consistent with notable variation in long COVID burden observed in the United States in 2022, revealed by a national survey (US Census Bureau's Household Pulse) of nearly half a million Americans: the all-age weighted mean proportion of "having had long COVID" ranged from 9.8% in urban Washington D.C. to 18.2% in rural West Virginia [31]. Moreover, our study found that rural Wyoming had the highest all-age and age-standardized YLD rates in 2021, aligning with the survey data indicating that Wyoming had the second-highest proportion of 'having had long COVID' (18.0%), just slightly lower than that in West Virginia [31], which showed a substantial YLD

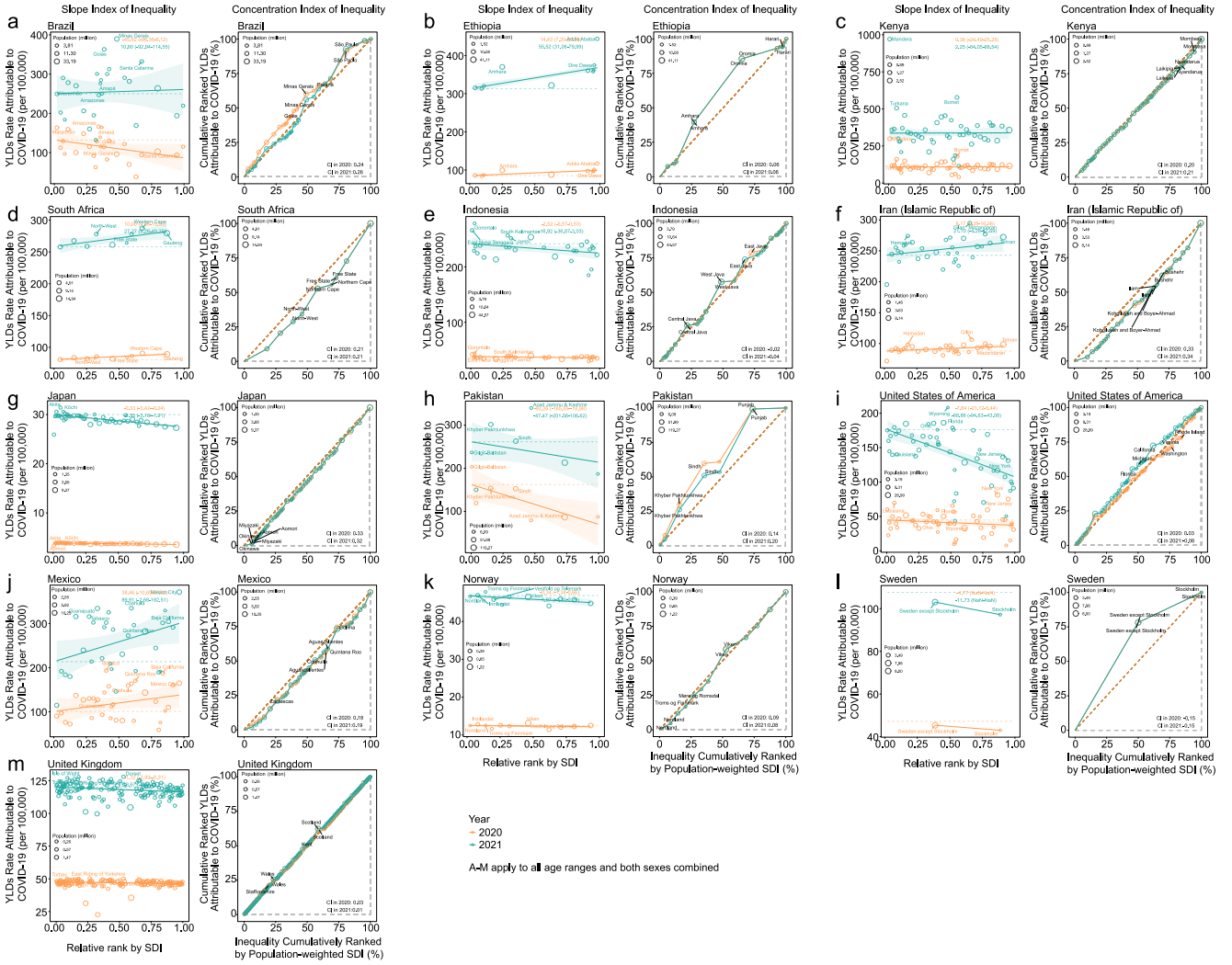

FIGURE 8 | Inequalities in COVID-19 YLD rates (2020–2021) within 13 countries (all ages, both sexes combined). Panels (a–m) illustrates the absolute and relative inequalities in YLD rates from 2020 to 2021 within 13 countries included in the inequality analysis, including (a) Brazil, (b) Ethiopia, (c) Kenya, (d) South Africa, (e) Indonesia, (f) Iran, (g) Japan, (h) Pakistan, (i) the United States, (j) Mexico, (k) Norway, (l) Sweden, and (m) the United Kingdom. This figure was adapted from Supporting Information of our previous study on global-to-local COVID-19 burden inequalities [6].

increase from 2020 to 2021 in our study. These localized disparities highlight the role of local healthcare inequalities, resource allocation, and socioeconomic conditions in shaping long COVID outcomes, underlining the need for context-specific public health interventions to alleviate disproportionate burden in underserved areas.

Other local units identified in our study as having higher COVID-19 YLD burden in 2021 (relative to counterparts within their countries) should also receive special attention, as this may signal a greater risk of a high long COVID burden in recent years. Hence, targeted interventions (such as bolstering clinic capacity, outreach, and rehabilitation services) should be considered in these hotspots to mitigate COVID-19's long-term effects. That said, further research and surveillance are needed to validate observations at the local level across multiple countries, especially within LMICs. Strengthening data collection on long COVID in resource-limited local settings will be crucial to ensure that emerging high-burden areas are recognized and supported appropriately.

4.2 | Public Health and Policy Implications

4.2.1 | International-Level Interventions

The COVID-19 pandemic exposed critical weaknesses in global supply chains for essential healthcare resources (e.g., personal protective equipment, vaccines, and testing kits), which disproportionately impacted LMICs [41, 42]. This underscores the need for stronger international cooperation. Global bodies could consider developing frameworks for equitable distribution of vaccines and other life-saving interventions during future health emergencies to ensure timely access worldwide—especially in low-resource settings—and mitigate the

inequalities observed during this pandemic [43–45]. Prior evidence indicated that COVID-19 vaccination may reduce the risk of developing long COVID symptoms [46]; however, lower vaccine coverage in many LMICs may have limited this potential protection effect [10]. Hence, international initiatives should prioritize rapid deployment of vaccines and therapeutics to underserved settings, protecting those at higher risk of severe acute outcomes (e.g., older adults ≥ 55 years, individuals with comorbidities) and of long COVID complications (e.g., women ≥ 20 years, as identified in this study), thereby promoting global resilience.

Beyond emergency response, sustained international support is needed to build long-term capacity for managing long COVID and future pandemics. Global health partnerships could strengthen healthcare infrastructure in LMICs by aiding the establishment of long COVID surveillance, diagnostic, and rehabilitation services. The highest age-standardized YLD rates observed in LMICs in 2021 may reflect systemic vulnerabilities and entrenched structural health disparities, potentially indicating a considerable and enduring long COVID burden that might continue to the present day, unless targeted and sustained interventions are implemented. Targeted investments in collaborative research (including studies led by LMIC scientists) are needed to better characterize long COVID's impacts on populations and on progress toward Sustainable Development Goals (SDGs). It is also prudent to invest not only in recovery but in preparedness; for instance, maintaining international stockpiles of critical medical supplies and knowledge-sharing platforms may help ensure LMICs are not disproportionately affected by future outbreaks [10]. Finally, as new therapeutics for preventing or treating long COVID are developed, international financing mechanisms and patent-sharing agreements could ensure these treatments are made available at affordable costs across all countries, avoiding repeats of past inequities in access to care [10].

4.2.2 | National-Level Policies

National governments and health agencies should translate global recommendations into context-specific strategies that strengthen health system responses to long COVID. One immediate step could be developing evidence-based clinical practice guidelines for long COVID diagnosis, management, and referral. Professional societies and ministries of health may collaborate on consensus guidelines and nationwide training programs for clinicians, especially in areas with low awareness of long COVID [9, 33]. By offering incentives and continuing education opportunities, authorities can improve providers' ability to recognize long COVID symptoms that might otherwise be misattributed—an important consideration in settings where the condition has been underdiagnosed (including many LMICs). Integrating up-to-date long COVID content into medical and nursing curricula, along with continuing education for current providers, is advisable to ensure new health professionals are equipped to manage this condition and that patients are not overlooked [47, 48].

Countries should also bolster healthcare services to support those affected by long COVID. Health systems could establish specialized multidisciplinary clinics or rehabilitation programs (at least in major centers) to address the physical, cognitive, social, and occupational dimensions of long COVID recovery. If resources are limited, pilot programs in high-burden areas could help optimize care pathways before scaling up successful models nationwide. Our findings indicate that even within high SDI countries, rural and socioeconomically disadvantaged communities may experience disproportionately high long COVID burden; thus, national policies should allocate extra support to these localities—for example, through mobile clinics or telehealth outreach. In formulating interventions, it is crucial to prioritize the demographic groups most impacted, such as older adults (≥ 55 years), who are at elevated risk of severe outcomes, and women aged ≥ 20 years, who have shown potentially higher susceptibility to long COVID compared to men, particularly in LMICs. Tailored outreach and prevention programs for these groups (such as targeted vaccination campaigns or post-acute follow-up initiatives) may help reduce overall long COVID morbidity. Furthermore, given the lack of widely validated therapies for long COVID, national research agencies should invest in studies to identify effective treatments and preventive strategies, ideally collaborating in international trials to accelerate results [49]. As evidence emerges, health authorities should update guidelines and rapidly integrate proven interventions into standard care. Once new therapeutics become available, governments could consider subsidizing them or negotiating affordable pricing to ensure broad access, so that low-income and marginalized patients are not left behind [10].

4.2.3 | Community-Level and Patient-Centered Actions

At the community level, public health efforts should engage local stakeholders and patients directly to improve awareness, reduce stigma, and facilitate access to care for long COVID. Grassroots health communication campaigns can be deployed to disseminate accurate, science-based information in local languages and via trusted community leaders, countering the "infodemic" of misinformation that has proliferated during the pandemic. Misleading narratives about long COVID may downplay the condition's seriousness, promote unproven remedies, or discourage individuals from seeking appropriate care. Combating this requires culturally sensitive education initiatives and proactive information campaigns (including on social media) to ensure communities understand long COVID's legitimate health impacts and the benefits of early medical consultation. By correcting misconceptions and highlighting patient testimonies of recovery, such initiatives may help reduce stigma, encourage timely diagnosis, and support more equitable uptake of available treatments.

Patient-centered care should be a cornerstone of community-level interventions. Healthcare providers and community health workers are encouraged to involve patients in decision-making and incorporate their lived experiences when planning long COVID management strategies. This participatory approach tailors interventions to what patients find practical and acceptable, avoiding one-size-fits-all recommendations that might be ineffective or harmful. For example, some individuals with long COVID experience post-exertional malaise (a worsening of symptoms like fatigue and cognitive impairment after even mild

exertion) [50]; for these patients, standard exercise-based rehabilitation protocols should be avoided or modified [51], even though graded exercise might benefit others with different post-COVID conditions [49]. Eliciting patient feedback may guide clinicians to adjust therapy plans—such as emphasizing pacing and rest for those with post-exertional symptoms—thereby preventing inadvertent harms and improving outcomes. In addition, communities could establish peer support networks or local support groups (facilitated by healthcare providers) where long COVID patients share experiences and coping strategies, helping to alleviate isolation and mental health burden. Such community support structures, combined with strengthened links between primary care and specialized services, would ensure that even patients in underserved areas can access appropriate guidance and rehabilitation resources. Ultimately, empowering patients and communities will improve long COVID management and build trust in public health guidance.

4.3 | Limitations and Future Directions

4.3.1 | Uncertainties in GBD COVID-19 Burden Estimates

Both this study and our previous GBD 2021 analysis of the global-to-local COVID-19 burden have several similar limitations [6], most of which reflect the methodological challenges and uncertainties inherent in official GBD reports [1–3, 52]. In particular, we would like to highlight that the GBD 2021 COVID-19 burden estimates, adjusted by IHME, were designed to account for potential underreporting and offer an alternative perspective on the pandemic's overall impact. These estimates complement those from official public health organizations, which primarily rely on officially confirmed case and death counts that may be subject to reporting limitations. However, like other modeling-based research, GBD estimates are influenced by methodological assumptions and model choices, which can introduce uncertainties, including potential biases such as analytic or researcher bias. For this reason, IHME's COVID-19 estimates should be interpreted with caution and considered alongside national and local epidemiological studies (where available), as well as officially confirmed data, to obtain a balanced understanding of the true impact of the COVID-19 pandemic on specific populations and locations [53, 54].

4.3.2 | Cross-National Comparability Issues

Although the GBD 2021 study sought to mitigate biases arising from cross-national variations in case definitions, testing strategies, data collection, reporting, and healthcare system capacities through modeling adjustments and uncertainty analyses, these efforts, while valuable, cannot completely eliminate the impact of such differences across countries. Therefore, caution is advised when using GBD 2021 estimates to compare COVID-19 burden (especially incidence and mortality) across nations, as these figures represent the best possible approximations within a standardized modeling framework rather than a directly comparable representation of the true pandemic burden.

4.3.3 | Interpretation of Uncertainty Intervals

Unlike conventional 95% confidence intervals, which primarily reflect sampling variability, the 95% uncertainty intervals encompass a broader range of uncertainties, including measurement errors, reporting inconsistencies, and modeling assumptions. Accordingly, comparisons should not be based solely on point estimates but should consider the extent of overlap between uncertainty intervals. Although nonoverlapping UIs may suggest evidence of meaningful differences, they do not, in themselves, establish statistical significance; more formal statistical testing or Bayesian approaches would be required for rigorous confirmation. In other words, while relative differences across geographic locations or temporal periods might suggest underlying trends, they should not be overinterpreted as statistically significant. Caution is particularly warranted when interpreting small differences or estimates with wide uncertainty intervals, as these may reflect data limitations or modeling sensitivities rather than true epidemiological variation. Strengthening the robustness and reliability of future estimates will require ongoing methodological refinements in subsequent iterations of the GBD study, such as GBD 2023 [52, 53]. Additionally, greater standardization in data collection and reporting across locations will be essential to mitigate systematic biases and enhance comparability. This is particularly pertinent for future research on the burden of long COVID in the coming years at local, national, regional, and global levels, given the current lack of consensus on its definition and diagnosis [55].

4.3.4 | Socioeconomic Inequalities and Modeling Limitations

Although SDI captures broad trends in socioeconomic development, substantial heterogeneity potentially persists within SDI groupings. Variations in employment, education, housing, and access to healthcare may be considerable even among countries classified within the same SDI tier, complicating cross-national comparisons. In our analysis, the High-SDI region exhibited the greatest between-country disparities in COVID-19 YLD burden, as indicated by the SII. These findings underscore the need for more granular data to elucidate and effectively address intra-regional and intra-national health inequalities. In addition, our approach to evaluating SII aligns with WHO-endorsed best practices [27], but it assumes a linear relationship between SDI and health outcomes. In reality, socioeconomic conditions interact with health outcomes in complex, potentially nonlinear ways. To mitigate biases and enhance reliability, we applied robust linear regression as a practical solution within the constraints of available data. However, as more validated methodologies emerge in the future, studies should explore advanced nonlinear modeling approaches to better capture these complex associations.

4.3.5 | Limitations in Long COVID Proxy Indicators

Because of limited availability of robust COVID-19 burden data across different geographic levels, we used GBD 2021 YLD burden estimates as a proxy indicator of populations and

locations that may be more vulnerable to long COVID in subsequent years. Although later SARS-CoV-2 variants (e.g., Omicron-related strains) may be associated with a relatively lower risk of post-acute sequelae compared to earlier strains [56, 57], this does not affect the validity of GBD/IHME's approach. The GBD methodology for estimating COVID-19 YLDs is based on the prevalence and severity of specific post-acute COVID-19 symptoms, weighted by disability scores (DWs), rather than on infection incidence or prevalence. Therefore, as the GBD 2023 and GBD 2025 estimates become available, they may provide valuable insights into which groups may be at higher risk of increased long COVID burden in the coming years. On the other hand, the GBD 2021 estimates focused on three major symptom clusters associated with long COVID. Although these clusters could reflect the most severe outcomes reported 3 months or more after the initial infection, they do not represent the full spectrum of long COVID symptoms [2]. This limitation may partly explain the discrepancies observed between the 2021 YLD rates and the actual long COVID burden that emerged in subsequent years across certain populations and locations. Hence, future iterations of the GBD should aim to refine burden estimates to more comprehensively reflect the diverse manifestations and impacts of long COVID.

4.3.6 | Lack of Individual-Level Validation

Because of the nature of this study as a secondary analysis based entirely on GBD 2021 estimates, we were unable to conduct individual-level predictive validation analyses or comparative modeling techniques such as sensitivity analyses based on the area under the receiver operating characteristic curve (AUC). The GBD framework does not provide disaggregated outcome data for long COVID in 2022–2023, nor does it support direct comparisons of different predictive indicators using external validation datasets. Nonetheless, the use of YLDs in 2021—already incorporating post-acute COVID-19 disability—may serve as a plausible and standardized proxy for the preliminary identification of populations and locations that might be vulnerable to long COVID in recent years. Future studies, particularly those based on forthcoming GBD iterations (e.g., GBD 2023 or GBD 2025) or large-scale individual-level datasets, will be essential to formally validate the predictive value of YLDs and assess alternative indicators using robust performance metrics.

4.3.7 | Need for Specific Long COVID Biomarkers

The presence of SARS-CoV-2 in the blood remains an imperfect biomarker for long COVID, as some asymptomatic individuals also exhibit signs of persistent viral presence [58]. This underscores the urgent need to identify reliable and specific biomarkers to diagnose long COVID, especially given that some clinicians still view these symptoms as primarily psychosomatic [58]. Establishing standardized definitions and clinical endpoints for long COVID is essential for accurately capturing its complexity and variability. Such consensus will not only improve patient care and research but also facilitate regulatory approvals, enhance pharmaceutical engagement, and enable meaningful cross-study comparisons [47].

4.3.8 | Future Access to Therapeutics and Long-Term Outcome Research

As efforts to identify effective interventions for long COVID advance, it is imperative that any new therapeutics, once demonstrated to be safe and effective, be made readily accessible at affordable costs—particularly in LMICs, where structural barriers have historically limited access to essential treatments [10]. Without deliberate global coordination, such inequities risk being perpetuated in the post-pandemic era, deepening the burden of chronic disability in the most vulnerable settings.

In parallel, further research is urgently needed to elucidate the full spectrum and mechanisms of long-term complications associated with COVID-19. While core symptom clusters such as fatigue, respiratory difficulties, and cognitive dysfunction are now well-recognized, a range of post-acute sequelae remains poorly characterized. These include potential neurodegenerative consequences such as new-onset dementia, as well as elevated risks of cardiovascular diseases (e.g., myocardial infarction, arrhythmias, thromboembolism), metabolic disorders including new-onset diabetes, immune dysregulation leading to autoimmune manifestations, and persistent inflammatory syndromes [7, 59–65]. Additionally, long COVID has been potentially linked to increased incidence of mental health conditions such as anxiety, depression, post-traumatic stress disorder, and sleep disturbances, which may exacerbate functional impairments and reduce quality of life, especially in younger and working-age populations [66, 67]. Notably, some of these complications may arise even in individuals with initially mild or asymptomatic infections, and may persist or evolve over extended periods. Addressing these complex outcomes will require sustained investment in longitudinal cohort studies, multi-system biomarker and imaging research, and cross-disciplinary mechanistic investigations. Moreover, global collaboration—including participation from underrepresented populations in LMICs—is essential to ensure scientific findings are broadly applicable and equity-focused. A coordinated research agenda integrating clinical, biological, and epidemiological data across diverse settings will be critical to inform targeted interventions, refine clinical guidelines, and ensure that future advances in prevention and treatment benefit all populations equitably.

5 | Conclusion

This study provides a comprehensive global-to-local analysis of the direct COVID-19 YLD burden and associated health inequalities from 2020 to 2021, with a novel emphasis on identifying locations and populations that may be at heightened risk for long COVID morbidity in more recent years, particularly in low- and middle-income countries. Crucially, given the potentially substantial and enduring burden of long COVID in LMICs, policymakers should consider immediate action to strengthen surveillance systems, expand access to rehabilitation services,

and promote equitable healthcare delivery. Long COVID should be integrated into universal health coverage discussions, accompanied by targeted resource allocation for high-risk groups. International collaboration is essential to standardize diagnostic criteria, advance research, and implement evidence-based interventions. A proactive, coordinated response will be critical to mitigating long-term health disparities and enhancing resilience for future pandemics. Although this study is not a substitute for formal long COVID surveillance based on individual-level data, it offers a valuable interim approach to identifying potential vulnerabilities, particularly in settings where direct surveillance is limited or unavailable. By using YLD rates from GBD 2021 and similar burden estimation strategies, researchers and policymakers may be able to flag at-risk populations and geographic areas that warrant closer monitoring and support. Looking ahead, future research leveraging forthcoming GBD iterations may help project the evolving impact of long COVID across geographic settings, thereby informing timely and targeted public health interventions.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

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Data Availability Statement

This study analyzes publicly available data obtained from the Global Burden of Disease Study 2021 (GBD 2021), accessible at: https://ghdx.healthdata.org/gbd-2021. Additional data not available through the GBD Results Tool (https://vizhub.healthdata.org/gbd-results/) can be requested from the Institute for Health Metrics and Evaluation (IHME).

Transparency Statement

Some of the figures in the main text (Figures 5, 7, and 8) were adapted from Supporting Information S3 (Figures S14, S40, and S46, respectively) of our

previous study (https://doi.org/10.1002/mdr2.70013), which was published in Med Research. These adaptations were made to address a distinct research question in the current manuscript.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.