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Association of the COVID-19 pandemic on stroke admissions and treatment globally: a systematic review

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ABSTRACT

Objectives The COVID-19 pandemic has highlighted insufficiencies and gaps within healthcare systems globally. In most countries, including high-income countries, healthcare facilities were over-run and occupied with too few resources beyond capacity. We carried out a systematic review with a primary aim to identify the influence of the COVID-19 pandemic on the presentation and treatment of stroke globally in populations≥65 years of age.

Design A systematic review was completed. In total, 38 papers were included following full-text screening.

Data sources PubMed, MEDLINE and Embase.

Eligibility criteria Eligible studies included observational and real-world evidence publications with a population who have experienced stroke treatment during the COVID-19 pandemic. Exclusion criteria included studies comparing the effect of the COVID-19 infection on stroke treatment and outcomes.

Data extraction and synthesis Primary outcome measures extracted were the number of admissions, treatment times and patient outcome. Secondary outcomes were severity on admission, population risk factors and destination on discharge. No meta-analysis was performed.

Results This review demonstrated that 84% of studies reported decreased admissions rates during the COVID-19 pandemic. However, among those admitted, on average, had higher severity of stroke. Additionally, in-hospital stroke treatment pathways were affected by the implementation of COVID-19 protocols, which resulted in increased treatment times in 60% of studies and increased in-hospital mortality in 82% of studies by 100% on average. The prevalence of stroke subtype (ischaemic or haemorrhagic) and primary treatment methods (thrombectomy or thrombolysis) did not vary due to the COVID-19 pandemic.

Conclusions During the COVID-19 pandemic, many populations hesitated to seek medical attention, decreasing hospital admissions for less severe strokes and increasing hospitalisation of more severe cases and mortality. The effect of the pandemic on society and healthcare systems needs to be addressed to improve stroke treatment pathways and prepare for potential future epidemics.

PROSPERO registration number CRD42021248564.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A broad comparison of global stroke treatment considering the pandemic.
⇒ Lack of data on low-income countries.
⇒ Difficulty in making comparisons across studies due to regional variation and study design.
⇒ Age limitations do not provide a broad scope of systems of care.

INTRODUCTION

The COVID-19 pandemic has influenced every aspect of healthcare and the general functioning of populations.[1] In December 2019, emerging cases of a new strain of coronavirus occurred in Wuhan, China, which spread across the globe within months.[2] A few effects of COVID-19 have been overcrowded hospitals and intensive care units, a lack of hospital resources and nationwide lockdowns. Such factors have directly influenced the stroke treatment pathways established within primary care centres. Initial reports have identified a decrease in stroke admission rates following the onset of the pandemic.[3 4] It is unclear whether stroke incidence has decreased or whether populations elicit avoidance behaviours for fear of viral infection.

This review will explore the global variation of stroke treatment and admission rates during the COVID-19 pandemic. Age is a key risk factor for stroke, and seniors over 65 years have been disproportionately affected by the pandemic.[5–7] This review will focus on ageing populations (65+ years). To date, no studies have explored the trends of stroke treatment within this population cohort as an effect of COVID-19 in both high-income countries and low-and-middle-income countries (HICs and LMICs). Considering systemic factors, this comparison may provide insight into the regional impacts of the pandemic and how varying interventions may have influenced

the stroke treatment pathway. The primary aim of this systematic review was to understand how the global and regional burden of stroke in seniors (aged 65+) has been affected by COVID-19. The secondary aim was to explore how the COVID-19 pandemic influenced the determinants of stroke.

METHODS

Search strategy

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[8] (online supplemental appendix table 1). The specific search queries for this protocol were registered on PROSPERO, an international database for prospectively detailing systematic reviews in health and social care (registration number: CRD42021248564). Three databases were used to search: Embase, MEDLINE and PubMed. No search restrictions about publication date were implemented, as results with COVID-19 as a medical subject heading (MeSH) begin in 2020. On 15 March 2021, each of the three databases was searched, and results were uploaded into Covidence. The search query for each database used the MeSH of stroke and COVID-19 and a subject heading of age 65 years and older. The abstract and title pertained to the presentation, treatment and management of stroke (full search strategy is shown in online supplemental appendix table 2).

Study selection

One reviewer (RAVD) screened search results based on titles, abstracts and full texts according to the established inclusion and exclusion criteria. A secondary reviewer (KA) completed 10% of the first reviewer's screening to decrease the risk of bias. Discussion and consensus among reviewers addressed discrepancies or resolved any concerns or discrepancies. The outcome of interest was patients who experienced a stroke, and the exposure of interest was the COVID-19 pandemic. The studied condition is stroke in patients located in regions affected by COVID-19. Selection criteria for study populations were those admitted and treated for a stroke during a specified time during the COVID-19 pandemic (variable depending on the study) and a control population sometime prior to the pandemic onset, usually in the same time range in 2019. The inclusion criteria are as follows:

- Study design—peer-reviewed and published observational studies.
- Population—patients with a reported stroke and a median age≥65 years.
- Comparator during the COVID-19 pandemic—patients with a reported stroke and median age≥65 years prior to the COVID-19 pandemic.

Exclusion criteria were study populations infected with the COVID-19 virus and cohorts with a transient ischaemic attack. Case studies and reports were also excluded.

Data extraction

One reviewer extracted data using a preset extraction template. A second reviewer checked extracted data to evaluate correctness and accuracy. Data were extracted, when available, according to the following categories: study characteristics (study design, location and economic status of country), population characteristics (size, median age and sex), cohort characteristics (type of stroke and risk factors), treatment characteristics (number of admissions, door to needle time, door to groin puncture time, door to neuroimaging time, treatment type and National Institute of Health Stroke Scale (NIHSS) Score on admission) and outcomes (in-hospital mortality rates and destination on discharge). The study's primary outcome is the number of patients with a reported stroke, treatment outcomes, risk factors during the COVID-19 pandemic and the geographic demographics associated with this occurrence.

Risk-of-bias assessment

Two authors evaluated the quality and risk of bias of selected papers based on the Newcastle Ottawa Scale (NOS) of assessment (RAVD and KA), commonly used for systematic reviews published in neurological and global health journals.[9–12] The NOS coding manual for case–control studies was used to reference the assessment[9] (online supplemental appendix table 3). The studies' selection, comparability and outcomes were analysed and assigned a star based on specific criteria within each section using the NOS. The selection was evaluated based on four questions and/or criteria in which a total of four stars could be awarded. Comparability was analysed based on one criterion; however, two stars could be awarded depending on the study controls' number of factors. Lastly, the outcome was evaluated concerning three criteria, with a potential for three stars. According to the NOS guidelines, stars were tallied and evaluated to classify each study as good or poor quality and/or bias risk as determined by the number of stars per category.

Synthesis of results

The aggregate data were extracted from each study. Continuous data were represented by mean with SD or median with IQR, whereas categorical data will be represented by a percentage. We provided a subgroup analysis for location, economic status of the country and type of stroke. Due to considerable variations in the study design, data collection procedures, reporting findings for different groups and population heterogeneity, we did not perform a meta-analysis of the reported effect sizes.[13] There were insufficient studies to carry out statistical testing for the risk-of-bias assessment, and data were interpreted independently and not in groups. Summary figures were created using Excel per data category.

Patient and public involvement

No patient was involved.

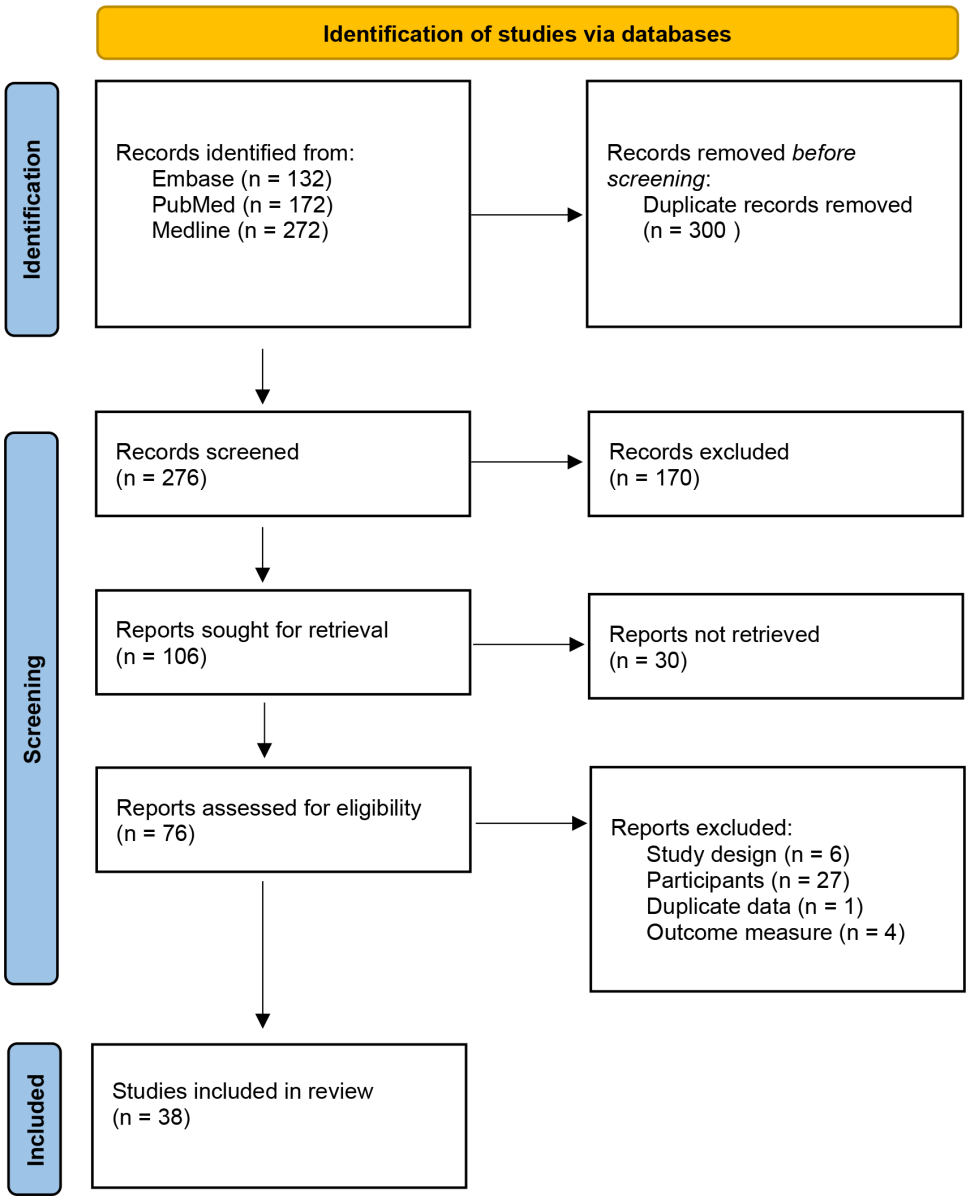

Figure 1 Schematic breakdown of systematic review study inclusion and exclusion process. Overall, 3 databases were used with the same search query, which resulted in a total of 576 papers. A total of 300 duplicates were removed, leaving 256 articles for the title and abstract review. Lastly, a full paper review resulted in a final inclusion of 38 studies.

RESULTS

Search results

The initial database searches using MEDLINE, Embase and PubMed resulted in 272, 132 and 172 results, respectively (figure 1). A total of 300 duplicates were removed, resulting in 276 papers screened by title and abstract; an additional 200 articles were removed following this screening as they did not meet the inclusion criteria. After the full-text screening, 38 papers were removed, resulting in a final 38 papers. Exclusions were made based on the study population (n=27 studies), study design (n=6), studies with duplicated data (n=1) and wrong outcome measures (n=4).

Study characteristics

Data were extracted from 38 studies, with study populations spanning 4 continents and 18 countries (online supplemental appendix table 4). The majority of studies were from HICs, and 5 (14%) were from LMICs (4 are upper-middle-income countries,[2 14–16] 1 is a lower-middle-income country[17] and none are from low-income countries) (figure 2). Over 100 000 patients are included across the studies, with a sample size ranging from 45 in Italy/Slovenia[18] to 69 412 in Germany.[19] The median age of patients (in years) within included studies ranged from 65 in France[20] (lowest threshold considered) to 78 in Italy/Slovenia.[18] Several studies separated data based on stroke subtype (ischaemic or haemorrhagic). Six studies reported an OR, and five reported an incidence rate ratio.

Risk of bias of individual studies

The breakdown of the risk-of-bias assessment, using the NOS for each study, is found in online supplemental appendix table 3. Of the 37 included studies, the majority

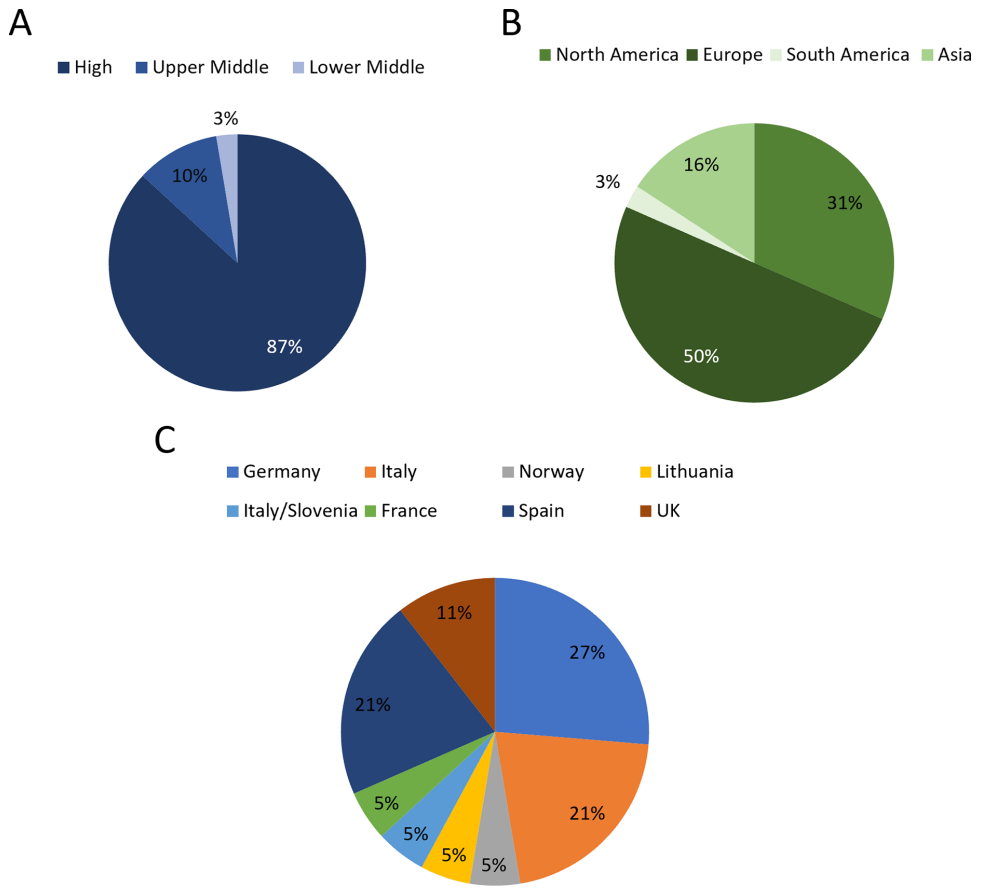

Figure 2 Characteristics of included studies. (A) The breakdown of the economic status of included studies as high-income country, upper-middle-income country or lower-middle-income country as classified by World Bank data. (B) The regional breakdown of included studies by continent. (C) The country breakdown of the Europe region.

scored an 8 out of 9,[15–18 20–35] 9 scored 7 out of 9[36–44] and 8 scored 9 out of 9.[14 19 45–50] Score(s) were most commonly lost in evaluating outcomes as the length and adequacy of follow-up was not often a factor considered within the studies. Despite this finding, due to the nature of the included studies, follow-up on cohorts is not an essential criterion as we are primarily investigating admission and treatment data. Data regarding the number of secondary strokes within each cohort would have been an interesting factor if a more extended follow-up did occur. Additionally, some scores were lost in the comparability category as not all studies controlled multiple confounding factors between cohorts. All individual studies evaluated were deemed acceptable for inclusion despite a non-perfect NOS Score.

Risk factors for stroke

The major risk factors measured across the studies were hypertension, diabetes and smoking, reported as prevalence percentages within the population (online supplemental appendix table 5). As reported by 12 studies, the most prevalent risk factor was hypertension. The prevalence ranged from the highest pre-COVID-19 rate of 85% in the USA to a COVID-19 rate of 79%.[43] In contrast, countries with a lower prevalence of hypertension increased from pre-COVID-19 to COVID-19 periods in the Netherlands (44%–50%)[32] and Iran (44%–56%).[15] The greatest COVID-19 rate was reported in Italy/Slovenia (76%–94%).[18]

Diabetes prevalence was reported in 11 studies and ranged from a pre-COVID-19 high of 42% in the USA[33] (43% in the COVID-19 cohort) to a low of 16% in the Netherlands[32] (18% in the COVID-19 cohort). In most studies, variation in the prevalence of diabetes between the pre-COVID-19 and COVID-19 cohorts was minimal; however, Italy/Slovenia reported a 9% increase from 28% during the pre-COVID-19 period.[18] The third risk factor, smoking, was reported in 7 studies, the highest (29%–30%) in the Netherlands[32] and the lowest in the USA (12%) in both the pre-COVID-19 and COVID-19 groups.[50] The greatest variation between pre-COVID-19 and COVID-19 cohorts was reported in Germany, decreasing from 18.3% in the pre-COVID-19 cohort to 14.7% in the COVID-19 cohort.[25]

Severity (NIHSS Score on onset)

The severity of the stroke on admission was measured by the NIHSS Score (online supplemental appendix table 6, figure 3A). A total of 24 studies reported NIHSS scores, with 67% reporting an increase from the pre-COVID-19 to COVID-19 cohort. The highest median score within the pre-COVID-19 group was 16 in Singapore, which

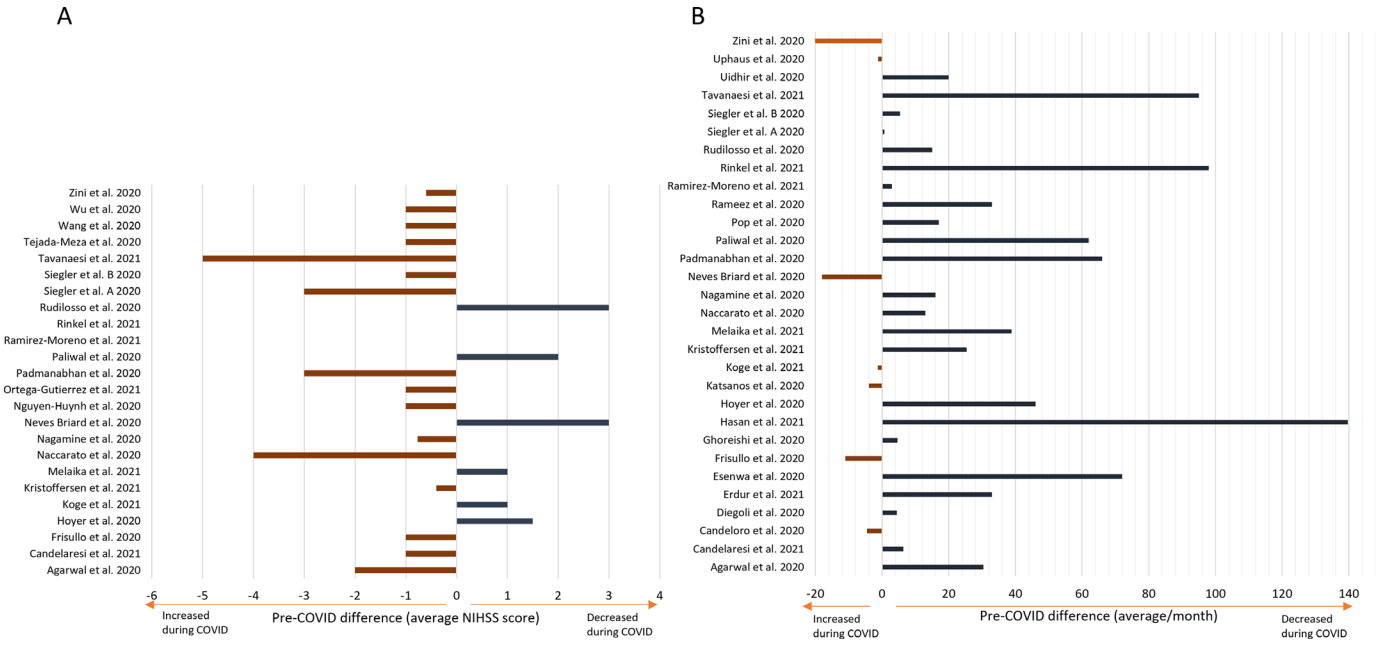

Figure 3 The difference in admission rates and stroke severity between pre-COVID-19 and COVID-19 groups. (A) The difference in the average number of stroke admissions per month between the pre-COVID-19 and COVID-19 groups. One outlier was removed, Rinkel *et al*, whose admissions rates greatly exceeded the rest. All data can be found in online supplemental appendix table 3. Admission rates were generally lower in the COVID-19 cohort than in the pre-COVID-19 cohort. (B) The difference in stroke severity on hospital admission between the pre-COVID-19 and COVID-19 groups was reported by average NIHSS Score. The average NIHSS Score was greater in the COVID-19 cohort compared with pre-COVID-19 for most studies.

decreased to 14 in the COVID-19 cohort.[42] The lowest median score in the pre-COVID-19 cohort was 3, found in two studies from the USA[48 50] followed by a score of 4 in a study from the Netherlands[32]; however, the scores in the two US studies increased to 5 and 4, respectively, in the COVID-19 group.

Evaluation and treatment

Admission rates

Admission rates were reported as average admissions per month; however, the variation between studies exists due to differences in study population sizes (online supplemental appendix table 6, figure 3B). A total of 26 out of the 32 studies that reported admission rates noted that rates decreased (average 31%) in the COVID-19 period compared with pre-COVID-19, with the largest decrease in Iran at 50%. Richter *et al*[19] analysed data from all of Germany reporting the highest admission rates, with an average of 17 608 stroke admissions per month in the pre-COVID-19 group, which decreased by over 26% to 13 015 per month during the COVID-19 period. The lowest monthly average from the pre-COVID-19 group was 6.9 and 11.4 patients per month for the COVID-19 group, reported from a single-centre study.[23]

Stroke subtypes

Stroke subtypes (ischaemic or haemorrhagic) were reported in 14 studies (online supplemental appendix table 7). Ischaemic strokes were the most common, with the highest percentage (97%) in Germany for pre-COVID-19 and COVID-19 cohorts,[25] the lowest prevalence was in the Netherlands at 61% during the pre-COVID-19 period (69% in the COVID-19 cohort)[32] and 62% in Spain (64% in the pre-COVID-19 cohort).[22] The proportion of patients who had a haemorrhagic stroke was the greatest in the UK (21.3% in the COVID-19 cohort vs 14.4% in pre-COVID-19),[31] followed by the USA (18% vs 19%)[38] and the lowest in Germany (2.9% vs 2.6%).[25]

Treatment

The primary treatment (thrombolysis or thrombectomy) was reported in 18 studies (online supplemental appendix table 7, figure 4). The highest percentage of patients receiving thrombolysis treatment in the pre-COVID-19 (60.4%), and COVID-19 (69%) cohorts were in China.[17] In contrast, thrombolysis treatment was lower (6%–11%) in the USA, with one study reporting a 6% decrease (vs 12% during pre-COVID-19) in thrombolysis treatment from the pre-COVID-19 to COVID-19 period.[33] In contrast, another study reported a 5% increase (6.3%–11.3%).[35] Thrombectomy treatment was most common in the USA in pre-COVID-19 (88%) and COVID-19 (90%) cohorts.[33] Unlike in the USA, thrombectomy treatments were lower in Iran (3.2% during pre-COVID-19 vs 7.4%)[15] and the UK (4.8% vs 5.9%)[31] during the COVID-19 period.

Treatment times

In-hospital treatment times were reported in 26 studies (online supplemental appendix table 8, figure 5). The door-to-head CT (DTCT) time (in monthly median) from the time of admission to the time of CT scan was reported

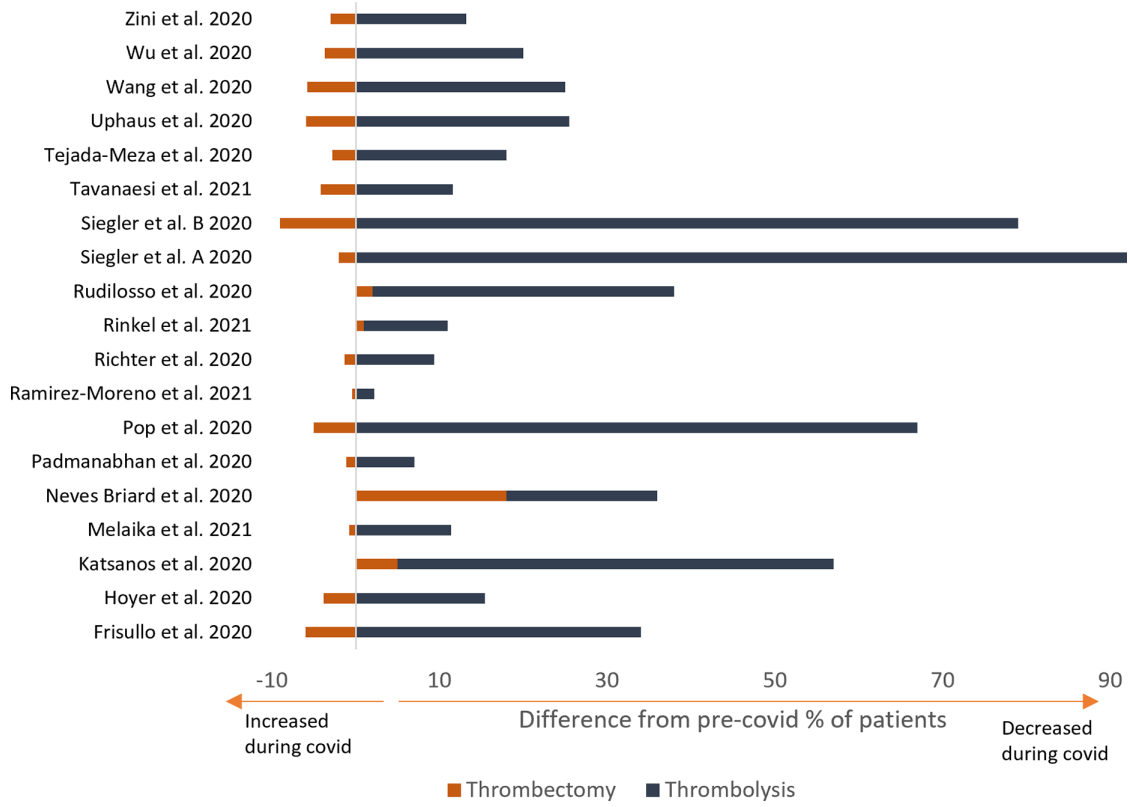

Figure 4 Difference in stroke treatment between pre-COVID-19 and COVID-19 groups. The difference in stroke treatment of either thrombolysis or thrombectomy was reported as a difference in percentage of patients receiving each treatment within each population cohort. The type of treatment received by patients did not greatly vary between pre-COVID-19 and COVID-19 cohorts, although several studies report an increase in thrombectomies in the COVID-19 group.

in seven studies. Canada's lowest median pre-COVID-19 time of 7.5 min increased to 19 min in the COVID-19 cohort.[45] The highest reported time in the pre-COVID-19 cohort was 45 (5–720) min in Italy, which increased to 54 (13–502) in the COVID-19 cohort.[24] The lowest median time in the COVID-19 cohort was reported in the USA at 16 min, slightly increasing from the pre-COVID-19 time of 12 min.[51] The highest median DTCT time in the COVID-19 cohort was in Italy at 55 min, an increase of 31 min from pre-COVID-19.[23] Of the 26 studies that reported the door-to-needle (DTN) time (time taken following admission to thrombolysis treatment) in the monthly median, 16 reported an increase from pre-COVID-19 to COVID-19. In both pre-COVID-19 and COVID-19 cohorts, the lowest median DTN time was in Iran at 18 (15–31) min and 20 (15–28) min, respectively.[15] The highest median time for pre-COVID-19 (147 min) and COVID-19 (165 min) was reported in Italy.[36] The door-to-groin puncture (DTGP) time (refers to the time it takes following admission to treatment via mechanical thrombectomy) varied across countries and was reported by a monthly median. The lowest median DTGP time within the pre-COVID-19 cohort of 50 (31–114) min was reported in Canada, which increased to 60 (33–110) min during COVID-19,[45] followed by Spain with the pre-COVID-19 time of 61 min which decreased to 56 (48–72) min during COVID-19.[22] The highest time pre-COVID-19 (242 min) was reported in Italy, which dropped to 162 min in the COVID-19 cohort,[36] unlike in Brazil, where median DGTP increased from pre-COVID-19 (137 min) to COVID-19 (189 min) in Brazil.[23]

Length of stay

The length of hospital stay was reported as mean days in 10 studies (online supplemental appendix table 9). In both pre-COVID-19 and COVID-19 cohorts, the lowest average stay was reported in the USA at 3.7 days, slightly increasing to 3.8 days in the COVID-19 cohort.[50] The longest average stay was reported in Italy/ Slovenia at 18 days pre-COVID-19 and 13 days during the COVID-19 period.[18]

Mortality

The in-hospital mortality rate was measured in 16 studies (online supplemental appendix table 10, figure 6). The highest pre-COVID-19 mortality rate was 10.8% in Iran, which decreased marginally to 10.5% in the COVID-19 cohort.[46] The lowest rate for both cohorts was reported in Spain at 0.6% pre-COVID-19 and slightly increased to 0.9% during COVID-19.[47] During the COVID-19 period, Italy's highest mortality rate (16.8%) was reported, a large increase from the pre-COVID-19 rate of 7.8%.[15] Of the studies that reported in-hospital mortality, 75% reported an increase in the COVID-19 cohort compared with the

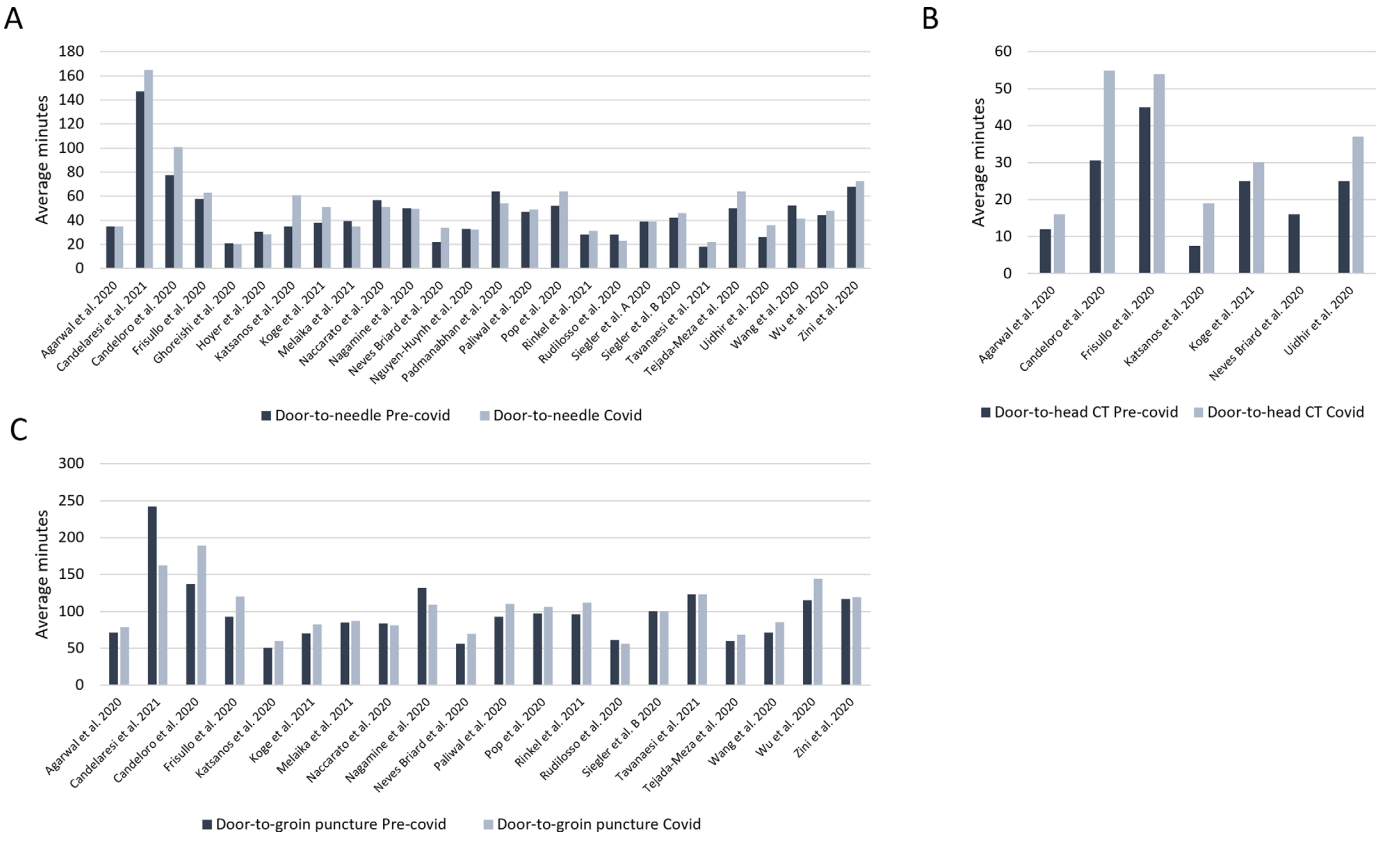

Figure 5 In-hospital treatment times. (A) Stroke pathway treatment times (door-to-needle time), (B) door-to-head CT time, (C) door-to-groin puncture time were reported in minutes in both pre-COVID-19 and COVID-19 cohorts. Treatment times generally increased in the majority of studies in the COVID-19 cohort compared with the pre-COVID-19 group.

pre-COVID-19 cohort. Some increases were modest at >5%; however, several increased by 50% or greater.

Destination on discharge

On discharge from the hospital, the destination of patients was reported in 6–8 studies (online supplemental appendix table 10). The UK reported the greatest percentage of patients returning home in pre-COVID-19 (63.5%) and COVID-19 (58.4%) cohorts.[31] The lowest percentage of patients returning home occurred in the USA at 34% in the pre-COVID-19 cohort, which increased to 50% during the COVID-19 period.[33] The lowest proportion (43%) of patients returning home in the COVID-19 cohort was reported in Italy/ Slovenia, a slight decrease from 46% pre-COVID-19.[18] There was a large variation in the number of patients discharged to a nursing home or long-term care facility. Wang *et al*[35] reported that 40% of patients in the pre-COVID-19 cohort and 43.1% of the COVID-19 cohort went to nursing homes, based on their study in the USA. In contrast, Rinkel *et al*[32] reported that 4% of patients were discharged to nursing homes during the pre-COVID-19 period and 3% in the COVID-19 period in their study in the Netherlands. Siegler *et al*[33] reported that only 2% of patients were discharged to long-term care facilities during a COVID-19 period, a large decrease from 10% in the pre-COVID-19 cohort from their multicentre study in the USA.

DISCUSSION

Our findings demonstrate that during the COVID-19 pandemic, admission rates for stroke decreased, and treatment times increased over half of the observed studies. The severity of stroke on admission increased in most studies, with a higher prevalence of hypertension among admitted patients. The pandemic also influenced outcome measures; most studies reported increased in-hospital mortality rates. There was also a large variation in the destination on discharge between the pre-COVID-19 and COVID-19 cohorts. Overall, there is a clear impact of the COVID-19 pandemic on the admission and treatment of patients who had a stroke globally.

The scope of this review includes populations with a median age of 65 years or greater to account for variability in aetiology and treatment and to limit potential confounding variables.[51 52] Future investigations should consider all population demographics to understand all cohorts better.

Stroke risk factors and severity

We excluded populations infected with the COVID-19 virus as the COVID-19 infection acts as a confounding factor to our treatment group during the COVID-19 period, as it cannot be compared with the control group pre-COVID-19 period. The studies chosen investigated treatment populations who did not test positive for the

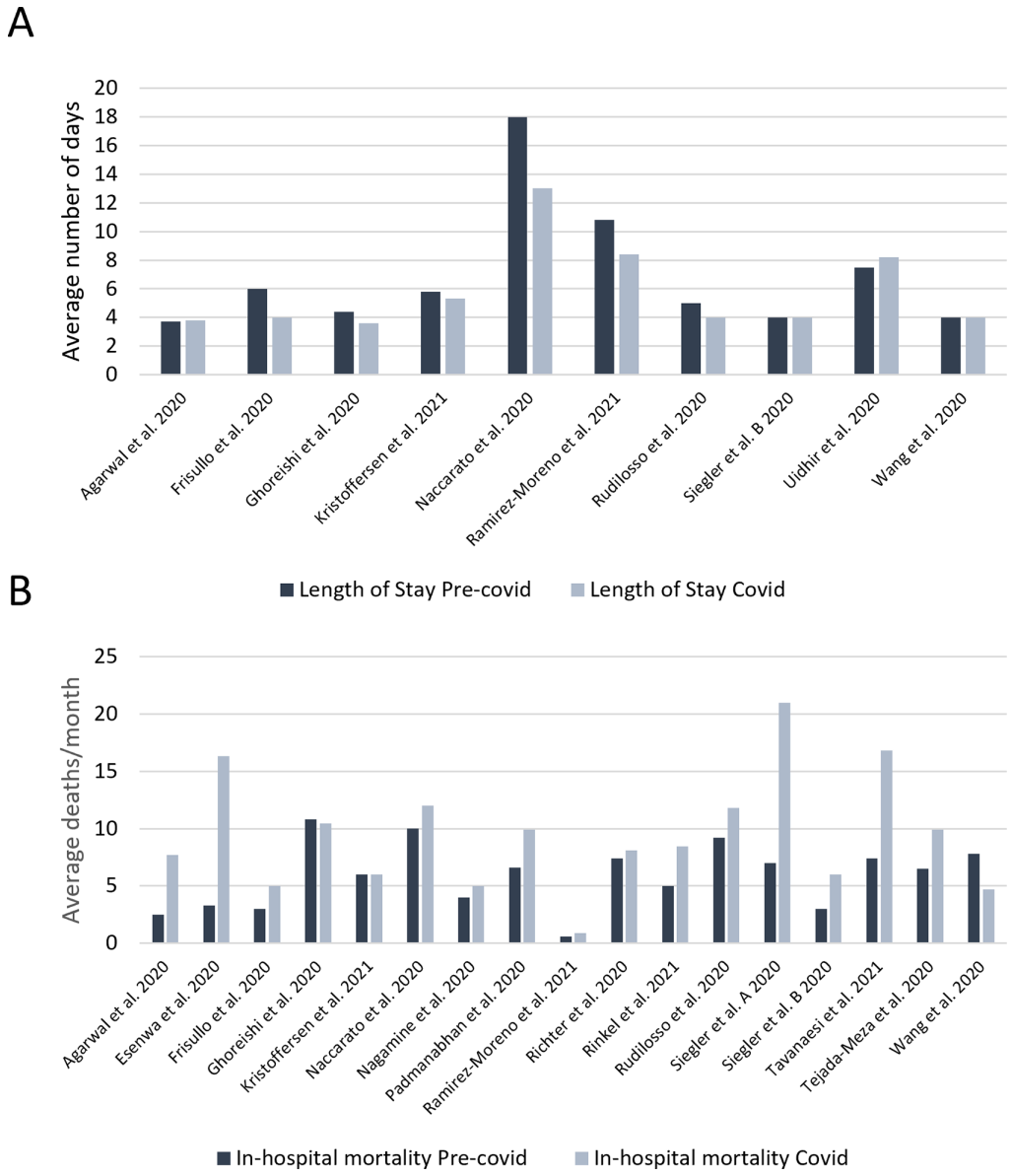

Figure 6 Length of stay and mortality rate. (A) The average length of stay in the hospital of admitted patients who had a stroke was reported as days in both pre-COVID-19 and COVID-19 cohorts. The length of stay did not vary greatly between the pre-COVID-19 and COVID-19 cohorts; however, some reported a decrease in the average length of hospital stay in the COVID-19 group. (B) In-hospital mortality was reported as a percentage of each population cohort in both pre-COVID-19 and COVID-19 groups. The in-hospital mortality generally increased in the COVID-19 group compared with pre-COVID-19.

COVID-19 virus; however, other reviews, such as Fridman *et al*,[53] examine the influence of COVID-19 infection on stroke phenotypes and outcomes.

Of the 12 studies that reported on risk factor prevalence, it is clear, and not surprising, that hypertension is the most prevalent across all regions and populations. However, the large differentiation between the highest and lowest prevalence may result from regional demographics and study population size. Siegler *et al*,[33] who report hypertension prevalence for pre-COVID-19 and COVID-19 groups of 85% and 79%, are at the top end of prevalence but are followed closely by other studies from the USA,[41 48] Germany[25] and Italy/Slovenia.[18] The countries demonstrating the lowest prevalence rates are Iran, the Netherlands[32] and Canada,[30] which fall below 70%, the average estimated prevalence of hypertension in patients who had a stroke worldwide.[54] In the general population, hypertension prevalence is greater in HICs than in LMICs,[55] which aligns with our current results. Diabetes prevalence displayed less variation among the studies. This may result from a more reliable diagnosis and reporting of diabetes than hypertension; in some studies, hypertension was reported as high blood pressure on admission, which can be largely variable. Smoking prevalence similarly displayed slight variation, with one observable outlier being the Netherlands, which reported higher rates of smoking closer to the national average of 25%.[56] Variations in risk factor prevalence between pre-COVID-19 and COVID-19 cohorts may indicate a change in the population seeking medical attention.

The prevalence of hypertension increased in 67% of the studies between pre-COVID-19 and COVID-19 periods. This finding suggests that those admitted for stroke treatment were at a higher risk.

The severity of stroke on admission displayed variation among countries, with the majority (88%) being classified as a moderate stroke in at least one cohort. The remaining 12% are classified as minor strokes. The literature regarding the regional distribution of stroke severity is not currently available; however, it may be affected by healthcare structures and population health campaigns. Regions or countries with poor access to medical care may increase the severity of patients who had a stroke seeking medical attention. This may occur in LMIC countries or those without government-funded insurance.

Several studies report observable decreases in mild and moderate stroke admissions during the COVID-19 pandemic period,[14 27 33 37 50] resulting in a rise in average severity. Of the 24 studies reporting average stroke severity, 16 reported increased severity in the COVID-19 group compared with the pre-COVID-19 group. Kristoffersen *et al*,[27] along with others, suspect this increase in severity is due to avoidance behaviour among the general public. As COVID-19 intervention measures were implemented, such as lockdowns and curfews, people became hesitant to leave home, especially to enter a hospital that COVID-19 patients may occupy. The other services, such as ambulance and accident and emergency, were overstretched beyond their capacity, which caused a very long waiting time for some cases, which in the absence of the pandemic, would have been attended to quickly. This may have resulted in those suffering minor strokes staying home despite feeling unwell until the symptom subsided or worsened, resulting in a more severe stroke on admission.

Evaluation and treatment

Average stroke admissions per month varied significantly between studies and countries. Several studies collected data from multiple healthcare centres across a region or even an entire nation, whereas other papers were based on single-centred studies. Additionally, some studies focused specifically on stroke hubs. When one hospital or healthcare facility is a large nation's primary stroke care centre, higher than typical admission rates will be found compared with other facilities. The highest admission rates come from a nationwide study of all stroke admissions within Germany,[19] resulting in a much greater admission rate than the other studies. In contrast, the lowest admission rates come from a single-centre study conducted in Varese, Italy, with a population of less than 100 000.[23] Due to this regional variation, comparing admission rates between studies is unreliable.

Of the 31 studies that reported admission rates, 26 (84%) reported decreased admissions during the COVID-19 pandemic. This trend has been discussed in the literature as many stroke centres and researchers have reported declining admissions since the beginning of the pandemic.[49 57–59] Perry *et al*[57] states that two hypotheses, or explanations, exist to account for the decline; first, there has been an actual decrease in stroke incidence, or second, an increased number of individuals suffering from a stroke do not reach and/or seek medical attention. It seems unlikely that stroke incidence has suddenly decreased across multiple populations and regions. As discussed previously, the COVID-19 pandemic has resulted in avoidance behaviour among many people, contributing to the decrease in stroke admissions. Coinciding with our findings regarding stroke severity, it may be likely that those suffering from minor strokes choose to stay home despite unwell feelings.

Additionally, Perry *et al*[57] describe that minor strokes may be missed or overlooked in COVID-19-positive patients suffering from more severe respiratory distress. These hypotheses were also speculated by Rudilosso *et al*,[22] who report moderate declines in stroke admissions and a decrease in the average age of patients, which may have been due to increased fear of infection or a positive outcome of isolation. The reduction in admissions may result from a combination of the two hypotheses, with a large amount associated with avoidance behaviour and some decrease in incidence due to lifestyle changes due to lockdowns. Implementing lockdown measures may have contributed to a reduction in stroke incidence as less air pollution occurred due to a decline in driving,[57] isolation may have resulted in more minor head injuries, and remote working conditions may have decreased daily stress.

Of the five studies that did not report decreased admissions during the pandemic period, two were within 1–2 entries per month of the pre-COVID-19 average and, therefore, do not demonstrate significant variance. The remaining three studies report slight increases in admissions rates, resulting from the timing of the study; some countries imposed lockdown measures later than others, and some regions did not experience their peak of infections until 2021. Of the three studies, two were based in Canada, which experienced its first wave from mid-November 2020 to the beginning of February 2021[60]; however, both studies were published in 2020 with data collected to the start of the first wave.[30 45] This timeline may account for the trend in admission data from these studies.

There was variation in the reported prevalence of ischaemic and haemorrhagic stroke between studies. Stroke subtypes followed expected trends, with ischaemic stroke being the most prevalent. However, slight variation existed between the pre-COVID-19 and COVID-19 cohorts. This indicates that despite changes in population behaviour, the pandemic did not significantly influence the occurrence of one subtype over another. The highest and lowest ischemic stroke and haemorrhagic stroke prevalence occurred in high-income western European countries. Therefore, the variation is likely a result of differences in study design.

Stroke treatment of either thrombolysis or thrombectomy varied considerably across studies. It is expected

that thrombolysis treatment will be more commonly performed due to the more recent establishment of thrombectomy as a standard of care. The occurrence of either treatment ranged from >10% to <60%. Stroke subtype, the timing of medical assessment and medical resources largely determine treatment type.[61] Baatiema *et al*[62 63] discuss their results regarding stroke treatment in Ghana. They report that none participating hospitals had the resources to perform thrombolytic therapy. Descriptive observation of the current data shows that the studies with the highest treatment percentages of either treatment were located in North America. In contrast, those with lower percentages were in Europe and Asia.

Between pre-COVID-19 and COVID-19 groups, there was a reduction in the percentage of thrombolysis treatment in all of the studies which reported data. In contrast, a slight increase in thrombectomy percentages was found in 78% of studies. Frisullo *et al*[24] report a 57.5% decrease in intravenous thrombolysis treatment during the COVID-19 pandemic; they attribute this decline to an increase in onset-to-door time. Due to the time sensitivity of stroke treatments, delays before hospital arrival or during the stroke pathway may significantly influence the availability of specific treatment options.

Timing within the stroke pathway was shown to vary across studies; however, much of this variation is likely due to the regional factors previously discussed. The greatest difference between pre-COVID-19 and COVID-19 groups was seen in the DTN time, where 61.5% of the studies reported an increase in time. Most increases were modest, with >5 min of variation between the cohorts. However, due to the importance of timeliness in stroke treatment, even modest increases in time can impact patient outcomes. Jahan *et al*[64] report that patient outcomes improved for every 15 min of faster treatment. The DTCT and DTGP times followed a similar trend. The time from stroke onset to intervention (ie, incorporating the prehospital phase of the stroke pathway) is important for the effective management of stroke. It is also likely that times from onset to intervention may also have varied under pandemic conditions due to some of the reasons mentioned above, including the hesitancy to seek treatment for minor strokes. It needs to be seriously considered for system sustainability in future pandemics.

The average hospital stay was relatively consistent between pre-COVID-19 and COVID-19 groups. One exception was a 5-day decrease in the average length of stay reported by Naccarato *et al*[18] in Italy/Slovenia. This decrease was attributed to a change in the stroke treatment pathway and general in-hospital protocols, which were set to minimise hospitalisation times where possible. A consequence of this decreased length of stay and limited access to advanced diagnostic examinations was a reduced number of patients discharged with a complete stroke work-up.[18] This may lead to later problems if the patients experience a secondary stroke or stroke-like symptoms.

Outcomes

In-hospital mortality rates increased between the pre-COVID-19 and COVID-19 periods in 82% of studies. This may result from increased severity of admitted strokes, patient risk factors and increased treatment times. Together, these factors may have contributed to increased mortality rates. The largest contributing factor is likely the general decrease in admission rates and increases in severity on admission; this results in a greater proportion of patients who had a moderate-to-severe stroke with a greater likelihood of poor outcome measures.

The destination on discharge varied greatly between studies; however, this is expected due to regional differences in healthcare structure and cultural norms. Similarly, there was variation when comparing pre-COVID-19 and COVID-19 cohorts; some reported decreases in those returning home on discharge, whereas others reported large increases. A decrease in those returning home may indicate the overall rise in stroke severity; those with more severe strokes require further rehabilitation and care. However, the increase in those returning home on discharge is not surprising either, as many nursing homes and long-term care facilities did not accept incoming patients during the COVID-19 pandemic. Nursing homes and long-term care facilities were greatly affected by the COVID-19 pandemic, with large outbreaks reported globally.[65] Due to this, security measures increased, and no new patients or occupants were permitted.

Study limitations

The current study had several limitations that must be considered during interpretation. No meta-analysis was carried out due to a lack of sufficient data. There are inconsistencies in the reporting of data between studies. Not all studies report on the same measures, which in some cases resulted in low data entries for specific measures. This limits the scope of the review and the ability to perform statistical analysis. The limited studies may be from a specific region due to the inclusion and exclusion criteria established during the study design. The median age restriction was set to achieve information on a vulnerable, more consistent population of patients; however, the median age of the general population is much lower in LMICs than HICs. Therefore, the median age of patients who had a stroke may also be lower. This may contribute to the lack of studies reporting from low-income countries. The age restriction is a limitation to the scope of the available data. Studies investigating populations with a median age below 65 are not included in the scope of the current study, which may contribute to bias. It is important to consider the lower availability or affordability of treatment and, thus, lower treatment reporting in LMICs, contributing to our lack of studies.

Another factor to consider between studies is the difference in healthcare structures that may influence data. Many populations cannot afford healthcare if uninsured and may be more hesitant to seek treatment. Similarly, this may result in an over-representation of research-intensive

countries such as the USA and Germany, which account for 33% of all our included studies.

Another limitation is the timing of studies associated with the spread of COVID-19. Due to the regional differences in the spread of COVID-19, different countries experienced their peak infection rate at other times. We did not adjust for the duration over which data was collected. This may influence the data within the studies while trying to compare. A retrospective study focussing on data from the peak time of infection in each respective region/country would eliminate this limitation. Also considered are the severe resource and time constraints resulting from COVID-19 on healthcare facilities, which could have impacted the quality and extent of data reporting during these times.

Another limitation of this review is in the screening protocol; the first author screened all articles, with 10% double-screened by a second reviewer. This could have introduced some errors; however, during the 10% double screening, no error was found and the chances of any significant error remained low. The other limitation could be due to the use of the Newcastle Ottawa Criteria, which is quite non-specific in certain studies, provides a quality score with unknown validity and gives more weightage to studies with community control than from other sources.

CONCLUSION

Long-term repercussions of the COVID-19 pandemic continue to present themselves, and the toll the pandemic has had on populations worldwide is still evolving. Here, it is demonstrated that the COVID-19 pandemic has influenced stroke admissions and treatment pathways in several world regions and is not uniform in access to care and management. Many studies reported decreased admissions rates, resulting from public hesitancy to seek medical attention during lockdown measures; however, the stoke pathway needs to be equally considered and strengthened, which seems to have broken to some degree during the pandemic. In-hospital stroke treatment pathways were affected by COVID-19 protocols, which generally increased treatment time and increased in-hospital mortality in most studies. The average stroke severity on admission increased, resulting from hesitancy to seek medical attention until symptoms worsened.

Regional variation is evident in every aspect of the stroke treatment pathway. Many LMICs lack the necessary resources to treat strokes effectively; there is a lack of medical personnel to accommodate the number of patients. Medical transport is not widely accessible, increasing onset-to-door time for patients, and medical supplies are not widely available to perform treatment procedures. These disparities have always been present in LMICs, well before the COVID-19 pandemic; however, the pandemic has highlighted how detrimental a lack of resources is on stroke treatment on a global scale. Perhaps this demonstration will allow policymakers to understand better the difficulties many LMICs face daily in stroke management. There must be a call to action to implement effective and efficient stroke treatment pathways globally to help reduce the burden of stroke and maintain timely and adequate treatment at all times.

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