Review

Effects of the COVID-19 pandemic on stroke response times: a systematic review and meta-analysis

Noah L A Nawabi,[1,2] Akiro H Duey,[1] John L Kilgallon,[1,3] Charissa Jessurun,[1,4] Joanne Doucette,[1,5] Rania A Mekary,[1,6] Mohammad Ali Aziz-Sultan[1,2]

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For numbered affiliations see end of article.

Correspondence to
Noah L A Nawabi, Computational Neuroscience Outcomes Center, Harvard Medical School, Boston, MA 02115, USA; nnawabi@bwh.harvard.edu

RAM and MAA-S are joint senior authors.

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ABSTRACT

Objectives COVID-19 presents a risk for delays to stroke treatment. We examined how COVID-19 affected stroke response times.

Methods A literature search was conducted to identify articles covering stroke during COVID-19 that included time metrics data pre- and post-pandemic. For each outcome, pooled relative change from baseline and 95% CI were calculated using random-effects models. Heterogeneity was explored through subgroup analyses comparing comprehensive stroke centers (CSCs) to non-CSCs.

Results 38 included studies reported on 6109 patients during COVID-19 and 14637 patients during the pre-COVID period. Pooled increases of 20.9% (95% CI 5.8% to 36.1%) in last-known-well (LKW) to arrival times, 1.2% (−2.9% to 5.3%) in door-to-imaging (DTI), 0.8% (−2.9% to 4.5%) in door-to-needle (DTN), 2.8% (−5.0% to 10.6%) in door-to-groin (DTG), and 19.7% (11.1% to 28.2%) in door-to-reperfusion (DTR) times were observed during COVID-19. At CSCs, LKW increased by 24.0% (−0.3% to 48.2%), DTI increased by 1.6% (−3.0% to 6.1%), DTN increased by 3.6% (1.2% to 6.0%), DTG increased by 4.6% (−5.9% to 15.1%), and DTR increased by 21.2% (12.3% to 30.1%). At non-CSCs, LKW increased by 12.4% (−1.0% to 25.7%), DTI increased by 0.2% (−2.0% to 2.4%), DTN decreased by −4.6% (−11.9% to 2.7%), DTG decreased by −0.6% (−8.3% to 7.1%), and DTR increased by 0.5% (−31.0% to 32.0%). The increases during COVID-19 in LKW (p=0.01) and DTR (p=0.00) were statistically significant, as was the difference in DTN delays between CSCs and non-CSCs (p=0.04).

Conclusions Factors during COVID-19 resulted in significantly delayed LKW and DTR, and mild delays in DTI, DTN, and DTG. CSCs experience more pronounced delays than non-CSCs.

INTRODUCTION

In a brain suffering from an ischemic stroke, 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated fibers are lost each minute.[1] Time is brain, and COVID-19 presents a threat to care teams' ability to treat stroke patients rapidly.

While virus-related precautions and a mass influx of COVID-19 patients into the world's hospitals will intuitively cause delays to stroke treatment, the precise extent of these delays is a measure of critical importance. Understanding if and when delays occurred, and what specifically they were attributed to, will help us appreciate potential unintended effects of viral spread precautions and will illuminate what factors leading to delays are truly in physicians' control. Achieving this understanding will allow for steps to be taken towards optimizing stroke response workflow for the remainder of the pandemic, and in any future disasters that may occur.

In this study, we set out to assess the effects of the COVID-19 pandemic on the systems approach to stroke care. This system is multifaceted and depends on factors that lie both in the hands of the patients and their network, and in the hands of physicians. We attempt to quantify how and where COVID-19 caused delays to stroke treatment by assessing the presence and extent of delays in individual stroke response time metrics reported by stroke centers across the globe.

METHODS

Search strategy

A systematic literature search was performed in PubMed, Embase, and Cochrane on November 19, 2021. The complete search can be found in online supplemental appendix 1.

Study selection

Study screening and data extraction were conducted by two independent reviewers (NN, JK) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist. In case of disagreement, a third reviewer (AK or CJ) was consulted. Articles were included in the analysis if they: (1) reported institutional stroke response time metrics during the COVID-19 study period and compared these values to a pre-pandemic period; (2) reported on stroke patients of any kind; and (3) reported on at least five participants per group in any study design. The primary outcome of this study was stroke response times as defined by the original study, including: last-known-well (LKW) to arrival time, defined for our purposes as stroke symptom onset to hospital arrival time; door-to-imaging (DTI) time, defined for our purposes as the time elapsed between hospital arrival and first imaging exam undergone; door-to-needle (DTN) time, defined for our purposes as the time elapsed from hospital arrival to administration of intravenous tissue plasminogen activator (tPA); door-to-groin (DTG) time, defined for our purposes as the time elapsed from hospital arrival to groin puncture for mechanical thrombectomy; and door-to-reperfusion (DTR) time, defined

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for our purposes as the time elapsed from hospital arrival to recanalization of the occluded vessel. Exclusion criteria were: (1) studies utilizing regional or national databases as a data source, or studies containing data from more than one comprehensive stroke center; (2) non-English publications; and (3) case reports and reviews.

Data extraction

The following information was extracted: study characteristics including study design, country, and sample size; time period data including the start and end dates of the defined COVID-19 period and pre-COVID-19 period and study duration; treatment characteristics including stroke response times; and institutional characteristics including academic status of hospital and inclusion of a comprehensive stroke center (CSC) in the study. Centers were deemed to be a CSC only if authors explicitly designated their centers as such. All other centers included in the analysis were assumed to be non-CSCs. Reported reasons for increases in response times, similar response times, or shorter response times before and during the pandemic were extracted from the results and discussion sections of the original studies.

Statistical analysis

To prepare the data for meta-analysis, all medians were converted to means using the method from Hozo *et al*.[2] All studies not reporting a measure of variance (eg, SD; IQR; range) in addition to a measure of central tendency (eg, mean; median) for any of the primary outcomes were excluded from the meta-analysis. The studies included in this meta-analysis reported significantly varied baseline stroke response times. To account for this heterogeneity in outcomes reporting, relative change from pre-COVID-19 (baseline) time (*100%) with 95% confidence intervals (95% CIs) were calculated for each of the original studies. As an extension of the central limit theorem, the difference between two means was assumed to approach a normal distribution with a mean difference equal to the difference in the true population means and a variance equal to the sum of the two variances. We assumed the two variances were not equal (heteroscedasticity). These relative changes from baseline*100% were entered in R and pooled using the DerSimonian and Laird random-effects model.[3]

The Higgins and Thompson I^2 was used to assess heterogeneity among studies; an I^2 >50% was considered to be high heterogeneity.[4] Pooled analyses were performed, both unstratified and stratified by stroke center status (CSCs vs non-CSCs), and the p value with 95% CI comparing the two strata was generated and reported. Meta-analysis was conducted using the 'metacont' function of the meta package in R v 4.0.3 (R Core Team, Vienna, Austria).[5] A two-sided p value <5% was considered statistically significant.

Risk of bias assessment

The quality assessment tool for before–after (pre–post) studies with no control group by the National Heart, Lung, and Blood

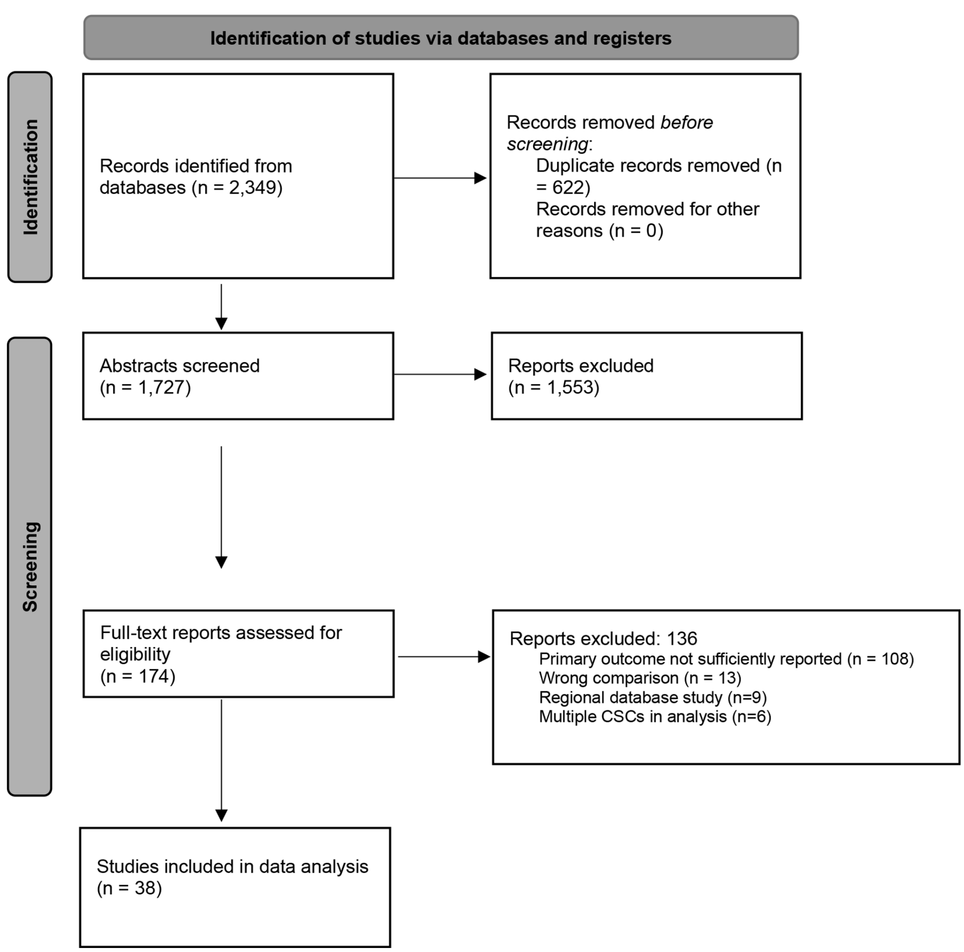

Figure 1 Results of the systematic review of the literature for this study. The database searches returned 1727 studies. Of these, 38 were ultimately included in the analysis. Reasons for exclusion are illustrated. CSCs, comprehensive stroke centers.

Table 1 Summary of included studies

Study	Country	COVID-19 period Patients (n)	Comparison period Patients (n)	Metrics included in meta-analysis	Included a CSC
Aboul-Nour 2021[18]	USA	121	264	LKW, DTI	Yes
Agarwal 2020[19]	USA	120	634	LKW, DTI, DTN, DTR, DTG	Yes
Altschul 2020[8]	USA	36	44	LKW, DTG	Yes
Amukotuwa 2020[11]	Australia	243	1818	DTI	Yes
Aref 2021[20]	Egypt	136	118	LKW	No
Candelaresi 2021[21]	Italy	148	327	DTI, DTN, DTG	Yes
Chen 2021[22]	China	135	128	LKW, DTI, DTN	No
Cummings 2020[23]	USA	613	5239	LKW, DTN	Yes
D'Anna 2021[24]	UK	514	353	LKW, DTI, DTN, DTG	Yes
Ghoreishi 2020[25]	Iran	232	355	LKW, DTN	No
Gu 2021[26]	China	99	153	LKW, DTN	No
Huo 2021[27]	China	36	70	LKW	Yes
Jasne 2020[28]	USA	211	167	LKW, DTN, DTR	Yes
John 2020[16]	UAE	130	109	LKW, DTN, DTG	Yes
Katsanos 2020[29]	Canada	18	11	LKW, DTI, DTN, DTR, DTG	Yes
Kwan 2020[30]	UK	28	33	DTR, DTG	No
Li 2021[31]	China	21	42	LKW, DTG	No
Luo 2021[32]	China	315	377	LKW, DTN, DTG	No
Mag Uidhir 2020[33]	UK	703	755	DTI, DTN	Yes
Mitra 2020[34]	Australia	52	57	LKW, DTI	Yes
Naccarato 2020[35]	Italy	16	29	LKW, DTN, DTG	No
Nagamine 2020[9]	USA	48	64	LKW, DTI, DTN, DTG	Yes
Neves-Briard 2020[17]	Canada	156	138	LKW, DTI, DTN, DTR, DTG	Yes
Padmanabhan 2020[36]	UK	101	167	LKW, DTN, DTG	Yes
Paliwal 2020[37]	Singapore	144	206	LKW, DTI, DTN, DTG	Yes
Plumereau 2020[38]	France	101	107	LKW, DTI, DTN, DTG	Yes
Rinkel 2020[39]	Netherlands	309	407	LKW, DTI, DTN, DTG	Yes
Rudilosso 2020[40]	Spain	68	83	LKW, DTI, DTN, DTG	Yes
Siegler 2020[41]	USA	53	275	LKW, DTI, DTN	Yes
Tan 2021[42]	China	110	173	LKW, DTN, DTG	Yes
Tejada-Meza 2020[43]	Spain	304	492	LKW, DTN, DTG	No
Teo 2020[10]	China	73	89	LKW, DTN, DTG	Yes
Uchino 2020[44]	USA	188	717	LKW, DTI, DTN, DTG	Yes
Velilla-Alonso 2021[45]	Spain	83	112	LKW, DTI, DTN, DTG	No
Wang 2020[46]	USA	255	320	DTN, DTG	No
Yang 2020[47]	China	21	34	LKW, DTR, DTG	Yes
Zhang 2021[48]	China	23	32	LKW, DTG	Yes
Zini 2020[49]	Italy	145	138	LKW, DTI, DTN, DTR, DTG	Yes
Total		6109	14637		

Studies are categorized in the following order: first author name and year, country of the first author's affiliation, the number of participants in the COVID-19 period and the pre-COVID-19 period, the time metrics that were reported in each study and included in analysis, and whether the study included a comprehensive stroke center.
CSC, comprehensive stroke center; DTG, door-to-groin; DTI, door-to-imaging; DTN, door-to-needle; DTR, door-to-reperfusion; LKW, last-known-well.

Institute[6] (NHLBI) was used to assess the quality of the studies. This tool consists of 12 questions focused on the key concepts for evaluating the internal validity of a study by assessing the clarity of the study question, inclusion and exclusion criteria, sample size, outcome measures, and the statistical methods that examine these outcomes. Questions not relevant to included studies were graded as 'yes' equally for all studies. The studies could be graded as poor (≤25%), fair (26–75%), and good (≥76%). To assess potential small-study bias, funnel plots and Egger's linear regression tests were used for pooled analyses with at least eight studies.[7]

RESULTS

Systematic review

After deduplication, we identified 1727 possible studies for inclusion in our meta-analysis. During title and abstract

Table 2 Summary of study time periods

Study	COVID-19 period start	Comparison period start	COVID-19 period end	Comparison period end	COVID-19 period length (days)	Comparison period length (days)
Aboul-Nour 2021[18]	3/20/20	3/20/19	5/20/20	5/20/19	61	61
Agarwal 2020[19]	3/1/20	6/1/19	5/15/20	2/29/20	75	273
Altschul 2020[8]	3/1/20	1/1/20	4/17/20	2/17/20	47	47
Amukotuwa 2020[11]	3/1/20	1/31/19	5/10/20	3/1/19	70	29
Aref 2021[20]	2/15/20	12/7/19	5/10/20	2/14/20	85	69
Candelaresi 2021[21]	3/9/20	3/9/19	4/16/20	4/16/19	38	38
Chen 2021[22]	1/1/20	1/1/18	9/30/20	12/31/19	273	729
Cummings 2020[23]	3/1/20	3/1/19	4/1/20	2/1/20	31	337
D'Anna 2021[24]	3/23/20	3/23/19	6/30/20	6/30/19	99	99
Ghoreishi 2020[25]	2/18/20	2/18/19	7/18/20	7/18/19	151	150
Gu 2021[26]	2/1/20	12/1/19	3/31/20	1/30/20	59	60
Huo 2021[27]	1/1/20	1/1/19	4/30/20	4/30/19	120	119
Jasne 2020[28]	3/1/20	2/1/20	4/28/20	4/28/20	58	87
John 2020[16]	3/1/20	3/1/19	5/10/20	5/10/19	70	70
Katsanos 2020[29]	3/17/20	3/1/19	4/30/20	3/16/20	44	381
Kwan 2020[30]	3/3/20	1/1/20	4/30/20	3/3/20	58	62
Li 2021[31]	1/23/20	2/3/20	4/8/20	4/17/20	76	74
Luo 2021[32]	1/1/20	1/1/19	5/31/20	5/31/19	151	150
Mag Uidhir 2020[33]	1/1/20	1/1/19	6/30/20	6/30/19	181	180
Mitra 2020[34]	3/26/20	3/26/19	4/23/20	4/23/19	28	28
Naccarato 2020[35]	3/9/20	3/9/19	4/9/20	4/9/19	31	31
Nagamine 2020[9]	3/1/20	3/1/19	4/30/20	4/3/19	60	33
Neves-Briard 2020[17]	3/30/20	3/30/19	5/31/20	5/31/19	62	62
Padmanabhan 2020[36]	3/15/20	3/15/19	4/14/20	4/14/19	30	30
Paliwal 2020[37]	2/7/20	11/1/19	4/30/20	2/6/20	83	97
Plumereau 2020[38]	2/29/20	2/28/19	5/10/20	5/10/19	71	71
Rinkel 2020[39]	3/16/20	10/21/19	5/3/20	12/8/19	48	48
Rudilosso 2020[40]	3/1/20	3/1/19	3/31/20	3/31/19	30	30
Siegler 2020[41]	3/1/20	10/1/19	4/15/20	2/29/20	45	151
Tan 2021[42]	1/24/20	1/24/19	3/10/20	3/10/19	46	45
Tejada-Meza 2020[43]	3/9/20	12/30/19	5/3/20	3/8/20	55	69
Teo 2020[10]	1/23/20	1/23/19	3/24/20	3/24/19	61	60
Uchino 2020[44]	3/9/20	1/1/20	4/2/20	3/8/20	24	67
Velilla-Alonso 2021[45]	3/14/20	3/14/19	5/14/20	5/14/19	61	61
Wang 2020[46]	3/12/20	12/1/19	6/30/20	3/11/20	110	101
Yang 2020[47]	1/23/20	12/1/19	3/7/20	1/14/20	44	44
Zhang 2021[48]	1/23/20	11/8/19	4/8/20	1/22/20	76	75
Zini 2020[49]	3/1/20	3/1/19	4/30/20	4/30/19	60	60

The COVID-19 and comparison period dates for each study are presented. The COVID-19 period was defined as the period of time occurring after the pandemic began, and the comparison period before the pandemic began. The length of each period in days for each study are also presented.

screening, 1553 studies were excluded, and during full-text screening, 136 studies were excluded. Reasons for exclusion at this level included insufficient time metrics reporting and reporting on differences in stroke response times between groups of patients in the COVID-19 period only (eg, time metrics for COVID-positive vs COVID-negative patients) as opposed to comparing time metrics between the COVID-19 period and a pre-COVID-19 time period. After screening, we extracted data from 38 studies for meta-analysis (figure 1).

Study characteristics

A wide range of countries were represented in our analysis. While the USA and China were the most common study setting (n=9), Australia, Canada, Italy, Spain, and the UK all had multiple studies included in our report. The number of patients presenting with stroke decreased by almost 60% during the study period, with 14 637 patients presenting with stroke during the collective pre-COVID-19 periods and only 6109 in the COVID-19 period. For all studies, the dates for the defined ‘COVID-19 period’ and

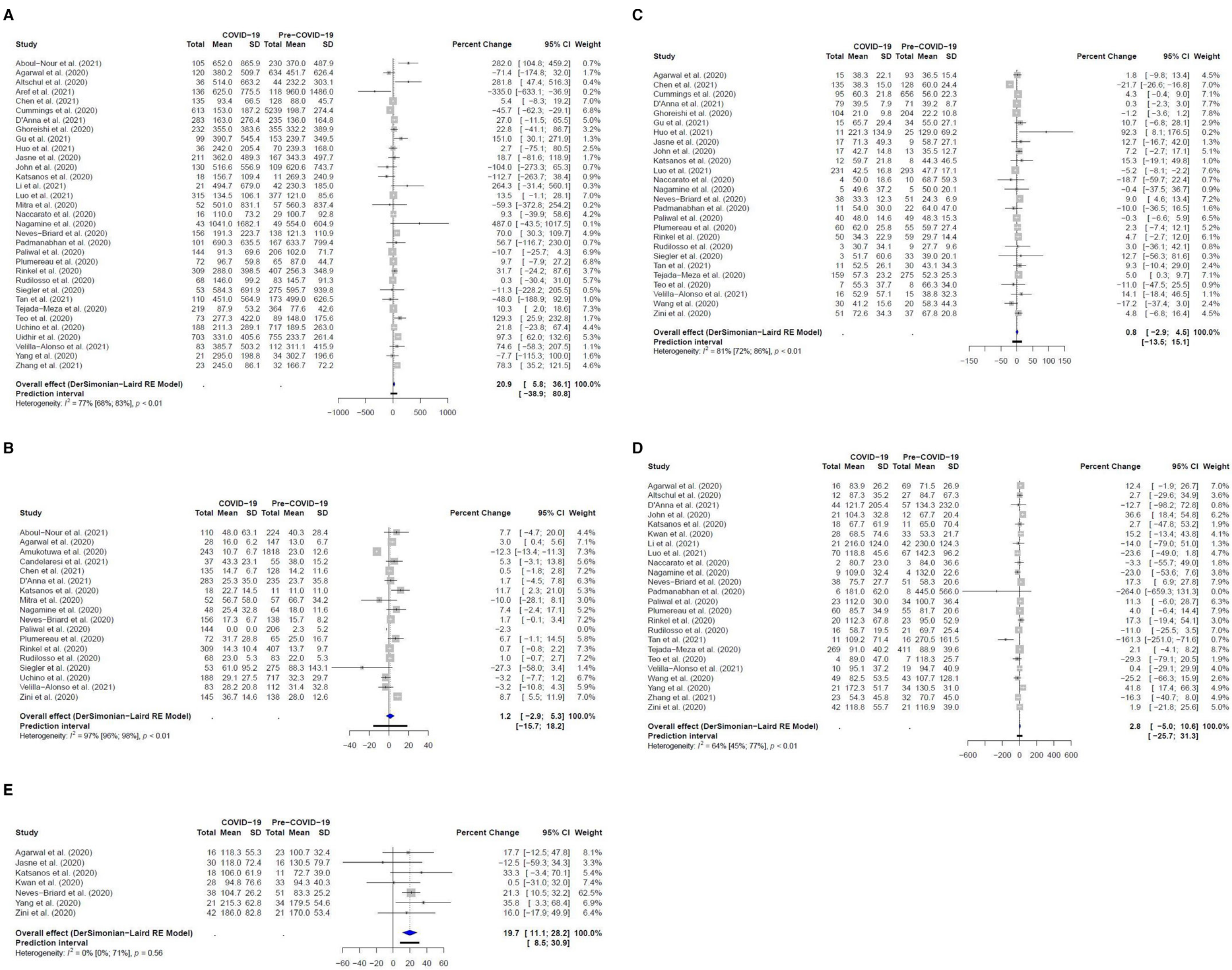

Figure 2 (A) Using the DerSimonian-Laird random-effects method, the normalized mean difference (percent change) in LKW to arrival time between the pre- and post-COVID-19 time periods was calculated for each study and pooled to determine the overall point estimate. The normalized means and SD were calculated by dividing by the baseline pre-COVID-19 mean for each study. (B) Using the DerSimonian-Laird random-effects method, the normalized mean difference (percent change) in DTI time between the pre- and post-COVID-19 time periods was calculated for each study and pooled to determine the overall point estimate. The normalized means and SD were calculated by dividing by the pre-COVID-19 mean for each study. (C) Using the DerSimonian-Laird random-effects method, the normalized mean difference (percent change) in DTN time between the pre- and post-COVID-19 time periods was calculated for each study and pooled to determine the overall point estimate. The normalized means and SD were calculated by dividing by the pre-COVID-19 mean for each study. (D) Using the DerSimonian-Laird random-effects method, the normalized mean difference (percent change) in DTG time between the pre- and post-COVID-19 time periods was calculated for each study and pooled to determine the overall point estimate. The normalized means and SD were calculated by dividing by the pre-COVID-19 mean for each study. (E) Using the DerSimonian-Laird random-effects method, the normalized mean difference (percent change) in DTR time between the pre- and post-COVID-19 time periods was calculated for each study and pooled to determine the overall point estimate. The normalized means and SD were calculated by dividing by the pre-COVID-19 mean for each study. DTG, door-to-groin; DTI, door-to-imaging; DTN, door-to-needle; DTR, door-to-reperfusion; LKW, last-known-well.

the 'pre-COVID-19 period' were recorded. Twenty-four studies reported on three or more time metrics that were included in the meta-analysis. Twenty-seven studies included a comprehensive stroke center in their review, while 11 did not (table 1).

Time periods

COVID-19 period start and end dates were similar across studies, with most of them encompassing the months of March through May 2020. The earliest COVID-19 period start date was January 1, 2020, and the latest was March 30, 2020. The earliest COVID-19 period end date was March 7, 2020, and the latest was September 30, 2020. Comparison period dates were more heterogeneous between studies and were either defined as the weeks and months directly preceding the COVID-19 period or the same time period of the previous year (2019), depending on the study. Five studies had a comparison period start date in 2020, 32 had a comparison period start date in 2019, and one had a comparison period start date in 2018 (table 2).

Time metrics meta-analysis

The following time metrics were included in the meta-analysis: LKW to arrival time, DTI time, DTN time, DTG time, and

Table 3 Relative change from baseline (95% CI) for overall and stratified center status (comprehensive; non-comprehensive)

	Center type		
Metric	Overall	CSC	Non-CSC
LKW	20.9% (5.8% to 36.1%)	24.0% (–0.3% to 48.2%)	12.4% (–1.0% to 25.7%)
DTI	1.2% (–2.9% to 5.3%)	1.6% (–3.0% to 6.1%)	0.2% (–2.0% to 2.4%)
DTN	0.8% (–2.9% to 4.5%)	3.6% (1.2% to 6.0%)	–4.6% (–11.9% to 2.7%)
DTG	2.8% (–5.0% to 10.6%)	4.6% (–5.9% to 15.1%)	–0.6% (–8.3% to 7.1%)
DTR	19.7% (11.1% to 28.2%)	21.2% (12.3% to 30.1%)	0.5% (–31.0% to 32.0%)

Results are presented as percent change in the COVID-19 period compared with the comparison period with 95% CI. A negative value indicates a decrease in time during the COVID-19 period compared with the comparison period.
CSC, comprehensive stroke center; DTG, door-to-groin; DTI, door-to-imaging; DTN, door-to-needle; DTR, door-to-reperfusion; LKW, last-known-well; Non-CSC, non-comprehensive stroke center.

DTR time. The absolute mean time metrics pre-COVID-19 and during COVID-19 for each included study are reported in online supplemental appendix 2.

Last-known-well to arrival

We analyzed 33 studies which reported LKW to arrival time as a stroke care metric. The median LKW to arrival time during the COVID-19 period was 295 min (range 88–1041 min) while the median pre-COVID-19 LKW to arrival time was 239.3 (78–960 min). Relative to each studies' baseline pre-COVID-19 LKW time, we reported a statistically significant 20.9% (95% CI 5.8% to 36.1%, p=0.01) pooled increase in mean LKW to arrival time during the COVID-19 period (figure 2A).

Door-to-imaging

We analyzed 18 studies reporting DTI time as a stroke care metric. The median DTI time during the COVID-19 period was 25 min (range 0–61 min) while the median pre-COVID-19 DTI time was 23 min (range 2.3–88.3 min). Relative to each studies' baseline pre-COVID-19 DTI time, we reported a pooled increase of 1.2% (95% CI –2.9% to 5.3%) in DTI time during the COVID-19 period (figure 2B).

Door-to-needle

We analyzed 26 studies reporting DTN time as a stroke care metric. The median DTN time during the COVID-19 period was 51 min (range 21–221 min) while the median pre-COVID-19 DTN time was 49 min (22–129 min). Relative to each studies' baseline pre-COVID-19 DTN time, we reported a pooled increase of 0.8% (95% CI –2.9% to 4.5%) in mean DTN time during the COVID-19 period (figure 2C).

Door-to-groin

We analyzed 24 studies reporting DTG time as a stroke care metric. The median DTG time during the COVID-19 period was 93 min (range 54–216 min) while the median DTG time during the pre-COVID-19 period was 95 min (53–445 min). Relative to each studies' baseline pre-COVID-19 DTG time, we reported a pooled increase of 2.8% (95% CI −5.0% to 10.6%) in mean DTG time during the COVID-19 period (figure 2D).

Door-to-reperfusion

We analyzed seven studies reporting DTR time as a stroke care metric. The median DTR time during the COVID-19 period was 118 min (range 95–215 min) while the median DTR time during the pre-COVID-19 period was 101 min (range 73–180 min). Relative to each studies' baseline pre-COVID-19 DTR time, we reported a statistically significant pooled increase of 19.7% (95% CI 11.1% to 28.2%, p=0.00) in mean DTR time during the COVID-19 period (figure 2E).

Time metric subgroup analysis

The following results were obtained after stratifying results by stroke center status. Overall analysis results are displayed in table 3.

Last-known-well to arrival

Mean LKW to arrival time increased by 24.0% (95% CI –0.3% to 48.2%) (I^2 81%, n=24 studies) at CSCs and by 12.4% (95% CI –1.0% to 25.7%) (I^2 46%, n=9 studies) at non-CSCs. There was no statistically significant difference in mean LKW to arrival time change between CSCs and non-CSCs (p=0.41).

Door-to-imaging

Mean DTI time increased by 1.6% (95% CI –3.0% to 6.1%) (I^2 97%, n=16 studies) at CSCs and by 0.2% (95% CI –2.0% to 2.4%) (I^2 0%; n=2 studies) at non-CSCs. There was no statistically significant difference in DTI time change between CSCs and non-CSCs (p=0.59).

Door-to-needle

Mean DTN time increased by 3.6% (95% CI 1.2% to 6.0%) (I^2 18%; n=18 studies) at CSCs, while mean DTN time decreased by 4.6% (95% CI –11.9% to 2.7%) (I^2 91%; n=8 studies) at non-CSCs. The reported difference between CSCs and non-CSCs was statistically significant (p=0.04).

Door-to-groin

Mean DTG time increased by 4.6% (95% CI –5.9% to 15.1%) (I^2 70%, n=17 studies) at CSCs and decreased by 0.6% (95% CI –8.3% to 7.1%) (I^2 7%, n=7 studies) at non-CSCs. There was no statistically significant difference in mean DTG time change between CSCs and non-CSCs (p=0.43).

Door-to-reperfusion

Mean DTR time increased by 21.2% (95% CI 12.3% to 30.1%) (I^2 0%, n=4 studies) at CSCs and by 0.5% (95% CI –31.0% to 32.0%) (I^2 33%, n=2 studies) at non-CSCs. There was no statistically significant difference in mean DTR time change between CSCs and non-CSCs (p=0.21).

Evaluation of study quality and small study effect

All included studies were found to be of 'good' study quality based on the quality assessment tool for before–after (pre–post) studies with no control group by the NHLBI.[6] Although the funnel plots for each time metric show minor signs of asymmetry (online supplemental appendix 3), Egger's test did not find any significant small study effect for any of these outcomes (see online supplemental appendix 4). A funnel plot was not constructed for DTR because fewer than eight studies were included in that analysis. It is possible that minor asymmetry is a result of the high heterogeneity among articles in our study.

DISCUSSION

Our results showed that all time metrics increased in the pandemic period, though LKW to arrival and DTR times were the only statistically significant delays, and the most pronounced. Several reasons were postulated by authors of included studies as to why certain metrics may have increased during the pandemic, with many of them being consistently reported across studies.

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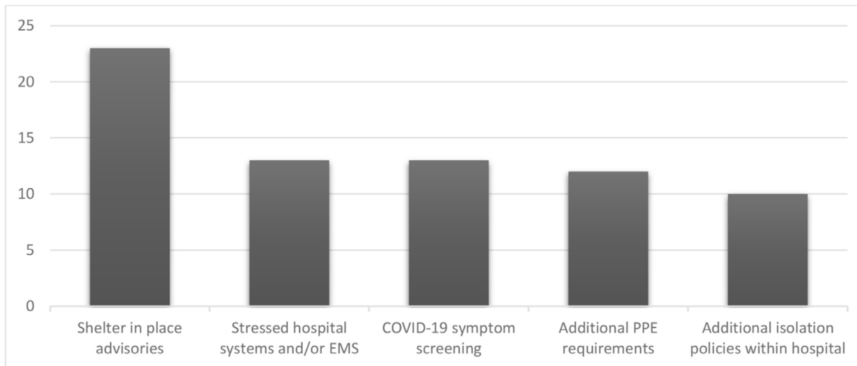
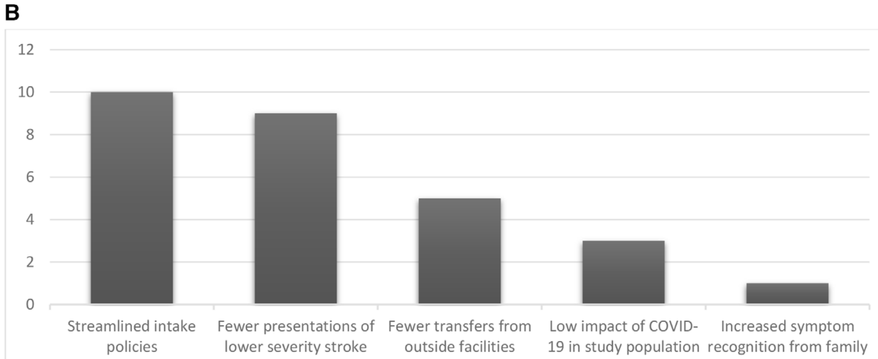


Rank	Reason for Delay	Studies (n=40)
1	Shelter-in-place advisories and/or patient fear of presentation	23 (59.0%)
2	Stressed hospital systems and/or EMS	13 (33.3%)
3	COVID-19 symptom screening	13 (33.3%)
4	Additional PPE requirements	12 (30.8%)
5	Additional isolation policies within hospital	10 (25.6%)

B



Rank	Reason for Steady State	Studies (n=40)
1	Streamlined intake policies	10 (25.6%)
2	Fewer presentations of lower severity stroke	9 (23.1%)
3	Fewer transfers from outside facilities	5 (12.8%)
4	Low impact of COVID-19 in study population	3 (7.7%)
5	Increased symptom recognition from family	1 (2.6%)

Figure 3 (A) Distribution of the number of studies that cited these reasons as potential drivers for delays. (B) Distribution of the number of studies that reported potential reasons for steady or improved times in the pandemic period. EMS, emergency medical services; PPE, personal protective equipment.

Delays in LKW to arrival time are largely out of the hands of the caretaker. Public health guidelines and patient discretion and perception have appeared to be the major player in stroke presentation decreases and delays during the pandemic. Twenty-three studies cited shelter-in-place advisories and/or patient fear of presentation as a perceived cause for delays to hospital presentation for stroke (figure 3A). The implications of increased presentation times were a topic of focus for authors, with multiple studies drawing the connection between longer times to presentation and thus fewer people presenting within the window for stroke treatment.[8–10] To address this, several studies called for the need for public awareness campaigns to stress the importance of seeking immediate medical attention for symptoms and to combat the misinterpretation of 'stay at home'.[10–12] Furthermore, 13 studies noted stressed hospital and EMS systems as a potential reason for delays to stroke treatment (figure 3A). A study out of Massachusetts assessing the impact of COVID-19 on statewide emergency medical services (EMS) found that EMS use decreased during COVID-19 irrespective of COVID-19 incidence, citing that 'measures must be taken to clearly inform the public that immediate emergency care for time-sensitive conditions remains imperative,'[13] further illustrating the importance of public perception in this matter.

In intra-hospital metrics where physicians and caretakers have more autonomy, delays were far less pronounced. Minor delays to DTI, DTN, and DTG were found in our pooled analysis. Across studies, these were widely attributed to precautions associated with COVID-19 such as symptom screening, additional PPE requirements, and isolation policies within hospitals (figure 3A). Minimal delays to stroke treatment during COVID-19 have also been identified in large multicenter studies,[14] further showing the ability of hospital systems to adapt workflow to maximize patient outcomes. Interestingly, our analysis showed only a 2.8% increase in mean DTG times, but a 19.7% increase in mean DTR times. While this trend must be noted with caution, as we had 24 studies included in the DTG analysis but only seven in the DTR analysis, this points to the fact that mechanical thrombectomy procedures were taking longer during COVID-19. Given that LKW increased by over 20% during this time period, it is possible that thrombi were given more time to solidify[15] and were thus harder to clear, another dangerous potential implication of increased presentation times.

When comparing CSCs to non-CSCs, our findings indicated that CSCs experienced more pronounced delays than non-CSCs during the pandemic. Although one might expect larger centers designated as CSCs to be better equipped for a mass influx of patients, and thus more prepared for public health crises, there were several factors working against them during the first phase of the pandemic. It was posited that CSCs experienced a disproportionate influx in stroke cases during the COVID-19 period as other nearby, smaller centers may have stopped taking in stroke patients to account for COVID-19 patients.[16 17] As noted above, stroke patients may have been more likely to delay seeking care until their symptoms became more serious, which could increase their chances of referral to a CSC.

There are potential limitations to our study. Given that we sought to focus on how COVID-19 affected the healthcare system's ability to respond to patients suffering from stroke, rather than stroke patients themselves, we did not analyze differences in clinical outcomes between the two study periods. As previously stated, only seven studies were included in the DTR analysis, and this was one of the statistically significant findings in this study.

This study's strengths include a wide variety of countries represented, stratification of the studies by stroke center status, and a specific focus on relative change from baseline (pre-COVID-19), rather than absolute change, in time metrics. As these data are often reported as secondary outcomes, our study is unique in that its primary endpoint is the relative change from baseline in stroke response times. Additional information about our review can be found in online supplemental appendix 5.

CONCLUSION

While delays were seen in stroke presentation times such as LKW and DTR, especially in CSCs, early multidisciplinary efforts to adapt the acute stroke treatment process resulted in keeping intra-hospital stroke response time metrics close to pre-pandemic levels. Delays were attributed to shelter in place advisories, stressed hospital systems, and COVID-19 associated precautions, among others. Potential future studies may include an analysis of subsequent waves in the pandemic to evaluate whether relative changes in response times persisted later into the pandemic, and institutional studies to assess viral spread rates at stroke centers where times were increased as a result of COVID-19 precautions.

Author affiliations
[1]Computational Neuroscience Outcomes Center, Harvard Medical School, Boston, Massachusetts, USA
[2]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts, USA
[3]Department of General Internal Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA
[4]Department of Neurosurgery, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands
[5]Department of Library and Learning Resources, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, USA
[6]Department of Pharmaceutical Business and Administrative Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, USA

Twitter Rania A Mekary @RMekary

Contributors All authors were involved in the design of the study, organization of the study, manuscript writing, and approval of final version of the manuscript. JD generated the search strategy and performed the search. NLAN and AHD independently performed the abstract and full text screening. NLAN and JLK performed the data extraction and summarized the data. AHD performed the data-analyses and RAM checked the data analysis and validity. NLAN, JLK, AD, and CJ wrote the manuscript.

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