Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Collateral Effect of Covid-19 on Stroke Evaluation in the United States

Supplementary Appendix

Table of Contents

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Supplementary Methods

RAPID in acute stroke

Non-invasive neurological imaging is a vital component of acute stroke evaluation. More than 850 U.S. hospitals that perform neurological imaging for stroke utilize RAPID, a software tool to process and disseminate this imaging to physicians caring for patients with suspected acute stroke. In routine use, neuroimaging for AIS—comprising non-contrast CT or MRI of the brain, CT or MR perfusion of the brain, and/or CT or MR angiography of the head and neck—is transmitted in real-time from the point of acquisition to a local server hosting RAPID imaging software (iSchemaView, Inc., Menlo Park, CA). Images are transmitted to the RAPID server in DICOM format with associated metadata that includes patient age, gender, site of imaging, and date and time of image acquisition. These data are processed by the RAPID server and sent to the appropriate clinical teams for patient care. Data are then anonymized by the RAPID server and transmitted to a central data warehouse. Multiple imaging studies occurring in the same patient are combined based on an anonymous patient identifier that is available to the local RAPID server but not the data warehouse.

RAPID imaging utilization has several features that make it attractive as an indicator of Covid-19 impact on stroke evaluation at national scale. RAPID imaging is performed in large numbers at centers distributed across 49 of 50 states in United States. The breadth and depth of sampling inherent in this data is therefore substantial. Moreover, RAPID imaging utilization is generally acquired at the time of presentation and provides nearly real-time insight through an interactive dashboard. In contrast, counts of patients undergoing stroke treatment or discharged with a diagnosis of acute ischemic stroke may lag by weeks or months due to hospitalization length and inherent delays in public data reporting, limiting their utility in shaping a response to time-sensitive public health emergencies.

Data collection

Complete data from the central data warehouse were available between July 1, 2019 and April 27, 2020. Within this interval, aggregated counts of unique patients imaged on each day were generated based on the timestamp of each imaging study in the time zone of the performing hospital. A patient was considered to have undergone imaging on a given day if RAPID was used to process any of the following types of imaging: non-contrast CT or MRI of the brain, CT or MR perfusion of the brain, or CT or MR angiography of the head and neck. Daily counts were subdivided into groups based on key patient demographics, imaging features, and hospital characteristics. Patient demographic data included age and gender. Hospital characteristics included U.S. state and typical daily imaging volume; closely affiliated hospitals that shared a single RAPID server were treated as a single site. Imaging data included automatically calculated volumes of ischemic core and hypoperfusion from CT perfusion data. Ischemic core, which

corresponds to acutely but irreversibly injured brain, is estimated within RAPID as regions with greater than 70% relative reduction in cerebral blood flow. Hypoperfusion volume, which corresponds to areas of the brain that are critically hypoperfused regardless of reversibility, is estimated within RAPID as regions with time to maximum of the residue function >6 seconds (Tmax >6 s). Studies with missing data were exceedingly rare (≤1.0% of data) and excluded only from those subgroups in which these missing data prevented categorization.

The local institutional review board determined that the investigators did not have access to protected health information and therefore this research did not meet the federal definition of human subjects research.

Data and statistical analysis

Outcome data were measured as daily counts of patients who underwent neuroimaging for AIS using the RAPID platform from July 1, 2019 to April 27, 2020. Percentage decline was calculated from the ratio of mean daily counts in a prepandemic epoch and an early-pandemic epoch. For the overall sample and for patient demographic subgroups, daily count data was normalized by the number of RAPID-connected hospitals prior to averaging. The number of RAPID-connected hospitals in the U.S. was available on a daily basis. For subgroups based on U.S. state and hospital volume, daily count data was not normalized as the number of RAPID-connected hospitals in each state and in each hospital volume subgroup was not reliably known.

The early-pandemic epoch was chosen as March 26, 2020 to April 8, 2020, corresponding to the two-week nadir of the two-week moving average of daily counts starting from November 2019.

The prepandemic epoch was chosen as February 1, 2020 to February 29, 2020, as data from this period did not reveal a deviation from baseline.

The choice to use a prior-month comparator instead of a prior-year comparator from 2019 was deliberate. Unlike treatment networks for other acute conditions that have been relatively stable for years, stroke networks and RAPID adoption have evolved significantly since the publication of the DAWN and DEFUSE 3 trials in 2018.[1,2] Compared to 2019, the demographic profile of RAPID-connected hospitals in 2020 includes a larger number of satellite hospitals that have relatively low stroke volumes and do not perform endovascular thrombectomy. Furthermore, RAPID imaging in 2020 encompasses automated analysis of other types of brain imaging studies besides CT or MR perfusion, which were much less common in early 2019. For example, among patients who underwent RAPID imaging with CT in February 2020, 18% underwent non-contrast head CT alone, 25% underwent CT angiography without CT perfusion, 34% underwent CT perfusion without CT angiography, and 23% underwent CT perfusion and CT angiography. Besides confounding the comparison of overall total counts to similar data from 2019, the broader coverage of stroke imaging types in recent RAPID data provides more reliable insight into overall stroke evaluation trends than is possible with only CTP.

Bootstrapped confidence intervals for the percentage change were determined from the averaged data in the prepandemic and early-pandemic epochs using a percentile bootstrap. All summary data are reported as point estimates and 95% confidence intervals. The widths of confidence intervals have not been adjusted for multiplicity. All analyses were performed in R (version 3.5.2).

Supplementary Figures

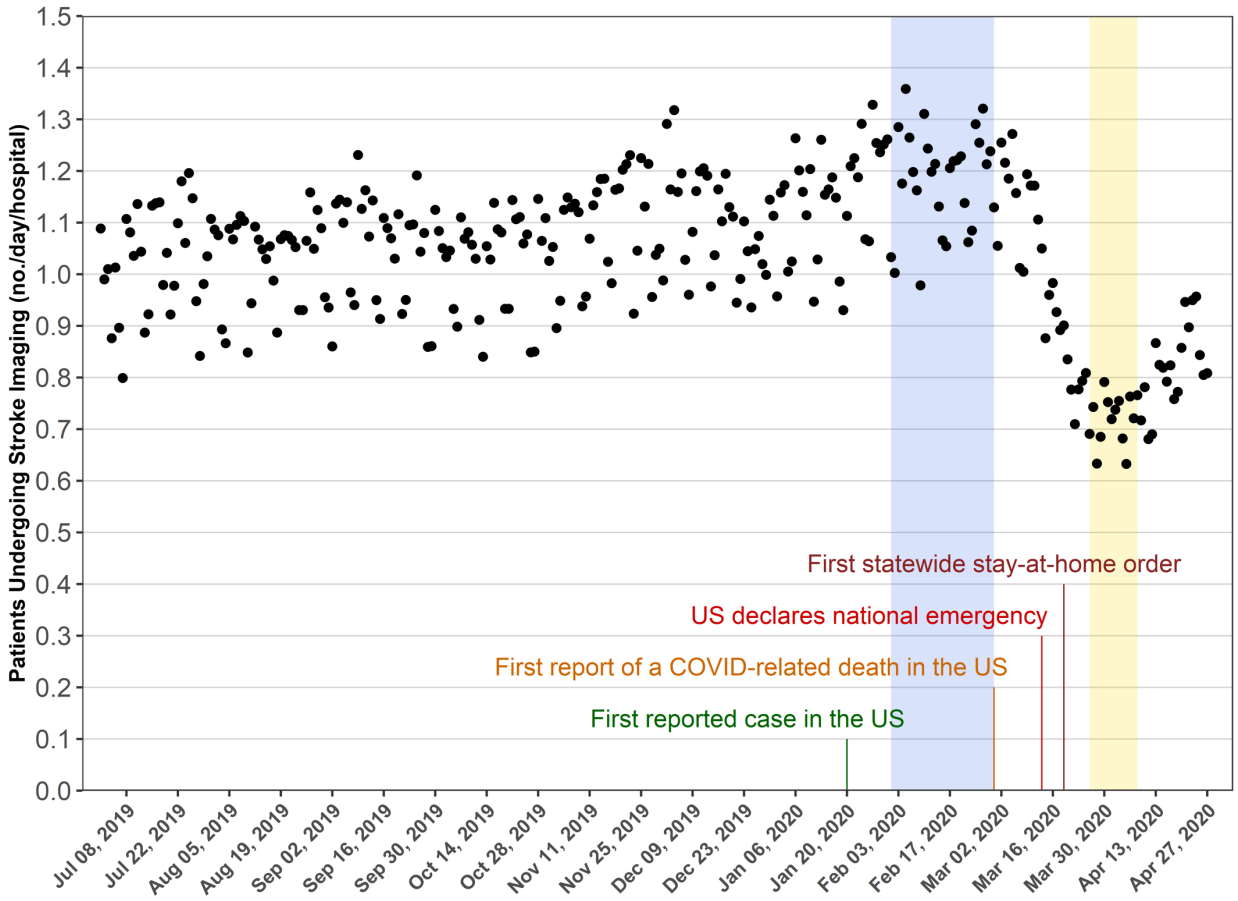

Figure S1. Normalized daily counts of unique patients who underwent neuroimaging for stroke with RAPID software in the United States, July 2019 through April 2020. Daily counts are normalized by the number of RAPID-connected U.S. hospitals on the corresponding day. Shaded regions correspond to the prepandemic (blue) and early-pandemic (yellow) epochs. Line markers indicate key dates of the pandemic in the U.S.

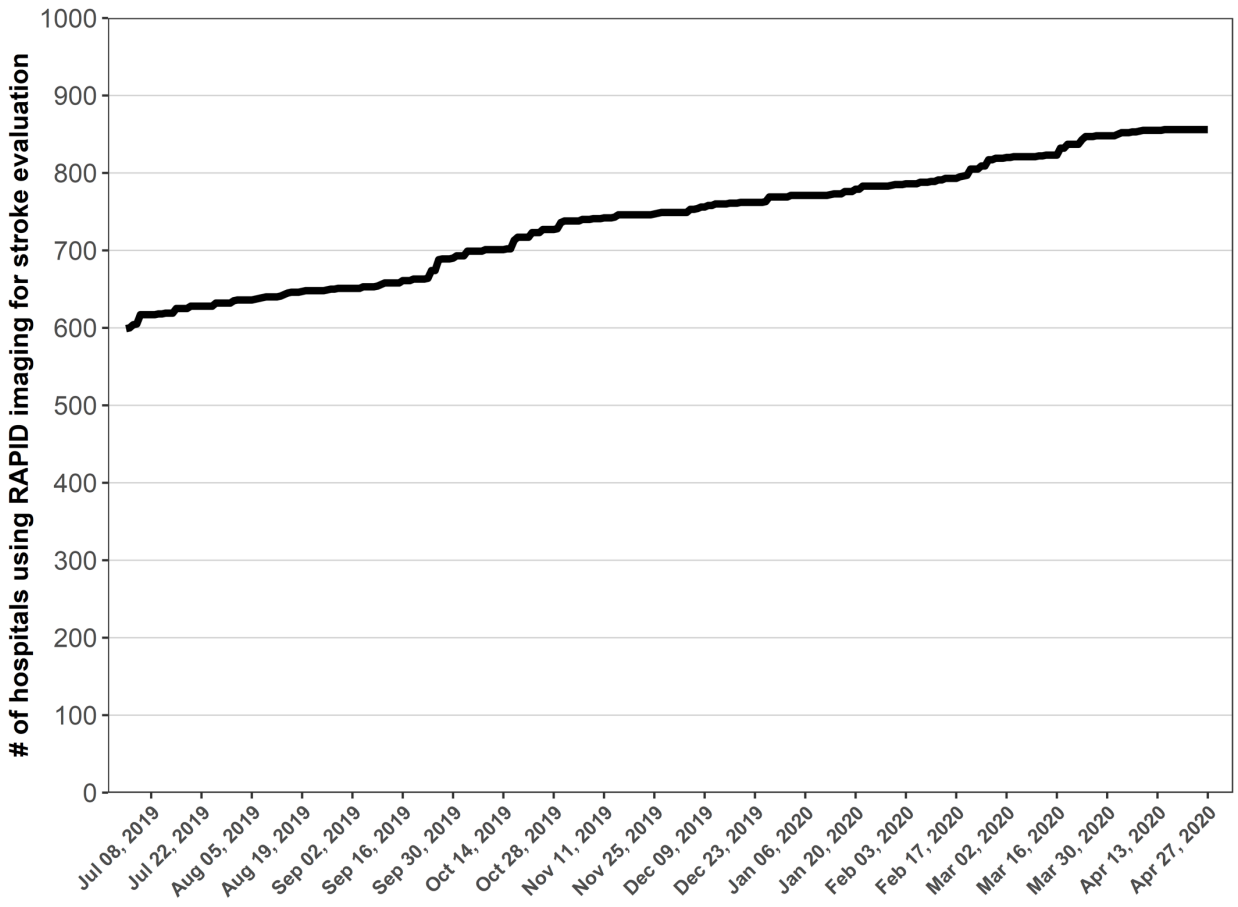

Figure S2. Number of RAPID-connected hospitals in the United States.

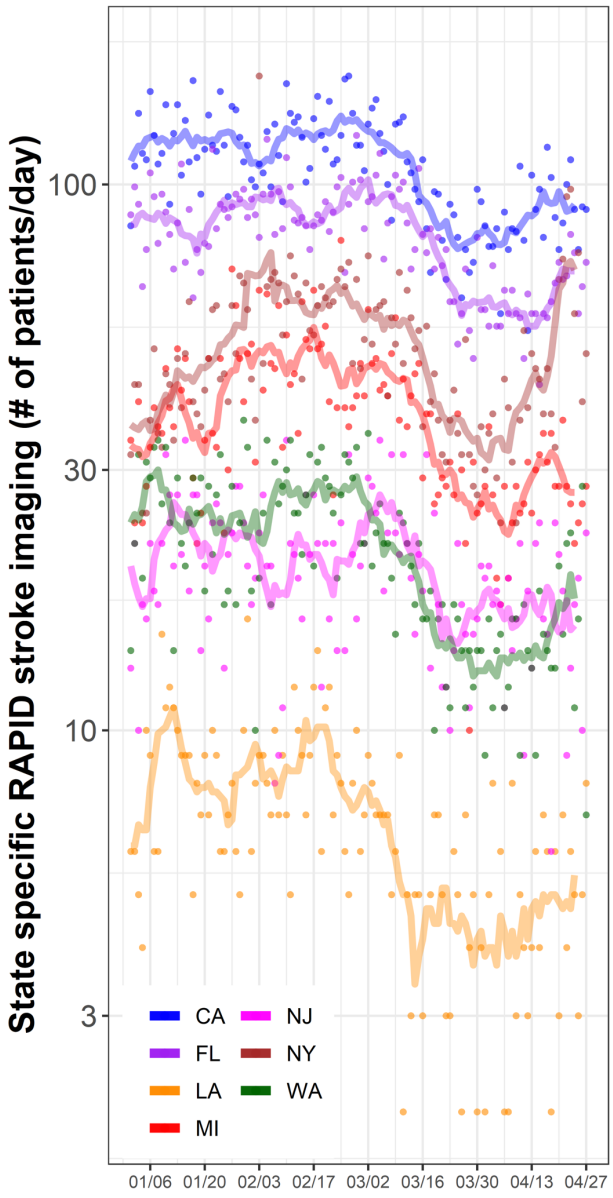

Figure S3. Patients evaluated daily with RAPID software in selected states. Trendlines are generated using a 1-week moving average of underlying daily counts.

Supplementary Tables

Table S1. Daily patient volume by patient demographic before and during the Covid-19 pandemic in the United States. Daily data are normalized by the number of RAPID-connected U.S. hospitals except where noted. All data reported as mean (95% CI).

	Daily patients (prepandemic)	*Daily patients (early-pandemic)*	*% change*
Overall			
Patients/day*	941.9 (911.7, 971.3)	611.6 (590.0, 632.1)	-35.1% (-32.0%, -38.0%)
Patients/day/hospital	1.182 (1.146, 1.217)	0.719 (0.693, 0.743)	-39.1% (-36.4%, -41.9%)
Age (patients/day/hospital)			
0-11 y	0.003 (0.002, 0.003)	0.002 (0.001, 0.003)	-20.8% (27.0%, -57.5%)
12-17 y	0.003 (0.002, 0.004)	0.002 (0.001, 0.003)	-45.0% (-9.6%, -69.3%)
18-24 y	0.015 (0.013, 0.017)	0.006 (0.004, 0.007)	-62.4% (-50.5%, -73.3%)
25-34 y	0.040 (0.037, 0.043)	0.019 (0.017, 0.022)	-52.3% (-43.8%, -59.6%)
35-44 y	0.075 (0.070, 0.080)	0.044 (0.040, 0.048)	-41.1% (-34.0%, -47.6%)
45-54 y	0.139 (0.131, 0.147)	0.083 (0.077, 0.088)	-40.6% (-35.2%, -45.6%)
55-64 y	0.226 (0.218, 0.234)	0.143 (0.136, 0.150)	-36.7% (-32.6%, -40.6%)
65-74 y	0.267 (0.257, 0.278)	0.167 (0.158, 0.175)	-37.6% (-33.4%, -41.6%)
75-84 y	0.232 (0.223, 0.239)	0.139 (0.133, 0.145)	-39.8% (-36.3%, -43.1%)
85+ y	0.169 (0.163, 0.174)	0.109 (0.101, 0.116)	-35.1% (-30.3%, -40.2%)
Gender (patients/day/hospital)			
Female	0.612 (0.590, 0.632)	0.348 (0.333, 0.361)	-43.1% (-40.1%, -46.2%)
Male	0.557 (0.539, 0.575)	0.361 (0.347, 0.374)	-35.1% (-31.9%, -38.3%)
Other	0.003 (0.002, 0.003)	0.002 (0.001, 0.002)	-30.1% (2.8%, -55.0%)
Hypoperfusion volume (patients/day/hospital)			
0-15 mL	0.450 (0.433, 0.469)	0.247 (0.238, 0.257)	-45.1% (-42.0%, -48.1%)
15+ mL	0.235 (0.227, 0.242)	0.163 (0.155, 0.172)	-30.4% (-26.0%, -34.6%)
15-30 mL	0.046 (0.044, 0.049)	0.030 (0.026, 0.034)	-35.8% (-26.0%, -45.2%)
30-50 mL	0.038 (0.035, 0.041)	0.028 (0.025, 0.030)	-26.6% (-18.1%, -35.0%)
50-100 mL	0.057 (0.054, 0.060)	0.041 (0.038, 0.043)	-28.4% (-22.3%, -34.0%)
100-150 mL	0.035 (0.033, 0.037)	0.026 (0.023, 0.029)	-24.4% (-14.4%, -33.9%)
150+ mL	0.059 (0.056, 0.061)	0.039 (0.034, 0.043)	-34.2% (-26.7%, -41.8%)
Ischemic core volume (patients/day/hospital)			
0-15 mL	0.559 (0.541, 0.577)	0.330 (0.321, 0.338)	-41.0% (-38.6%, -43.4%)
15+ mL	0.071 (0.067, 0.075)	0.053 (0.050, 0.057)	-25.0% (-18.3%, -31.1%)
15-30 mL	0.026 (0.024, 0.028)	0.019 (0.017, 0.022)	-25.6% (-12.4%, -37.1%)
30-50 mL	0.017 (0.015, 0.019)	0.014 (0.012, 0.016)	-16.6% (1.3%, -31.8%)
50-100 mL	0.015 (0.014, 0.017)	0.013 (0.011, 0.014)	-18.9% (-4.5%, -32.1%)
100-150 mL	0.007 (0.006, 0.008)	0.004 (0.003, 0.005)	-39.2% (-20.3%, -55.7%)
150+ mL	0.006 (0.005, 0.007)	0.003 (0.002, 0.004)	-45.5% (-19.4%, -64.6%)

* Not normalized by number of hospitals.

Table S2. Daily patient volume by location before and during the Covid-19 pandemic in the United States. Daily data are not normalized. All data reported as mean (95% CI).

	Daily patients (prepandemic)	*Daily patients (early-pandemic)*	*% change*
Site volume* (patients/day)			
Low (0-1)	222.9 (211.5, 234.7)	170.0 (160.6, 180.2)	-23.7% (-17.6%, -29.6%)
Medium (1-5)	551.1 (531.0, 570.7)	360.4 (350.6, 368.4)	-34.6% (-31.7%, -37.4%)
High (5+)	240.2 (230.8, 250.1)	126.9 (114.6, 139.6)	-47.2% (-41.5%, -52.8%)
State			
CA	122.1 (115.7, 128.5)	78.4 (72.8, 84.0)	-35.8% (-30.1%, -41.4%)
FL	92.3 (88.0, 96.9)	60.7 (56.7, 65.2)	-34.2% (-28.5%, -39.4%)
TX	63.3 (60.2, 66.5)	43.1 (40.1, 46.2)	-31.8% (-25.8%, -37.6%)
NY	63.1 (57.0, 71.5)	34.1 (30.6, 38.1)	-46.0% (-37.1%, -54.2%)
WI	54.1 (50.2, 57.8)	33.6 (29.3, 38.1)	-37.9% (-28.3%, -46.4%)
MI	47.7 (43.6, 52.0)	24.4 (21.0, 27.6)	-48.8% (-39.9%, -57.2%)
OH	38.9 (36.1, 41.7)	30.4 (27.1, 33.5)	-22.0% (-11.4%, -31.8%)
PA	37.2 (32.6, 43.1)	22.1 (18.4, 26.1)	-40.4% (-25.9%, -52.9%)
TN	29.3 (27.2, 31.7)	20.1 (17.5, 22.4)	-31.6% (-21.7%, -41.1%)
WA	26.2 (24.0, 28.3)	13.1 (12.0, 14.1)	-50.2% (-43.8%, -55.6%)
NC	24.7 (22.5, 26.9)	18.9 (16.9, 20.9)	-23.5% (-12.4%, -33.7%)
IL	22.7 (20.6, 25.0)	14.0 (12.1, 15.9)	-38.4% (-27.9%, -47.9%)
IN	20.8 (18.3, 23.2)	9.0 (7.6, 10.6)	-56.7% (-47.1%, -64.7%)
NJ	19.9 (17.7, 22.1)	16.4 (14.9, 17.8)	-17.6% (-4.6%, -28.5%)
VA	19.5 (17.5, 21.6)	13.1 (10.8, 15.7)	-33.0% (-17.0%, -45.9%)
MO	19.4 (17.6, 21.2)	12.5 (11.3, 13.8)	-35.5% (-25.6%, -43.7%)
AZ	18.9 (17.1, 20.8)	19.7 (17.0, 22.6)	4.1% (23.3%, -12.5%)
GA	18.2 (16.4, 20.1)	12.9 (9.9, 16.0)	-29.1% (-10.2%, -46.7%)
KY	16.6 (15.2, 18.0)	10.4 (9.4, 11.7)	-37.0% (-27.6%, -44.9%)
MS	12.9 (11.6, 14.2)	6.7 (4.9, 8.7)	-47.9% (-31.0%, -63.0%)
NV	12.8 (11.4, 14.2)	10.3 (8.9, 11.8)	-19.6% (-3.7%, -33.4%)
CT	12.6 (11.1, 14.0)	7.9 (6.4, 9.4)	-37.4% (-21.9%, -50.1%)
NE	11.6 (10.2, 13.0)	8.1 (6.8, 9.5)	-30.3% (-13.9%, -43.9%)
AL	11.1 (9.7, 12.5)	7.7 (6.0, 9.6)	-30.5% (-10.8%, -47.3%)
AR	11.0 (9.5, 12.6)	5.8 (4.4, 7.2)	-47.6% (-31.5%, -61.1%)
MD	10.5 (9.4, 11.7)	6.0 (4.9, 7.2)	-43.0% (-29.3%, -54.5%)
KS	10.4 (9.3, 11.6)	7.9 (6.4, 9.5)	-23.9% (-5.8%, -39.6%)
MN	10.1 (8.8, 11.4)	5.6 (4.6, 6.6)	-44.1% (-30.7%, -55.2%)
SC	9.8 (8.8, 10.7)	6.4 (4.9, 8.1)	-34.4% (-15.9%, -50.9%)
CO	9.5 (8.1, 10.9)	4.7 (3.3, 6.4)	-50.3% (-30.6%, -66.3%)
LA	8.5 (7.7, 9.3)	4.1 (3.0, 5.4)	-51.2% (-35.0%, -65.3%)
OK	8.2 (6.8, 9.6)	4.7 (3.9, 5.6)	-42.3% (-25.7%, -55.6%)
MA	7.3 (6.4, 8.1)	4.2 (3.1, 5.4)	-42.1% (-23.0%, -58.2%)
IA	7.0 (6.0, 8.1)	4.0 (3.0, 5.1)	-43.1% (-23.9%, -58.0%)
DC	5.8 (4.6, 7.0)	6.3 (5.0, 7.6)	8.5% (48.0%, -19.7%)
ID	4.5 (3.7, 5.3)	4.9 (3.6, 6.2)	7.5% (48.2%, -23.8%)

HI	3.5 (2.8, 4.2)	2.2 (1.4, 2.9)	-36.4% (-9.1%, -59.8%)
OR	3.4 (2.8, 4.0)	2.7 (1.9, 3.6)	-20.5% (14.4%, -48.7%)
UT	3.1 (2.4, 3.8)	2.1 (1.5, 2.6)	-32.5% (-4.4%, -53.2%)
AK	2.1 (1.5, 2.7)	1.3 (0.9, 1.7)	-37.9% (-4.7%, -62.6%)
SD	2.0 (1.5, 2.6)	2.0 (1.5, 2.5)	-1.7% (42.7%, -32.3%)
WV	2.0 (1.6, 2.4)	1.6 (1.1, 2.1)	-20.1% (15.5%, -49.1%)
ME	1.7 (1.2, 2.2)	0.9 (0.4, 1.4)	-49.3% (-9.4%, -79.3%)
DE	1.2 (0.9, 1.7)	0.8 (0.3, 1.4)	-36.7% (25.4%, -77.5%)
MT	1.0 (0.7, 1.4)	0.6 (0.3, 1.1)	-37.9% (26.6%, -75.6%)
NM	1.0 (0.6, 1.3)	3.2 (2.1, 4.4)	232.9% (488.7%, 90.3%)
RI	0.9 (0.6, 1.2)	1.2 (0.6, 1.9)	40.9% (164.7%, -33.4%)
WY	0.6 (0.2, 1.0)	0.1 (0.0, 0.4)	-75.6% (-14.7%, -100.0%)
ND	0.6 (0.3, 0.9)	0.4 (0.1, 0.7)	-35.3% (81.3%, -87.1%)
VT	0.4 (0.2, 0.6)	0.3 (0.0, 0.6)	-24.7% (107.1%, -100.0%)

* Sites correspond to unique RAPID servers. In some cases, one RAPID server may serve multiple closely affiliated hospitals.

Supplementary References

1. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. The New England Journal of Medicine 2018;378:708-18.

2. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. The New England Journal of Medicine 2018;378:11-21.