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ORIGINAL ARTICLE

Sex differences in acute stroke metrics and outcome dependent on COVID status

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Abstract

Background and purpose: Biological sex is known to have an impact on quality metrics of acute stroke. We aimed to determine whether COVID positivity accentuates this effect and constitutes worse outcome.

Methods: The present analysis was based on the Global COVID-19 Stroke Registry, a retrospective, international, cohort study of consecutive ischemic stroke patients receiving intravenous thrombolysis and/or endovascular thrombectomy between 1 March 2020 and 30 June 2021. We investigated differences between the sexes in patient characteristics, acute stroke metrics as well as post-stroke outcome in COVID-positive and COVID-negative stroke patients undergoing acute revascularization procedures.

Results: A total of 15,128 patients from 106 centers were recorded in the Global COVID-19 Stroke Registry, 853 (5.6%) of whom were COVID-positive. Overall, COVID-positive individuals were treated significantly slower according to every acute stroke metric compared to COVID-negative patients. We were able to show that key quality indicators in acute stroke treatment were unfavorable for COVID-negative women compared to men (last-seen-well-to-door time + 11 min in women). Furthermore, COVID-negative women had worse 3-month outcomes (3-month modified Rankin Scale score [interquartile range] 3.0 [4.0] vs. 2.0 [3.0]; $p < 0.01$), even after adjusting for confounders. In COVID-positive individuals no such difference between the sexes, either in acute management metrics or in 3-month outcome, was seen.

Conclusion: Known sex-related differences in acute stroke management exist and extend to times of crisis. Nevertheless, if patients were COVID-19-positive at stroke onset, women and men were treated the same, which could be attributed to structured treatment pathways.

KEYWORDS
COVID-19, metrics, outcome, sex, stroke

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INTRODUCTION

Patient demographics, such as biological sex, are known to have an impact on quality metrics of acute stroke management as well as post-stroke outcome, placing certain individuals at a disadvantage [1-6]. Such effects are not limited to acute ischemic stroke, but extend to global health crises, most recently the coronavirus disease 2019 (COVID-19) pandemic [7,8]. In ischemic stroke, the quest to treat patients as quickly and effectively as possible has made stroke systems more intricate and, in some cases, as seen during the initial months of the COVID-19 pandemic, vulnerable to outside factors [9-11]. Even though the initial difference in stroke treatment metrics between COVID-positive and -negative patients seems to have passed, the impact of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) on stroke has not [12]. Recently, an increased risk of intracerebral or subarachnoid hemorrhage as well as 24-h mortality in COVID-19-positive stroke patients undergoing recanalization was reported [13]. Whether COVID positivity accentuates the impact of patient demographics on quality metrics of acute stroke management is hitherto unknown. Furthermore, it is unclear if sex-related differences in treatment may cause the negative impact of COVID-19 positivity on post-stroke outcomes. Therefore, our goal was to assess whether biological sex had an impact on (i) stroke treatment time metrics or (ii) outcome of SARS-CoV-2-positive patients with ischemic stroke receiving acute recanalization treatments when compared to SARS-CoV-2-negative patients.

METHODS

Study design, patient selection and study variables

Details of the Global COVID-19 Stroke Registry have been published previously [13]. In short, the data stem from a retrospective, international, cohort study of consecutive ischemic stroke patients receiving intravenous thrombolysis (IVT) and/or endovascular thrombectomy (EVT) between 1 March 2020 and 30 June 2021. Each participating center had to have included at least one patient undergoing either IVT or EVT with concomitant COVID-19. Patients were considered COVID-19-positive if polymerase chain reaction (PCR) and/or antigen test were positive within 7 days before hospital admission (i.e., at-home testing), at hospital admission, irrespective of COVID-19 symptoms, or within the first 7 days after treatment if signs of respiratory infection attributable to COVID-19 were evident at admission. The COVID-19-negative control group comprised all other stroke patients without any signs of COVID-19-compatible symptoms and with negative testing. Patients excluded from this analysis were: (i) those who had symptomatic COVID-19 with symptom resolution more than 7 days prior to hospital admission; (ii) those with asymptomatic COVID-19 and positive testing more than 10 days prior to hospital admission; (iii) those who were not tested within the first 7 days after admission; and (iv) those who became positive after the initial 7 days after hospital admission (i.e., nosocomial COVID-19 infection).

Variable definitions

Within the present study, we investigate differences between COVID-positive and COVID-negative male and female ischemic stroke patients with regard to: (i) patient characteristics: age at stroke onset, pre-stroke modified Rankin Scale (mRS) score, pre-existing risk factors and conditions (atrial fibrillation, hypertension, diabetes, hyperlipidemia, coronary heart disease); (ii) stroke characteristics including etiology (expanded Trial of ORG 10172 in Acute Stroke Treatment [TOAST] criteria, i.e., atherosclerosis, lacunar, cardioembolism, dissection, other determined, undertermined), National Institutes of Health Stroke Scale (NIHSS) score and Alberta Stroke Programme Early Computed Tomography Score (ASPECTS); (iii) acute management metrics: last-seen-well (LSW)-to-door time, LSW-to-needle time (if IVT), LSW-to-puncture time (if EVT) and LSW-to-reperfusion (if EVT); (iv) outcome characteristics including 24-h mortality, mRS score at 3 months and 3-month mortality.

Statistical analysis

Characteristics of the cohort are shown as count (percentage), mean (±standard deviation), or median (interquartile range). Differences in characteristics between subgroups were tested using the chi-squared test, Fisher's exact test, *t*-test or Wilcoxon test, as appropriate. Differences in time indices were investigated after adjustment for age, sex and pre-stroke mRS score. For outcome parameters, NIHSS score at baseline was added to the adjustment. We accounted for the clustered data structure based on multicenter data assessment using linear mixed models for continuous, conditional logistic regression for binary, and proportional odds mixed models for ordinal outcomes, in each case conditioning on center of data assessment. Accordingly, time metrics were analyzed using linear mixed models. Effect modification was investigated by including appropriate interaction effects in models, and linear combinations of model parameters were used to simultaneously obtain interaction and main effects. All *p* values are two-sided and an alpha level of 0.05 was used. Analysis was conducted using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Standard protocol approvals, registration, and patient consents

Each participating center was responsible for ethical approval of data collection and data sharing. Due to the retrospective cohort design, informed consent was not necessary on an individual patient level. All study-related activities adhered to the principles of the Declaration of Helsinki (World Medical Association 2013) and

the guidelines of Good Clinical Practice issued by the International Council for Harmonization. The study was registered at ClinicalTrials.gov with the identifier NCT04895462. Anonymized patient data were handled by the coordinating center (Stroke Centre, Department of Neurology, Lausanne University Hospital, Lausanne, Switzerland).

RESULTS

In total, 15,128 patients from 106 centers were recorded in the Global COVID-19 Stroke Registry, 853 (5.6%) of whom were COVID-positive. Differences in patient and stroke characteristics between COVID-positive and -negative patients within our registry have previously been reported (Table 1).

COVID-positive individuals were younger, more frequently male, and had a higher prevalence of diabetes mellitus and dyslipidemia. Stroke severity, based on NIHSS score and ASPECTS, was higher, and stroke was more frequently considered to be of other determined etiology, while undetermined etiology was less common in COVID-positive patients. Table 2 presents the differences in patient, stroke and treatment characteristics between male and female individuals according to their COVID status.

Both in COVID-positive and -negative individuals, women were older than men at stroke onset and more frequently had atrial fibrillation as a pre-existing condition, which led to cardioembolic stroke being a more common stroke etiology. Compared to their COVID-negative counterparts, COVID-positive women were more frequently functionally independent prior to stroke (mRS score ≤2) and treatment types did not differ from those received by COVID-positive men. NIHSS score at stroke onset was significantly higher in COVID-negative women compared to COVID-negative men, which was not the case in COVID-positive individuals with stroke. Regarding acute stroke treatment, Figure 1 shows the differences in stroke management quality metrics between COVID-positive and -negative patients, while Figure 2 shows the subgroup analysis concerning biological sex. Overall, we report that

TABLE 1 Differences between COVID-negative and COVID-positive patients overall.

	COVID-positive (*N* = 853)	COVID-negative (*N* = 14,275)	*p* Value
Patient characteristics			
Male[a]	494 (57.9)	7273 (51.0)	<0.01
Age, years[b]	70 ± 14	72 ± 14	<0.01
Pre-stroke mRS score > 2[a]	74 (8.7)	1246 (8.7)	1.00
Risk factors[a]			
Atrial fibrillation	244 (28.7)	4310 (30.3)	0.33
Hypertension	579 (67.9)	10,087 (71.0)	0.06
Diabetes	284 (33.3)	3531 (24.9)	<0.01
Dyslipidemia	361 (42.3)	6594 (46.5)	0.02
Coronary heart disease	137 (17.0)	2298 (16.6)	0.82
Stroke characteristics			
Etiology[a]			
Atherosclerosis ≥50%	157 (18.4)	2626 (18.4)	<0.01
Cardioembolism	309 (36.2)	5657 (39.6)	
Lacunar	34 (4.0)	667 (4.7)	
Dissection	15 (1.8)	273 (1.9)	
Other determined	118 (13.8)	644 (4.5)	
Undetermined	220 (25.8)	4408 (30.9)	
NIHSS[b]	14 ± 7	13 ± 7	<0.01
ASPECTS[b]	8.6 ± 1.8	8.8 ± 1.6	<0.01
Treatment[a]			
IVT only	329 (38.6)	5519 (38.7)	0.99
Bridging	225 (26.4)	4214 (29.5)	0.06
Direct EVT	299 (35.1)	4542 (31.8)	0.05

Abbreviations: ASPECTS, Alberta Stroke Programme Early Computed Tomography Score; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a]Values given as *N* (%).

[b]Values given as mean ± standard deviation.

TABLE 2 Differences between male and female stroke patients according to their COVID status.

	COVID-negative			COVID-positive		
	Men (*N* = 7277)	Women (*N* = 6998)	*p* Value	Men (*N* = 494)	Women (*N* = 359)	*p* Value
Patient characteristics						
Age, years[a]	69.2 ± 13.3	74.3 ± 13.9	<0.01	68.0 ± 13.0	71.9 ± 14.7	<0.01
Pre-stroke mRS score ≤ 2[b]	6828 (93.8)	6201 (88.6)	<0.01	31 (6.3)	43 (12.0)	<0.01
Risk factors[b]						
Atrial fibrillation	1901 (26.2)	2409 (34.6)	<0.01	128 (26.0)	116 (32.4)	0.05
Hypertension	5001 (69.1)	5086 (73.0)	<0.01	321 (65.0)	258 (71.9)	0.04
Diabetes	1818 (25.1)	1713 (24.6)	0.47	169 (34.2)	115 (32.0)	0.55
Dyslipidemia	3458 (47.8)	3136 (45.1)	0.01	205 (41.5)	156 (43.5)	0.62
Coronary heart disease	1394 (19.8)	904 (13.4)	<0.01	88 (18.8)	49 (14.5)	0.14
Stroke characteristics						
Etiology[b]						
Atherosclerosis ≥50%	1593 (21.9)	1033 (14.8)	<0.01	113 (22.9)	44 (12.3)	<0.01
Cardioembolism	2530 (34.8)	3127 (44.7)		161 (32.6)	148 (41.2)	
Lacunar	408 (5.6)	259 (3.7)		21 (4.3)	13 (3.6)	
Dissection	172 (2.4)	101 (1.4)		11 (2.2)	4 (1.1)	
Other determined	348 (4.8)	296 (4.2)		66 (13.4)	52 (14.5)	
Undetermined	2226 (30.6)	2182 (31.2)		122 (24.7)	98 (27.3)	
NIHSS[a]	11.9 ± 7.5	13.1 ± 7.2	<0.01	14.5 ± 7.6	13.8 ± 7.1	0.13
ASPECTS[a]	8.9 ± 1.6	8.8 ± 1.6	0.02	8.5 ± 1.8	8.7 ± 1.8	0.33
Treatment[b]						
IVT only	3033 (41.7)	2486 (35.5)	<0.01	190 (38.5)	139 (38.7)	1.00
Bridging	2098 (28.8)	2116 (30.2)	0.07	128 (25.9)	97 (27.0)	0.78
Direct EVT	2146 (29.5)	2396 (34.2)	<0.01	176 (35.6)	123 (34.3)	0.73

Abbreviations: ASPECTS, Alberta Stroke Programme Early Computed Tomography Score; EVT, endovascular thrombectomy; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a]Values given as mean ± standard deviation.

[b]Values given as *N* (%).

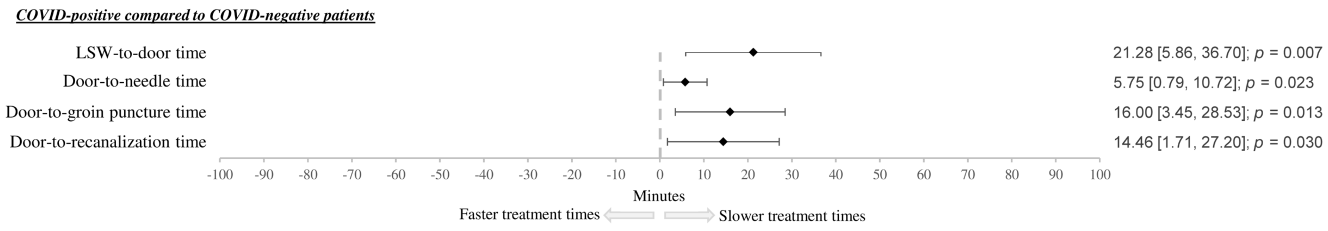

FIGURE 1 Differences in treatment metrics of acute stroke management between COVID-positive and COVID-negative patients. LSW, last seen well.

COVID-positive patients in general were treated significantly slower than COVID-negative patients (LSW-to-door time + 21.3 min; door-to-needle time + 5.8 min; door-to-puncture time + 16.0 min; door-to-recanalization time + 14.5 min [Figure 1]). Concerning biological sex, women had longer LSW-to-door times if they were COVID-negative (+11.0 min), while other treatment metrics did not differ. This was not true for COVID-positive women, as none of the acute management times differed between the sexes (Figure 2). An interaction analysis between COVID status and individual treatment times did not show significant results in any of the subgroups (*p* value > 0.15 throughout, data not shown). In accordance with these differences in treatment times and after adjusting for confounders, COVID-negative women were more likely to have worse 3-month functional outcome and mortality compared to COVID-negative men (3-month mRS

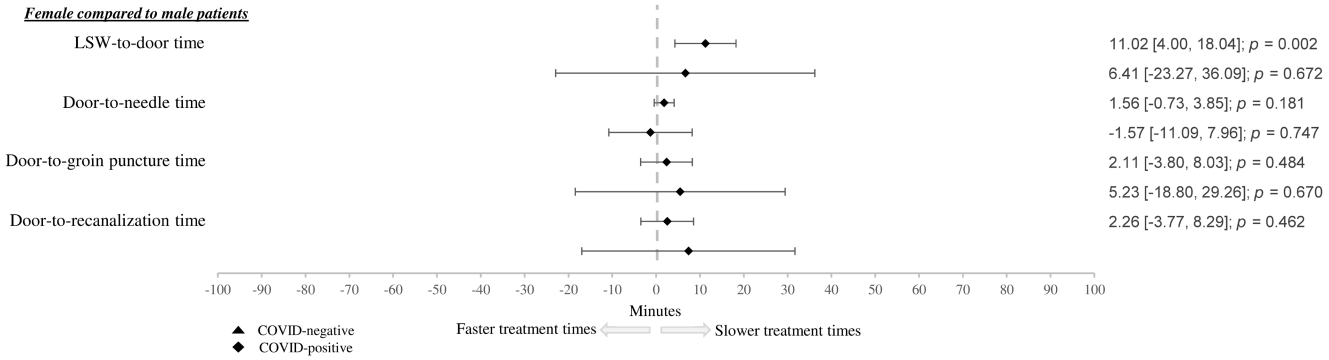

FIGURE 2 Differences in treatment metrics of acute stroke management between female and male patients according to their COVID status. LSW, last seen well.

TABLE 3 Differences in outcome between men and women according to their COVID status.

	COVID-negative			COVID-positive		
	Men ($N=7277$)	Women ($N=6998$)	*p* Value	Men ($N=494$)	Women ($N=359$)	*p* Value
Outcome						
24-h mortality[a]	95 (1.4)	83 (1.2)	0.56	18 (3.8)	13 (3.7)	1.00
3-month mRS score[b]	2.00 (3.00)	3.00 (4.00)	<0.01	3.00 (5.00)	4.00 (4.00)	0.74
mRS score[a]						
0	1375 (21.1)	988 (15.7)		52 (11.0)	37 (10.6)	
1	1212 (18.6)	1022 (16.3)		67 (14.1)	48 (13.7)	
2	993 (15.2)	801 (12.8)		63 (13.3)	32 (9.1)	
3	789 (12.1)	879 (14.0)		64 (13.5)	55 (15.7)	
4	651 (10.0)	801 (12.8)		45 (9.5)	45 (12.9)	
5	336 (5.2)	448 (7.1)		24 (5.1)	27 (7.7)	
3-month mortality[a]	1161 (17.8)	1336 (21.3)	<0.01	159 (33.5)	106 (30.3)	0.36

Note: Adjusted *p* values (age, pre-stroke mRS score, admission NIHSS score).

[a]Values given as *N* (%).

[b]Values given as median (interquartile range).

score 2.58 ± 2.13 vs. 2.98 ± 2.13, $p < 0.01$; 3-month mortality 17.8% vs. 21.3%, $p < 0.01$), while COVID-positive women did not differ in these measures compared to COVID-positive men (3-month mRS score 3.46 ± 2.19 vs. 3.51 ± 2.12, $p = 0.74$; 3-month mortality 33.5% vs. 30.3%, $p = 0.36$ [Table 3]).

DISCUSSION

In our analysis of the Global COVID-19 Stroke Registry, the largest registry containing data on consecutive COVID-positive ischemic stroke patients to date, we were able to show that key quality indicators in acute stroke treatment were unfavorable for COVID-negative women compared to men during the first 15 months of the COVID pandemic. COVID-negative women also had worse 3-month outcomes. Unexpectedly, in COVID-positive individuals, no such difference between the sexes, either in acute management metrics or in 3-month outcome, were seen (Figure 2 and Table 3).

Overall, ischemic stroke remains one of the most time-critical medical emergencies worldwide but prompt application of acute revascularization measures (IVT and/or EVT) has the potential to reduce ischemic stroke burden through reducing post-stroke morbidity and mortality [14-16]. Therefore, each factor that can potentially stall the timely treatment of stroke patients needs to be addressed. Several studies have investigated the effect of the COVID pandemic itself on acute stroke care, most recently two large-scale retrospective cohort assessments that revealed a decrease in stroke admissions and decline in reperfusion strategies through in-house delays in patient work-ups NCBI 37821520/36932121 [17-19]. Furthermore, patient demographics have been linked to lower quality of treatment and worse outcomes in COVID-19 patients and those with other time-critical emergencies, such as myocardial infarction, and concomitant COVID-19 [17,20,21]. In the case of stroke, it is also well known that treatment times can differ solely due to demographic factors, for instance, clinical presentation of cerebral ischemia may differ between the sexes and personal or institutional biases in

healthcare may decelerate access to acute stroke care in some patients [3,22,23,24].

Considering biological sex, our data extrapolate a known negative impact of female sex on ischemic stroke management quality metrics at times of crisis as outpatient emergency services were found to be slower for COVID-negative women, which subsequently affected outcome (Figure 2 and Table 3) [3,22,23,24]. However, if patients were COVID-positive, outpatient and inpatient acute management metrics were similar, resulting in 3-month outcome being the same between the sexes (Figure 2 and Table 3). It is possible that, as the COVID-19 pandemic led to the establishment of treatment pathways for COVID-19 patients (i.e., structured in-house management of patients with suspected or manifest COVID-19 to avoid spreading), there was a shift in focus, potentially reducing biases in the emergency setting [25,26]. This would be in line with stroke care pathways structuring stroke care from the outpatient to post-stroke rehabilitation having a clear positive impact on quality of stroke management, which has recently been shown to be consistent in times of crises [27,28].

Strengths of our analysis include the sample size of COVID-positive stroke patients undergoing treatment and the global nature of recruitment, with centers from Europe, Asia, North and South America, and Africa included within the Global COVID-19 Stroke Registry. Overall, the registry holds the largest set of data on ischemic stroke patients with concomitant COVID-19 to date.

Nevertheless, limitations associated with our retrospective design, namely, registration and reporting bias, the missing data on patients not receiving acute revascularization treatment and self-reporting of COVID-19 PCR/antigen testing, should also be noted. Even though our registry houses the largest cohort of COVID-positive stroke patients undergoing acute recanalization therapy, absolute numbers limit statistical power, and confidence intervals for point estimations in the multivariable linear mixed model are broad, therefore, the results should be interpreted with caution. In addition, patients' social support environment after stroke was not measured. As women are often older than men at the time of stroke, they may have outlived their spouses and have less family support in the recovery of their stroke [22,29,30]. Lastly, there is a potential for regional differences in acute stroke treatment, which is why we adjusted for centers involved in our mixed model analysis.

In conclusion, known sex-related differences in acute stroke management exist and extend to times of crisis, such as the COVID-19 pandemic. However, if patients were COVID-19-positive at stroke onset, women and men were treated the same.

AUTHOR CONTRIBUTIONS

Lukas Mayer-Suess: Data curation; conceptualization; investigation; formal analysis; visualization; project administration; writing – original draft. **João Pedro Marto:** Conceptualization; data curation; investigation; project administration; writing – review and editing. **Davide Strambo:** Methodology; software; data curation; writing – review and editing. **George Ntaios:** Data curation; investigation; writing – review and editing. **Thanh Nguyen:** Data curation; investigation; writing – review and editing. **Stefan Kiechl:** Data curation; supervision; writing – review and editing; resources. **Raimund Pechlaner:** Methodology; formal analysis; validation; writing – review and editing. **Raul Nogueira:** Methodology; investigation; writing – review and editing. **Patrik Michel:** Methodology; conceptualization; supervision; validation; project administration; writing – review and editing; resources. **Michael Knoflach:** Conceptualization; methodology; validation; supervision; writing – review and editing; resources; project administration.

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CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

DATA AVAILABILITY STATEMENT

Anonymized data not published within this article will be made available to any qualified investigator upon reasonable request.

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