





REVIEW

The impact of COVID 19 on the outcomes of thrombectomy in stroke patients: A systematic review and meta-analysis

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Abstract

We aimed to conduct the current meta-analysis to provide better insight into the efficacy of mechanical thrombectomy (MT) in managing COVID-19 patients suffering from a stroke. An electronic search was conducted through eight databases for collecting the current evidence about the efficacy of MT in stroke patients with COVID-19 until 18 December 2021. The results were reported as the pooled prevalence rates and the odds ratios (ORs), with their corresponding 95% confidence intervals (CI). Out of 648 records, we included nine studies. The prevalence of stroke patients with COVID-19 who received MT treatment was with TIC1 ≥ 2 79% (95%CI: 73–85), symptomatic intracranial haemorrhage 6% (95%CI: 3–11), parenchymal haematoma type 1, 11.1% (95%CI: 5–23), and mortality 29% (95%CI: 24–35). On further comparison of MT procedure between stroke patients with COVID 19 to those without COVID-19, we found no significant difference in terms of TIC1 ≥ 2 score (OR: 0.85; 95%CI: 0.03–23; $p = 0.9$). However, we found that stroke patients with COVID-19 had a significantly higher mortality rate than stroke patients without COVID-19 after MT procedure (OR: 2.99; 95%CI: 2.01–4.45; $p < 0.001$). Stroke patients with COVID-19 can be safely and effectively treated with MT, with comparable reperfusion and complication rates to those without the disease.

KEYWORDS

COVID-19, mechanical thrombectomy, meta-analysis, stroke, systematic review

1 | INTRODUCTION

Since the first case of Coronavirus Disease 2019 (COVID-19), owing to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, subsequent reports indicated the significant burden of the

disease secondary to the huge number of the reported cases and the wide variety of the associated complications.^{1–3} Accordingly, the disease was marked as a pandemic by the World Health Organization, and different measures were declared to reduce the severity of the condition. Although many approaches have been

Abbreviations: AIS, acute ischaemic stroke; CI, confidence intervals; COVID-19, Coronavirus Disease 2019; DIC, disseminated intravascular coagulopathy; ICTRP, International Clinical Trials Registry Platform; ISI, Web of Science; IV-tPA, intravenous tissue plasminogen activator; LVO, large vessel occlusion; mRCT, metaRegister of Controlled Trials; mRS (0–2), Modified Rankin Score; MT, mechanical thrombectomy; NIHSS, National Institute of Health Stroke Scale; NYAM, New York Academy of Medicine; ORs, odds ratios; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; sICH, symptomatic intracranial haemorrhage; TIC1, thrombolysis in cerebral infarction; VHL, Virtual Health Library; WHO, World Health Organisation.

reported, including the development of the reportedly efficacious vaccines, many cases and associated complications are still being reported.⁴⁻⁶

Among settings with high-in-hospital mortality rates, the prevalence of acute ischaemic stroke (AIS) among COVID-19 patients ranged between 1% and 2.5%.⁷⁻⁹ It should be noted that among these cases, most cases are usually attributed to large vessel occlusion.¹⁰ The quality of care of stroke patients is also essential when estimating the burden of COVID-19 in these settings as the disease has reduced the frequency of admissions and urgency of management of mild and severe stroke cases, respectively.¹¹⁻¹³ The association between SARS-CoV-2 infection and the development of stroke is not adequately understood. However, some authors reported that the induction of stroke secondary to COVID-19 might be evidenced by the presence of endothelial cell dysfunction and antiphospholipid antibodies.^{14,15} Moreover, a histological analysis of the cerebral thrombi of stroke patients with and without COVID-19 indicated the role of neutrophils in the pathogenesis of the cerebral thrombi of stroke with concomitant COVID-19 infection, as an increase of the neutrophils count was found in the COVID-19 group rather than the non-COVID-19 group.¹⁶ The same findings were demonstrated by Desilles et al, where the thrombi of COVID-19 patients had a high number of neutrophils in addition to neutrophil extracellular traps; however the efficacy of thrombolysis was similar in the thrombi of the stroke patients with or without COVID-19 infection.¹⁷

Mortality rates and worsened functional outcomes have been more significantly associated with AIS in COVID-19 patients.^{9,18} Besides, reports showed that a pre-existing stroke increases the severity and worsens the outcomes of COVID-19.¹⁹ Accordingly, prompt management is critical in managing these patients. Furthermore, reports show that many modifications have been introduced to the management protocols of stroke in the COVID-19 pandemic. However, it is still unclear whether these modifications impact the treatment outcomes. In this context, different studies investigated the effect of managing stroke with mechanical thrombectomy (MT) during COVID-19 settings with conflicting findings.^{9,20-27}

Accordingly, we aimed to conduct the current meta-analysis to provide better insight into the efficacy of MT in managing COVID-19 patients suffering from a stroke. We believe that the intended outcomes can enhance the quality of evidence and might help physicians and healthcare authorities decide whether the current management protocols are effective or further efforts are needed to enhance the outcomes and reduce the mortality rates among affected patients.

2 | METHOD

2.1 | Definition of outcomes

The main outcome of this study was to study the outcomes of MT in managing stroke in COVID-19 patients. Individual outcomes included the rates of patients that had thrombolysis in cerebral infarction (TICI) score $\geq 2b$, the rates of Modified Rankin Score (0-2) or

functional independence, the rates of symptomatic intracranial haemorrhage (sICH), the rates of parenchymal haematoma type 1 and type 2, and the rates of mortality. These outcomes were extracted for both COVID-19 and non-COVID-19 (if reported) patients. Therefore, we aimed to collect the relevant studies in the literature to conduct our meta-analysis.

2.2 | Search strategy

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for conducting the steps of this systematic review.²⁸ The first step was conducted according to a search strategy through the different databases in 18 December 2021, including PubMed, Web of Science (ISI), [Clinicaltrials.gov](https://www.clinicaltrials.gov), Google Scholar, Virtual Health Library, International Clinical Trials Registry Platform-, Grey Literature database by the New York Academy of Medicine, and metaRegister of Controlled Trials (mRCT). This has been done through developing a comprehensive search term based on the requirements of the search strategy per each database. For example, the used search term for PubMed was (COVID-19 odds ratio (OR) "COVID 19" OR "novel coronavirus" OR "SARS-CoV-2") AND (stroke) AND (thrombectomy OR "endovascular therapy"). We furtherly conducted a manual search of the references of the included studies and the relevant reviews to find any potentially missed articles during the electronic search strategy.

2.3 | Criteria of inclusion

Based on our intended outcomes, we decided to include studies that: 1) were original with no limitations regarding study design or sample size, 2) included patients with COVID-19 and concomitant stroke, 3) investigated the outcomes of stroke after the application of MT therapy, and 4) included human subjects only. On the other hand, we decided to exclude studies that 1) were non-original (including reviews, abstract-only articles, thesis, commentary, editorials, and protocols), 2) included patients with stroke only or with COVID-19 only, 3) did not study the efficacy of MT therapy on stroke outcomes in COVID-19 patients, 4) were non-English studies, and 5) did not include human data. We also excluded studies containing overlapping data and outcomes or cases when there are no available full-texts. However, we included all studies that included patients with stroke and COVID-19 that were treated with MT, regardless of being compared with non-COVID-19 patients or not.

2.4 | Screening and data extraction

At least two independent reviewers took part in this step. After the search strategy, we first screened all the imported items from the relevant databases. The endnote programme excluded all potential duplicates among the different imported results of the relevant

databases mentioned above. Next, we conducted title/abstract and full-text screening to simplify the screening process and avoid missing relevant articles based on our inclusion and exclusion criteria. Finally, we designed an extraction sheet based on the outcomes of this study. It included three parts, including a part for baseline characteristics and study population, one for the included outcomes, and another for the items of the quality assessment tool. The part for baseline characteristics included the ID of each article after the screening, the first author's last name, publication year, study design, sample size, the approach of COVID-19 diagnosis, age, gender, associated comorbidities, the rate of patients that administered intravenous thrombolysis and intravenous tissue plasminogen activator (IV-tPA) therapies and other outcomes as we previously emphasised. A discussion was conducted among members whenever a disagreement on any of these steps was present to make the best conclusion.

2.5 | Quality assessment

This constituted the third part of the extraction sheet and was consistent with the items of the National Institute of Health tool for quality assessment of cohort studies. The tool consisted of 14 items (resembling 14 questions) (Table S1). Each of these items was given a one or 0 score, and the cumulative score resembled the summation of the total scores for each included investigation. All articles were rated based on their total scores. This step was also conducted by at least two reviewers with a public discussion whenever there was a disagreement.

2.6 | Statistical analysis

All data were analysed using Comprehensive meta-analysis software version 3. we calculated pooled prevalence rates and ORs, with their corresponding 95% confidence intervals. Heterogeneity was assessed using Q statistics and the I^2 test, where $I^2 > 50\%$ or p -value < 0.05 were considered significant, and a random model was adopted.²⁹ Publication bias (Egger's regression test) and meta-regression were not possible due to the small number of the included studies (< 10).

3 | RESULTS

3.1 | Study selection and characteristics

Database search resulted in 648 records after removing 247 duplicates. After performing title and abstract and full-text screening, we included seven articles together with another two articles after manual search trials (Figure 1).^{9,20-27}

We included eight retrospective cohort studies and one prospective cohort study with a total sample size of 309 COVID 19 patients (Table 1). COVID 19 was diagnosed by polymerase chain

reaction (PCR) in five studies, PCR, symptoms, and chest CT in one study and not reported in three studies. Regarding the quality of the included papers, all studies were considered fair quality with a score ranging from (10–11) points (Table S1).

3.2 | Thrombolysis in cerebral infarction $\geq 2b$

Seven studies reported a TICI $\geq 2b$ score in stroke patients with COVID-19 who underwent MT. The prevalence of patients that attained TICI $\geq 2b$ was 79% (95%CI: 73–85) (Figure 2a). No heterogeneity was detected ($p = 0.13$, $I^2 = 38$). On further comparison of MT procedure between stroke patients with COVID 19 to those without COVID-19, we found no significant difference in terms of TICI $\geq 2b$ score (OR: 0.85; 95%CI: 0.03–23; $p = 0.9$) (Figure 2b). Significant heterogeneity was observed; therefore random effect model was adopted ($p = 0.05$, $I^2 = 77$).

3.3 | sICH

The prevalence of sICH in stroke patients with COVID-19 that received MT was 6% 95%CI: 3–11) (Figure 3), without any source of heterogeneity ($p = 0.49$, $I^2 = 0$).

3.4 | Mortality

Mortality was reported in 9 studies. The prevalence of mortality in COVID-19 patients with stroke treated with MT was 29% (95%CI: 24–35) (Figure 4a). Heterogeneity was not observed ($p = 0.7$, $I^2 = 0$). Stroke patients with COVID-19 had a significantly higher mortality rate than stroke patients without COVID-19 after MT procedure (OR: 2.99; 95%CI: 2.01–4.45; $p < 0.001$) (Figure 4b). We used the fixed-effect model due to the absence of heterogeneity ($p = 0.75$, $I^2 = 0$).

3.5 | Functional independence

Only one study reported functional independence in stroke patients with COVID-19. The prevalence of functional independence after MT was higher in stroke patients without COVID-19 rather than those with COVID-19 (29.7% vs. 16.7%); however, the comparison did not yield statistical significance ($p = 0.5$).²¹

3.6 | Parenchymal haematoma

The prevalence of parenchymal haematoma type 1 in stroke patients with COVID-19 who were treated with MT was 11.1% (95%CI: 5–23) using the fixed-effect model ($p = 0.67$, $I^2 = 0$) (Figure 5). Moreover, only one study reported parenchymal haemorrhage type 2 with a prevalence of 0% in stroke patients with COVID-19.²⁴

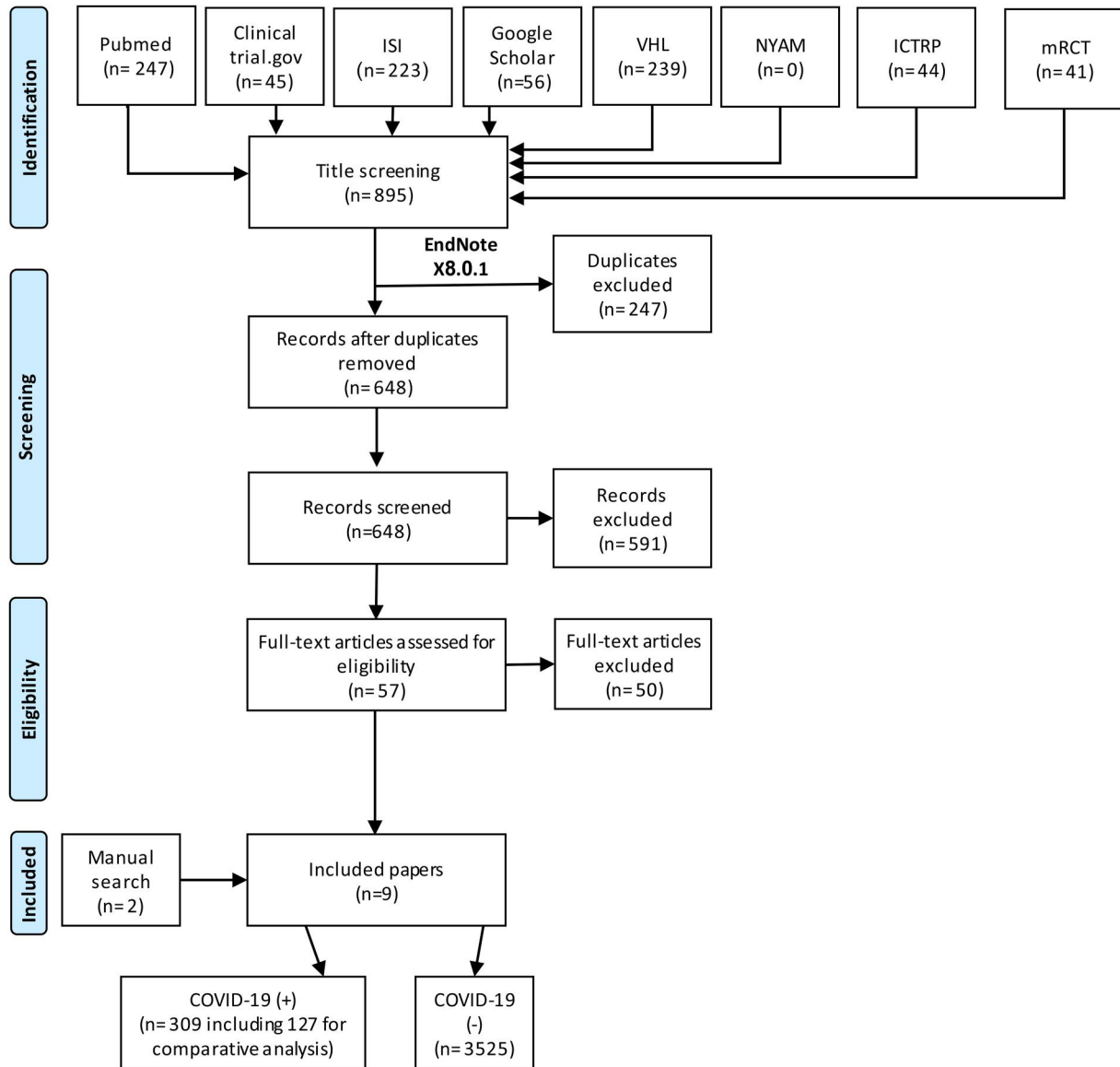


FIGURE 1 PRISMA flow diagram of the study process

4 | DISCUSSION

The main outcome of the current study was to investigate the outcomes of COVID-19 patients with stroke events after being treated with MT. Overall, our findings indicate that MT therapy can significantly enhance the outcomes of COVID-19 patients with stroke. For instance, it has been shown that the prevalence of patients that attained $\text{TICI} \geq 2b$ was 79%. No significant difference was observed between COVID-19 and non-COVID-19 patients. Moreover, although the rate of functional independence was higher among non-COVID-19 than COVID-19 patients treated with MT, no significant difference was detected between the two groups. We found a higher mortality rate in the COVID-19 group compared to the non-COVID-19 group. Finally, only 11.1% had parenchymal haematoma, and 0% had parenchymal haemorrhage type 2. Different studies in the literature reported that COVID-19 significantly worsens the

outcomes of patients suffering from stroke and other diseases.^{10,18,30-32} This can explain the remarkable benefits of MT therapy for COVID-19 patients because of the high rate of complications usually reported with these patients, which might worsen their outcomes.

In a large scale meta-analysis that included 33 studies with more than 55 thousands COVID-19 patients, the stroke incidence in patients with COVID-19 was 1.7% which was more common in males with a median age of patients 66.5 years. Approximately, two thirds of stroke patients with COVID-19 will need intensive care unit admission while one third will develop mortality outcome.³³

Despite having similar $\text{TICI} \geq 2b$ outcomes in our study, the mortality rate was higher after MT procedure in the stroke group with COVID-19 rather than the stroke group without COVID-19. Such high mortality can be explained by numerous causes. To our knowledge, a high National Institute of Health Stroke Scale (NIHSS) at admission is

TABLE 1 Characteristics of the included studies

Author/year published/ country of patients	Compared groups	Study design	Sample size	Age (mean (SD))	Gender (male)	Diagnostic method
Requena-2020-Spain	COVID 19 (+)	Retrospective cohort	10	70.8 (14.8)	6	PCR
	COVID 19 (-)		19	71 (15.9)	11	PCR
Al Kasab-2021-multicenter	COVID 19 (+)	Prospective cohort	13	58*	8	NR
	COVID 19 (-)		445	72*	240	NR
Havenon-2020-USA	COVID 19 (+)	Retrospective cohort	104	18->75#	71	NR
	COVID 19 (-)		3061		1571	NR
Sweid-2020-USA	COVID 19 (+)	Retrospective cohort	16	NR	NR	NR
Pop-2020-France	COVID 19 (+)	Retrospective cohort	13	78*	5	PCR, symptoms and chest CT
Khandelwal-2021-multicenter	COVID 19 (+)	Retrospective cohort	42	54*		NR
Yaghi-2020-USA	COVID 19 (+)	Retrospective cohort	6	55		PCR
Cagnazzo-2020-multicenter	COVID 19 (+)	Retrospective cohort	93	71*	63	PCR
Escalard-2020-Paris	COVID 19 (+)	Retrospective cohort	12	60.1 (12.6)	10	PCR

Note: *median, # range, PCR: polymerase chain reaction, CT: computed tomography, NR: not reported.

associated with adverse stroke outcomes including mortality.³⁴ In two of the three studies included in the mortality outcome, the stroke patients with COVID-19 had a higher admission NIHSS compared to the stroke patients without COVID-19.^{20,21} Moreover, comorbidities play a substantial role in the survival of COVID-19 patients.³⁵ In our study, we could not rule out the role of comorbidities in the prognosis of stroke patients with COVID-19 as certain comorbidities were higher in the stroke patients with COVID-19 rather than their peers without COVID-19 (Table 2).^{20,21} In addition, a higher proportion of the stroke patients without COVID-19 received additional stroke treatment to thrombectomy such as IV-tPA which is associated with favourable outcomes in stroke patients (Table 2).^{20,21,36} Moreover, only one study described the MT procedure duration between stroke patients with or without COVID-19 which did not differ between the two groups ($p = 0.45$). However, the stroke patients with COVID-19 had a clinical but not a statistically significant mortality rate than the stroke patients without COVID-19 (33% vs. 24%; $p = 0.5$).²¹ Furthermore, various investigations indicate that COVID-19 severity is associated with many factors, including comorbidities and quality of care provided for these patients.^{37,38} Finally, the diagnosis and interventions for COVID-19 patients are usually delayed because of the high rates of respiratory diseases and associated intubation and sedation.³⁹

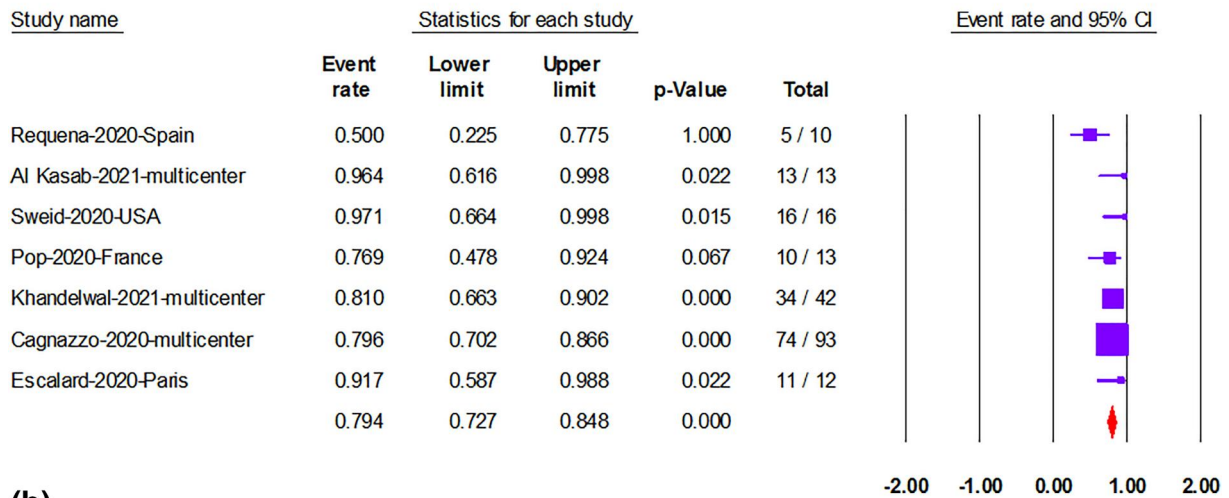
Our analysis indicated that 6% of COVID-19 group with stroke that underwent MT had sICH. We did not find any current studies that compared this rate and patients without COVID-19. The rate of sICH among stroke patients is remarkably variable among the different studies in the literature. This is usually attributed to the variable criteria defining sICH and the design of these studies. For instance, a previous systematic review reported that the incidence of sICH following intravenous thrombolysis was 5.6%, and the rates

were higher among randomized controlled trials.⁴⁰ Evidence indicated that comorbidities such as diabetes mellitus and medication use are all significant risk factors for sICH in stroke patients,⁴¹⁻⁴³ which might also explain the rate of sICH in our COVID-19 population since most severe cases of COVID-19 usually have similar characteristics.

Vascular occlusive events should be highly suspected in COVID-19 patients to adequately establish an early diagnosis and apply proper management interventions, which might be the most vital step in managing COVID-19 patients with stroke. Due to COVID-19, evidence indicated that disseminated intravascular coagulopathy (DIC) is usually observed in critically-ill patients.⁴⁴ Although detecting inflammatory markers might represent a good investigation for detecting these events, it has been reported that these do not establish an adequate diagnosis of DIC in the current population.⁴⁵ In this context, it is still controversial whether COVID-19 increases the incidence of stroke by inducing a generalised hypercoagulable state or by weakening the intima of arterial walls and increasing the risk of dissection.⁴⁶ Accordingly, understanding the mechanism of such events can direct clinicians to conduct proper diagnostic and therapeutic approaches to early manage these patients.

The present study represents cumulative evidence from all the potentially related data in the current literature regarding the efficacy of MT therapy in COVID-19 patients with stroke. However, the current study has many limitations. Firstly, only one of the included studies is prospective, and some studies did not report the method of COVID-19 diagnosis. Secondly, the number of included studies and sample size in some studies is very small and is not adequate to establish a good evidence regarding the effect of MT on stroke outcomes in COVID-19 patients. Thirdly, not all studies compared patients with COVID-19 and others without COVID-19, and the

(a)



(b)

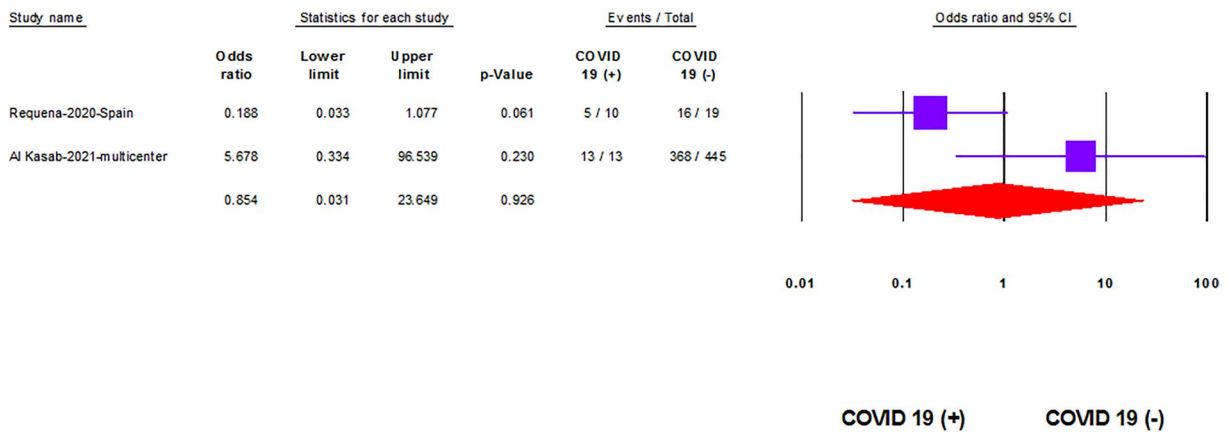


FIGURE 2 (a) The prevalence of stroke patients with COVID-19 who attained thrombolysis in cerebral infarction (TICI) $\geq 2b$ represented with the event rate % and 95% confidence interval (95%CI). (b) The association of stroke patients with COVID-19 and TICI $\geq 2b$ represented with the odds ratio (OR) and 95% confidence interval (95%CI)

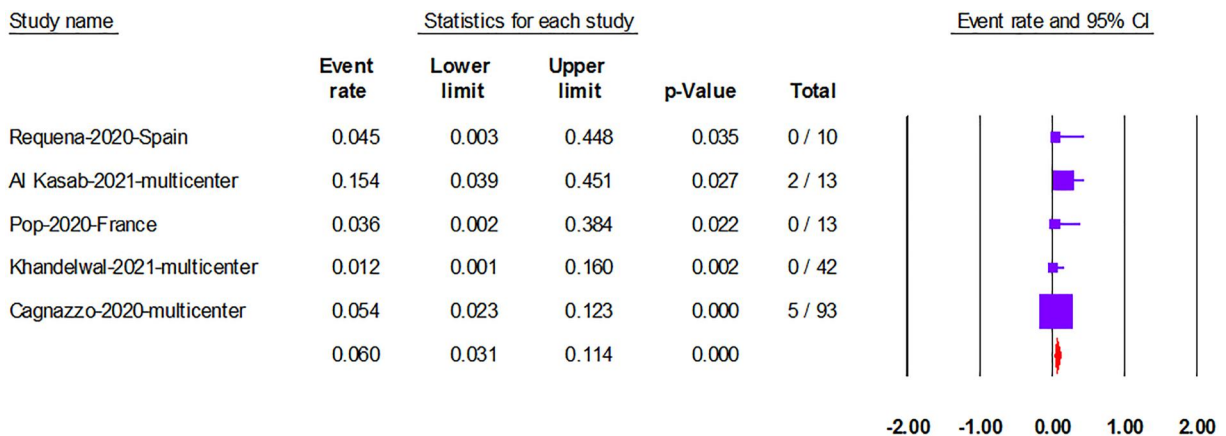
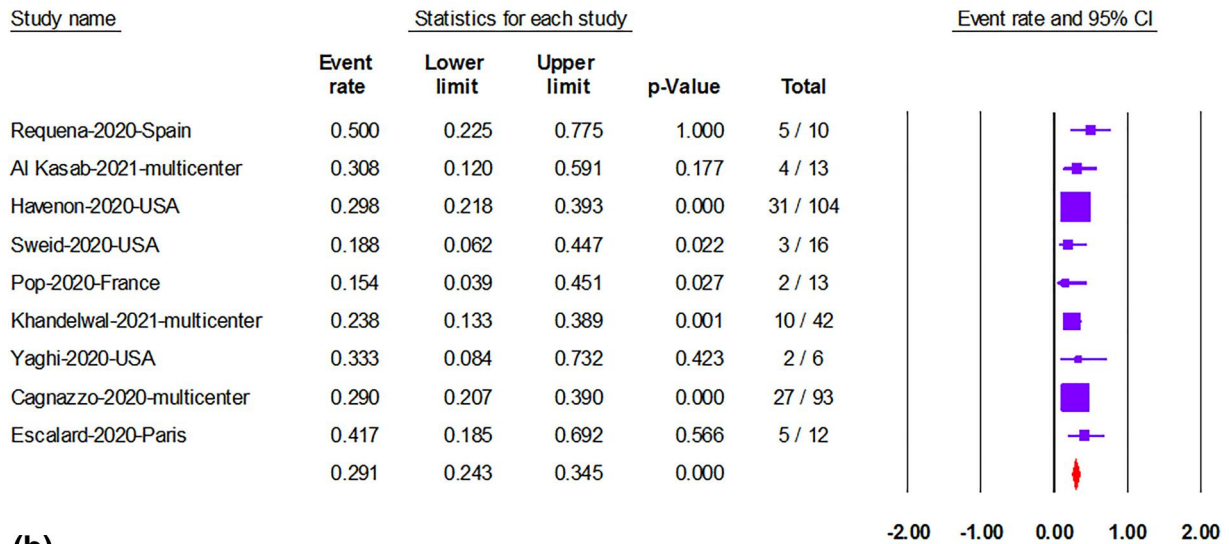


FIGURE 3 The prevalence of sICH in stroke patients with COVID-19 represented with the event rate % and 95% confidence interval (95%CI)

(a)



(b)

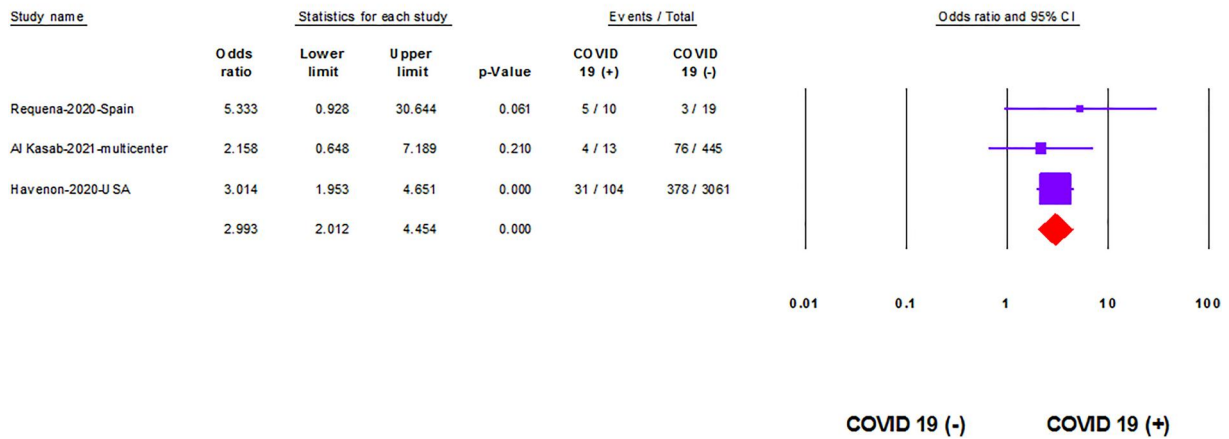


FIGURE 4 (a) The prevalence of mortality in stroke patients with COVID-19 represented with the event rate % and 95% confidence interval (95%CI). (b) The association of stroke patients with COVID-19 and mortality represented with the odds ratio (OR) and 95% confidence interval (95%CI)

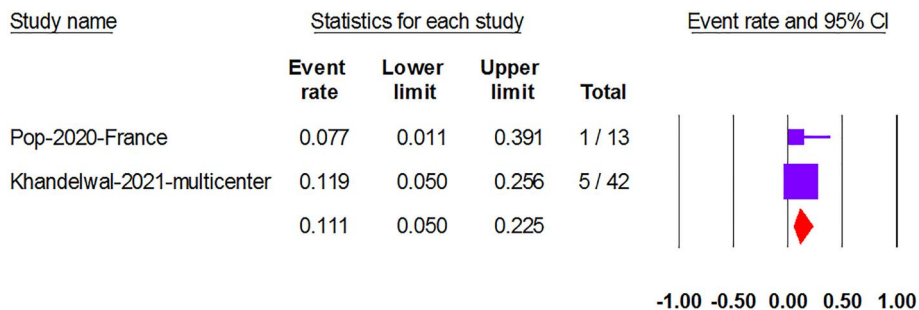


FIGURE 5 The prevalence parenchymal haemorrhage of stroke patients with COVID-19 represented with the event rate % and 95% confidence interval (95%CI)

randomisation of patients was not approached (based on the potential impact of several variables on the outcomes and efficacy of interventions). Fourthly, all the studies who compared stroke patients with or without COVID-19 did not adjust mortality outcome

for potential confounders such as comorbidities, age, sex and NIHSS at admission. Fifthly, more studies are needed to describe the difference between stroke patients with or without COVID-19 in terms of symptoms to recanalisation onset, procedural duration and door to

TABLE 2 Comorbid risk factors and additional treatment to thrombectomy

Author/year published/country of patients	Compared groups	Hypertension (%)	Diabetes mellitus (%)	Atrial fibrillation (%)	Hyperlipedemia/hypercholesterolaemia (%)	Smoker (%)	IV thrombolysis (%)	IV-tPA (%)	NIHSS (Median)
Requena-2020-Spain	COVID 19 (+)	60	40	20	50	30	-	10	18
	COVID 19 (-)	53	21	21	37	32	-	26	17
Al Kasab-2021-multicenter	COVID 19 (+)	-	-	-	-	-	-	31	19
	COVID 19 (-)	-	-	-	-	-	-	40	15
Havenon-2020-USA	COVID 19 (+)	71	47	29	56	-	-	-	-
	COVID 19 (-)	76	34	43	64	-	-	-	-
Sweid-2020-USA	COVID 19 (+)	-	-	-	-	-	-	-	-
Pop-2020-France	COVID 19 (+)	62	15	-	23	23	31	-	13
Khandelwal-2021-multicenter	COVID 19 (+)	-	-	-	-	-	-	-	-
Yaghi-2020-USA	COVID 19 (+)	100	33.3	33.3	50	-	83	67	-
Cagnazzo-2020-multicenter	COVID 19 (+)	67	22	-	30	23	39	-	17
Escalard-2020-Paris	COVID 19 (+)	42	42	8	25	0	67	-	19

Note: IV-tPA = intravenous tissue plasminogen activator, - = not reported, NIHSS: National Institutes of Health Stroke Scale.

recanalisation time which can significantly influence the MT outcomes. Sixthly, some stroke patients with or without COVID-19 who were treated with MT, had received additional stroke treatment including tPA which can influence the pooled results. Therefore, more studies are needed to assess the most appropriate treatment for the stroke patients with COVID-19 regarding MT alone, in combination with medical therapy or the medical therapy alone. Finally, due to the limited number of the included studies (less than 10 studies), meta-regression for the detection of the potential confounders of our pooled results was not feasible. Accordingly, further studies with proper sampling and randomisation of patients (considering their demographics, the presence of co-morbidities, quality of care, and applied interventions) are encouraged.

5 | CONCLUSION

Stroke patients with COVID-19 can be safely and effectively treated with MT, with comparable reperfusion and complication rates to those without the disease. The increased mortality among COVID-19 patients does not seem to be procedure-related and further investigation is needed in this regard.

AUTHOR CONTRIBUTION

Amr Ehab El-Qushayri was responsible for the idea and the study design. All authors shared in screening, extraction, and writing of the full text. Sherief Ghozy supervised all steps, and all authors approved the final version before submission.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: El-Qushayri AE, Reda A, Dahy A, Azzam AY, Ghozy S. The impact of COVID 19 on the outcomes of thrombectomy in stroke patients: a systematic review and meta-analysis. *Rev Med Virol*. 2022:e2379. <https://doi.org/10.1002/rmv.2379>