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Systematic review and meta-analysis of current rates of First Pass Effect by thrombectomy technique and associations with clinical outcomes

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Abstract

Background: First pass effect (FPE) in mechanical thrombectomy is thought to be associated with good clinical outcomes. We performed this study to determine FPE rates as a function of thrombectomy technique and to compare clinical outcomes between patients with and without FPE.

Methods: In July 2020, a literature search on FPE (defined as mTICI2c-3 after single pass) and modified FPE (mFPE, defined as TICI2b-3 after single pass) and mechanical thrombectomy for stroke was performed. Using random-effects meta-analysis, we evaluated following outcomes for both FPE and mFPE: overall rates, rates by thrombectomy technique, rates of good neurologic outcome (modified Rankin Scale (mRS) ≥ 2 at day 90), mortality, and sICH rate.

Results: Sixty seven studies comprising 16,870 patients were included. Overall rates of FPE and mFPE were 28% and 45% respectively. Thrombectomy techniques shared a similar FPE ($p=.17$) and mFPE ($p=.20$) rates. Higher odds of good neurologic outcome were found when we compared FPE with non-FPE (56% vs 41%, OR 1.78) and mFPE with non-mFPE (57% vs 44%, OR 1.73). FPE had lower mortality rate (17% vs 25%, OR 0.62) than non-FPE. FPE and mFPE were not associated with lower sICH rate compared to non-FPE and non-mFPE (4% vs 18%, OR 0.41 for FPE; 5% vs 7%, OR 0.98 for mFPE).

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Conclusions: Our findings suggest that approximately one-third of patients achieve FPE and around half of patients achieve mFPE, with equivalent results throughout thrombectomy techniques. FPE and mFPE are associated with better clinical outcomes.

Keywords

First pass effect; modified first pass effect; thrombectomy; stroke; modified Rankin Scale

Introduction:

With mechanical thrombectomy (MT) becoming the standard of care for patients suffering from stroke due to large vessel occlusion (LVO), optimizing MT techniques to achieve better clinical outcomes has become increasingly important over the last couple of years. Previous studies have demonstrated the importance of minimizing delays to endovascular treatment and keeping thrombectomy procedural times less than 60 minutes (1). A shorter time to revascularization has been linked with better outcomes (2). Additionally, the number of passes to achieve successful angiographic outcomes has been suggested to affect clinical outcomes (3). Notably, first pass effect (FPE), first introduced by Zaidat, et al. and defined as complete revascularization of large vessel occlusion (mTICI 3) in a single thrombectomy pass, has been shown to be associated with better clinical outcomes compared to non-FPE (4). The impact of FPE on outcomes, as well as rates of FPE by thrombectomy device, is gaining widespread attention. FPE has become key index in evaluating the efficacy of new generation of devices in thrombectomy. Many studies have reported FPE is associated with better neurological outcome (mRS score 0–2 at 90 days) and lower mortality rate (5–7). We performed a systematic review and meta-analysis of studies providing data on FPE to assess overall rates and rates by type of thrombectomy technique, as well as to correlate clinical outcomes with presence or absence of FPE or mFPE.

Methods

Literature search and study selection

This study is reported in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines. We performed a comprehensive literature search through July 2020. Several databases including PubMed, Ovid MEDLINE, and Ovid EMBASE were used to identify relevant articles. Keywords including first pass efficiency, first pass success, first pass revascularization, first pass recanalization, first pass effect, single pass success, first pass attempt, TICI-2b, TICI-2c, TICI-3, acute ischemic stroke, large vessel occlusion, thrombectomy were used in both ‘AND’ and ‘OR’ combinations. Identified studies were then further evaluated for inclusion in the meta-analysis. We searched the reference lists of included articles for additional papers. Inclusion criteria for studies in the analysis were the following: 1) acute ischemic stroke (AIS) patients with large vessel occlusion defined as occlusion of middle and anterior cerebral arteries, the vertebral, basilar and carotid terminus, as determined by MR angiography or, CT angiography, 2) retrospective or prospective articles or conference abstracts with at least ten patients, and 3) published in English. Exclusion criteria were the following: 1) studies

with <10 patients, 2) animal/In-vitro studies only, and 3) case reports, letters, editorial comments, or review articles.

Two investigators independently reviewed the initial search results and selected relevant articles based on title and abstract for detailed review. In a case of duplication or overlapping study population (studies published on the same registry), studies with the largest patients' population or the most amount of data relevant to our outcome were selected. The process of database search, study selection, data extraction, and final inclusion were reviewed in consensus with two investigators and was overseen by a board-certified interventional neuroradiologist.

Outcome variables

For the purpose of current study, we calculated the overall rate of FPE and mFPE (defined as achieving TIC1 2b or greater after a single pass of device) and then correlated rates of FPE and mFPE with the type of thrombectomy technique (aspiration, stent-retriever, combination). We compared rates of clinical outcomes between FPE/non-FPE, mFPE/non-mFPE, FPE/ recanalized non-FPE, and mFPE/ recanalized non-mFPE. Recanalized non-FPE was defined as achieving mTICI 2c or higher on multiple passes and recanalized non-mFPE was considered as mTICI 2b or higher on multiple device passes. The clinical outcomes we evaluated in this study were the good neurologic outcome, defined as an mRS of ≤ 2 at 90 days following MT, mortality rate, and symptomatic intracerebral hemorrhage (sICH) rate.

Statistical analysis

Meta-analysis results were expressed as Odds Ratio (OR) for clinical outcomes and the rate for continuous outcomes with respective 95% Confidence Intervals (CIs). Random-effects meta-analysis was used for pooling across studies (8). The I^2 statistic was used to express the proportion of heterogeneity that is not attributable to chance (9). We explored the impact of publication bias by constructing funnel plots and checking for symmetry. Egger's regression test was also used to evaluate publication bias. Meta-analysis was conducted using STATA version 14 (Stata Corp LP, College Station TX, USA).

Results

Literature search

A total of 151 articles were identified. After removing duplications, 87 were excluded based on abstract, title and full-text article assessment. A total of 67 articles reporting 16,870 patients were included for meta-analysis (Supplementary Table 1). A study selection flow diagram is provided in Figure 1.

All patients in the included studies were treated with direct aspiration, stent-retriever, or combination of stent-retriever/aspiration techniques. Twenty-six studies comprising 3708 patients were treated with aspiration alone (7, 10–34), while 34 studies including 6669 patients were stent-retriever technique alone (3–5, 7, 12, 15, 16, 18, 19, 22, 26–28, 30, 31, 35–53). Eight studies reported using combination of stent-retriever/aspiration for a total of 545 patients (12, 15, 18, 26, 31, 54–56). Eleven studies consisting of 5948 patients did not

specify the technique that was used (6, 49, 57–63). Twenty-three studies which included 7299 patients provided direct comparative data between FPE and non-FPE (3–5, 7, 11, 16, 19, 26, 29, 33, 45, 53, 55, 59–68). Twelve studies provided additional data on mortality rate and complications (4, 7, 11, 16, 19, 50, 60–63, 65, 67, 68). Most studies were assessed as having a moderate risk of bias based on their non-randomized design. No studies were excluded for the high-risk of bias.

FPE Rate

As summarized in Figure 2 and Table 1, among 67 studies that reported mFPE and FPE rates, the overall rate was 28% (2440/ 9082) for FPE and 47% (5351/11689) for mFPE. FPE rate for aspiration, stent retriever, and combination technique was 29% (516/2147), 34% (1038/3312), and 26% (58/229) respectively. No statistically significant difference was noted when comparing FPE rate by thrombectomy techniques ($p=.17$). mFPE rates were 48% (1653/3191) for aspiration, 48% (2211/4584) for stent retriever, and 58% (193/333) for combination technique. mFPE rate was not significantly different across thrombectomy techniques ($p=.22$, Supplementary Table 1).

Clinical outcomes

Comparison of mFPE vs non-mFPE and FPE vs non-FPE—Findings are presented in Table 2. The rate of mRS 0–2 at 90 days was 56% (431/774) for FPE group compared with 41% (933/2285) for the non-FPE group (OR 1.78, 95% CI 1.50 to 2.11, $p<0.01$). Patients with mFPE had higher rate of mRS 0–2 at 90 days compared with non-mFPE patients (339 / 591 [57%] vs 402/ 91 [44%], OR 1.73, 95% CI 1.44 to 2.1, $p<0.01$; Figure 3). Compared to non-FPE group, patients with FPE had significantly lower mortality (129/771 [17%] vs 610/2457[25%] OR 0.62, 95% CI 0.50 to 0.76, $p<0.01$). sICH rate was not different between FPE and non-FPE group (28/651 [4%] vs 389/2118 [18%] 0.41 (0.09–1.93), OR 0.41, 95% CI 0.09 to 1.93, $p= .26$). The rate of mortality was (16%) 40/244 in the mFPE group and (21%) 132/634 for the non-mFPE group (OR 0.98, 95% CI 0.66 to 1.49, $p= .96$) and the rate of sICH was 5% (13/245) (5%) vs 0.98(0.51 -1.88)for the mFPE group and 7% (47/670) for the non-mFPE group (OR 0.98, 95% CI 0.51 to 1.88, $p= .95$; Figure 4). (Supplementary Tables 2–4).

Comparison of mFPE vs recanalized non-mFPE and FPE vs recanalized non-FPE—Patients with FPE had higher rate of mRS 0–2 at 90 days compared with recanalized non-FPE (323/524 [61%] vs 369/714 [51%], OR 1.75, 95% CI 1.37 to 2.25, $p<0.01$). The rate of mRS 0–2 at 90 days was 53% (387/734) for mFPE group compared with 42% (389/916) for the recanalized non-mFPE group (OR 1.6, 95% CI 1.31 to 1.96, $p<0.01$; supplementary Figure 1). The rate of sICH was 3.9% (9/233) in the FPE group and 3.8% (15/391) for the recanalized non-FPE group (OR 1.1, 95% CI 0.46 to 2.62, $p= .82$) and the rate of mortality was 11% (68/577) for the FPE group and 15% (105/681) for the recanalized non-FPE group (OR 0.53, 95% CI 0.37 to 0.75, $p<0.01$). sICH rate was not different between mFPE and the recanalized non-mFPE group (16/256 [6%] vs 25/316 [8%], OR 0.81, 95% CI 0.42 to 1.56, $p= .54$). Compared to recanalized non-mFPE group, patients with mFPE had significantly lower mortality (121/1043 [11%] vs 223/1331 [16%], OR 0.55, 95% CI 0.38 to 0.79, $p<0.01$; ; supplementary Figure 2) (Supplementary Tables 5–7).

Heterogeneity and publication bias

The I^2 values were higher than 80% for FPE and mFPE rates, suggesting high heterogeneity. The I^2 values were 0% for mRS(0–2) at 90 days indicating low heterogeneity (Table 2). The P-values for publication bias using Egger’s regression were higher than 0.05 for FPE rate, mFPE rate, and clinical outcomes, suggesting no bias.

Discussion

Our meta-analysis demonstrated a number of clinically relevant findings. First, as the literature stands, FPE and mFPE are achieved in only about one third and one-half of patients respectively. Notably, rates of both FPE and mFPE are fairly similar across thrombectomy techniques. Second, regarding clinical outcomes, patients in whom FPE or mFPE was achieved had statistically significant and clinically relevant improvements in the neurologic outcome as compared to those in whom these angiographic outcomes were not achieved. Also, the mortality rate was lower in the FPE group compared to the non-FPE group. Taken together, results of the current meta-analysis indicate that there is substantial room for improvement in the efficacy of all types of thrombectomy techniques with regard to FPE rate. Increasing the likelihood of successful revascularization on the first through development of new MT technique or newer devices would result in better outcomes for patients as FPE is associated with better clinical outcome.

Numerous, previous studies have focused on FPE (3–5, 7, 11, 16, 19, 26, 29, 33, 45, 55, 59–66). In general, rates of FPE and mFPE ranged from 13% to 85%, and 19% to 97% respectively. Furthermore, rates of FPE were noted to influence rates of good neurologic outcome. Zaidat, et al. (4), who introduced FPE as a key metric for the angiographic outcome, reported an FPE rate of 25% for 354 patients who were treated with stent-retriever (Solitaire FR) and they also showed that FPE is a predictor of good neurologic outcome (mRS score ≥ 2 at 30 days). In another study by Haussen, et al. authors noted a rate of 59% for mFPE (36). Also, in two studies in 2019, greater odds of achieving mRS 0–2 at 90 days were reported for both mFPE and FPE (11, 62). Our results provide clarity regarding the contemporary rates of FPE and mFPE, as well as confirm the strong relationship between FPE and good neurological outcome.

Conversely, results regarding the association of mortality and sICH rate with FPE and mFPE are inconsistent in the literature. In one study by Kang, et al., FPE was associated with higher odds of sICH (65) while five other articles reported lower odds of sICH (4, 7, 16, 60, 62). For mortality rate, only one article showed no correlation of mFPE with mortality rate, (4) whereas other articles mentioned positive correlation with either mFPE or FPE (4, 7, 11, 16, 19, 60–62). Our current study confirmed a lower mortality rate with FPE but not with mFPE, as well as the association between FPE and a reduction in the ‘other complications’ category.

Our study has limitations that need to be taken into consideration when interpreting our findings. First, we did not include assessments of other potential factors that might impact rates of FPE, including Symptom onset to reperfusion, location of occlusion, the size of aspiration catheter lumen(69), adjunctive devices such as balloon guiding catheters, imaging

characteristics such as baseline ASPECTS (67), clot perviousness (22), better collateral grade (70), and clot surface phenotypic (19). Further understanding of factors associated with FPE may influence choice of thrombectomy device and technique. Included studies in our meta-analysis may suffer from biases such as ascertainment bias due to not having core laboratory angiographic outcome adjustment or selection bias due to the retrospective nature of some studies and heterogeneous stroke population.

Conclusion

Our systematic review and meta-analysis demonstrated that patients with FPE or mFPE have better clinical outcomes compared with non-FPE or non-mFPE patients. Additionally, FPE rate is approximately thirty percent overall, and based on the current data available in the literature, existing endovascular techniques (aspiration, stent retriever, and combination) appear closely efficient in achieving successful revascularization on the first pass.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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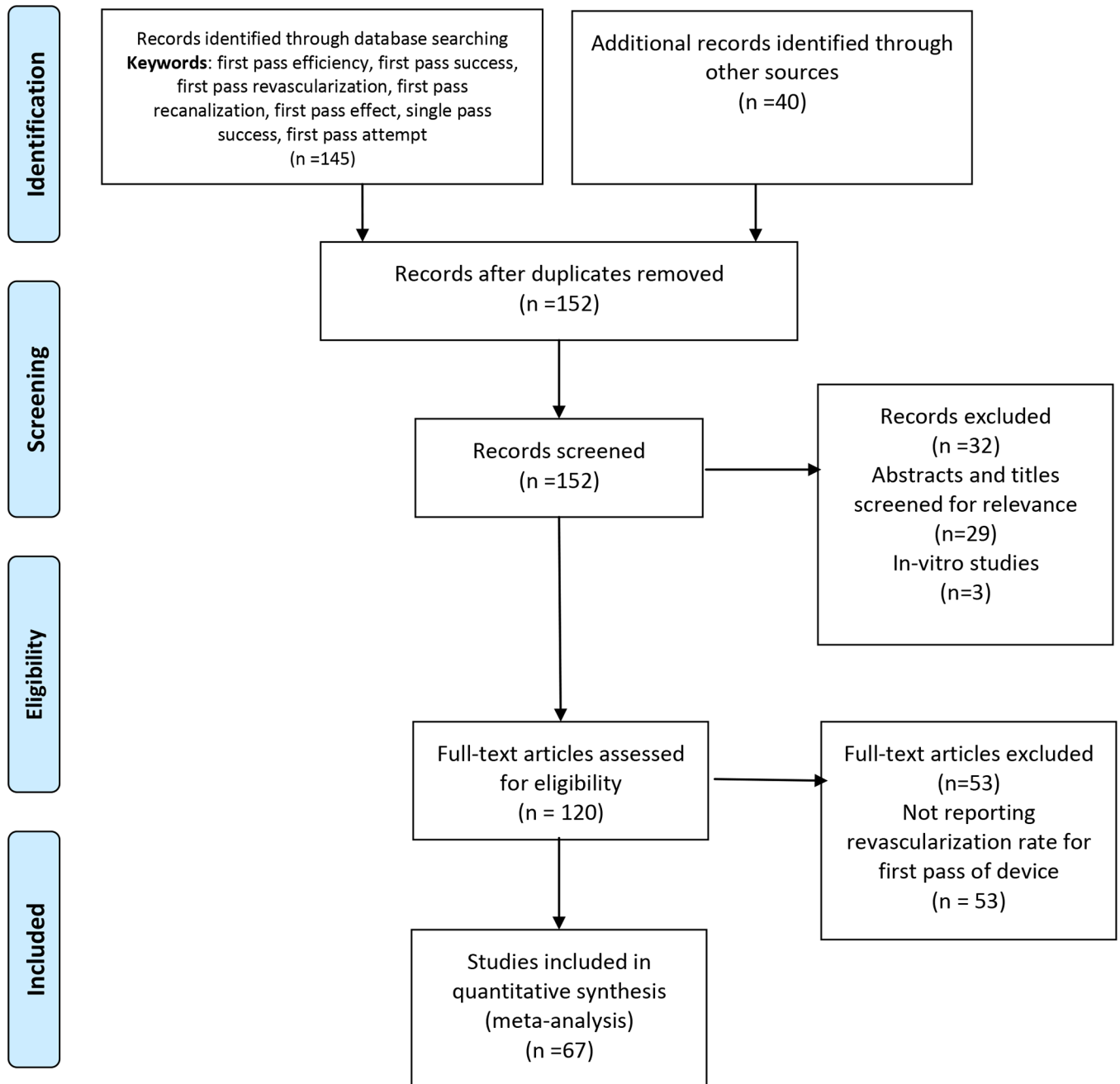


Figure 1).
PRISMA flow diagram

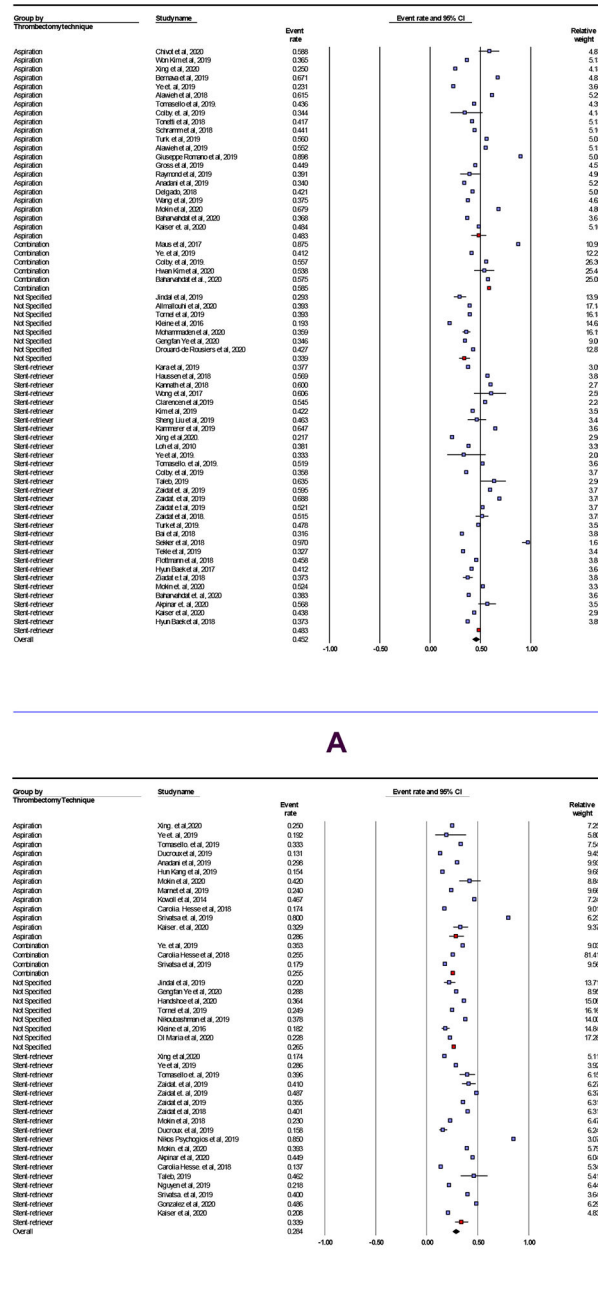


Figure 2). this forest plot compares mFPE (A) and FPE (B) rate between aspiration, stent-Retriever, Combination and, not specified groups.

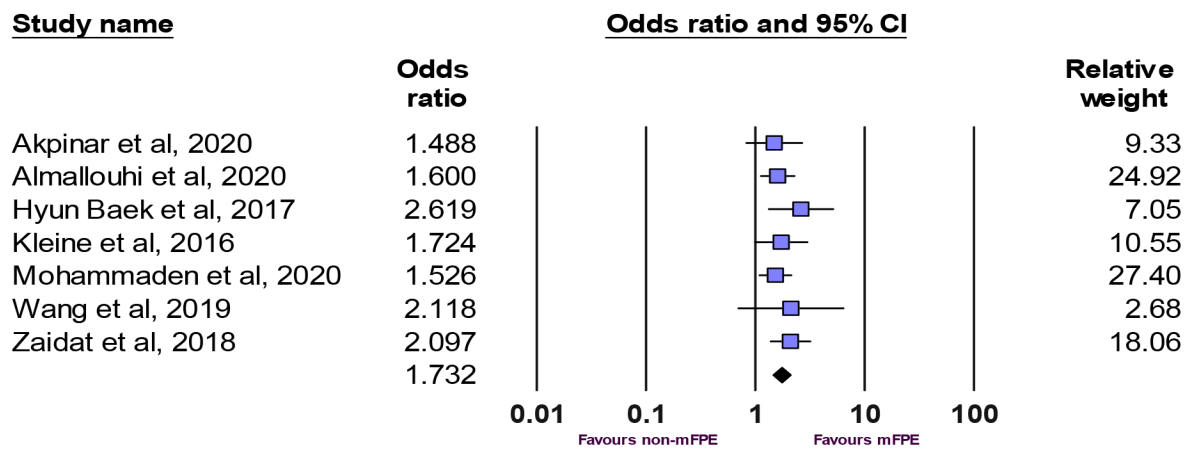
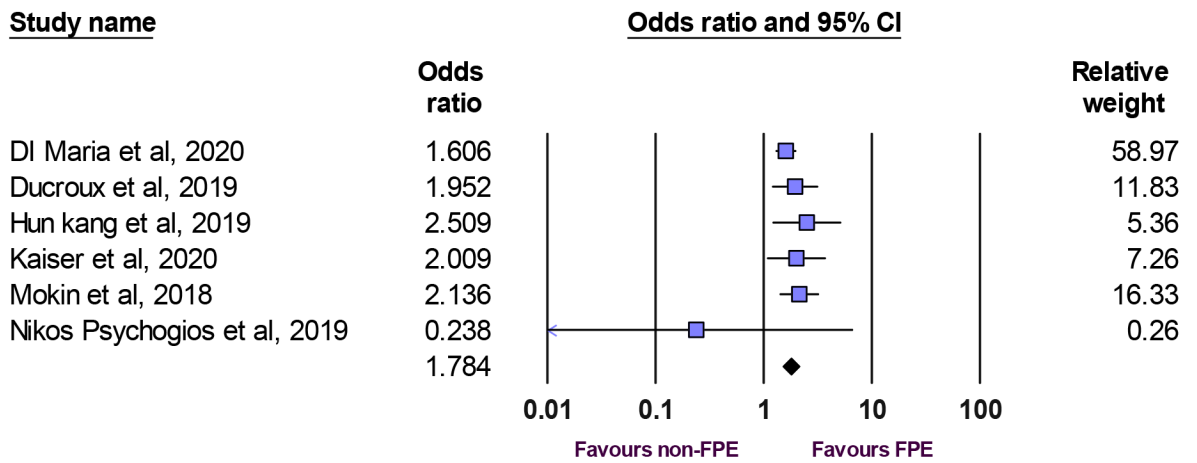
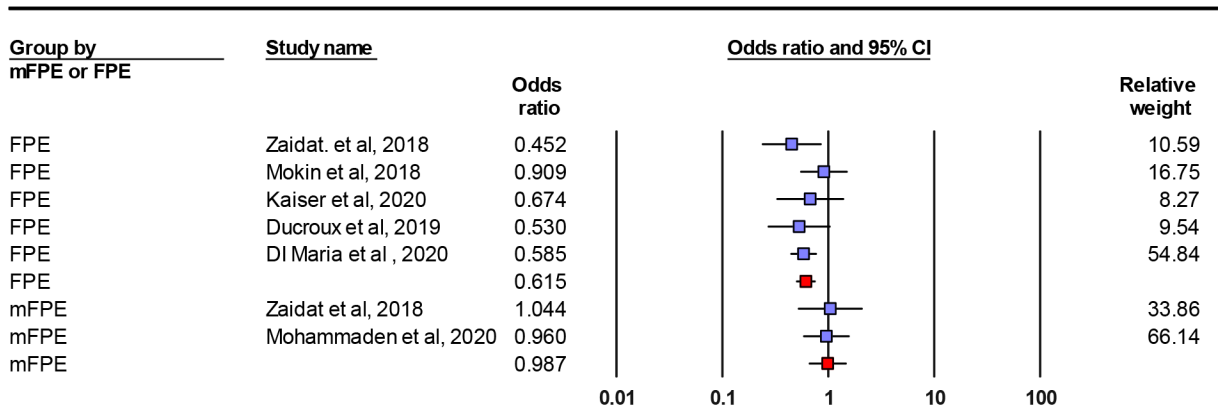
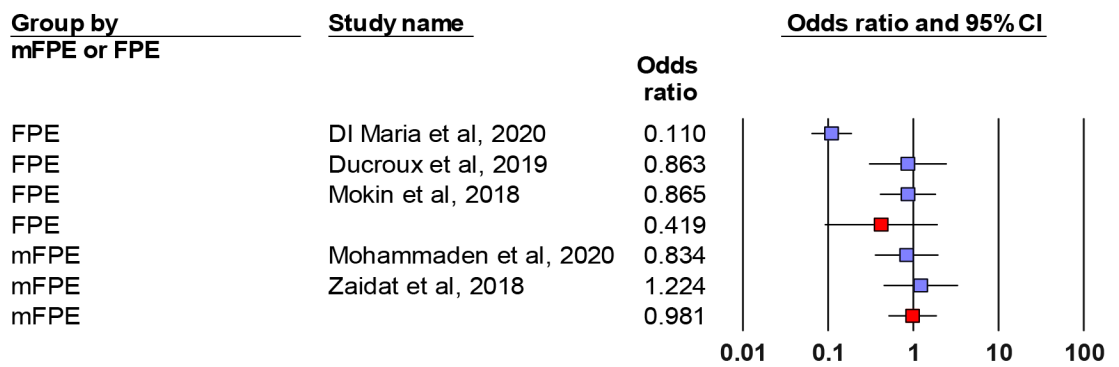


Figure 3). mRS (0–2) 90 days for FPE vs non-FPE (A), mFPE vs non-mFPE (B).



A



B

Figure 4).
mortality at 90 days (A), sICH (B).

TABLE 1.**FPE AND MFPE RATES**

THROMBECTOMY TECHNIQUE	Number of Studies (percentage)	FPE Rate (95% CI)	I² heterogeneity	P-value
ASPIRATION	12 (30 %)	29 (22–37)%	90%	0.17
STENT RETRIEVER	18 (45%)	34 (28–40)%	92%	
COMBINATION	3 (7.5%)	26 (20–32)%	0%	
NOT SPECIFIED	7 (17.5%)	27 (22–32)%	87%	
OVERALL	40	28 (26–32)%	90%	
mFPE Rate (95% CI)				
ASPIRATION	21 (34%)	48% (40–55)	93%	0.20
STENT RETRIEVER	30 (48%)	48% (44–53)	90%	
COMBINATION	5 (8%)	58% (48–68)	66%	
NOT SPECIFIED	7 (10%)	34% (28–40)	89%	
OVERALL	63	45% (42–48)	92%	

FPE: First pass effect; mFPE: modified first pass effect.

TABLE 2.

CLINICAL OUTCOMES

	Number Studies	Events/Total (percentage)		Odds ratio (CI 95%)	I ² heterogeneity	P-value
		FPE	Non-FPE	FPE vs Non-FPE		
MRS(0–2) 90 DAYS	6	431/774 (56%)	933/2285(41%)	1.78 (1.50–2.11)	0	<0.01
SICH	3	28/651 (4%)	389/2118 (18%)	0.41 (0.09–1.93)	91	0.26
MORTALITY	5	129/771 (17%)	610/2457(25%)	0.62 (0.50–0.76)	0	<0.01
		mFPE	Non-mFPE	mFPE vs Non-FPE		
MRS(0–2) 90 DAYS	7	339 / 591 (57%)	402/ 917 (44%)	1.73 (1.44–2.1)	0.00	<0.01
SICH	2	13 / 245 (5%)	47 / 670 (7%)	0.98(0.51 –1.88)	0.00	0.95
MORTALITY	2	40 / 244(16%)	132 / 634(21%)	0.98 (0.66–1.49)	0.00	0.95

FPE: First pass effect, mFPE: modified first pass effect, non-FPE: non-First pass effect, non-mFPE: non-modified first pass effect, mRS: modified Rankin Score, sICH: symptomatic intracranial hemorrhage.