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RESEARCH ARTICLE

DIFFERENCES IN OUTCOMES BETWEEN MALES AND FEMALES WITH ACUTE STROKE TREATED WITH MECHANICAL THROMBECTOMY OR INTRAVENOUS THROMBOLYSIS: A SYSTEMATIC REVIEW

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Abstract

Introduction: Multiple studies have shown that following acute stroke, females tend to have poor outcomes as compared to males. Our study aims to discover whether these differences in outcomes are associated with the type of treatment, either mechanical thrombectomy or intravenous thrombolysis, received by the females.

Methods: As per the PRISMA guidelines, we searched the PubMed/Medline and Google scholar databases to identify studies that reported differences in outcomes between males and females with stroke, undergoing either mechanical thrombectomy or intravenous thrombolysis.

Results: Nine studies met out eligibility criteria, including a total of 17648 participants, out of which 9798 (55.52%) were males and 7850 (44.48%) were females. Seven studies stated that males and females had similar treatment outcomes post stroke, while two studies stated that males had better treatment outcomes as compared to females.

Conclusion: We strongly suggest the need to investigate the specific cause(s) of these outcome discrepancies between males and females, and to tailor a sex-specific treatment protocol to optimize care and improve outcomes for both sexes, with particular attention to improving outcomes in females.

Introduction:-

- In 2019, Acute stroke was the second leading cause of death worldwide. It was also the second most common cause of disability-adjusted life years. [1] The incidence of Acute stroke increases with the aging of the population. In 2030, there may be about 10 million stroke survivors just in the United States [2] Globally, 13.7 million strokes occur each year with 60% occurring in people under the age of 70 years [3] Despite major

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improvements in both prevention and acute management over the last decades, stroke remains a devastating disease. [6] The American Heart Association and American Stroke Association projected that by 2030 the prevalence of stroke in the US would be 3.9%. Moreover, the economic burden of stroke was projected to rise by 129% from 2013 to 2030, with an increase in the direct economic burden of stroke-related medical costs, from $71.6 billion in 2013 to $184.1 billion in 2030. [1]

- Two major treatment modalities for Acute ischemic stroke have been Endovascular thrombectomy (EVT) and Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA). Endovascular thrombectomy (EVT) is the standard of care for majority of the patients with ischemic stroke within 6 h from the time of symptom onset, and for selected patients with favorable perfusion imaging up to 24 h from symptom onset. [9] Intravenous recombinant tissue plasminogen activator (rtPA), has been the standard thrombolysis treatment of acute ischaemic stroke (AIS) since the early 2000s in Europe and a few years earlier in the US. [7]
- It has been established that stroke affects men and women differently. In the US, stroke was the 3rd leading cause of death in women, compared with 5th in men. [1] As per the 2015 Greater Cincinnati Northern Kentucky Stroke Study (GCNKSS), stroke case fatality in women exceeded that of men. [1] Women have a poorer quality of life than men, both in the short- and long-term after stroke.[4] Females have been reported to have higher prevalence of dementia as well as worse post-stroke functional outcomes, compared to males.[5] Moreover, women are more likely to have a higher degree of disability in their activities of daily living than men at the time of their stroke. [1] Women were found to have higher risk of Post stroke dysphagia as compared to men. [3] The 1- and 10-year mortality and stroke recurrence rates were higher in female patients than in male patients after stroke. In the US, projections suggest that ~200,000 more women will be disabled after stroke than men by 2030.[10]
- Also, women feature a higher risk of cardioembolic stroke due to atrial fibrillation, which may contribute to the often-observed higher acute ischemic stroke (AIS) severity in female patients. [10] Due to a longer life expectancy, more women than men experience a stroke each year. [10]
- The prevalence of dementia at 90 days after first-ever stroke was high, with women having significantly worse cognitive outcomes compared with men. In an untreated control population, women ischemic stroke patients present with worse functional outcomes than men, but when treated with a tissue plasminogen activator (rtPA), no difference in outcomes was reported. [11]
- As mentioned above, there have been differences in outcomes between men and women with stroke. However, no cause has been found till date to explain these discrepancies in outcomes. It is supposed to be multifactorial. In general, the observed gender differences have been attributed to several factors such as age, comorbidity, prestroke functional status, and stroke severity. [12] Women also have a significant higher odds of presenting with non focal symptoms during acute stroke compared with men. [13]
- It is also unknown if treatment with EVT or IVT causes different outcomes between men and women, and if these treatment modalities are responsible for causing poor outcomes in women following stroke.
- Out study is trying to discover if the discrepancies in outcomes between males and females with Stroke are associated with the treatment modalities received by these patients, either mechanical thrombectomy or IV thrombolysis.

Methods:-

Literature search

Search terms were formulated using the Population, Intervention, Comparator, and Outcome framework to identify papers mentioning Acute stroke, gender and outcome. The databases searched were PubMed/MEDLINE and Google scholar from 2018 through June 2023.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and recommended guidelines were used to guide this search. [14,15]

The terms used were ((Acute stroke) AND (Gender)) AND (Outcomes). The identified studies were screened with a backward citation done by checking the references of the included studies. All the studies selected for this analysis were chosen after application of the inclusion and exclusion criteria through the different phases of screening.

PICOs Framework:

Population:

Patients(males and females) with Stroke.

Intervention:
Mechanical thrombectomy or IV thrombolysis.

Comparison:
Males vs females

Outcomes: Primary outcome:
Mortality rate, good functional outcome.
2nd: Disability Associated Life Years, depression, functional independence.

Inclusion criteria:
1. Clinical trials and Observational Cohort studies (prospective or retrospective) were included.
2. Only studies available as free full text were included.
3. Only adult male and female patients with stroke that were intervened with Endovascular thrombectomy or IV thrombolysis were included.
4. Studies must have reported at least one sex-based comparative outcome following EVT or IVT.
5. The number of study subjects for both male and female groups should be clearly defined.
6. The published study must be in English.
7. Only studies involving human participants were included.

Exclusion criteria:
1. Studies published in languages other than English.
2. Studies involving intervention or treatment other than EVT or IVT.
3. Studies that do not provide sex-stratified data for the treatment outcomes.
4. Excluded study designs included case reports/series, editorials, study protocols, and abstracts that do not meet the inclusion criteria.
5. Studies that were published prior to 2018.

Selection of studies for inclusion in the review
The screening of the articles was carried out by two researchers who independently reviewed the titles and abstracts of the identified studies. Any disagreements were resolved through discussion and consensus between the two reviewers. In cases where a consensus could not be reached, a third reviewer, was involved in providing a final decision. This ensured a thorough evaluation of all potentially relevant records and minimized bias. Throughout the screening process, detailed notes were taken to record the specific reasons for excluding research studies from the review.

Risk of Bias assessment
To assess the quality of the included studies, we employed the New Castle Ottawa Scale (NOS) risk of bias assessment tool for Cohort studies and the AMSTAR tool for Systemic review & Meta analysis. Two independent reviewers evaluated the risk of bias, and a final table was constructed based on their agreement which is provided in Table 2.

Results:-

A systematic search yielded a total of 1773 records from two databases, Pubmed/Medline (n=1761) and Google scholar (n=12). After removing duplicates (n=6) and conducting initial screening based on title and abstracts, 1709 irrelevant records were excluded, leaving 58 records for full text retrieval. Out of these, 1 record was not retrieved and other 57 records underwent full text screening. Of these, 48 records were excluded during full text screening leaving 9 records that successfully underwent quality assessment and were ultimately included in the study.

Figure 1 shows the PRISMA flowchart process of filtering from the original literature search to the final included studies.

A total of 17648 participants were included in our study, out of which 9798 (55.52%) were males and 7850 (44.48%) were females.

Table 1 shows the baseline characteristics of included studies.

Table 1:- Baseline characteristics of included studies.

Sr	Study ID	Year	Study design	Study size	Intervention	Males	Age	Females	Age	Outcomes
1	Hahn	2022	Cohort	606	EVT	438	55	168	51.5	Absolute percentages of reemployment 3 months after MT did not differ significantly in women versus men (34.5% versus 36.1%; unadjusted OR, 0.934 [95% CI, 0.643–1.357]; P=0.722) Females reached a higher share of excellent functional outcome by discharge (48.1% versus 37.1%, P=0.015), while at 90-day follow-up, no sex differences in functional outcome parameters were observed.
2	Chalos	2019	SR & Meta analysis	1762	EVT	929	66	833	70	The effect of EVT on the ordinal modified Rankin Scale was similar in women (adjusted common odds ratio [acOR], 2.13; 95% CI, 1.47–3.07) and men (acOR, 2.16; 95% CI, 1.59–2.96), with a P for interaction of 0.926
3	Tan	2022	Retrospective Cohort	322	EVT	206	65.6 ± 133.6	116	70.9 ± 14.3 years	The outcomes were similar in terms of functional status and mortality although females tended to present at an older age with higher rates of atrial fibrillation.
4	Demeestere	2021	Prospective Cohort	198	EVT	107	64 [±15]	91	n 68 [±14]	Female sex was associated with a favorable shift on the modified Rankin Scale (adjusted cOR 1.79 [1.04 – 3.08; p = 0.04]) and lower odds of severe disability or death (adjusted OR 0.29 [0.10 – 0.81]; p = 0.02).
5	Bala	2022	Multicenter analysis	608	EVT	301	68 (IQR, 58–76)	307	72 (IQR: 58–80)	Sex was not associated with functional outcome. Functional independence at 90 days was achieved by 43.5% women 46.4% men. Mortality at 90 days [18.5%] versus [16.5%]) and symptomatic intracranial hemorrhage [13.3%] versus [11.6%]) were similar between women and men.
6	Dmytriw	2021	SR & Meta analysis	7335	EVT	3858	NA	3477	NA	Pooled 90-day good outcomes (mRS # 2) were better for men than women (OR =1.29; 95% CI, 1.09–1.53; P <.001, I2 = 56.95%).
7	Zhou	2021	Prospective Cohort	1440	EVT	899	61.0±11.3	541	(66.2± 11.2	For Chinese patients with IS, although women are older and more severe at the time of onset, the prognosis after intravenous thrombolysis is not significantly different from men.

8	Noseda	2023	Prospective Cohort	4996	IVT	2872	71	2124	79	Males had higher odds of functional independence at 3 months (AOR 1.34, 95 % CI 1.09–1.65),The proportion of patients who were independent at 3 months after discharge (mRS score 0–2) was 44.21 % (939/2124) of females and 54.70 % (1571/2872) of males ($p < 0.0001$).
9	W Regenhardt	2022	Retrospective Observational	381	EVT	188	64 (IQR 56–75	193	75 IQR 62–82	In a real-world analysis of ELVO stroke patients treated with EVT, we found that despite advanced age and more pre-stroke disability, women have comparable reperfusion rates and functional outcomes compared to men

Discussion:-

For years, stroke has affected both males and females differently. This includes difference in risk factors, stroke presentation, treatment received and outcomes post-stroke. Our study tried to explain if the differences in the outcomes post-stroke between males and females were related to the treatment that they received and if a particular treatment was associated with poor outcomes in females than in males.

We included a total of 9 studies which compared various outcomes between males and females with stroke treated with either EVT or IVT.

Hahn et all, 2022 compared the re-employment status post stroke between males and females treated with mechanical thrombectomy or EVT. As per them, patients treated with intravenous thrombolysis post EVT had better re-employment rates (73.6% versus 55.4%, P<0.001). Posttreatment functional outcome as assessed by NIHSS and modified Rankin Scale (mRS) at 24 hours follow-up and discharge were much better in patients re-employed by 90 day follow-up with 69.5% versus 23.9% reaching excellent functional outcome (mRS score of 0–1) by discharge (P<0.001).

At 3 months after MT, 93.5% of patients being employed at that time had reached excellent functional outcome, whereas only 34.9% of patients not working had reached this level of recovery (P<0.001). Thus suggesting that reemployment post stroke is associated with better functional outcomes. They also found that female sex (OR, 0.427 [95% CI, 0.229–0.794]; P=0.007) was a negative predictor of reemployment, and thus a negative predictor of better functional outcome post stroke. However, absolute percentages of reemployment 3 months after MT did not differ significantly in women versus men (34.5% versus 36.1%; unadjusted OR, 0.934 [95% CI, 0.643–1.357]; P=0.722). Moreover, females reached a higher share of excellent functional outcome by discharge (48.1% versus 37.1%, P=0.015), while at 90-day follow-up, no sex differences in functional outcome parameters were observed. Hence suggesting that female sex despite being a negative predictor of better functional outcomes, females had similar functional outcomes at 90-day follow-up. [16]

Chalos et all, 2019 studied the effect of sex on the post stroke outcomes including functional independence as measured by the modified Rankin scale score 0-2 as well as mortality. As per their study, the functional independence was reached by similar percentage of men and women (39%) at 90 days. And the mortality at 90 days was 15% for women and 16% for men. Thus suggesting that sex does not influence clinical outcome after EVT and does not modify treatment effect of EVT. [17]

Tan et all, 2022 performed a retrospective analysis of patients with basilar artery occlusion who had undergone mechanical thrombectomy. They found that females were older than males (mean ± SD 70.9 ± 14.3 years vs. 65.6 ± 133.6 years; p = 0.001) and had higher rates of atrial fibrillation (38.9% vs. 24.2%; p = 0.012). Time from groin puncture to reperfusion was shorter in females than males (mean ± SD 57.2 ± 37.2 min vs. 71.1 ± 50.9 min; p = 0.021). Despite these differences, primary and secondary outcome measures were similar in females and males, with comparable rates of favorable 90-day mRS scores (OR = 1.20; 95% confidence interval [CI] = 0.59–2.43; p =

0.611); favorable discharge mRS scores (OR = 1.38; 95% CI = 0.69–2.78; p = 0.368) and in-hospital mortality (OR = 1.15; 95% CI = 0.55–2.43; p = 0.710. Thus proving that females achieved comparable functional outcomes compared with males after undergoing MT for BAO acute ischemic stroke. [18]

Demeestere et all, 2021 stated that women experienced less ischemic core growth (median 15 mL vs. 29 mL, p < 0.01) and had smaller final infarct volumes (median 26 mL vs. 50 mL, p < 0.01). They found that female sex was associated with a favorable shift on the modified Rankin Scale (adjusted cOR 1.79 [1.04 – 3.08; p = 0.04]) and lower odds of severe disability or death (adjusted OR 0.29 [0.10 – 0.81]; p = 0.02). Moreover, good functional outcome (mRS 0–2) did not differ between men and women (adjusted p = 0.35). The results suggest that women have better collaterals and, therefore, more often exhibit a favorable imaging profile on baseline imaging, experience less lesion growth, and have better clinical outcomes following endovascular therapy. This was in contrast to the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial, which showed higher rates of severe disability and mortality among women in the intervention arm , the DEFUSE 3 trial, which showed lower rates of good functional outcome (mRS 0–2) in women (38%) compared to men (67%, p = 0.02). [19]

Bala et all, 2022 investigated the differences in outcomes between women and men treated with endovascular treatment in the late time window. They found that adjusted outcomes did not differ between women and men. Functional independence at 90 days was achieved by 127 out of 292 women (43.5%) and 135 out of 291 men (46.4%). Mortality at 90 days (54 [18.5%] versus 48 [16.5%]) and symptomatic intracranial hemorrhage (37 [13.3%] versus 33 [11.6%]) were similar between women and men. Thus, concluding that Sex did not influence the relation between successful reperfusion and outcomes. This was in line with a pooled analysis of 7 clinical trials within the HERMES (Highly Effective Reperfusion Using Multiple Endovascular Devices) collaboration that concluded that sex did not influence clinical outcomes or modify EVT treatment effect among those treated within 6 hours from onset. [20]

Dmytriw et all, 2021 performed a systematic review and meta-analysis of endovascular thrombectomy studies to determine whether sex influences the outcome of patients with large-vessel occlusion stroke undergoing endovascular thrombectomy. They included 33 articles with 7335 patients and found that Pooled 90-day good outcomes (mRS # 2) were better for men than women (OR=1.29; 95% CI, 1.09–1.53; P<.001, I2 = 56.95%). These results are in contrast to those of other studies. [18,19,20] This suggests that future Large-scale prospective cohort studies should be carried out with attention to sex.

Zhou et all, 2021 investigated the relationship between sex differences and the prognosis of intravenous thrombolysis in Chinese patients with acute ischaemic stroke. According to the prognosis analysis of unsatisfactory functional recovery, there was no significant difference between women and men (45.9% vs 37.1%; adjusted OR 1.01, 95%CI 0.75 to 1.37). As for the safe outcome, the proportion of SICH and mortality in women is relatively high but did not reach statistical significance. Thus concluded that for Chinese patients with ischaemic stroke, although women are older and more severe at the time of onset, the prognosis after intravenous thrombolysis is not significantly different from men. The influence of sex differences in stroke is also related to age. Recent studies proved that the age-related ischaemic stroke (IS) mortality rate of young women is lower than that of men, while of old women is higher than that of men. This should be studied more in the future studies [22]

Noseda et all, 2023 compared the safety and functional outcomes of intravenous thrombolysis (IVT) between females and males with acute ischaemic stroke (AIS). They found that in total, 3.06 % females and 2.47 % males developed in-hospital sICH (p = 0.19), with similar odds (adjusted odds ratio, [AOR] 0.93, 95 % confdence interval, [CI] 0.63–1.39). Males had higher odds of functional independence at 3 months (AOR 1.34, 95 % CI 1.09–1.65), regardless of preadmission use of antiplatelets. The proportion of patients who were independent at 3 months after discharge (mRS score 0–2) was 44.21 % of females and 54.70 % of males (p < 0.0001). This study suggested that males had better outcomes post stroke as compared to women when treated with IVT. [23]

Regenhardt et all, 2022 investigated the sex differences in the determinants of reperfusion and functional outcomes after endovascular thrombectomy (EVT) for emergent large-vessel occlusion ischemic stroke (ELVO). They found that Women (N=193) were older (75 vs 64, p<0.0001), had more pre-stroke disability (17% vs 9%, p=0.032), more atrial fibrillation (41% vs 30%, p=0.033), but less carotid atherosclerosis (8% vs 16%, p=0.027). However, good outcomes were similar between sexes. Rates of both 90-day functional independence (39% vs 44%, p=0.377) and

90-day good outcomes (49% vs 50%, p=0.828) were similar between sexes, however there was a strong trend for women to have higher mortality (27% vs 18%, p=0.052) [24]

As mentioned in the above studies, males and females have comparable outcomes following treatment for stroke, either with mechanical thrombectomy or intravenous thrombolysis. However, there are still differences in the overall outcomes between them following stroke. These differences in outcomes between them are due to multifactorial causes and more research should be carried out to identify the cause of these outcome discrepancies between males and females with stroke and to address them efficiently. If needed, research should be carried out to modify the treatment guidelines for female patients with stroke and to deliver more intensive treatment to such patients to improve outcomes post stroke. Tailoring treatment strategies to address the specific needs of each sex can potentially lead to improved outcomes and enhanced quality of life. Investigating the time from symptom onset to intervention can offer valuable insights into the reasons behind the older age at presentation and poorer survival rates among women. It helps determine if these differences are due to diagnostic and therapeutic delays or truly indicative of delayed disease onset and progression in females.

Limitations

Our study has a few limitations. First, we were able to include published studies from only two databases, PubMed/Medline and google scholar, due to restricted access. Second, we included only Cohort studies and Systematic reviews as there were no randomized control trials comparing the treatment outcomes between males and females with stroke following mechanical thrombectomy or intravenous thrombolysis. Third, most of the outcomes were not consistently available across the included studies.

Conclusion:-

Our study shed some light on the sex based discrepancies in treatment outcomes following stroke. Seven of the included nine studies stated that females with stroke have similar treatment outcomes as compared to males. Two studies stated that males have better treatment outcomes following stroke. These results strongly emphasize the need to investigate the specific cause(s) of these outcome discrepancies between males and females, and to tailor a sex-specific treatment protocol to optimize care and improve outcomes for both sexes, with particular attention to improving outcomes in females.

Figure 1:- Prisma Flowchart.

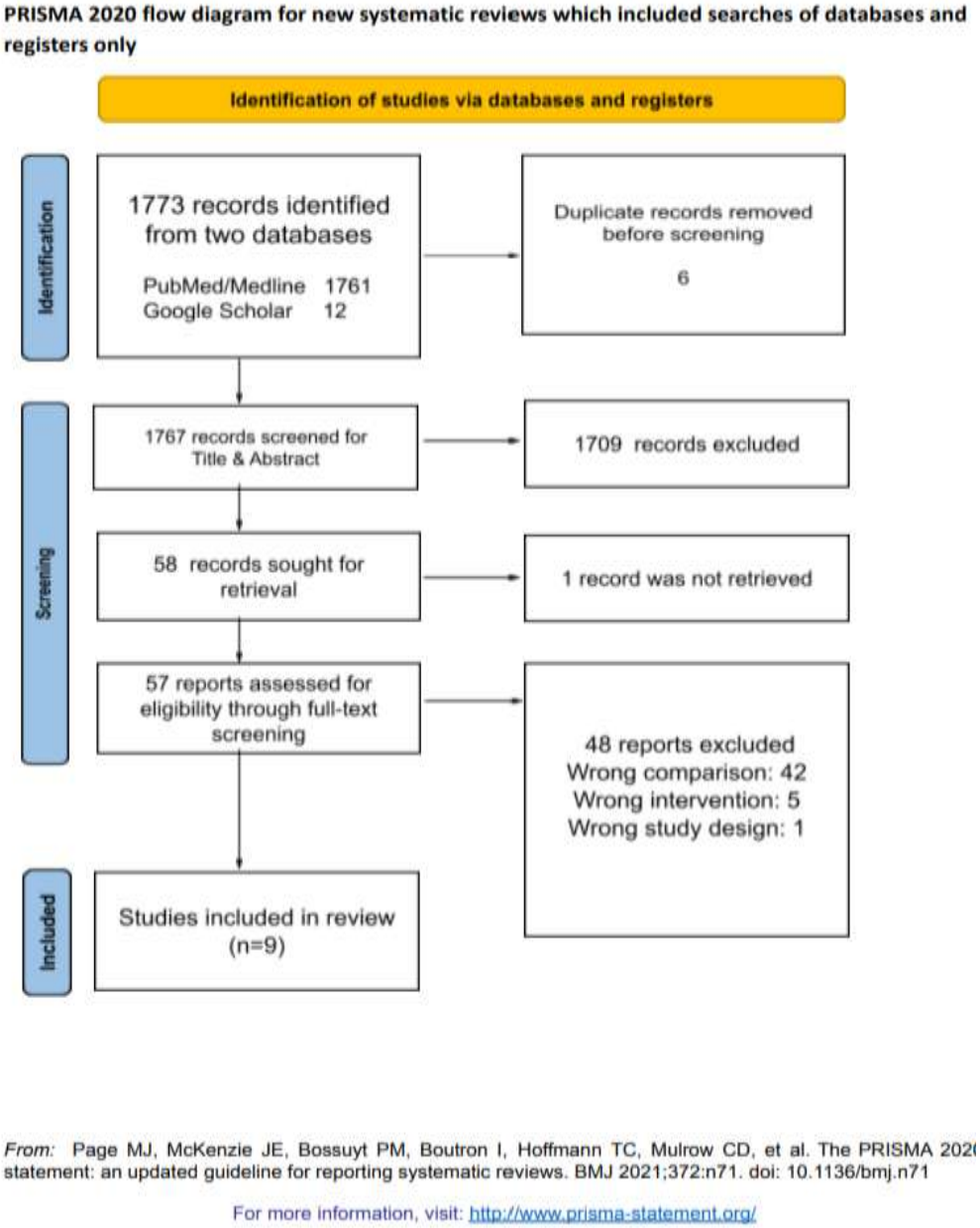

Table 2:- Quality Appraisal of included studies.

Author	Publication year	Report type	Quality assessment tool used	Score
Chalos et all	2019	Systematic review and Meta Analysis	AMSTAR	8
Dmytriw et all	2021	Systematic review and Meta Analysis	AMSTAR	9

Hahn et all	2022	Cohort study	Newcastle Ottawa scale	7
Tan et all	2022	Cohort study	Newcastle Ottawa scale	8
Demeestere et all	2021	Cohort study	Newcastle Ottawa scale	8
Zhou et all	2021	Cohort study	Newcastle Ottawa scale	6
Noseda et all	2023	Observational study	Newcastle Ottawa scale	8
W Regenhardt et all	2022	Cohort study	Newcastle Ottawa scale	7
#Newcastle Ottawa scale accepted score (>=70%): Minimum score 6 out of 9; **AMSTAR checklist accepted score (>=70%): Minimum score 8 out of 11				

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Conflict of interest:
The authors declare no conflict of interests related to this manuscript.

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