

Review Article

PROGNOSTIC VALUE OF MEAN PLATELET VOLUME IN ACUTE ISCHEMIC STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: Acute ischemic stroke (AIS), a significant public health concern, causes severe functional impairments. Mean platelet volume (MPV), a marker of platelet activity, is associated with increased platelet aggregation and elevated thromboxane-A₂ and β -thromboglobulin levels, factors linked to heightened stroke risk and potentially its severity. This review aims to evaluate the prognostic value of MPV in predicting functional outcome in acute ischemic stroke patients.

Methods: A comprehensive systematic search of MEDLINE, Google Scholar, ScienceDirect, and Europe PMC databases was conducted using keywords related to MPV, ischemic stroke, and outcome. Cross-sectional, retrospective, and prospective studies from 2016 to 2023 reporting association of MPV with functional outcome measured with modified Rankin scale (mRS) in AIS patients were included. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for certainty assessment.

Discussion: Nine good-quality studies with 1,514 participants and six good-quality studies with 1,030 participants were included in the systematic review and meta-analysis, respectively, with very low certainty based on GRADE. Pooled results demonstrated a significantly lower MPV in the good outcome group than in the poor outcome group at 3-month follow-up (SMD -0.38; 95% CI -0.72, -0.04; $p=0.03$; I^2 84%). Subgroup analysis showed no significant differences in MPV among patients receiving thrombolysis.

Conclusion: While lower MPV appeared associated with better outcomes, these findings are insufficient to support its use as a prognostic marker of AIS due to marked heterogeneity and inconsistency. Further studies are warranted to validate its clinical utility.

Keywords: Mean platelet volume; Acute ischemic stroke; Modified rankin scale; Prognosis

INTRODUCTION

Among neurological conditions, stroke is the most common worldwide and stands as a primary contributor to mortality and long-term disability, following coronary artery disease. Acute

ischemic stroke (AIS) accounts for approximately 62% of stroke cases, intracerebral hemorrhage (ICH) 28%, and subarachnoid hemorrhage (SAH) the remainder.¹ Ischemic strokes are brought on by a reduction in cerebral blood supply,

often due to a clot formed by thrombosis or carried by an embolism.² The leading risk factor is hypertension, followed by diabetes mellitus, hyperlipidemia, coronary artery disease, atrial fibrillation, and prior stroke history.³ Atherosclerosis and thrombosis, potential initiators of ischemic stroke, are associated with marked platelet activation, wherein aggregation and adhesion play key roles in disease progression.⁴

Larger platelets are characterized by an abundance of dense granules, elevated glycoprotein IIb/IIIa receptor expression, increased thromboxane A₂, and enhanced aggregation capacity. One of the measures of platelet size, mean platelet volume (MPV), is correlated with platelet activation.⁵ The presence of this condition may be relevant to the pathological processes involved in AIS. Multiple prior studies have indicated that MPV may serve as a predictive marker for poor clinical outcomes in acute ischemic stroke (AIS), particularly among patients who do not receive thrombolytic therapy.⁶ This study aimed to evaluate the prognostic

value of MPV in predicting functional outcome in AIS patients.

METHODS

This systematic review and meta-analysis study was conducted using observational studies. We utilized the following eligibility criteria for study inclusion: (a) patients with acute ischemic stroke; (b) mean platelet volume (MPV) level assessed upon admission and categorized according to functional outcomes measured by modified Rankin scale (mRS), with mRS <3 classified as a good outcome and mRS ≥3 as a poor outcome; (c) cross-sectional, case-control, or cohort study designs. Exclusion criteria included patients with hemorrhagic stroke, animal studies, randomized or non-randomized clinical trials, articles without full text, reviews, letters, editorials, poster presentations, non-English publications, MPV was not assessed upon admission, and studies using mRS cut-offs other than 3.

Search strategy and study selection

This study protocol is registered in

PROSPERO

(CRD420251033942). A comprehensive search was done based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) on MEDLINE, Google Scholar, ScienceDirect, and Europe PMC databases for studies published from inception to November 2024. Relevant studies were gathered using the search terms and MeSH keywords “(Mean platelet volume) AND (ischemic stroke) AND (outcome OR outcomes)” (Supplementary Table 1). Two authors (MCE and DAW) initially searched the databases on November 16, 2024. The articles were then screened independently by three authors (MCE, DAW, and BS), and any disagreements were resolved via discussion to reach a consensus. Additional studies were acquired through manual searching of references from eligible studies.

Data extraction

All authors conducted the data extraction. Relevant variables were extracted into a Microsoft Excel sheet and included the first author, publication year, study design, sample size, mean age, type of

intervention, and follow-up interval. The outcome of interest is the mean MPV value categorized according to good functional outcome (mRS <3) and poor functional outcome (mRS ≥3). Other patient characteristics, such as gender, comorbidities, stroke type according to TOAST, and laboratory parameters, were also collected.

Quality assessment

All authors independently assessed study quality using the Newcastle-Ottawa Scale (NOS) for cohort studies. A cohort study is graded good if it scores ≥7 in the NOS. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of this review.

Statistical analyses

Review Manager 5.4 (Cochrane) was used for the meta-analysis of this study. An inverse-variance formula with a random-effects model was employed to calculate the standard mean difference and 95% confidence interval (CI). Data demonstrated using median and interquartile range were converted

to mean and standard deviation using the formula by Wan et al.⁷ A subgroup analysis was also conducted based on the type of intervention. This study used a two-tailed *p*-value with a statistical significance of ≤ 0.05 . Heterogeneity was assessed using the I^2 test, with $I^2 > 50\%$ considered significant heterogeneity. A funnel plot analysis was not done as there were fewer than ten studies included.

RESULTS

Study selection and characteristics

Figure 1 depicts the process of

study selection. The initial search identified 4368 records, and after removing 685 duplicates, 3683 records remained for title and abstract screening. Subsequently, 58 records were sought for retrieval, and eight records could not be retrieved. A total of 50 reports were thoroughly assessed for eligibility, resulting in six included studies.^{8–13} Manual identification through citation screening identified four records, of which three met the eligibility criteria.^{14–16}

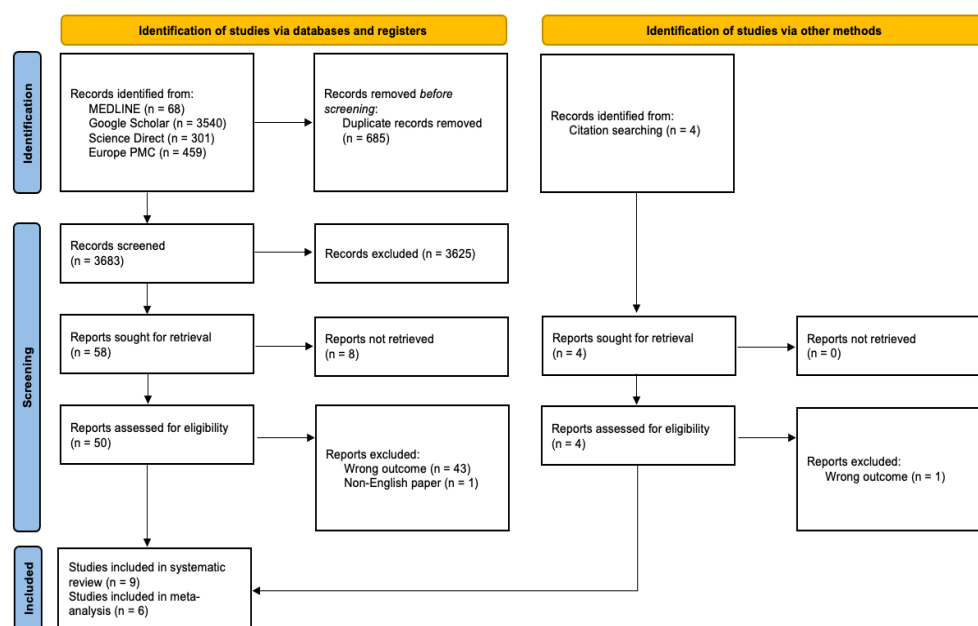


Figure 1. PRISMA Diagram

In total, this systematic review included nine studies with 1,514 participants and the meta-analysis included six studies with 1,030 participants. Out of 9 studies, four were retrospective cohort and five were prospective cohort. The sample size of each study ranged from 74 to 241. Functional outcomes were assessed using mRS at different time points across studies: after two weeks in one study, after one month in one

study, and after 12 months in the other. Six studies evaluated the functional outcomes three months after initial admission. Characteristics of the included studies are provided in Table 1.

Quality of study assessment

The nine cohort studies were assessed using NOS; all were deemed good quality (Table 2).

Table 1. Included Studies Characteristics

Author (year)	Study design	Sample size	Age (years), mean $\pm$ SD		Mean Platelet Volume (fl), mean $\pm$ SD		Intervention	Follow-up interval
			Good outcome (mRS <3)	Poor outcome (mRS $\geq$ 3)	Good outcome (mRS <3)	Poor outcome (mRS $\geq$ 3)		
Zhai et al (2023)	Prospective cohort	222	62.27 $\pm$ 13.84	66.59 $\pm$ 10.64	10 $\pm$ 1.4	10.5 $\pm$ 1.8	Thrombolysis	12 months
Butt et al (2023)	Prospective cohort	225	64 $\pm$ 10.4	64 $\pm$ 10.1	8.37 $\pm$ 0.65	8.55 $\pm$ 0.67	NS	3 months
Nara et al (2023)	Retrospective cohort	74	60.89 $\pm$ 11.348	60.38 $\pm$ 11.16	9.935 $\pm$ 0.758	9.789 $\pm$ 0.612*	NS	1 month
Xue et al (2022)	Retrospective cohort	188	50.1 $\pm$ 9.6	50.3 $\pm$ 10.0	9.6 $\pm$ 1.11	11.35 $\pm$ 1.01	NS	2 weeks
Yao et al (2022)	Prospective cohort	241	66.6 $\pm$ 0.9	70.1 $\pm$ 1.3	11.4 $\pm$ 1.2	12.4 $\pm$ 1.2	Thrombolysis	3 months
Mohamed et al (2019)	Prospective cohort	157	51 $\pm$ 17.8	62.7 $\pm$ 11.6	8.7 $\pm$ 1.3	10.4 $\pm$ 2.3	NS	3 months
Chen et al (2019)	Prospective cohort	241	63.6 $\pm$ 12.2	70.2 $\pm$ 10.6	9.2 $\pm$ 1.4	9.5 $\pm$ 1.5*	Thrombolysis	3 months
Gao et al (2018)	Retrospective cohort	74	58.8 $\pm$ 13.1	66 $\pm$ 11	11.784 $\pm$ 1.692	11.3 $\pm$ 0.929*	Thrombolysis	3 months
Lim et al (2018)	Retrospective cohort	92	65.32 $\pm$ 12	70.11 $\pm$ 10.83	8.45 $\pm$ 1.42	8.77 $\pm$ 0.96*	NS	3 months

NS, not specified; *p value >0.05; OR, odds ratio; CI, confidence interval

Table 2. Quality appraisal for included studies using Newcastle Ottawa Scale

Author (year)	Study design	Selection ^a	Comparability ^b	Outcome ^c	Total score	Result
Zhai et al. (2023)	Cohort	***	**	***	8	Good
Butt et al. (2023)	Cohort	***	**	**	7	Good
Nara et al. (2023)	Cohort	***	**	***	8	Good
Xue et al. (2022)	Cohort	***	**	***	8	Good
Yao et al. (2022)	Cohort	***	**	***	8	Good
Mohammed et al. (2019)	Cohort	***	**	***	8	Good
Chen et al. (2019)	Cohort	***	**	***	8	Good
Gao et al. (2018)	Cohort	***	**	***	8	Good
Lim et al. (2018)	Cohort	***	**	***	8	Good

^a, representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; demonstration that outcome of interest was not present at start of study

^b, comparability of cohorts on the basis of design or analysis (maximum of two stars)

^c, assessment of outcome; was follow-up long enough for outcomes to occur; adequacy of follow up of cohorts

Outcome results

Table 3 describes the baseline characteristics of the 1,514 included participants. The mean age of participants was 60.39 years in the good functional outcome group and 65.73 years in the poor functional outcome group. More than half of the participants were male in both groups. Several comorbidities for stroke, such as a history of smoking (37.2%), alcoholism (29.1%), and hypertension (58%), were more common in the good functional outcome group. On the other hand, dyslipidemia (37%), coronary artery

disease (19.0%), and atrial fibrillation (19.2%) were seen more in the poor functional outcome group. The good

functional outcome group reported more small artery occlusion (SAO) stroke compared to the poor functional outcome group (37%). Meanwhile, the poor functional group had more large-artery atherosclerosis (LAA) and cardioembolism (CE) stroke than the good functional outcome group (49.3% and 29%, respectively). MPV was higher in the poor outcome group (10.202 ± 1.924) than in the

good outcome group (9.724 ± 1.605). Five studies reported mean platelet count and demonstrated lower platelet count in the poor outcome

group (194.057 ± 58.275) than in the good outcome group (202.204 ± 66.614).^{8,10,14–16}

Table 3. Baseline characteristics of included patients

Variables	Number of data available		Good outcome (mRS <3)	Poor outcome (mRS ≥3)
	Good outcome (mRS <3)	Poor outcome (mRS ≥3)		
Age (years), mean ± SD	944	570	60.39 ± 12.922	65.73 ± 11.042
Male, n (%)	944	570	593 (62.8)	327 (57.4)
History of smoking, n (%)	771	444	287 (37.2)	149 (33.6)
Alcoholism, n (%)	350	134	102 (29.1)	38 (28.4)
Hypertension, n (%)	688	360	399 (58.0)	200 (55.6)
Diabetes, n (%)	700	348	168 (24)	129 (37.1)
Dyslipidemia, n (%)	607	284	197 (32.5)	105 (37.0)
Coronary artery disease, n (%)	690	411	74 (10.7)	78 (19.0)
Atrial fibrillation, n (%)	544	326	94 (17.3)	122 (37.4)
Stroke history, n (%)	488	290	114 (23.4)	71 (24.5)
TOAST				
LAA	408	221	125 (30.6)	109 (49.3)
CE	408	221	49 (12.0)	64 (29.0)
SAO	408	221	151 (37.0)	25 (11.3)
Undetermined	408	221	83 (20.3)	25 (11.3)
Laboratory parameter				
Platelet ($\times 10^9/L$), mean ± SD	544	326	202.204 ± 66.614	194.057 ± 58.275
MPV (fL), mean ± SD	944	570	9.724 ± 1.605	10.202 ± 1.924

Abbreviation, TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small artery occlusion; MPV, mean platelet volume
lower MPV in the good functional

Nine studies (n = 1696) reported the MPV levels according to functional outcomes. Our meta-analysis of MPV levels was done for studies with 3-month follow-up interval (Fig. 2). Pooled estimate showed

outcome group (mRS <3) compared with the poor functional outcome group, although with considerable heterogeneity (SMD -0.38; 95% CI -0.72, -0.04; p=0.03, random-effect model; $I^2 = 84\%$).

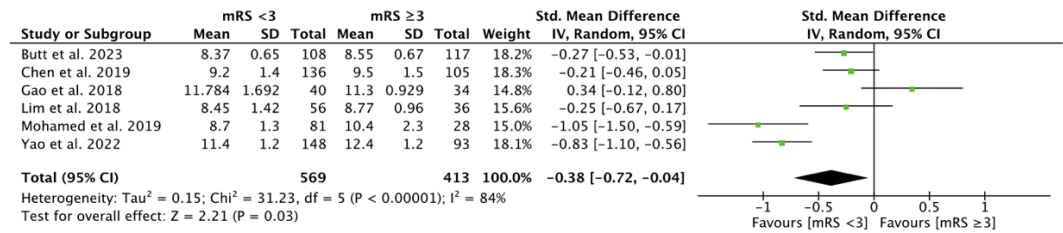


Figure 2. Forest plot analysis of MPV levels in good and poor functional outcome groups based on 3-month follow-up

Four studies (n = 778) analyzed MPV levels in AIS patients undergoing thrombolysis. Of these, three studies assessed functional outcome at a 3-month follow-up interval, and one study did a 12-month follow-up interval. Subgroup analysis of MPV levels in thrombolysis patients showed no significant MPV levels difference in

the good and poor functional outcome group (SMD -0.25; 95% CI -0.86, 0.35; p=0.41, random-effect model; I² = 91%). (Fig. 3)

The GRADE assessment showed a very low certainty of this review due to strong suspicion of publication bias and inconsistency among studies (Table 4).

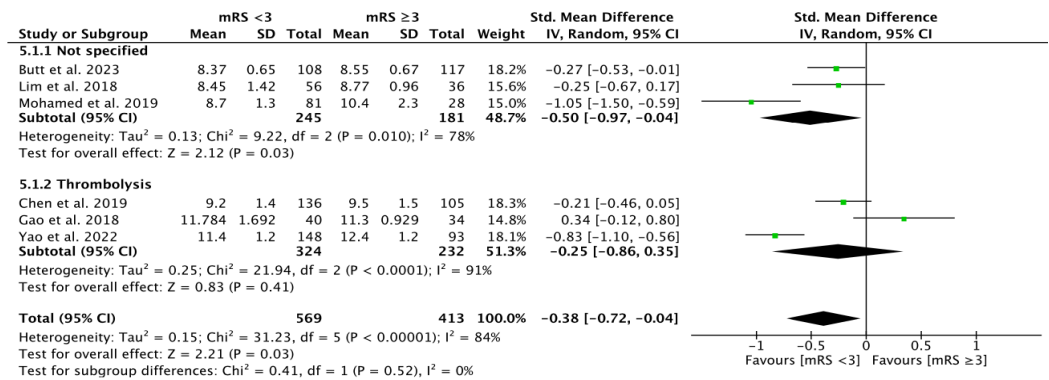


Figure 3. Forest plot of subgroup analysis of MPV levels in good and poor functional outcome groups based on intervention

Table 4. GRADE Evidence Assessment

Certainty assessment						No of patients			Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	mRS <3	mRS ≥3	Relative (95% CI)	Absolute (95% CI)	
6	Non randomised studies	Not serious	Serious	Non serious	Serious	Publication bias strongly suspected All plausible residual confounding would reduce the demonstrated effect Dose response gradient	569	413	-	SMD 0.38 lower (0.72 lower to 0.04 lower)	⊕○○○ Very low

Abbreviation, CI, confidence interval; MPV, mean platelet volume; SMD, standard mean difference

DISCUSSION

AIS occurs after a loss of blood supply caused by obstruction of the blood vessel due to clots formed from thrombosis or embolism. This obstruction initiates a cascade of cellular injury due to impaired energy metabolism and oxidative stress. The ensuing damage is exacerbated by the release of reactive oxygen species, chemokines, and cytokines that provoke neuroinflammation, leading to further insult to the cells. While conventional risk factors such as a history of diabetes, hypertension, and dyslipidemia are well-established contributors to the formation of clots in the blood vessels, several newer studies have found that platelet indices, such as

the mean platelet volume (MPV), are also correlated with clot formation.

Previous studies have also shown that cases of AIS with higher MPV are associated with more severe sequelae of stroke compared to those patients with a lower MPV, and also worse functional long-term outcomes. These results may be attributed to the MPV, a parameter that reflects the size of platelets. The larger a platelet is, the higher amounts of β -thromboglobulin it can release and the more P-selectin and glycoprotein IIIa it can express, thereby enhancing platelet aggregation and promoting the inflammatory cascade. Elevated MPV level is also a sign of

increased inflammatory response in the body, as IL-6 regulates the production of larger platelets. Although neuroinflammation is essential for tissue regeneration, it may also impair neuroplasticity and exacerbate the neurologic deficit in AIS.^{17,18} These findings suggest that MPV may have a role in predicting the outcome of AIS by indirectly being a marker of the neuroinflammation occurring during AIS.

In our systematic review of 9 studies, we observed a lower MPV in the good outcome group compared to the poor outcome group, even in different follow-up intervals. Our meta-analysis also demonstrated lower MPV in the good outcome group at the 3-month follow-up interval. However, it should be noted that the analysis has high heterogeneity. Except for two studies^{13,15}, the majority of included studies demonstrated a significant difference between the MPV of the good and the poor outcome group. This result aligns with the proposed pathophysiology whereby elevated MPV, reflecting larger platelet size and increased neuroinflammation, is associated with higher cellular injury and worse outcomes. Notably,

higher MPV is associated with both short- and long-term poor functional outcomes. Butt et al., Mohamed et al., Chen et al., Lim et al., and Zhai et al. demonstrated poor outcomes at 3 to 12 months with higher MPV.^{8,11,12,14,16} These findings highlight the potential utility of MPV as a prognostic biomarker to help plan interventions following AIS. Interestingly, studies by Gao et al. and Nara et al. found no significant difference between MPV values between the outcome groups, with both even observing higher MPV levels in the group with good outcomes.^{13,15} This conflicting finding may be due to smaller sample sizes in both studies compared to others included in this review. Additionally, differences in treatment received by the patients, specifically the administration of vitamin B12 in addition to regular antiplatelets, may have influenced the results. Both studies were retrospective, meaning various confounding variables were not accounted for.

While MPV level has been shown to influence functional outcomes in AIS patients significantly, our subgroup analysis suggests that this association may not hold among

those treated with intravenous thrombolysis. Zhai et al., through multivariate logistic regression analysis, concluded that MPV was not predictive of poor outcomes after intravenous thrombolysis.⁸ Likewise, Chen et al. and Gao et al. found no significant association between MPV and outcomes at three months post-thrombolytic therapy.^{15,16} In AIS, the process of thrombosis depletes circulating platelets due to ongoing activation and aggregation, often resulting in decreased platelet counts, as observed in our population (Table 3). This stimulates megakaryocytic hyperplasia and the release of oversized, granule-rich platelets, thereby increasing MPV.⁸ While thrombolytic agents effectively suppress platelet aggregation and clot retraction, they do not significantly alter platelet activation or the expression of surface glycoproteins such as GPIb α , GPVI, and α IIb β 3. Evidence from acute myocardial infarction studies further suggests that thrombolysis may exert anti-aggregatory effects that override platelet activation.⁵ The prognostic relevance of MPV in the functional outcomes of AIS is driven by its role in promoting platelet

aggregation and neuroinflammation. As thrombolysis attenuates platelet aggregation, it may consequently dampen the predictive value of MPV on functional outcomes, as reflected in the findings of our subgroup analysis.

Our study shows several strengths, one of which is MPV's accessibility and cost-effectiveness as a prognostic biomarker in AIS.^{19,20} This systematic review and meta-analysis also includes a diverse range of populations across multiple regions, which may enhance the external validity and applicability of our findings. The subgroup analysis based on the type of intervention adds clinical relevance, which could help tailor the clinical approach to individual cases, as MPV in patients receiving thrombolysis may not be as reliable as in non-thrombolysis patients.

This study has several limitations that need to be acknowledged. First, the heterogeneity of the analysis in this study was significantly high, and the GRADE evidence assessment showed a very low certainty of this review, due to the inconsistency and possible bias,

indicating that no firm conclusion can be drawn. The included studies also had a relatively short follow-up interval. Additionally, we could not adjust for variations in MPV measurement techniques or the timing of blood sample collections, which could introduce bias due to laboratory heterogeneity. All included studies were observational cohorts, which limits the ability to establish causality. Future studies would benefit from the inclusion of randomized controlled trials with a larger sample size and a more extended follow-up period, as well as accounting for the differences in laboratory methods.

CONCLUSION

Our review demonstrates an association between mean platelet volume (MPV) and acute ischemic stroke (AIS) outcomes. MPV values were significantly higher in groups

with unfavorable outcomes compared to those with favorable outcomes. However, subgroup analysis revealed no significant difference in patients treated with thrombolysis. While these findings appeared to show an association between lower MPV and better outcomes, they are still insufficient to support its use as a prognostic marker of AIS due to marked heterogeneity and inconsistency. Further studies are recommended to elucidate this relationship for long-term outcomes, investigate the association in patients receiving thrombolysis, adjust for biases in laboratory measurements, and assess MPV's role in the progression of AIS outcomes.

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