



# Clinical Practice Guidelines for the Prehospital Stage of Acute Stroke in Korea II : Transport Decisions for Patients with Acute Ischemic Stroke

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The mothership (MS) model, where patients are directly transferred to a thrombectomy-capable center, and the drip-and-ship (DS) model, where thrombolysis is initiated at the nearest primary stroke center before transfer for thrombectomy, are the primary transport modes for patients with stroke. We aimed to establish guidelines for selecting the appropriate transfer strategy based on emergent large vessel occlusion (LVO). We developed this guideline based on evidence from systematic reviews and meta-analyses via a *de novo* process. A systematic literature review was conducted across four databases (MEDLINE, Embase, Cochrane, and KoreaMed) to answer three Population, Intervention, Comparison, and Outcome questions comparing MS and DS models. The risk of bias was assessed using the Newcastle-Ottawa Scale. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagrams and meta-analyses were generated for functional outcomes, mortality, and successful recanalization. Twenty-six non-randomized controlled studies showed that the MS model improved good functional outcomes by approximately 14% compared with the DS model (odds ratio [OR], 1.14; 95% confidence interval [CI], 1.00–1.30). Fifteen studies reported that mortality in the MS and DS models showed no significant differences (OR, 0.97; 95% CI, 0.84–1.11). Twenty-four studies revealed no significant difference in successful recanalization between the MS and DS models (OR, 0.87; 95% CI, 0.68–1.10). The MS model should be considered first to improve the functional outcome of patients with LVO. However, if thrombectomy cannot be performed immediately after thrombolysis, or if a thrombectomy-enabled hospital is not nearby, the DS model should be considered by stroke specialists depending on transportation time and regional factors. We suggest a mixed approach with the DS model based on specific circumstances or regions to ensure the optimum treatment of patients with acute ischemic stroke (AIS). Appropriate transport for patients with LVO improves the prognosis of AIS.

**Key Words :** Guideline · Ischemic stroke · Cerebral infarction · Thrombectomy · Emergencies.

## INTRODUCTION

Concurrent acute ischemic stroke (AIS) and large vessel occlusion (LVO) require two major acute-phase treatments: intravenous thrombolysis (IVT) and mechanical thrombectomy (MT). There are two primary transport strategies for these recanalization therapies. First, the “mothership (MS)” model, where the patient is directly transferred to an IVT- and MT-enabled comprehensive stroke center (CSC). The other is the “drip-and-ship (DS)” model, where IVT is first administered at a nearby primary stroke center (PSC), and the patient is subsequently transferred to an MT-capable center. Studies have evaluated the clinical effectiveness of each model; however, the results varied depending on regional infrastructure, transport times, and institutional capacity. Korea has an efficient national health insurance system and an increasing number of certified endovascular neurosurgeons, neurointerventionists, and stroke centers. However, optimal emergency transport strategies for patients with AIS are inadequately standardized. Furthermore, disparities in geographical accessibility to thrombectomy-capable centers hinder the establishment of a nationwide unified protocol. This guideline aims to provide evidence-based recommendations for selecting the most appropriate hospital transfer strategy for patients with concurrent AIS and LVO. We

aim to offer a practical framework adaptable to various clinical and geographic settings in Korea by systematically reviewing the current literature and incorporating expert consensus. We hope that this guideline will facilitate the development of a national protocol, which will be updated regularly to reflect emerging evidence and changes in healthcare delivery systems.

## MATERIALS AND METHODS

### Development of clinical practice guidelines

This guideline was developed using the methodology recommended by the relevant Korean medical society. Four key questions were established, and four recommendations were derived. For areas where recommendations could not be drawn from meta-analyses, a systematic review was conducted. Continuous revisions and further guideline development will be conducted subsequently with related society and experts. This guideline was approved by the Institutional Review Board (UC24ZISE0069), and the requirement for informed consent was waived. The participants and progress in developing this guideline are described in detail in Supplementary Material 1.

## Rationale for developing guidelines

Emergency patient transfer has become a significant social concern in Korea, as highlighted by the ongoing media reports about emergency room crises. In addition, since February 2024, legislative conflicts have exacerbated the shortage of specialists, intensifying the crises in essential medical services. Thus, the challenge of transferring patients between hospitals has emerged as a major concern in Korea's healthcare system. Therefore, developing guidelines about decisions for patients with LVO is crucial to addressing this social challenge.

## Selection of key questions

The selection of key questions for the clinical practice guideline topic began with a survey among all members of the society. The survey was conducted before and after ASCENT (Annual Summer Conference on Endovascular Neurosurgical Therapy) between May and June 2024. Following the survey and the collection of topics by the Working Committee, two rounds of meetings were held among the development committee members to finalize the key questions. The key questions for each recommendation were formulated based on the PICO (Population, Intervention, Comparison, and Outcome) framework, and a systematic literature search was conducted. Our key questions are described in Supplementary Table 1. In the hyperacute treatment of AIS, prompt and appropriate therapy is critical. For patients eligible for IVT and MT, thrombolysis is required before thrombectomy. Deciding on the suitable approach is a daily challenge for emergency physicians. When determining the transport strategy to a stroke center for the initial reperfusion therapy, does a DS model approach—administering thrombolysis followed by a transfer to a thrombectomy-capable center—affect prognosis? Or is it preferable to transport the patient directly to a thrombectomy-capable center (MS model) to receive both treatments in one setting and potentially improve outcomes? This dilemma highlights the importance of choosing between the MS and DS models. The clinical question addressed in this guideline was structured according to the PICO format as follows: we included patients diagnosed with AIS requiring IVT and MT. The intervention group comprised patients managed using the MS model, and the comparison group consisted of patients treated with the DS model. The primary outcomes evaluated were good functional outcome, defined as a modified Rankin scale (mRS) score of less than 3, all-cause mortality at 3 months, and successful recanalization

(thrombolysis in cerebral infarction [TICI] 2b or higher). Furthermore, through systematic review, we assessed whether these outcomes varied according to transfer time and distance between the PSC and the thrombectomy-capable center (Supplementary Material 1). A summary of each key question and its corresponding recommendation is provided in Table 1.

## Literature search and selection

The selection of relevant studies was conducted separately for each key question, with two, seven, or three development committee members assigned depending on the volume of the literature available for each topic. Duplicate exclusion and literature selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig. 1). The inclusion and exclusion criteria for each key question were formulated and applied based on the PICO framework.

## Systematic review

For each subtopic selected by the Clinical Practice Guideline Executive Committee, at least two responsible reviewers were designated. Subsequently, a systematic review was conducted based on key questions, literature selection processes, supporting evidence, and meeting records. In Korea, where hospitals are predominantly located in urban centers, distinguishing between urban and rural settings is crucial when comparing the MS and DS models. A meta-analysis showed that available data were insufficient; therefore, we conducted a systematic review to examine the effects of transfer time and distance under the MS and DS paradigms.

## Financial support and independence in clinical practice guideline development

The development of this guideline was funded by the Korean Neuroendovascular Society (KoNES) and the Korea Health Industry Development Institute, and no conflicts of interest were associated with this funding. The Clinical Practice Guideline Development Committee operated independently from KoNES, and during the guideline development process, the funding sources had no direct, indirect, or potential influence on the content of the guideline or the development process.

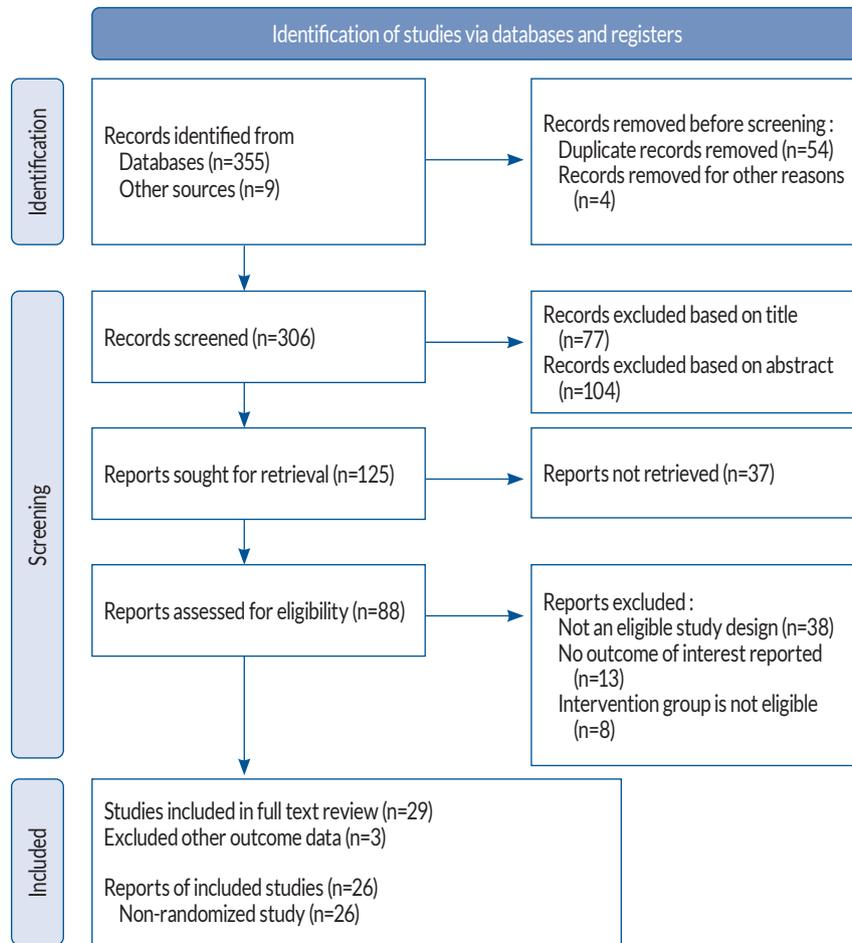
## Publication and future updates of the clinical practice guideline

This clinical practice guideline will be published in medical

**Table 1.** Summary of key questions and recommendations

Key question	Recommendation	GOR	LOE
In the hyperacute treatment of acute ischemic stroke (AIS) with large vessel occlusion (LVO), prompt and appropriate therapy is critical. For patients eligible for thrombolysis and thrombectomy, thrombolysis should precede thrombectomy. Selecting the appropriate transport strategy remains a daily challenge for emergency physicians. When determining transport to stroke centers for initial reperfusion, does a drip-and-ship (DS) model—administering thrombolysis followed by transfer to a thrombectomy-capable center—affect prognosis? Or is it preferable to transport the patient directly to a thrombectomy-capable center (mothership [MS] model) to receive both treatments in a single setting and potentially improve outcomes?	The MS model improves patient prognosis compared with the effect of the DS model by enhancing good functional outcomes.	B	Moderate
Does the MS model improve functional outcomes compared with the effectiveness of the DS model?	MS and DS models do not differ in terms of mortality for AIS with LVO.	C	Moderate
Does the MS model reduce mortality compared with the efficiency of the DS model?	MS and DS models do not differ in terms of successful recanalization among treatment outcomes for AIS with LVO.	C	Low
Does the MS model increase the recanalization rate compared with the effect under the DS model?			
Can the application of the MS and DS models vary depending on different regions and factors such as time and distance of transfer to thrombectomy-capable hospitals?	In urban areas or regions with multiple well-equipped hospitals—such as thrombectomy-capable or comprehensive stroke centers—the MS model is likely to be more effective. However, in rural regions, areas with a shortage of stroke centers and medical personnel, or locations where the distance to a thrombectomy-capable center is significantly greater, the DS model may be more effective, particularly when a nearby primary stroke center (PSC) can initiate thrombolysis before transfer. The appropriate model should be selected based on the transport time and distance to PSCs and thrombectomy-capable centers, under the discretion of a stroke specialist.	C	Very low

GOR : grade of recommendation, LOE : level of evidence



**Fig. 1.** The Preferred Reporting Items for Systematic reviews and Meta-Analyses flow.

journals affiliated with one of the Korean Neurosurgical Society. Additionally, it will be made publicly available on the society’s official website, Instagram, and other online platforms, ensuring that physicians, healthcare professionals, and the general public can easily download and access the guidelines.

Furthermore, the guidelines will be registered on the official website of KoNES for promotional purposes. A summary booklet will also be produced and actively distributed at future academic conferences and events.

The KoNES Academic Committee and the Clinical Practice Guideline Committee will continue to monitor research findings in specific areas, including early diagnosis, the transfer of patients with emergency stroke, and treatment selection for subarachnoid hemorrhage. Additionally, they will track updates from international clinical guidelines. If new research accumulates, warranting additions or modifications to the recommendations, a Clinical Guideline Revision Committee

under the society will be formed to revise the guideline every 5 years.

## RESULTS

When considering IVT and MT, we identified 26 studies comparing the MS and the DS models, all of which were non-randomized studies (NRS). Among the studies, 26 evaluated functional outcomes at 3 months, 15 assessed mortality, and 24 compared successful recanalization. A good functional outcome was defined as a mRS score of less than 3, and successful recanalization was defined as a TICI grade of 2b or 3 on angiographic results after MT. In Korea, where hospitals are predominantly in urban centers, differentiating between urban and rural settings is crucial when comparing the MS and DS models. A preliminary meta-analysis revealed insufficient data; there-

fore, we conducted a systematic review to examine the effects of transfer time and distance under each model.

**Functional outcomes**

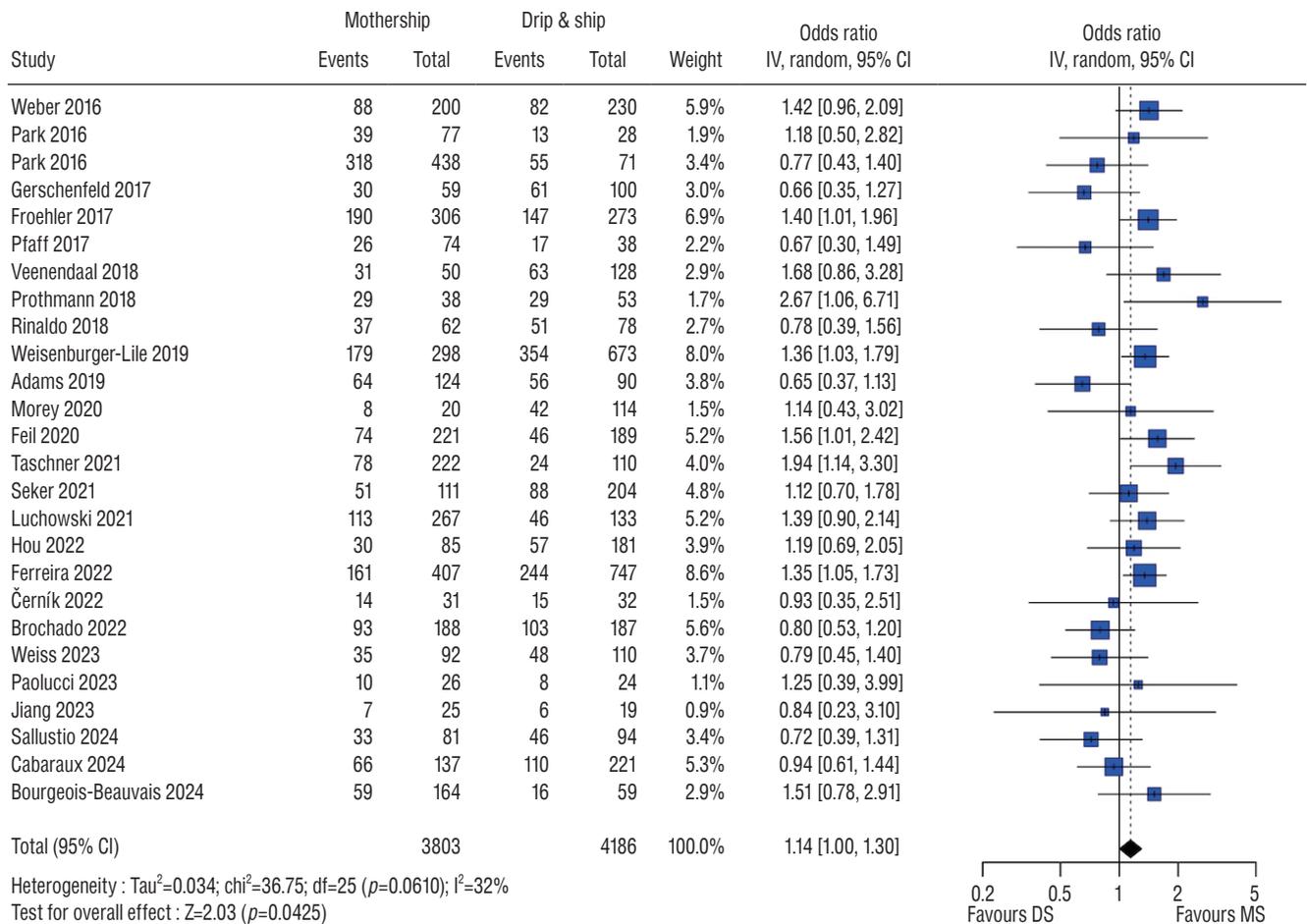
For patients with concurrent AIS and LVO requiring MT, transfer to a thrombectomy-capable center should be prioritized to improve post-treatment functional outcomes (level of evidence [LOE], moderate; grade of recommendation [GOR], B).

Twenty-six studies<sup>1-12,14-18,20-22,24-29)</sup> compared the functional outcomes of the MS and DS models, with moderate heterogeneity observed. A follow-up at 3 months after AIS treatment showed that 1863 of 3803 patients (49.0%) in the MS model group achieved a good functional outcome, compared with 1827 out of 4186 patients (43.6%) in the DS model group. A meta-analysis of these 26 studies showed that the MS model improved good functional outcomes by approximately 14% com-

pared with the effect of the DS model (odds ratio [OR], 1.14; 95% confidence interval [CI], 1.00–1.30) (Fig. 2).

A good functional outcome is a primary endpoint in studies on MT. In AIS, the two major treatments should be delivered within a limited time, requiring the simultaneous efforts of a large medical team and sufficient healthcare resources. The MS model improves functional outcomes; therefore, providing both key treatments immediately after stroke in one comprehensive center improves outcomes. Additionally, receiving acute-phase care at hospitals with specialists and modern facilities improves outcomes. The MS model may be associated with adequate medical systems for immediate intervention, post-procedural patient care, and standardized clinical pathways. Therefore, patients should receive treatment at a CSC where IVT and MT are feasible to improve functional outcomes in cases of LVO-associated ischemic strokes.

However, treating LVO-induced AIS has a high risk of reper-



**Fig. 2.** Forest plot of functional outcome between mothership (MS) and drip-and-ship (DS) model. CI : confidence interval.

fusion injury and disability if recanalization is delayed. In addition to high recanalization rates and good post-procedural care, patients should receive IVT and MT sequentially within an optimal time window. If the time from symptom onset to recanalization exceeds a specific time limit, patients are less likely to achieve favorable outcomes, including those with good collateral circulation. Furthermore, in some cases, IVT alone may lead to successful recanalization. Therefore, the DS model should be considered first if MT cannot be performed immediately after thrombolysis or if thrombectomy-capable hospitals are not nearby.

For LVO-associated AIS, transporting the patient to the nearest MS hospital improves functional outcomes. However, the DS model should be considered if the transportation time is expected to be long or the distance is considerably long (LOE, moderate; GOR, B).

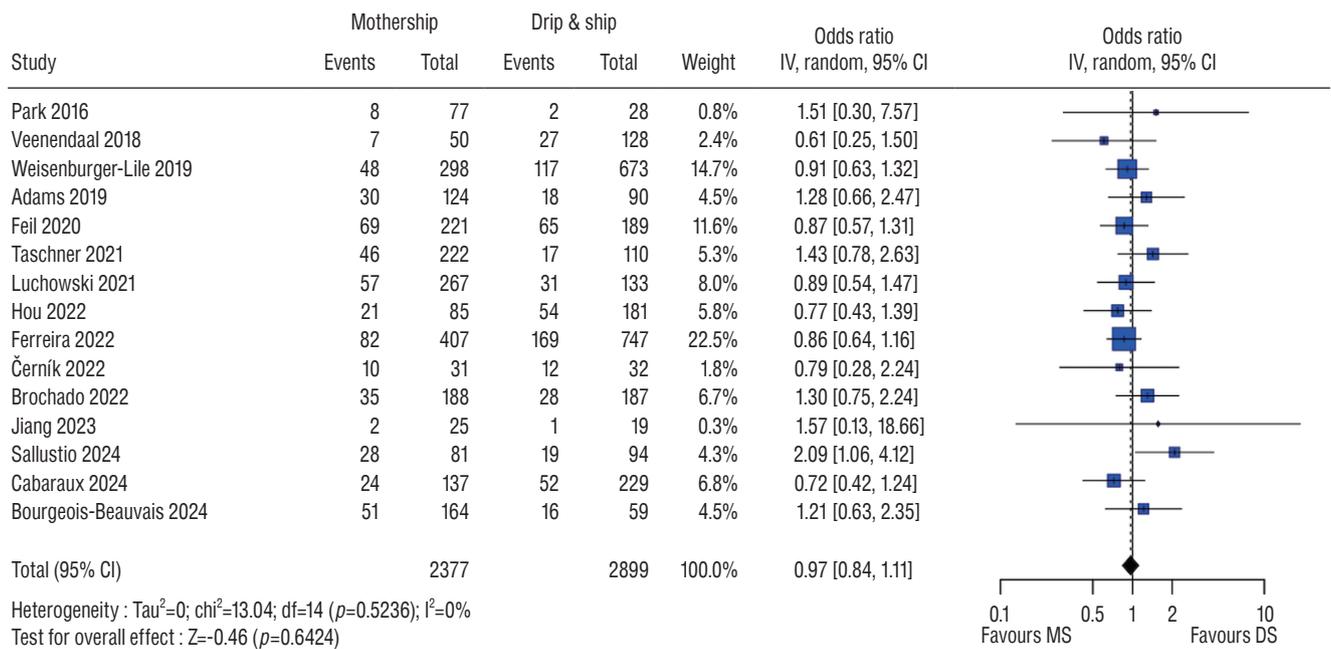
**Mortality**

MS and DS models do not differ in terms of mortality for AIS with LVO. Consequently, the selection of the MS or DS Model should be based on local infrastructure, expertise, and specialist assessment, with emphasis on minimizing delays through a well-coordinated transport protocol (LOE, moderate; GOR, C).

Fifteen studies reported mortality outcomes, and all were NRS with low heterogeneity. The follow-up was 3 months. Among 2377 patients in the MS model group, 518 (21.8%) died. In the DS model group, 628 (21.7%) of 2899 patients died. The MS model mortality was not significantly different from that of the DS model (OR, 0.97; 95% CI, 0.84–1.11) (LOE, moderate) (Fig. 3). Previous studies on patients with stroke and LVO undertaking thrombectomy showed that mortality risk is influenced by initial patient condition and other factors, including age, time of treatment, and hospital infrastructure. Although previous major randomized control trials on MT revealed reduced mortality with aggressive treatment, mortality reductions between the MS and DS models were statistically insignificant. Therefore, in this study, there were no significant differences in mortality between the MS and DS models, consistent with the findings of previous thrombectomy studies (LOE, moderate; GOR, C).

**Recanalization rate**

No significant differences in successful recanalization rates of reperfusion therapy were observed between the MS and DS models. This guideline emphasizes the integration of thrombolysis and thrombectomy and recommends a good transport strategy to ensure that either procedure is performed promptly



**Fig. 3.** Forest plot of mortality between mothership (MS) and drip-and-ship (DS) model. CI : confidence interval.

by stroke specialists (LOE, low; GOR, C).

Twenty-four NRS with high heterogeneity reported recanalization rates. Among 3123 and 3515 patients in the MS and DS model groups, 2486 (79.6%) and 2889 (82.2%) achieved successful recanalization, respectively. A meta-analysis revealed no significant difference in successful recanalization between the MS and DS models (OR, 0.87; 95% CI, 0.68–1.10) (LOE, low) (Fig. 4), possibly because both models recommended rapid and active treatments. MT was ultimately performed in all cases; therefore, the recanalization rates exhibited no differences. Thus, we concluded that there were no significant differences in the successful recanalization rate between the MS and DS models, consistent with the findings of previous studies (LOE, low; GOR, C).

### Distance and time

MS models are effective in urban areas or regions with many

IVT- and MT-enabled hospitals—such as CSC or thrombectomy-capable centers. However, in rural areas with insufficient stroke centers and medical personnel or locations where the distance to a thrombectomy-capable center is significantly far, the DS model may be more effective, particularly when a PSC is nearby and can initiate thrombolysis before transfer. The appropriate model should be selected based on the transport time and distance to CSC or thrombectomy-capable centers that provide definitive treatment in each region (LOE, very low; GOR, C).

In patients with AIS, short transfer distances and reduced time to revascularization directly impact functional outcomes. Previous studies have revealed that long transfer distance is associated with poor functional outcomes and high mortality. Rinaldo et al.<sup>21)</sup> reported a significantly shorter time to revascularization under the MS model than under the DS model (277.4 vs. 420.4 minutes;  $p \leq 0.0001$ ). Among the transferred patients,

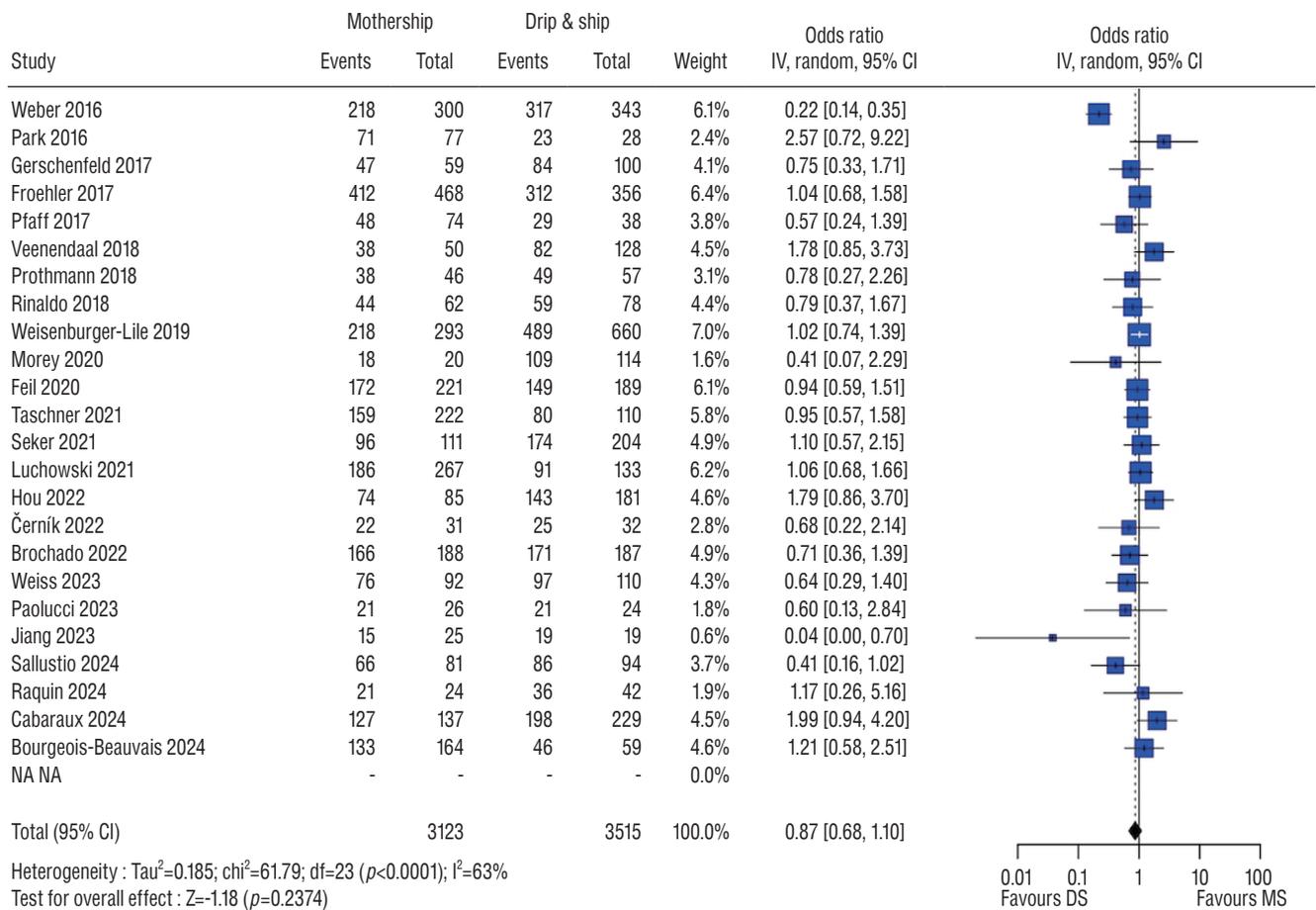


Fig. 4. Forest plot of successful recanalization between mothership (MS) and drip-and-ship (DS) model. CI : confidence interval.

the long distance between the transferring and receiving hospitals was associated with a high mortality risk (unit OR, 1.26; 95% CI, 1.07–1.54;  $p=0.0061$ ). As long transfer distances were associated with high mortality, the MS model is more effective under such conditions. According to a multicenter observational study on Endovascular Treatment in Ischemic Stroke in France, the MS model resulted in greater functional independence than that of the DS model among patients traveling over 20 km between the PSC and CSC (adjusted relative risk, 0.82; 95% CI, 0.71–0.94)<sup>28</sup>. In the DS group with transfer distances under 20 km, outcomes did not differ significantly from those in the MS group, indicating that the MS model exhibited better outcomes as the transfer distance increased. Schlemm et al.<sup>23</sup> reported that long door-to-needle time (DNT) or door-out time at the PSC was associated with poor outcomes. Furthermore, if there were treatment delays (e.g., DNT and door-out time) at the PSC, better outcomes were observed when patients were directly transferred to a CSC<sup>23</sup>. Previous studies have revealed that MT alone is not inferior to combined IVT and MT therapies. Based on these findings, recent guidelines (although limited) recommend direct transfer (MS model). Consequently, clinical practice is shifting toward the MS model to expedite MT, which may improve outcomes. Per previous studies, the MS model outperforms the DS model in time metrics, including DNT, onset-to-needle time (ONT), and onset-to-groin puncture time (OGT), resulting in reduced treatment time and improved functional outcomes. Therefore, physicians suggest that the choice of transfer model reduces the time to recanalization and improves patient prognosis. These studies share a common conclusion. For patients with LVO residing far from stroke centers or likely to experience a prolonged ONT, the MS model, which directs transportation to a thrombectomy-capable center, is recommended.

Other studies have reported contradictory results, exhibiting no significant differences in transport time or patient outcomes. The 2019 American Heart Association guideline suggests that the treatment of LVO-associated AIS is affected by door-in-door-out time, DNT, interhospital transport time, and various other factors, such as the allocation of medical resources<sup>19</sup>. Sallustio et al.<sup>22</sup> compared cases with transport times to the CSC within 30 minutes versus >30 minutes, regardless of the transport method, and found no significant difference in 90-day functional outcomes and mortality or successful reperfusion rates. Milne et al.<sup>13</sup> revealed that the distance between

medical institutions and the swiftness of treatment are critical in choosing between DS and MS models. When the PSC is close to the CSC and intravenous alteplase can be administered within 30 minutes, the DS model may be effective.

If treatment is promptly administered in the DS model, outcomes may not significantly differ from those of the MS model. Simulation models have revealed no significant difference in prognoses between the two models when the transport time is <60 minutes<sup>13</sup>. Cabaraux conducted a single-center retrospective observational study by dividing 229 DS group patients into subgroups based on transport time to a CSC (within or >20 minutes) and comparing them with the MS model group patients and revealed no significant difference in functional outcomes between the models when the transport time was under 20 minutes<sup>4</sup>. Gerschenfeld et al.<sup>9</sup> conducted a retrospective cohort study of 159 patients and found no significant differences in functional outcomes between the two models despite a treatment delay (approximately 50 minutes) in the DS group (MS, 240 minutes; interquartile range [IQR], 202–285 vs. DS, 297 minutes; IQR, 255–357). In another retrospective cohort study, Adams et al.<sup>1</sup> analyzed data from 214 patients and found no significant differences in functional outcomes despite a mean delay of 147 minutes in EVT for the DS model owing to transfer. These findings indicate that the DS model is not inferior to the MS model and, depending on the situation, can be an effective transport strategy. Thus, the optimal strategy may vary depending on the local medical infrastructure and transport time from the site of stroke onset.

These discrepancies among studies may be owing to the differences in regional and national settings where the models were studied. The DS model is used in rural areas without a nearby thrombectomy-capable center and 24-hour on-site medical personnel, resulting in longer transport times. Delays in DNT, OGT, and onset-to-reperfusion time worsen outcomes. Therefore, we conclude that the MS model is effective in urban areas or regions with multiple hospitals where IVT and MT can be performed—such as CSC or thrombectomy-capable centers. However, in rural areas with insufficient stroke centers and medical personnel or locations where the distance to a thrombectomy-capable center is significantly far, the DS model may be more effective, particularly when a PSC is nearby and can initiate thrombolysis before transfer. The appropriate model should be selected based on the transport time and distance to CSC or thrombectomy-capable center capable of providing de-

definitive treatment in each region (LOE, very low; GOR, C).

## DISCUSSION

This clinical practice guideline primarily intends to guide paramedics responsible for emergency transport, emergency room medical staff, and specialists in emergency medicine, neurology, and neurosurgery who treat AIS. In cases of LVO-induced AIS, the rapid selection of an appropriate treatment hospital for timely intervention greatly improves functional outcomes. Through this guideline, we recommend transporting patients to the nearest hospital using the MS model when feasible. However, in instances where transport time to a thrombectomy-capable center is significantly prolonged or the distance is long, we suggest a mixed approach with the DS model based on the specific circumstances to ensure the optimal treatment of patients.

The KoNES has established certification systems for neuroendovascular surgeons and stroke intervention-certified hospitals capable of performing thrombectomy (<https://www.kone-online.or.kr/certification/certiList.php>; Supplementary Material 1). As of November 29, 2024, there were 311 certified stroke interventionists and 106 certified institutions. In Korea, IVT and thrombectomy can be performed at centers certified by academic societies. When transferring emergency patients with LVO to certified centers, they should be transported to a nearby stroke intervention-certified hospital within an hour if acute severe cerebral infarction is suspected. KoNES plans to investigate and monitor the acute-phase major treatments and the current status of transferred patients and hospitals for patients with AIS and will actively introduce this guideline to its members. Although implementing the human network project in collaboration with the Ministry of Health and Welfare since 2024, KoNES will inform medical professionals and its members of the guidelines that actively incorporate the MS model or, depending on the state of the hospital or regional differences, allow for the application of the DS model, and will monitor their implementation. The final PICO was developed through a public hearing that included emergency medicine specialists and experts from relevant fields. The recommendation was formulated based on expert consensus, taking into account the unique healthcare environment and characteristics of Korea. Because of the limited availability of data, a meta-analysis

could not be conducted for this topic.

Through the guidelines developed in this study, we aim to support clinical decision-making in the early treatment of patients with AIS and restructure the patient transport system for those requiring urgent and critical care. Thus, we intend to redistribute medical resources more efficiently while improving the quality of stroke treatment, enhancing the health of patients and the general public.

## CONCLUSION

IVT and MT, the primary treatments for LVO-induced AIS, are crucial. Thrombectomy requires consistently available infrastructure, personnel, and equipment, making the MS model challenging to implement without adequate resources. If a nearby facility can apply the MS model with minimal distance and transport time, immediate treatment implementation is recommended. However, if transport time is prolonged, the MS model may not be feasible. Similarly, if the thrombectomy-capable center is excessively distant or time-consuming to reach, the DS model should be prioritized. The appropriate model should be determined by a stroke specialist based on transport time and distance to thrombectomy-capable centers that provide definitive treatment in each region.

## AUTHOR'S DECLARATION

### Conflicts of interest

Won-Sang Cho has been editorial board of JKNS since September 2021 and Sukh Que Park has been editorial board of JKNS since May 2017. They were not involved in the review process of this original article. No potential conflict of interest relevant to this article was reported.

### Informed consent

This type of study does not require informed consent.

### Author contributions

Conceptualization : JSO; Data curation : JSO, YJ; Formal analysis : JSO; Funding acquisition : JSO; Methodology : JSO; Project administration : JSO, JML, YJ, HSA, JJK, KMJ, GYY, JHK, DS, HJL, JJ, KCC, YSC, SJK, JP, WSC, HK, YWK, SHS,

SWL, JWL, TGK, SKH, SQP, SCK; Visualization : JSO; Writing - original draft : JSO, YJ; Writing - review & editing : JSO, YJ

## Data sharing

None

## Preprint

None

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## • Supplementary materials

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