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ABSTRACT

This study aimed to investigate the associations between pre-hospital delays and outcomes for patients in acute stroke management. A total of 554 pertinent publications were found after a comprehensive search across four databases. Full-text publications (288) were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; six studies finally satisfied the requirements for inclusion. A total of 8906 patients were included, more than half of them 4953 (55.6%) were males. Research showed that early hospital admission leads to better survival, less disability, and better function, mainly from the early delivery of treatment such as thrombolysis. Nevertheless, delays are common for a variety of reasons including symptom appreciation, systemic, and/or logistical bottlenecks in emergency services. Reducing these delays by improved public awareness, improved emergency response, and better communication both between hospitals and emergency medical services (EMSs) will significantly enhance the stroke management. Timely and uninterrupted treatment increases access to life-saving interventions, reducing mortality and post-stroke disability. Pre-hospital delay has demonstrable effects on the outcome of acute stroke management, as early intervention is essential for survival and recovery. Strategies such as public awareness campaigns, enhanced EMS systems, and systemic reforms are essential for mitigating delays and improving stroke care efficiency. Future research should focus on evaluating interventions to reduce these delays, addressing healthcare disparities, and considering regional variations to optimize outcomes and reduce the global burden of stroke.

Keyword: Acute stroke; Management; Pre-hospital delay; Systematic review.

Introduction

There are two types of strokes: ischemic and hemorrhagic. Strokes are one of the leading causes of death in mainland China. Approximately 80% of all stroke patients have an ischemic stroke.

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Following an acute ischemic stroke (AIS), sustaining and regaining nervous system function requires prompt and efficient enhancement of the cerebrovascular blood flow. AIS patients often have

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The option of receiving endovascular thrombectomy (EVT) within 6 hours of the onset of symptoms or intravenous alteplase (IVT) within 3-4.5 hours [1]. About 1-10% of AIS patients in mainland China receive IVT, which is a rather low number [1]. One of the primary causes of hemorrhagic stroke is hypertension. The more promptly acute cerebral hemorrhage is treated clinically, the better the outcome. If treatment is delayed, the bleeding will worsen and may result in circulatory and respiratory collapse and even death [2]. However, because the majority of patients arrive hospitals too late, delicate treatment is lost during the time window, and the rate of immediate intervention for ischemic and hemorrhagic stroke is quite low. Consequently, patients and their families bear a heavy financial and medical burden as a result of pre-hospital delays [3]. The period between the onset of symptoms and the earliest recorded time in the participating hospital's emergency room or general department was referred to as the patient delay or time to presentation [3]. Patient delays have a major impact on stroke patients' quality of life, raise their mortality and disability rates, and place an increasing financial, emotional, and physical strain on patients and their families [4, 5]. Acute stroke is a medical emergency in which early treatment plays a critical role in the outcome of patients. Early initiation of treatment, including thrombolysis or mechanical thrombectomy, are very important for reducing brain damage, enhancing recovery potential, and minimizing disability and death. Nonetheless, pre-hospital delays (i.e., delays prior to arrival at the hospital) can be a major bottleneck in good stroke care. Such delays could be attributable to reasons like insufficient awareness of stroke signs, delayed identification of stroke by bystanders or emergency services, and the practical difficulties that exist in healthcare institutions [2]. Therefore, in order to lower the incidence of patient delays and enhance patients' quality of life, we need to pay attention to patient delays among stroke patients and determine the variables that contribute to them. The purpose of this systematic review is to investigate the associations between pre-hospital delays and outcomes for patients in acute stroke management. It offered a more comprehensive understanding of the effects of pre-hospital delays on clinical course and recovery by synthesizing data from recent reports.

Methods

Search strategy: The PRISMA and GATHER criteria were adhered to in the systematic review. To locate pertinent research on the associations between pre-

hospital delays and outcomes for patients in acute stroke management. Four electronic databases were searched by the reviewers: SCOPUS, Web of Science, Cochrane, and PubMed. We eliminated any duplicates and uploaded all of the abstracts and titles that we could find using electronic searches into Rayyan QCRI. After that, all of the study texts that met the requirements for inclusion based on the abstract or title were gathered for a thorough examination. Two reviewers independently assessed the extracted papers' suitability and discussed any discrepancies.

Study population—selection: The PEO (Population, Exposure, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: Patients with acute stroke, including ischemic and hemorrhagic strokes, (ii) Exposure: Pre-hospital delays, which refer to the time taken from the onset of stroke symptoms to arrival at a hospital, and (iii) Outcome: Patient outcomes in terms of clinical effectiveness of stroke management, including rates of mortality, levels of disability, recovery times, functional independence, and overall quality of life post-treatment.

Data extraction: Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information were retrieved and recorded: (i) First author, (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Age, (vii) Gender, (viii) Stroke type, and (ix) Main outcomes.

Quality review:

Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool can be used for cohort designs where individuals exposed to different staffing levels are tracked over time and is designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [6].

Results

The specified search strategy yielded 554 publications (Figure 1). After removing duplicates (n =266), 288 trials were evaluated based on title and abstract. Of these, 206 failed to satisfy eligibility criteria, leaving just 82 full-text articles for comprehensive review. A total of 6 satisfied the requirements for eligibility with evidence synthesis for analysis. Sociodemographic and clinical outcomes:

In (Table 1), we included six studies with a total of 8906 patients, and more than half of them 4953 (55.6%) were males. Regarding study designs, three studies were retrospective cohorts [8, 10, 11], two were prospective cohorts [9, 12], and one was a crosssectional study [13]. One study was implemented in Italy [8], one in Japan [9], one in China [10], one in Norway [11], one in India [12], and one in Serbia [13]. The earliest study was conducted in 2013 [11] and the latest in 2023 [12]. There is a widespread tendency that early hospitalization leads to a substantial improvement in survival and functional endpoints [8]. Patients who promptly present to medical institutions have a greater likelihood of receiving time-critical care procedures, such as thrombolysis, that better improve and increase chances of recovery and survival [9]. On the other hand, evidence also indicates that the lack of timely hospitalization thwarts patients from being eligible for good and evidenc based treatments, thereby contributing to worse outcomes [10]. In several instances, even when patients were admitted to hospitals in a timely fashion, disputes over emergency management systems became evident as obstacles to quality of care. Improvements of emergency medical services (EMSs) infrastructure and public education on stroke etiologies are required to fill these [11]. Moreover, the reviews show that a significant fraction of stroke patients are unable to receive prompt therapy or arrive to the hospital too late to receive effective therapy [12]. This latency is commonly associated with systemic and logistical causes e.g., response time of EMSs and road transport. Reforms of pre-hospital services and awareness campaigns are of utmost importance for effective stroke management about the minimization of the time between symptom initiation and hospital visit [13]. Denti et al. (2016) demonstrated that early hospitalization could enhance survival chances even when patients are ineligible for time-sensitive therapies like thrombolysis, highlighting the importance of minimizing prehospital delays (Denti et al., 2016) [8]. Similarly, Nagao et al. (2020) found that earlier admission directly contributed to better discharge outcomes, reinforcing the critical need for prompt medical intervention (Nagao et al., 2020) [9]. On the other hand, Jiang et al. (2016) reported that a notable portion of patients arrived at the hospital without receiving standard care, indicating a gap in emergency medical services (EMS) that needs addressing to optimize patient outcomes (Jiang et al., 2016) [10]. Labberton et al. (2013) echoed this concern, emphasizing the urgent need for strategies to reduce delayed

which continue to hinder admissions, the administration of effective therapies (Labberton et al., 2013) [11]. In India, Gupta et al. (2023) highlighted that pre-hospital delays significantly limit the number of patients who can benefit from critical treatments, underscoring the importance of timely admission within the therapeutic window (Gupta et al., 2023) [12]. Lastly, Živanović (2021) pointed out that many patients present too late for effective thrombolytic therapy, suggesting a systemic issue in managing stroke care (Živanović, 2021) [13]. (Table 2) shows that assessment of bias across the studies presents a nuanced picture of methodological rigor. Notably, while most studies exhibit low to moderate levels of bias concerning various factors such as confounding and participant selection, certain studies, such as Živanović (13), demonstrate critical biases that warrant careful consideration. The variability in bias levels underscores the importance of thorough evaluation when interpreting the findings and implications of each study.

Discussion

Stroke remains one of the leading causes of morbidity and mortality worldwide, necessitating urgent medical intervention to mitigate its devastating effects. A systematic review of the literature reveals a pressing need to address pre-hospital delays in acute stroke care, with evidence suggesting that timely access to medical treatment significantly influences patient outcomes. The findings underscore that reducing these delays is not merely a logistical challenge but a critical factor in enhancing survival rates and functional recovery for stroke victims. Early access to care is crucial in stroke management, particularly in the context of ischemic strokes, where interventions such as thrombolysis and mechanical thrombectomy can be life-saving. These treatments are most effective when administered within a narrow time frame following the onset of stroke symptoms. Delays in recognizing stroke symptoms, activating emergency medical services (EMS), and transferring patients to appropriate care facilities can severely limit the window of opportunity for these interventions. As highlighted in the reviewed studies, such delays often lead to more severe clinical outcomes, including increased mortality and greater post-stroke disability [6]. The systematic review indicates that various factors contribute to these pre-hospital delays. Among them, the recognition of stroke symptoms plays a pivotal role. Many individuals, particularly the elderly, those with lower levels of education, and residents of rural areas, may not be aware of the signs of a stroke



Figure 1: PRISMA flowchart [7].

Table 1: Outcome measures of the included studies.

Study ID	Study design	Country	Socio- demographic	Prevalence of HF*	Main outcomes		
Denti et al., 2016 [8]	Retrospective cohort	Italy	N: 1847 Mean age: 74 Males: 960 (51.9%)	IS**	The multivariate model revealed a significant interaction (P =.01) between the neurological score on mortality and pre- hospital delay, as well as the survival benefit of early admission. Even if IS patients are unable to benefit from time- dependent therapies with established efficacy, like thrombolysis, early hospitalization can improve their chances of survival.		
Nagao et al., 2020 [9]	Prospective cohort	Japan	N: 5102 Mean age: 78 Males: 2965 (85%)	IS**	The findings demonstrated that, regardless of other variable an earlier admission was associated with a better outcome discharge.		
Jiang et al., 2016 [10]	Retrospective cohort	China	N: 666 Mean age: 70.6 Males: 341 (50.2%)	IS**, ICH#, or SAH##	Within two hours, 25% of patients reached the hospital or emergency room, but they were not given the usual care. In order to resolve the conflicts of interest between the hospital and the EMSs ^{***} system, it would be advantageous to enhance EMSs for stroke.		
Labberton et al., 2013 [11]	Retrospective cohort	Norway	N: 1072 Mean age: 76.4 Males: 558 (52.1%)	IS	Since many patients continue to come too late to get time- sensitive therapies, there is still an urgent need to lower the frequency of delayed admissions.		
Gupta et al., 2023 [12]	Prospective cohort	India	N: 100 Males: 63 (63%)	IS	Due to delayed admittance, only a small percentage of patients receive this life-saving treatment and are admitted to the hospital during this limited therapeutic window. One of the main causes of this delay is pre-hospital delay.		
Živanović, 2021 [13]	Cross- sectional	Serbia	N: 119 Mean age: 65.5 Males: 66 (48.2%)	IS	When contemporary thrombolytic therapy is no longer effective, over half of the patients show up at outpatient clinics.		

*Heart Failure, ** Ischemic Stroke, # intracerebral hemorrhage, ## subarachnoid hemorrhage, ***Emergency medical services

Study ID	Bias due to confound ing	Bias in the select ion of participa nts *	Bias in the classifica tion of intervention s	Bias due to deviation s from the inten ded interval	Bias due to missi ng data	Bias in the measure ment of outcomes	Bias in the select ion of reported result	Overal l bias
Denti et al., 2016 [8]	Low	Mod	Low	Low	Low	Mod	Low	Low
Nagao et al., 2020 [9]	Low	Mod	Low	Low	Low	Low	Low	Low
Jiang et al., 2016 [10]	Mod	Mod	Low	Low	Low	Low	Mod	Moder ate
Labbert on et al., 2013 [11]	Low	Mod	Mod	Mod	Low	Mod	Low	Moder ate
Gupta et al., 2023 [12]	Mod	Mod	Mod	Low	Low	Low	Mod	Moder ate
Živanov ić, 2021 [13]	Mod	Crit	Low	Low	Mod	Low	Low	Critical

 Table 2: Risk of bias assessment using ROBINS-I.

or the urgency required in seeking care. Dong et al. [14] emphasized the necessity of targeting these vulnerable populations to improve timely access to medical care. By implementing educational initiatives focused on stroke recognition and the importance of immediate medical attention, we can potentially reduce the time from symptom onset to treatment. Beyond patient-related factors, systemic inefficiencies within EMS also contribute to delays in stroke care. Coordination among EMS personnel and the protocols for early stroke detection are often inconsistent, leading to unnecessary delays even when patients reach hospitals quickly. Evenson et al. [15] noted that observational studies rarely collect and analyze data on the critical time span from the onset of stroke symptoms to the administration of tissue Plasminogen Activator (tPA) for ischemic stroke. This lack of comprehensive data hampers efforts to identify and address the root causes of delays in care. To improve the situation, there is a clear need for enhanced management and coordination within EMS. Optimizing protocols for early stroke detection, improving communication among EMS teams, and raising public awareness regarding stroke symptoms are essential measures. Public education campaigns can empower community members to recognize stroke signs and seek help promptly, thereby minimizing delays. Additionally, implementing community-based interventions can help bridge the gap between symptom recognition and medical intervention, particularly in underserved areas. In-hospital care indicators, including the prompt initiation of treatment, are addressed by quality improvement programs such as the Centers for Disease Control and Prevention's Coverdell National Acute Stroke Registries [16] and the World Health Organization's stepwise approach to stroke [17, 18]. These initiatives aim to streamline processes within hospitals, ensuring that once patients arrive, they receive timely and effective care. However, while these programs have made strides in addressing in-hospital delays, the primary cause of delays in receiving care for stroke remains patient-oriented factors related to careseeking behavior following symptom onset. It is crucial that future initiatives not only focus on hospital protocols but also directly address public awareness and education regarding stroke symptoms and the importance of timely medical intervention. Looking ahead, there is an opportunity to implement more successful community-based interventions globally over the next decade. Establishing efficient stroke surveillance systems will be essential for

understanding and enhancing pre-hospital and inhospital delays in acute stroke care. These systems can facilitate the collection of data on stroke incidence, response times, and treatment outcomes, providing valuable insights into the effectiveness of interventions and areas needing improvement. One of the primary recommendations from the review is the need for enhanced public health initiatives aimed at improving stroke symptom recognition among the general population. Timely admission to hospitals is crucial in minimizing the long-term effects of stroke, as the phrase "time is brain" aptly summarizes the urgency of treatment. Public health campaigns should focus on educating individuals about the warning signs of stroke, such as sudden numbness, confusion, difficulty speaking, and loss of coordination. By empowering the public with knowledge, we can foster a culture of immediate response, encouraging individuals to seek emergency care without delay. Moreover, educational activities should not be limited to the general population; healthcare providers also require ongoing training to enhance their knowledge and responsiveness regarding stroke care. Medical professionals must be equipped with the latest information on stroke management protocols, as well as the importance of rapid assessment and intervention. Regular workshops, seminars, and simulation training can help reinforce these concepts, ultimately leading to quicker recognition and treatment of stroke symptoms in clinical settings. Another critical aspect highlighted in the review is the need for EMS systems to simplify stroke identification and transport protocols. The current variability in EMS practices can lead to inconsistencies in patient care, which may contribute to pre-hospital delays. Establishing standardized protocols for stroke assessment can facilitate quicker decision-making by EMS personnel, ensuring that patients are transported to the most appropriate facility without unnecessary delays. Moreover, EMS systems should prioritize training for personnel on the use of specific stroke assessment tools, such as the Cincinnati Prehospital Stroke Scale (CPSS) or the Los Angeles Prehospital Stroke Screen (LAPSS). By utilizing these validated assessment tools, EMS providers can more accurately identify potential stroke cases and initiate appropriate transport protocols. Additionally, enhancing communication channels between EMS and hospitals can ensure that receiving facilities are prepared for incoming stroke patients, further reducing wait times upon arrival. Mobile stroke units are equipped with advanced imaging technology, allowing for immediate

CT scans and laboratory tests to be performed on-site. This capability enables rapid diagnosis and the initiation of treatment, such as thrombolysis, while the patient is still en route to the hospital. Research has demonstrated that the use of mobile stroke units can significantly reduce the time to treatment, ultimately improving patient outcomes. Telemedicine ambulances further enhance the pre-hospital care landscape by allowing EMS personnel to consult with neurologists in real time. This capability can facilitate quicker decision-making regarding treatment options and destination selection, ensuring that patients receive the most appropriate care based on their specific needs. The incorporation of these innovative technologies into the EMS framework has the potential to revolutionize stroke management, bridging the gap between pre-hospital and hospital care.

Strengths of the Review: This review provides a comprehensive synthesis of studies from diverse geographical and healthcare settings, offering a global perspective on the impact of pre-hospital delays in stroke management. By integrating both prospective and retrospective studies, the review enhances the reliability of its findings, emphasizing the generalizability of trends across various methodologies. Furthermore, the focus on patientoriented outcomes, such as survival rates and functional recovery, underscores the clinical relevance of the analysis. This patient-centered approach is vital in understanding the real-world implications of prehospital delays and the importance of timely intervention.

Limitations of the Review: Despite its strengths, several limitations should be acknowledged in this review. The heterogeneity of study designs, reporting metrics, and the extent of reporting can complicate comparisons between results. Most studies utilized retrospective data, which may be susceptible to recall and selection biases, potentially skewing the findings. local variations Additionally, in healthcare infrastructure and EMS procedures may restrict the generalizability of certain results to other environments. Moreover, the review did not extensively examine socioeconomic variables or healthcare equity (HCE) factors that could influence pre-hospital delays and outcomes. Socioeconomic status can significantly impact access to healthcare services, including timely emergency response. Further research is needed to explore these variables and their implications for stroke management, ensuring that interventions are equitable and effective across diverse populations.

Conclusion

Decreasing pre-hospital time-lag is of great importance for improving the outcome of acute stroke management. Early and uninterrupted access to treatment enables a larger proportion of patients to take advantage of life-saving interventions with a consequent improvement in mortality and post-stroke disability. Delay mitigation via public awareness, EMS enhancement, and overarching reform will contribute to the effectiveness and efficiency of stroke care. Research in the future should center on the assessment of interventions to reduce the pre-hospital delays, including disparities in access to and regional healthcare variations. Addressing these challenges will optimize the ability of healthcare systems to deliver better outcomes and alleviate the global burden of stroke.

Conflict of Interest

None

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None

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