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Post-traumatic Stress Disorder Following Acute Stroke

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Abstract

Purpose of Review Stroke is a devastating event that annually affects over 800,000 million individuals in the USA and is associated with significant individual and social costs. In this narrative review, we summarize current evidence regarding post-traumatic stress disorder (PTSD) following acute stroke.

Recent Findings In addition to the long-term physical consequences, it is increasingly recognized that psychological distress is common after stroke and transient ischemic attack (TIA). Nearly 1 in 4 survivors of TIA and stroke report elevated symptoms of PTSD in the first year following their cerebrovascular event. Those individuals with PTSD symptoms are at elevated risk for not only sustained psychological distress but also increased risk for non-adherence to medication. Factors in the emergency department, such as crowding, may influence the development of PTSD following acute stroke and TIA. We also summarize the rationale and clinical importance of developing and implementing quantitative predictive models of post-stroke PTSD symptoms in the ED setting.

Summary The potential of promising early interventions to prevent PTSD critically hinges on the accurate and precise identification of patients at risk for PTSD. Predictive modeling of PTSD risk may greatly facilitate the prospective management of mental health care in ED patients after stroke.

Keywords Post-traumatic stress disorder · Stroke · Transient ischemic attack · Emergency medicine · Prognostic models · Computational medicine · Acute care

Introduction

Stroke is the leading cause of serious disability and the fifth leading cause of death in the United States (US), with nearly 800,000 new cases annually [1••]. Transient ischemic attack (TIA), one of the major precursors to ischemic stroke, is also common, with an estimated 250,000–300,000 TIA events occurring each year in the US, and a median survival time of 8 years [2]. The public health burden of stroke and TIA is high, and the total annual costs of stroke are anticipated to increase about 129% to $240.67 billion by 2030 [3].

In the US, many acute and recurrent presentations of stroke and TIA present first to the emergency department (ED). In the 3 years between 2010 and 2013, there were 2.50 million ED visits for acute ischemic stroke in the US [4], over 297,000 annual ED visits attributed to TIA alone [5], leading to nearly 200,000 total inpatient admissions (via the ED and outpatient direct admission), and associated total health care costs totaling $2.6 billion per year [1, 6].

The short- and long-term medical complications of acute stroke, including increased risk of recurrent stroke, myocardial infarction (MI), and mortality, are well established [7]. Recent research has noted the common occurrence of psychological consequences of stroke and TIA, including post-traumatic stress disorder (PTSD) [8••, 9]. These adverse psychological reactions may be associated with increased risk of non-adherence to medication [10•]. In addition, PTSD has been shown to be associated with overall negative health outcomes, such as an increased risk for re-admission and

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recurrence of cardiovascular diseases as shown in patients with PTSD after acute coronary syndrome [11, 12]. This review summarizes recent research describing the prevalence and impact of PTSD symptoms following stroke and TIA. We highlight the challenges and the opportunities of developing quantitative prediction models for early identification of patients at risk of post-stroke PTSD based on factors available in the ED setting. Reliable and accurate predictive models are crucial to estimating individual PTSD risk after stroke. Such models will enable the identification of patients who can benefit [9] from timely, tailored psychological treatments that are personalized to the individual patients' PTSD risk.

Stroke and TIA Are Psychologically Stressful Events

Stroke and TIAs result in sudden and often progressive loss of bodily control and cognitive function. In qualitative investigations of the subjective experience of stroke, survivors interviewed within 72 h of stroke onset consistently described the terror of being awake and alert as an affected arm or leg became weaker to the point of paralysis [13]. During the acute phase, stroke patients report experiencing extreme anxiety, despair, and shock [14, 15]. In the aftermath of the acute phase, patients may experience long-lasting fear of the long-term health consequences of stroke such as physical disability, fear of recurrent stroke, and also the impact of stroke on longevity as well as social functioning and quality of life. They often report fear of losing control over their bodies and their future [13]. These psychological consequences have also been shown in TIA patients who have transient functional impairments [14].

Stroke and TIA May Induce PTSD

PTSD is a severe stress pathology triggered by emotional reactions to life-threatening events. PTSD is characterized by symptoms of repeated burdensome re-experiencing of the event (e.g., intrusive thoughts, nightmares) along with cognitive and behavioral avoidance of cues reminding the patient of the event, detrimental alterations in patients' cognition and mood, and hyperarousal [16]. PTSD symptoms lasting for 3 days to 1 month are classified as acute stress disorder, and longer-lasting symptoms are classified as PTSD. Both early and long-lasting symptoms are classified as trauma- and stressor-related disorders by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [17].

While historically, a large body of work on PTSD has focused on the presence of external traumatic events as triggers of PTSD, such as wartime exposure or sexual trauma, it is increasingly recognized that internal stressful events, such as the psychologically stressful experience of an acute stroke or other acute medical events, may also give rise to PTSD [18, 19]. According to the trauma criteria of categorical psychiatric nosology (DSM-5), qualifying trauma events are limited to incidents that qualify as "sudden, catastrophic"; medical events such as life-threatening stroke events requiring immediate ED admission satisfy this criterion [20, 21•]. Similar to external traumatic events, TIA or stroke can lead to high levels of psychological distress. Enduring somatic threat [22] is a characteristic of PTSD induced by acute medical events, defined as concerns of being unable to escape the threat of future events given the somatic source of the traumatic event. As such, the perceived or actual life-threatening experience of stroke and TIA and patients' psychological reactions, such as intense fear and anxiety, warrant high attention in acute care.

Based on a meta-analysis of 1014 patients from seven studies, the 1-year incidence of post-stroke PTSD ranges between 15 and 34% (mean 23%) in moderate severity stroke and TIA survivors [8••]. Up to 14% may experience persistent PTSD symptoms for more than 1 year after the stroke event [8••]. These rates indicate that post-stroke PTSD is considerably higher than the US 1-year PTSD prevalence of 4.7% [23] and the US lifetime prevalence of 6.8% [24]. In a prospective study that screened 108 patients for PTSD 3 months after experiencing TIA, the prevalence of PTSD was 29.6% [25], which is 10 times higher than the lifetime prevalence of PTSD (2.9%) in the German general population using the same screening instrument [25, 26].

In the US, the lost productivity due to PTSD is estimated as high as $3 billion (US dollars of the fiscal year 2000, i.e., inflation corrected to $4.7 billion in 2019) [27]. In turn, the secondary prevention of post-stroke PTSD after ED discharge is not only clinically important for the mitigation of individual disease burden in stroke patients but also a key for reducing public health costs. In sum, mounting evidence shows that PTSD after stroke may have negative impact on the prognosis of stroke rehabilitation and the mental health status of stroke patients presented in the ED with high downstream public health costs [8••, 28, 29].

Assessment for Post-stroke PTSD in the ED

Long-lasting PTSD symptoms after ED discharge, such as severe emotional distress, are among the most burdensome psychological sequelae in stroke and TIA patients as well as their caregivers [30]. However, since PTSD is conditional on trauma exposure, it offers an important opportunity for initiating early interventions to prevent PTSD [29]. In particular, ED clinicians have a unique opportunity to assess and mitigate

the risk of PTSD in the wake of the potential traumatic experience itself. However, since most moderate stroke and TIA survivors (i.e., about 77%) do not screen positive for PTSD after stroke [8••] and since the prevalence of stroke and TIA in ED patients is very high, blanket interventions launched early in the course of ED care are unlikely to be cost-effective or feasible [31, 32].

Quantitative clinical prediction models are important tools [33] to guide risk-targeted interventions for those stroke patients in the ED who are at the highest risk for developing PTSD. However, at the moment, it is challenging even for experienced ED physicians to reliably assess the future risk of psychiatric sequelae. Little is known about the natural progression of traumatic stress symptoms over time in the particular population of ED patients who experienced an actual or perceived life-threatening stroke and TIA event. Previous research on ED patient populations indicates important heterogeneity in the temporal evolution of PTSD symptomatology [34].

Typically, this heterogeneity can be decomposed into a *resilient trajectory*, as the majority of stroke or TIA patients will not screen positive for full-fledged PTSD, whereas a portion of trauma survivors with initial high stress symptoms can be expected to follow a *chronic trajectory* of non-remitting symptoms lasting for several months or even years [35]. What complicates the prognosis, however, is that significant numbers of patients may show unanticipated remission of initially high symptoms without any intervention (*rapid remission trajectory*) while an important fraction may develop delayed-onset PTSD, but without immediate high symptoms being observable in the ED in response to the trauma exposure [35]. Prospective longitudinal cohort studies, such as the Reactions to Acute Care and Hospitalizations (REACH) study examining stroke outcomes [21•], are promising to identify and describe such natural fluctuations and between-patient heterogeneity with regard to trauma- and stressor-related symptoms of ED patients having experienced stroke or TIA.

The prospective prognosis of post-stroke PTSD is further complicated by the inherent complexity of the psychiatric disorder which may present itself in numerous different phenotypes. Mathematically, there are 636,120 distinct symptom combinations that can qualify as PTSD according to DSM-5 [36]. At times, this complexity may further hamper the prediction of PTSD occurrence because currently no simple symptom-based prediction rule for the specific stroke population can be formulated. To address these potential challenges, data-driven machine learning and statistical modeling may be a valuable approach to discover sets of predictors with high accurate and reliable probabilistic information [37]. Below we provide a brief overview about what is already known about implicated candidate predictor variables and about the knowledge gaps that still remain.

Predictors of PTSD After Stroke and TIA Are Diverse

Previous narrative reviews identified multiple candidate predictor variables and risk factors but high between-study heterogeneity. The reviewed studies were mostly of limited sample size and mostly cross-sectional [28, 38]. The reported candidate predictors can be categorized into five broad clusters (Table 1): (1) general sociodemographic group-level PTSD risk factors, such as female gender, or education; (2) individual pre- and peri-traumatic risk factors, such as high perceived somatic threat or maladaptive coping strategies; (3) stroke-related risk factors, such as stroke localization; and finally (4) ED environment–related risk factors, such as time-to-treatment or ED crowding.

First findings on several variables have been reported in the literature as candidate clinical predictors (Table 1). However, it remains uncertain how these findings translate into a prediction model for the specific population of ED patients with an index event of stroke or TIA. Due to heterogeneity in study designs and clinical outcome measures, the quantitative synthesis of the existing findings presented in Table 1 is hampered. Further research on quantitative risk prediction models for PTSD after stroke is needed. In particular, high-quality systematic reviews are warranted to summarize what is already known and to assess the strength of evidence of existing findings and reported associations. Variables that are, in isolation, clinical predictors for PTSD quite generally may be uninformative in specific subpopulations or when combined with other relevant information. For instance, studies consistently report that younger age and female gender are clinical predictors of PTSD [16]. In theory, this could be driven by a special "high-risk" age range in female trauma survivors of age 30 or younger and may strongly interact with trauma type such as sexual assault or interpersonal violence. Whether younger age and gender have any positive predictive value in stroke survivors, where 3 out of 4 patients are likely above 65 years of age, needs to be shown independently. In contrast, biological risk factors of stress and fear maladaptation such as a genetic susceptibility or the dysregulation of the hypothalamic-pituitary-adrenal axis [49] may be stable predictors across different clinical contexts. The latter may be particularly promising as stroke leads to acute sympathetic hyperactivation [50–53].

To our best knowledge, there is currently no accurate, reliable, and externally validated clinical prediction model to prospectively estimate the risk of PTSD specifically in ED patients suffering from stroke or TIA. In light of the high individual burden and costs associated with psychiatric sequelae after stroke, such models are urgently needed.

Table 1 First evidence of predictors for PTSD after stroke/TIA

Predictor category	Candidate predictor	Evidentiary status (e.g., study design; sample size)	PTSD measure	Patient population	Reference
(1) Sociodemographic characteristics	Age	Cross-sectional cohort study; $N = 535$	PCL-S	Stroke and TIA survivors	Goldfinger et al. [14]
		Narrative review reporting findings of multiple studies	Not applicable	Post-stroke PTSD	Garton et al. [28]
	Gender	Consecutive sample, longitudinal study ($N = 94$)	IES-R, PTSD-Interview Scale	Stroke or TIA survivors	Favrole et al. [39]
		Cross-sectional cohort study; $N = 49$	IES	Stroke survivors	Bruggimann et al. [40]
		Longitudinal study; $N = 32$	PCL	Stroke survivors	Letamendia et al. [41]
		Narrative review reporting findings of multiple studies	Not applicable	Post-stroke PTSD	Garton et al. [28]
	Insurance status Education Marital status	Cross-sectional cohort study; $N = 535$	PCL-S	Stroke or TIA survivors	Goldfinger et al. [14]
(2) Psychological pre-, peri-, and post-traumatic risk factors	Alexithymia	Longitudinal study; $N = 90$	PDS	Stroke or TIA survivors	Wang et al. [42]
	Maladaptive coping	Narrative review reporting findings of multiple studies	Not applicable	Post-stroke PTSD	Garton et al. [28]
	Negative appraisal	Cross-sectional cohort study; $N = 49$	IES	Stroke survivors	Bruggimann et al. [40]
	Perceived somatic threat and emotional or psychological distress	Consecutive sample, longitudinal study ($N = 94$)	IES-R, PTSD-Interview Scale	Stroke or TIA survivors	Favrole et al. [34]
		Cross-sectional cohort study; $N = 49$	IES	Stroke survivors	Bruggimann et al. [35]
		Longitudinal study; $N = 32$	PCL	Stroke survivors	Letamendia et al. [36]
	Negative cognitions about the self and the world	Longitudinal study; $N = 81$	PDS	Stroke survivors	Field et al. [43]
	Negative affect	Cross-sectional study; $N = 102$	PDS	Stroke survivors	Merriman et al. [44]
(3) Stroke-related risk factors of unfavorable neurological outcomes	Stroke location	Cross-sectional cohort study; $N = 49$	IES	Stroke survivors	Bruggimann et al. [40]
		Consecutive sample; $N = 85$	PCL-S	Stroke survivors	Rutovic et al. [45]
		Cross-sectional study; $N = 102$	PDS	Stroke survivors	Merriman et al. [44]
		Cross-sectional telephone survey; $N = 352$	PCL-S	Stroke survivors	Merriman et al. [44]
(4) ED environment–related risk factors	Perceiving other ED patients are dying	Longitudinal study, REACH cohort; $N = 763$	PCL-C	Acute Coronary Syndrome survivors	Konrad et al. [46]
	Health care provider compassion	Patients admitted to the ED between January and December 2018 with who needed a life-sustaining intervention; $N = 99$; prospective cohort study	PCL-5	Life-threatening illness in the ED	Moss et al. [47]
	ED crowding	Longitudinal, observational cohort study; $N = 135$	IES-R	Acute coronary syndrome survivors	Edmondson et al. [48]

This is not a systematic review. *IES*, Impact of Event Scale; *PCL*, PTSD CheckList; *CAPS*, Clinician-Administered PTSD Scale; *PDS*, Post-traumatic Stress Disorder Scale

Future Directions: Towards Risk Mitigation of Post-stroke PTSD in the ED

Prospective risk estimation bears great potential to inform treatment choices and can enable risk stratification that increases the efficiency of identifying vulnerable patients for planned interventions. Research in other cardiovascular diseases, such as acute coronary syndrome, has found that ED environmental factors, ranging from ED crowding [48], clinician-patient communication [54, 55, 56•], and hallway care [57], may be associated with increased risk for development of post-traumatic stress. Exploring these variables in stroke patients may reveal similar relations. Additionally, a prediction model is a computational combination of multiple predictors from which the probabilistic risk of a specific PTSD symptom severity can be calculated for individual patients [58]. The concept of "risk" refers to the probability of the occurrence of an uncertain harm combined with the magnitude of that harm [59]. Such harms could comprise the non-remission of initially high PTSD symptoms in ED patients following stroke or, respectively, the potential delayed onset of PTSD symptoms after initial asymptomatic presentation.

The first step of building a prediction model is to understand the heterogeneity in the response of stroke survivors with regard to their experience of the index event as potential trauma. What is the typical response and what is the mean symptom severity to be expected at different times of follow-up? Are there distinct latent profiles of symptom trajectories such as *resilience*, *rapid recovery*, *non-remission*, and *delayed onset?* Large prospective cohort studies such as the REACH [21•, 32] and the AURORA [60] studies are well suited to provide important insights about those questions. In addition, data sharing of already available datasets on mental health in stroke survivors collected in ED setting should complement these efforts in identifying clinical predictors. Since the ED is at times a very hectic place, it may sometimes be difficult to obtain clinical interview data for research purposes. It may come handy that many candidate predictors (Table 1) are routinely collected and extractable from electronic medical records. Machine learning offers opportunities to use readily available electronic medical records to identify probabilistic information and risk factors in data-driven approaches [37].

Computational advanced approaches to predictive modeling are increasingly widespread across many fields of medicine, from radiology to cancer research and stress research [37]. Machine learning applications have shown the potential to outperform traditional statistical models such as logistic regression for predicting PTSD [61]. Leveraging machine learning tools on ED data to predict the probability, time course, and severity of PTSD symptoms after stroke are particularly promising because these versatile modeling approaches are suitable to unravel higher-order interactions among candidate predictors [37] and are able to shed light on new hypotheses to be tested for secondary prevention in the ED setting [15]. In particular, machine learning can be attuned to identify individual patients at high and highest risk which may warrant special care. Recent advances in the field have greatly improved the clinical interpretability of machine learning prediction models by providing patients and clinicians with explanations of individual predictions [62] and promote risk-aware shared decision-making. Such risk stratification may be very beneficial for existing prevention measures [32] and increase the likelihood of success of therapeutic approaches such as trauma-specific cognitive-behavioral intervention and symptom-based adjuvant psychopharmacological treatment.

Early Treatments and Rehabilitation for Post-stroke PTSD

To date, there are no evidence-based recommendations on specific treatments for preventing post-stroke PTSD after ED discharge [31, 32]. Some initial exploratory hypotheses can be based on the pathophysiology of stroke, PTSD, and post-stroke PTSD, which may jointly suggest a common role

Table 2 Planned, ongoing, or completed registered studies

Clinicaltrials.gov identifier	Evidentiary status (e.g., study design; sample size) and patient population
NCT03496480	A retrospective observational study of acute ischemic stroke patients ($N = 636$) at 9–13 months to investigate the association between PTSD symptoms and prior traumatization
NCT01187342	A prospective case-control observational study ($N = 120$) to compare the occurrence of depression in a striatal lesion group versus a non-striatal lesion group
NCT02797509	A randomized controlled trial in acute stroke (hemorrhagic and ischemic) patients ($N = 15$) investigating psychosocial skills–based intervention for preventing chronic depression, anxiety, PTSD, and decreased quality of life in patient and informal caregiver dyads at risk
NCT03605693	A randomized controlled trial in patients with stroke, TIA, or cardiovascular disease ($N = 10$) investigating written exposure therapy

for cortisol and serotonin. Initially, a Cochrane meta-analysis of 52 trials found that SSRIs significantly improved post-stroke outcomes of anxiety, depression, and neurological deficits [63] while SSRIs have also been shown to alleviate PTSD symptoms [64, 65]. However, much of the evidence was based on small samples and less rigorous study designs [66] and although SSRIs are low cost, risks such as risk of seizure, bleeding, and hyponatremia need to be considered in stroke patients [63]. A recent large double-blind randomized placebo-controlled trial ($N = 3127$) in acute stroke did not find improvement of daily 20 mg of fluoxetine on functional outcome at 6 months [67] but suggestive evidence on a potential to reduce the occurrence of depressive symptoms [67].

Little research has directly investigated early interventions to mitigate post-stroke PTSD symptoms (Table 2).

In light of the high burden and cost of PTSD and a relative research paucity, there remain great opportunities for new discovery in this area. Predictive models that accurately and reliably identify ED patients at highest PTSD risk shortly after stroke or TIA exposure could identify cost-effective potential interventions. Moreover, rehabilitation has been shown to aid the improvement of psychomotor and linguistic capabilities following treatment for acute stroke [42]. Future work may evaluate the potential impact integrating psychological interventions directly into rehabilitation programs immediately following stroke. This may give rise to a multi-disciplinary approach that goes beyond acute care and functional outcomes and incorporates behavioral and emotional recovery in order to restore and maintain quality of life.

Conclusion

Stroke and TIA are often experienced as unexpected, uncontrollable, and life-threatening events that can act as triggers for PTSD [43]. The timely identification of risk for psychological sequelae following stroke/TIA can inform clinical management in the ED setting and potentially alter the trajectory of long-term mental health outcomes. Besides the evident neurological consequences, stroke is associated with psychological, emotional, and behavioral consequences that go beyond acute fear and anxiety. Eventually, the long-term psychiatric needs of stroke patients may be disguised behind a veil of a "anhedonic and dysphoric," "externalizing angry and aggressive," or "dissociative" symptom phenotype [17] or of an unstable or non-linear pattern of symptom progression that is not immediately clinically apparent. If unpredictable and thus not timely treated, post-stroke PTSD can lead to long-term distress and substantial individual disease burden and costs. Further epidemiological research must focus on identifying etiological and modifiable risk factors to guide early interventions that are precisely targeted at improving the mental health of those patients at the highest risk of psychiatric care. Accurate and reliable risk prediction rules for ED clinicians are needed for increased likelihood of future early interventions to be clinically beneficial and cost-effective. Further research in this area is of high clinical importance and public health relevance. With 800,000 stroke incidence per year in the US and 1 out of 4 stroke and TIA patients being at risk of PTSD, the ED plays a key role in the early screening and potential implementation of primary and secondary interventions to improve patient outcomes. Increased knowledge of such psychological sequelae of stroke and TIA among acute care providers will ideally lead to further innovations in this important area of psychological and neurologic health.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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