 https://doi.org/10.21601/ejbms/10817

Pre-Hospital Delay and Associated Factors of Ischemic Stroke in Northern Mediterranean Countries: A Literature Review

Ahmed Kharbach [1]*, Majdouline Obtel [1,2], Mohamed Amine Baba [3,4], Laila Lahlou [4], Rachid Razin [1,2]

[1] Laboratory of Biostatistics, Clinical Research and Epidemiology (LBRCE), Faculty of Medicine and Pharmacy of Rabat, Mohammed V University of Rabat, MOROCCO

[2] Laboratory of Social Medicine (Public Health, Hygiene and Preventive Medicine), Faculty of Medicine and Pharmacy of Rabat, Mohammed V University of Rabat, MOROCCO

[3] Laboratory of Health Sciences, National School Applied Sciences, Ibn Zohr University, Agadir, MOROCCO

[4] Faculty of Medicine and Pharmacy of Agadir, University Ibn Zohr, Agadir, MOROCCO

* Corresponding author:
Kharbach.a.lbrce@gmail.com

EUROPEAN JOURNAL OF BASIC MEDICAL SCIENCE

Eur J Basic Med Sci 2019;9(1):5-16

Received: 10 Sep 2019

Accepted: 25 Dec 2019

ABSTRACT

The emergence of new therapeutic protocols for reperfusion requires the respect of a therapeutic window which consists of an optimal admission time of 4.5 hours, and which should not exceed 6 hours according to the latest clinical trials. The objective of this narrative review of the literature is to identify the time of admission of patients arriving at emergency departments for ischemic stroke after the onset of symptoms, as well as the factors that influence it in four European countries of the Northern Mediterranean (Spain, France, Italy, and Turkey).

Twenty-two studies published between 2004 and 2018 were included. The mean pre-hospital delay ranged from 7.65 hours to 22.5 hours. The median prehospital delay ranged from 1.54 to 6.08 hours. The proportion of patients consulting after the first 3 hours ranged from 31.6 to 96.29%. Almost half of the studies (45%) associated the transport used with early admission delay. More than a third of the studies (36%) revealed an association of this delay with the destination of the first call after the signs related to the stroke was noticed. Whereas, 32% of the studies showed that vigilance (consciousness) disorders were the symptoms most related to early admission due to their severity. In addition, advanced age was implicated in 27% of the studies as a determinant contributing to a reduction of the time to arrival of patients. Besides, the lack of awareness and underestimation of symptoms was reported in 13% of the studies, constituting the main barrier affecting negatively early admission.

These findings show that the optimal therapeutic window recommended is not always respected even if in developed countries, and that ignorance about the symptoms evocative of ischemic stroke still remains in Northern Mediterranean countries. This implies that measures ought to be implemented in order to improve care in the best possible way, focusing mainly on educating and raising the awareness of the population about the signs of this disabling disease and the actions to be taken.

Keywords: Ischemic stroke, prehospital delay, associated factors, therapeutic window, Northern Mediterranean countries

INTRODUCTION

Early diagnosis and treatment of acute ischemic stroke (AIS) is critical to survival and disability [1]. Despite recent advances in the management of AIS, reperfusion therapy is administered only to 1 to 8% of patients [2]. Furthermore, despite the availability of thrombolytic and endovascular treatments for stroke in the acute phase, many patients are ineligible due to the late arrival at the hospital [3]. Similarly, the main barrier to this fibrinolytic protocol is the delayed arrival of patients to the emergency departments (ED) of hospitals, which have the capacity to deliver it [4]. Reducing this pre-hospital delay is a major challenge for healthcare systems all over the world [5].

Identifying the factors influencing early or late arrival at hospital facilities and raising public awareness of these determinants can contribute to the successful management of ischemic stroke (IS) [1]. A systematic review of the literature showed that the major factors affecting pre-hospital time were related to patient pathways and pathways of emergency care, patient health characteristics, clinical characteristics (symptoms) of stroke, patient and witness behaviors at the time of stroke-related symptom onset, and level of stroke knowledge [6]. Studies have demonstrated that delays in admission to ED are due to a late decision to seek medical care [7]. This may be facilitated by the paucity of general knowledge about symptoms and risk factors for IS, which is considered a major hindrance to care access [8]; whereas, other studies have attributed early admission to the use of the Emergency Medical Services (EMS) [9].

The present narrative review of the literature aims to summarize all the studies conducted between 2004 and 2018 in four Northern Mediterranean countries (Spain, France, Italy, and Turkey) and to identify the factors influencing the pre-hospital delay of patients with IS.

DELAY OF PATIENT'S CONSULTATION WITH ISCHEMIC STROKE IN NORTHERN MEDITERRANEAN COUNTRIES

Twenty-two studies quantified the time to admission for patients with IS, either as a percentage of patients arriving within a 3-hour or 6-hour time frame, and/or as a mean and median [1,4,5,7-25].

According to the studies conducted in France (n=9) [4, 10, 12-18], the median time to admission was reported in (n=5) studies, and was found to be between 3.25 hours and 6.08 hours [5,10,13,16,20]. In addition, only one study explored a median pre-hospital admission time of 22 h 30 min, according to the study conducted by Griesser et al. (2005) [13]. Furthermore, studies of Desseigne et al. (2012), Redjaline et al. (2015), Luis (2004) and Julié (2004) have shown that less than half of the population does not exceed the 3-hour treatment window [4,12,16,18], while only one study of Laribi et al. (2004) found a small proportion of recruited patients arriving within 3 hours (3.7%) [17].

The French study, which was conducted in Tours by Charaa et al. (2004), revealed that the median admission time was 6 h 05 min for the Reception and Emergency Center (Commonly known locally by the acronym "CAU") and 2 h 25 min for the proximity unit for emergency treatment and orientation (Commonly known locally by the acronym "UPATOU"). Therefore, the UPATOU is associated with an early delay [10].

In Italy, (n=4) studies showed that the median pre-hospital delay was between 1 h 53 min and 5.4 h [9,11,24,25], of which two studies also reported an average admission time of 7.65 hours [11,24]. Besides, two other studies reported the proportion of patients admitted within 3 hours. In this sense, 37.6% of patients were admitted in less than 3 hours [22], whereas in the study by Maestroni et al. (2008), 28% of patients were admitted in less than 3 hours [9]. Another study demonstrated that 60.8% arrive before 6 hours [23].

In Spain, the investigation performed in the Castilla region by Ruiz Garcia et al. (2017), indicated that the median time was 3 hrs 11 min and 48.7% accessed within 3 hours [21]. Another investigation indicated a median time of 5.73 hours [5]. The study carried by Palomeras et al. (2008), in the Catalonia region, showed that 57.5% of patients arrived at the hospital in less than 3 hours [20]. The study carried out by Geffner et al. (2012) revealed a proportion of 39.2% of patients arriving before 3 hours [5].

For Turkey, the study by Keskin et al. (2005), and Koksal et al. (2014), explored respectively a median admission time of 1h33min and 2h33min [7,26]. On the other hand, the study by Korkmaz et al. (2010), found a mean time to admission of 9.5 hours [8]. In a similar vein, the studies by Memis, Koksal and Korkmaz reported respectively 68.4%, 44%, and 55% of patients arriving within 3 hours [1,8,19].

The results are detailed in **Table 1**.

***Table 1**. Mean and median pre-hospital delay (from symptom onset to arrival in the emergency department) and percentage of patients with ischemic stroke arriving within 3, and 6 hours*

Studies	Country	Design of the study	Sample size	Median delay (H)	Mean delay (H)	% < 3H delay	% > 3H delay	% < 6H delay	% > 6H delay
Laribi, Chicheportiche et al., 2004 [17]	France	Retrospective	27	-	-	3,7	96,2	-	-
Charaa, Bonnaud et al. 2004 [10]	France	Prospective	598	6h5min^{CAU}/ 2h52min^{UPATOU}	-	-	-	-	-
Julié, Bonnaud et al., 2004 [16]	France	Prospective	598	4,86	-	40	60	-	-
Luis, Paule et al., 2004 [18]	France	Prospective	-	-	-	47	53	-	-
Griesser et al. 2005 [13]	France	Prospective	329	3,25	22,5	-	-	-	-
Heydenreich et al., 2008 [14]	France	Prospective	201	1h10min /1h51min^{SMUR}	-	-	-	-	-
Desseigne et al., 2012 [12]	France	Prospective	536	4	-	31	69	-	-
Joux et al., 2013 [15]	France	Prospective	313	-	-	-	-	-	-
Redjaline et al., 2015 [4]	France	Prospective	339	5,25	-	31	69	-	-
Silvestrelli et al., 2006 [22]	Italy	Prospective	1364	-	-	37,6	62,4	-	-
Silvestrelli et al., 2006 [23]	Italy	Prospective	1479	-	-	-	-	60,8	39,2
Maestroni et al., 2008 [9]	Italy	Prospective	375	5,4	-	28	72	-	-
Vidale et al., 2013 [25]	Italy	Prospective	573	2	-	-	-	-	-
Vidale et al., 2016 [24]	Italy	Retrospective	2114	4,86	7,65	-	-	-	-
Denti et al., 2016 [11]	Italy	Prospective	914	1,88	7,65	-	-	-	-
Palomeras et al., 2008 [20]	Spain	Prospective	292	-	-	57,5	42,5	-	-
Geffner et al., 2012 [5]	Spain	Prospective	382	5,73	-	39,2	61	-	-
Ruiz, Fernández et al. 2018 [2]	Spain	Prospective	263	3,18	-	48,7	-	-	-
Keskin et al., 2005 [7]	Turkey	Prospective	229	1,54	-	-	-	-	-
Memis et al., 2008 [19]	Turkey	Prospective	98	-	-	68,4	31,6	-	-
Korkmaz et al., 2010 [8]	Turkey	Prospective	117	-	9,5	44	56	58,1	41,9
Koksal et al., 2014 [1]	Turkey	Prospective	106	2,55	-	55	45	-	-

CAU: Emergency Reception Center; **UPATOU:** Proximity emergency reception, treatment and orientation unit; **VSAV:** Victim Assistance and Rescue Vehicle; **SMUR:** Mobile Emergency and Reanimation Service

FACTORS ASSOCIATED WITH PRE-HOSPITAL DELAY OF ISCHEMIC STROKE PATIENTS IN NORTHERN MEDITERRANEAN COUNTRIES

Socio-Demographic Factors Associated with Pre-Hospital Delay of Ischemic Stroke Patients in Northern Mediterranean Countries

Age as a determinant associated with the time to admission for ischemic stroke

Several studies have confirmed the existence of a significant relationship between patient age and admission time. The study conducted in Turkey by Keskin et al. (2005), showed that age below 65 years is associated with the short consultation time ($p<0.001$) [7]. Similarly, the Italian study of Silvestrelli et al. (2006) indicated that the mean age of patients arriving within the first 6 hours was higher than those arriving after 6 hours ($p<0.05$) [23]. Also, another study conducted by the same author found that patients arriving within 3 hours were significantly older than those arriving after 12 hours ($p <0.01$), a result which could be explained by the fact that the elderly had more severe clinical signs [22].

On the other hand, the Spanish study by Garcia et al. (2017) mentioned that the average age of 69.62 years is related to a consultation time of less than 1 hour ($p<0.05$) [2]. Palomeras et al. (2008) in turn confirmed that age averaging 75.7 years was associated with a delay of less than 3 hours ($p=0.04$) [20]. Finally, the study by Vidale et al. (2013) reported that the time from onset to activation of EMS was significantly longer for patients aged 80 years and more compared to younger subjects ($p<0.05$) [25].

Contrary to these aforementioned, other studies have shown that there is no significant relationship between age and consultation time. By this logic, the three Turkish studies by Koksal et al. (2014), Memis et al. (2008), and Korkmaz et al. (2011) did not explain any association between age range and pre-hospital delay with ($p>0.05$) [1,8,19]. In addition, two other Italian investigations by Vidale et al. (2016) and Maestroni et al. (2008), as well as the French study by Joux et al. (2012), found the same result [9,15,24].

Gender as a determinant associated with time of admission for ischemic stroke

Sex is undoubtedly a very important factor to consider. Three studies have reported a significant association between patient consultation time and gender, including the study by Silvestrelli et al. (2006), which indicated that men had a long consultation time compared to women in the group arriving more than 12 hours ($p<0.01$) [22]. Moreover, the Spanish study by

Garcia et al. (2017) has shown that the female sex was a predictor factor for consultation seeking more than 60 min (p=0.007) [21]. By contrast, the study of Memis indicated that gender had no effect on time to hospital arrival (p>0.05) [19]. Similarly, studies by Koksal, Palmeras, Denti, Desseigne, Maestroni et al. showed no significant association between gender and admission time of less than 3 hours (p=0.09) [1,9,11,12,20]. Another study reported that EMS was activated more in women than in men (58% vs. 47%; p<0.001) [24].

Is There an Association Between the Clinical Characteristics of Patients (Symptoms) and the Co-morbidities Associated with the Delay of Patients' Admission to Hospital Facilities?

Several studies have reported a significant association between motor disorders and pre-hospital delay in patients with IS. The first study by Keskin et al. (2005) confirmed the existence of a significant association between motor disorders and a short admission delay [7]. In the same vein, the second and third study conducted by Denti et al. (2016) in the city of Parmie and Palomeras et al. (2008) in Maresme, indicated that motor disorders combined with neurological disabilities were also related to early delay with (p=0.0009) and (p=0.028), respectively [11,20]. However, the investigation conducted by Desseigne et al. (2012) concluded that motor disorders had not influenced patient admission time [12].

For vigilance disorders. Studies have confirmed that this type of disorder has a positive influence on the consultation time. Certainly, in the French study by Desseigne et al. (2012), patients admitted in less than 3 hours had a very high frequency of vigilance disorders (p=0.0001) [12]. Similarly, the study by Maestroni et al. (2008) and Redjaline et al. (2015) found that altered level of consciousness is associated with consultation times less than 3 hours with (p=0.005), (p=0.03), respectively [4,9]. Other studies found that patients with vigilance disorders to the point of consciousness impairment had a tendency to arrive at the hospital more quickly (p<0.05) [1,20,22,23]. By contrast, two other investigations showed no significant association between the level of consciousness and the time of patients' admission, with (p>0.05) [15,24].

Speech impairments, too, have been highlighted in four studies as an important factor contributing to early admission. The French study by Desseigne et al. (2012), Garcia et al. (2017), Korkmaz et al. (2011) and the Spanish study by Palomeras et al. confirmed that people with aphasia as the main sign arrive at the hospital earlier than those with other clinical signs suggestive of stroke with a p-value of less than 0.05 [8,20,21].

In addition to the symptoms that appeared, risk factors or co-morbidities or medical history had a significant association with pre-hospital delay. Personal history of stroke was reported in three studies to be associated with a delay in admission of less than three hours with a p-value of <0.05 [7,21,22]. Nevertheless, three other studies by Koksal et al. (2014), Joux et al. (2012), and Desseigne et al. (2012) reported a non-significant association between stroke history and time to visit with p>0.05 [1,12,15].

A history of transient ischemic attack (TIA) was also reported in four studies. In this respect, Garcia et al. (2017), indicates that a history of TIA is associated with an admission delay of less than 3 hours (p=0.02) [21]. Also, a similar result was found in two studies by Silvestrelli et al. (2006) [22,23]. Conversely, only one study by Redjaline et al. (2015) indicated the opposite result with p=0.41 [4].

The other factors that have been implicated, including hypertension and diabetes have been reported in several studies. Therefore, the study by Joux et al. (2012), confirmed that the presence of diabetes has influenced positively the time between the onset of signs and hospital admission between the two groups of patients transported by the FD and the EMS [15]. The same result featured in the study by Silvestrelli et al. (2006), as well as in the study by Denti et al. (2016), with p<0.05 and p=0.01, respectively [11,23].

However, the studies performed by Koksal et al. (2014), Maestroni et al. (2008), and Desseigne et al. (2012) indicate that hypertension and diabetes did not have a significant association on the time to admission, with (p>0.05) [1,9,12]. Furthermore, Joux et al. (2012) and Denti et al. (2016) have observed that hypertension is not associated with admission delay, with p > 0.05 [11,15].

With respect to dyslipidemia, the Palomeras et al. (2008) indicated that among vascular risk factors, only dyslipidemia was associated with a delay of more than 3 hours (p = 0.019) [20]. By contrast, Silvestrelli et al. (2006) demonstrated that dyslipidemia had no significant influence on arrival time (p >0.05) [23].

Compared to the heart disease, the Spanish study conducted by Palomeras et al. (2008) showed a significant association with a short pre-hospital delay with a (p=0.047) [20]. Likewise, Ruiz Garcia et al. (2017) noted that among the factors independently associated with a prehospital delay of 180 minutes or less was the fact of having a pre-existing heart disease (p=0.03) [21]. Two other studies of Silvestrelli et al. (2006) found out that ischemic heart disease influenced significantly earlier arrival time (p<0.05) [22,23]. In turn, the study conducted by Koksal et al. (2014) explored that among the risk factors of stroke, a history of coronary artery disease and atrial fibrillation were statistically more frequent in the first group of patients admitted to hospital (p<0.05) [1].

Patients' Perceptions, Recognition of Stroke Symptoms, and Behaviors at Stroke Symptom Onset

Keskin et al. (2005) revealed that patient recognition of symptoms contributed to decreased pre-hospital delay (p<0.01) [7]. Following the same line of thought, Koksal et al. (2014) joined Keskin et al. (2005) in demonstrating that recognition of symptoms as stroke (p = 0.01), feelings of fear and panic (p = 0.001) were higher in the early arrivals group than in the late arrivals group, and that recognition of stroke symptoms was an independent factor associated with early hospital arrival. Besides, patients who recognized symptoms as stroke were 3.4 times more likely (95% CI, 1.2-9.3) to arrive at hospital earlier than those who did not recognize symptoms as stroke [1].

In addition, Gressier's study confirmed that patients who recognize their symptoms as stroke symptoms are more likely to use a cardiomobile, rather than an ambulance, and that the "symptom-arrival time at the ED" is significantly shorter if the patient is transported by the cardiomobile or ambulance than using their own means [13].

Palomeras et al. (2008) reported in their study in Maresme, Spain, that perceptions of the urgency of the situation were strongly associated with a prehospital delay of less than 1 hour and 3 hours (p=0.000) in the onset of stroke symptoms [20]. Similarly, Geffner et al. (2012) showed in their study in Castellon, that consideration of the attack as a serious event was associated with a shorter decision delay and arrival time (p = 0.005); as well as the identification of the event as a stroke was also associated with reduced delay in both of the above-mentioned delays [5].

In regard to patient behaviors at symptom onset, the study of Korkmaz et al. (2011) concluded that among patients who arrived at the hospital for more than three hours (45.9%), most of them had waited for symptoms to disappear or were hesitant to attend the hospital [8]. By the same token, Memis et al. (2008) concluded that the most common reason given by patients for long pre-hospital delay was waiting for symptoms to disappear (35.5%) [19]. According to the study by Silvestrelli et al. (2006), and more specifically in relation to the reasons for pre-hospital delay (> 6 hours), underestimation of symptoms was the most frequent cause with a percentage of 48.7% [23].

Does Lifestyle Influence the Admission Time for Stroke Patients?

For the Korkmaz study, hospital arrival within the first three hours was statistically significant for those living with family members (p = 0.008) [8]. In a similar vein, Denti et al. (2016) found that patients who arrived at the hospital earlier differed from those who arrived after 2 hours in terms of their living conditions, since the majority of the latter lived alone (p=0.04) [11]. Likewise, in the study by Garcia et al. (2017), the onset of symptoms at the time of the presence of a son or daughter (witness) was independently associated with earlier arrival and more specifically with a prehospital delay ≤180 minutes (OR 3.84; 95% CI 1.90-7.76; P < 0.001) [21]. Along with that, the study of Desseigne et al. (2012) indicated a significant difference between the group arriving before 3 hours and the group arriving after 3 hours based on the presence of a member of the entourage at the onset of functional signs of stroke (58% vs. 39%, p < 0.01) **[12]**.

Whereas, other studies have concluded that there is no significant correlation between a person's social status and admission time. This finding was corroborated by Memis et al. (2008), who revealed that marital status and occupation are not associated with a delay shorter than 3 hours [19]. The same findings were reported in the study of Koksal et al. (2014), who found that there were no significant differences between the group arriving in less than 3 hours and those arriving more than 3 hours with respect to marital status (p=0.06), occupation status (p=0.34), and living alone (p=0.7) [1]. Also, Keskin et al. (2005) and Geffner et al. (2012) have shown that living alone has no significant association with hospital admission time (p=0.342) [5, 7], and in the

study of Palomeras et al. (2008), confirmed that marital status, living alone or accompanied, presence of stairs or elevator in the home, as well as level of education, did not influence pre-hospital delay [20]. On the other hand, the study by korkmaz et al. (2010), did not find any association with admission time as regards employment and level of education [8].

Factors Related to the Type of Alert, First Recourse to the Health Care System, Transfer Circuit Type and Orientation After Symptom Onset

In two French studies. The first conducted by Redjaline et al. (2015), showed that the factors significantly associated with a pre-hospital delay of 3h30 min were : a first call to the center 15 (33% [95% CI, 24-42] vs. 22% [95% CI, 17-28], p=0.03), to the FD (19% [95% CI, 11-26] vs. 7% [95% CI, 4-11], p<0.01), or to relatives (19% [95% CI, 12-27] vs. 11% [95% CI, 7-14], p=0.02) [4]. The second conducted by Desseigne et al. (2012) confirmed that regardless of the destination of the first call, an admission delay of more than 3 hours was associated with a medicalized intervention before admission to the ED (p=0.0001). What is more, the absence of this intervention (direct transport to the ED by the FD, a private ambulance or by relatives) was significantly associated with the 82 (49%) patients in group I versus the 42 (12%) patients in group II (p=0.0001). Hence, when the physician was the recipient of the first call, patients tended to arrive late. However, a delay of < 3 hours was associated with a caller who was from the patient's family and friends (p=0.0001) [12].

A study carried by Vidale et al. (2013) in cities in the macro region of northern Italy showed that the implementation of a triage system based on a set of codes (EMS code) favors rapid access to hospital facilities and in particular the use of the red code reserved for extreme emergencies, which has certainly reduced pre-hospital delays (p<0.05) [25]. The same author, in another study, conducted in 2016 found that the yellow code for emergencies was also associated with early arrival. This code contributed to a significant reduction in pre-hospital time (p < 0.001) [24].

Garcia et al. (2017) in turn demonstrated that calling 112-EES (Extrahospital Emergency Services) was associated with a pre-hospital delay of 60 minutes or less (OR 5.69; 95% CI 2.41-13.45; P <0001). The use of a pre-notification system (Stroke code) (OR 8.18; 95% CI 2.95-22.70) and the composition of 112-EES (OR 3.86; 95% CI 1.47-10.11; P = 0.006) were also independently associated with earlier arrival (Prehospital delay ≤180 minutes) [21]. In a similar study, Geffner et al. (2012) showed that the median time to ED arrival was significantly shorter when calling the EMS: 117 minutes compared to 285 minutes for patients who attended hospital alone and 546 minutes for those who visited their general practitioner first (p = 0.000) [5]. On the other hand, Palomeras et al. (2008) showed that patients who decided to go immediately to the ED were more susceptible to reach the ED within 3 hours (P = 0.001) [20].

Other studies have pointed to determinants related to late admission. In this sense, the study of Griesser et al. (2005) affirmed that the delay between the onset of symptoms and arrival at the ED was longer when the patient called a general practitioner or SOS physicians (p<0.004) [13].

Factors Related to the Mode of Transportation Used by Patients After the Onset of Stroke Symptoms

The Italian studies by Vidale et al. (2013), Maestroni et al. (2008), and the Turkish study by Koksal et al. (2014), confirmed that the use of EMS is significantly associated with a shorter delay compared to other available means of transport with (p<0.001) [1, 9, 24, 25].

The first study by Vidale et al. (2013) showed that pre-hospital time was reduced by half in patients hospitalized by the EMS (p < 0.001) [25]. The second study by Maestroni et al. (2008), indicated that the arrival time was significantly shorter in patients using EMS (p<0.001) [9]. The third investigation by Koksal et al. (2014) reported that Seventy-two patients representing 63.7% arrived at the hospital by private car and 41 (36.3%) by ambulance, and that the median pre-hospital delay for those using private vehicles was significantly longer than for ambulances (p = 0.03). In addition, the use of EMS-Ambulance was associated with a delay of less than 3 hours (p=0.04) [26].

However, another study conducted in Geneva by Griesser et al. (2005) showed that the duration of "symptoms-arrival at "CAU" was significantly shorter if the patient was transported by the Cardiomobile Ambulance or by an ambulance than if the patient transported by his/her own means. Therefore, if the transport is performed by the Cardiomobile Ambulance or by an ambulance, the admission to the ED is respectively 2.4 and 1.8 times shorter than if the

transport is performed by the patient's own means (p<0.0005). However, even though the use of ambulance in general significantly shortens the delays, there is still an important difference between the specific use of the cardiomobile and that of a "non-medical" ambulance. This difference lies mainly in the time between the onset of symptoms and the time of calling 144 (53 minutes for the cardiomobile versus 107 minutes for other types of ambulance) [13].

Another French study done in Martinique by Joux et al. (2012) found that EMS transported 61.6% of patients and 38.4% were transported by the FD, mostly diabetics, and a similarly comparable difference in the time from symptom onset to call, which was 67 minutes for EMS and 77 minutes for FD, but the average time from call to hospital arrival was shorter in the FD group than in the EMS group. And a similarly comparable difference in the time from symptom onset to call, which were 67 minutes for EMS and 77 minutes for FD, but the average time from call to hospital arrival was shorter in the FD group than in the EMS group. The average time from call to hospital was slightly shorter in the FD group than in the EMS group [15].

Regarding the study conducted by Hydenreich et al. (2008) in Bordeaux, It was confirmed that the comparison between the time taken to transport by private ambulance and the Victim Assistance and Rescue Vehicle (Commonly known locally by the acronym " VSAV") did not reveal any significant difference, except that persons prefer the VSAV because of its accessibility compared to the other [14].

While the study of Redjaline et al. (2015), reported that among the factors significantly associated with patients in the group (<3h30min) was transport to the hospital by the FD (41% [IC 95%, 32-51] vs. 25% [IC 95%, 19-30], p<0.01) [4]. Conversely in Turkey, in the city of Aydin, Memis et al. (2008) found that patients arriving within 3 hours of symptom onset were more likely to come by ambulance (22.4%) or private vehicle (77.6%) (Ki2= 5.697, p <0.05) [19]. Furthermore, only one study, namely that of Korkmaz et al. (2011), demonstrated the absence of a significant association between the time of admission of stroke patients and the mode of transport used [8].

Circumstantial or Contextual Factors and the Pre-hospital Delay

Stroke symptom onset timing and pre-hospital delay

Based on the study of Garcia et al. (2017), the onset of symptoms on non-work days was associated with a pre-hospital delay of less than 3 hours (OR 1.91; 95% CI 1.08-3.37; P = 0.026) [21]. In the same vein, the Palomeras et al. study (2008) found that having a stroke on Sunday was an independently predictor factor of a delay less than one hour (OR 3.46; 95% CI 1.56-7.66 p= 0.002) [20].

The French study conducted in Sainte Etienne by Desseigne et al. (2012) also reported that diurnal onset of stroke signs appeared to be more frequently associated with admission before the third hour (p=0.001) [12].

According to the study of Silvestrelli et al. (2006), patients who suffered a stroke in the morning and afternoon tended to arrive earlier (<3 hours): 38.5% (301/782, P <0.01) and 40.2% (281/700, P <0.01), respectively [22]. Another study by Silvestrelli et al. (2006) reported that 38.3% of all stroke patients arrived in the morning, 34.3% in the afternoon, 22.8% at night and 4.6% for an unknown time. Patients with overnight stroke arrived later [23].

The study conducted in Izmir by Korkmaz et al. (2011) showed that the time between 00:01 and 6:00 am was the period when patients arrived 4 times later than the other periods ((from 6:01 to 12:00), (12:01 to 18:00) and (18:00 to 00:00) (p=0.06), OR=4.03) [8]. For other researchers such as Memis et al. (2008), day of the week and time of day have no effect on the time to hospital arrival (p>0.05) [19]. Similarly, Vidale et al. (2013), showed that the occurrence of stroke during working or non-working days or time of day (day or night) had no significant association with time to ED arrival [25]. Also, studies by Maestroni et al. (2008) and Koksal et al. (2014) indicate that the onset of signs of stroke during the day or at night, as well as during working and non-working days, do not influence pre-hospital admission time (p>0.05) [1,9].

The site of symptom onset and pre-hospital delay

According to the study of Desseigne et al. (2012), the occurrence of symptoms in a public location contributed to rapid admission (<3 hours) (p=0.05) [12].

On the other hand, Memis et al. (2008) reported that the patients' place of residence had no influence on admission time (p>0.05) [19]. Similarly, Silvestrelli et al. (2006), in two separate studies, showed that the area where patients live, whether urban or rural, had no influence on admission time after the onset of stroke symptoms [22,23].

DISCUSSION

The results of the present review show, firstly, that the median pre-hospital delay in Northern Mediterranean countries is between 1 hour 10 min and 6 hours 5 min, and between 2 hours 36 min 22 hours 30 min for the mean pre-hospital delay. These findings, however, appeared to be better than those found in other African studies. By this logic, a systematic literature review revealed that the median pre-hospital delay in Africa was 31 hours [27]. Furthermore, the median pre-hospital delays revealed in this literature review were higher than those recorded in other studies [11,21,24,28,29]. However, they are lower than other pre-hospital delays obtained in other investigations [30-34].

As for the average pre-hospital period, it varies between 26 and 61.9 hours in Morocco, according to the results of a recent literature review [35]. This suggests that the average pre-hospital delays in northern Mediterranean countries, recorded in the current literature review (2 hours 36 min to 22 hours 30 min) is considerably lower than the range revealed by the systematic literature review performed in Morocco.

This prehospital time lost outside the hospital is mainly due to several factors [36]. Moreover, the determinants influencing this delay vary considerably between populations and regions [37]. Similarly, the factors identified as influencing pre-hospital delay were different, even contradictory, according to studies conducted in this sense [38]. Furthermore, despite the global nature of the problem, solutions must respect the specificities of each context in order to address the different barriers preventing the implementation of rapid reperfusion therapy at the local level [39].

According to this narrative review of the literature, almost half of the studies selected (45% of the studies) showed a significant association between the transport used and early admission delay, and more particularly the use of EMS or other types of ambulances. This goes in utter congruency with the results of a study that demonstrated through multivariate logistic regression analysis that ambulance use (OR 1,961, 95% CI 1,176-3,270) was among the factors significantly associated with early arrival at the ED [40]. Furthermore, the use of ambulance transport reduced significantly the time to admission compared to using the patient's own means (OR 2.4, 95% CI 1.6-3.7) according to another investigation [41].

In a similar context, transport by EMS (adjusted OR 0.28, 95% CI 0.19-0.41]) is among the factors most strongly associated with a shorter extrahospital time interval [42]. Also, the use of EMS has been associated with shorter pre-hospital delay according to another study [43]. In addition, another study confirmed that the use of EMS for transportation to hospital was among the factors independently associated with a presentation within 3 hours (OR 6.24, 95% CI 2.52-16.63, p = 0.0001) [44].

Globally, prehospital delays recorded in these Northern Mediterranean countries remain lower than prehospital delays in other developing countries. This could be attributed to the use of most patients in low- and middle-income countries of their own vehicle(s) (personal or rented) to obtain medical care [45-48]. Furthermore, ambulances in these countries predominantly transport the traumatized patients and obstetric emergencies, while medical emergencies such as stroke are not a priority [49,50].

In fact, more than a third of the studies included (36% of the investigations) unveiled a significant a significant association between pre-hospital delay and the destination of the first call after stroke-related symptoms were observed. A literature review of surveys on knowledge regarding measures appropriate at stroke symptom onset showed that although the majority of respondents reported having called an EMS, a significant proportion responded by contacting their general practitioner [51].

Approximately a third (32%) of the studies included in the present narrative review of the literature showed that vigilance disorders (consciousness) were the symptoms most associated with early admission, given their severity. This is consistent with the results of a study conducted in Korea which found that patients, who had altered consciousness as the first symptoms appeared, arrived earlier [52]. However, in Tunisia, a study showed that initial clinical presentation (presence of motor deficit, p = 0.03; high NIHSS score, p = 0.04) was associated with early presentation to the ED [53].

Moreover, older age was also identified in almost one-third (27%) of the studies as a determinant contributing to a reduction of the time of patients' arrival. This is corroborated by the results of several studies, which confirmed that hospital arrival time was significantly earlier in older patients [54]. Also, older age (OR 0.99 [95% CI 0.98-0.99]) was among the factors most strongly associated with a short extra-hospital interval according to another study [42]. In addition, another investigation found that age < 65 years was among the most significant factors associated with delayed arrival at the ED [55].

The lack of understanding and underestimation of symptoms is indicated in 13% of studies, constituting the main barrier that affects negatively early admission. By this, late recognition of stroke symptoms by patients (or the inability to attribute symptoms to stroke) has been consistently identified as a major cause of delay in the pre-hospital phase [56-60]. Moreover, the majority of IS patients do not arrive at the hospital on time to receive thrombolytic therapy. A major factor responsible for this delay is the misinterpretation of stroke symptoms by patients or bystanders. While studies focusing on stroke patients and surveys of the general population have reported a low level of knowledge about the warning signs of stroke [61-63], a recent study conducted in Morocco, concluded that there is a lack of knowledge about the warning signs of stroke [64]. It is also important to highlight that lack of symptom recognition and low levels of public awareness were among the main reasons for pre-hospital delay [65]. In view of these findings, further investigation of patient perceptions of their own symptoms at the time of stroke is needed [66].

CONCLUSION

Despite the pre-hospital delays' decrease recorded in these Northern Mediterranean countries compared to those recorded in other African and Southern Mediterranean countries, increased proportions of patients do not arrive at hospital facilities within the recommended therapeutic windows. Therefore, to reduce pre-hospital delay and increase the proportions of patients' eligible for reperfusion therapy protocols, it is time for healthcare systems to address the three essential elements: the individual component (cultural factors, perceptions), the mode of transport, and a healthcare pathway for stroke management. Also, it is recommended that they intensify investigations of cultural factors and perceptions associated with stroke, specifically symptoms.

ABBREVIATIONS

AIS : Acute ischemic stroke

ED : Emergency department

CAU : Centre d'accueil des urgences

EES : Extrahospital Emergency Services

EMS : Emergency medical services

FD : Fire department

VSAV : véhicule de secours et d'assistance aux victimes

IS : Ischemic stroke

TIA : transient ischemic attack

UPATOU : Unité de proximité, d'accueil, de traitement et d'orientation des urgences

Author contributions: All authors contributed equally. All authors confirmed the final article.

Conflict of Interest: The authors declare that they have no competing interests.

Source of funding: There was no funding for this study.

Acknowledgements: The authors would like to thank Professor Acim Rachid (Ibn Zohr University, Agadir, Morocco) for their assistance in reviewing the quality of the English language manuscript.

Ethics approval and consent to participate: Not applicable.

Availability of data and materials: All data used in the publication of this work were obtained from published studies.

REFERENCES

1. Koksal EK, et al. Factors associated with early hospital arrival in acute ischemic stroke patients. Neurological Sciences, 2014; 35(10): 1567-72. doi: 10.1007/s10072-014-1796-3.
2. Ruiz RG, et al. Response to Symptoms and Prehospital Delay in Stroke Patients. Is It Time to Reconsider Stroke Awareness Campaigns? J Stroke Cereb Dis, 2018; 27(3): 625-32. doi: 10.1016/j.jstrokecerebrovasdis.2017.09.036.

3. Pulvers JN, Watson JDG. If time is brain where is the improvement in prehospital time after stroke? Frontiers in neurology, 2017; 8: 617. doi: 10.3389/fneur.2017.00617.

4. Redjaline A, et al. Délais d'admission et profil des patients présentant un accident vasculaire cérébral admis aux urgences d'hôpitaux ne disposant pas d'une unité neurovasculaire Admission time and profile of patients presenting with acute stroke admitted to emergency department with no neurovascular unit. Annales françaises de médecine d'urgence, 2015; 5(5): 214-22. doi: 10.1007/s13341-015-0576-x.

5. Geffner D, et al. Delay in seeking treatment by patients with stroke: who decides, where they go, and how long it takes. Clinical neurology and neurosurgery, 2012; 114(1): 21-5. doi: 10.1016/j.clineuro.2011.08.014.

6. Pulvers JNaW, John DG. If time is brain where is the improvement in prehospital time after stroke? Frontiers in neurology, 2017; 8: 617. doi: 10.3389/fneur.2017.00617.

7. Keskin Ö, Kalemoğlu M, Ulusoy RE. A clinic investigation into prehospital and emergency department delays in acute stroke care. Medical Principles and Practice, 2005; 14(6): 408-12. doi: 10.1159/000088114.

8. Korkmaz T, et al. An evaluation of pre-admission factors affecting the admission time of patients with stroke symptoms. Turk J Emerg Med, 2010; 10(3): 106-11.

9. Maestroni A, et al. Factors influencing delay in presentation for acute stroke in an emergency department in Milan, Italy. Emergency Medicine Journal, 2008; 25(6): 340-5. doi: 10.1136/emj.2007.048389.

10. Charaa A, et al. 294 Accidents Vasculaires Cérébraux (AVC) en région centre: devenir selon les modalités de prise en charge. Journal Européen des Urgences, 2004; 17: 110. doi: 10.1016/S0993-9857(04)97282-2.

11. Denti L, et al. Pre-hospital delay as determinant of ischemic stroke outcome in an Italian cohort of patients not receiving thrombolysis. Journal of Stroke and Cerebrovascular Diseases, 2016; 25(6): 1458-66.

12. Desseigne N, et al. Quels sont les facteurs influençant les délais d'admission des patients arrivant aux urgences pour une suspicion d'accident vasculaire cérébral. La Presse Médicale, 2012; 41(11): e559-e567. doi: 10.1016/j.lpm.2012.01.041.

13. Griesser A-C, et al. Identification des facteurs qui influencent favorablement ou défavorablement le délai de la prise en charge et du traitement d'un patient victime d'un accident vasculaire cérébral (AVC).

14. Heydenreich C, et al. Évaluation des délais et des stratégies de prise en charge des accidents vasculaires cérébraux: de la régulation à la thrombolyse. Journal Européen des Urgences, 2008; 21: A27. doi: 10.1016/j.jeur.2008.03.384.

15. Joux J, et al. Prehospital transfer medicalization increases thrombolysis rate in acute ischemic stroke. A French stroke unit experience. Clinical neurology and neurosurgery, 2013; 115(9): 1583-5. doi: 10.1016/j.clineuro.2013.02.010.

16. Julié V, et al. 297 Les accidents vasculaires cérébraux (avc) aux urgences: étude épidémiologique dans la région centre (étude avc-centre). 2004; 17: 111. doi: 10.1016/S0993-9857(04)97285-8.

17. Laribi S, et al. 293 Accidents vasculaires cérébraux ischémiques et thrombolyse: les délais de prise en charge par le smur sont-ils compatibles? Journal Européen des Urgences, 2004; 17: 110. doi: 10.1016/S0993-9857(04)97281-0.

18. Luis D, et al. 296 Prise en charge des accidents vasculaires cérébraux dans 5 hôpitaux généraux d'ile de france: états des lieux et dysfonctionnement de la filière. 2004; 17: 111. doi: 10.1016/S0993-9857(04)97284-6.

19. Memis S, et al. Multiple causes for delay in arrival at hospital in acute stroke patients in Aydin, Turkey. BMC neurology, 2008; 8(1): 15. doi: 10.1186/1471-2377-8-15.

20. Palomeras E, et al. Emergency perception and other variables associated with extra-hospital delay in stroke patients in the Maresme region (Spain). European journal of neurology, 2008; 15(4): 329-35. doi: 10.1111/j.1468-1331.2008.02082.x.

21. Ruiz RG, et al. Response to symptoms and prehospital delay in stroke patients. Is it time to reconsider stroke awareness campaigns? 2018; 27(3): 625-32.

22. Silvestrelli G, et al. Early admission to stroke unit influences clinical outcome. 2006; 13(3): 250-5. doi: 10.1111/j.1468-1331.2006.01187.x.

23. Silvestrelli G, et al. Characteristics of delayed admission to stroke unit. 2006; 28(3-4): 405-11. doi: 10.1080/10641960600549892.

24. Vidale S, et al. Reducing time delays in the management of ischemic stroke patients in Northern Italy. International journal of cardiology, 2016; 215: 431-4.

25. Vidale S, et al. Time to hospital admission and start of treatment in patients with ischemic stroke in northern Italy and predictors of delay. European neurology, 2013; 70(5-6): 349-55. doi: 10.1159/000353300.

26. Koksal EK, et al. Factors associated with early hospital arrival in acute ischemic stroke patients. 2014; 35(10): 1567-72. doi: 10.1007/s10072-014-1796-3.

27. Urimubenshi G, et al. Stroke care in Africa: A systematic review of the literature. 2018; 13(8): 797-805. doi: 10.1177/1747493018772747.

28. Fladt J, et al. Reasons for Prehospital Delay in Acute Ischemic Stroke. 2019; 8(20): e013101. doi: 10.1161/JAHA.119.013101.

29. Abraham SV, et al. Factors delaying management of acute stroke: An Indian scenario. Int J Crit Illn Inj Sci, 2017; 7(4): 224-30. doi: 10.4103/IJCIIS.IJCIIS_20_17.

30. Fekadu G, et al. Stroke event factors among adult patients admitted to Stroke Unit of Jimma University Medical Center: prospective observational study. 2019; 2019. doi: 10.21203/rs.2.9228/v1.

31. Ashraf V, et al. Factors delaying hospital arrival of patients with acute stroke. 2015; 18(2): 162. doi: 10.4103/0972-2327.150627.

32. Arulprakash N, Umaiorubahan M. Causes of delayed arrival with acute ischemic stroke beyond the window period of thrombolysis. J Family Med Prim Care. 2018; 7(6): 1248. doi: 10.4103/jfmpc.jfmpc_122_18.

33. Sim J, et al. Factors associated with the hospital arrival time in patients with ischemic stroke in Korea. 2016; 31(5): E10-E16. doi: 10.1097/JCN.0000000000000313.

34. Fang J, et al. Time interval between stroke onset and hospital arrival in acute ischemic stroke patients in Shanghai, China. 2011; 113(2): 85-8. doi: 10.1016/j.clineuro.2010.09.004.

35. Kharbach A, et al. Ischemic stroke in Morocco: a systematic review. 2019; 19(1): 1-15. doi: 10.1186/s12883-019-1558-1.

36. Kurz M, Kurz K, Farbu E, Acute ischemic stroke–from symptom recognition to thrombolysis. Acta Neurol Scand Suppl. 2013; 127: 57-64. doi: 10.1111/ane.12051.

37. Zhou Y, et al. Pre-hospital Delay after Acute Ischemic Stroke in Central Urban China: Prevalence and Risk Factors. Mol Neurobiol, 2017; 54(4): 3007-16. doi: 10.1007/s12035-016-9750-4.

38. Evenson KR, et al. A comprehensive review of prehospital and in-hospital delay times in acute stroke care. 2009; 4(3): 187-99. doi: 10.1111/j.1747-4949.2009.00276.x.

39. Zhou Y, et al. Pre-hospital delay after acute ischemic stroke in central urban China: Prevalence and risk factors. 2017; 54(4): 3007-16. doi: 10.1007/s12035-016-9750-4.

40. Kim YS, et al. Stroke awareness decreases prehospital delay after acute ischemic stroke in Korea. 2011; 11(1): 2. doi: 10.1186/1471-2377-11-2.

41. Sekoranja L, et al. Factors influencing emergency delays in acute stroke management. Swiss Med Wkly, 2009; 139(27-28): 393-9.

42. Rossnagel K, et al. Out-of-hospital delays in patients with acute stroke. 2004; 44(5): 476-83. doi: 10.1016/j.annemergmed.2004.06.019.

43. Yanagida T, et al. Causes of prehospital delay in stroke patients in an urban aging society. 2014; 5(3): 77-81. doi: 10.1016/j.jcgg.2014.02.001.

44. Dimitriou P, et al. Factors associated with delayed presentation at the emergency department in patients with acute ischemic stroke. 2019; 33(9): 1257-61. doi: 10.1080/02699052.2019.1641226.

45. Pandian JD, et al. Factors delaying admission to a hospital-based stroke unit in India. 2006; 15(3): 81-7.

46. Nkoke C, et al. Stroke mortality and its determinants in a resource-limited setting: A prospective cohort study in Yaounde, Cameroon. 2015; 358(1-2): 113-7. doi: 10.1016/j.jns.2015.08.033.

47. Jin H, et al. Factors associated with prehospital delays in the presentation of acute stroke in urban China. 2012; 43(2): 362-70. doi: 10.1161/STROKEAHA.111.623512.

48. Razzak JA, Cone DC, Rehmani R. Emergency medical services and cultural determinants of and emergency in Karachi, Pakistan. 2001; 5(3): 312-6.

49. Peyravi M, et al. An overview of shiraz emergency medical services, dispatch to treatment. 2013; 15(9): 823. doi: 10.5812/ircmj.10982.

50. Waseem H, et al. Epidemiology of major incidents: an EMS study from Pakistan. 2011; 4(1): 48. doi: 10.1186/1865-1380-4-48.

51. Jones SP, et al. Stroke knowledge and awareness: an integrative review of the evidence. 2010; 39(1): 11-22. doi: 10.1093/ageing/afp196.

52. Kim HJ, et al. Factors associated with prehospital delay for acute stroke in Ulsan, Korea. 2011; 41(1): 59-63. doi: 10.1016/j.jemermed.2010.04.001.

53. Jemaa HB, et al. Délais de prise en charge des accidents vasculaires cérébraux: Expérience de la région du centre tunisien. 2008; 37(10): 1502-3. doi: 10.1016/j.lpm.2008.05.003.

54. Nowacki P, et al. Patients' and bystanders' awareness of stroke and pre-hospital delay after stroke onset: perspectives for thrombolysis in West Pomerania Province, Poland. 2007; 58(3): 159-65. doi: 10.1159/000104717.

55. Chen C-H, et al. Pre-hospital and in-hospital delays after onset of acute ischemic stroke—A Hospital-based study in Southern Taiwan. 2007; 23(11): 552-9. doi: 10.1016/S1607-551X(08)70002-0.

56. Nedeltchev K, et al. Pre-and in-hospital delays from stroke onset to intra-arterial thrombolysis. 2003; 34(5): 1230-4.

57. Hong ES, et al. Factors associated with prehospital delay in acute stroke. 2011; 28(9): 790-3. doi: 10.1136/emj.2010.094425.

58. Sauser K, et al. Hospital variation in thrombolysis times among patients with acute ischemic stroke: the contributions of door-to-imaging time and imaging-to-needle time. 2014; 71(9): 1155-61. doi: 10.1001/jamaneurol.2014.1528.

59. Inatomi Y, et al. Pre-hospital delay in the use of intravenous rt-PA for acute ischemic stroke in Japan. 2008; 270(1-2): 127-32. doi: 10.1016/j.jns.2008.02.018.

60. California Acute Stroke Pilot Registry (CASPR) Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. Neurology. 2005; 64(4): 654-9. doi: 10.1212/01.WNL.0000151850.39648.51.

61. Pandian JD, et al. Knowledge of stroke among stroke patients and their relatives in Northwest India. 2006; 54(2): 152.

62. De Dominicis L, et al. What do Italians at high risk of stroke know about ischaemic stroke? A survey among a group of subjects undergoing neuro-sonographic examination. 2006; 27(1): 7-13. doi: 10.1007/s10072-006-0558-2.

63. Centers for Disease Control and Prevention (CDC). Awareness of stroke warning signs--17 states and the US Virgin Islands, 2001. MMWR Morb Mortal Wkly Rep. 2004; 53(17): 359.

64. Kharbach A, et al. Speech disorders and stroke in the Souss Massa Region in Morocco. Afr J of Health Sci. 2019; 1(1). doi: 10.5334/aogh.2885.

65. Bouckaert M, Lemmens R, Thijs V. Reducing prehospital delay in acute stroke. Nat Rev Neurol. 2009; 5(9): 477-83.

66. Faiz KW, et al. Factors related to decision delay in acute stroke. 2014; 23(3): 534-9. doi: 10.1016/j.jstrokecerebrovasdis.2013.05.007.