Ischemic stroke in Morocco: A systematic review

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Abstract

**Background:** To main objective of this systematic review is to determine; the epidemiological and the etiological profile, the influential factors of the prehospital delay, thrombolysis management, the acute and 3-month mortality rate and the genetic aspect of ischemic stroke in Morocco.

**Methods:** A systematic review was conducted according to the recommendations of the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) through the consultation of the Pubmed, Sciencedirect, Scopus, Clinicalkey, and Google scholar databases for the raking of the gray literature during the period between 2009 and 2018. The protocol of the review was registered in the PROSPERO register (CRD42018115206).

These studies were assessed based on: Age, sex ratio, risk factors, etiological profile according to Trial of ORG classification 10172 in Acute Stroke Treatment (TOAST), prehospital delay average and it’s influential factors, thrombolyzed patients proportion, acute and 3-month mortality and the genetic factors of ischemic stroke in Morocco.

**Results:** Twenty-nine (n = 29) studies were selected. And the average age ranged from 49±15.28 to 67.3 ± 9.91 years. Also, a male predominance was recorded in 13 studies of all ages. High blood pressure, diabetes, smoking and heart disease are the four main risk factors identified throughout the studies. Atherosclerosis and cardioembolic origin seem to be the main etiologies of cerebral ischemia. And the average prehospital time ranged from 26 to 61.95 hours. In addition, the proportion of thrombolyzed patients ranged from 1.8% according to the Azdad et al (2012) study to 2.9% according to the Rachdi’s (2015) study. Finally, the mortality rate in the acute phase varied between 3 and 13%. And the 3-month mortality ranged from 4.30 to 32.5%. It is also important to note that most of studies have a reduced sample size, conducted in hospital environment, and with no confidence interval.

**Conclusions:** Ischemic stroke is affecting more and more the young population with male predominance. Moreover, the long prehospital delay and the low proportion of thrombolysed patients are alarming, indicating the need to deepen investigations on the determinants that influence patient’s access to care in Morocco in order to improve the management of this pathology.

**Background**
Stroke has become a major public health problem and is a real and growing burden in African countries [1, 2]. Regarding its cost on the social, psychological, and economic level [3]. The incidence of stroke continues to increase in developing countries, including the North Africa region [4]. From an etiological point of view, multiple causes of stroke exist [5]. According to the epidemiological survey on population, conducted in the two major Moroccan cities (Casablanca and Rabat); ischemic stroke (IS) represents 70.9% of the studied strokes [6]. The multidisciplinarity and speed required in terms of therapeutic management condition the prognosis and evolution of the disease [7]. In addition, the care management of the Ischemic stroke is experiencing an unprecedented evolution in recent years. The main two advances were the approval of intravenous thrombolysis in 1995 and that of intra-arterial mechanical thrombectomy in 2015 [8]. Stroke, thus, represents a major challenge in terms of prevention and organization of management in acute phase in order to improve the mortality and morbidity of this pathology [7, 9].

Despite the enormous burden of stroke in developing countries, only 15% of research on this disease is done between these countries compared to 85% in high-income countries [10]. In addition, no data is available on temporal trends in the incidence or long-term outcomes of this debilitating disease in Morocco [11]. Since ischemic stroke is largely preventable, it is essential to know the epidemiological and other aspects of care to reduce the incidence rate and the resulting burden in our kingdom. It is important to know that no systematic review of the literature on stroke in Morocco has been conducted. So, the objective of this work is to evaluate by a systematic review, the epidemiological, etiological profile, the factors that influence the prehospital delay, the thrombolysis management, the mortality rate in the acute phase and at 3 months, and the genetic aspect of ischemic stroke in Morocco.

Methods

Research Strategy

This systematic review was conducted in accordance with the methodological criteria of the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) [12]. The protocol has been previously registered and published (PROSPERO:
This is a systematic review of the literature by adopting a multisource research strategy, consulting the databases of Pubmed, Sciencedirect, Scopus, Clinicalkey, and Google scholar for raking gray literature (Scientific research work national as master, doctorate or theses of medicine) between 2009 and 2018. (Last questioning on the 29th, November 2018).

The key words used were: (Ischemic stroke) or (cerebral infarction) or (Cerebral ischemia) or (ischemic stroke) or (ischemic attack) or (Cerebral ischemia) or (Cerebral infarction) and (Morocco) or indicating specific cities of the kingdom.

Two authors (KA and OM) independently verified titles and abstracts to identify eligible studies.

Complete articles of the potential studies were retrieved for a more detailed evaluation. And the references in all relevant articles were examined for additional documents as well as the works citing them. No restrictions were made on the language of publication.

Inclusion and exclusion criteria

1. All studies in Morocco concerning stroke that were published after 2009.

2. Studies on the following data: age, sex ratio, risk factors, etiologic profile, prehospital delay and the management of cerebral ischemia including thrombolysis.

3. Studies on genetic polymorphisms related to the occurrence of cerebral ischemia in Morocco.

4. Studies on ischemic stroke in patients less than 15 years of age and cerebral venous thromboses have been excluded.

Extraction and analysis of data

The data extracted from the identified documents were the following: average age, sex ratio, risk factors, etiological profile according to the TOAST classification, prehospital delay, stroke management (thrombolysis), mortality rate at the acute phase and at 3 months (according to the modified Rankin score), and genes involved in the occurrence of cerebral ischemia in Morocco.

Risk of bias in individual studies
Bias risk assessment was conducted by two authors independently through the use of “Quality Assessment Tool for Case Series Studies”, “Quality Assessment Tool for Cross-Sectional Studies” and “Newcastle-Ottawa Quality Assessment Scale Case-Control Studies”.

Two reviewers (KA and OM) assessed the methodological quality of the studies independently and then the agreement between the two examiners’ results was analyzed by the Kappa statistical coefficient (κ).

**Results**

The flow-chart is shown in Figure 1. Twenty-nine (n = 29) studies were selected. Based on study type: Full papers (n = 13), conference abstracts (n = 6), medical theses (n = 10). By locations: Rabat (n = 5), Casablanca (n = 7), Casablanca and Rabat (n = 1), Marrakech (n = 7), Fez (n = 8), Meknes (n = 1). According to the study design: (n = 15) were retrospective case series, (n = 8) were prospective case series, (n = 1) were prospective cross sectional study, and (n = 5) were prospective case-control studies. According to the age of the target population of the selected studies, (n = 25) studies targeted all ages combined (Greater than 15 years) and (n = 4) studies focused on the young population (15 - 45 years old). All studies were hospital series.

The Kappa statistical coefficient (κ = 0.64). The Quality Rating of “case series”, “cas-control” and “cross-sectional” studies were considered “good” with an average score of 7.5/9 (the results of the methodological evaluation of case series studies are shown in Table 1).

**Mean age and sex ratio of patients with ischemic stroke in Morocco**

Twenty-three studies focusing on ischemic stroke in all age groups revealed an average age ranging from 49 ± 15.28 to 67.3 ± 9.91 years. Thus, the average age is listed in the fifth and sixth decade [13–35].

However, two studies did not specify the average age of patients. The first study is that of Chraa (2010), reporting that the age was below 45 years in 36% of cases and more than 45 years in 64% of cases, and the second by Bourazza (2013) indicated an age between the two extreme 24 and 104 years [36, 37].
As for the sex ratio (n = 13) studies were in favor of a male with a ratio of between 1.23 and 3.45 [16–19, 22, 24–28, 33, 37, 38]. A ratio of 1 has been reported in (n = 3) studies [23, 33, 34]. Similarly, a slight female predominance with a ratio between 0.756 and 0.95 was found in (n = 9) studies [13, 15, 20–22, 30, 31, 35, 36].

Concerning ischemic stroke in the young adult, four studies included patients aged between 15 and 45 years. The first of Mbagui (2009) with an age ranging between 15 and 45, the second of Ibouajbane (2014) between 16 and 45, the third of Chraa (2014) with an age between 18 and 45 and the fourth of Allaoui (2018) which included all patients under age 45 admitted to internal medicine [39–43].

According to studies of ischemic stroke in young people, the mean age ranged from 28.3 ± 4.2 to 39 years (Extremes: 16–45 years) [39–43].

In what concerns the sex-ratio of ischemic stroke in young cases, (n = 2) studies reported values less than 1.

The first is that of Ibouajbane (2014) with a clear female predominance including a sex -ratio of 0.43 [39], and the second study is that of Allaoui (2018), which showed a slight predominance of women, with a sex ratio of 0.73 [43].

A male predominance was recorded in the Chraa (2014) study with a sex ratio of 1.46 [40]. In addition, the Mbagui (2009) study did not show a significant difference between the two sexes [42].

**Risk factors for ischemic stroke in Morocco according to selected studies**

Studies in this literature review have identified several risk factors for cerebral ischemia in the studied populations. Indeed, high blood pressure, diabetes, smoking and heart disease were the four main risk factors listed and are as follows: Hypertension was reported in (n = 20) studies (31 to 65.45%) [13–16, 18–23, 25, 26, 28–30, 32–34, 36, 38], diabetes in (n = 20) studies (12- 41.8%) [13–16, 18–23, 25, 26, 28–30, 32–34, 36, 38], cardiac pathologies in 14 studies (7- 44.3%) [13–15, 18, 20–23, 28–30, 32, 36, 38], and smoking in (n = 19) studies (4- 41.8%) (4- 41.8%) [13–15, 18–23, 25, 26, 28–30, 32–34, 36, 38].
In addition to these risk factors, other risk factors have been reported, such as dyslipidemia in \((n = 16)\) studies (0–61.8%) [13-16, 18-20, 22, 23, 25, 28-30, 32, 36, 38], obesity in \((n = 6)\) studies (10.70–26.10%) [13, 18, 19, 28, 32, 36], the notion of an earlier stroke was noted in \((n = 10)\) hospital series (5–26.6%) [13, 14, 22, 23, 28-30, 32, 35, 36], alcoholism in \((n = 10)\) studies [13-15, 20, 22, 26, 32–35], oral contraception in \((n = 3)\) studies (6.64–12.21%) [15, 35, 36], and migraine in a single study at 6.53% [36].

Concerning the young population, reported risk factors were smoking in \((n = 4)\) studies (5–40.6%) [39–42]. high blood pressure in \((n = 4)\) studies (8% - 49.2%) [39–43]. Oral contraception was revealed in \((n = 4)\) studies (12–31.25%) [39–43]. Cardiac diseases were identified in a single Chraa (2014) study with a percentage of 17.9% [40]. Diabetes in \((n = 4)\) studies (7.5–13.2%) [39–43]. Migraine in \((n = 4)\) studies (1.56–24%) [39–43]. Dyslipidemia in \((n = 3)\) studies (0–15.38%) [39, 40, 42]. Alcoholism was found in \((n = 3)\) studies (5–8%) [39, 40, 42]. The obesity was noted in \((n = 1)\) Study of Ibouajbane (2014) with a percentage of 2.5% [39]. The notion of previous stroke in \((n = 2)\) studies of Chraa (2014) and Ibouajbane (2014) with respectively of 2.34% and 2.5% [39, 40]. The notion of first-degree family history of stroke was reported in a single Allaoui study (2018) with a percentage of 25% [43]. The pregnancy was found in \((n = 2)\) studies of Mbagui (2009) and Chraa (2014) with percentages respectively of 0.96% and 1.56% [40, 42]. (The results are detailed in Table 2)

**Genetic risk factors for ischemic stroke in Moroccan studies**

In this systematic review, \((n = 5)\) studies only focused on the genetic factors associated with ischemic stroke in Morocco.

The first study by They et al (2011) suggested that the \textit{MTHFR} C677T variant could be a determinant of the atherothrombotic event of ischemic stroke in Morocco [33]. The second was that of They et al (2013), which demonstrated an interactive effect between the \textit{MTHFR} C677TT and \textit{F2} 20210GA polymorphisms and the increased risk of ischemic stroke [32]. The third study by Diakite et al (2014) suggested another statistically significant association between \textit{G894T} polymorphism at the \textit{eNOS} gene level and ischemic stroke in the recessive, dominant and additive models [27].
In addition, another genetic study of Diakite et al (2015) evaluated the association of the *FVF C2491T* mutation with the risk of ischemic stroke, suggesting that carriers of the mutated T allele were associated with a high risk of ischemic stroke. But this risk was 8.95 times higher when the subject had the TT genotype (P < 0.0001) and 4.08 times higher with the CT genotype, and he concluded that the *FVF C2491T* mutation could be a genetic risk factor for ischemic stroke in the Moroccan population [25].

The fourth genetic research was conducted by Diakite (2016) on *T–1131C APOA5* polymorphism, which observed a modest risk of ischemic stroke with CC and C alleles. In addition, the same study and more specifically related to with *SG13S114 ALOX5AP*, a significant association was observed in subjects with TT and T alleles. Overall, despite the reduced sample size, variants *T–1131C APOA5* and *SG13S114* could be considered as an independent genetic risk factor ischemic stroke in the Moroccan population [26]. The fifth study of Balar (2014), showed that *MTHFR* (patients with *MTHFR CT/TT* patients without CT/TT) and other factors (sex, age, hypertension, diabetes, smoking, alcoholism, dyslipidemia) did not revealed significant correlation [16]. (Results are detailed in Table 3)

[Insert Table 3 Here]

**TOAST etiological classification of ischemic stroke in Moroccan studies**

The most dominant etiology is atherosclerosis of large arteries according to (n = 16) studies (16-57.8%) [15, 17, 18, 22, 23, 25-33, 35, 36].

The cardioembolic origin comes second in (n = 17) studies (8.8-50 %) [15, 17, 18, 20, 22, 23, 25-33, 35, 36]. Undetermined causes were present in (n = 12) studies (5.55-34%) [15, 17, 18, 22, 23, 28-30, 32, 33, 35, 36]. Lacunar ischemic stroke was found in (n = 12) studies (0-39%) [17, 18, 23, 25-28, 30, 32, 33, 35, 36]. Other identified causes are recorded in (n = 13) studies (0–27.4%) [15, 17, 22, 23, 25–27, 29, 30, 32, 33, 35, 36].

In details concerning the etiology category “Other determinate causes”, five studies have specified the pathologies involved in the genesis of ischemic stroke [22, 29, 30, 32, 36].

The first study of Chraa (2010) reported 14 cases of syphilitic arteritis, 12 cases related to disorders
of clotting factors, 5 cases of arterial dissection, 4 cases of systemic diseases, 4 cases of migraine, 1
case of chemotherapy, and 1 case of human immunodeficiency virus. The second from Chtau (2012),
mentioned 2% of cases were related to arterial dissections. The third of Rachdi (2012), 1 case of
Vaquez disease has been notified. The fourth study of Saraya (2013), revealed 1 case of
polycythemia, 1 case with interhemispheric Meningioma, a toxic ischemic stroke after taking
Cannabis, and an ischemic stroke after cerebral angiography as part of the assessment of a C3
Neuroma. Fifth of Rachdi (2015), 5% of cases were related to carotid stenosis greater than 50%. In
addition, six other studies did not break down the other identified causes [15, 25–27, 33, 35].
Concerning the young population (15–45 years), the undetermined causes are identified in four
studies. The first study is that of Mbagui (2009) with a proportion of 29.03% [42]. The second of Chraa
(2014) with a proportion of 40.62% [40]. The third of Ibouajbane (2014) with a proportion of 55% [39].
The fourth study of Allaoui (2018) with a proportion of 24% [43].
The ischemic stroke of cardioembolic origin was also highlighted in four studies; the first study was
that of Mbagui (2009) with a proportion of 21.51% [42]. The second was the Ibouajbane (2014) study
with a proportion of 15% [39]. The third study was inherent to that of Chraa (2014) with a proportion
of 33.59% [40]. The fourth study of Allaoui (2018) with a proportion of 4% [43].
As for the other determinate causes, they were identified in (n = 4) studies of Mbagui (2009), Chraa
(2014), Ibouajbane (2014) and Allaoui (2018) with proportions of 21.51%, 14.06%, 15% and 72% [39,
40, 42, 43].
Concerning the details on the etiological class “other specific causes”, four studies specified the
causes involved in the occurrence of ischemic stroke in young population. The first of Mbagui (2009)
pointed the finger on blood diseases, vasculitis, oral contraception and carotid dissections with
proportions of respectively 35%, 25% (2 cases of Behcet, 1 case of Takayashu, 2 cases of
undetermined vasculitis), and 15%. In addition, 1 case of sneddon syndrome, and 1 post partum case
have also been reported [42].
The second of Ibouajbane (2014), angiitis accounted for 5% of cases, hematological disorders
accounted for 5% of the cases, one case is observed during pregnancy and especially in the sixth
month, and thrombophlebitis in another case [39].
The third of Chraa (2014), 11 cases of syphilis, 3 cases of carotid dissections, 2 cases of coagulation protein deficiency (C), 1 case of sneddon syndrome, and 1 case of anti-phospholipids’ antibody syndrome were identified [40].
The fourth study of Allaoui (2018) with a proportion of determinate causes of 72%. The etiologies in this study were dominated by systemic lupus (32%) associated with antiphospholipid syndrome (80%), Behcet’s disease (16%), Takayasu’s disease (12%) [43].
In what concerns atherosclerosis of large arteries, it has been reported in (n = 3) studies, Chraa (2014), Ibouajbane (2014) and Mbagui (2009) with proportions respectively of 11.72%, 12, 5% and 25.81% [39, 40, 42].
For lacunar ischemic stroke it was found in (n = 2) studies, including that of Mbagui (2009) and Ibouajbane (2014) with ratios of 2.15 and 2.50%, respectively [39, 42].
In the Allaoui study (2018), TOAST III (lacunary) patients were 73% smokers, 8% had type II diabetes and / or High blood pressure, and 12% had oestroprogestative contraception at the time of diagnosis [43]. (Results are detailed in Table 4)

Prehospital delay in patients with ischemic stroke in Morocco

Since the notion of time is very important in the management of cerebral ischemia, (n = 5) studies quantified the prehospital delay, which extends between the time of the symptoms onset and the arrival to the emergency department of the different hospital structures [15, 28, 30, 31, 35].
In this perspective, a minimum prehospital average delay was 26 hours [Extremes: 15 Minutes- 8 months] according to the study made by Azdad (2012) [15] and a maximum mean prehospital delay was 61.95 hours [Extreme: 0.5 hour–216 hours] which was listed in the Yonmadji (2016) study [35]. (The results are detailed in Table 5)
Between the youth, the consultation period was quantified in two studies [39, 42]. Mbagui’s first study (2009) and Ibouajbane’s second study (2014) reported 134.4 hours and 342 hours respectively [39, 42]. Moreover, the Allaoui study (2018) showed that the delay between the installation of symptoms
and the first cerebral imaging exceeded 12 hours in 100% of cases [43].

No study has investigated the factors influencing the consultation and admission time of patients with ischemic stroke.

[Insert Table 5 Here]

The proportion of patients with thrombolyzed ischemic stroke in Morocco

Four studies conducted at the neurology department of the University Hospital Hassan II of Fez, focused on the thrombolysis management. The proportion of thrombolysed patients ranged from 1.8% in the Azdad (2012) [15] to 2.9% in the Rachdi (2015) study [30]. In addition, two studies by Yonmadji (2016) and Daouda (2017) respectively revealed two intermediate proportions of thrombolysed patients of 1.94% and 2.8% [24, 35].

Mortality in the acute phase and mortality in the chronic phase (3 months) in Morocco

Six articles have reported the mortality rates in the acute phase, which ranged from 3% for the Yonmadji (2016) study to 13% for the Chraa (2010) study. In addition, four studies by Saraya (2013), Rhissassi (2010), Chtaou (2016) and Azdad (2012) have revealed intermediate values of 5.8%, 9.9%, 10% and 10.8% respectively [15, 23, 31, 32, 35, 36].

The rates of mortality after 3 months were reported in seven studies. Three studies by Bendriss (2012), Rachdi (2015), and Hadi (2018) reported respectively the mortality rates of 5.45%, 10%, and 8%. Moreover, four studies by Daouda (2018), Yonmadji (2016), Chtaou (2016), and Rachdi (2012), respectively reported mortality rates of 4.3%, 21.7%, 29%, and 32.5% in ischemic strokes treated with thrombolysis [18, 23, 24, 28-30, 35].

The mortality during the acute phase in the young population, was indicated in (n = 3) studies. The first from Ibouajbane with a mortality rate of 0% [39], the second from Mbagui (2009) at 1.07% [42] and the third from Chraa (2014) with a mortality rate of 16.4% [40].

For mortality after three months, no study has attempted to elucidate this parameter.

Discussion
The average onset age of ischemic stroke in Morocco is between 49 ± 15.28 and 67.3 ± 9.91 years. The studies by Mbagui (2009), Chraa (2010) and Chraa (2014) showed proportions of 12.3%, 28.9% and 36% respectively of a population under 45 [36, 40, 42]. The early onset of ischemic stroke in Morocco according to the studies could probably be due to the young age of the Moroccan population and the low percentage of the elderly (over 60 years old), which represents 9.4% according to the results of the last census of the population of 2014 [18, 36, 44]. Young age could also be explained by the high frequency of embolic heart disease, rheumatic heart disease and sexually transmitted infections (syphilis, and acquired immunodeficiency syndrome) in Morocco [15, 40]. In addition, cardioembolic disease is the leading cause of ischemic stroke in the young population in our country due to the preponderance of rheumatic heart disease [43]. Similarly, it may also be due to the very high level of consanguinity and the significant association with the incidence of health conditions in the Moroccan population [45].

Furthermore, the average onset age of cerebral ischemia in Morocco is still lower in comparison to the average age of patients hospitalized for ischemic stroke in France in 2014 which was 74 ± 15 years [46] and in comparison to the average age identified in a systematic review in the Arab countries that ranged between 58.5 and 63 years [11]. In addition, the average age of the young population ranged between 28 and 39 years, and therefore joining the results of several hospital series carried out in North Africa and the Middle East [47–49].

Most Moroccan studies showed a male predominance. And this goes is in line with the results of a literature review in the Arab world, which indicated that men were most often victims of stroke (between 55.9 to 75%) [11].

These revelations are also consistent with the results of a literature review at the level of the Eastern Mediterranean countries, which has explored a higher prevalence of stroke between men than women with a sex ratio of up to 3.55 [50]. Moreover, the same finding is consistent with the results of a literature review in the Middle East between 1980 and 2015 reporting gender differences, and that 75% of studies reported a high sex ratio in patients with stroke [51]. This may be the result of the hormonal factors whose estrogen seems to have protective effects on both the vascular system and
cerebral ischemia [52].

High blood pressure is the main risk factor for ischemic stroke in Morocco in addition to diabetes, smoking, and heart disease which represent the other risk factors identified. In this regard, in Africa more than half of patients with ischemic stroke have high blood pressure [53].

Which joins the results of the literature review of studies conducted in the Middle East between 1980 and 2015, showing hypertension was the most common risk factor, followed by diabetes in Africa [51]. This is also consistent with data from the literature in the Eastern Mediterranean countries, where the prevalence of hypertension was above 50% in 38 studies, diabetes was greater than 25% in 36 studies, and smoking was higher at 15% in 26 studies [50]. The preponderance of these vascular risk factors in Morocco could be due to the phenomenon of urbanization which reaches a percentage of 60.3%, and the change of lifestyle in the Moroccan population [44], as well as the westernization of the behavior and the food habits between Moroccans [54]. however, a study conducted in Casablanca showed that fast foods have a high composition of sodium and saturated fatty acids but a small amount of unsaturated fatty acids, which would contribute to the increase in the prevalence of cardiovascular diseases and strokes in Morocco [55].

In what concerns the risk factors ischemic stroke between young people, and in addition to high blood pressure, smoking remains the most reported factor. This can be justified by the fact that Morocco is considered one of the highest tobacco consuming in the countries in the Mediterranean area with more than 15 billion cigarettes a year, and that 42% of men in the age group 30 –39 years old are smokers [56].

Oral contraception is also a preponderant risk factor between the young subjects; these results can be justified in Morocco by the massive use of hormonal contraceptive methods. For this reason, and according to the performance of the national family planning program in 2015, the pill represents a percentage of 90% of all contraceptive methods used [57]. Similarly, a meta-analysis of 16 studies conducted in America in 2015 showed that oral contraceptives are associated with an increased relative risk of cerebral infarction of 2.75 [58].

Genetically speaking, studies have suggested that MTHFR C677T variant could be a determining
event of atherothrombotic ischemic stroke in Morocco, which is superimposed the results of a recent meta-analysis which concluded that the \textit{MTHFR C677T} mutation increases the risk of ischemic stroke adults, particularly in atherosclerosis of large arteries [59]. The study by Diakite et al (2014) suggested a statistically significant association between \textit{G894T eNOS} polymorphism and ischemic stroke, which is consistent with the results of a meta-analysis that confirmed that polymorphism \textit{eNOS G894T} is associated with risk of ischemic stroke in Asians [60]. Moreover, the \textit{T-1131C APOA5} mutation could be considered as a genetic risk factor nondependent on ischemic stroke between the Moroccan population. The same observation has been revealed between the Chinese population [61]. For \textit{SG13S114 ALOX5AP}, a significant association was observed in subjects with TT and T alleles in Morocco. The same result was concluded in the Iberian population [62].

As for the etiological TOAST classification, atherosclerosis of large arteries is the most dominant etiology in this review. This is probably due to: First, an increased prevalence of arterial hypertension in Morocco, which is estimated at 29.3% according to the national survey of common risk factors for noncommunicable diseases (NCDs) of the years 2017 and 2018, and also to a high prevalence of diabetes which is 10.6% according to the same survey. Second, atherosclerosis is probably related to poor compliance with antihypertensive therapy or poor glycemic control.

In this sense, the percentage of people with hypertension who do not take medication in Morocco is estimated at 71.4% [CI: 69.1–73.7%]. In addition, the proportion of people who have never measured blood glucose is 63.2% [CI: 61.8–64.6%] according to the same survey of risk factors common to NCDs [63].

The average prehospital delay for patients with ischemic stroke in Morocco has ranged between 26 to 61.95 hours, which far exceeds the therapeutic window recommended by randomized clinical trials [64]. This finding coincides with the median admission time (31 hours) mentioned in a review of literature on the African continent [65]. In addition, it joins the average consultation time mentioned in a prospective cross-sectional study conducted at the University Hospital Center of Brazzaville in the Republic of Congo, which was 28.2 hours [66]. Moreover, a longer period was also recorded in a study conducted at the Sahloul Hospital Center in Sousse, Tunisia, which was 16 hours [67]. These very long
delays listed in our review, are recorded mainly in the two university hospitals Fez and Marrakech, which could be explained by the lack of knowledge of the warning signs of cerebral infarction. Furthermore, this delay of consultation in the Moroccan population could be linked to a lack of awareness [15, 35]. This finding was confirmed by a survey conducted at the Mohamed VI University Hospital Center in Marrakech, in which 59.8% of the interviewees could not name any revealing signs of cerebral ischemia [68]. However, these different findings could probably be due to the illiteracy rate of 32.2% according to the results of the last census of the Moroccan population [44]. This could also be explained by the fact that most of the patients arrived at the emergency rooms by non medical vehicles (taxi, personal car), and only a minority having arrived by ambulance (3.5%)[24]. Besides, a recent literature review found that low awareness of the signs and symptoms of stroke, the shortage of medical transportation, health care staff and stroke management units, as well as the cost of High levels of brain imaging services and thrombolysis have been reported as major barriers to accessing quality stroke care in Africa [65]. Concerning the management of cerebral ischemia patients, all the studies dealing thrombolysis as reference technique, are conducted at the University Hospital of Fez. For that, the proportion of thrombolysis patients ranged between 1.8 and 2.9%. These minimal recruitment percentages for thrombolysis may be due to the beginning of this procedure at the University Hospital Hassan II in Fès in 2010 [15]. In the same perspective, the Daouda study (2017), 11% of cerebral infarctions did not benefit from thrombolysis because they were admitted beyond 4.5 hours [24]. Moreover, the Rachdi (2015) study also showed that the majority of patients were not thrombolysed because of the long consultation time and other interfering factors such as lack of patient’s information about clinical signs suggestive of ischemic stroke [30]. Besides, the transportation of patients by their own means (car, taxi, private ambulance) due to the lack of organization of emergency medical service (EMS), the difficulties in the recognition of symptoms of ischemic stroke by the patient, the delays in seeking appropriate emergency care, delays in obtaining an urgent brain imaging scanner and cost constraints ; non-assurance coverage of rt-PA in Morocco are the causes involved in the non-access of the population to thrombolysis [23].
Moreover, these performance figures of this Moroccan neurovascular unit are superimposable to the data offered by the literature. In this respect, reperfusion treatments (thrombolysis) are administered only to a proportion of 1 to 8% of admitted patients [69]. In addition, 3% (95% CI 2–4) of patients were thrombolysed based on the results of a literature review with recent meta-analysis [70]. Therefore, awareness-raising of the public on a large scale on the neurological signs of the disease are needed, and the organization of pre-hospital medical care from the perspective of reducing admission time and increase the number of thrombolyzed patients [24].

So, and according to our review, mortality in the acute phase varied between 3 and 13%. These results are low compared to the mortality rates recorded in other studies in the Arab and African countries (In Algeria, which was 39%) [71], Senegal (a mortality rate of 37.5%) [72]. The hospital mortality rate in the first week between 2000 and 2013 increased from 45.8 to 18% in sub-Saharan Africa [73]. The overall lethality rate in one month was 12–32% according to a systematic review in the Middle East countries between 1980 and 2015 [51].

The fatality rate in the acute phase in our review remains low despite the preponderance of atherosclerotic ischemic and embolic origin in the study population which are normally characterized by a greater lethality compared to the occlusion of small arteries which represents a minority in our review [74]. This finding could be due to the implementation of a strategy of diagnosis and effective etiological treatment of cerebral ischemia in the studies included in our review. These low mortality rates could also be explained by the lack of studies evaluating the mortality rate attributed to ischemic stroke in Morocco [70]. Three-month mortality in thrombolyzed patients exceeded 20%, according to most studies. This is higher than the mortality rate recorded in a meta-analysis, which was 13.4% according to a meta-analysis [75].

Conclusions
The cerebrovascular accident remains a multi-factorial affection in Morocco. Overall, available data show a concentration of all studies in cities with university hospitals. Also, they suggest that cerebral ischemia in Morocco is characterized by precocious onset (begins at an early age), male predominance, and etiologies and vascular risk factors observed in patients with ischemic stroke in
Morocco which is generally similar to findings in other Arab and African countries. In addition, several genetic markers have been suggested as predisposing factors of cerebral infarction in Morocco. The prehospital delays are very long, in comparison to the different deadlines listed in developed countries with pathways for the management of ischemic stroke. Therefore, the expansion of epidemiological studies, particularly in other regions of the Kingdom, will provide an opportunity for investigation of incidence and prevalence figures. Finally, it is time to further investigate the determinants associated with long hospital admission delays in this invalidating pathology to increase the level of brain infarction eligibility for thrombolysis.

Declarations

List of abbreviations

TOAST: Trial of ORG classification 10172 in Acute Stroke Treatment; IS: Ischemic stroke; YIS: Young Ischemic Stroke; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; NCDs: Noncommunicable diseases; HBP: High Blood Pressure.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this article

Competing interests

The author(s) declare that they have no competing interests.

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Authors’ contributions

KA participated in the conceptualization and design of the review, performed the selection of studies, data-extraction, and drafted the review. OM involved in the conceptualization and design of the review, data-extraction, involved in the evaluation of the risk of bias for each included study,
reviewed the article in different steps. LL involved in the evaluation of the risk of bias for each included study, participate in the writing of the protocol of the systematic review. AJ participated in revising the manuscript and more specifically the clinical component. MN participated in revising the manuscript. RR involved in the conceptualization and design of the review, supervised the review, reviewed the results and the final approval of the manuscript. All authors participated in revising the manuscript and the final approval of the manuscript.

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Tables
Due to technical limitations, all tables are only available for download from the Supplementary Files section.

Figures
Figure 1 PRISMA 2009 Flow Diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

For more information, visit www.prisma-statement.org,

Figure 1

PRISMA 2009 Flow Diagram
Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Table 2 Risk factors for ischemic stroke in Morocco.pdf
Table 4 TOAST etiological classification of ischemic stroke.pdf
Table 3.pdf
Table 5.pdf
Table 1 Quality Assessment Tool for Case Series Studies.pdf
PRISMA 2009 checklist.pdf