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REVIEW

Exploring Factors Associated with Falls in Multiple Sclerosis: Insights from a Scoping Review

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory condition that causes demyelination of the central nervous system accompanied by a wide range of symptoms. The high prevalence of falls among patients diagnosed with MS within the initial six months highlights the importance of this issue. The objective of this study is to identify factors associated with falls in MS patients in order to increase awareness and reduce the risk of falls. This scoping review used specific Mesh terms to formulate the literature search around falls and MS using Medline, Google Scholar, Scopus, and Embase search engines. English papers published between 2012 and 2022, studies with a clear definition of falls, McDonald's diagnostic criteria for MS, and those with Expanded Disability Status Scale (EDSS) or Patient Determined Disease Steps (PDDS) scores were included. Critical data from the selected articles were extracted and classified according to the different factors associated with falls in MS patients. Eighteen articles were included in this review. The most important factors associated with falls in MS patients identified were the severity and progression of the disease, mobility and balance problems, bladder dysfunction, fear of falling, fatigue, and cognitive dysfunction. In conclusion, this scoping review yielded the most common factors associated with falls in patients with MS. Study findings can be used to develop future interventions focusing on improving mobility, proprioception, and balance to decrease fall risk and injury amongst MS patients.

Keywords: multiple sclerosis, falls, causes, risk factors, neurological disorders

Introduction

Multiple sclerosis (MS) is a chronic inflammatory condition characterized by demyelination of the central nervous system.[1] It is an immune-mediated disease and is the main cause of disability in young adults, with women being three times more likely affected compared to men.[2,3] MS presents with a wide scope of symptoms including gait abnormalities, vertigo, vision problems, and fatigue all of which could be disabling to the patient and lead to impairment in their quality of life. As a result of the wide range of symptoms experienced, falls in MS patients are frequent, with research suggesting more than 50% of patients fall in 6 months after initial diagnosis.[4] A study that recruited 52 participants with MS with a mean age of 39.7 years, and 49 healthy controls with a mean age of 38.7 years observed the difference in falls between the two groups and reported 145 falls in MS patients, compared to only 55 falls in healthy individuals.[5] Approximately half of the patients with an MS-related fall sustained orthopedic injuries, most commonly fractures of the lower extremity, as well as musculoskeletal injuries including bruises, lacerations, muscle strains, and sprains.[6,7] Furthermore, patients with MS (PwMS) reported a higher incidence of injury, such as cuts, grazes, and bruises, which can be attributed to the higher incidence of falling increasing the likelihood of injuries occurring.[4] Therefore,

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interventions to prevent and reduce falls in PwMS were the interest of several articles within the last few years.[8,9] Despite these studies, falls in PwMS remain a medical challenge due to the poor understanding of the complex factors associated with MS-related falls. These unsuccessful interventions necessitate a more in-depth comprehension of falls in PwMS to provide more efficient solutions in future studies.

The risk factors of falls in PwMS are often multifactorial and biologically interrelated.[10] However, studies have shown that fatigue, vision loss, and balance abnormalities due to dizziness, vertigo, and gait abnormalities were mainly associated with an increased risk of falls in patients diagnosed with MS.[10] Moreover, fear of falling (FOF) due to recurrent falls significantly decreases physical activity which further reduces motor function and stability thereby increasing the risk of falling.[11] The literature has consistently indicated that falls and injuries due to falls are under-reported in neurological diseases including ataxia, Parkinson's disease, and MS.[10,11] A cross-sectional study involving 455 patients with MS demonstrated that only 50% of patients who fell reported the fall to their healthcare provider.[11] This was mainly due to the physicians not asking about falls and due to the patient thinking that there were no interventions or strategies available to decrease the risk of MS-related falls.[11]

Despite being discussed by some previous articles, risk factors of falls in PwMS remain under-identified with limited discussed categories, deficient standardization of falls definitions and MS diagnostic criteria and high variations in study designs.[12] For example, two meta-analyses identified only two and four categories of factors associated with falls in PwMS respectively.[12,13] Although a review looked at more factors associated with falls in a narrative review, no standardization of fall definition or MS diagnostic criteria (like McDonald's criteria) were used in the article, which adds bias to the study and limits the finding's reliability.[7] Hence, this review is designed using a methodology aimed to meticulously curate a selection of the highest quality and most recent studies. The objective is to identify the most reliable factors associated with falls in individuals with Multiple Sclerosis. Through this comprehensive approach, the review aims to contribute essential novel insights that will enhance awareness among both patients and healthcare providers. Furthermore, it seeks to inform the development of interventions tailored to reducing the risk of falls and associated injuries in the context of Multiple Sclerosis.

Methods

Scoping Review Question

"What are the factors that are associated with falls in PwMS?"

A search was undertaken on Medline, Scopus, and Embase using the Mesh terms: "Multiple sclerosis" or "MS" in combination with "falls", "fall", "near falls", "near fall", "causes of falls", "causes of fall", "causes of near falls", causes of near fall", "risk of falls", "risk of fall", "risk of near falls", and "risk of near fall". Review articles were manually screened by the authors for relevant articles.

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria of this scoping review was specifically designed to include only studies in the past ten years, with the highest quality. Therefore, only a minute number of studies were selected from a wide range that were found through the literature screening. This was designed to provide the reader with the most reliable and highest quality evidence of the different factors associated with falls in PwMS. Other studies that did not fulfill all our inclusion/exclusion criteria were selectively curated after discussion with the authors and were included in the discussion section for a more comprehensive scope.

1. Studies related to factors/associations/risk/causes of falls in PwMS.
2. Studies written in English.
3. Studies published from 1st January 2012 to 1st January 2023.
4. Studies that included definitions of falls "event where the participant unintentionally comes to rest on the ground or at a lower level or similar definitions with different descriptive words to define a fall".
5. Studies that used McDonald's criteria to diagnose MS.

6. Studies that included the Expanded Disability Status Scale (EDSS) or the Patient Determined Disease Steps (PDDS) to quantify neurological impairments in MS patients.
7. Studies that were not reviews, scoping, literature, systematic, or meta-analysis reviews.

Three independent reviewers (Rachid Kaddoura (RK), Hanan Faraji (HF), and Amin Abu Hijleh (AA)) manually screened the titles and abstracts of studies retrieved from the search. Studies considered eligible for full-text screening were retrieved for full-text review. Any conflicts were resolved by discussion between the three researchers and the senior author (Hani Benamer (HB)). A flow chart illustrates the literature search in Figure 1.

A standardized data extraction template sheet was developed and completed by one author (RK) and crosschecked by another (HF). Descriptive data for the characterization of studies included information on the author, year of publication, number of MS patients, female sample size, age range, mean age, the definition and duration of fall, the severity of MS, type of MS, and the factors associated with falls identified from each article.

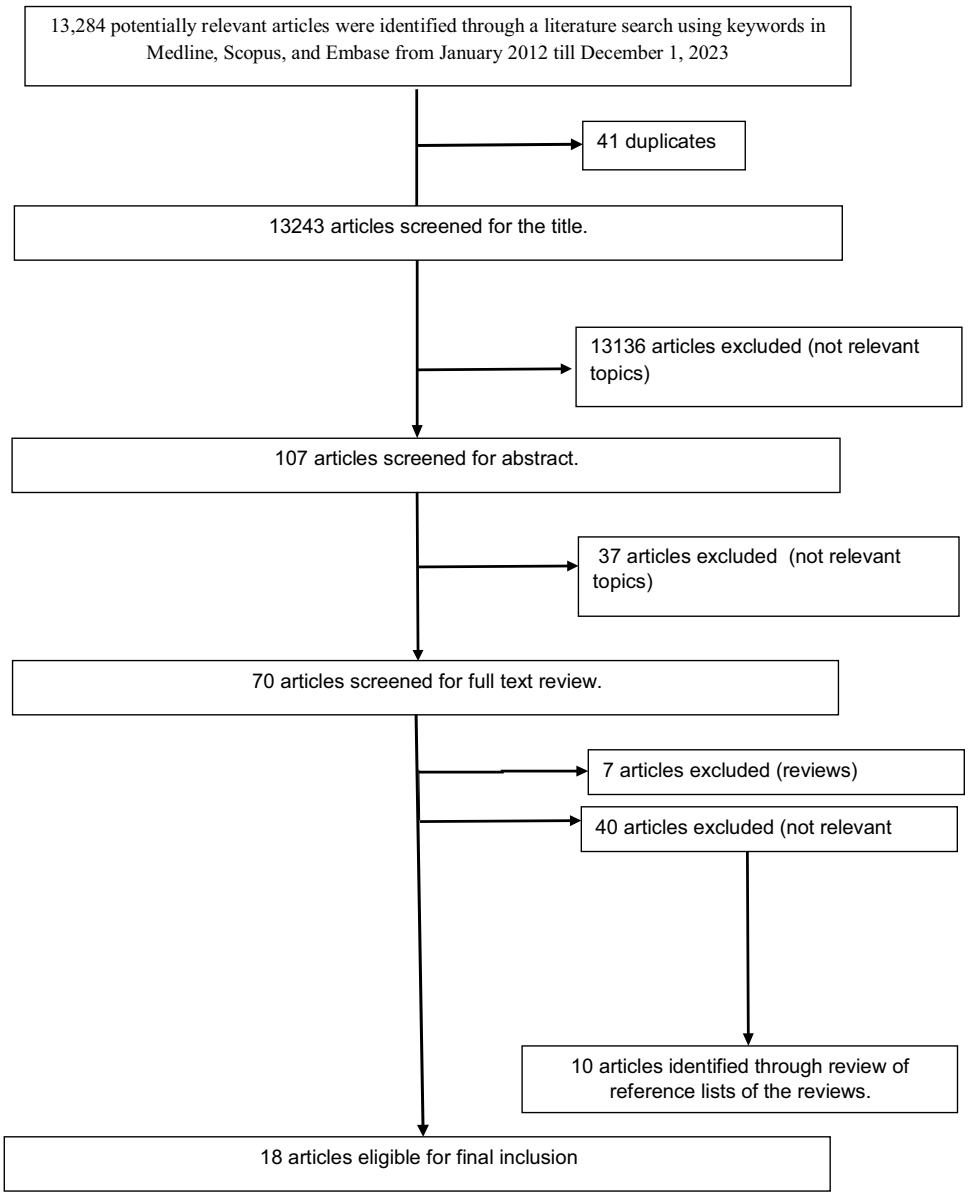

Figure 1 Literature search flowchart.

Table 1 An Overview of the 18 Studies Included in the Scoping Review

Study Author/Year (Reference)	Study design	Number of MS Patients/ Female	Age range / Mean in Years	Duration of Falls	Severity of MS (EDSS)	Type of MS	Association Factors or the Cause of Falls
Abasıyanık et al 2021[10]	Cross-sectional study	104/ F:77	Mean: 33.41 F 35.96 NF: 32.56	3 months	Range: ≤ 1.5 mean: 0.69	RRMS	• EDSS score
Soll et al 2021[14]	Cross -sectional study	44/ F:44	Mean: 46	1 year	Range:3.0–6.0. median: 4.5	NR	• Fear of falling in patient with bladder dysfunction
Gunn et al 2013[15]	Prospective cohort study	148/ F:114	Mean: 57.9 F: 57 NF: 59	3 months	Range: 3.5–6.5	RRMS PPMS SPMS	• Loss of balance • Using walking stick or elbow crutch
Kalron et al 2013[12]	Cross-sectional study	107/ F: 62	F: 45.3 NF: 47	6 months	Mean: 2.8	RRMS	• Old age • Longer disease duration • Greater level of EDSS • impairment in pyramidal, cerebellar, and sensory function • concern of falling
Kalron et al 2017[16]	Cross-sectional study	540/ F:333	NR	1 year	Median: 2.5	NR	• Lower global cognitive performance
Mofateh et al 2017[17]	Retrospective cohort study	50/ F:40	Range: ≥ 18	6 months	Mean: 4.16	RRMS	• Higher EDSS • Gait variability • Decreased muscle strength • Spasticity • Fatigue • Increased postural sway
Zelaya et al 2017[14]	Prospective cohort study	51/ F:36	Range: 18–50 Mean: 39.6 F: 39.8 NF: 39.1	3 months	Median: 3	RRMS	• Urinary urgency with incontinence
Gunn et al 2018[18]	Secondary analysis of data from prospective cohort studies	416/ F: 305	Range: ≥ 18 Mean: 51.5	3 months	Median: 4.0	RRMS	• Impaired proprioception, quadriceps muscle strength, simple reaction time, visual contrast sensitivity, and postural sway
Karlon et al 2018[19]	Cross-sectional study	122/ F:75	Mean: 43	1 year	Mean: 2.9	NR	• Depression

Mazumder et al 2014[4]	Prospective cohort study	58/ F:34	Range: 18–50 Mean: 39.7	6 months	Median 3.0	RRMS	• Loss of balance (most common) • Fatigue • Heat • Tripping • Distraction
Kalron et al 2014[13]	Retrospective cohort study	101/ F:60	F: 43.2 NF: 38.8	1 year	Mean: 3.0 F: 3.6 NF: 2.2	RRMS	• EDSS • Concern of falling • Cognitive performance less (attention and verbal function)
Kalron et al 2018[20]	Cross-sectional study	355/ F:218	Mean: 41.1 F: 43.6 NF: 39.5	1 year	Median: 2.5	NR	• Higher EDSS • Longer disease duration • Slower walking speed
Karlon et al, 2016[21]	Cross-sectional study	342/ F:211	Mean: 46.6	1 year	Mean 3.8	NR	• MS affected in pyramidal system • EDSS
Cameron et al 2015[22]	Prospective cohort study	248/ F:178	Range: 21–74 Mean: 48.5 F: 48.8 NF: 48.1	6 months	Mean: 3.10	RRMS PPMS SPMS	• The use of more medications • The use of MS disease-modifying therapies is associated with fewer falls • Antidepressants was associated with 96% increased odds of falling
Mazumder et al 2015[15]	Prospective cohort study	58/ F:37	Range: 18–50 Mean: 39.6 F: 40.4 NF: 38.25	6 months	Mean: 2.7	RRMS PPMS SPMS	• Fear of falling
Karlon et al 2019[23]	Cross-sectional study	88/ F:50	Mean: 39.8 F: 42.1 NF: 38.5	3 months	Mean: 2.0	RRMS	• Higher step length variability
Khalil et al 2017[24]	Cross-sectional study	70/ F:50	Mean: 34.3	12 months	Mean: 2.3	RRMS	• Fear of falling
Gunn et al/ 2014[11]	Prospective cohort study	148/ F: 114	Mean: 57 F: 57 NF: 59	3 months	Median F: 5.5 NF: 5.5	RRMS PPMS SPMS	• Continence issues • History of falls • Men

Abbreviations: No, Number; MS, Multiple sclerosis; EDSS, Expanded disability status scale; F, Female; EDSS, Expanded Disability Status Scale; NR, Not reported; RRMS, Relapse-remitting MS; PPMS, Primary-progressive MS; SPMS, Secondary-progressive MS; BMS, Benign MS. F, Fallers; NF, Non-fallers; MS1, no clinical gait impairment; MS2, clinical gait impairment.

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Results

The search revealed 1482 potentially relevant articles. After title and abstract screening, 70 articles remained for full-text review, of which 40 articles were excluded as they did not fulfill the inclusion criteria. Seven reviews were identified, and their references were screened, with a total of 10 articles added Figure 1. In total, 18 papers were eligible for final inclusion in this scoping review Table 1.

Sociodemographic

A total of 3050 patients were included in this scoping review with 66.8% (N=2038) being females. Moreover, 14 articles included the mean age of the participants (mean=43.4 years), and 10 articles included the mean age of fallers and non-fallers, 45.3 and 44.0 years, respectively.

Severity Scale, and MS Type

All studies included the mean EDSS with an average of 2.75. Two studies included a separate EDSS mean of fallers and non-fallers. Moreover, the type of MS was identified in 13 studies, while the others did not report any specific type. 13 studies included relapse-remitting MS patients, and only four studies included primary-progressive MS, as well as secondary-progressive MS.

Definitions and Duration of Falls

Eight studies defined a fall as an event where the participant unintentionally comes to rest on the ground or at a lower level. The remainder 10 articles used similar definitions with different descriptive words to define a fall. All studies reported the duration of reported falls ranging from three months to one year.

Summary of the Identified Factors Associated with Falls in MS

Each of the 18 articles included in this scoping review identified at least one factor associated with falls in PwMS. In summary, the following are the factors that were identified: mobility and balance impairment, severity and progression of the disease, fear of falling, bladder dysfunction, fatigue, and cognitive dysfunction. Mobility and balance impairment was identified as the most common cause of falls across the 18 articles. Other causes were also identified including age, gender, depressive symptoms, and medications, which could not be grouped under any specific cause and thus were grouped under miscellaneous. Figure 2 illustrates a schematic diagram of the seven factors associated with falls and their interplay in PwMS.

Severity and Progression

Six studies showed an association between falls and the severity of MS. The severity of MS was analyzed using the EDSS scale which was used by all studied included in this review for unanimity of the results. One study demonstrated that the probability of being classified as a faller was more than six times higher for those with a score of 1.5 compared to an EDSS of 0.[20] Another study also reported more falls in patients with higher EDSS compared to those with lower scores, however, the results were not statistically significant.[17] Four studies reported that the mean EDSS for fallers (3.72) was significantly higher than that of non-fallers (2.24).[18,21,23,25] One study quantified the affected functional system in patients with MS based on the EDSS score, namely, pyramidal, cerebellar, or sensory group.[14] As for fall status, 48.5% of the total sample were considered as a faller and had a significantly higher EDSS score compared to non-fallers.

Results showed that patients with only sensory impairment are less prone to falls (19.5%) in comparison to patients with pyramidal (44.3%) or cerebellar dysfunction.[14]

Disease duration and its impact on falls were also reported in two articles.[21,25] The mean disease duration was found to be significantly higher in the MS fallers group (7.7) compared to the non-fallers group (4.4).[21,25]

Mobility and Balance

Seven studies established an association between mobility dysfunction and falls in patients with MS. One study reported that 37% of patients with recurrent falls scored highly on the Physiological Profile Assessment (PPA) and the Falls Efficacy Scale-international (FESi) which measures and assesses vision, peripheral sensation, muscle force, reaction

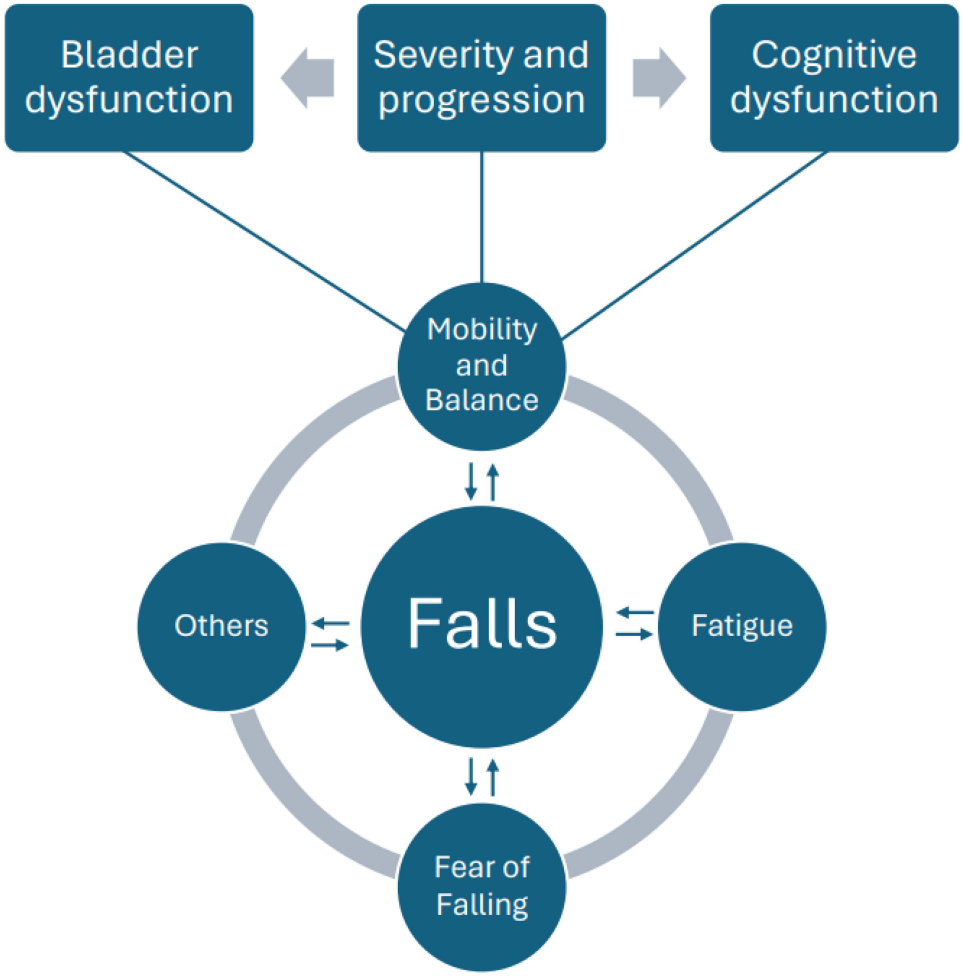

Figure 2 Factors associated with falls in Multiple Sclerosis.

time, and postural sway. These tests are used to identify people at risk for falls and those people who are not at risk of falls.[26,27] Another study concluded that patients with MS who ambulate with increased variability between steps expend more energy than normal to control the body's irregular center of mass sway.[15]

Fallers exhibited increased centre of pressure (CoP) path length, sway velocity, and greater sway area compared to non-fallers.[21] These are common instrumented measures of balance used to identify definite balance components. Two prospective studies[5,17] had the participants use a fall calendar to record the fall frequency and causes. A study found that 27.6% of MS patients sustained falls while performing mobility activities rather than activities demanding less movement.[17] Moreover, another study concluded that loss of balance was the most reported cause of falls in 43% of the participants based on fall calendars that noted fall location, fall-related injuries, and the cause of falls.[25]

Bladder Dysfunction

A significant association was reported between urinary urgency with incontinence and recurrent falls. The most likely mechanism described was that PwMS were rushing to the bathroom to avoid incontinent episodes, and therefore were more likely to fall.[24] Moreover, the odds ratio of fallers was significantly higher in PwMS with frequent urinary incontinence, compared to those without.[28] On the contrary, one study showed no significant difference between fallers and non-fallers, using the Urinary Incontinence Quality of Life Scale (I-QoL) and Bladder Control Scale (BLCS),

however, a significant correlation was shown between bladder dysfunction and FOF.[24] Out of all static balance measures in this study, only post-urography when standing on a firm surface with eyes closed was significantly associated with I-QoL scores.[16]

Fear of Falling

Four studies[18,19,21,29] explored the association between falls and FOF in patients with MS. To identify patients with FOF, three articles used the FES-i questionnaire,[18,19,21] and one article used the 7-item FES-i.[29] A higher score on the FES-i reflects a higher concern of falling as opposed to the ABC scale in which higher scores show higher walking confidence. Two studies reported that fallers had 70% higher FES-i scores compared to non-fallers.[18,21] FOF was significantly associated with EDSS and most of the postural control parameters that were measured.[21] Furthermore, FES-i scores were significantly correlated to multiple cognitive variables such as memory and motor skills.[18] A study found that recurrent fallers had a significantly higher 7-item FES-i mean score.[29] With each point increase in the 7-item FES-i score, the odds ratio of recurrent falls in the following three and six months increased by 25% and 19%, respectively, and FOF was significantly linked with falls only during the following three months.[29] An FES-i score of 20 was considered the cut-off point for high concern of falling in another study.[19] Nearly two thirds (65.4%) of non-fallers and 86.7% of fallers with MS were highly concerned about falling, reflecting high FOF even in patients who did not experience falls or recurrent falls in the previous year. Fall history, motor characteristics, and affective outcomes were significantly correlated with FOF.[19]

Fatigue

Two studies reported a relationship between fatigue and falls in MS patients using a 4-point ordinal scale where the participants reported their perceived rates of fatigue (not at all, as usual, somewhat more than usual, and much more than usual).[5,17] One study reported that 27.8% of fallers felt somewhat more fatigued than usual, and 13.3% of fallers reported their fatigue to be much more than usual.[17] Another study used healthy controls and reported fatigue as the cause of falls in 14% of MS patients and none of the controls.[5] Both studies found that a significant number of participants who reported a fall also reported an increased level of fatigue.[5,17]

Cognitive Dysfunction

Five studies[18,22,23,25,30] reported an association between cognitive dysfunction and falls. The studies utilized different tools to measure cognitive domains which included verbal memory and learning, visual memory, working memory, verbal fluency, processing speed, and executive functions. One study reported lower cognitive function test scores in the fallers compared to non-fallers.[18] However, a significant difference was observed only in attention and verbal function domains. Furthermore, those who scored lowest in processing speed, executive functions, and working memory had decreased walking speed, which was correlated with higher risk of falls. One study found no significant differences in cognition when comparing fallers and non-fallers.[30]

Three studies reported that falling in patients with MS was related to impaired cognition on gait. A study desecrated that worse cognitive performance was related to a slower walking speed and to increased fall frequency in patients with MS.[22] This was further supported by another study which illustrated that cognitive function was associated with gait variability only in patients with MS without a fall history.[25] Finally, the last study investigated the cognitive effect on gait, where the participants underwent three distinct tests: single-task gait (participants walked on a treadmill without any distractions), cognitive dual-task gait (participants were instructed to count backward while walking), and motor dual-task gait (participants walked while holding a tray with four empty glasses). The study found that spatiotemporal gait parameters were different in MS patients compared to healthy individuals regardless of fall history. All participants demonstrated increased walk ratio scores during cognition dual-task compared to motor dual-task and single walking conditions.[23]

Others

One study reported that increased age was positively associated with the risk of falls.[21] Another study showed that the mean age of MS fallers (45.3 years) was higher compared to the mean age of non-fallers (39.6 years).[21] Two studies showed a correlation between depressive symptoms and increased risk of falls.[31,32] One study used the Hospital Anxiety and Depression Scale and found that fallers were the most prevalent in the group classified as anxious/depressed. However, PwMS who were categorized in the anxiety/non-depressed subgroup were six times less likely to fall than non-depressive or non-anxious.[32]

One study reported a significantly increased risk of falls in males with MS compared to females.[17] Two studies reported that medications increased falls in particular the anti-depressant medications such as SNRI and SSRI.[28,33]

Discussion

This section of the scoping review provides an overview of the different factors associated with falls in PwMS. It is aimed to help clarify the etiologies and pathophysiological mechanisms that could directly or indirectly predispose falls. However, certain gaps in the available literature are highlighted, with the hope of encouraging further research. The findings have been systematically organized into seven distinct themes for a structured presentation and analysis.

Severity and Progression

The severity and progression of MS significantly contribute to falls among patients.[21,25] Higher EDSS scores indicate greater disease severity and progression correlating to an increase in fall incidence.[17,20] Elevated EDSS scores were also associated with worse postural control and an increased frequency of falls, which reflects an indirect relationship between disease severity and falls.[21] Additionally, greater MS severity was found to exacerbate pre-existing gait abnormalities during cognitive and motor dual-task activities, increasing susceptibility to falls.[23] This progression may also impair cognitive functions, such as processing speed and attention, further elevating the risk of falls during challenging motor tasks.[18] While there are significant overlaps between measures of disability and frailty,[34] it has been reasonably theorized that cumulative disability may be one of the main drivers of frailty in MS.[35] People with elevated scores (≥7.0) on the EDSS or patient-determined disease steps (PDDS) almost exclusively rely on wheelchairs and/or other assistive devices to support mobility. The inability to ambulate independently can lead to a cascade of negative health outcomes, including an increased risk of falls, which could accelerate the onset and severity of frailty. The frailty index, was in turn, found to be strongly associated with fall history, which indirectly suggests that frailty measurement can be used to predict clinical adverse outcomes in MS patients with advanced disability.[36]

Mobility and Balance

Gait and balance disturbance are among the most frequent symptoms reported by PwMS.[37] One study reported that 50–80% of PwMS experience gait and balance disturbances.[38] A self-reported nationwide study conducted in 2023 found that balance issues account for the majority of falls in MS.[39] Notably, falls tend to occur during dynamic events, particularly in activities such as transferring and transitioning between positions.[40] A high percentage of falls in PwMS are similarly associated with general mobility tasks such as standing, turning, and walking.[17,28,41] In a cohort study of younger and less disabled PwMS, outdoor falls predominate due to increased engagement in activities.[5] Gait variability in PwMS (greater stride-to-stride fluctuations in walking) is also associated with higher energy costs and increased fatigue, which emerges as a notable risk factor for falls.[15]

MS leads to mobility and balance disturbance through lesions in the gray and white matter which cause atrophy and slow the somatosensory conduction. This leads to impaired central gait integration which might explain the increased incidence of falls in PwMS.[42,43] CoP path length can thus serve as a potential predictor of falls in PwMS as it is linked to degree of white matter damage.[21] Furthermore, falls in MS can be classified by the affected neurological system, with pyramidal system involvement correlating with reduced stability and an increased tendency to fall compared to cerebellar and sensory dysfunctions.[14] This can be identified using magnetic resonance imaging (MRI) and help tailor the specific patients that are more likely to benefit from fall prevention interventions.

In exploring the link between cognitive performance and gait variability, a study found a statistical relationship only in non-faller.[25] However, limitations in methodology, such as the exclusion of factors like static and dynamic balance, spasticity, or sensory deficits, may account for these results. While impaired gait and spasticity are recognized risk factors for falls in MS, instrumented tests may not always capture these physiological nuances. Therefore, future management of fall risk in MS necessitates the measurement of both perceived and physiological factors.[26]

Bladder Dysfunction

Urinary symptoms are common among individuals with Multiple Sclerosis (MS), affecting a substantial proportion (32–97%) and significantly impacting their quality of life.[44] Two prospective cohort studies explored the association between falls and baseline urinary symptoms over a duration of three months.[16,24] One study found a significant association between urinary urgency with incontinence and recurrent (two or more) falls.[24] However, no association was found between urinary urgency with incontinence, and any (one or more) falls after baseline, indicating that urinary symptoms might only be linked to a higher fall frequency. In addition, this observation might explain the discrepancy found in another study, in which lower fall frequency measured by I-QoL and BLCS (at least one fall within the last year) had no association between falls and bladder dysfunction.[28] The study included female MS patients with mild bladder dysfunction symptoms, providing another possible explanation for this controversy.[28]

Incontinence leading to falls in patients with MS can be explained by several mechanisms. Primarily, bladder dysfunction induces a sense of urgency, compelling patients to rush to restroom facilities, thereby elevating the likelihood of falls.[24] Moreover, environmental hazards, such as wet floors, and physiological factors associated with bladder dysfunction symptoms can independently contribute to the occurrence of falls.[45] Another contributing factor lies in the potential side effects of medications prescribed for bladder issues, used for neurogenic bladder dysfunction in PwMS.[46]

Such medications mainly include anticholinergic drugs such as oxybutynin which works through competitive acetylcholine antagonism at postganglionic muscarinic receptors, leading to the relaxation of the smooth muscles of the bladder. These medications are known to impact the central nervous system and have been consistently linked to an increased risk of falls due to dizziness and lightheadedness.[47] Furthermore, concurrent MS-related issues can amplify the risk of falls and exacerbate urinary symptoms.[24] For instance, a study a significant correlation between post-urography on a firm surface with eyes closed and scores on the Incontinence Quality of Life (I-QoL) assessment, suggesting a potential association between spinal cord pathology, bladder dysfunction, and diminished postural control.[28] In the same study, bladder dysfunction and FOF were statistically correlated, indicating that FOF in the setting of bladder dysfunction could also lead to falls.[28] On the contrary, a study did not establish a direct relationship between urinary urgency and falls in the absence of incontinence or frequency, indicating that the presence of incontinence may be a crucial factor in the increased risk of falls.[24] The study also highlighted the progression from urinary urgency to incontinence in patients with MS, emphasizing the consequential nature of urgency in the context of falls.[24]

Fear of Falling

FOF increases among patients with previous falls and is an important indicator of health outcomes and quality of life in patients with MS.[48,49] FOF is defined as "a lasting concern about falling that leads to an individual avoiding activities that they remain capable of performing".[50] Several scales have been developed to quantitatively assess FOF, with the Modified Falls Efficacy Scale (MFES) emerging as particularly accurate for evaluating both indoor and outdoor activities.[51] Notably, a study revealed a robust association between heightened FOF scores, assessed by the Falls Efficacy Scale-International (FES-I), and an increased frequency of falls.[51] Four studies[18,19,21,29] in this scoping review illustrates a significant correlation between FOF and falls in patients with MS.

The association between FOF and the occurrence of falls in individuals with MS can be elucidated through multifaceted factors. The behavioral consequences of FOF in MS patients precipitate mobility constraints, thereby exacerbating functional decline and contributing to deconditioning. This is evident in patients with FOF, who exhibit diminished walking speed, reduced physical capacity, compromised lower limb function, and impaired balance.[19]

Further evidence supports these clinical observations, as FOF is significantly correlated with objective measures indicative of compromised static postural control. Individuals with FOF demonstrate an augmented ellipse sway area,

increased CoP path length, elevated sway rate, and differences in pressure distribution all of which contribute to falls. These objective metrics collectively illustrate the profound impact of FOF on the intricacies of static postural control.[21] The genesis of FOF in individuals with Multiple Sclerosis (MS) can be traced to previous falls, wherein the awareness of potential injuries and the consequential devastation stemming from past experiences contribute to the development of FOF.[46] Moreover, disease severity and affective characteristics namely, fatigue, and sleep quality were significantly correlated with FOF.[19] Other factors including depression and impaired cognitive function can also contribute to FOF and will be further elaborated at their designated sections in this review.

It is important to note that although most studies indicate a robust association between FOF and falls, one study did not establish this correlation.[44] However, the use of different tools to assess FOF and variations in mobility in patients with MS among studies previously mentioned can explain this finding. For instance, one study used a single question to assess FOF,[4] while the five studies in this review used multi-item scales systems for this purpose. Single-item questions were shown to be less sensitive than a multi-item questionnaire in FOF assessment.[52]

Fatigue

More than 70% of patients with MS experience symptomatic fatigue which is characterized by an overwhelming sense of tiredness that can worsen over the course of the day.[53,54] This is shown to impact a patients' quality of life and interfere with their daily functioning.[4,55] This scoping review identified two articles that found fatigue to be one of the causes of falls in MS patients.[5,17]

Specific fatigue scales, such as the Modified Fatigue Impact Scale (MFIS), Fatigue Severity Scale (FSS), and Pittsburgh Fatigue Scale, offer new insights into the nature of fatigue experienced by individuals with MS, and several studies indicate increased fatigue in PwMS.[56] Notably, one study found that higher MFIS scores were correlated with increased risk of falls in PwMS.[57] Another study that utilized the FSS scale found that increased fatigue induced by physical activity has a major impact on postural control in patients with MS during challenging tasks that require motor functions increasing the likelihood of these patients sustaining falls.[58] Therefore, more difficult tasks that require higher motor functions predispose patients with MS and fatigue to an increased risk of falls.

Numerous studies have outlined a relationship between fatigue and autonomic dysfunction in people with MS.[59] It was found that cardiac autonomic dysfunction in MS patients could result in fatigue-related processes and result in falls.[60] A study observed that patients with MS displayed lower blood pressure response, compared to that fatigue-free.[60] Fatigue and impaired upright postural balance are the hallmarks of MS, which all increases risk of MS-related falls.[61]

Cognitive Dysfunction

The prevalence of cognitive dysfunction in MS patients is high affecting an estimate 43–65% of MS patients.[62] Moreover, MS patients demonstrated reduced performance in all aspects of cognitive domains, as well as global cognitive scores.[18,25] In turn, studies have found that reduced cognitive capacity is associated with instability and disturbed motor control, especially while performing a motor function, therefore increasing the likelihood of falls.[22,23]

The relationship between cognitive impairment and falls could be attributed to brain lesions in the cerebellum and brainstem which results in instability in gait, and several trials found that cerebellar abnormalities are related to cognitive impairments.[63] MS often engenders cognitive impairments attributable to both white and gray matter pathology. Demyelination disrupts efficient neural transmission, leading to compromised attention, executive function, and processing speed. Concurrently, motor deficits in MS manifest as disruptions in sensorimotor integration, proprioception, and altered muscle recruitment patterns.[64,65] It is important to note that some studies did not find relationship between cognitive impairments and falls.[30] However, this could be explained by the variability of the areas that MS lesions can pertain to.

Several studies have explored the relationship between Fear of Falling (FOF) and cognitive performance, yielding divergent findings. Some investigations have indicated a correlation between FOF and impaired cognitive performance,[18,30] while contrasting results have been reported by other studies that found no significant association.[19,28] The current body of evidence, though informative, lacks robust consistency in establishing a clear and

unequivocal link between FOF and cognitive performance. Further research with larger sample sizes and standardized cognitive assessment tests is warranted.

Others

This scoping review identified four other causes that were briefly touched upon in the selected articles. Older patients had a greater risk of falling, which may be attributed to prolonged disease duration and severity predisposing to a greater risk of falls (as outlined in the severity and disease progression).[21] Nevertheless, it's important to note that elderly people are more likely to fall, and thus the observed relationship could be independent of the disease itself.

Depression is another factor that was found to be associated with falls.[31,32] Processing speed task is impaired in depressed MS patients, which means that they must take more time to complete tasks that require motor functioning, reflecting an increased risk of falls.[66] Furthermore, the dysregulation of neurotransmitters, particularly serotonin, implicated in mood disorders like depression, plays a crucial role in both affective states and motor control.[67] Studies have emphasized the impact of serotonergic dysfunction in MS-related depression, further affecting the neural circuits involved in motor coordination and balance in MS patients.[67] The presence of depression in MS is intricately linked to disruptions in the hypothalamic-pituitary-adrenal (HPA) axis, as evidenced by altered cortisol levels.[68] This dysregulation not only contributes to the emotional and cognitive aspects of depression but also has implications for the physiological processes involved in motor planning and execution. Interestingly, anxiousness level in MS patients was found to be correlated with a decreased risk of falls, this observation could be due to an increased sense of awareness among those subsets of patients.[32] Depression, as well as fatigue, and sleep quality were also found to be significantly correlated with FOF, which by itself is a risk factor for falls in PwMS.[19]

The prevalence ratio of females to males with MS has markedly increased over the last decades. This reflects a true increase in MS amongst females but not males.[69–71] However, regarding falls, males had a significantly increased risk compared to females.[17] This could be due to more regionally gray matter atrophy in male patients and thus worse disease severity.[3] Furthermore, men are generally less physically active and demonstrate lower self-efficacy for physical activity compared to females, which could be a contributing factor to the increased overall risk of falls.[72] In addition to that, patients with MS with certain ethnicities and races; Black and Latinx are predisposed to an increased risk of falls.[73]

Medications, in particular anti-depressants such as SNRI and SSRI, increase fall risk in MS patients.[28,33] SSRIs tend to cause orthostatic hypotension, as well as predispose patients to syncope and falls due to their co-current inhibition of sodium and calcium channels.[74] However, it is important to note that the falls in those patients could be due to the disease itself "depression" as discussed earlier rather than the medication per se. Therefore, more research focusing on pathophysiology regarding medication and the risk of falls is warranted.

In addition to understanding the physiological aspects of MS leading to falls, it is crucial to acknowledge environmental factors that contribute to this issue.[7] These factors, though not directly related to MS pathophysiology, play a significant role, particularly in environments that predispose to falls such as slippery or uneven surfaces. Furthermore, objects including furniture, pets, and flooring all have been shown to contribute to falls in PwMS. Patients are more likely to slip/trip in such settings particularly when patients are not paying attention and rushing to get somewhere.[75] The use of walking aids amongst PwMS has also been shown to increase the risk of falls. This could be due to the increased disease progression in this subset of patients. However, it also indicates difficulty maneuvering through challenging environmental settings which may include uneven or different floor types and obstacles.[76] The combination of all or any of the factors associated with falls in PwMS in combination with challenging environments has also been shown to increase fall risk. Hence, we would like to emphasize the importance of considering the environmental challenges in addition to the various factors discussed earlier when managing fall risk amongst PwMS.

Limitations

While this scoping review has provided key points into the common factors associated with falls in patients with MS and their potential correlations, it is important to consider several limitations that may impact the generalizability and robustness of our findings. For instance, the quality of evidence included in this review differs between studies, as it

encompasses a wide range of studies with varied methodologies and sample sizes. This heterogeneity may introduce potential biases and limitations in interpreting the relevant findings. Moreover, many of the studies included in this scoping review were cross-sectional or retrospective in nature, limiting the ability to establish causal relationships between the identified factors and falls in patients with MS. Therefore, longitudinal studies and randomized controlled trials are needed to further elucidate these associations.

Conclusion

The current scoping review highlighted the most common factors associated with falls that might be significantly correlated in patients with MS. The evidence assembled and synthesized in this review indicates that severity and progression, mobility and balance, bladder dysfunction, fear of falling, fatigue, cognitive dysfunction, and other miscellaneous causes are amongst the most common factors associated with falls in MS patients. Identifying the risk of falls can aid in developing future interventions to decrease fall risk and improve the overall quality of life. Therefore, it is important to increase awareness regarding falls in MS amongst both physicians and patients.

Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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