



# End of life in multiple sclerosis: Disability, causes and place of death among cases diagnosed from 1981 to 2010 in Pirkanmaa hospital district in Western Finland

Annukka Murtonen<sup>a,\*</sup>, Juho T. Lehto<sup>a,b</sup>, Marja-Liisa Sumelahti<sup>a</sup>

<sup>a</sup> Faculty of Medicine and Health Technology, Tampere University, 33014 Finland

<sup>b</sup> Palliative Care Centre and Department of Oncology, Tampere University Hospital, Tampere, Finland

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## ABSTRACT

**Background:** Mortality risk and causes of death have been widely studied in MS. Surveys on conditions related to approaching death have not been conducted before in Finland.

**Objective:** Our aim was to sort out the possible needs for end of life (EOL) care in MS by examining causes, place of death and level of hospitalization by age and MS related disability before approaching death.

**Materials:** Data included information for MS patients diagnosed from 1981 to 2010 in a Finnish university hospital district. Information on place and causes of death and care prior to death was based on death certificates from Statistics Finland. Decedents initial disease course, disease modifying treatment (DMT) use and MS related disability status by using EDSS were achieved from hospital records.

**Results:** Data included 113 decedents. Level of disability showed EDSS 6.0 or higher in 54% of the patients. In relapsing onset MS (N 93, 80%) DMTs were used in 11%. Infections, respiratory or other, were the main immediate cause of death (51.3%, n 58) among cases with varying disability. Central or university hospital (42.5%) or community hospital ward (28.3%) were places of death in majority of cases and nursing home (13.3%), home (9.7%) or hospice (3.7%) less often. Place of death did not significantly differ between age-groups (Chi square  $p = 0.86$ ). Mean age at death was 57 years (range 28–90, SD 13.86). Cardiovascular causes of death were reported mainly in age group 60 years or more and suicide in age group younger than 50 years.

**Conclusion:** The level of hospitalization was high at end of life in all age-groups. High MS related disability and immobility among decedents likely relates to infections as the most common cause of death. Along with our and earlier surveys in this field, we showed that places of death and level of disability before death share similarities in both younger and older age groups highlighting the need of palliative care and end of life care plans in all MS patients with triggers of poor survival. The recently published consensus definition featuring palliative care guideline in MS is aimed at improving end of life care in MS. Our results point at need for future studies in order to assess the impact of palliative care treatment guidelines in MS.

## 1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system, starting in early adulthood and affecting 2.3 million people worldwide. Initial disease course is relapsing-remitting (RRMS) in a majority of cases (Scalfari et al., 2014).

At its later stage MS may show a progressive and debilitating course (Leray et al., 2010), accompanied by heterogenous neurological symptoms of varying severity, that cause decrease in quality of life (Kobelt et al., 2006; Ruutiainen et al., 2016), early retirement (Pfleger et al.,

2010) and higher mortality ratios as compared to general population (Brønnum-Hansen et al., 2004; Hirst et al., 2008; Lunde et al., 2017; Smestad et al., 2009; Sumelahti et al., 2010). Surveys point that there is an increased risk of infection-related hospitalizations (Pirttialo et al., 2020) and infection related mortality in MS (Lalmohamed et al., 2012; Montgomery et al., 2013; Nelson et al., 2015).

There is increasing understanding on circumstances and complex patterns that contribute to death due to MS (Harding et al., 2020). Also, the complex conditions related to advanced disability and immobility (Harding et al., 2020) point at need for individual advanced care

\* Corresponding author.

E-mail address: [annukka.murtonen@tuni.fi](mailto:annukka.murtonen@tuni.fi) (A. Murtonen).

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planning in MS (Davies et al., 2016; Sleeman et al., 2013; Strupp et al., 2014). The recently published guidelines for palliative care (PC) of people with severe, progressive multiple sclerosis and studies up to 2017 present evidence-based recommendations for several MS related symptoms (Solari et al., 2020). However, publications or trials are lacking for recommendations in several common symptoms, for example respiratory or swallowing difficulties.

In this study we aim to study the reported conditions related to approaching death in MS by using data from death certificates and hospital patient records among deceased cases in MS cohort diagnosed from 1981 to 2010 at the university health care district Pirkanmaa in Western Finland. We aim to study the immediate and other causes of death by age and MS related disability level in relation to patients' need for end of life hospital care and place of death.

## 2. Material and methods

### 2.1. Data collection

This is a retrospective observational study including confirmed MS patients from 1.1.1981 to 31.12.2010 with a death certificate at University Hospital District of Tampere in Pirkanmaa. The end of follow-up is 31.12.2010. The examination of identified patient records at hospitals and the linkage to Statistics Finland and the Population Register Centre's Population Information System for deaths were approved by The National Institute for Health and Welfare and The Ethics Committee of the Tampere University Hospital District.

Data in this study includes deceased incident MS cases, a detailed description of the catchment population is reported earlier (Holmberg et al., 2013). Cases with ICD-code of multiple sclerosis (codes 340, 341, 377, G35 in the International Classification of Disease, versions 8 to 10) from January 1, 1981, to December 31, 2010, were first identified from administrative registries in hospitals belonging to the University Hospital district of Tampere in Pirkanmaa. Patients who fulfilled the criteria of definite MS at the timepoint of diagnosis were included (McDonald et al., 2001; Polman et al., 2005; Poser et al., 1983).

All included cases had a confirmed MS diagnosis and a Finnish death certificate. If a patient had visited other neurologist in Finland or abroad, information on this was detectable in the patient record. We were able to control for patient information available from all hospitals in the catchment area based on personal identification code of cases.

Linkage of the MS cohort to the Statistics Finland death database from 1 January 1981 until 31 December 2010 was done automatically by using the patient's personal identity code as the key. All residents of Finland have since 1 January 1967 had this unique personal identity code. This code is used in all main registers in Finland and allows reliable computerized record linkages.

### 2.2. Death certificate process in finland

Any health care unit or licensed physician must immediately report any decease and causes of death to Population Register centre of Finland and National Institute for Health and Welfare, where reports are sent onwards to Statistics Finland. This certificate is on paper form up to 2014 and electronic from 2015. Approximately 80% of all death certificates are issued by the attending physician. A forensic autopsy is performed in 20% of the cases (Korpisaari, 2016).

Statistics Finland maintains Finnish residents' death certificate archives from where death certificate data or copies of death certificates are released for purposes defined by law. Since 1996, the statistics have been compiled based on the 10th revision of the International Classification of Diseases (ICD-10). Between 1987 and 1995, the data were classified using the national classification of diseases 1987 and from 1969 to 1986, the international classification ICD-8 was in use.

Death certificate contains data of the deceased, including sex, age, timepoint and causes of death by immediate, intermediate, and

underlying causes, other notable diseases, injuries and contributing factors to death, manner, and place of death. The medical case history during the EOL is reported in these certificates in a form of epicrisis.

### 2.3. Methods

Death certificates (N 113 in paper form) were scrutinized by authors (AM, MLS). For purposes in this study information was included for the timepoint, place and causes of death by immediate, intermediate, and underlying causes. Data from epicrisis was collected for the final institution of care, disability, contributing diseases and treatments at end of life.

Hospital records were scrutinized (AM, MLS) to collect demographic information for birth year, initial disease course (relapsing-remitting, RRMS or primary progressive, PPMS) (Lublin et al., 2014), MS duration from diagnosis, any exposure to disease modifying treatments (DMT) and last assessment of disability. Disability status at last evaluation was based on given Expanded Disability Status Scale (EDSS) value (Kurtzke, 1983) or description of disability in patient document based on status signs, patient reported symptoms and symptomatic treatment shown in the patient record. Disability categorization into mild, moderate, or severe was used in a similar manner than in our previous prevalence study (Murtonen and Sumelahti, 2020). In case there was no description of handicap at any central nervous system level or any symptoms that needed treatment or rehabilitation, or when the described symptoms and signs could be graded as mild, we categorized patient into a mild disability group, corresponding to EDSS grades < 3.0. Categorization to moderate disability group concerned cases with a reported handicap in several functions, corresponding EDSS grades 3.0–5.5. Severe disability group here included cases with a significant handicap, constant bilateral support required to walk 20 m without resting, corresponding EDSS 6.0 or greater (Solari et al., 2020).

#### 2.3.1. Statistical methods

Statistical analyses were conducted with SPSS version 26. Descriptive statistics, distributions and appropriate tests for significance were used: T-tests to compare two independent groups with a single variable and Chi-Square when there were several categories.

## 3. Results

During the 30-year follow-up from 1981 to 2010 among 684 confirmed MS cases from the catchment area, a total of 113 cases with death records were scrutinized. Mean age at MS onset was 36.2 years (min 15, max 62, SD 11.2). Mean age at death was 57.4 years (min 28, max 90, SD 13.86). Women (N 63) were slightly older at death, mean 59 years, than men (N 50) 57 years, difference was not significant (T-test  $p = 0.244$ ). Initial disease course was RRMS in 90 (79.6%) and PPMS in 23 (20.4%) cases. Half of the mortality cohort were working aged and reported a marital status, while half were single, divorced or widows. Majority had children.

Distribution of immediate causes and places of death in three age-groups are shown in Table 1. As immediate cause of death MS was recorded in 13 (11.5%) cases. Infections were recorded in a majority of 58 (51.3%) cases. Infections were mainly respiratory in 52 cases (46.0%), gastrointestinal and urinary infections in 2 (1.8%) and sepsis with unknown focus in 4 (3.5%). Cardiovascular causes in 10 cases (11%) were mainly seen in the oldest age group (60 years or older) and suicide in three cases (2.7%) in the youngest group. Group differences by immediate causes of death in age-groups were statistically significant (Chi square  $p = 0.006$ ).

MS as an underlying cause of death (not shown) was recorded in 65 death certificates (57.5%). Other underlying causes were infection in 5, cancer in 13, vascular cause in 19, gastrointestinal cause, other neurological disorder, trauma, and suicide altogether in 14 cases.

Overall, ICD codes for MS were mentioned in 92% of death

**Table 1**  
Characteristics in the study cohort.

	Agegroups, n (%)			Total	%
	0–49 years	50–59 years	60 and over		
N (%)	34 (30.1)	33 (29.2)	46 (40.7)	113	
Mean age at death (SD) years	41.3 (6.1)	55.1 (2.3)	71.0 (7.6)	57.4	
Mean duration of MS (SD) years	10.9 (5.2)	15.7 (7.2)	21.1 (8.7)	16.5 (8.5)	
Disability (N,%)					
EDSS < 3.0	7 (28)	7 (28)	11 (44)	25 (100)	22.1%
EDSS 3.0–5.5	8 (38.1)	5 (23.8)	8 (38.1)	21 (100)	18.6%
EDSS 6.0 or greater	19 (31.1)	18 (29.5)	24 (39.3)	61 (100)	54.0%
Immediate cause of death (N)					
Infection	16	22	20	58	51.3%
MS	4	5	4	13	11.5%
Cardiovascular	2	0	10	12	10.6%
Cancer	3	2	5	10	8.8%
Accident	3	0	2	5	4.4%
Pulmonary embolism	3	2	0	5	4.4%
Cerebrovascular	0	0	4	4	3.5%
Gastrointestinal	0	2	0	3	2.7%
Suicide	3	0	0	3	2.7%
Place of death (N)					
Central or university hospital ward	17	15	16	48	42.5%
Community hospital ward	6	14	12	32	28.3%
Nursing home	1	0	14	15	13.3%
Home	6	3	2	11	9.7%
Hospice	2	1	1	4	3.5%
Other	2	0	1	3	2.7%

certificates. MS was not shown for 9/113 (7.96%) decedents, where mean age of death was 46.8 years and immediate causes of death were accident or suicide (N 3), acute myocardial infarction (N 3), pulmonary embolism (N1) and cancer (N1).

Do Not Resuscitate (DNR) statement was mentioned in 5/113 cases

(4.4%) in the death certificate.

The place of death was central or university (42.5%) or community hospital ward (28.3%), while nursing home (13.3%), home (9.7%) and hospice care (3.7%) represented a minority. No significant difference between place of death existed by age-groups (Chi square  $p = 0.86$ ). Place of death by immediate cause of death is shown in Fig. 1.

Information on the latest hospital recorded disability status at the neurological or other clinic before death was compared with information available in the death record. Based on this information disability before death was mild in 22.1%, (corresponding to EDSS < 3.0, N 25), moderate in 18.6% (corresponding EDSS 3.0–5.5, N 21) and severe in 54% (corresponding EDSS 6.0 or more, N 61). In 5.3% information on disability was not available (not classified, NC, N 6). Distribution of disability using this classification was similar in the three age-groups (<50 years, 50–59 years, 60> years) (Chi-square  $p = 0.72$ ), by initial disease course (RRMS, PPMS) ( $p = 0.42$ ) and by sex ( $p = 0.56$ ), showing statistically nonsignificant differences. Disability distribution by cause of death is shown in Fig. 2 and in by initial disease course in Fig. 3.

#### 4. Discussion

In this MS cohort, care of dying patients and deaths took place mainly at hospital wards. MS related disability was high among majority of decedents and the main immediate cause of death were respiratory infections in all age groups. Result in our report supports earlier observations that MS patients with a severe, progressive disease die in hospital rather than at home (Campbell et al., 2010; Lunde et al., 2017) and confirms the observation on increased risk of infection-related hospitalizations and infection related mortality in MS (Lalmohamed et al., 2012; Montgomery et al., 2013; Nelson et al., 2015). Along with results in earlier surveys, we showed here that this concerns patients in both young age-groups, where end of life care plans are not usually necessitated, and also in older age groups, where slow disease progression may disperse observation of the triggers for palliative care.

The level of hospitalization was high, as almost half (42.5%) of all deaths took place at central or university hospital ward, where the main causes of death were respiratory infections. Majority of reported deaths in all age-groups during the follow-up took place at any health care institutions. Among the four decedents in hospice care, MS and cancer were reported as causes of death. Deaths that took place outside health care institutions related to acute vascular diseases, suicide, and accidents.

This is the first Finnish survey on characteristics of dying MS patients

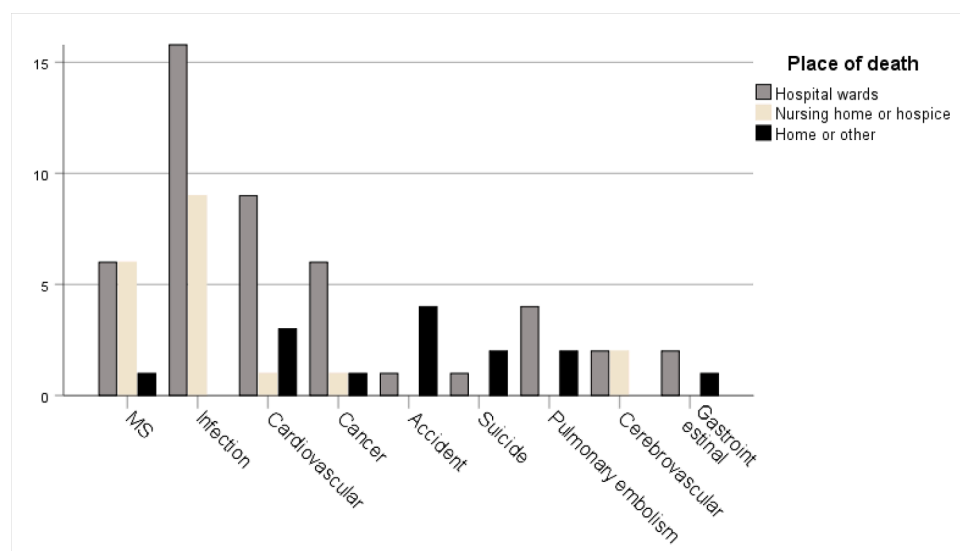


Fig. 1. Place of death by immediate causes of death. Number of cases treated for infections in hospital wards is 49.

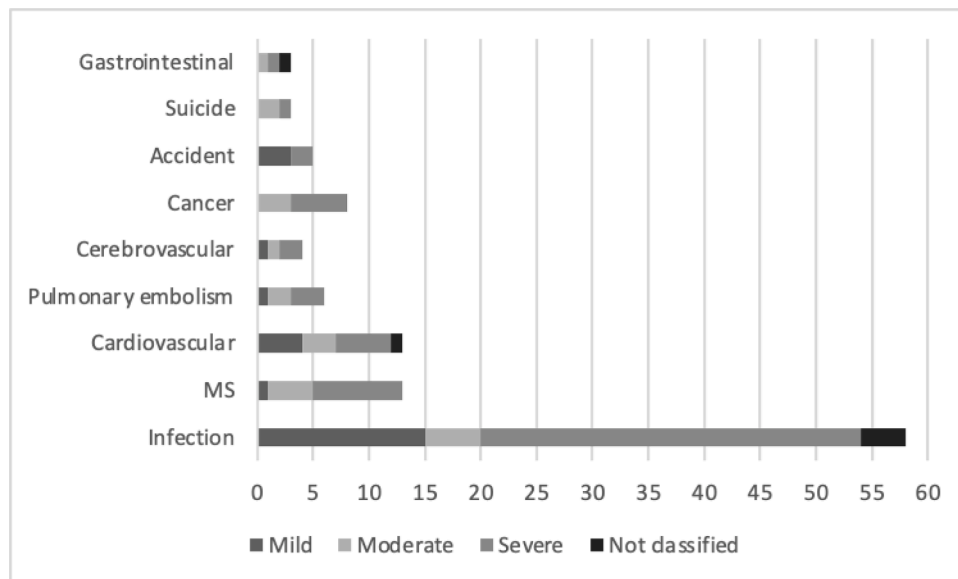


Fig. 2. Distribution of disability before care period prior to death by immediate cause of death.

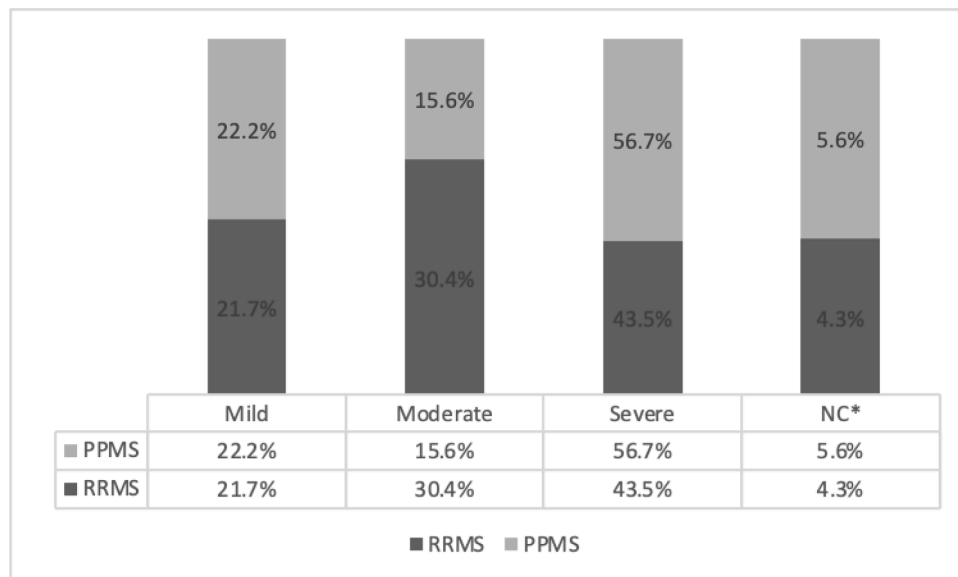


Fig. 3. Disability distribution before care period prior to death by disease course.

covering a long follow up for 30 years in a cohort of 113 decedents. During the follow up the structure of health care system by large has remained unchanged, and facilities are comparable to those in other Scandinavian and North European countries. Finland offers its residents a universal healthcare, which consists of a highly decentralized three-level publicly funded healthcare system and a much smaller private sector. The diagnosis of MS is practically always confirmed in public health care neurology clinics, where regular control visits also take place. The death certificate procedure has been described earlier in this report and it follows the international standards (World Health Organization, 1979).

In our data the ICD code for MS was mentioned in 92% of death certificates, rate being somewhat higher than reported elsewhere, 80–90% (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Harding et al., 2020). MS as an immediate cause of death was recorded in 11.5% of decedents, which was similar to previously reported 9% (Hirst et al., 2008). As an underlying cause of death MS was mentioned in 57.5% of

records, being similar or a bit higher than reported previously, 34–56% (Brønnum-Hansen et al., 2004; Cutter et al., 2015; Hirst et al., 2008; Smestad et al., 2009).

Mean age at death, 57.4 years, was lower than reported in two previous studies: 74.5 years (Harding et al., 2020) and 65.3 years (Hirst et al., 2008). In our data the mean age of death was lowest (not shown in results, 46.8 years) among cases with a missing MS ICD code. High inclusion rate of diagnosed cases in this set of data could be among explanations for the observed low mean age of death. However, the standardized mortality rate (SMR) of 2.8 reported in several populations is true also in Finland (Brønnum-Hansen et al., 2004; Lunde et al., 2017; Sumelahti et al., 2010). In line with earlier reports, infections (51.3%) were the main cause of death here in our cohort, followed by cardiovascular causes (10.6%) (Brønnum-Hansen et al., 2004; Harding et al., 2020; Hirst et al., 2008; Smestad et al., 2009).

We believe to have a full coverage of MS cases and their disease course in the study district (Holmberg et al., 2013; Murtonen and

Sumelahti, 2020). The cohort was followed retrospectively from disease onset by using hospital records. The earlier reported high MS mortality and distribution of causes of death in other Finnish districts (Sumelahti et al., 2010) and our present data on causes of death from Pirkanmaa district are similar to results in other medium-to high MS risk areas (Cutter et al., 2015; Lalmohamed et al., 2012; Lunde et al., 2017; Sumelahti et al., 2010), why we believe that our results here are reliable for comparisons.

Exploration of determinants of place of death is important for public health policy, which aims at improving the quality of end of life care. Our aim here was to assess the characteristics of MS patients approaching death, and specify their place of death by healthcare level, which is supposed to relate to the complexity of the medical needs as well as the skills and specialties of the providers. This information and causes of death were based on death certificates and hospital patient records and information was sorted out to evaluate the possible needs and unmet needs for end of life care in MS. Much of the information for the purposes in this study was available from these sources (Davies et al., 2016). The domains for specific symptoms at advanced stages of MS, or information on patients' living conditions, changes in social or working status and need for medical care and support, along with differences in caregiver roles were not available from the sources used in this study. In our hospital record data, the specific MS symptoms such as fatigue, cognitive symptoms, pain, spasticity, bladder symptoms, dysphagia, dyspnea or other respiratory symptoms prior to the dying phase, were randomly reported. During the care period prior to death recordings of recurrent infections, aspiration pneumonia and description for respiratory insufficiency were found in the epicrisis in the death certificate. However, the specific triggers in order to evaluate the applicable healthcare level for patients approaching death were randomly reported in hospital records, and information is thus deficient for research purposes. We also lacked some information on patients' sociodemographic status. This information in some studies has shown to be associated with cause and place of death, and includes factors such as age and marital status, and degree of urbanization and healthcare system, while social status plays lesser role (Gomes and Higginson, 2006; Houttekier et al., 2011).

Use of more structured information is thus needed in future studies. In addition, national registers in Finland, such as the Care Register for Healthcare informing about hospital admissions, National Health Insurance registry providing information on retirement, rehabilitation and other health related support and data from Finnish MS patient Register will be useful sources in future register-based studies.

This research is subject to several limitations mentioned above, such as lack of detailed information on specific symptoms and need of care. However, despite these shortcomings, disability status and information on ambulation were described in majority of hospital records and death certificates. Although information on disability or the EDSS score offer a limited description on need of care, increased disability seems to be a solid indicator for a permanently advanced disability and immobility in MS. In our cohort over half of decedents showed a severe disability before death up to end of follow-up in 2010, while mild and moderate disability were shown in the rest of the cases. As no uniform definition for progressive, severe MS exists, we used the definition used in EAN guideline, where severe MS was assessed when a constant bilateral support required to walk 20 m without resting corresponding to EDSS > 6.0 or higher (Solari et al., 2020). This classification has been used earlier also in the prevalence study in Western Finland in 2010, including the catchment area in this study (Murtonen and Sumelahti, 2020). The disability status was moderate or severe among almost half of the prevalent cases, where mean age was 50.2 years. Such information on disability from prevalence cohorts could be useful for future health care planning (Murtonen and Sumelahti, 2020).

In our data severe disability was observed in both RRMS and PPMS, nor were there differences by immediate causes of death or place of death by disease course. The severe disability in 44% in RRMS is

explained by development of secondary progressive course, generally shown in 40% after 15 years in relapsing–remitting disease (Scalfari et al., 2014). The DMT effect may be considered minor as only 11% among deceased RRMS patients had used DMTs. It may be expected that increasing use of available immunomodulatory treatments, such as DMTs, may suppress inflammation, prolong patients' performance and time to retirement (Heinonen et al., 2020) but it is unknown how these effects are reflected over the entire disease trajectory. Considering the high number of aging treatment naïve MS patients in many current MS cohorts, the awareness of risk factors and progressive symptoms in all disease course groups remains important. Information on the common risk factors may be derived from the earlier reported causes of death in progressive MS, which include infections, such as aspiration pneumonia or urinary tract infections, and complications of falls and fractures, and sepsis secondary to pressure ulcers (Hirst et al., 2008; Sumelahti et al., 2010).

A good proportion of decedents in our cohort had died in hospital settings in spite of a progressed disability which raises the question of unplanned hospitalizations (Seeber et al., 2019; Veronese et al., 2017). At present we do not know how MS patients engage in the process of decision-making, but it is suspected that also in our cohort there is a need for increasing awareness of advance care planning (ACP), supported by reported benefits and the generally low use in neurological diseases (Higginson et al., 2009; Hussain et al., 2018; Seeber et al., 2019). In recent studies contexts and mechanisms underpinning engagement in ACP have been identified in MS, indicating the crucial role of health care professionals and communication throughout the whole course of progressive disease (Seeber et al., 2019; Solari et al., 2018; Veronese et al., 2017). Similar to benefits in ACP, early referral to PC has shown advantages such as better pain management, quality of life, less aggressive EOL care and reduced late-life acute-hospital use (Qureshi et al., 2019; Rosenwax et al., 2015; Spilsbury et al., 2017). PC is a fairly new concept in MS (Solari et al., 2020; Strupp et al., 2016, 2014). The qualifications have only recently been assessed in 2016 by Strupp J et al. (Strupp et al., 2016) indicating benefits in severe MS (Higginson et al., 2009). General triggers for need of PC relate to common symptoms in progressing MS such as deteriorating physical function, weight loss, dysphagia and recurrent infections and aspiration pneumonia (Hussain et al., 2018). Effectiveness of PC among late stage MS patients is expected to be similar than in other neurological diseases (Strupp et al., 2014). In 2014 the Delphi study group reached consensus that specialized PC in MS should begin once the disease has progressed up to EDSS > 6 and nursing care required, and a specialized PC should be consulted when the need exists for communication about disease progression, psychological support, relatives support and pain medication (Strupp et al., 2014). This common lack of integration of PC in EOL may call for a need for standardized referral criteria (Ahmed et al., 2004) and a more widespread empowerment (Westerlund et al., 2018).

#### 4.1. Limitations

As discussed above, this study is subject to several limitations. Detailed information concerning symptoms, all medications and need of care during the days prior to death is lacking in hospital patient records or death certificates. Similarly, information on living conditions, social status, or specific triggers to evaluate the appropriate place of care for patients approaching death were not available or reported randomly. Same is true for detailed information about MS-symptoms and disability among those decedents, whose MS was progressed and were mainly treated in primary health care. Information of possible DNR-statement may as well be lacking from our sources of information. However, in majority of cases there was enough information to categorize the disability into one of the three EDSS-classes discussed above.

## 5. Conclusions

High disability, hospital deaths and infections were common characteristics of the dying MS patients in all age groups in this cohort. Our results thus reflect the need for better integration of advanced care planning on the comprehensive care of MS patients showing severe disease progression. Our results also point need for future studies in order to assess the impact of palliative care treatment guidelines in MS (Strupp et al., 2016).

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## Credit author statement

Annukka Murtonen: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing  
Juho Lehto: Conceptualization, Writing – Original Draft, Writing – Review & Editing

Marja-Liisa Sumelahti: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration, Funding acquisition

## Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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