Primary Progressive Multiple Sclerosis Evolving from Radiologically Isolated Syndrome

Primary Progressive MS evolving from Radiologically Isolated Syndrome

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ABSTRACT:

Objective: To evaluate the pre-progressive phase in subjects with radiologically isolated syndrome (RIS) who evolve to primary progressive MS (PPMS).

Methods: A multicenter RIS cohort was previously established. Demographic, clinical and radiological characteristics of subjects with RIS that evolved directly to PPMS were compared to those that developed a relapsing from onset disease (clinically isolated syndrome (CIS) or relapsing-remitting MS), and were also compared to two other population-based and clinic-based PPMS cohorts.

Results: Of the 453 subjects with RIS, 128 evolved to symptomatic MS during the follow-up (113 developed a first acute clinical event consistent with CIS/MS, 15 evolved to PPMS). PPMS prevalence (11.7%) and onset age (mean ± SD; 49.1 ± 12.1) in the RIS group was comparable to other PPMS populations ($p>0.05$). Median time to PPMS was 3.5 years (range: 1.6-5.4). RIS evolved to PPMS more commonly in men ($p=0.005$) and at an older age ($p<0.001$) when compared to CIS/MS, independent of follow-up duration. Subjects who evolved to PPMS had more spinal cord lesions (100%) before symptomatic evolution then those that developed CIS/MS (64%) and those that remained asymptomatic (23%) within the follow-up period ($p=0.005$). Other MRI characteristics in the pre-progressive phase of PPMS were indistinguishable from CIS/MS.

Interpretation: Subjects with RIS evolve to PPMS at the same frequency as expected from general MS populations in an age dependent manner. Besides age unequivocal presence of spinal cord lesions and being male predicts evolution to PPMS. Our findings further suggest that RIS is biologically part of the MS spectrum.

INTRODUCTION:

Multiple sclerosis (MS) is a heterogeneous immune-mediated central nervous system (CNS) demyelinating disease that is punctuated by four phases: i) a phase of MS risk, ii) an asymptomatic-preclinical phase, iii) a relapsing-remitting phase (RRMS) and iv) a progressive phase. In the latest revision of the diagnostic criteria for MS, asymptomatic sub-clinical activity, appreciated via magnetic resonance imaging (MRI), is proposed to fulfill both spatial and temporal dissemination requirements for MS.[1-3] Therefore, inactivity within all phases is implied based on the absence of both new MRI and clinical events suggestive of acute inflammatory demyelination within the last year.[4]

Many patients with MS, who are evaluated for the first time for a symptomatic syndrome suggestive of inflammatory-demyelinating disease, already have clinically silent lesions on MRI suggesting an asymptomatic prodrome of unknown duration. The early manifestations of CNS demyelination may also be appreciated in subjects who have an MRI as healthy control subjects for the investigation of symptoms that are incongruent with an inflammatory demyelinating syndrome. Such subjects are described as having radiologically isolated syndrome (RIS), when 3 or 4 of the 4 radiological criteria for dissemination in space are met.[5-7] These subjects may remain asymptomatic, or develop clinically isolated syndrome (CIS) and RRMS.[8, 9] Therefore, RIS may represent the earliest presentation of MS during the asymptomatic-preclinical phase. We recently reported asymptomatic to symptomatic evolution typical of demyelination in 34% of subjects with RIS within the first 5 years of follow-up.[10] Risk factors for developing a first symptomatic event included male sex, younger age at the time of RIS diagnosis (< 37 years), and the presence of spinal cord lesions.[10]

The progressive phase of MS is currently classified by the temporal relationship between clinical phenotypes of symptomatic relapses and progression.[11] Secondary progressive MS (SPMS) follows RRMS, while single attack progressive MS (SAPMS) occurs after a single demyelinating event - CIS.[12] In primary progressive MS (PPMS), a decline in physical abilities occurs without preceding relapses. Pure PPMS excluding SAPMS, a group that could have been included in the PPMS definition in the past, constitutes about 10% of all MS patients at presentation.[13, 14] While PPMS generally is accepted to be related to spinal-cord dominant form of MS [15], many PPMS patients present with multiple brain or spinal cord lesions similar to that of bout-onset progressive MS (SPMS + SAPMS), suggesting a protracted asymptomatic-preclinical phase of MS. Several recent studies have also established that PPMS, SAPMS and SPMS are strikingly similar in terms of age at progressive disease course onset.[14, 16, 17] It is likely that PPMS and other bout-onset forms of progressive MS are presentations of the same biology of a progressive phenotype, differentiated only by the resistance to acute symptomatic manifestations as relapses.

We hypothesize that subclinical disease activity in PPMS during the pre-progressive phase is similar to that of other MS patients. For SPMS, the pre-progressive phase is better defined in natural history studies involving those with RRMS. It is predicted that approximately 25% of RRMS patients will never evolve to SPMS, highlighting disease heterogeneity. [14] An unbiased natural history study aimed at investigating the temporal profile of disease activity from incidentally identified radiological anomalies to the development of non-acute symptoms typical for the onset of PPMS is difficult. A population-based imaging effort to identify such subjects in the pre-progressive phase of PPMS is simply resource prohibitive. We present demographic and imaging findings collected during the pre-progressive phase from subjects prospectively followed

and enrolled in a multinational RIS cohort who developed PPMS, in comparison to those who experienced a first acute symptomatic demyelinating episode.

METHODS:

Ethical statement:

All data were collected with written informed consent to access medical information from all patients under a protocol approved by appropriate institutional review boards from each center.

Definition of terms:

RIS was defined according to the previously established criteria.[7] Outcome of symptomatic evolution was assigned to any individual that developed a clinical syndrome that could not be explained by any neurological disease other than a CNS demyelinating disorder. In those subjects with symptomatic evolution as an acute demyelinating event, a diagnosis of CIS/MS was assigned according to established criteria. [1-3] In those subjects with symptomatic evolution as insidious neurological worsening for at least a 12-month period, a diagnosis of PPMS was assigned according to the established criteria. [3]

Study populations:

Data were ascertained from three previously published cohorts; An RIS cohort that originated from 22 clinical sites within 5 countries (n=453) [10]; a population-based cohort of all MS patients from Olmsted County, MN with a longitudinal follow-up of more than 20 years (n=210)[14, 18, 19] and a recently established large clinic-based cohort of progressive MS patients (n=754).[14, 20]

Data collection:

MRI data was collected as previously described. [10] Information on lesions location, number and enhancement characteristics were described and coded for the brain and spinal cord MRIs when available according to diagnostic criteria.[5, 6] Cerebrospinal fluid information was coded as

positive when patients had presence of either oligoclonal bands or elevated IgG index according to local standards at each clinical laboratory.

Data analyses:

We compared demographic and clinical features in different populations by χ^2, Fischer's exact test or Student-T tests as appropriate to the variable. We studied probability of evolution from RIS to PPMS vs. RIS to CIS/MS according to age and time by the Kaplan-Meier and Cox regression analyses.

RESULTS:

Prevalence of evolution to PPMS among subjects with RIS:

Of the 453 subjects with RIS identified between multiple centers[10], 128 developed symptomatic MS (Figue-1). Of these 113 developed a first acute clinical event related to CNS demyelination consistent with CIS/MS diagnosis while 15 evolved to PPMS. Thus, among subjects with RIS who developed a symptomatic demyelinating syndrome, the prevalence of PPMS was 11.7%.

Demographic, Clinical and MRI characteristics of subjects who evolved to PPMS:

In subjects who evolved to PPMS, 6 were women, median age (range) at RIS was 43.3 (range: 20-66) years, median duration of follow-up was 5.8 (range: 1.1-18.0) years, and median time to conversion was 3.5 (range: 1.6-5.4) years.

The reasons for obtaining the initial MRI leading to a diagnosis of RIS were as follows; primary headache (n=4), trauma (n=5), low back pain (n=1), radiculopathy (n=1), history of childhood epilepsy (n=1), non-neurological spells (n=1), non-central hearing impairment (n=1) and malignancy screening (n=1).

The initial MRI screening could have been one of various spinal cord levels. However, identification of a demyelinating lesion at any level led to an additional brain MRI fulfilling the previously established RIS criteria in all 15 subjects. Also an initial MRI may have been done

without gadolinium but following MRIs establishing the diagnosis of RIS could have been completed with gadolinium.

At the time of first brain MRI fulfilling RIS criteria, all 15 subjects had periventricular lesions (8/15 had >10 lesions; 5/15 had 6-10 lesions, 2/15 had 1-6 lesions), 13 subjects had subcortical / juxta-cortical lesions (3/13 had >10 lesions, 5/13 had 6-10 lesions, 7/13 had 1-6 lesions) and 9 subjects had infra-tentorial lesions (0/9 had >10 lesions, 1/9 had 6-10 lesions, 8/9 had 1-6 lesions).

Only 12 of 15 subjects had a spinal cord MRI at the time of first brain MRI or before conversion to symptomatic MS. All 12 subjects had cervical cord lesions (3/12 had >10 lesions, 5/12 had 6-10 lesions, 4/12 had 1-6 lesions) while 9 of 11 subjects who had thoracic cord MRI had thoracic cord lesions (2/9 had >10 lesions, 0/9 had 6-10 lesions, 7/9 had 1-6 lesions).

In Figure-2, we illustrate the typical time-course with imaging findings from a subject followed for 9 years with a diagnosis of RIS prior to developing neurological symptoms related to progressive myelopathy/ataxia and fulfilling a diagnosis of PPMS.

Comparison of Demographic, Clinical and MRI characteristics of subjects who evolved to PPMS versus those that developed CIS/MS:

Subjects who evolved to PPMS were more commonly men ($p=0.005$) when compared to those that developed CIS/MS (Table-1). Both the median age at RIS ($p<0.001$) and median age at symptomatic evolution ($p<0.001$) was older by approximately 10 years for subjects that evolved to

PPMS than those that developed CIS/MS. While evolution to PPMS happened at an older age, the observation did not appear to be related to follow-up time after RIS diagnosis (p=0.21) (Figure-3).

When spinal cord MRIs were available before conversion to symptomatic MS, the presence of spinal cord lesions at the time of first RIS MRI highly correlated with evolution of symptomatic MS in the whole group of RIS subjects (HR=3.33, 95%CI= 2.22-4.99, p<0.001). However, there was also a highly significant difference in the presence of spinal cord lesions between subjects that evolved to PPMS (100%) and those that developed CIS/MS (64%) (p=0.005) (Table-1).

On baseline brain MRI studies, if gadolinium was administered, at least one enhancing lesion was observed in 76 of 277 subjects that remained asymptomatic (27.4%), 30 of 91 that developed CIS/MS (33.0%) and 2 of 13 that evolved to PPMS (15.4%) (p=0.32). On baseline spinal cord MRIs, if gadolinium was administered, 14 of 255 subjects that remained asymptomatic (5.5%), 25 of 101 that developed CIS/MS (24.8%) and 6 of 15 that evolved to PPMS (40.0%) had at least one enhancing lesion (p<0.001). However, when the enhancing spinal cord lesions were considered as a fraction of total spinal cord lesions and compared among subjects that remained asymptomatic, those that developed CIS/MS and those that evolved to PPMS, the results were not significant (p>0.05). There was also no specific difference among subjects that developed CIS/MS and those that evolved to PPMS (Table-1).

Comparison of Demographic, Clinical characteristics of subjects with RIS who evolved to PPMS with other populations of PPMS:

The mean age at onset of PPMS (n=15; mean ± SD; 49.1 ± 12.1) in the RIS cohort was comparable to the population-based patients with PPMS (n=15; mean ± SD; 41.1 ± 11.6)

(p=0.076), and the clinic-based patients with PPMS (n=308; mean ± SD; 45.9 ± 10.8) (p=0.274) (Figure-4). The ratio of women to men was lower for subjects with RIS that evolved to PPMS than it is in the other two populations (Figure-4).

DISCUSSION:

This is the first report of the temporal course within the pre-progression phase for an extremely rare group of subjects originally identified by MRI as having asymptomatic disease, who ultimately experienced progressive symptom evolution consistent with PPMS that could not otherwise be explained by any other mechanism (excessive alcohol use, vitamin deficiencies etc). Within the existing scientific literature, only a single case report exists with low resolution MRI evidence of possible MS from an earlier imaging study done 10 years before for unrelated reasons. [21]

The 12% prevalence of PPMS in this large RIS cohort, as well as age at PPMS onset, are strikingly similar to that of large clinical studies in MS. [13] The current RIS diagnostic criteria [7] appears to be adequately sensitive in identifying potential PPMS patients before they become symptomatic at the same rate as already symptomatic clinic populations, further supporting the growing evidence that RIS, when characterized accurately, is pre-symptomatic MS. [10] Studying RIS, therefore, provides an opportunity to better understand the onset of clinical MS and to test early intervention.

Our current study illustrates that the pre-progressive phase in PPMS is characterized by active but asymptomatic lesion development that is similar to RRMS. For many PPMS patients, being older, male and having a spinal cord dominant lesion load profile is characteristic. [15] We established that just like evolution from RIS to a first acute event related to CNS demyelination consistent with CIS/MS, the strongest predictors of evolution of PPMS included male sex, a more advanced age, and the presence of initially asymptomatic spinal cord disease long before the onset of progressive MS. [10] All subjects that evolved to PPMS in our study had undoubtedly high load of

asymptomatic spinal cord disease in addition to brain lesions fulfilling diagnostic criteria for MS. While we did not observe the often mentioned paucity of brain lesion development in PPMS, this could be driven by our RIS criteria, which biases our study towards the higher brain lesion load patients, or as originally reported, it may be due to the fact that many patients with PPMS indeed have very similar lesion loads to that of bout-onset progressive MS albeit with smaller lesions. [22]

Expectedly, subjects who developed symptomatic MS were more likely to have had at least one enhancing lesion on baseline MRI studies when compared to those who remained asymptomatic in the same period. This was independent of development of PPMS or CIS/MS. Subjects who evolved to PPMS were more likely to have had at least one enhancing spinal cord lesion than those who developed CIS/MS or remained asymptomatic. However when corrected for the increased lesion load in the spinal cord for subjects who evolved to PPMS, this difference was not significant. Our findings suggest that the proportion of contrast enhancing lesions are not different between subjects who develop CIS/MS and those who evolve to PPMS during the early pre-symptomatic phase of the disease, suggesting that it is the location of lesion load that seems to make a difference.

In this study, the older age at onset of progressive MS evolving from RIS compared to age at onset of acute clinical events developing in RIS was clearly independent of follow-up times. This age dependence of progressive MS development, in the absence of previous clinical relapses despite having clear sub-clinically active MS, suggests that biological aging mechanisms may be a significant contributor for development of progressive MS. Together with the strikingly similar age-at-onset of the progressive phase of MS, regardless of the presence or absence of acute relapses [14, 16, 17], our study suggests that progression mechanisms in PPMS are indeed similar to other progressive MS forms of SAPMS and SPMS.

Furthermore, the progressive disease course contributes strongly, but relatively equally, to the long-term cumulative disability among PPMS, SAPMS and SPMS. [20] The difference in long-term cumulative disability outcome among PPMS, SAPMS and SPMS is than explained primarily by the presence or absence of pre-progression clinical manifestations or ongoing clinical relapses after progressive MS onset. [20] Ongoing clinically active MS or relapses can be present in 14% of patients after the onset of progressive phase of MS.[20] While ongoing relapses after progressive MS onset are less common in patients with PPMS than those with SAPMS or SPMS, when present, the last relapse also remarkably manifests around the same age group in PPMS, SAPMS or SPMS.[14, 20]

Given similar ages at the onset of progression and termination of relapses, progressive MS patients without preceding clinical relapses likely have subclinical disease activity at similar ages as patients with preceding clinical relapses. This hypothesis needs to be studied further with longer term follow-up of subjects with RIS. The main limitation of our study without doubt is the randomness of the detection of RIS and the difficulty to design a prospective study of natural history of RIS at a population-based level. However, our results are nevertheless intriguing in suggesting that a yet to be defined intervention at RIS phase could potentially delay or ideally prevent PPMS onset.

Together with findings of this study we conclude that subclinical disease activity and progression mechanisms in PPMS, SPMS and SAPMS are likely indistinguishable from each other. The only difference seems to be whether or not active MS manifests clinically as relapses. The relationship between the two relatively specific characteristics of PPMS, resistance to acute clinical relapses and early spinal cord dominance of lesions need to be studied further.

Why some lesions, indistinguishable from their counterparts in symptomatic subjects, never become symptomatic as relapses but still cause enough CNS injury later to lead to progressive disease course remains largely unexplained. Many potential mechanism exist that need to be further studied. These include, but are not limited to, synaptic plasticity exhaustion induced by injury or energy failure due to mitochondrial dysfunction leading to loss of white matter and neuronal integrity maintenance associated with aging. [23-26]

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AUTHOR CONTRIBUTIONS:

Conception and design of the study: OK, CL, AS, DP, DO

Data acquisition and analyses: OK, MS, CL, AS, DP, DO, MK, CA, MI, MT, BN, FDD, MA, NDS

Drafting the manuscript, tables and figures: OK, MS, CL, AS, DP, DO

POTENTIAL CONFLICTS OF INTEREST:

The authors declare no conflicts of interest related to this work.

TABLE 1: Comparative demographics and clinical characteristics of the study population

	Non-converters	All converters	RIS to CIS/MS (15 years)	RIS to PPMS (15 years)	P (CIS/MS vs PPMS)
N	324	128	113	15	NA
F%	81	71	75	40	P§ = 0.005
Median (yrs) age at RIS (range)	38.6 (14-74)	32.5 (11-70)	32.0 (11-70)	43.3 (20-66)	P^ < 0.001
Median (yrs) follow-up (range)	2.0 (0-20)	5.2 (0.2-21.1)	5.2 (0.2-21.1)	5.8 (1.1-18.0)	P^ = 0.66
Median (yrs) time to symptomatic MS* (range)	NA	2.4 (2.0-2.8)	2.3 (1.7-2.9)	3.5 (1.6-5.4)	P** = 0.21
CSF+(%)	61	75	73	85	P§ = 0.37
Spinal cord lesions at the time of RIS (%)	23	69	64	100	P§ = 0.005
(Gd+) spinal cord lesions at the time of RIS (% of all spinal cord lesions)	3.1	17.4	19	27	P§ = 0.48

§ Chi square test, ^ Mann Whitney U test, *KM estimates, **logrank test; NA= not applicable

Supplementary table-1: SFSEP/OFSEP members in alphabetical order

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FIGURE LEGENDS:

Figure-1: Structure of the study populations. MS= multiple sclerosis, PPMS = primary progressive multiple sclerosis.

Figure-2: An example of a subject with RIS that has been followed for 9 years before developing PPMS. The multiple active but asymptomatic lesions that have evolved during this time indistinguishable from any RRMS patient are illustrated. The notable spinal cord atrophy in later follow-up MRIs is in keeping with the clinically observed progressive myelopathy and ataxia is shown.

Figure-3: Age at and time to evolution from RIS to PPMS or CIS/MS are shown

Figure-4: Age at onset of progressive MS distribution in; RIS evolving to PPMS, population-based PPMS and clinic-based PPMS cohorts is shown

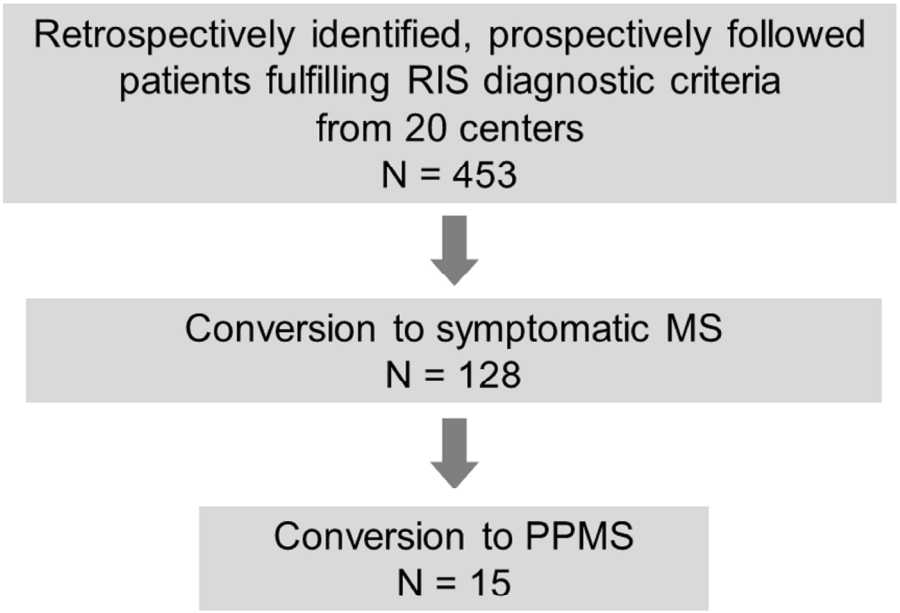

Figure-1 in BW
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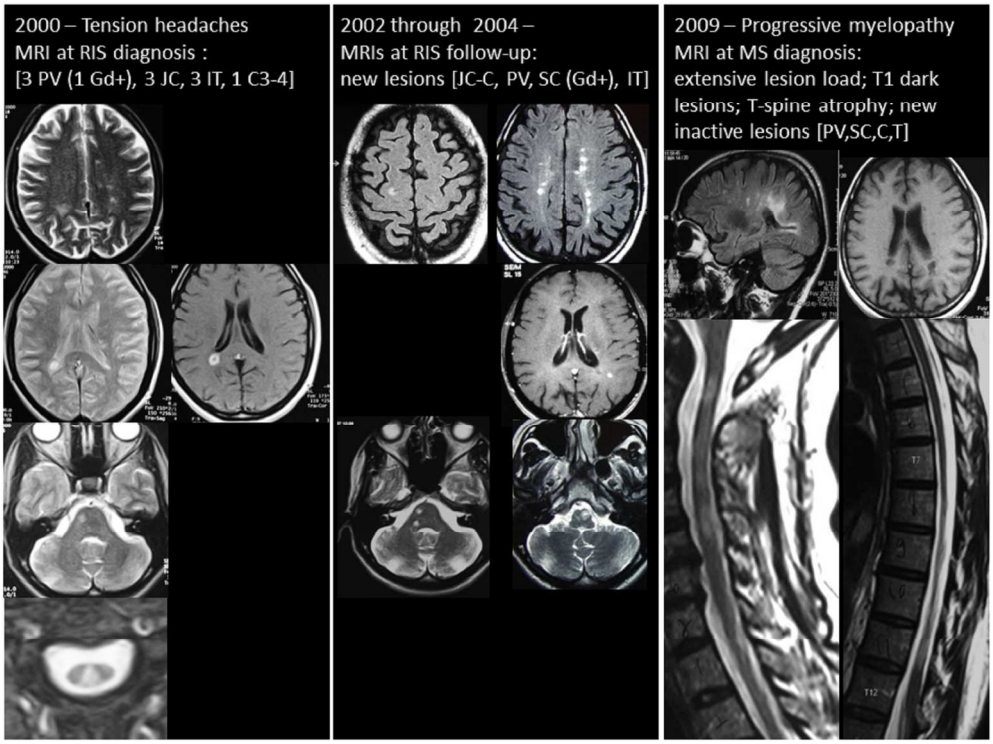

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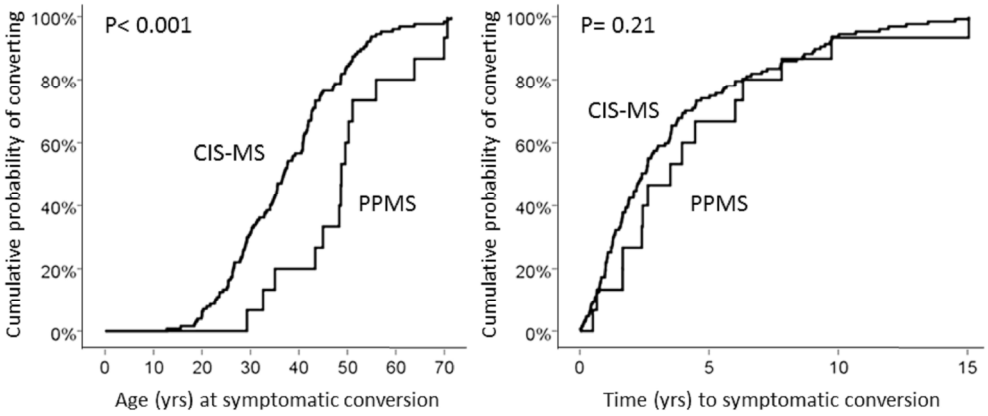

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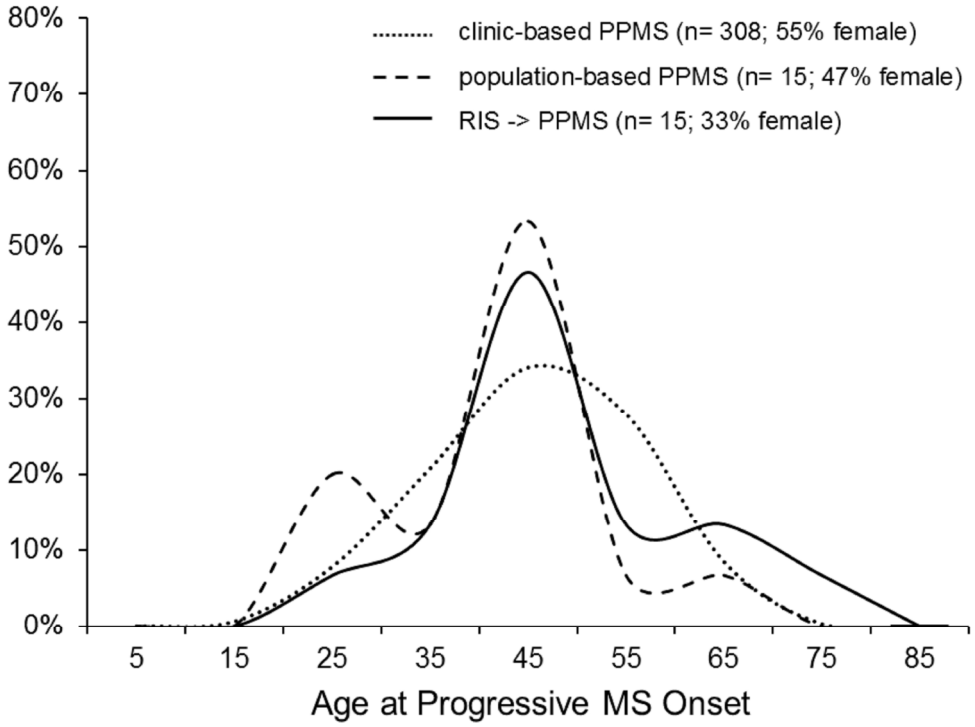

Figure-4 in BW
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