Clinical Disability Outcome Measures in PML

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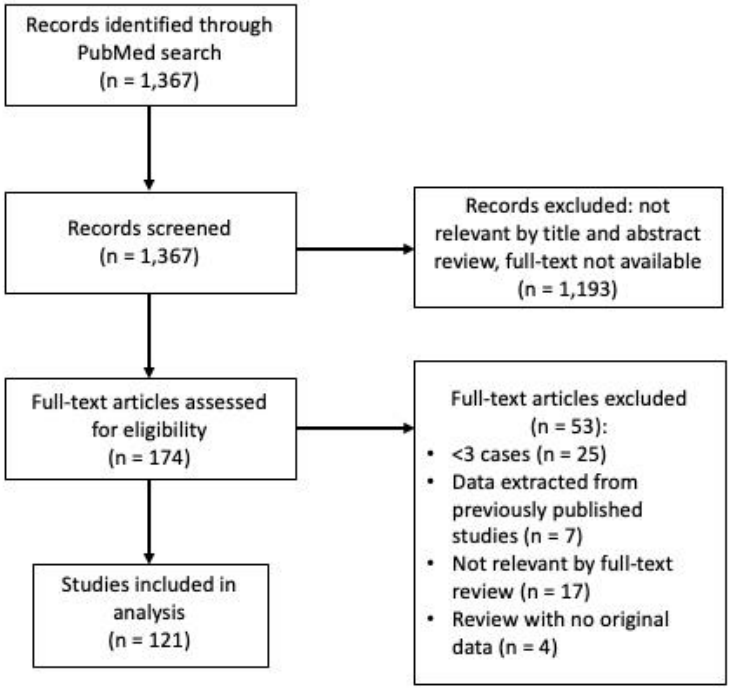
Introduction

- In PML patient populations with higher survival rates, assessment of PML-related disability is a more meaningful outcome measure than survival
- Standardized measurement of PML-related functional outcomes has not been established
- The PML Clinical Outcomes Working Group sought to evaluate the use of disability measures in PML in existing literature, as well as the potential suitability of these measures as clinical trial endpoints

Methods

- Systematic review to evaluate clinical outcomes in PML
- Inclusion criteria:
  - Published 1990-present
  - English language
  - Clinical outcomes (e.g., survival, disability scale) reported
  - At least 3 patients
- Outcomes:
  - Survival
  - Mean/median values for clinical disability outcomes
  - Prevalence of PML symptoms among key neurological domains



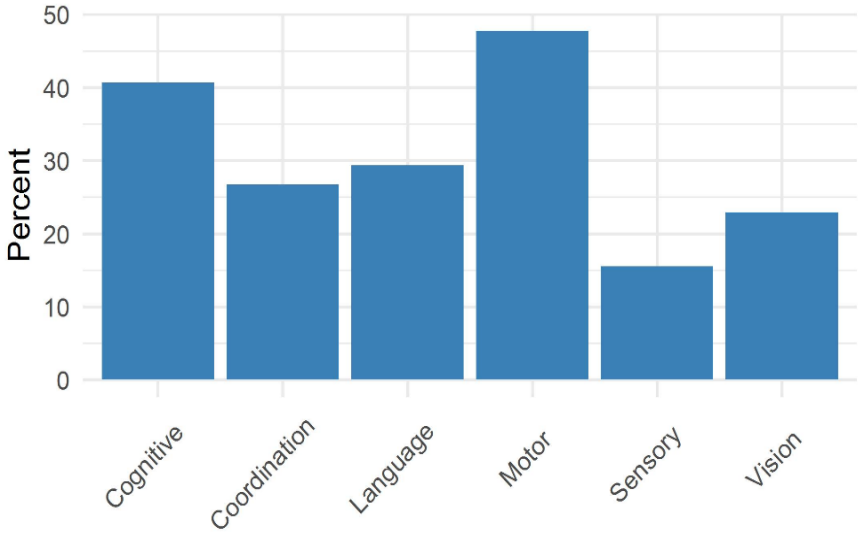
Results: Study Information

- 6517 patients across 121 studies included in final analysis
- Mean cohort size 53.9 (SD 98.6)
- Most studies were retrospective cohorts (40.5%) and case series (33.1%)
- Most common patient populations included were HIV, mixed population, and MS

Underlying Disease	# Studies	# Patients
HIV	55	3412
Mixed population	25	766
Multiple sclerosis	17	1944
Oncological (hematologic)	9	196
Other rheumatology	3	48
Transplant (solid organ)	3	32
Sarcoidosis	2	13
Transplant (bone marrow)	2	35
Primary immunodeficiency	2	36
Idiopathic lymphopenia	2	33
Oncological (non-hematologic)	1	2

Results: PML Symptoms

- Common signs and symptoms of PML were evaluated across available studies, comprising 2217 patients
- Motor (47.8%) and cognitive impairment (40.7%) were the most frequently reported across all disease populations
- Visual impairment was reported in 22.9%

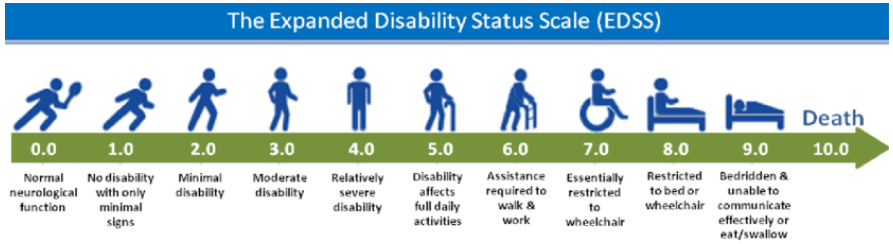


Results: Disability Outcomes

- Most studies (71.9%) did not report a quantitative clinical disability outcome
- Many studies indicated a global impression of whether patients improved or worsened neurologically, but without quantitative assessment
- Clinical disability outcomes reported:
  - 17 (14.0%) reported Expanded Disability Status Scale (EDSS)
  - 14 (11.6%) reported Karnofsky Performance Score
  - 5 (4.1%) reported Modified Rankin Scale
  - 3 (2.5%) reported a novel scale
- Disability scale used and severity of disability varied by underlying disease

Expanded Disability Status Scale (EDSS)

- Developed for use in Multiple Sclerosis
- 10-step scale based on standardized neurological exam
- Overall score determined by evaluation of 8 functional systems, including ambulation
- Driven by ambulation in upper range of scale



https://my-ms.org/ms_progression.htm

Score	Description
0	Normal neurological exam
1.0	No disability, one FS grade 1 (minimal signs)
1.5	No disability, >1 FS grade 1 (minimal signs)
2.0	Minimal disability (grade 2) in 1 FS
2.5	Minimal disability (grade 2) in 2 FS
3.0	Fully ambulatory, but moderate disability (grade 3) in 1 FS or mild disability in 3 or 4 FS
3.5	Fully ambulatory, but moderate disability (grade 3) in 1 FS and 1 or 2 FS grade 2, or 2 FS grade 3, or five FS grade 2 (others 0 or 1)
4.0	Ambulatory with aid/rest for ≥500m; 1 FS grade 4 and up 12 hours/day; exceeding prev. steps
4.5	Ambulatory with aid/rest for ≥300m; 1 FS grade 4 and up 12 hours/day; exceeding prev. steps
5.0	Ambulatory with aid/rest for ≥200m (usually 1 FS grade 5, or combination exceeding step 4.5)
5.5	Ambulatory with aid/rest for ≥100m
6.0	Unilateral assistance required to walk at least 100m with or without resting
6.5	Constant bilateral assistance required to walk at least 20m without resting
7.0	Unable to walk 5m with aid, essentially restricted to wheelchair, can wheel self and transfer
7.5	Unable to take more than a few steps, restricted to wheelchair, needs help transferring
8.0	Essentially restricted to bed/chair/WC, but out of bed most of day; retains self-care functions, effective use of arms
8.5	Essentially restricted to bed most of day, some effective use of arms, some self-care functions
8.0	Restricted to bed, can communicate and eat
9.5	Restricted to bed, unable to communicate effectively or eat/swallow
10.0	Death due to MS

Expanded Disability Status Scale (EDSS)

Advantages

- Accounts for multifocal central nervous system disease
- Broad range of outcomes
- Clinically meaningful changes defined
- Commonly utilized outcome in phase 3 trials for MS and included in labeling

Limitations

- Intended as MS-specific outcome
- Lack of assessment in domains relevant to PML (e.g., behavior, cognition, cortical visual function, seizures)
- Largely driven by ambulatory status
- Interrater variability
- Non-linear scale
- Bimodal distribution

Karnofsky Performance Score

- 11-point functional scale
- Based on ability to perform activities of daily living
- Developed for use in patients with cancer

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

http://www.npcrc.org/files/news/karnofsky_performance_scale.pdf

Karnofsky Performance Score

Advantages

- Not specific to underlying disease
- Broad range of outcomes
- Reasonable assessment of overall disability and need for assistance
- Well-understood and commonly utilized

Limitations

- Lack of assessment in domains relevant to PML (e.g., behavior, cognition, cortical visual function, seizures)
- Categories are coarse and may not sensitively capture clinically meaningful change in PML patients

Modified Rankin Scale

- 7-point functional scale
- Based on ability to perform activities of daily living
- Developed for use in patients with stroke

Score	Definition
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

Hatefi D, et al. Surg Neurol Int 2014; 5:72.

Modified Rankin Scale

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- Broad range of outcomes
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- Clinically meaningful changes defined

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Development of a PML-Specific Scale

- Given lack of suitable existing functional/disability scales in the context of PML, development of a PML-specific scale is a consideration
- Ideally, this disability scale would quantify and weight severity of common neurological symptoms seen with PML in terms of contribution to overall disability
  - Cognition, behavior, seizures, cortical visual function, brainstem signs, weakness, sensory changes, gait impairment, and ataxia
- Development challenges
  - Rarity of PML may limit availability of cohorts for scale development
  - Choice of an appropriate comparator scale for anchoring
  - Dedicated process of scale development

Conclusions and Future Directions

- Systematic review of literature demonstrated limited and heterogeneous application of clinical outcome measures across PML clinical studies
- Existing functional scales lack granularity and specificity for domains relevant to PML
- Development of a novel, PML-specific multidomain scale that assesses the full spectrum of disease may facilitate clinical trial design and endpoint selection
- Systematic review currently ongoing for comprehensive assessment of PML clinical outcomes in literature

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