Clinical Outcomes Among PML Patient Populations

Bryan Smith, MD

Associate Research Physician

National Institute of Neurological Disorders and Stroke

Section of Infections of the Nervous System

Topics

- PML Clinical Outcomes Working Group

- PML patient populations

- Importance of underlying disease

- Outcomes over time

- Beyond survival

- IRIS

Clinical Outcomes in PML: Introduction

- Historically, survival in PML has been uniformly dismal.

- Limited attention has been paid to establishing measurements of functional outcomes in PML.

Clinical Outcomes in PML: Introduction

- For some PML populations with poor prognosis, survival is a meaningful outcome measure.

- For others—those in whom PML has higher survival rates—measuring the PML-related disability is a more meaningful outcome measure.

•PML Clinical Outcomes Working Group

Laura Baldassari, MD, MHS
Ana Maria Cabal, MD
Irene Cortese, MD
Paul Lee, MD, PhD
Farrah Mateen, MD, PhD
Gina Norato, ScM
Bryan Smith, MD
Yair Mina, MD

- To evaluate the differences in outcomes among PML disease populations

- To see which measures have been used and for which diseases

- To evaluate the suitability of these as endpoints in PML trials.
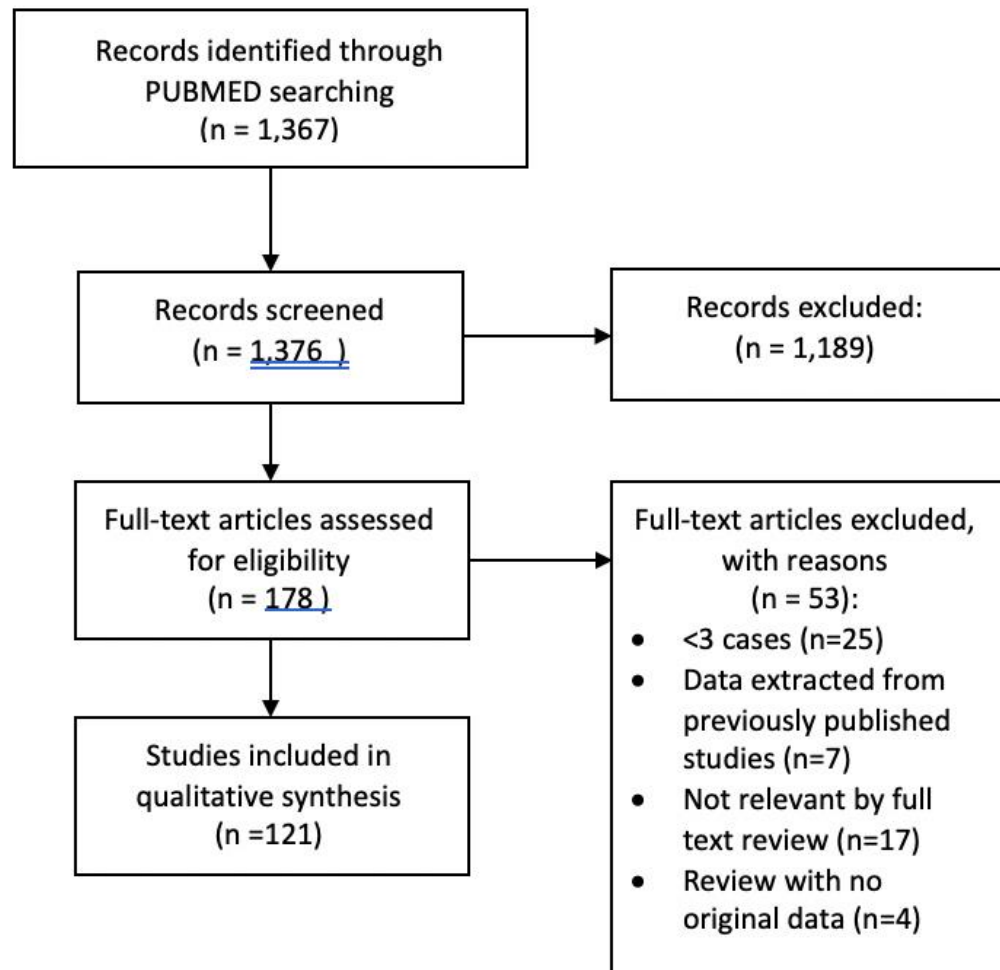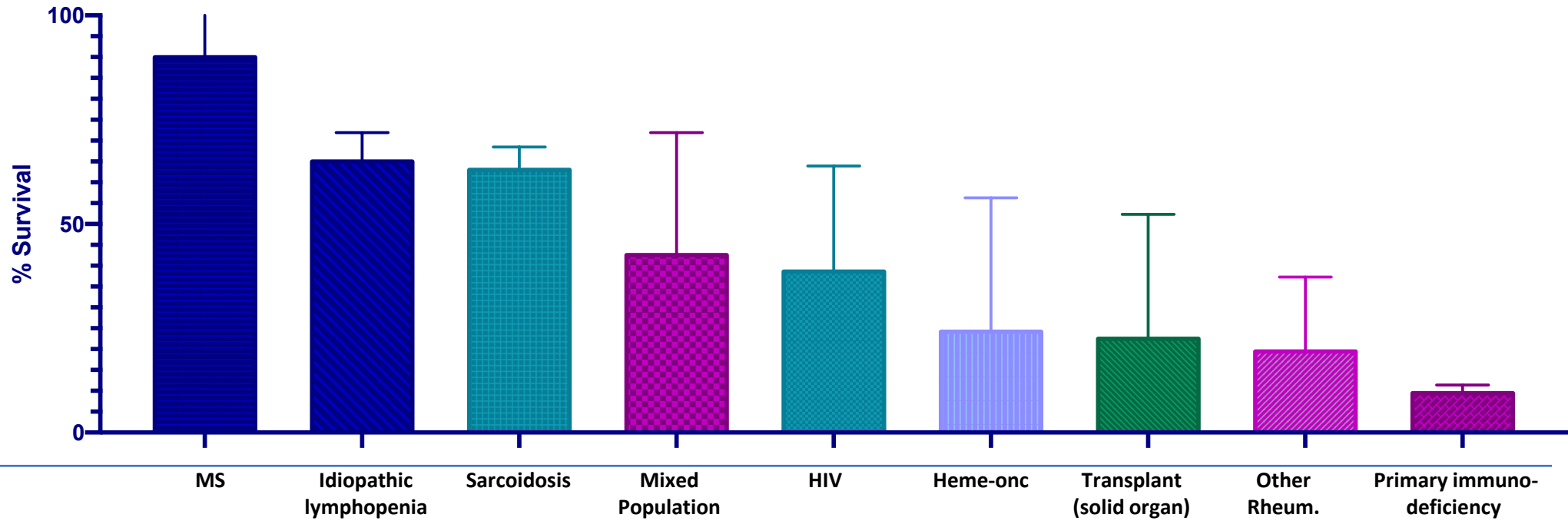
Systematic Review: Methods

Systematic Review: Studies Reviewed

Number of Studies	121
Publication year- median [min-max]	2009 [1991 – 2019]
Total number of patients	6517
Cohort Size- mean (SD)	53.9 (98.6)
Cohort Size (binned); N (%)	
0-9	34 (28)
10-19	18 (15)
20-29	16 (13)
30-39	11 (9)
40-49	9 (7)
50-99	21 (17)
100-199	6 (5)
200+	6 (5)

Systematic Review: Underlying Diseases

Underlying Disease	Number of Studies	Number of Patients
HIV	55	3412
Mixed Population	25	766
MS	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

Survival Rates Vary by Underlying Disease

	MS	Idiopathic lymphopenia	Sarcoidosis	Mixed Population	HIV	Heme-onc	Transplant (solid organ)	Other Rheum.	Primary immuno-deficiency
Survival, mean (SD)	90.5 (12.3)	65.5 (6.4)	63.5 (5.0)	43.1 (28.8)	39.1 (24.8)	25.7 (31.6)	23.0 (29.3)	20.0 (17.3)	10.0 (1.4)
Patient total	1118	33	13	600	2716	175	32	48	36

PML: Survival in HIV Has Improved with ART
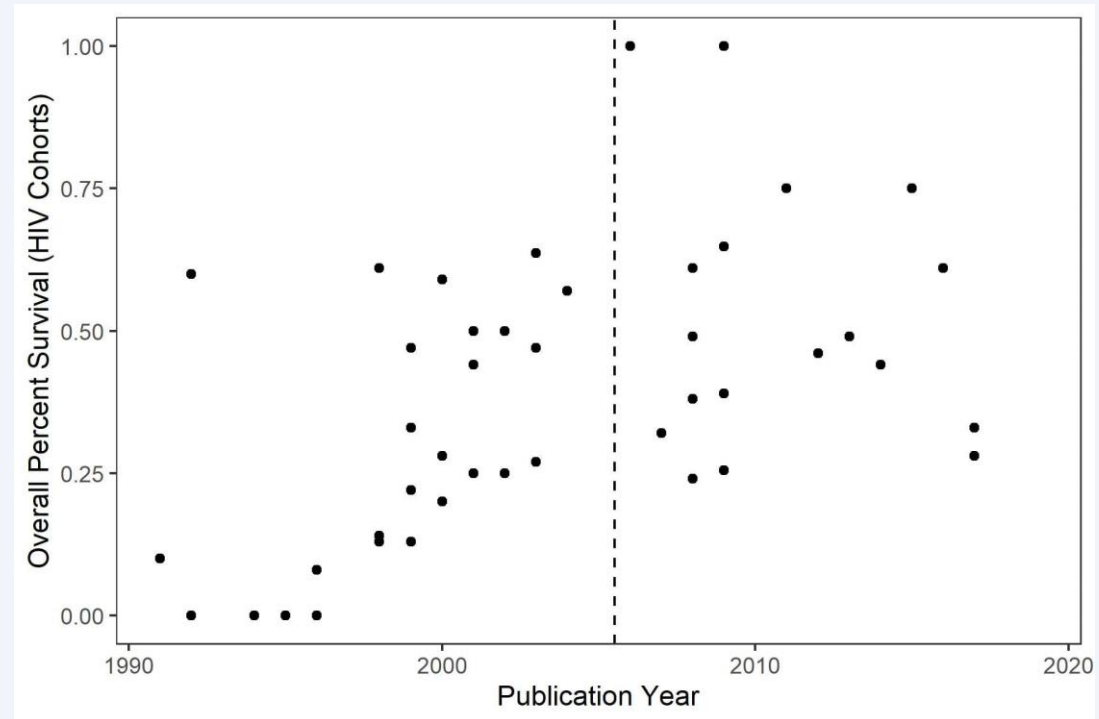
	HIV pre 2006 (n=33)	HIV 2006 and later (n=22)
% Survival, mean (SD)	29.9 (21.6)	52.5 (23.4)
Patient total	1512	1204

PML: Limited Survival Data Beyond % Survival

- Data on other survival outcomes (e.g. time to death, risk factors for death) is more limited:
  - Inconsistent definitions
  - Inconsistent summary methods
  - Consistent with percent survival, the results vary across underlying diseases.

Disability: Background

Survival does not capture the full spectrum of clinical outcomes across PML populations.

Measuring function depends on accurately capturing quantitative information related to:

- Symptoms
- Neurologic exam abnormalities
- Functional status

	Modified Rankin Scale	Karnofsky Performance Score	Expanded Disability Status Scale
Type of Scale	Functional disability		Disease-specific
Description	7-point functional scale based on ability to perform activities of daily living.	11-point functional scale based on ability to perform activities of daily living.	Scale based on a standardized neurological exam.
Primary Use	Neurological patients	Cancer patients	MS patients
Advantages to use in PML	• Well understood • Not specific to underlying disease • Provides reasonable assessment of patient's overall disability and need for assistance		• Accounts for multifocal CNS disease
Disadvantages to use in PML	• Categories are coarse, insensitive to change • No measurement of many domains relevant to PML		• Specific to MS pathophysiology • No measurement of many domains relevant to PML • Poor interrater reliability

PML-Associated Disability Varies by Underlying Disease

Disease	Karnofsky Performance Score			EDSS		
	n	Mean	Median	n	Mean	Median
HIV	564	61.4	60.0	92	5.9	6.0
Multiple Sclerosis	336	79.7	n/a	684	4.8	4.0

IRIS and PML Clinical Outcomes

- No consensus definition.

- IRIS may negatively impact a disability scale despite a positive effect of the intervention.

- The likelihood of IRIS during a trial will depend on the intervention <u>and the underlying disease.</u>

- A standardized way to define and report IRIS for trials should be established.

Conclusions

- PML prognosis varies widely
  - The underlying disease drives much of this variability
- There is no ideal clinical endpoint for use in a trial, though a disease-specific scale will be of tremendous value.
- IRIS must be recognized and accounted for when measuring and reporting clinical outcomes.

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