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SHORT COMMUNICATION

Progressive multifocal leukoencephalopathy and Creutzfeldt-Jakob disease: population-wide incidences, comorbidities, costs of care, and outcomes

J. A. Bakal[1] · C. L. Charlton[2,3,4] · B. Hlavay[5] · G. H. Jansen[6] · L. W. Svenson[5,7,8,9] · C. Power[5]

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Abstract

Neurological disorders associated with chronic infections are often progressive as well as challenging to diagnose and manage. Among 4.4 million persons from 2004 to 2019 receiving universal health, progressive multifocal leukoencephalopathy (PML, $n=58$) and Creutzfeldt-Jakob disease (CJD, $n=93$) cases were identified, revealing stable yearly incidence rates with divergent comorbidities: HIV/AIDS affected 37.8% of PML cases while cerebrovascular disease affected 26.9% of CJD cases. Most CJD cases died within 1 year (73%) although PML cases lived beyond 5 years (34.1%) despite higher initial costs of care. PML and CJD represent important neurological disorders with evolving risk variables and impact on health care.

Keywords Progressive multifocal leukoencephalopathy · Creutzfeldt-Jakob disease · Population epidemiology · Outcomes · Costs of care · Comorbidities

Introduction

Progressive neurological diseases associated with infectious agents are among the most challenging disorders to diagnose and manage because of their complex presentations and the paucity of available diagnostic biomarkers. Progressive multifocal leukoencephalopathy (PML) is a rare disorder caused by a ubiquitous polyomavirus, JC virus, that usually occurs in the setting of immunosuppression including HIV/AIDS, cancer, transplantation, and more recently with immunosuppressive disease modifying therapies (Grebenciucova and Berger 2018). Creutzfeldt-Jakob disease (CJD) is also an infrequently encountered disorder, caused by aberrant infectious transmissible proteins termed prions and occurs as an inherited, acquired, or sporadic disorder (Asher and Gregori 2018). The sporadic type of CJD is the most common, approximately 85% of cases, although it can manifest as specific clinical-pathological subtypes (Bizzi et al. 2020). Variant CJD emerged in the early 2000s, likely a consequence of bovine spongiform encephalopathy (BSE) in cattle, concentrated in the UK and Europe with few cases elsewhere. Both PML and CJD are prototypic progressive neurological disorders caused by infectious agents with high morbidity and mortality that require substantial effort to verify the diagnosis and are without proven treatments.

Given the low incidence of both PML and CJD, it is difficult to determine their actual incidences and associated outcomes in defined populations as well their comorbidities and costs of care. Moreover, as western populations' median age increases and new therapeutic options surface with immunosuppressive effects, it is imperative to understand

✉ C. Power
chris.power@ualberta.ca

1 Provincial Research Data Services-Alberta Health Services, Edmonton, AB, Canada

2 Public Health Laboratory, Alberta Precision Laboratories, Edmonton, AB, Canada

3 Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada

4 Li Ki Sheng Institute of Virology, Edmonton, AB, Canada

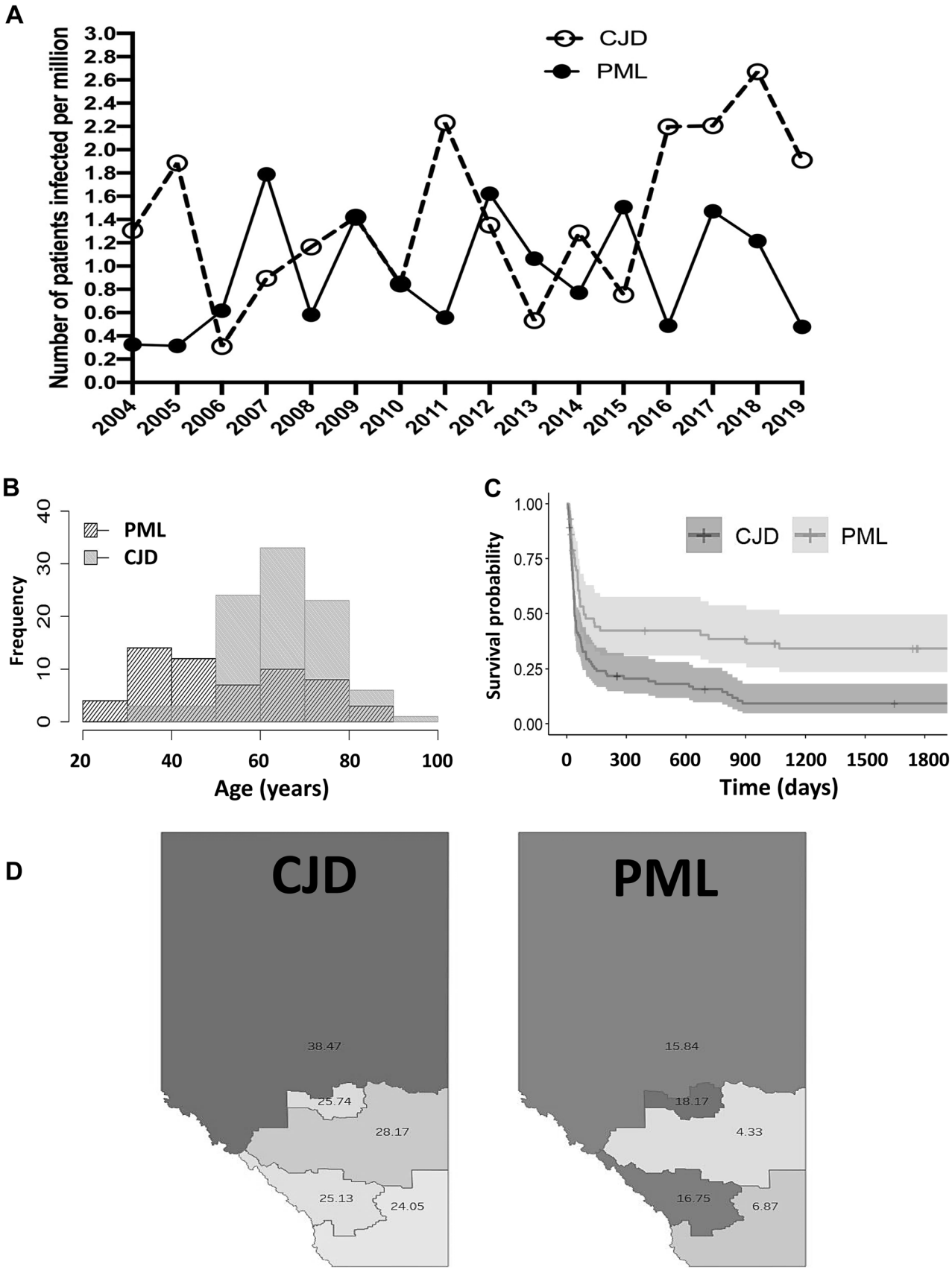
5 Department of Medicine, Medical Research Centre, University of Alberta, 6-11 Heritage, Edmonton, AB, Canada

6 Division of Anatomical Pathology, University of Ottawa, Ottawa, ON, Canada

7 Analytics & Performance Reporting Branch, Alberta Health, Edmonton, AB, Canada

8 School of Public Health, University of Alberta, Edmonton, AB, Canada

9 Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada


A
Number of patients infected per million
CJD
PML
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
B
Frequency
PML
CJD
Age (years)
C
Survival probability
CJD
PML
Time (days)
D
CJD
38.47
25.74
28.17
25.13
24.05
PML
15.84
18.17
4.33
16.75
6.87

◂**Fig. 1** Incidence, age onset, and survival among cases with CJD and PML. **a** The annual incidence per million people in Alberta varied over the course of the study period with a persistent rise in incidence among CJD cases. **b** CJD cases showed a trend toward disease onset at older ages with a peak in the 60–70-year group. **c** Kaplan-Meir curves for survival with PML and CJD revealed that, while most cases died early after the disease onset, over a third of PML cases lived longer than 5 years after the diagnosis, and approximately 9% of CJD cases showed long term survival. **d** CJD case numbers ($/10^5$) in Alberta showed were higher in the northern region of the province while PML case numbers ($/10^5$) were the highest in the two major urban regions (Calgary and Edmonton) with fewer identified cases in the less populated areas of the province

disease occurrence for debilitating and fatal disorders such as PML and CJD. Herein, we conducted a population-wide epidemiological longitudinal analysis of CJD and PML using population-based administrative health and laboratory data, together with verification of the diagnosis from corroborative databases. Notably, we selected these two disorders for in depth analysis because of their poor outcomes and the availability of corroborative datasets by which we could validate our findings. The purpose of the present study was to provide contemporary population-based estimates of incidence, outcomes, and comorbidities for PML and CJD. Our rationale for conducting this study was multifold and included the availability of a longitudinal province-wide electronic medical record (15 years) allowing population- and geography-based studies to be performed of rare diseases' (e.g., PML, CJD) incidence, prevalence, and related variables; the ongoing concern that CJD might be associated with Chronic Wasting Disease for which Alberta is a good location to examine this issue because of the mix of urban and rural populations with a strong hunting community in the province, and finally, when examining rare diseases, it is important to include comparator and corroborative datasets by way of validating the study's data.

Methods

The study was approved by the Institutional Ethics Review board at the University of Alberta (Study ID: Pro0094810). The province of Alberta maintains a publicly funded, universally available, and free at the point of care healthcare system for its population of 4.4 million residents. The data and analytics group in Alberta Health Services maintains several linkable population-based administrative databases. The following databases were included: discharge abstract database (DAD), which records all inpatient admissions, diagnoses, discharges, and relevant interventions; physician claims (fee for service), which records all visits to physicians; the National Ambulatory Care Reporting System (NACRS), which records Emergency Department and specialty outpatient clinic visits; the Pharmaceutical Information Network (PIN) which records all community prescription dispensations; Alberta Precision Laboratory data which stores the results of cerebrospinal fluid analyses including PCR for JC virus and real-time quaking-induced conversion (RT-QuIC); and Alberta Health Care Insurance Program Central Stakeholder Registry, which holds demographic data including date of emigration or death for the population eligible for public health insurance. The study included all individuals residing in the province of Alberta, ages 18 to 99 years from 2004 to 2019. The data collection algorithm used data starting from 2002 to provide a 2-year washout period to ensure accuracy of incidence and prevalence. The main descriptors were year of incidence, age, sex, geographic location of home, and co-comorbidities summarized as the Charlson index (Quan et al. 2011). Outcomes included the following: cost of care (Sarnecki and Gordon 2009), post-presentation days alive, days out of hospital (Fanaroff et al. 2018), and survival. The date of first emergency department visit or hospitalization for PML or CJD, as a most responsible diagnosis (ICD-10-CA A81.0 for CJD and A81.2 for PML), was based on case chart review at discharge and used to determine incidence. Prior hospitalization, Emergency Department and physician claims records were used to identify patient comorbidities before the index date. Costs (in Canadian dollars) were determined by combining resource intensity weights from the index hospitalization and follow-up billings from physician claims. Location data was based on the patients' home postal code and divided into 5 geographic zones used by Alberta Health Services. The Data and Research Services Platform of the Alberta Strategy for Patient Oriented Research Support Unit (AbSPORU) performed the data analyses. Data were verified in other available datasets: for CJD in the national CJD Surveillance Service and for PML in the Alberta Precision Laboratory database. All analyses were completed using SAS 9.4 software (SAS Institute Inc., Cary, USA).

Results

We identified PML ($n = 58$) and CJD ($n = 93$) cases over the 15-year study period. Based on annual population measures over the 15-year study period, the incidences of PML and CJD did not change substantially for both diseases, ranging from 0.3 to 2.6 cases per million although there was a trend toward increased absolute and relative CJD case numbers (Spearman $r = 0.43$, $p = 0.099$) during this period (Fig. 1a). Comparison of mean age of disease onset showed the CJD group was 12 years (95% CI, 7.5–17.2, $p < 0.001$) higher than PML (Table 1) with a predominance of disease onset at older ages; peak frequency of CJD cases occurred within the 60–70-year interval, while the PML group showed a peak frequency

Table 1 Comparative demographic, risk factors and outcomes for CJD and PML in Alberta from 2004 to 2019

Groups	CJD ($n=93$)	PML ($n=58$)
Age of onset mean (±SD) yr	65.29 (10.88)	52.88 (16.61)
Sex		
F (%)	41 (44.1)	23 (39.7)
M (%)	52 (55.9)	35 (60.3)
Comorbidities (%)		
Charlson Index mean (±SD)	1.80 (1.88)	4.34 (3.02)
HIV/AIDS (%)	< 5	22 (37.9)
Multiple sclerosis (%)	< 5	6 (10.3)
Diabetes (%)	19 (20.4)	10 (18.9)
Cancer (%)	11 (11.8)	18 (31.0)
Cerebrovascular disease (%)	25 (26.9)	9 (15.5)
Chronic pulmonary disease (%)	10 (10.8)	10 (17.2)
Cost of healthcare utilization 1 yr post-diagnosis mean (±SD)	$52,232 (47,563)	$71,957 (70,054)
Median (IQR)	$36,439 (20,238–62,790)	$51,834 (29,169–86,760)
Died ≤ 1 yr post-diagnosis (%)	73 (78.5)	32 (55.2)
Time to death mean (±SD) days	154.4 (374.02)	240.65 (660.62)
DAOH mean (±SD) days[a]	203.61 (172.43)	244.83 (158.22)

[a]Days alive and out of hospital in the year following discharge

at 30–40 years of age, but its incidence was relatively consistent across all age groups (Fig. 1b). For both the PML and CJD groups, the likelihood of disease was higher in males than in females (Table 1).

Among associated comorbidities, PML cases displayed a higher risk of comorbidity including HIV/AIDS (37.9%; OR = 56.2 96, 95% CI 7.3–432.7; $p < 0.001$) and cancer (31%; OR = 3.4, 95% CI; $p = 0.007$) although there were several other associated comorbidities, which were more evident in the CJD group (e.g., cerebrovascular disease (26.9%; OR = 2.0, 95% CI 0.9–4.7; $p = 0.1$)). The mean Charlson index was higher in the PML (4.34 ± 3.02) compared to the CJD (1.80 ± 1.88) group (95% CI, 1.7–3.4; $p < 0.001$) (Table 1). As an indicator of cost of care, resource intensity weight measures revealed that the median cost of PML was greater during the first year post-diagnosis, showing a 40% increase (median difference $131,106; 95% CI 1197–26,635; $p = 0.03$). Mean survival rate and time were less in the CJD group compared to the PML group (Table 1). Kaplan-Meir curves showed high early mortality in both groups with a median survival of 39 days (95% CI 35–69) for the CJD group and 86 days (95% CI 57–1069) for the PML group (Fig. 1c). At 5 years post-diagnosis, CJD survival was 9.2% (95% CI, 4.7–18.1%), and PML survival was 34.1% (95% CI, 23.4–49.5%). Geographic assessments of disease occurrence based on case postal code showed PML cases that were distributed uniformly across the province (Fig. 1d), although the absolute numbers for both diseases were highest in the major urban centers (Fig. 1d). CJD case prevalence (38.1 per 100,000) was the highest in the northern region of the province (Fig. 1d).

Discussion

To the best of our knowledge, this study represents the first population-based comparative and long-term longitudinal analysis of two severe neurological disorders associated with infectious agents that were verified with corroborative datasets. Importantly, while the overall incidences of both disorders did not change substantially over time, these data are informative in that CJD incidence is rising, as reported for other studies, and survival with PML is improving in this well defined, albeit growing population with over a third of PML patients living beyond 5 years. Although these disorders exhibited differing comorbidities, the findings were surprising as cerebrovascular disease as a comorbidity for CJD was unprecedented and HIV/AIDS remains the chief comorbidity for PML despite the availability of free and contemporary antiretroviral therapy in Alberta. The current findings recapitulate reports from previous studies (Anand et al. 2019; Ladogana et al. 2005; Uttley et al. 2020) but also raise several issues that warrant consideration as discussed below.

The incidence of CJD is rising, likely a consequence of an ageing population and perhaps improved diagnostic testing (e.g., RT-QuIC) assays of cerebrospinal fluid, with recent incidence rates ranging from 1.7 to 2.2 per million (Hermann et al. 2018). Indeed, CJD incidence in

the present Alberta data was similar to that observed in the national CJD Surveillance System (Coulthart et al. 2015). Nonetheless, a notable outcome of the present study was the finding of increased CJD incidence in northern Alberta; this area displays sparse population density and is a mixture of farmland as well as forested regions. The underlying explanation for this high incidence rate is unclear although it could represent a biased artefact associated because of the low overall population. Cerebrovascular disease was the chief comorbidity observed in the CJD, which likely reflects the ageing population affected with CJD. Of interest, almost 10% of CJD cases lived beyond 5 years although we could not find evidence for any familial and geographic clustering among these long-term CJD survivors.

PML has been regarded as a largely fatal disease in the past, but the present studies suggest that PML survival has improved and that a third of PML cases showed a greater than 5-year survival. Earlier studies reported PML prevalence ranging from 1.1 to 2.6/1,000,000 among persons in the general population (Power et al. 2000) or with rheumatic diseases (Bharat et al. 2012), respectively. While this finding was reassuring, it was evident from our dataset that PML affected relatively few patients with autoimmune diseases (e.g., multiple sclerosis), primary immunodeficiency disorders, or patients who were receiving immunosuppressive disease modify therapies; of note, on review of the six cases of multiple sclerosis and PML, their occurrence was evenly scattered over the 15-year study period. Only two cases with MS and PML received immunosuppressive disease-modifying therapies that included cyclophosphamide and rituximab and none received natalizumab, which is remarkable given that over 15,000 patients with multiple sclerosis resided in Alberta during the study period (2004–2019). PML in HIV/AIDS was distributed over the entire study period without apparent temporal clustering at any specific time point despite widely available antiretroviral therapy (Khanna et al. 2009).

The present study also faced several challenges. Although it was a population-based analysis, Alberta's total population was small, ranging from 3.07 to 4.4×10^6 persons from 2004 to 2019, which precluded definitive quantification of diseases in select populations including immigrant and indigenous persons. In addition, the diagnosis of both PML and CJD evolved over the study period, predicated on improved diagnostic tools and deeper understanding of the disease presentations. It is also plausible that cases of CJD or PML were overlooked or misdiagnosed; the former shortcoming is possible because of personal preference or administrative oversight although the likelihood of misdiagnosis is less because of the centralized and universal healthcare delivery structure in Alberta with two tertiary care centers in the province. Future studies that incorporate larger datasets and cutting-edge diagnostic tools will likely obviate these issues.

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Declarations

Conflict of interest The authors declare no competing interests.

References

Anand P, Hotan GC, Vogel A, Venna N, Mateen FJ (2019) Progressive multifocal leukoencephalopathy: a 25-year retrospective cohort study. Neurol Neuroimmunol Neuroinflamm 6(6):e618

Asher DM, Gregori L (2018) Human transmissible spongiform encephalopathies: historic view. Handb Clin Neurol 153:1–17

Bharat A, Xie F, Baddley JW, Beukelman T, Chen L, Calabrese L, Delzell E, Grijalva CG, Patkar NM, Saag K, Winthrop KL, Curtis JR (2012) Incidence and risk factors for progressive multifocal leukoencephalopathy among patients with selected rheumatic diseases. Arthritis Care Res (Hoboken) 64:612–615

Bizzi A, Pascuzzo R, Blevins J, Grisoli M, Lodi R, Moscatelli MEM, Castelli G, Cohen ML, Schonberger LB, Foutz A, Safar JG, Appleby BS, Gambetti P (2020) Evaluation of a new criterion for detecting prion disease with diffusion magnetic resonance imaging. JAMA Neurol 77:1141–1149

Coulthart MB, Jansen GH, Connolly T, D'Amour R, Kruse J, Lynch J, Sabourin S, Wang Z, Giulivi A, Ricketts MN, Cashman NR (2015) Creutzfeldt-Jakob disease mortality in Canada, 1998 to 2013. Can Commun Dis Rep 41:182–191

Fanaroff AC, Cyr D, Neely ML, Bakal J, White HD, Fox KAA, Armstrong PW, Lopes RD, Ohman EM, Roe MT (2018) Days alive and out of hospital: exploring a patient-centered, pragmatic outcome in a clinical trial of patients with acute coronary syndromes. Circ Cardiovasc Qual Outcomes 11:e004755

Grebenciucova E, Berger JR (2018) Progressive multifocal leukoencephalopathy. Neurol Clin 36:739–750

Hermann P, Laux M, Glatzel M, Matschke J, Knipper T, Goebel S, Treig J, Schulz-Schaeffer W, Cramm M, Schmitz M, Zerr I (2018) Validation and utilization of amended diagnostic criteria in Creutzfeldt-Jakob disease surveillance. Neurology 91:e331–e338

Khanna N, Elzi L, Mueller NJ, Garzoni C, Cavassini M, Fux CA, Vernazza P, Bernasconi E, Battegay M, Hirsch HH, Swiss HIVCS (2009) Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Clin Infect Dis 48:1459–1466

Ladogana A, Puopolo M, Croes EA, Budka H, Jarius C, Collins S, Klug GM, Sutcliffe T, Giulivi A, Alperovitch A, Delasnerie-Laupretre N, Brandel JP, Poser S, Kretzschmar H, Rietveld I, Mitrova E, de Pedro Cuesta J, Martinez-Martin P, Glatzel M, Aguzzi A, Knight R, Ward H, Pocchiari M, van Duijn CM, Will RG, Zerr I (2005) Mortality from Creutzfeldt-Jakob disease and related disorders in Europe, Australia, and Canada. Neurology 64:1586–1591

Power C, Gladden JG, Halliday W, Del Bigio MR, Nath A, Ni W, Major EO, Blanchard J, Mowat M (2000) AIDS- and non-AIDS-related PML association with distinct p53 polymorphism. Neurology 54:743–746

Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, Januel JM, Sundararajan V (2011) Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 173:676–682

Sarnecki L, Gordon L (2009) Analysis of acuity trends using resource intensity weights via the CIHI portal. Stud Health Technol Inform 143:42–46

Uttley L, Carroll C, Wong R, Hilton DA, Stevenson M (2020) Creutzfeldt-Jakob disease: a systematic review of global incidence, prevalence, infectivity, and incubation. Lancet Infect Dis 20:e2–e10