Research Article

Etiologies of rapidly progressive dementias: A systematic review and meta-analysis of causes in worldwide and Latin America

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Abstract

Background: Rapidly progressive dementia (RPD) is a group of neurological diseases, where three etiologies are particularly relevant: neurodegenerative, prion and autoimmune encephalitis (AIE) diseases.

Objective: The aim of this study is to conduct a systematic review and meta-analysis of the frequency of these etiologies causing RPD in worldwide and Latin America (LatAm).

Methods: A systematic review and meta-analysis were conducted. A bibliographic search of publications related to the etiologies of RPD was done. The etiologies, the timeframe definition (<1 year versus <2 years) and the study's place of origin were analyzed.

Results: A total of 10 articles were selected for the analysis in this study (n = 1006 patients). Three studies were originated in LatAm cohorts (two from Argentina and one from Brazil). The global prevalence of RPD due to neurodegenerative disease was 23% CI95% [11%; 42%]; prion diseases, 16% CI95% [9%; 28%]; and AIE, 12% CI95% [6%; 22%]. Comparing each overall proportion of etiologies of LatAm versus non-LatAm there were statistically significant differences for AIE (25% versus 8%, respectively, $p < 0.01$). In the case of timeframe definitions, the comparison of the etiological percentage did not show statistically significant differences.

Conclusions: From our results, approximately a half of the causes of RPD were due to neurodegenerative, prion, and AIE diseases. Future studies will be needed to analyze this issue both globally and regionally.

Keywords

Alzheimer's disease, encephalitis, etiology, prion diseases, rapidly progressive dementia

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Introduction

Rapidly progressive dementia (RPD) is a group of neurological diseases characterized by rapid cognitive decline leading to dementia within a short period of time.[1] This timeframe definition is still controversial, with publications reporting an evolution period ranging from 1 to 2 years.[2] There are multiple causes of this condition. Medical literature often uses the mnemonic "VITAMINS" to refer to the various causes: vascular, infectious, toxic-metabolic, autoimmune, metastases/neoplasm, iatrogenic/inborn error of metabolism, neurodegenerative, or systemic/seizures.[1] However, three etiologies are particularly significant due to their etiological contribution. They are prion diseases like Creutzfeldt-Jakob disease (CJD), neurodegenerative disorders, and autoimmune encephalitis (AIE). These three causes often suppose a diagnostic challenge, leading to treatments and prognoses that are diametrically opposed. While CJD has a grim prognosis with virtually no treatment alternatives, neurodegenerative diseases tend to progress into long-term disorders requiring symptomatic management, and many autoimmune conditions have potentially curative treatments. Additionally, the diagnosis of autoimmune diseases is elusive and often requires extensive studies for detection.[3] Therefore, it is of paramount importance in medical practice to be able to accurately identify the causes underlying a case of RPD in patients. Knowledge of the etiological frequency will also enable the optimization of the diagnostic approach, allowing for the necessary studies to be requested for the patient's diagnosis. Providing clinicians with knowledge of the frequency of this presentation allows for the estimation of the cost-effectiveness of extensive work-up and would allow the creation of diagnostic and treatment guidelines based on the probabilities of each etiology.

There are different regions in the world with unique demographic characteristics. Among these, Latin America (LatAm) is characterized by its own health and socio-environmental conditions. Various factors, such as mortality rates, the environment, education, nutrition, and population genetics, influence the incidence and prevalence of various diseases. This region encompasses countries with low to moderate incomes. Difficulties in accessing healthcare systems, lack of infrastructure, and other factors also affect the quality of care for patients with diseases such as RPD. Publications have indicated that these demographic conditions can alter the frequency of different pathologies. Ribeiro et al. conducted a meta-analysis on the prevalence of dementia in Latin America and the Caribbean, comparing it with other regions showing a higher prevalence in Latin America compared to Europe and the USA.[4]

For the above, the aim of this study is to conduct a systematic review and meta-analysis of the frequency of etiologies causing RPD worldwide and compare them with those in LatAm to provide clinicians with the necessary evidence regarding which diagnosis is most probable facing a subject with RPD.

Methods

The present study was *a priori* registered in the international prospective register of systematic reviews PROSPERO (ID PROSPERO 2024 CRD42024539079) This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations.

Search strategy

A bibliographic search of publications related to the etiologies of RPD was conducted. Due to the nature of our aim, to explore frequencies of etiologies, the SPIDER tool for search strategy was employed. Our definition of search implies: S) sample: subjects presenting with RPD according to the researcher's criteria; PI) phenomenon of interest, etiologies, RPD definitions D) design: Cohorts; E) evaluation: definition of etiology by work-up, R) research type, quantitative. Our search strategy was: ("rapidly progressive dementia" OR "rapidly progressive cognitive impairment" OR "rapidly progressive cognitive dysfunction") AND ("etiology" OR "causality" OR "causes" OR "pathogenesis" OR "diagnosis" OR "diagnoses").

The academic databases were PubMed, LILACS, Science Direct, Scielo, and EMBASE. Additionally, groups identified as key stakeholders in the field were contacted whether they had ongoing studies worthy of inclusion. It was decided not to include gray literature in the analysis of our study due to the heterogeneity of access to studies conducted in LatAm.

Eligibility criteria

The inclusion criteria for articles were as follows: 1) research studies investigating the causes of RPD and reporting the prevalence of diagnosis, 2) publications written in English, Spanish, or Portuguese, and 3) published between the years 2013–2023. The exclusion criteria were: 1) case reports, 2) studies involving pediatric patients (under 18 years of age), 3) reviews, 4) studies whose inclusion criterion is to belong to a specific etiology of RPD, 5) studies presented only as posters or abstracts, and 6) animal studies.

In recent times, several discoveries have impacted the way we study the etiology of RPD. Firstly, AIE criteria were developed during this period.[5] Secondly, biomarkers of neurodegenerative diseases have been extensively developed.[6] Lastly, new autoimmune etiologies (some even mimicking, for example, CJD) have been described along with the necessary antibodies for diagnosis. This newfound sensitivity towards certain etiologies can significantly influence how subjects are classified compared to how they were in the past. To avoid this noise originating from lack of sensitivity, the study restricted the sample to the last 10 years.

Selection article process

For article selection, a panel of 10 expert neurologists in cognitive disorders evaluated the articles in pairs. Each article was reviewed by a pair of reviewers who were blinded to other opinions. A paper was included or excluded when a consensus was reached. Discrepancies were mediated by a third reviewer. All the selection processes were conducted using Rayyan platform.

Data extraction

For each selected article, the number of cases of RPD was extracted according to the etiology with which they were classified. The etiologies were grouped into three categories according to our objective of interest: neurodegenerative, prion and AIE diseases. Neurodegenerative causes encompassed all diagnoses of neurodegenerative etiology, including, for example, Alzheimer's disease (AD) and frontotemporal dementia. AIE entities were classified as any cause associated with antibodies against components of the nervous system (including paraneoplastic encephalitis) or those in which the authors of the article considered in this category with varying levels of certainty (response to immunotherapy or detection of inflammatory components). As the measure to be studied, it was decided to use the observed proportion for each etiology out of the total cases classified as RPD. Other variables of interest for the analysis included the clinical setting where the etiologies were identified, the timeframe definition of RPD used (with a primary emphasis on the time frame used to define 'rapidly'), and the study's place of origin (LatAm or Non- LatAm).

Finally, a description of the percentage of other causes of RPD published but not previously analyzed was conducted. Only those etiologies described in two or more studies were considered.

Statistical analysis

Statistical analysis was conducted in R version 4.3.2 with the meta, readxl, tidyverse, rstatix, ggoplot2, metafor, dmetar, gt and grid packages. From each study, the sample size and the number of cases in each of the three mentioned categories were extracted. The global pooled proportion of any of the kinds of etiologies (view data extraction section) were determined conducting independent meta-analytic studies with a proportion meta-analysis random-effects model based on inverse variance method and Freeman-Tukey double arcsine transformation for variance stability. Two sub-analyses were conducted. One compared the proportions in LatAm versus non-LatAm regions, and the other compared the timeframe definition of <1 year versus <2 years. The objective was to determine if these variables influenced the frequency of causes. The subgroups were analyzed using the same methodology as for the overall proportion. Heterogeneity estimation was performed through the DerSimonian-Laird estimator for τ^2 statistics and tested with Cochran's Q test. The Jackson method was applied for the confidence interval of τ^2 calculation. The detection of outliers was carried out through the calculation of the Clopper-Pearson confidence interval for individual studies. Studies were defined as outliers when their 95% confidence interval lies outside the 95% confidence interval of the pooled effect. When outliers were detected, the meta-analysis was recalculated with their exclusion. To avoid misinterpretation with other situations such as publication bias, both sets of results (with and without the exclusion of outliers) are shown. The influence effects of the studies were analyzed using the Leave-One-Out methodology.

It was defined a statistical significance level of $p < 0.05$ (2-sided) and effects and predictions are presented with a 95% confidence interval.

Risk of bias assessment

Publication bias with funnel plot and Egger's test for asymmetry were assessed.

To analyze the quality of the studies included in our meta-analysis, the Newcastle-Ottawa Scale (NOS) was used and converted it to AHQR standards. This tool is employed in non-randomized studies through a "star system." It evaluates three aspects of each study: the selection of patients, the comparability of groups, and, in our case, the exposure of interest. The final score was agreed upon by two reviewers from the research team.

Results

Overview of the included studies

A total of 934 studies were identified from the search. Figure 1 shows the PRISMA flowchart depicting the selection process in our analysis.

After excluding duplicated articles (n = 300), the remaining 634 articles were screened by title, abstract, review eligibility according to the inclusion and exclusion criteria, resulting in a total of 10 articles selected for the analysis in this study.[7–16] Table 1 summarize the general features of the selected studies.

Except for Tagliapietra et al. (2013) and Grau-Rivera et al. (2015), all the studies analyzed were published between 2017 and 2023. The publication with the largest number of patients was by Anuja et al., with 187 participants and with the lower was Tagliapietra et al. with 37. Three studies published in LatAm were identified, two from Argentina (Da Prat et al. and Acosta et al.) and one from Brazil (Studart-Neto et al.). Considering only neurodegenerative diseases, prion diseases, and AIE, the first was the most frequent cause in the publications by Da Prat et al., Day et al., Stamatelos et al., and Liu et al. In the works of Acosta et al., Grau-Rivera et al., and Tagliapietra et al., prion disease was the leading cause. Meanwhile, in the studies by Anuja et al., Chandra et al., and Studart-Neto et al., the most frequent etiology was immune-mediated. All collected results were based on

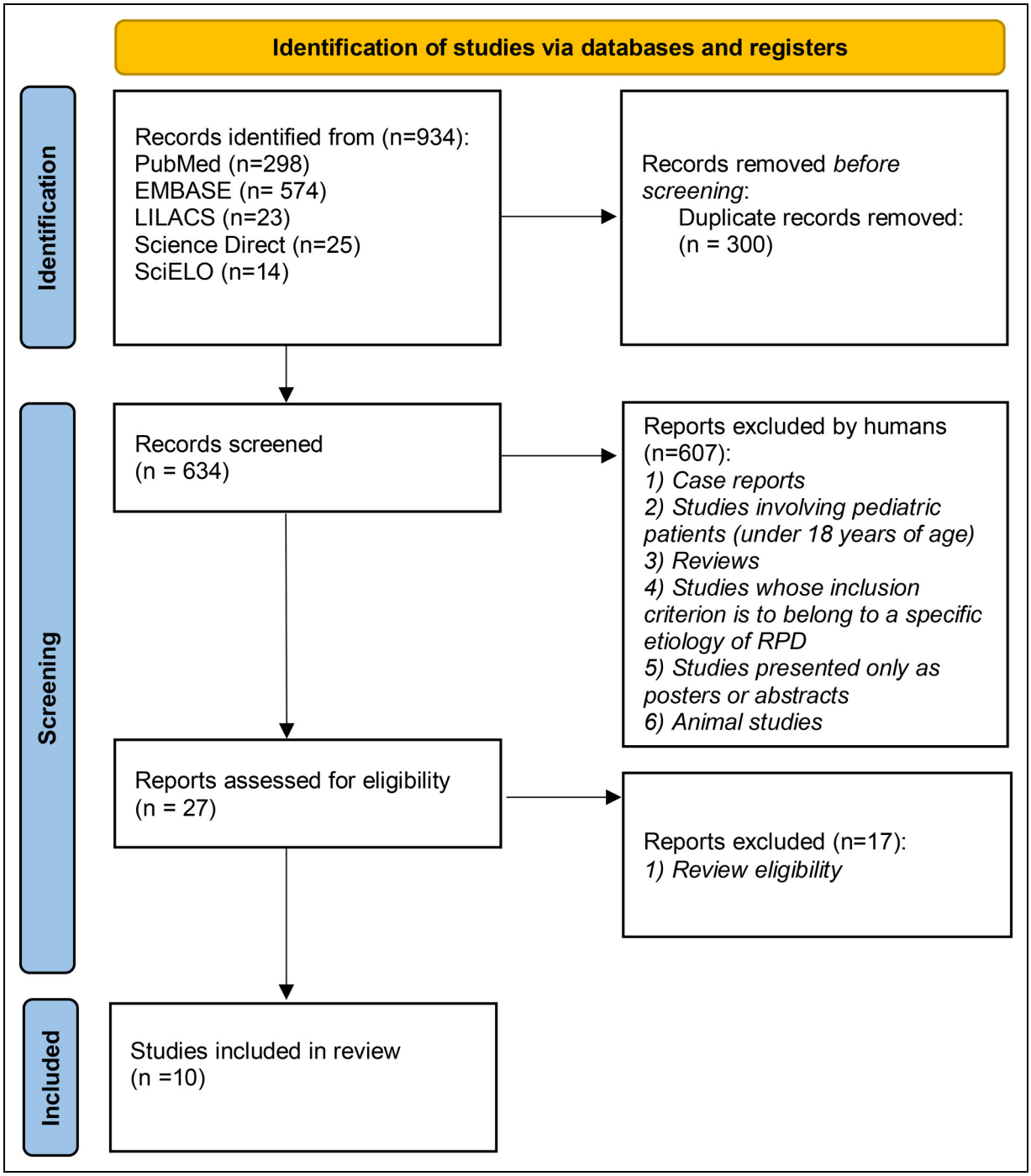

Figure 1. Flow chart of study inclusion.

clinical diagnoses supported by complementary studies, except for the Spanish study by Grau-Rivera et al., which was based on pathological anatomy results.

Proportion of RPD etiologies

A total of 1006 patients were included in the analysis. Using a random effects model, a global prevalence of RPD due to neurodegenerative disease was 23% CI95% [11%; 42%], with an $I^2 = 92\%$, $\tau^2 = 1.94$, and $p < 0.01$. The study by Day et al. exhibited the highest proportion at 90% CI95% [80%; 96%], while the study by Chandra et al. showed the lowest proportion with 2% CI95% [0%; 6%]. In the context of prion diseases, a prevalence of 16% CI95% [9%; 28%] was observed, with an $I^2 = 95\%$, $\tau^2 = 1.09$, and $p < 0.01$. The study conducted by Grau-Rivera et al. reported the highest proportion, 68% CI95% [60%; 75%],

Table 1. Study characteristics.

Article	First Author	Year	Country	Methods	Participants	Definition of RPD	nCJD	nND	nAI	nTotal	Latin America	Definition of timeframe of RPD
Accuracy of Diagnostic Criteria for Sporadic Creutzfeldt-Jakob Disease Among Rapidly Progressive Dementia	Tagliapietra	2013	Italy	Retrospective	Clinical records of patients with RPD referred to Memory Clinic between 2007 and 2012	The diagnosis of RPD was made according to the following definition: cognitive, behavioral, or motor impairment with disease course of less than 24 months from first reported symptom to functional dependence	11	10	2	37	No	< 2 Years
Clinicopathological Correlations and Concomitant Pathologies in Rapidly Progressive Dementia: A Brain Bank Series	Grau-Rivera	2015	Spain	Retrospective	Analysis of 160 brain donors with RPD (defined as 2 years of disease duration from the first symptom to death) registered at the Neurological Tissue Bank of the Biobanc-Hospital Clínic-IDIBAPS, from 2001 to 2011	The term RPD encompasses a heterogeneous group of medical conditions that cause progressive cognitive impairment, leading to functional disability or death within a short period of time, usually less than 24 months	108	27	4	160	No	< 2 Years
Estudio de registro de las demencias rápidamente progresivas en un centro de alta complejidad: hacia un diagnóstico adecuado de las demencias autoinmunes en nuestro país	Da Prat	2017	Argentina	Retrospective	Clinical records of patients with RPD referred to Sanatorio de la Trinidad Mitre between 2009 to 2016	Rapidly progressive cognitive decline lasting more than one month and less than two years of evolution.	2	16	12	50	Yes	< 2 Years
Rapidly Progressive Dementia: Prevalence and causes in a Neurologic Unit of a Tertiary Hospital in Brazil	Studart-Neto	2017	Brazil	Retrospective	Database of patients with RPD referred to neurologic unit of a tertiary center (Hospital das Clínicas, Universidade de Sao Paulo, Sao Paulo, Brazil) between 2012 to 2015	Patients who had progressed from initial symptoms to moderate [Mini-Mental State Examination (MMSE) < 20] or severe dementia (MMSE < 10 or inability to respond to MMSE) within a period ranging from a few months to 2	7	5	18	61	Yes	< 2 Years

(continued)

Table 1. Continued.

Article	First Author	Year	Country	Methods	Participants	Definition of RPD	nCJD	nND	nAI	nTotal	Latin America	Definition of timeframe of RPD
						years, upon hospitalization						
Syndromes of Rapidly Progressive Cognitive Decline-Our Experience	Chandra	2017	India	Retrospective	Patients with RPD referred to Departments of Neurology and Neuromicrobiology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India between January 2011 to December 2016 were evaluated	Patients who presented to us with features of rapidly progressive cognitive decline in weeks to 1 year	18	3	42	144	No	< 1 Year
Rapidly progressive dementia: An eight year (2008–2016) retrospective study	Anuja	2018	India	Retrospective	Medical records of patients admitted at a tertiary care center in north India (Postgraduate Institute of Medical Education and Research) from 2008 to 2016	Dementia was defined using the Diagnostic and Statistical manual of mental disorders- 5 (DSM-V) criteria for major neurocognitive impairment (decline in one or more cognitive domains with functional impairment). Those patients presenting within one year of symptom onset were selected for evaluation.	14	27	34	187	No	< 1 Year
Rapidly Progressive Dementia in the Outpatient Clinic: More than Prions	Day	2018	USA	Retrospective	Patients with suspected RPD were assessed within the Washington University School of Medicine (Saint Louis, Missouri, USA) outpatient memory clinic from February 2006 to February 2016.	RPD was diagnosed when dementia developed within 2 years of the onset of the first symptom, or when symptoms progressed at a greater-than-expected rate for a known dementing illness (defined as an increase of	4	60	0	67	No	< 2 Years

(continued)

Table 1. Continued.

Article	First Author	Year	Country	Methods	Participants	Definition of RPD	nCJD	nND	nAI	nTotal	Latin America	Definition of timeframe of RPD
						more than two global CDR stages in ≤2 years						
Diagnosis of Rapidly Progressive Dementia in a Referral Center in Argentina	Acosta	2020	Argentina	Retrospective	Adult patients diagnosed with RPD between June 2011 and May 2017 at Fleni Institute were included	RPD was defined as the progression from first cognitive symptom to dementia in ≤2 years, independently of etiology.	31	29	24	104	Yes	< 2 Years
Evolving Causes of Rapidly Progressive Dementia A 5-Year Comparative Study	Stamatelos	2021	Greece	Retrospective	Medical records of patients who were hospitalized in the Second Department of Neurology, Attikon University General Hospital, during a 5-year period (January 2012 to March 2017) for suspected RPD	RPD was defined as a dementia that evolved in <12 months since the first symptom appeared.	9	18	8	47	No	< 1 Year
Prevalence and outcomes of rapidly progressive dementia: a retrospective cohort study in a neurologic unit in China	Liu	2023	China	Retrospective	RPD patients by referring to a database including all participants hospitalized in the Neurology Department of the First Affiliated Hospital, Zhejiang University School of Medicine, in Southern China between January 2015 and December 2019 and identifying RPD patients	Inclusion criteria were as follows: (1) chief complaints of cognitive decline and progression to dementia with Mini-Mental State Examination (MMSE) scores < 20 or inability to respond within 2 years; or (2) rapidly progressive Alzheimer's disease (rpAD) with a loss of ≥ 6 points per year	20	31	15	149	No	< 2 Years

n: number; ND: neurodegenerative diseases; AIE: autoimmune encephalitis; RPD: rapidly progressive dementia.

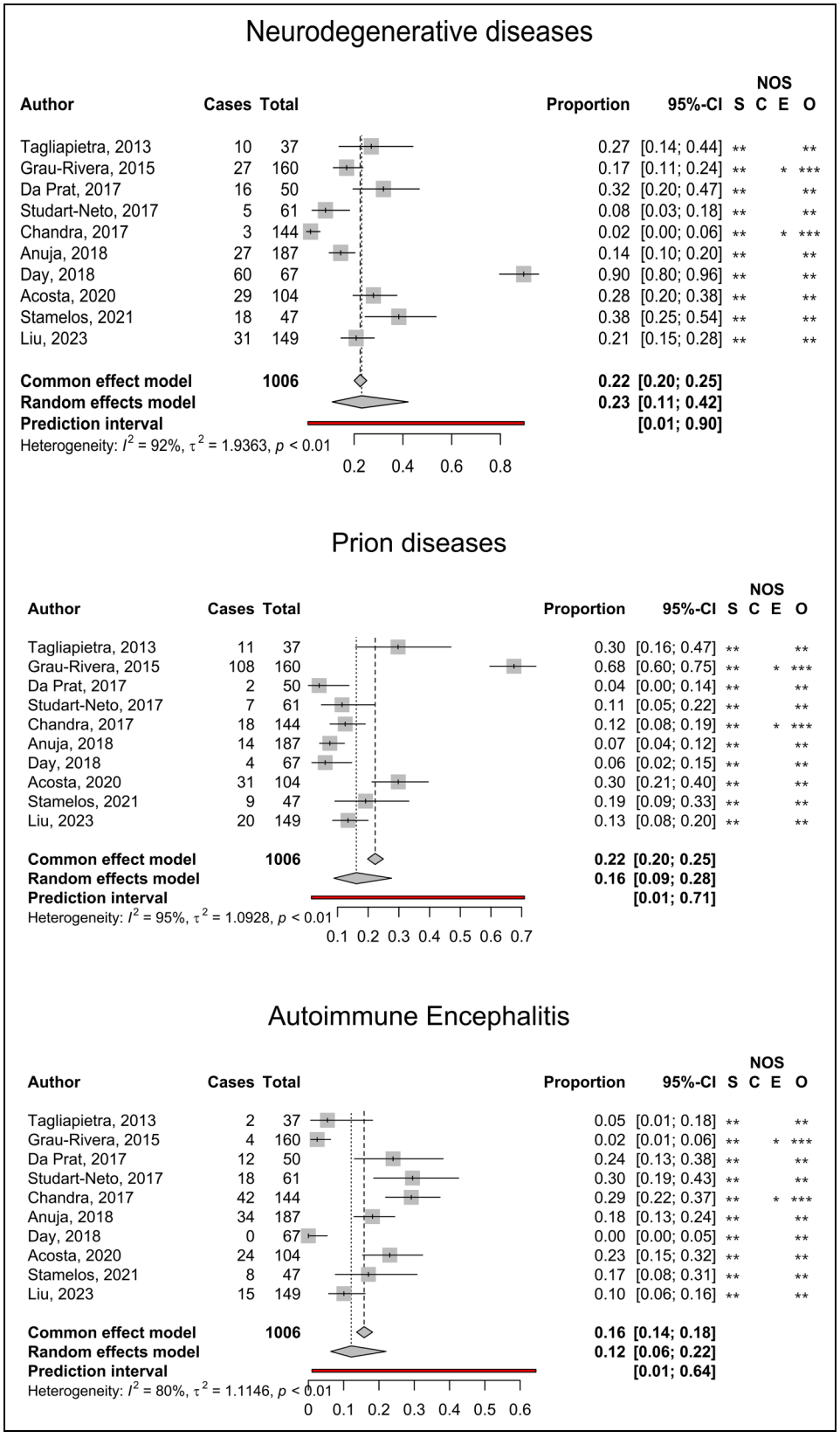

Figure 2. Forest plot of rapidly progressive dementia etiologies.

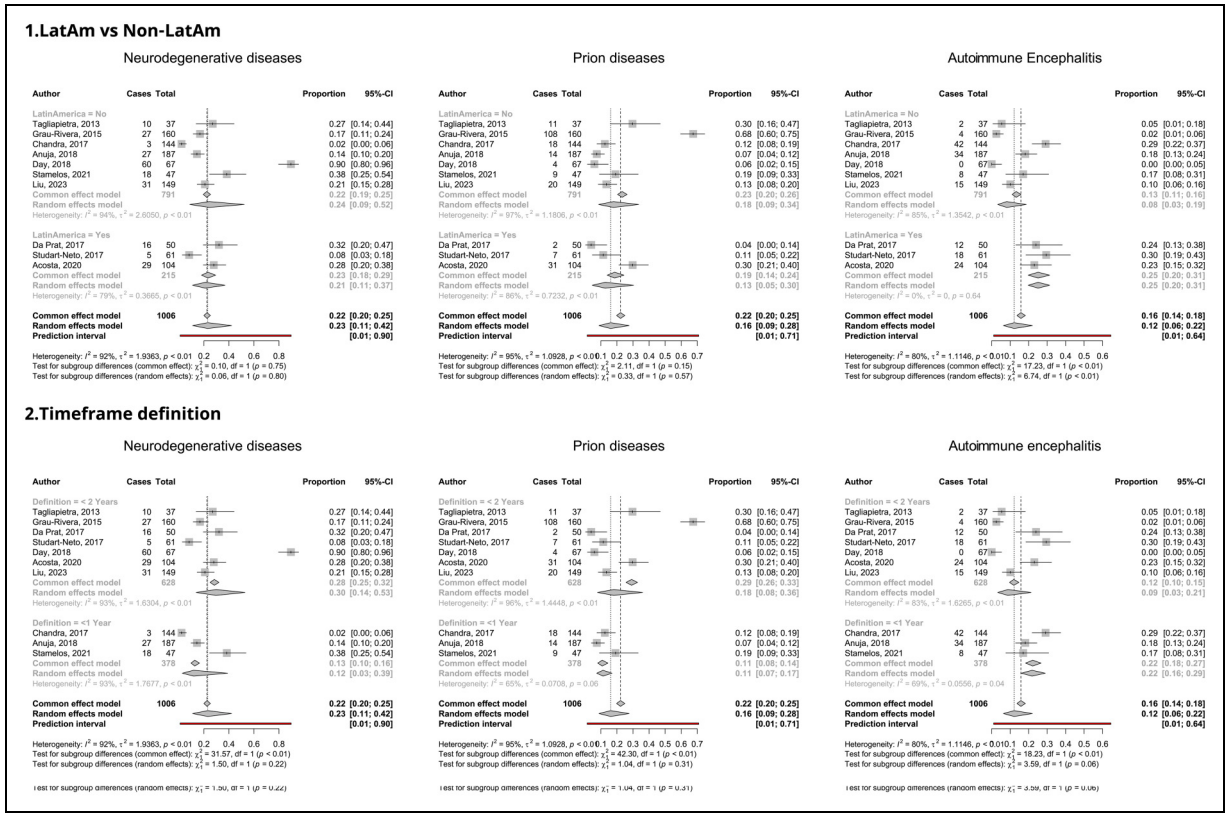

Figure 3. Forest plot of rapidly progressive dementia etiologies in Latin America and non-Latin America and timeframe definition.

whereas Da Prat et al. reported the lowest proportion,4% CI95% [0%; 14%]. Finally, the prevalence of AIE was 12% CI95% [6%; 22%] with an $I^2 = 80\%$, $\tau^2 = 1.11$, $p < 0.01$. The study by Studart-Neto et al. showed the highest prevalence of 30% CI95% [19%; 43%], while the study by Day et al. did not report any cases of AIE. Figure 2 illustrates the forest plots with the proportions by study of the causes of RPD analyzed above and their NOS assessment.

Comparative analysis of Latin America and worldwide

The proportion of etiologies was compared based on whether the cohort was from LatAm or not. From our review, only three out of 10 studies were conducted in LatAm (Da Prat et al., Studart-Neto et al., Acosta et al.). Of this group, the global prevalence of RPD due to neurodegenerative diseases was 21% CI95% [11%; 37%], with an $I^2 = 79\%$, $\tau^2 = 0.37$, and $p < 0.01$. Regarding prion diseases, the proportion was 13% CI95 [5%; 30%] with an $I^2 = 86\%$, $\tau^2 = 0.72$, $p < 0.01$. For AIE, it was 25% CI95% [20%; 31%] with an $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.64$.

In parallel, the results of studies not conducted in LatAm were analyzed. The countries included were Italy, Spain, India, USA, Greece and China. In this group, the prevalence of RPD due to neurodegenerative diseases was 24% CI95% [9%; 52%], with an $I^2 = 94\%$, $\tau^2 = 2.61$, and $p < 0.01$. Regarding prion diseases, the proportion was 18% CI95% [9%; 34%] with an $I^2 = 97\%$, $\tau^2 = 1.18$, $p < 0.01$. For AIE, it was 8% CI95% [3%: 19%] with an $I^2 = 85\%$, $\tau^2 = 1.35$, $p < 0.01$.

Comparing each overall proportion of etiologies of LatAm and non-LatAm there were no statistically significant differences except for AIE. LatAm had a significantly ($\chi^2 = 6.72$, df = 1, $p < 0.01$) higher proportion of AIE (25%) than the rest (8%). Figure 3 shows the forest plots for each etiology comparing the region of origin of the study.

Comparative analysis of timeframe definition of RPD

Comparing the definition of RPD considering a temporal cutoff of <1 year versus <2 years yielded different results. In the first group, three studies were included. Herein, global prevalence of RPD due to neurodegenerative diseases was 12% (95% CI [3%; 39%]), with an $I^2 = 93\%$, $\tau^2 = 1.77$, and $p < 0.01$. Regarding prion diseases, the proportion causing RPD was 11% CI95% [7%; 17%] with an $I^2 = 65\%$, $\tau^2 = 0.07$, $p = 0.06$. As for AIE, the percentage was 22% CI95% [16%; 29%] with an $I^2 = 69\%$; $\tau^2 = 0.06$, $p = 0.04$.

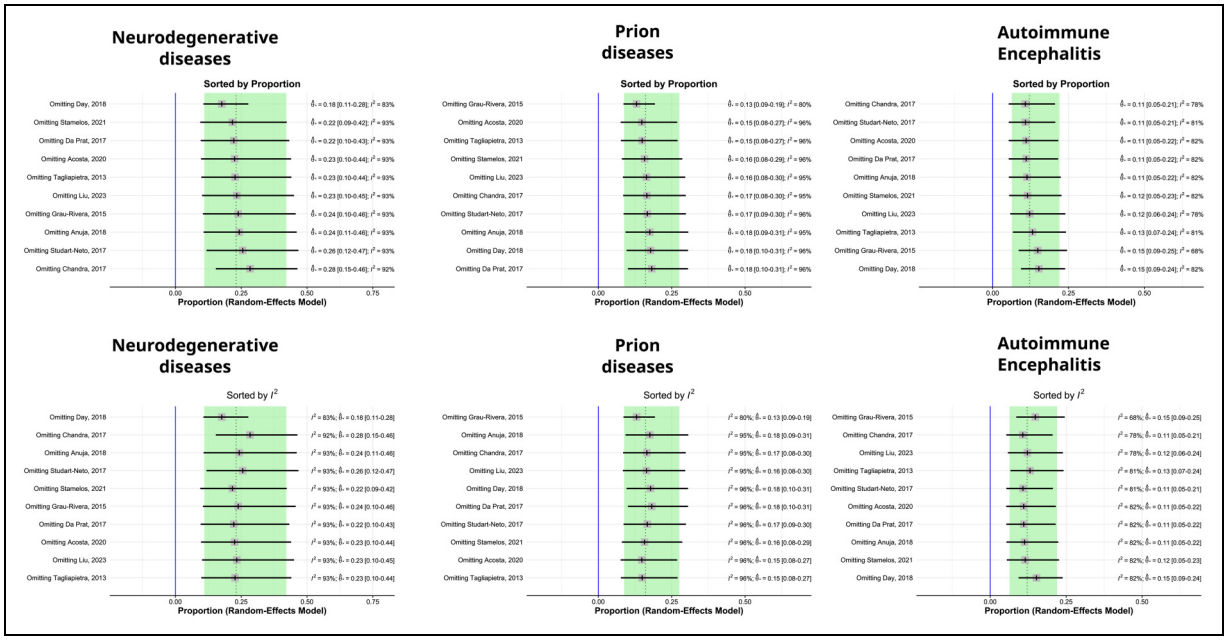

Figure 4. Influence analysis of each rapidly progressive dementia etiology.

When considering the RPD development range of <2 years, seven studies were included. The etiological proportion results were as follows. For neurodegenerative diseases, 30% 95% CI [14%; 53%], with an $I^2 = 93\%$, $\tau^2 = 1.63$, and $p < 0.01$. For prion diseases, 18% CI95% [8%; 36%] with an $I^2 = 96\%$, $\tau^2 = 1.44$, $p < 0.01$. For AIE, 9% CI95% [3%; 21%] with an $I^2 = 83\%$, $\tau^2 = 1.63$, $p < 0.01$.

In this case, the comparison of the etiological percentage of RPD did not show statistically significant differences between timeframe definitions. Figure 3 shows the forest plots of the causes according to the temporal range used.

Outliers of studies

As it was described previously, there is heterogeneity among the publications analyzed according to etiology proportion. Outlier studies for each cause group were identified. In the case of neurodegenerative diseases, the studies by Chandra et al. and Day et al. stand out as outliers. Excluding these studies, the proportion causing RPD would be 22% CI95% [16%; 28%] with n = 795, $I^2 = 74\%$, $\tau^2 = 0.2$, $p < 0.01$. Regarding prion diseases, the outlier study is the one by Grau-Rivera et al. If excluded, the proportion causing RPD would be 13% CI95% [9%; 19%] with n = 846, $I^2 = 80\%$, $\tau^2 = 0.38$, $p < 0.01$. Finally, in AIE, the outlier is the study by Chandra et al. Excluding this publication, the proportion would be 11% CI 95% [5%; 21%] with n = 862; $I^2 = 78\%$, $\tau^2 = 1.13$, $p < 0.01$. In Supplemental Figure 1, forest plots of the analyzed studies are presented excluding the outliers.

Influence analysis

The influence analysis of the results of each publication was conducted using the Leave-one-out method. Figure 4 illustrates this for each analyzed etiology, sorted by proportion and I^2. In the case of neurodegenerative diseases, it was observed that the studies by Day et al. and Chandra et al. have a positive and negative influence on the pooled effect (18% and 28%, omitting each study respectively), with the former contributing to the greatest heterogeneity ($I^2 = 83\%$, when omitted from the analysis). In prion diseases, the study by Grau-Rivera produces a positive influence in the effect and contributes to heterogeneity (13% of proportion and $I^2 = 80\%$, omitting it). Finally, in the AIE group, the studies by Day et al. and Grau-Rivera et al. have a negative influence on the pooled effect (omitting either of the first two, the proportion would be 15%). This last study contributes more to heterogeneity, as omitting it from the analysis results in an I^2 of 68%.

Publication bias

A potential risk of publication bias was detected. Figure 5 illustrates the contour-enhanced funnel plot for each cause. Asymmetry is observed in the publications of prion diseases and AIE.

Egger's test of the analysis of neurodegenerative diseases revealed an intercept of 1.08 CI95% [−6.5; −8.65], τ=0.28; $p = 0.79$. For prion diseases, the intercept was −8.04 CI95% [−14.35; −1.73], τ=−2.5; $p = 0.04$. Lastly, for AIE, the intercept was −3.623 CI95% [−6.35; −0.89], τ=−2.6, $p = 0.03$.

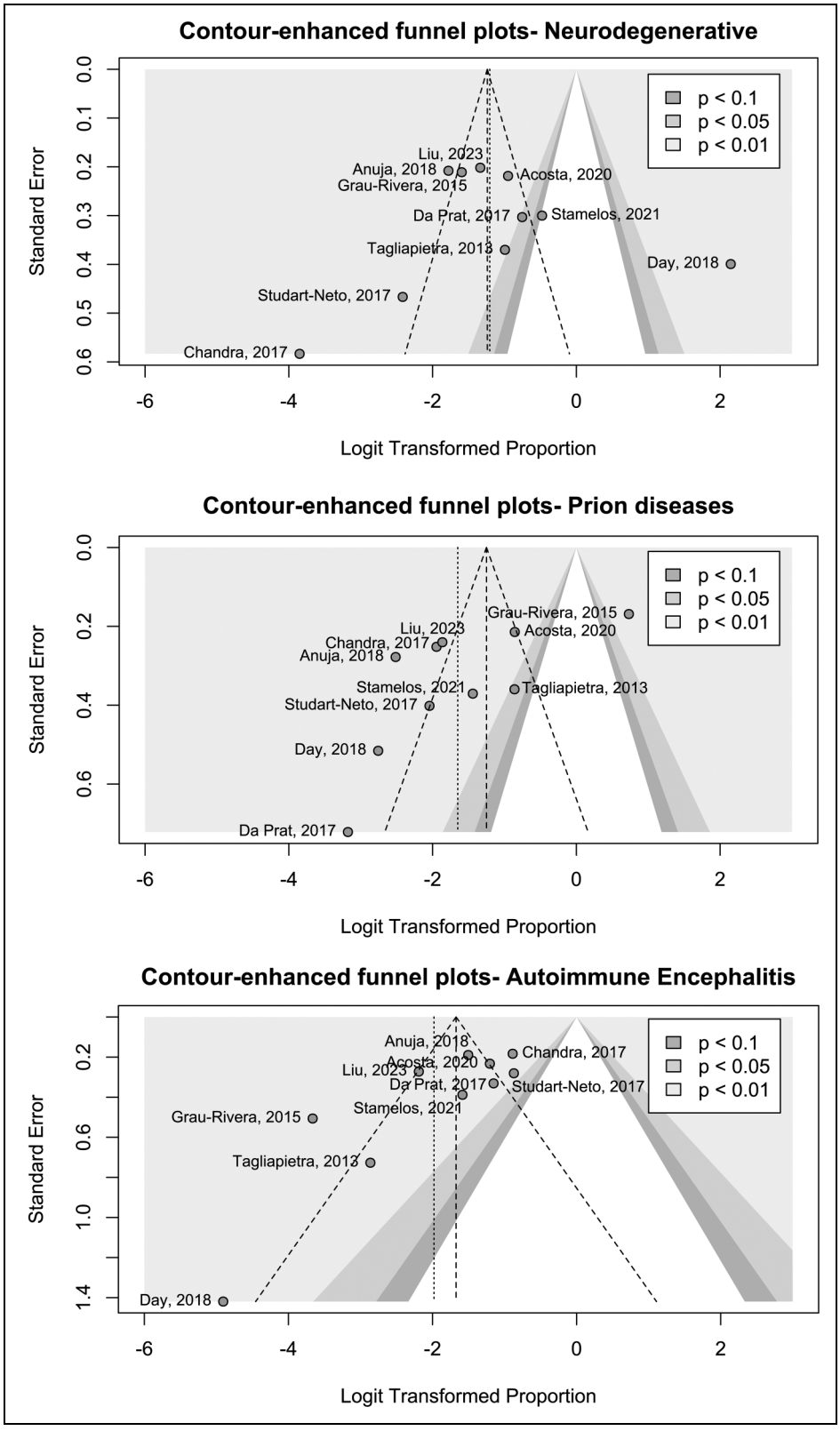

Figure 5. Contour-enhanced funnel plot for each rapidly progressive dementia etiology.

Table 2. Other causes of rapidly progressive dementia.

Article	First Author	Sample Size	Vascular, n (%)	Depression, n (%)	Cerebral vasculitis, n (%)	Limbic encephalitis, n (%)	Neoplastic diseases, n (%)	Infection, n (%)	Toxic-metabolic, n (%)
Accuracy of Diagnostic Criteria for Sporadic Creutzfeldt-Jakob Disease Among Rapidly Progressive Dementia	Tagliapietra	37	4 (10.8)	1 (2.7)	1 (2.7)	5 (13.5)	NA	NA	NA
Clinicopathological Correlations and Concomitant Pathologies in Rapidly Progressive Dementia: A Brain Bank Series	Grau-Rivera	160	7 (4.38)	NA	NA	3 (1.88)	4 (2.5)	4 (2.5)	3 (1.88)
Estudio de registro de las demencias rápidamente progresivas en un centro de alta complejidad: hacia un diagnóstico adecuado de las demencias autoinmunes en nuestro país	Da Prat	50	2(4)	NA	NA	NA	3(6)	6 (12)	1 (2)
Rapidly Progressive Dementia: Prevalence and causes in a Neurologic Unit of a Tertiary Hospital in Brazil	Studart-Neto	61	NA	NA	3 (4.92)	NA	NA	12 (19.7)	NA
Syndromes of Rapidly Progressive Cognitive Decline-Our Experience	Chandra	144	3 (2.08)	NA	NA	NA	NA	76 (52.78)	3 (2.08)
Rapidly progressive dementia: An eight year (2008–2016) retrospective study	Anuja	187	18 (9.63)	5 (2.67)	10 (5.35)	NA	25 (13.37)	39 (20.86)	7 (3.74)
Rapidly Progressive Dementia in the Outpatient Clinic: More than Prions	Day	67	NA	NA	NA	NA	NA	NA	NA
Diagnosis of Rapidly Progressive Dementia in a Referral Center in Argentina	Acosta	104	3 (2.88)	NA	NA	NA	7 (6.73)	3 (2.88)	6 (5.77)
Evolving Causes of Rapidly Progressive Dementia A 5-Year Comparative Study	Stamatelos	47	6 (12.77)	NA	NA	NA	NA	NA	NA
Prevalence and outcomes of rapidly progressive dementia: a retrospective cohort study in a neurologic unit in China	Liu	149	13 (8.72)	NA	1 (0.67)	2 (1.34)	5 (3.35)	19 (12.75)	25 (16.77)

NA: not applicable

Other causes of RPD

Table 2 provides the etiological distribution of other significant causes of RPD that were not analyzed in detail in this study. It is noteworthy that, in certain studies, these alternative etiologies demonstrated a proportion exceeding that of the entities analyzed in this work. For example, in the two studies from India (Chandra et al. and Anuja et al.), infectious causes accounted for a higher percentage compared to neurodegenerative, prion, or AIE causes individually.

Discussion

From our study, approximately half of the causes of RPD were due to neurodegenerative, prion, and AIE diseases. Comparing by region, LatAm had a statistically higher frequency only in AIE compared to non-LatAm regions. We also observed that of the three etiologies in this region, it was the one with the highest percentage.

While no significant statistical differences were observed among the etiologies when analyzed according to the timeframe definitions of RPD, some patterns emerged. Notably, the proportion of neurodegenerative and prion diseases surged when the onset of dementia was evaluated within a 2-year period. Conversely, in the AIE, the frequency rate was markedly elevated when the threshold was set at 1 year.

This meta-analysis presented several limitations. Firstly, the number of studies analyzed was limited, and the geographical representation within Latin America was restricted to only Argentina and Brazil. Secondly there was a significant heterogeneity among the publications which included influential effects, outliers, and noticeable publication biases. Thirdly, there is limited neuropathological data available for this condition. Among all the studies reviewed, only one included an analysis of a brain bank. The absence of neuropathological confirmation limits diagnostic accuracy, particularly in diseases with overlapping clinical presentations. Most studies rely on clinical criteria and biomarkers, which can vary between centers, thereby hindering comparability. Encouraging multicenter studies that incorporate autopsy data could significantly enhance the understanding of RPD etiologies and validate clinical and radiological findings. Lastly, the assessment of the quality of each study revealed a generally low standard.

Determining the proportion of RPD etiologies has several advantages for clinical management. In the context of advancing the development of new therapies against amyloid-β, one-third of the causes (represented by neurodegenerative, specifically AD, and AIE) have actually potential disease-modifying treatments.[17,18] However, it remains a complex situation, as new treatments for AD have been approved for typical forms of the disease. This is currently an area of ongoing research that requires a deeper understanding, especially for cases where cognitive impairment progresses rapidly. This is relevant because the prompt detection and management of these diseases is not only crucial due to the rapid patient disability but also because new therapies capable of altering the course of the disease are available. At time of this publication, a disease-modifying treatment for prion disease is not available. The only therapeutic option remains symptomatic and palliative management. However, early diagnosis is important because the prognostic implications are grim for the patient and their family members.

The differing frequencies of AIE between LatAm and worldwide can be attributed to several factors. Firstly, as initially mentioned, epidemiological characteristics, such as environmental exposures and genetics could influence disease occurrence. Secondly, studies from Latin America and the rest of the world differ in the timing of their conduct. The diagnostic criteria for AIE were only defined in 2016, resulting in potential selection biases from earlier publications (e.g., Tagliapietra et al. and Grau-Rivera et al.). Furthermore, there have been reports highlighting diagnostic errors due to the misuse of these criteria. Misinterpretation of functional/psychiatric symptoms or nonspecific cognitive dysfunction as encephalopathy also contributes significantly to diagnostic inaccuracies. Flanagan et al. found that 72% of patients misdiagnosed with AIE in their cohort did not meet the established criteria for the condition.[19] Lastly, the accessibility of specific diagnostic methods. The detection of antibodies against surface and onconeural antigens complements the with the diagnosis of AIE but not necessary. The identification of new antibodies has enhanced the diagnostic sensitivity for AIE; however, specificity fluctuates depending on antibody type, test methodology, and pretest probability. Consequently, there exists a risk of false-positive autoantibody outcomes in patients with conditions other than AIE, potentially leading to misdiagnosis.[20–22] Furthermore, in recent years, diagnostic methods for several diseases have also been refined. Currently, diagnostic approaches include the use of biomarkers for AD, such as PET-PIB studies and the measurement of amyloid protein or total and phosphorylated tau in cerebrospinal fluid. The RT-QuIC assay in cerebrospinal fluid has been developed in recent years and is a highly sensitive and specific method for the diagnosis of CJD. Nevertheless, there are also publications that alert us to diagnostic errors in some patients diagnosed with prion disease but who have other diagnoses such as neurodegenerative diseases, encephalitis, among others.[23] However, despite the recent development of these approaches to improve accuracy, they are still not readily accessible in many parts of the world, including LatAm. Therefore, precise characterization of the aforementioned neurological diseases is not entirely feasible in most healthcare centers.

As highlighted earlier, the medical community has not reached a unanimous agreement on the timeframe used to

categorize dementia as RPD. The criteria vary across studies. This issue was addressed by our meta-analysis. Despite the limitations of our analysis, it could be inferred that time could be a variable in determining the underlying cause of RPD. This is consistent with the typical rapid evolution of AIE (according to diagnostic criteria of 3 months) compared to the slow development of neurodegenerative conditions. Therefore, a more accurate temporal definition of RPD is essential, not only for future research studies but also because the proportion of causes could vary.

In conclusion, our systematic review shows that the majority of the RPD cases fall within the neurodegenerative, prion, and AIE categories. Despite our efforts to build robust estimators, the recruited studies exhibit high heterogeneity among them, which limits the results. Our findings underscore the importance of considering regional epidemiological factors, the evolving diagnostic criteria, and the accessibility of advanced diagnostic methods when evaluating the causes of RPD. The notable differences in the frequency of AIE between LatAm and non-LatAm regions highlight the need for more inclusive research that spans diverse geographical areas. Additionally, the variability in defining the timeframe for RPD classification suggests that a standardized temporal definition is crucial for ensuring accurate diagnosis and effective clinical management. By addressing these disparities and refining diagnostic protocols, we can enhance our understanding of RPD etiologies, ultimately improving patient outcomes through timely and targeted therapeutic interventions. Future research should focus on expanding the geographical scope, standardizing diagnostic criteria.

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Statements and declarations

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Data availability

The data and code that support the findings of this study are available in Github at https://github.com/icalandri/rapidly_progressive_dementias_meta-analysis/blob/main/README.md. These data were collected by the authors of this paper according to the review methodology.

Supplemental material

Supplemental material for this article is available online.

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