











# Clinical, radiological and immunohistological distinctions between limbic-predominant and typical Alzheimer's disease: A systematic review

Guilherme Linha Secco<sup>1</sup>, Lucas Ribas Lachman<sup>1</sup>, Leticia Alves de Oliveira<sup>1</sup>, Maisa Baldinu Caramujo<sup>2</sup>, Lunna Giovanna Gonçalves Campos<sup>2</sup>, Alana Barroso de Carvalho<sup>2</sup>, Giovanna Moreira Nascimento de Castro<sup>2</sup>, Fábio Henrique Malinoski<sup>1</sup>, Caroline de Oliveira Christoff<sup>3</sup>, Mateus Cordeiro Merlim da Silva<sup>4</sup>

1 State University of Ponta Grossa, Ponta Grossa, Brazil

2 São Leopoldo Mandic, Campinas, Brazil

3 Universidade Positivo, Curitiba, Brazil

4 Maringa, Brazil

Corresponding author: Guilherme Linha Secco ([seccolg@gmail.com](mailto:seccolg@gmail.com))



Academic editor: Galya Stavreva

Received: 31 December 2025

Accepted: 10 February 2026

Published: 1 April 2026

**Citation:** Secco GL, Lachman LR, de Oliveira LA, Caramujo MB, Campos LGG, de Carvalho AB, de Castro GMN, Malinoski FH, Christoff CdeO, da Silva MCM (2026) Clinical, radiological and immunohistological distinctions between limbic-predominant and typical Alzheimer's disease: A systematic review. Journal of Biomedical and Clinical Research 19: 153–172. <https://doi.org/10.3897/jbcr.e183988>

Copyright: © Guilherme Linha Secco et al.  
This is an open access article distributed under terms of the Creative Commons Attribution License (Attribution 4.0 International – CC BY 4.0).

## Summary

**Background:** Alzheimer's disease (AD) is the leading cause of dementia worldwide, with prominent hippocampal and medial temporal lobe atrophy. Although limbic-predominant (LP) AD has been proposed as a distinct subtype, distinctions from typical AD remain unclear. This systematic review evaluates clinical, radiological, and immunohistological differences between LP and typical AD.

**Methods:** Following PRISMA guidelines, Medline, Embase, and Web of Science were searched. Data on baseline characteristics, clinical, radiological, and immunohistological features were extracted. Screening was performed with Rayyan.ai, and study quality was assessed using the Newcastle–Ottawa Scale.

**Results:** Of 211 articles, 21 studies were included, totaling 11,315 patients: 1,178 (15.7%) with LP, 4,159 (36.7%) with typical AD, and 5,378 (47.6%) with other presentations. Weighted averages included: education 24.31 years (LP) vs. 17.15 years (AD); age at onset 77.36 years (LP) vs. 72.33 years (AD); disease duration 8.43 years (LP) vs. 8.95 years (AD). Clinical presentations were similar, with predominant cognitive impairment and memory deficits. MRI and FDG-PET revealed lower hippocampal volume and higher metabolism in LP. Tau-PET showed lower R2 relaxation in parietal, cingulate, and cuneus regions and elevated hippocampal neurofibrillary tangles. Immunohistology revealed greater hippocampal tau burden and more TDP-43 inclusions in LP than in typical AD.

**Conclusion:** LP and typical AD exhibit notable radiological and immunohistological differences, despite overlapping clinical presentations. Current evidence cannot definitively classify LP as a distinct subtype or separate disease. Further studies are required to clarify these distinctions.

**Key words:** Alzheimer's disease, LATE neuropathological change, neurofibrillary tangles, TDP-43 proteinopathies

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide and a major contributor to morbidity and mortality among older adults. It is primarily characterized by progressive brain atrophy, particularly affecting the hippocampus and medial temporal lobe (UpToDate 2024). However, AD is not a single, uniform condition. Accumulating evidence supports the existence of distinct pathological subtypes, including limbic-predominant Alzheimer's disease (LP-AD). LP-AD is characterized by a disproportionate burden of neurofibrillary tangles within the hippocampus and other limbic regions, in contrast to the more diffuse cortical involvement typically observed in typical AD (Murray et al. 2011).

These differences are associated with distinct clinical phenotypes. Patients with LP-AD tend to exhibit earlier and more pronounced episodic memory impairment, whereas individuals with typical AD more frequently present with widespread cognitive deficits across multiple domains (Carlos et al. 2023). Although both phenotypes share core AD biomarkers, such as  $\beta$ -amyloid, differences in their distribution and regional burden complicate reliable clinical differentiation (Tondo et al. 2020). In addition, LP-AD is more frequently associated with TDP-43 inclusions and distinct patterns of tau pathology, suggesting partially divergent molecular mechanisms (Carlos et al. 2023). TDP-43 pathology, in particular, has been linked to accelerated hippocampal atrophy and may contribute to the more rapid clinical deterioration observed in a subset of LP-AD cases.

Imaging studies further support phenotypic divergence between LP-AD and typical AD. Patients with LP-AD commonly demonstrate a characteristic radiological profile marked by pronounced medial temporal lobe atrophy and regionally specific metabolic abnormalities on FDG-PET imaging (Corriveau-Le-cavalier et al. 2023). Recent advances in molecular imaging, including tau PET, have improved the *in vivo* characterization of these patterns, facilitating more precise differentiation between LP-AD and typical AD.

Collectively, these findings challenge the traditional view of LP-AD as merely a variant within the Alzheimer's disease spectrum and raise the possibility that it may represent a partially distinct pathological entity. While LP-AD and typical AD share overlapping biological mechanisms, growing evidence suggests only partial convergence in their underlying pathophysiology, with important implications for therapeutic strategies. Diagnostic misclassification remains common, as neuropathological studies have demonstrated that a substantial proportion of patients clinically diagnosed with AD exhibit limbic-predominant pathology at autopsy (Pagnotti et al. 2023). These findings underscore the need for improved diagnostic frameworks that capture phenotypic heterogeneity and reduce inappropriate treatment allocation. Differences in disease trajectory have also been reported. Patients with LP-AD may present with distinct performance patterns on global cognitive measures such as the Mini-Mental State Examination (MMSE), further supporting the need for refined diagnostic criteria (Hiya et al. 2023). Longitudinal studies suggest that cognitive decline in LP-AD may be slower overall compared with typical AD, although progression rates vary considerably depending on coexisting pathologies, including cerebrovascular disease.

Despite advances in the understanding of neurodegenerative disorders, significant gaps remain regarding the early pathological development and longitudinal clinical trajectories of LP-AD and typical AD. Accordingly, this systematic

review aims to synthesize the available evidence on the clinical, radiological, and immunohistological differences between LP-AD and typical AD, and clarify whether LP-AD should be regarded as a subtype within the AD spectrum or as a distinct pathological entity.

## Methods

### Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2010). We searched the literature using Medical Subject Headings (MeSH) terms and free-text keywords across the MEDLINE (via PubMed), Embase, and Web of Science databases, covering 10 years from January 2015 to January 2025. The search strategy was designed to identify studies addressing limbic-predominant and typical Alzheimer's disease phenotypes.

The full electronic search strategy for MEDLINE (PubMed) was as follows: ("Alzheimer Disease" [MeSH] OR "Alzheimer" [Title/Abstract]) AND ("Limbic System" [MeSH] OR limbic [Title/Abstract] OR "limbic-predominant" [Title/Abstract]) AND ("Neuroimaging" [MeSH] OR imaging [Title/Abstract] OR MRI [Title/Abstract] OR PET [Title/Abstract]). Equivalent search strategies, adapted to the syntax and controlled vocabulary of each database, were applied to Embase and Web of Science. Forward and backward snowballing techniques were not systematically performed. However, the comprehensive database search strategy was designed to ensure broad coverage of the relevant literature, and no additional eligible studies were identified outside the indexed databases.

The search aimed to capture studies that describe imaging, clinical, or pathological characteristics distinguishing limbic-predominant from typical Alzheimer's disease. Further details of the study selection process are presented in Fig. 1. This review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; reference number: CRD42024622149).

### Study selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2010). The literature search was performed using Medical Subject Headings (MeSH) terms and free-text keywords across the MEDLINE (via PubMed), Embase, and Web of Science databases, covering 10 years from January 2015 to January 2025. The search strategy was designed to identify studies addressing limbic-predominant Alzheimer's disease (LP-AD) and typical Alzheimer's disease (typical AD) phenotypes.

The full electronic search strategy for MEDLINE (PubMed) was as follows: ("Alzheimer Disease"[MeSH] OR "Alzheimer"[Title/Abstract]) AND ("Limbic System"[MeSH] OR limbic [Title/Abstract] OR "limbic-predominant"[Title/Abstract]) AND ("Neuroimaging"[MeSH] OR imaging[Title/Abstract] OR MRI[Title/Abstract] OR PET [Title/Abstract]). Equivalent search strategies, adapted to the syntax and controlling the vocabulary of each database, were applied to Embase and

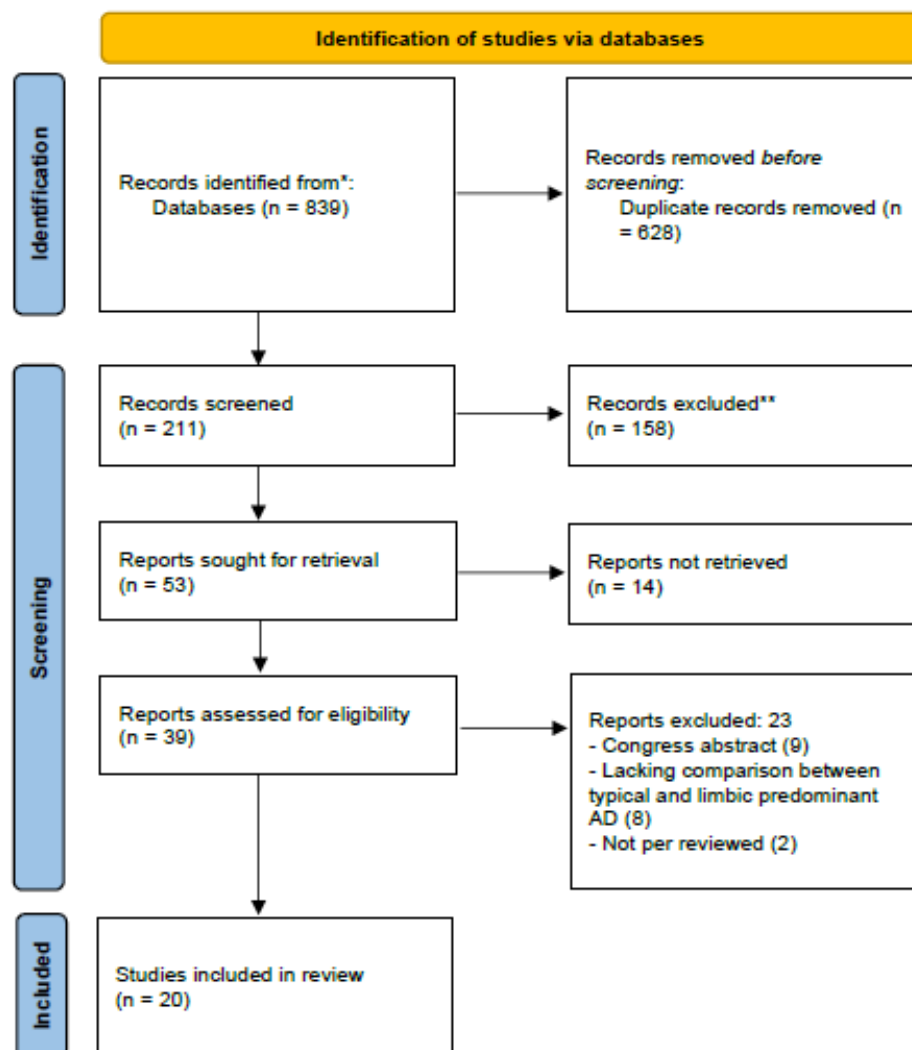


Figure 1. Flow diagram of study screening and selection. PRISMA flow diagram illustrating the study selection process for the systematic review, including numbers of records identified, screened, assessed for eligibility, and included in the review.

Web of Science. Forward and backward snowballing techniques were not systematically performed. However, the comprehensive database search strategy was designed to ensure broad coverage of the relevant literature, and no additional eligible studies were identified outside the indexed databases.

The search aimed to capture studies describing imaging, clinical, neuropathological, or biomarker characteristics distinguishing LP-AD from typical AD. Further details of the study selection process are presented in Fig. 1. This review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; reference number: CRD42024622149).

### Data extraction

Data were collected using a predefined, standardized extraction spreadsheet, and all variables were mapped to the prespecified primary and secondary outcomes. The following information was extracted from each included study: authors, year of publication, journal, country or region, study design, sample

size, age at diagnosis, sex, years of education, clinical presentation, disease duration, imaging and/or neuropathological features, biomarkers assessed, neurological and cognitive measures used and their corresponding outcomes, follow-up duration, key findings, and authors' conclusions. Detailed information on the characteristics of the included studies is provided in Table 1.

**Table 1.** Summary of included studies.

Author/year	DOI	Journal	Country	Study Design
Carlos et al. 2023	<a href="https://doi.org/10.3233/JAD-221094">https://doi.org/10.3233/JAD-221094</a>	Journal of Alzheimer's Disease	USA	Retrospective cohort
Tondo et al. 2020	<a href="https://doi.org/10.1111/ene.14639">https://doi.org/10.1111/ene.14639</a>	European Journal of Neurology	Italy	Retrospective cohort
Pagnotti et al. 2023	<a href="https://doi.org/10.1212/WNL.000000000207159">https://doi.org/10.1212/WNL.000000000207159</a>	Neurology	USA	Retrospective cohort
Hiya et al. 2023	<a href="https://doi.org/10.1093/jnen/nlad098">https://doi.org/10.1093/jnen/nlad098</a>	Journal of Neuropathology & Experimental Neurology	USA	Retrospective cohort
Lagarde et al. 2023	<a href="https://doi.org/10.1186/s13195-024-01466-z">https://doi.org/10.1186/s13195-024-01466-z</a>	Alzheimer's Research & Therapy	France	Retrospective cohort
Levin et al. 2021	<a href="https://doi.org/10.1186/s13195-021-00785-9">https://doi.org/10.1186/s13195-021-00785-9</a>	Alzheimer's Research & Therapy	Spain	Retrospective cohort
Uretsky et al. 2021	<a href="https://doi.org/10.1002/trc2.12201">https://doi.org/10.1002/trc2.12201</a>	Alzheimer's & Dementia: Translational Research & Clinical Interventions	USA	Retrospective cohort
Kouri, 2024	<a href="https://doi.org/10.1001/jamaneurol.2024.0784">https://doi.org/10.1001/jamaneurol.2024.0784</a>	JAMA Neurology	USA	Retrospective cohort
Nag et al. 2020	<a href="https://doi.org/10.1212/WNL.000000000010602">https://doi.org/10.1212/WNL.000000000010602</a>	Neurology	USA	Observational
Machado et al. 2020	<a href="https://doi.org/10.1186/s13195-020-00620-7">https://doi.org/10.1186/s13195-020-00620-7</a>	Alzheimer's Research & Therapy	Sweden, USA, German, Canada	Observational
Agrawal et al. 2021	<a href="https://doi.org/10.1186/s40478-021-01260-0">https://doi.org/10.1186/s40478-021-01260-0</a>	Acta Neuropathologica Communications	USA	Observational
Nelson 2021	<a href="https://doi.org/10.1093/jnen/nlab050">https://doi.org/10.1093/jnen/nlab050</a>	Journal of Neuropathology & Experimental Neurology	USA	Retrospective cohort
Persson et al. 2017	<a href="https://doi.org/10.1371/journal.pone.0186595">https://doi.org/10.1371/journal.pone.0186595</a>	PLOS ONE	Norway, Sweden	Observational
Mohanty et al. 2022	<a href="https://doi.org/10.1212/WNL.000000000200573">https://doi.org/10.1212/WNL.000000000200573</a>	Neurology	Sweden, USA, German, Spain, UK	Observational
Besser et al. 2020	<a href="https://doi.org/10.1093/jnen/nlz126">https://doi.org/10.1093/jnen/nlz126</a>	Journal of Neuropathology and Experimental Neurology	USA	Observational
Mikhailenko et al. 2024	<a href="https://doi.org/10.1093/brain/awae212">https://doi.org/10.1093/brain/awae212</a>	Brain	Finland	Retrospective cohort
Gauthreaux et al. 2022	<a href="https://doi.org/10.1212/WNL.000000000200001">https://doi.org/10.1212/WNL.000000000200001</a>	Neurology	USA	Retrospective cohort
Tazwar et al. 2022	<a href="https://doi.org/10.1016/j.neurobiolaging.2022.05.009">https://doi.org/10.1016/j.neurobiolaging.2022.05.009</a>	Neurobiology of Aging	USA	Observational
Robinson et al. 2021	<a href="https://doi.org/10.1093/brain/awaa438">https://doi.org/10.1093/brain/awaa438</a>	Brain	USA	Retrospective cohort
Estades Ayuso et al. 2023	<a href="https://doi.org/10.1186/s13024-023-00646-z">https://doi.org/10.1186/s13024-023-00646-z</a>	Molecular Neurodegeneration	USA	Observational

Summary of the included studies, presenting author, year of publication, DOI, journal, country, and study design.

### Quality assessment

Two independent reviewers assessed the risk of bias and methodological quality of the included studies using the Newcastle–Ottawa Scale (NOS). Disagreements between reviewers were resolved through discussion and consensus; when consensus could not be reached, a third senior reviewer made the final decision. Studies were evaluated across the NOS domains of selection, comparability, and exposure. Total scores ranged from 0 to 9, and higher scores indicated better methodological quality. Detailed results of the quality assessment are presented in Table 2.

**Table 2.** Newcastle Ottawa Scale summary.

Studies	Items								Score
	Selection				Comparability	Exposure			
	1	2	3	4	1	1	2	3	
6		*	*	*	**	*	*	*	8/9
8	*		*	*	*	*	*	*	7/9
9	*	*	*	*	*	*	*	*	8/9
10	*	*	*		*	*	*	*	7/9
11	*	*	*	*	*	*	*	*	8/9
12	*	*	*	*	*	*	*	*	8/9
13	*	*	*	*	**	*	*	*	9/9
20	*	*				*	*		4/9
21	*	*	*	*	**	*	*	*	9/9
24	*	*	*		**	*	*	*	8/9
25	*	*	*	*	**	*	*	*	9-9
26		*	*	*	*	*	*	*	7/9
27		*	*	*	**		*	*	7/9
28		*	*	*	**	*	*	*	8/9
31	*			*	*	*	*	*	6/9
32	*			*	**	*	*	*	7/9
35		*	*		*	*	*	*	6/9
36	*	*	*	*	**	*	*	*	9/9
37		*	*	*	*	*	*	*	7/9
39	*	*	*	*	**	*	*	*	9/9

Summary of methodological quality assessment of the included studies using the Newcastle –Ottawa Scale (NOS). Scores are presented as asterisks, with each asterisk representing one point awarded according to the scale criteria.

Although the ROBINS-I tool is recommended for assessing risk of bias in non-randomized studies of interventions, the NOS was selected because the included studies were predominantly observational, descriptive, and neuropathological, rather than interventional or comparative effectiveness studies. The NOS is widely used and validated for cohort and case–control designs and enables a structured and consistent appraisal of selection, comparability, and exposure domains across heterogeneous observational methodologies. Given the descriptive and exploratory objectives of this systematic review, as well as the absence of causal effect estimation or quantitative synthesis, the NOS was considered appropriate and sufficient for evaluating study quality and risk of bias.

## Outcomes

The primary outcomes were differences between limbic-predominant Alzheimer's disease (LP-AD) and typical Alzheimer's disease (typical AD) in neuropathological and neuroimaging characteristics, specifically the regional distribution and burden of neurofibrillary tangles, patterns of hippocampal and limbic system involvement, and imaging features such as hippocampal atrophy assessed by magnetic resonance imaging (MRI) or metabolic patterns assessed by positron emission tomography (PET).

The secondary outcomes included clinical and demographic characteristics, such as age at symptom onset, clinical presentation, disease duration, and trajectories of cognitive decline, as well as the presence of associated neuropathological biomarkers, including tau and TDP-43 pathology. Additional secondary outcomes included follow-up duration, when available, and the overall conclusions of the included studies regarding Alzheimer's disease subtype differentiation.

## Data synthesis and rationale for not performing a meta-analysis

Although several of the included studies reported quantitative data, a formal meta-analysis was not performed due to substantial clinical, methodological, and outcome heterogeneity across studies. The included articles varied considerably with respect to study design, sample size, definitions of limbic-predominant Alzheimer's disease (LP-AD) and typical Alzheimer's disease (typical AD), imaging modalities (magnetic resonance imaging versus positron emission tomography), neuropathological assessment methods, outcome measures, and reporting formats.

In addition, many studies did not provide effect estimates or measures of variance in a sufficiently consistent or comparable manner to allow for meaningful statistical pooling. Given these sources of heterogeneity, quantitative synthesis was deemed inappropriate, and a narrative synthesis was adopted to summarize and compare findings across studies qualitatively.

## Diagnostic definitions of Alzheimer's disease subtypes

Across the included studies, the definition of limbic-predominant Alzheimer's disease (LP-AD) and typical Alzheimer's disease (typical AD) was highly heterogeneous. Subtype classification was based on neuropathological criteria (postmortem regional distribution and density of tau and/or TDP-43 pathology, frequently informed by Braak staging), imaging-based criteria (patterns of hippocampal or limbic-predominant atrophy on MRI or hypometabolism on FDG-PET), or combined biomarker-imaging approaches.

Although clinical diagnostic criteria for Alzheimer's disease generally followed established frameworks such as the NIA-AA, subtype differentiation was predominantly driven by regional pathological or neuroimaging features, rather than by clinical phenotype alone. Consequently, no single diagnostic framework or standardized set of criteria for LP-AD or typical AD was consistently applied across all included studies, contributing to substantial clinical and methodological heterogeneity (Table 3).

**Table 3.** Diagnostic frameworks and terminology used to define LP-AD and typical AD across included studies.

Study	Primary diagnostic modality	Framework/criteria applied	Terminology used	Operational definition of LP-AD vs typical AD
Carlos et al. 2023	Neuropathological	Regional distribution of tau and TDP-43 pathology	Limbic-predominant AD	Postmortem classification based on disproportionate involvement of limbic regions compared with neocortical areas
Tondo et al. 2020	Imaging + biomarkers	FDG-PET and CSF biomarkers	Limbic-predominant (prodromal AD)	Limbic-predominant hypometabolism in amnesic MCI with AD biomarker profile
Pagnotti et al. 2023	Neuroimaging	MRI/PET (data-driven subtyping)	Limbic-predominant AD	Imaging-based subtype characterized by greater limbic involvement relative to cortical regions
Hiya et al. 2023	Neuropathological	Neurofibrillary tangle (NFT) distribution	Limbic-predominant AD	Regional predominance of NFT burden in limbic structures on postmortem analysis
Lagarde et al. 2023	Neuropathological	Regional tau pathology mapping	Limbic-predominant AD	Disproportionate tau burden in limbic regions compared with neocortex
Levin et al. 2021	Functional imaging	FDG-PET clustering	Typical AD; Limbic-predominant AD	Data-driven metabolic patterns distinguishing limbic-predominant from typical cortical involvement
Uretsky et al. 2021	Neuroimaging	MRI-based subtyping	Limbic-predominant AD	Predominant hippocampal and limbic atrophy on structural MRI
Kouri, 2024	Neuropathological	Postmortem tau and TDP-43 assessment	Limbic-focused AD	Pathological phenotype with primary limbic involvement
Nag et al. 2020	Neuropathological	Braak-based NFT staging	Limbic-predominant AD	Braak stage distribution emphasizing limbic NFT burden
Machado et al. 2020	Neuroimaging	Volumetric MRI analysis	Limbic-predominant AD	Reduced hippocampal volume relative to cortical regions
Agrawal et al. 2021	Neuropathological	Regional tau burden	Limbic-predominant AD	Higher tau density in limbic structures
Nelson 2021	Neuropathological	Braak staging + TDP-43 pathology	Limbic-predominant AD	Combined tau and TDP-43 pathology predominating in limbic areas
Persson et al. 2017	Neuroimaging	MRI and PET imaging	Typical AD; Limbic-predominant AD	Structural and metabolic patterns differentiating limbic and typical phenotypes
Mohanty et al. 2022	Neuropathological	NFT density analysis	Limbic-predominant AD	Increased NFT density in limbic regions
Besser et al. 2020	Neuropathological	Tau pathology distribution	Limbic-predominant AD	Limbic-weighted tau pathology
Mikhailenko et al. 2024	Neuroimaging	MRI-based classification	Limbic-predominant AD	Limbic-predominant atrophy pattern
Gauthreaux et al. 2022	Functional imaging	PET-based subtyping	Limbic-predominant AD	Limbic-predominant hypometabolism
Tazwar et al. 2022	Neuropathological	Postmortem pathological assessment	Limbic-predominant AD	Regional predominance of limbic pathology
Robinson et al. 2021	Neuropathological	Braak staging / NFT distribution	Limbic-predominant AD	Limbic-weighted neurofibrillary pathology
Estades Ayuso et al. 2023	Genetics + imaging	Imaging-genotype correlation	Limbic-predominant AD	Limbic-predominant phenotype associated with genetic variants

Subtype terminology and diagnostic criteria varied substantially across studies. Definitions were reported as described in the original publications and were not assumed to be interchangeable. LP-AD classification was primarily driven by regional neuropathological or imaging features rather than clinical phenotype alone.

## Results

### Patient information

After the initial identification of 211 records, title and abstract screening followed by full-text assessment resulted in the inclusion of 21 studies, comprising a total of 11,315 patients. The mean age ( $\pm$  SD) was  $74.53 \pm 5.46$  years for the typical Alzheimer's disease (typical AD) group and  $78.81 \pm 5.07$  years for the limbic-predominant Alzheimer's disease (LP-AD) group.

The mean follow-up duration was 151 months (range: 24–336 months) for the typical AD group and 176.6 months (range: 24–456 months) for the LP-AD group. Among the included patients, 1,178 (15.7%) were classified as LP-AD and 4,159 (36.7%) as typical AD. The remaining 5,378 patients (47.6%) presented with alternative pathological or imaging patterns, including hippocampal-sparing AD and mixed presentations combining features of LP-AD and typical AD.

The weighted mean years of education were higher in the LP-AD group (24.31 years) compared with the typical AD group (17.15 years). The proportion of female patients was similar across groups, at 52.3% in the typical AD group and 51.5% in the LP-AD group. The weighted mean age at symptom onset was 72.33 years for typical AD and 77.36 years for LP-AD. Mean disease duration was comparable across groups, with weighted averages of 8.95 years for typical AD and 8.43 years for LP-AD.

Across studies, no consistent differences were observed in clinical presentation between LP-AD and typical AD, with cognitive impairment and memory deficits being the most frequently reported manifestations in both groups. Detailed demographic and clinical characteristics are summarized in Tables 4, 5.

**Table 4.** Summary of information from Typical AD patients.

Study	Number of patients (n)	Female (%)	Age at onset (mean)	Education in years (mean)	Disease Duration in years (mean)	Clinical Presentation
Tondo et al. 2020	62	56.4%	71.14	13.95	4.05	N/A
Kouri et al. 2024	1090	39.7%	71	15.3	9.3	AS; MCI
Pagnotti et al. 2023	391	50.4%	72.5	15.5	7.5	MS; BS; AS
Hyia et al. 2023	243	44.7%	N/A	16.0 $\pm$ 0.2	N/A	CI
Lagarde et al. 2023	23	47.8%	70.4	N/A	N/A	AS; CI
Carlos et al. 2023	196	64%	77	14	11	CI
Levin et al. 2021	87	38%	73.2	15.5	N/A	CI
Mikhailenko et al. 2024	33	82.7%	86.8	N/A	4.4	CI
Uretsky et al. 2021	213	74%	81.3	80.7	16.2	AS; CI
Persson et al. 2017	59	56%	71.4	11.9	3.2	CI; AS
Mohanty et al. 2022	31	25.8%	80	16.1	N/A	CI; AS
Machado et al. 2020	90	47.7%	74.2	15.2	N/A	N/A
Robinson et al. 2021	522	53.4%	69.5	N/A	9.5	CI; AS

Summary of demographic and clinical information from patients with typical Alzheimer's disease (AD), including number of patients (n), proportion of females (%), mean age at onset, mean years of education, mean disease duration (years), and clinical presentation. AS: Amnesic syndrome; MCI: Mild cognitive impairment; MS: Motor symptoms; BS: Behavior symptoms; CI: Cognitive impairment.

**Table 5.** Summary of information from limbic predominant AD patients.

Study	Number of patients (n)	Female (%)	Age at onset (mean)	Education in years (mean)	Disease Duration in years (mean)	Clinical Presentation
Tondo et al. 2020	80	40%	74.2	13.69	4.05	N/A
Kouri et al. 2024	204	9.4%	78.3*	14.2*	8.76*	AS; CI
Pagnotti et al. 2023	27	54.8%	78.8	16.8	8.9	MS; BS; AS
Hyia et al. 2023	31	51.7%	N/A	16.9	N/A	CI
Lagarde et al. 2023	17	35.3%	77.3	N/A	N/A	AS; CI
Carlos et al. 2023	167	59%	75	15	9	CI
Levin et al. 2021	80	49%	75.4	15.4	N/A	CI
Nelson 2021	34	N/A	N/A	N/A	N/A	CI
Tazwar et al. 2022	419	72.%	N/A	15.7	N/A	AS
Gauthreaux et al. 2022	221	51.6	86.9	N/A	N/A	CI
Mikhailenko et al. 2024	20	75.9%	87.3	N/A	2.5	CI
Nag et al. 2020	228	76.3%	82.8	14.7	N/A	CI; AS
Uretsky et al. 2021	57	67%	83	16.3	N/A	CI; AS
Persson et al. 2017	29	58.6%	72.2	11.4	2.9	CI; AS
Agrawal et al. 2021	1.670	68.62%	N/A	16.9	N/A	CI; AS
Machado et al. 2020	18	56%	74.5	15.1	N/A	CI; AS

Summary of demographic and clinical information from patients with limbic-predominant Alzheimer's disease (AD), including number of patients (n), proportion of females (%), mean age at onset, mean years of education, mean disease duration (years), and clinical presentation.

AS: Amnesic syndrome; MCI: mild cognitive impairment; MS: motor symptoms; BS: Behavior symptoms; CI: Cognitive impairment.

\* Weighted average of the mean values of three cohorts from the same study.

## Imaging, histological, cognitive and biomarker outcomes

### Imaging outcomes

Magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) were the most frequently employed imaging modalities across the included studies. Neuroimaging findings consistently demonstrated greater hippocampal atrophy in patients with limbic-predominant Alzheimer's disease (LP-AD) compared with those with typical Alzheimer's disease (typical AD). Reduced volumes of the amygdala and entorhinal cortex were also more pronounced in LP-AD patients than in cognitively normal controls.

In contrast, patients with typical AD exhibited more diffuse cortical atrophy, whereas LP-AD patients showed predominant involvement of medial temporal lobe structures. Functional imaging studies using FDG-PET further revealed higher rates of hypometabolism in LP-AD patients, particularly within limbic regions, compared with typical AD patients.

Overall, neuroimaging findings across studies converge on a pattern of medial temporal lobe–predominant structural and metabolic involvement in LP-AD, rather than the more widespread cortical changes observed in typical AD. A summary of imaging findings is presented in Table 6.

Imaging findings across studies indicate more diffuse neocortical involvement in typical AD, whereas limbic-predominant AD shows disproportionate medial temporal lobe degeneration, particularly affecting the hippocampus and amygdala.

**Table 6.** Imaging findings in typical Alzheimer's disease and limbic-predominant Alzheimer's disease.

Study	Typical AD	Limbic-predominant AD
Kouri et al. 2024	Reduced hippocampal volume (-1.7); increased tau-PET uptake in parietal cortex and posterior cingulate	Greater hippocampal volume loss (-2.2), with predominant medial temporal involvement
Lagarde et al. 2023	Diffuse cortical atrophy involving temporal and parietal regions	Predominant hippocampal, amygdala, and entorhinal atrophy; relatively less neocortical involvement
Levin et al. 2021	FDG-PET hypometabolism in 22.6%	FDG-PET hypometabolism in 49.8%
Persson et al. 2017	Temporal and frontal lobe atrophy	Medial temporal lobe atrophy
Machado et al. 2020	Atrophy in basal forebrain, hippocampus, and precuneus	Medial temporal and basal forebrain degeneration
Tazwar et al. 2022	—	Reduced R2 relaxation in amygdala, hippocampus, and temporal white matter

### Histological and pathological outcomes

Histological analyses demonstrated no significant differences between LP-AD and typical AD patients with respect to overall brain weight or the presence of cerebrovascular pathology, including arteriosclerosis. However, LP-AD patients consistently showed a higher corticolimbic index, indicating disproportionate involvement of limbic regions compared with neocortical areas.

Regarding proteinopathies, no major between-group differences were observed in the presence of amyloid- $\beta$  plaques,  $\alpha$ -synuclein/Lewy body pathology, or overall neurofibrillary tangle burden. In contrast, TDP-43 inclusions were more frequently associated with LP-AD than with typical AD.

Furthermore, the regional distribution of neurofibrillary tangles differed between phenotypes: LP-AD showed a more restricted distribution to hippocampal and limbic structures, whereas typical AD showed a more diffuse neocortical distribution. A summary of histological and pathological findings is presented in Table 7.

Histological analyses consistently demonstrate a limbic-weighted burden in limbic-predominant AD, particularly hippocampal sclerosis and higher corticolimbic indices, while typical AD shows more widespread cortical involvement.

### Biomarker outcomes

Across studies reporting biomarker data, no substantial differences were identified between LP-AD and typical AD in classical Alzheimer's disease biomarkers, including amyloid- $\beta$  and tau-related measures. Biomarker profiles largely overlapped across phenotypes, reinforcing the notion that subtype differentiation was primarily driven by regional distribution patterns rather than absolute biomarker burden.

An exception was the higher prevalence of TDP-43 pathology in LP-AD, which emerged as a consistent finding across neuropathological studies and may represent a distinguishing biological feature of the limbic-predominant phenotype. A summary of biomarker findings is presented in Table 8.

Biomarker findings suggest comparable amyloid and tau profiles between groups, while limbic-predominant AD is more strongly associated with TDP-43 pathology and hippocampal-restricted neurofibrillary tangle burden.

**Table 7.** Histological findings in typical Alzheimer's disease and limbic-predominant Alzheimer's disease.

Study	Typical AD	Limbic-predominant AD
Kouri et al. 2024	Lower corticolimbic index; Braak stages V–VI; frequent CERAD plaques	Higher corticolimbic index; Braak stage VI predominance
Pagnotti et al. 2023	Microinfarcts, arteriosclerosis, hippocampal sclerosis	More frequent hippocampal sclerosis and limbic vascular pathology
Carlos et al. 2023	Hippocampal sclerosis, infarcts, microinfarcts	Similar vascular pathology with greater limbic involvement
Nelson 2021	–	Hippocampal sclerosis
Mikhailenko et al. 2024	Advanced AD neuropathologic changes	Arteriolosclerosis, predominantly affecting the hippocampus and amygdala

**Table 8.** Biomarker findings in typical Alzheimer's disease and limbic-predominant Alzheimer's disease.

Study	Typical AD	Limbic-predominant AD
Kouri et al. 2024	Amyloid pathology, Lewy bodies, TDP-43 positivity	Higher frequency of TDP-43 positivity (up to 68%)
Lagarde et al. 2023	Low CSF Aβ42 and high tau levels	Mostly negative tau-PET; limited amyloid-PET positivity
Levin et al. 2021	AV45 PET positivity; CSF Aβ and t-tau alterations	Similar amyloid and tau CSF profiles
Tazwar et al. 2022	–	TDP-43 inclusions in amygdala, hippocampus, and neocortex
Nag et al. 2020	TDP-43 occasionally present	TDP-43 frequently present
Uretsky et al. 2021	Greater neocortical NFT burden	Higher hippocampal NFT burden

### Cognitive outcomes

Cognitive outcomes were primarily assessed using the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) scale. Across studies, no substantial differences were observed between LP-AD and typical AD patients in global cognitive performance, as reflected by comparable MMSE and CDR scores.

Mean MMSE values were similar between groups (20.18 in typical AD versus 20.29 in LP-AD). While LP-AD patients generally performed better than typical AD patients on several neuropsychological measures, poorer performance was observed on tasks assessing executive function and processing speed, particularly the Trail Making Test parts A (TMT-A) and B (TMT-B).

These findings suggest that global cognitive impairment is comparable between phenotypes, whereas domain-specific differences may exist, particularly in executive function. A summary of cognitive findings is presented in Table 9.

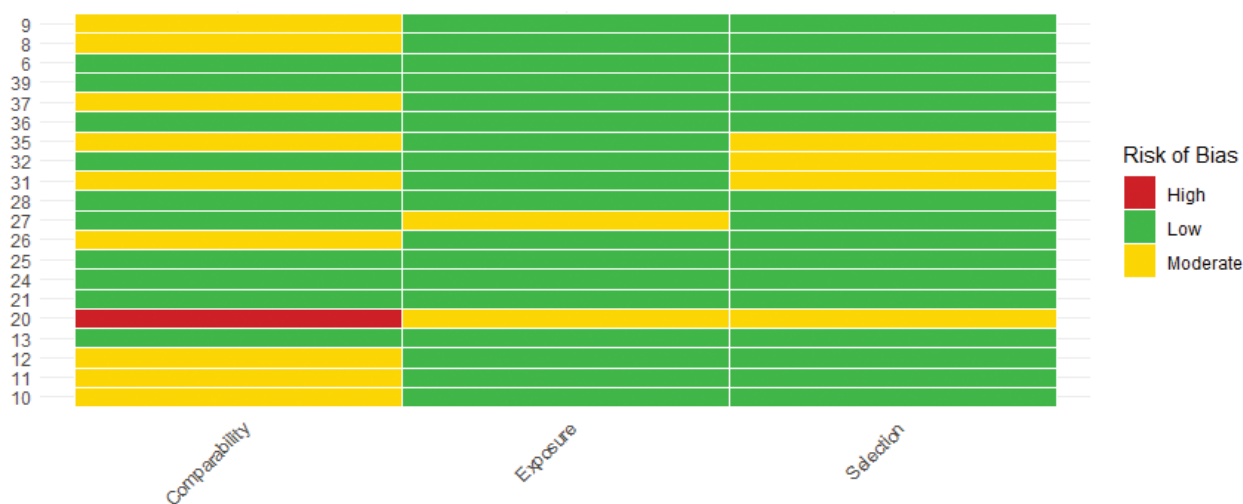
Despite broadly similar global cognitive scores, limbic-predominant AD tends to show relatively preserved executive function and slower decline in some domains. In contrast, typical AD shows faster, more generalized cognitive deterioration.

### Quality assessment

Overall, the methodological quality of the included studies was moderate to high. Most studies scored highly in the selection domain, reflecting adequate case definition and representativeness. Comparability scores varied across studies, primarily due to differences in adjustment for potential confounders. Assessment

**Table 9.** Cognitive outcomes in typical Alzheimer's disease and limbic-predominant Alzheimer's disease.

Study	Typical AD	Limbic-predominant AD
Tondo et al. 2020	MMSE: 25.40 ± 1.81; CDR: 0.50	MMSE: 25.73 ± 2.06; CDR: 0.50
Kouri et al. 2024	Lower MMSE scores and faster decline	Slightly higher MMSE scores and slower decline
Pagnotti et al. 2023	Worse performance across most domains	Better performance except for TMT-A and TMT-B
Hyia et al. 2023	Progressive decline across domains	Similar pattern of decline
Persson et al. 2017	MMSE: 22.1 ± 4.3; faster CDR progression	MMSE: 22.1 ± 4.7; higher CDR scores
Mohanty et al. 2022	MMSE: 18.16 ± 6.74	Similar cognitive outcomes
Uretsky et al. 2021	Faster cognitive decline	Slower decline compared with typical AD



**Figure 2.** Risk of bias assessment of included studies. Traffic-light plot summarizing the risk of bias of the included studies based on the Newcastle–Ottawa Scale domains (selection, comparability, and outcome/exposure). Green indicates low risk of bias, yellow indicates moderate risk, and red indicates high risk of bias.

of exposure and outcome domains was generally of good quality, although some studies lacked detailed reporting of follow-up duration or outcome ascertainment.

A detailed quality assessment for each included study is presented in Table 2, and a visual summary of the risk of bias assessment across studies is shown as a traffic-light plot in Fig. 2.

### Diagnostic criteria heterogeneity

Substantial heterogeneity in diagnostic criteria and subtype definitions was observed across the included studies. Studies employing neuropathological assessment relied on postmortem characterization of neurofibrillary tangle and/or TDP-43 distribution. In contrast, imaging-based studies utilized MRI or FDG-PET patterns to differentiate limbic-predominant from typical AD phenotypes. Biomarker-based subtyping, particularly in amnesic mild cognitive impairment (aMCI) populations, incorporated cerebrospinal fluid or metabolic biomarkers.

Terminology such as limbic-predominant AD, cortical-predominant AD, and typical AD was applied variably across studies, reflecting differences in operational definitions, diagnostic frameworks, and imaging modalities. These inconsistencies contribute to heterogeneity in study populations and outcomes, as summarized in Table 3.

## Discussion

This systematic review analyzed 21 articles to investigate whether the limbic-predominant (LP) presentation of dementia represents a subtype of Alzheimer's disease (AD) or a distinct pathological entity. Among the 11,315 patients included, 15.7% were classified as having LP-AD, whereas 36.7% were classified as having typical AD. Patients with LP-AD demonstrated a later age at symptom onset and higher educational attainment, while disease duration and clinical presentation were largely comparable between groups.

Neuroimaging findings consistently revealed greater involvement of the hippocampus, amygdala, and entorhinal cortex, as well as more pronounced limbic hypometabolism in LP-AD patients. In contrast, typical AD patients exhibited more diffuse cortical atrophy. Histopathological analyses demonstrated a higher prevalence of TDP-43 inclusions and greater concentrations of neurofibrillary tangles in the hippocampus and limbic regions in LP-AD. In the cognitive domain, LP-AD patients showed global cognitive performance similar to that of typical AD patients, although domain-specific differences were observed. Collectively, these findings highlight important distinctions between LP-AD and typical AD in neuroimaging, histopathology, biomarker distribution, and cognition, despite overlapping clinical features.

Age at onset emerged as one of the most relevant distinguishing factors between the two groups. In this review, the mean age at onset was 72.33 years for typical AD and 77.36 years for LP-AD. Two included studies reported statistically significant differences, identifying age at onset as a key factor differentiating typical AD from LP-AD (Tondo et al. 2020; Pagnotti et al. 2023). These results are supported by several additional studies demonstrating a later onset of dementia symptoms in LP-AD patients (Levin et al. 2021; Uretsky et al. 2021; Lagarde et al. 2023). Furthermore, a recent retrospective cohort study reported that, among patients with AD pathology, greater limbic system involvement was associated with progressively later ages of onset, reinforcing the relevance of regional pathological burden in clinical expression (Boon et al. 2023)

Regarding disease duration, no substantial differences were observed between LP-AD and typical AD. This finding aligns with most published studies, which report similar disease durations between phenotypes (Uretsky et al. 2021; Boon et al. 2023; Pagnotti et al. 2023). An exception was reported by Carlos et al., who identified a longer disease duration in patients with typical AD combined with TDP-43 encephalopathy ( $p = 0.02$ ). Overall, current evidence suggests that disease duration alone does not reliably differentiate LP-AD from typical AD.

Educational level also differed between groups in this review, with LP-AD patients showing a higher weighted mean number of years of education. However, this finding should be interpreted cautiously, as many individual studies did not report significant differences in educational attainment, and no consistent association between education level and LP-AD stage or severity has been established (Nag et al. 2020; Tondo et al. 2020; Levin et al. 2021; Pagnotti et al. 2023; Carlos et al. 2023). This discrepancy may reflect methodological differences and the influence of weighted averages rather than a true biological association.

Neuroimaging analyses revealed marked differences between LP-AD and typical AD, particularly involving the hippocampus, amygdala, and medial temporal lobe. Several studies have demonstrated correlations between these

regional differences and other brain structures, including higher rates of basal forebrain atrophy in LP-AD compared with typical AD (Lagarde et al. 2023). Nonetheless, overlapping features were also observed. A retrospective cohort study identified volume reduction in the nucleus basalis of Meynert, an early marker of typical AD, as well as varying degrees of atrophy in the hippocampus, amygdala, and entorhinal cortex in both phenotypes (Nag et al. 2020).

Functional imaging studies have further demonstrated that global hypometabolism is more pronounced in LP-AD. In contrast, hypometabolism in typical AD, when present, appears to be more strongly associated with progression of dementia (Tondo et al. 2020). Additionally, a recent cohort study reported that patients with LATE-NC pathology exhibited lower R2 relaxation rates on MRI, particularly in advanced disease stages, affecting temporal, frontal, and occipital lobes, as well as the basal ganglia. The hippocampus, parahippocampal cortex, entorhinal cortex, and temporal lobes were the most severely affected regions (Machado et al. 2020; Agrawal et al. 2021). Consistent with these findings, two studies reported that larger hippocampal volume and higher cortical flortaucipir PET standardized uptake value ratios (SUVR) were associated with less severe limbic system impairment, while hippocampal sclerosis was more frequent in LATE-NC than in typical AD (Tondo et al. 2020; Boon et al. 2024).

Histological findings were highly heterogeneous across the included studies, limiting the ability to perform quantitative synthesis. Nevertheless, several consistent patterns emerged. LP-AD tended to be associated with arteriosclerosis, but showed a lower association with amyloid angiopathy (Woodworth et al. 2024). Although prior studies comparing AD and LATE-NC have demonstrated superior cognitive performance in LATE-NC patients, particularly on global cognitive tests such as the MMSE, this review did not identify significant differences in MMSE or CDR scores between LP-AD and typical AD (Pagnotti et al. 2023). This discrepancy may reflect the limited specificity of global cognitive scales or the fact that many studies were not designed to detect subtle neurocognitive differences between phenotypes.

When domain-specific cognitive tests were examined, LP-AD and LATE-NC patients demonstrated better performance on tasks assessing processing speed and executive function, particularly the Trail Making Test parts A (TMT-A) and B (TMT-B). These findings suggest that executive function measures may offer greater discriminatory power than global cognitive scales in distinguishing LP-AD from typical AD. Further studies employing comprehensive neuropsychological batteries are needed to clarify these distinctions.

Regarding biomarkers, amyloid pathology was consistently observed in both LP-AD and typical AD across studies, as demonstrated by amyloid PET imaging and postmortem amyloid staining (Persson et al. 2017; Machado et al. 2020; Levin et al. 2021; Carlos et al. 2023; Lagarde et al. 2023). Tau pathology was similarly present in both phenotypes and was confirmed by tau-PET imaging and Braak staging of neurofibrillary tangles (Agrawal et al. 2021; Boon et al. 2024). Other proteinopathies, including  $\alpha$ -synuclein and Lewy body pathology, were also identified in both groups, with no significant differences in prevalence (Mohanty et al. 2022; Carlos et al. 2023; Boon et al. 2024).

In contrast, TDP-43 pathology emerged as a key differentiating feature. Although TDP-43 inclusions can be present in typical AD, they were significantly more frequent and regionally concentrated in LP-AD, particularly within limbic

structures such as the hippocampus, amygdala, and entorhinal cortex (Nag et al. 2020; Agrawal et al. 2021; Mikhailenko et al. 2024; Boon et al. 2024). In typical AD, TDP-43 pathology tended to show a more diffuse cortical distribution. This differential pattern mirrors neuroimaging findings, in which LP-AD is characterized by medial temporal lobe atrophy and hypometabolism, whereas typical AD demonstrates widespread cortical involvement (Persson et al. 2017; Machado et al. 2020; Agrawal et al. 2021; Levin et al. 2021; Boon et al. 2024).

Taken together, the greater burden and limbic predominance of TDP-43 pathology, combined with distinct neuroimaging and histopathological patterns, support the hypothesis that LP-AD may represent a biologically distinct entity within the Alzheimer's disease spectrum, rather than a simple anatomical subtype of typical AD.

However, several important limitations should be acknowledged. First, this review is characterized by substantial clinical and methodological heterogeneity across the included studies. Considerable variability was observed in sample sizes, study designs, and the availability of longitudinal follow-up data, with several studies adopting only cross-sectional or postmortem approaches. In addition, diagnostic frameworks varied widely, encompassing neuropathological criteria (e.g., Braak staging, CERAD scores, ADNC), imaging-based classifications (structural MRI, FDG-PET, tau- and amyloid-PET), and biomarker-driven definitions (CSF and PET biomarkers). Similarly, heterogeneity in immunohistochemical techniques, targeted proteins (e.g., tau, amyloid- $\beta$ , TDP-43,  $\alpha$ -synuclein), and quantification methods further limited cross-study comparability. Cognitive outcomes were assessed using a wide range of scales and batteries, including global, domain-specific, and composite measures, contributing additional methodological variability.

Second, publication bias cannot be ruled out, as studies reporting clear phenotypic distinctions between limbic-predominant and typical Alzheimer's disease may be more likely to be published. Moreover, several studies were subject to potential confounding factors, including age at onset, disease duration, comorbid cerebrovascular pathology, and overlapping neurodegenerative processes such as LATE or Lewy body disease. Selective reporting of outcomes, particularly regarding imaging or neuropathological findings, may also have influenced the overall synthesis.

Third, no randomized controlled trials (RCTs) were included. This absence reflects the predominantly observational and neuropathological nature of the literature addressing Alzheimer's disease subtypes. However, it nonetheless limits causal inference and the ability to evaluate intervention effects across phenotypes. In addition, a meta-analysis was not performed. Although several studies reported quantitative outcomes, the marked heterogeneity in diagnostic criteria, outcome definitions, imaging modalities, and reporting formats precluded meaningful statistical pooling. They would have risked producing misleading summary estimates.

Finally, a major source of heterogeneity stems from the lack of standardized definitions and outcome measures for Alzheimer's disease subtypes. While most studies applied well-established criteria to diagnose Alzheimer's disease overall, subtype classification varied substantially across neuropathological, imaging-based, and biomarker-driven frameworks. Importantly, diagnostic labels such as limbic-predominant, typical, and related terms were not interchangeable across studies and often reflected modality-specific opera-

tional definitions. This variability limits direct comparability across studies and underscores the urgent need for harmonized diagnostic criteria and standardized outcome measures in future research.

## Conclusion

Our analysis of clinical, radiological, and immunohistological features revealed significant differences between LP and typical AD presentations. However, those findings alone cannot, with high accuracy, rule out the possibility that both presentations are stages of the same pathology or different diseases. More studies are needed to explore this topic further.

## Additional information

### Conflict of interest

The authors have declared that no competing interests exist.

### Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

### Use of AI

No use of AI was reported.

### Funding

No funding was reported.

### Author contributions

Conceptualization: GMNC, GLS. Data curation: GLS, LRL, ABC, MBC. Funding acquisition: GLS. Investigation: LGGC, MCMS, GLS. Methodology: LAO, MCMS, GLS. Supervision: GLS. Validation: MCMS, COC. Visualization: MBC, FHM, ABC. Writing – original draft: LAO, GLS, MCMS, FHM, LRL, LGGC, MBC, GMNC, ABC, COC. Writing – review and editing: MBC, LGGC, LAO, ABC, LRL, GMNC, FHM, COC, MCMS, GLS.

### Author ORCIDs

Guilherme Linha Secco  <https://orcid.org/0000-0001-8866-4546>

Lucas Ribas Lachman  <https://orcid.org/0009-0006-9146-1655>

Leticia Alves de Oliveira  <https://orcid.org/0009-0004-8199-3987>

Maisa Baldinu Caramujo  <https://orcid.org/0009-0005-3792-9301>

Lunna Giovanna Gonçalves Campos  <https://orcid.org/0009-0008-3598-5424>

Alana Barroso de Carvalho  <https://orcid.org/0009-0005-2833-9721>

Giovanna Moreira Nascimento de Castro  <https://orcid.org/0009-0007-2513-2543>

Fábio Henrique Malinoski  <https://orcid.org/0009-0000-9262-5822>

Caroline de Oliveira Christoff  <https://orcid.org/0009-0002-5364-2835>

Mateus Cordeiro Merlim da Silva  <https://orcid.org/0009-0001-4478-5175>

## Data availability

All of the data that support the findings of this study are available in the main text.

## References

- Agrawal S, Yu L, Nag S, Arfanakis K, Arfanakis K, Barnes LL, Bennett DA, Schneider JA (2021) The association of Lewy bodies with limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes and their role in cognition and Alzheimer's dementia in older persons. *Acta neuropathologica communications* 9: 156. <https://doi.org/10.1186/S40478-021-01260-0>
- Besser LM, Teylan MA, Nelson PT (2020) Limbic predominant age-related TDP-43 encephalopathy (LATE): clinical and neuropathological associations. *Journal of Neuro pathology & Experimental Neurology* 79: 305–313. <https://doi.org/10.1093/jnen/nlz126>
- Boon BD, Labuzan SA, Peng Z, Matchett BJ, Kouri N, Hinkle KM, Lachner C, Ross OA, Ertekin-Taner N, Carter RE, Ferman TJ (2023) Retrospective evaluation of neuropathologic proxies of the minimal atrophy subtype compared with corticolimbic Alzheimer disease subtypes. *Neurology* 101: 1412–23. <https://doi.org/10.1212/WNL.000000000207685>
- Boon BD, Frigerio I, de Gooijer D, Morrema TH, Bol J, Galis-de Graaf Y, Heymans M, Netherlands Brain Bank, Murray ME, Normal Aging Brain Collection Amsterdam, van der Lee SJ (2024) Alzheimer's disease clinical variants show distinct neuroinflammatory profiles with neuropathology. *Neuropathology and applied neurobiology* 50: 13009. <https://doi.org/10.1111/nan.13009>
- Carlos AF, Machulda MM, Rutledge MH, Nguyen AT, Reichard RR, Baker MC, Rademakers R, Dickson DW, Petersen RC, Josephs KA (2023) Comparison of clinical, genetic, and pathologic features of limbic and diffuse transactive response DNA-binding protein 43 pathology in Alzheimer's disease neuropathologic spectrum. *Journal of Alzheimer's disease* 93: 1521–1535. <https://doi.org/10.3233/JAD-221094>
- Corriveau-Lecavalier N, Botha H, Graff-Radford J, Switzer AR, Przybelski SA, Wiste HJ, Murray ME, Reichard RR, Dickson DW, Nguyen A, Ramanan V, McCarter SJ, Boeve B, Machulda MM, Fields JA, Stricker NS, Nelson PT, Grothe MJ, Knopman DS, Lowe AJ, Petersen RC, Jack CR, Jones DT (2023) A limbic-predominant amnestic neurodegenerative syndrome associated with TDP-43 pathology. *The preprint server for health sciences* 2023.11.19.23298314. <https://doi.org/10.1101/2023.11.19.23298314>
- Estades Ayuso V, Pickles S, Todd T, Yue M, Jansen-West K, Song Y, González Bejarano J, Rawlinson B, DeTure M, Graff-Radford NR, Boeve BF, Knopman DS, Petersen RC, Dickson DW, Josephs KA, Petrucelli L, Prudencio M (2023) TDP-43-regulated cryptic RNAs accumulate in Alzheimer's disease brains. *Molecular Neurodegeneration* 18: 57. <https://doi.org/10.1186/s13024-023-00646-z>
- Gauthreaux KM, Teylan MA, Katsumata Y, Mock C, Culhane JE, Chen YC, Chan KC, Fardo DW, Dugan AJ, Cykowski MD, Jicha GA (2022) Limbic-predominant age-related TDP-43 encephalopathy: medical and pathologic factors associated with comorbid hippocampal sclerosis. *Neurology* 98: 1422–1433. <https://doi.org/10.1212/WNL.000000000200001>

- Hiya S, Maldonado-Díaz C, Walker JM, Richardson TE (2023) Cognitive symptoms progress with limbic-predominant age-related TDP-43 encephalopathy stage and co-occurrence with Alzheimer disease. *Journal of Neuropathology and Experimental Neurology*. <https://doi.org/10.1093/jnen/nlad098>
- Kouri N, Frankenhauser I, Peng Z, Labuzan SA, Boon BD, Moloney CM, Pottier C, Wickland DP, Caetano-Anolles K, Corriveau-Lecavalier N, Tranovich JF (2024) Clinicopathologic heterogeneity and glial activation patterns in Alzheimer disease. *JAMA Neurology* 81: 619–629. <https://doi.org/10.1001/jamaneurol.2024.0784>
- Lagarde J, Olivieri P, Tonietto M, Lehericy S, Moussion M, Caillé F, Gervais P, Bottlaender M, Sarazin M (2023) In vivo MRI assessment of locus coeruleus and nucleus basalis of Meynert integrity in frontotemporal degeneration and corticobasal syndrome. *Alzheimer's & Dementia* 19(S17): e077310. <https://doi.org/10.1002/alz.077310>
- Levin F, Ferreira D, Lange C, Lange C, Dyrba M, Westman E, Buchert R, Teipel SJ, Grothe MJ, Alzheimer's Disease Neuroimaging Initiative (2021) Data-driven FDG-PET subtypes of Alzheimer's disease-related neurodegeneration. *Alzheimer's Research & Therapy* 13: 49. <https://doi.org/10.1186/S13195-021-00785-9>
- Machado A, Ferreira D, Grothe MJ, Eyjolfsdottir H, Almqvist P, Cavallin L, Lind G, Linderoth B, Seiger Å, Teipel SJ, Wahlberg L, Wahlund L-O, Westman E, Eriksson M, Alzheimer's Disease Neuroimaging Initiative (2020) The cholinergic system in subtypes of Alzheimer's disease: an in vivo longitudinal MRI study. *Alzheimer's Research & Therapy* 12: 51. <https://doi.org/10.1186/S13195-020-00620-7>
- Mikhailenko E, Colangelo K, Tuimala J, Kero M, Savola S, Raunio A, Kok E, Tanskanen M, Mäkelä M, Puttonen H, Mäyränpää MI, Kumar D, Kaivola K, Paetau A, Tienari P, Polvikoski T, Myllykangas L (2024) Limbic-predominant age-related TDP-43 encephalopathy in the oldest old: a population-based study. *Brain* 148: 154–167. <https://doi.org/10.1093/brain/awae212>
- Mohanty R, Ferreira D, Frerich S, Muehlboeck J-S, Grothe MJ, Westman E, Alzheimer's Disease Neuroimaging Initiative (2022) Neuropathologic features of antemortem atrophy-based subtypes of Alzheimer disease. *Neurology* 99: 323–333. <https://doi.org/10.1212/WNL.0000000000200573>
- Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International Journal of Surgery* 8: 336–341. <https://doi.org/10.1016/j.ijssu.2010.02.007>
- Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW (2011) Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. *Lancet Neurology* 10: 785–796. [https://doi.org/10.1016/S1474-4422\(11\)70156-9](https://doi.org/10.1016/S1474-4422(11)70156-9)
- Nag S, Barnes LL, Yu L, Wilson RS, Bennett DA, Schneider JA (2020) Limbic-predominant age-related TDP-43 encephalopathy in black and white decedents. *Neurology* 95: 2056–2064. <https://doi.org/10.1212/WNL.000000000010602>
- Nelson PT (2021) LATE neuropathologic changes with little or no Alzheimer disease is common and is associated with cognitive impairment but not frontotemporal dementia. *Journal of Neuropathology & Experimental Neurology* 80: 649–651. <https://doi.org/10.1093/jnen/nlab050>
- Pagnotti RB, Pudumjee SB, Cross CL, Miller JB (2023) Cognitive and clinical characteristics of patients with limbic-predominant age-related TDP-43 encephalopathy. *Neurology* 100: 2027–2035. <https://doi.org/10.1212/WNL.0000000000207159>
- Persson K, Eldholm RS, Barca ML, Cavallin L, Ferreira D, Knapkog AB, Selbæk G, Brækhus A, Saltvedt I, Westman E, Engedal K (2017) MRI-assessed atrophy subtypes in Alz-

- heimer's disease and the cognitive reserve hypothesis. PLOS ONE 12: e0186595. <https://doi.org/10.1371/JOURNAL.PONE.0186595>
- Robinson JL, Richardson H, Xie SX, Suh E, Van Deerlin VM, Alfaro B, Loh N, Porras-Paniagua M, Nirschl JJ, Wolk D, Lee VM (2021) The development and convergence of co-pathologies in Alzheimer's disease. *Brain* 144: 953–962. <https://doi.org/10.1093/brain/awaa438>
- Tazwar M, Evia AM, Tamhane AA, Ridwan AR, Leurgans SE, Bennett DA, Schneider JA, Arfanakis K (2022) Limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC) is associated with lower R2 relaxation rate: an ex-vivo MRI and pathology investigation. *Neurobiology of Aging* 117: 128–138. <https://doi.org/10.1016/j.neurobiolaging.2022.05.009>
- Tondo G, Carli G, Santangelo R, Mattoli MV, Presotto L, Filippi M, Magnani G, Iannaccone S, Cerami C, Perani D, Alzheimer's Disease Neuroimaging Initiative (2020) Biomarker-based stability in limbic-predominant amnesic mild cognitive impairment. *European Journal of Neurology* 28: 1123–1133. <https://doi.org/10.1111/ENE.14639>
- UpToDate (2024) Clinical features and diagnosis of Alzheimer disease. UpToDate.com. <https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-alzheimer-disease/print>
- Uretsky M, Gibbons LE, Mukherjee S, Trittschuh EH, Fardo DW, Boyle PA, Keene CD, Saykin AJ, Crane PK, Schneider JA, Mez J (2021) Longitudinal cognitive performance of Alzheimer's disease neuropathological subtypes. *Alzheimer's & Dementia* 7: e12201. <https://doi.org/10.1002/TRC2.12201>
- Woodworth DC, Nguyen KM, Sordo L, Scambray KA, Head E, Kawas CH, Corrada MM, Nelson PT, Sajjadi SA (2024) Comprehensive assessment of TDP-43 neuropathology data in the National Alzheimer's Coordinating Center database. *Acta Neuropathologica* 147: 103. <https://doi.org/10.1007/s00401-024-02728-8>