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Featured Article

Determining the impact of psychosis on rates of false-positive and false-negative diagnosis in Alzheimer's disease

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Abstract

Introduction: The rate of clinical misdiagnosis of Alzheimer's disease (AD) and how psychosis impacts that clinical judgment is unclear.

Methods: Using data from National Alzheimer's Coordinating Center, we compared the clinical and neuropathologic diagnosis in patients with a diagnosis of AD with autopsy and in neuropathology-confirmed AD cases (n = 961). We determined the rate of true positives, false positives, and false negatives in patients with and without psychosis.

Results: A total of 76% received a correct AD diagnosis, 11.9% had a false-negative diagnosis, and 12.1% had a false-positive diagnosis of AD. Psychotic patients had a higher rate of false-negative diagnosis and a lower rate of false-positive diagnosis of AD compared with nonpsychotic patients.

Discussion: Patients with psychosis were five times more likely to be misdiagnosed as dementia with Lewy bodies, whereas patients without psychosis were more likely to be falsely diagnosed with AD when vascular pathology is the underlying neuropathologic cause of dementia.

Keywords: Psychosis; Alzheimer's disease; Misdiagnosis; Neuropathology; Delusions; Hallucinations; Diagnosis

1. Introduction

Rates of misdiagnosis of Alzheimer's disease (AD) in general are uncertain. Patients may be erroneously diagnosed with AD during life (false positive) in the presence of high loads of other pathology such as cerebrovascular disease, Lewy bodies (LBs), and so forth. Conversely, AD may be missed if the

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clinical features resemble other forms of dementia such as frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and so forth (false negatives). Many factors may contribute to high rates of misdiagnosis, both in terms of false-positive and false-negative rates. It has been estimated based on prior studies that only 20% to 50% of patients with dementia ever receive an actual specific diagnosis [1]. Moreover, several studies indicate that patients may be inaccurately given a diagnosis of AD when in fact based on postmortem analyses of brain tissue the actual diagnosis is that of vascular dementia (VaD) [2,3] or dementia with LBs [3–5]. On the basis of the analyses of data from the National Alzheimer's Coordinating Center (NACC) database, it has been estimated that sensitivity rates for an AD diagnosis are in the range of 71% to 87% whereas specificity rates range from 44% to 71%, leaving much to be desired [6]. How psychosis impacts rates of misdiagnosis is not clear. One could speculate the association of psychosis with alternative pathologies, mainly DLB, but also cerebrovascular disease might contribute to high rates of misdiagnosis. Alternatively, it is possible that psychosis is more strongly associated with other forms of pathology, such as tau. There is an emerging literature suggesting this may be the case [7,8].

Although psychotic symptoms occur in AD, they are observed more frequently in other forms of dementia, such as Parkinson's disease–related dementia, DLB, and VaD [9,10]. Conversely, the prevalence of psychosis in other forms of dementia, such as FTD, tends to be quite low [11]. One of the challenges related to identifying the prevalence of psychosis in various forms of dementia is that most studies to date have relied on clinical diagnosis when making such assertions, as opposed to cohorts that are neuropathologically verified. This may lead to erroneous assumptions. A second challenge is that many patients have overlapping pathologies at autopsy, thus making it more challenging to identify prevalence rates for different etiologies of dementia.

In our previous article [12] we established that psychosis in neuropathologically confirmed AD was not statistically significantly associated with increase in Alzheimer pathology load (i.e., plaques and tangles), but this finding was not replicated in patients with clinically attributed AD. One potential reason for the discrepancy may relate to high rates of misdiagnosis among patients with clinically attributed AD, specifically in patients without psychosis.

Misdiagnosis of AD has significant implications for clinical care as patients may not receive appropriate treatment and this may impact clinical outcomes. For example, treatment with existing cholinesterase inhibitors has shown some effectiveness in AD [13] but limited effectiveness in other forms of dementia such as VaD [14] or FTD [15]. With the advent of new disease-modifying therapies that may be specific to the etiology of dementia, this issue is likely to become more important in the years to come. There are increasing studies showing that correct conclusions are only reached when using autopsy-based neuropathologic diagnoses in research and not when clinical AD criteria are used [16,17]. The purpose of our article is to examine rates of misdiagnosis in AD patients with and without psychotic features using data from the NACC database. We predict based on the association of psychosis with overlapping pathologies such as LBs and cerebrovascular disease that psychosis will be associated with lower rates of false-positive diagnosis and higher rate of false-negative diagnosis.

2. Methods

2.1. Data source

We used data from the NACC Uniform Data Set and Neuropathology Data Set, collected between the September 2005 and May 2012 data freeze [18]. The data were pooled from 29 National Institute of Aging (NIA) Alzheimer's disease Centers in the United States that collect standardized clinical and pathologic data on participants with normal cognition, mild cognitive impairment, AD, and other dementias. Subjects were recruited from clinical referrals, self-referrals, community organizations, and volunteers. All subjects from NACC were followed approximately annually by the Alzheimer's disease Centers for as long as they are able to participate.

2.2. Participants

We included subjects who received a clinical diagnosis of probable AD [19] before death and who have neuropathologic data collected at autopsy, as well as subjects who met neuropathologic criteria for AD at autopsy, according to the NIA-Reagan Institute neuropathologic criteria [20] ($n = 961$). The clinical diagnosis stratified subjects as having "probable AD," "possible AD," or "not AD" (either another type of dementia or no dementia diagnosis). The neuropathologically diagnosis stratified subjects as having a "high likelihood of AD," "intermediate likelihood of AD," "low likelihood of AD," or "criteria not met". The demographic data are summarized in Table 1.

2.3. Misdiagnosis definitions

Subjects with both a clinical probable AD diagnosis and high likelihood of dementia due to AD on the NIA-Reagan Institute neuropathologic criteria were considered as having received a correct diagnosis, even if there are other coexisting pathologies (e.g., AD-VaD). Subjects with a clinical probable AD diagnosis but who did not meet the neuropathologic criteria for AD (i.e., low likelihood of AD or criteria not met) were considered false positives. All cases with a neuropathologic intermediate likelihood of AD were not included in the analyses. Subjects with a neuropathologic high likelihood of AD but who were not clinically diagnosed with probable AD were considered false negatives. A clinical diagnosis of possible AD has a much lower index of suspicion than probable AD in the eyes of clinicians. Therefore, it is debatable if possible AD with "high probability of AD" on neuropathology should be considered a correct diagnosis (specifically, a

Table 1
Demographic data of all participants, subdivided into psychosis group

Demographic variable	AD − P (n = 606)	AD + D (n = 173)	AD + H (n = 79)	AD + DH (n = 103)
Age of death	81.1 ± 10.0	80.5 ± 10.8	78.6 ± 9.9	78.8 ± 9.9
Age of cognitive decline	71.4 ± 10.1	70.3 ± 11.0	69.2 ± 9.4	68.6 ± 9.8
Race	89.9% White 4.6% Black 0.8% Asian 4.7% Hispanic	92.1% White 4.0% Black 0.6% Native Hawaiian/Pacific Islander 3.4% Hispanic	92.4% White 7.5% Black	81.2% White 9.9% Black 5.0% Asian 4.0% Hispanic
Gender	57.5% Male 42.5% Female	54.2% Male 45.8% Female	55.2% Male 44.8% Female	57.4% Male 42.6% Female
MMSE score at last clinical visit	14.3 ± 8.2	15.3 ± 7.2	10.8 ± 7.8	10.4 ± 6.4

Abbreviations: AD − P, never psychotic; AD + D, delusion-only psychosis; AD + H, hallucination-only psychosis; AD + DH, delusion and hallucination psychosis; MMSE, Mini–Mental State Examination.

false-negative diagnosis). Thus, we have included the results of both, if possible AD is considered an incorrect diagnosis (Table 2) as well as a correct diagnosis (Table 3).

The false-positive group was further examined to determine their correct neuropathologic diagnosis using the available fields in the NACC database, including assessment of LBs, vascular pathology, medial temporal lobe sclerosis, and FTD-related pathology. LB pathology was assessed with α-synuclein immunohistochemistry according to the DLB Consortium criteria [21], which categorizes subjects into those with no pathology, brainstem predominant, limbic, or neocortical LB pathology. Subjects who showed LBs in any region were considered to be positive for LBs.

A total of 1147 subjects from the NACC database met inclusion and exclusion criteria. Of these, 186 received a clinical diagnosis of AD and an intermediate likelihood of AD on neuropathology and were subsequently excluded from analysis, resulting in a current sample of 961. A total of 731 subjects received a correct clinical diagnosis of AD based on neuropathologic confirmation (i.e., probable AD clinical diagnosis and "definite AD" at autopsy). There were 116 (12.1%) subjects with a false-positive diagnosis of AD; 114 (11.9%) subjects with a false-negative diagnosis of AD if possible AD is considered an incorrect diagnosis; and 66 (6.9%) subjects with a false-negative diagnosis of AD if possible AD is considered a correct diagnosis. Rates of misdiagnosis within specific psychosis groups are shown in Tables 2 and 3. In Table 2, possible AD cases with a high likelihood of AD on neuropathology were considered false negatives, whereas in Table 3, possible AD cases were considered as having received a correct diagnosis.

2.4. Psychosis

Our sample was further categorized by their psychosis status. The presence of psychosis was determined using the delusion and hallucination items of the Neuropsychiatric Inventory Questionnaire (NPI-Q) completed by a study informant who responded "yes" to each item if the subject had demonstrated the symptom in the previous month and "no" if he/she had not. The NPI-Q is a validated measure for psychosis and has been extensively used in the literature [22]. Subjects with delusions indicated at any time over the course of follow-up were categorized as AD + D; subjects with hallucinations at any time were designated AD + H; and those with delusions and hallucinations (not necessarily on the same visit) were designated AD + DH. Never-psychotic subjects with neither delusions nor hallucinations at any time were designated as AD − P.

2.5. Statistical analysis

The rates of false positives versus false negatives between psychosis groups were compared using the Pearson chi-square test for categorical variables (Fisher exact test was used if a cell included less than five subjects). Post hoc pairwise comparisons were made if the overall comparison between all

Table 2
Rates of misdiagnosis between psychosis groups: possible AD considered incorrect diagnosis/false negatives

	Group											
Diagnosis	AD − P		AD + P		AD + D		AD + H		AD + DH		Total	
Correct diagnosis	447	73.8%	284	80.0%*	141	81.5%*	64	81.0%	79	76.7%*	731	76.1%
Incorrect diagnosis	159	26.2%	71	20.0%*	32	18.5%*	15	19.0%	24	23.3%*	230	23.9%
False negative	66	10.9%	48	13.5%	20	11.6%	11	13.9%	17	16.5%	114	11.9%
False positive	93	15.3%	23	6.5%†	12	6.9%†	4	5.1%*	7	6.8%*	116	12.1%
Total	606	63.1%	355	36.9%	173	18.0%	79	8.2%	103	10.7%	961	100%

Abbreviations: AD − P, never psychotic; AD + D, delusion-only psychosis; AD + H, hallucination-only psychosis; AD + DH, delusion and hallucination psychosis.

*$P < .05$ compared with AD − P.

†$P < .01$ compared with AD − P.

Table 3
Rates of misdiagnosis between psychosis groups: possible AD considered correct diagnosis

	Group											
Diagnosis	AD − P		AD + P		AD + D		AD + H		AD + DH		Total	
Correct diagnosis	487	80.4%	292	82.3%	146	84.4%	66	83.5%	80	77.7%	779	81.1%
Incorrect diagnosis	119	19.6%	63	17.8%	27	15.6%	13	16.5%	23	22.3%	182	18.9%
False negative	26	4.3%	40	11.3%*	15	8.7%*	9	11.4%*	16	15.5%*	66	6.9%
False positive	93	15.3%	23	6.5%*	12	6.9%*	4	5.1%†	7	6.8%†	116	12.1%
Total	606	63.1%	355	36.9%	173	18.0%	79	8.2%	103	10.7%	961	100%

Abbreviations: AD − P, never psychotic; AD + D, delusion-only psychosis; AD + H, hallucination-only psychosis; AD + DH, delusion and hallucination psychosis.
*$P < .01$ compared with AD − P.
†$P < .05$ compared with AD − P.

groups was significant. All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS), version 21. For all tests, significance was set at $P < .05$.

3. Results

3.1. Demographic

There were no significant demographic differences between AD − P and AD + D with respect to age of death, age of cognitive decline, sex, and Mini–Mental State Examination score. The AD + H and AD + DH groups had a significantly younger age of death ($U = 17{,}890.5$, $P = .032$; $U = 27{,}088.5$, $P = .012$, respectively) and a lower Mini–Mental State Examination score ($U = 6753.0$, $P = .011$; $U = 10{,}961.5$, $P < .001$) compared with AD − P.

3.2. Overall rates of misdiagnosis

There was a significant difference in rates of misdiagnosis between psychosis groups, if possible AD is considered an incorrect diagnosis (χ^2=29.5, $P = .0003$; Table 2). Post hoc pairwise analysis showed that the AD + P, AD + D, and AD + DH groups had a higher proportion of correct diagnoses compared with AD − P ($P = .029$, $P = .037$, $P = .034$, respectively). Although AD + H had a higher proportion of correct diagnosis than AD − P, it was not statistically different ($P = .164$; Table 2). The proportion of false positives significantly differed between the psychosis groups. If possible AD is considered an incorrect diagnosis, the false-positive rate in the AD − P group (15.5%) was significantly higher than AD + P (6.5%, $P < .001$), AD + D (6.9%, $P = .006$), AD + H (6.8%, $P = .019$), and AD + DH (6.8%, $P = .019$) groups (Table 2, Fig. 1A). There were no significant differences in rates of false negatives between psychosis groups (Table 2).

If possible AD cases with high likelihood of AD on neuropathology is considered a correct diagnosis, there is no difference in the overall misdiagnosis rate between psychosis groups (Table 3, Fig. 1A). However, by parsing the type of misdiagnosis, we found that all psychotic groups had lower rates of false positives (Fig. 1B), but higher rates of false negatives (Fig. 1C), than AD − P (Table 3, Fig. 1).

3.3. False-positive cases by pathologic diagnosis

The pathologic substrates of the false positive cases organized by the presence and type of psychoses is presented in Table 4. The main finding is that vascular pathology is the main cause of misdiagnosis in the group without psychosis, whereas many patients with delusions and delusions plus hallucinations fall under a mixed group with the designation "other."

3.4. False-negative cases

The results for the false-negative group are presented in Table 5. The most common clinical diagnoses in subjects with a pathologic diagnosis of AD who did not manifest psychoses was possible AD, whereas the most common diagnoses in all three subgroups of psychoses was DLB.

4. Discussion

Most patients in the NACC database have been examined by clinicians with particular expertise in dementia, and the diagnosis rendered is the last one before death. Thus, the rates of misdiagnosis in our study should be considered to represent the minimum, reached under very favorable conditions. We compared rates of false-positive and false-negative diagnosis of AD in AD − P versus AD + P using data from the NACC database. We also examined rates of misdiagnosis in AD + D, AD + H, and AD + DH. As we had both clinical and neuropathologic data available to us, we were able calculate rates of false-positive and false-negative diagnoses in both groups. Consistent with our predictions, the presence of psychotic symptoms was associated with a lower false positive diagnosis of AD and a higher false negative diagnosis of AD. Our findings are also consistent with the findings from our previous study [12]. In that article, we demonstrated that high rates of misdiagnosis in the clinically diagnosed AD cohort likely explained the discrepancy in our findings between the clinically and neuropathologically diagnosed AD cohorts. In this study, we demonstrated higher rates of misdiagnosis among patients without psychosis—inclusion of these patients in the clinically diagnosed AD sample likely created a false impression that AD patients

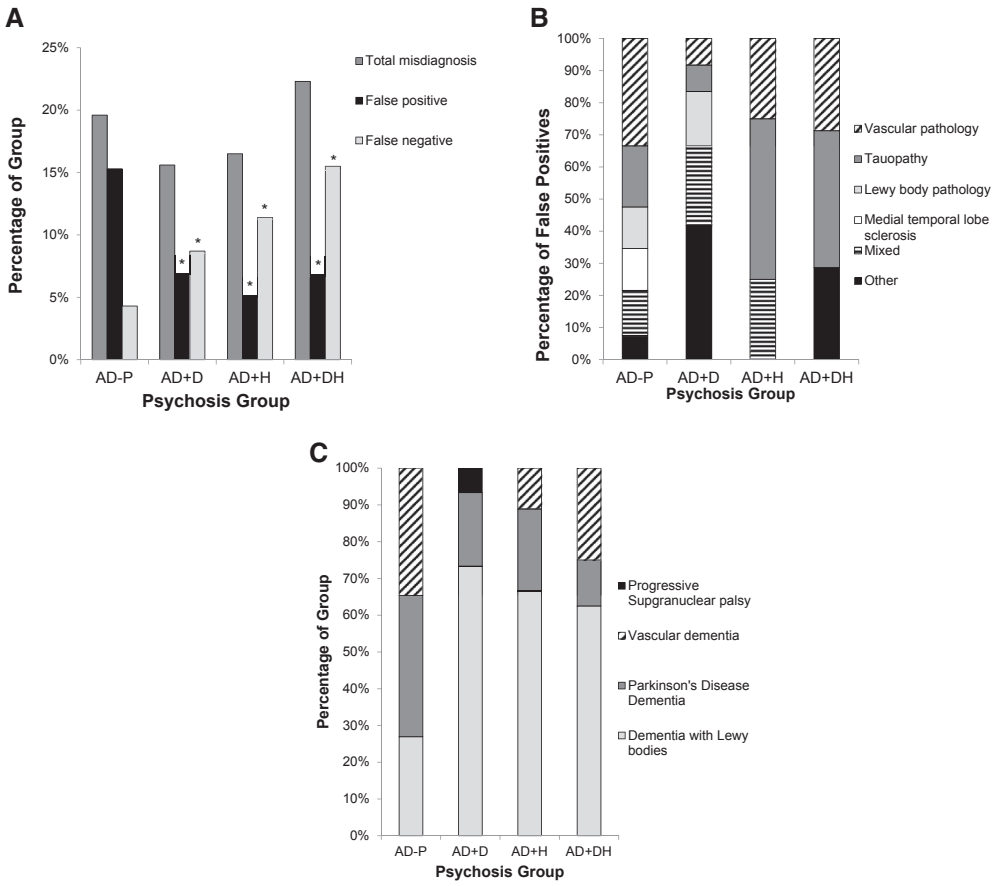

Fig. 1. (A) Rates of total misdiagnosis, false positives, and false negatives of Alzheimer's disease (AD) between psychosis groups. Probable AD and possible AD with neuropathologic evidence of AD are considered correct clinical diagnoses. Asterisk represents significance ($P < .05$) compared with AD − P. (B) Neuropathologic diagnoses of false-positive cases of AD, separated by psychosis group. (C) Clinical diagnoses of false-negative cases of AD, separated by psychosis group.

with psychosis were more likely to meet clinical criteria for neuropathologically verified AD.

The implications of our findings are significant. Psychosis is highly prevalent among VaD [10,12] and DLB [4,5] patients; as such clinicians may be more compelled to diagnose psychotic AD patients with these other forms of dementias. Our results showed that patients with a history of psychosis were more likely to be clinically misdiagnosed with other forms of dementias. Specifically, psychotic AD patients were five times more likely to be misdiagnosed with DLB than patients without psychosis, when there was clear neuropathologic evidence of AD. This suggests that in the presence of psychosis in a patient with progressive cognitive decline and no other clinical features suggestive of another

Table 4
Neuropathologic diagnosis of false-positive cases by psychosis group breakdown

	AD − P (n = 93)		AD + D (n = 12)		AD + H (n = 4)		AD + DH (n = 7)	
Neuropathologic diagnosis	n	%	n	%	n	%	n	%
Vascular	31	47.0	1	8.3	1	25.0	2	28.6
LB	12	18.2	2	16.7	0	0.0	0	0.0
Medial temporal lobe sclerosis	12	18.2	0	0.0	0	0.0	0	0.0
Tau	11	16.7	1	8.3	1	25.0	1	14.3
Mixed	13	19.7	3	25.0	1	25.0	0	0.0
FTD	7	10.6	0	0.0	1	25.0	2	28.6
FTD specific	3 PSP	3.2	0	0.0	1 FTD	25.0	1 PSP	14.3
	2 FTD	2.2						
	2 CBD	2.2					1 Pick's	14.3
Other	7	7.5	5	41.7	0	0.0	5	71.4

Abbreviations: AD − P, never psychotic; AD + D, delusion-only psychosis; AD + H, hallucination-only psychosis; AD + DH, delusion and hallucination psychosis; CBD, corticobasal degeneration; FTD, frontotemporal dementia; LB, Lewy body; Pick's, Pick's disease; PSP, progressive supranuclear palsy.

Table 5
Clinical diagnosis of false-negative cases by psychosis group breakdown

	AD − P (n = 66)		AD + D (n = 20)		AD + H (n = 11)		AD + DH (n = 17)	
Clinical diagnosis	n	%	n	%	n	%	n	%
Parkinson's dementia	10	15	3	15.0	2	18.2	2	11.8
VaD	9	13.6	0	0.0	1	9.1	4	23.5
DLB	7	10.6	11	55.0	6	54.5	10	58.8
Possible AD	40	60.1	5	25.0	2	18.2	1	5.9
PSP	0	0.0	1	5.0	0	0.0	0	0.0

Abbreviations: AD − P, never psychotic; AD + D, delusion-only psychosis; AD + H, hallucination-only psychosis; AD + DH, delusion and hallucination psychosis; DLB, dementia with Lewy bodies; PSP, progressive supranuclear palsy; VaD, vascular dementia.

form of dementia, a diagnosis of AD should be given more consideration, and existing symptomatic treatments, such as cholinesterase inhibitors, should be potentially prescribed. The issue of false-negative diagnosis has more important treatment implications as failure to diagnose AD clinically may lead to limited use of existing symptomatic treatments. There is existing rationale for intervening early with AD + P patients based on research to date. Studies have suggested that AD + P patients as a group have excess cognitive decline and progress much more rapidly than those without psychosis [23]. As well, psychosis is a common feature in AD, estimated to occur in as many as 50% of patients [23]. Recent studies have suggested in fact an incidence rate of 10% per year [24]. Thus, it is possible that the high prevalence of psychosis in AD may partially explain the observed findings. Recent research suggests that psychosis may be present in the very earliest stages of dementia, even at the mild cognitive impairment phase [25], and that its presence may be associated with increased risk of progression to AD [26]. Our research provides further support for the idea that psychosis may be a presenting feature of AD, given that its presence is more likely to be associated with a neuropathologic diagnosis of AD.

We also found that the absence of psychosis increased the false-positive diagnosis of AD when there is no neuropathologic evidence. The neuropathologic diagnoses driving the false positives differed between AD − P and AD + P groups. Although in the AD − P group false positivity was driven largely by missed vascular disease, in the AD + D group a neuropathologic diagnosis of other was the major driver. The other designation was given for unspecified pathology or when no major neuropathology was identified. Our findings of increased false positives in the nonpsychotic patients reflect that AD is overdiagnosed in this group to the detriment of VaD. Because expensive neuroimaging tools like magnetic resonance imaging are required to detect silent cerebrovascular disease and subcortical cerebrovascular disease, it is possible that many patients were scanned with computed tomography, which may not have detected these vascular brain changes. As a result, these patients were diagnosed with AD. Alternatively, the diagnostic criteria for VaD may be too stringent that clinicians opt for a diagnosis of AD instead.

Although the results of our study are informative, some limitations should be pointed out. The NPI-Q focuses on symptoms experienced in the last month; thus, it is possible that patients with psychosis may be missed if they did not display active symptoms in the past month. Most patients in the sample had moderate to advanced AD, so it is hard to know whether our findings could be extrapolated to patients with milder symptoms or preclinical disease. Moreover, we relied on neuropathologic and clinical assessments conducted at multiple sites throughout the United States, and while approaches were standardized, it is possible that there was some variability across sites in terms of diagnostic approaches, and so forth. Finally, although we looked at global neuropathologic measures, we did not consider regional specificity, which may be a limitation in AD + P patients given the established link with hypofrontality [27].

In conclusion, our research demonstrates that in patients with neuropathologically validated diagnosis of AD, those with psychosis are much more likely to be misdiagnosed with other forms of dementia. Specifically, psychotic patients were five times more likely to be diagnosed with DLB compared with patients without psychosis. Conversely, in the absence of psychosis, patients were more likely to be misdiagnosed as AD when no neuropathologic evidence of AD is present. The false positivity in nonpsychotic patients was driven largely by missed vascular disease. Our study raised concern that there may be an underappreciation of how common psychotic symptoms are in AD. Therefore, clinicians should be less hasty to diagnose a psychotic patient in the context of cognitive impairments with DLB and take more time to consider other causes when psychosis is not present.

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RESEARCH IN CONTEXT

1. Systematic review: Patients may be erroneously diagnosed with Alzheimer's disease (AD) during life if there are high rates of other pathology such as cerebrovascular disease, Lewy bodies, and so forth (false-positive diagnosis). Conversely, AD may be missed if the clinical features resemble other forms of dementia such as frontotemporal dementia, dementia with Lewy bodies, and so forth (false-negative diagnosis). Recent studies suggest that the rate of misdiagnosis in AD ranges from 12% to 23% in pathologically confirmed studies.
2. Interpretation: In our study, we investigated how the presence of psychosis impacts the rate of misdiagnosis of AD. In our large sample of patients with neuropathology data, we found the rate of misdiagnosis of 24%, which is slightly higher than these previously reported. An advantage of our study is that the final clinical diagnosis after years of follow-up is used. Therefore, the rate of misdiagnosis is under ideal conditions and should represent a minimum. Some limitations of previous studies include a smaller sample size, not following up patients longitudinally to assess their final clinical diagnosis, or not looking at the alternative diagnoses. Our study was also the first to examine how psychosis impacts rates of misdiagnosis. Consistent with our hypotheses, the presence of psychosis was associated with a higher rate of false-negative diagnosis of AD, but a lower rate of false-positive diagnosis of AD compared with nonpsychotic patients. Our findings suggest that clinicians are more reluctant to diagnose psychotic patients with AD when AD should have been the diagnosis, and instead often opting for dementia with Lewy bodies as a clinical diagnosis. When psychosis is not present, clinicians are more likely to falsely diagnose patients with AD when other neuropathologic causes, such as vascular pathology, are present. We concluded there may be an underappreciation of how common psychosis is in AD, which has important clinical implications.
3. Future directions: Future studies should investigate the neuropathological and imaging correlates of psychosis.

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