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Mortality in dementia with Lewy bodies compared to Alzheimer's dementia: a naturalistic cohort study

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ABSTRACT

Objectives: To use routine clinical data to investigate survival in dementia with Lewy bodies (DLB) compared with Alzheimer's dementia (AD).

DLB is the second most common dementia subtype after AD accounting for 1/13 dementia diagnoses in secondary care, though studies suggest that it is underdiagnosed by up to 50%. Most previous studies of DLB have been based on select research cohorts, so little is known about the naturalistic patterns, characteristics and outcomes of the disease in routine healthcare settings.

Setting: Cambridgeshire & Peterborough NHS Foundation Trust, a mental health Trust providing secondary mental health care in England.

Sample: 251 DLB and 222 AD cases identified from an anonymised database derived from electronic clinical case records across an eight year period (2005-2012), with mortality data updated to May 2015.

Results: The model-predicted median survival for DLB was 3.3 years for males and 4.0 years for females, while median survival for AD was 6.7 years for males and 7.0 years for females, controlling for age, sex, physical comorbidity, and antipsychotic prescribing.

Conclusion: Survival was markedly shorter in DLB compared with AD, independent of age, sex, physical comorbidity, or antipsychotic prescribing. This finding, in one of the largest clinical cohorts of DLB cases assembled to date, adds to existing evidence for poorer survival for DLB vs AD. There is an urgent need for further research to understand possible mechanisms accounting for this finding.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large clinical cohort of DLB cases
- Naturalistic study design reflecting clinical conditions
- Cases identified by treating clinician diagnosis; therefore undiagnosed/wrongly diagnosed cases may have been missed
- Possibility of bias introduced by secondary care study setting

INTRODUCTION

Background/rationale

Dementia with Lewy bodies (DLB) accounts for 7.5% of dementia cases in secondary care, according to clinic-based prevalence studies (1), though other studies have suggested that DLB is underdiagnosed, with up to 50% of cases missed. (2)

Health services in the UK National Health Service (NHS) comprise primary care (provided in general practice settings), secondary care (specialist care including outpatient services such as memory clinics and inpatient services such as acute psychiatric wards), and tertiary care (subspecialist care provided in selected centres). In UK practice, new dementia diagnoses are usually made by clinicians working in secondary care, most commonly old-age psychiatrists and neurologists. There is no clear demarcation between which specialties diagnose which dementia subtypes, and new diagnoses are made in a range of secondary care settings.

Compared to Alzheimer's disease (AD), studies have suggested that DLB cases have accelerated cognitive decline, more cormorbid conditions, a higher mortality rate, greater service use, and poorer quality of life. (3-7) Until recently it was generally accepted that DLB was more common in males than females, though recent studies have challenged this. (1)

Most previous studies of DLB have been based on select research cohorts, so less is known about the naturalistic patterns, characteristics and outcomes of the disease in routine clinical settings, though recent studies have used dementia registry and population data to examine subtype specific mortality and comorbidity patterns. (6)

The emergence of electronic case records and the technology to make these records searchable gives the potential to bring together larger patient cohorts in order to study clinical populations that are otherwise difficult to identify. Routine clinical data can now be used to track referral and diagnostic patterns in order to characterise diagnostic trends better and to use these data to inform development of dementia services.

Objectives

This study aimed to identify a naturalistic cohort of patients with a diagnosis of DLB within a secondary care sample, describe their demographic and clinical characteristics, determine the temporal trend in diagnosis rate, and measure survival, using as a comparator group a cohort of patients with AD diagnosed over the same time period.

METHODS

Study design

A naturalistic cohort design was used. The cohort was identified from the electronic clinical records of Cambridge and Peterborough NHS Foundation Trust (CPFT), which provides secondary mental health care to a local population of approximately 900,000 people in the UK.

CPFT's electronic records from 2005-2012 were de-identified using Case Records Interactive Search (CRIS) software (8) into a research database (UK NHS National Research Ethics Service reference 12/EE/0407). This process removes identifying information such as names and addresses from the records and assigns an arbitrary patient-specific research identifier. Such anonymised electronic

records methods have been successfully used in secondary mental health care to examine areas such as mortality (9, 10) and incidence of treatment complications.(11)

Data entered onto the system by CPFT clinicians (mental health specialists including doctors, nurses, allied health specialities and social workers) related only to patients currently under the care of secondary mental health services, though they may have been cared for in a number of settings (e.g. outpatient clinics, inpatient units, and in the community). Some data entered onto the clinical system were recorded in a systematic and structured way (e.g. date of birth), whilst others were recorded as required clinically and in free text (e.g. contemporaneous case records, cognitive scores, medical history). Frequency of data entry was guided by clinical necessity and not further specified. The corresponding research database therefore contains some structured data fields (including demographic variables and diagnosis if coded) but the majority of clinical information was found within free-text fields.

Population

All patients with electronic clinical records in CPFT between 2005 and 2012 (inclusive) were eligible for inclusion in the study.

Study sample

All patients with a clinician-recorded diagnosis of DLB within this timeframe were included, with a comparator cohort of patients with a clinician-recorded diagnosis of AD (sampled randomly from all possible such patients; see below).

Dementia diagnoses in CPFT were made by psychiatrists specialising in old-age psychiatry.

Case identification

Key word, phrase and acronym searches based on the diagnosis of DLB (e.g. 'Lewy', 'LBD', 'DLB') were applied to the full dataset. Unique document identifiers containing these key words were extracted, with surrounding text containing the key word, phrase or acronym. The same process was repeated for AD. Only records in which the key words or phrases appeared in the initial search were examined further.

An initial manual scan of the extracted text fragments excluded definite non-cases (e.g. 'does not have Lewy body dementia'). For the remaining documents, a manual search of the anonymised patient record related to that document was performed.

Manual case identification was then carried out on the records identified by experienced clinicians (AP and VM), with knowledge of both diagnostic criteria (12, 13) and symptom presentation in dementia. Cases were positively identified if a diagnosis had been given by a CPFT clinician and it was the most recently recorded diagnosis in the patient record (i.e. not later changed to another diagnosis that excluded the diagnosis of interest). Any cases thought to be incorrectly diagnosed on scrutiny of the clinical record were not included in the final study cohorts.

Variables

Once cases had been positively identified, demographic, clinical and temporal data were extracted from the corresponding anonymised case record. Basic demographic data (e.g. date of birth and gender) were extracted automatically using SQL (Structured Query Language) queries, and clinical data were extracted by clinicians manually by searching the anonymised case records.

Cognitive status was measured using the Mini-Mental State Examination (MMSE).(14) The MMSE score recorded closest to recorded diagnosis was taken as the MMSE score at diagnosis.

We recorded the date of the first consultation where cognitive impairment was recorded as a problem, and the date of diagnosis, thereby calculating time from presentation with cognitive impairment to diagnosis.

Physical comorbidy was measured using the Charlson comorbidity index. (15) We calculated the score that best reflected the physical comorbidities documented in the patient record at the time of diagnosis. All cases were assigned at least a score of 1 due to their dementia diagnosis.

Antipsychotic prescribing was recorded as present if any such drugs were documented as being prescribed at any time in the clinical record. Antidementia drug prescribing was recorded as present if the patient had received such a drug (cholinesterase inhibitor or memantine) and continued to take it beyond the initiation phase. Parkinson's disease drug prescribing (dopamine precursor or agonist) was recorded as present if documented at any time in the clinical record.

Mortality data in the database were derived from automatic updates of the source clinical records from the NHS Spine (16), providing mortality data including for patients who were discharged from the service before death. The study end date was May 2015.

Statistical methods

Baseline demographic and clinical data were analysed using Microsoft's Excel Analysis Toolpak. Within each diagnostic group, we calculated the sex ratio, mean age at diagnosis, mean MMSE at diagnosis, proportions of patients prescribed antipsychotic and antidementia medications, and proportions of those with high vs low comorbidity scores on the Charlson index. Continuous variables were compared between the two diagnostic groups using t-tests; binary variables were compared using χ^2 tests.

We analysed survival data using the Cox proportional hazards model, with R version 3.3.0 (17) and the "survival" package. We defined each patient's start time as the date (month/year) that they presented with cognitive impairment. If this was not known then the date of diagnosis was used instead. The end time was either the date of death, or the study end time for surviving patients (May 2015, the data set's most recent update of NHS spine mortality data).

Baseline differences in potential predictors between the AD and DLB groups were tested for individually using analysis of variance (for continuous variables) or χ^2 tests (for binary variables).

Survival was predicted using discrete factors of diagnosis (AD versus DLB), sex, physical comorbidity (dichotomized as: "low" Charlson score <=2 versus "high" score of >2), and antipsychotic prescribing at any time (yes/no). The "diagnosis" predictor was allowed to interact with each of the other binary predictors (but interactions between sex, comorbidity, and antipsychotic prescribing were not included). Age was included as a continuous covariate (not interacting with other predictors). Data are displayed using survival (Kaplan-Meier) plots.

Patient involvement

Patients were not involved directly in this study and patient level data was not identifiable due to the anonymisation process. The authors worked closely with a CPFT dementia patient and carer advisory group who advised on research priorities and agenda setting during the project.

RESULTS

Sample

The initial text word search in the DLB case identification process yielded 2276 separate clinical documents (e.g. clinic letters) pertaining to 983 unique patient records. Manual searching of these records excluding non-cases yielded a total of 304 individual cases in the database. Over the 8 year study period (2005-2012) there were 251 new diagnoses of DLB made within CPFT.

For the AD group the initial text search yielded 21,424 unique clinical documents pertaining to 7442 unique patient records. If a similar case-finding ratio is assumed then there would be approximately 2304 cases of AD in the database in total. Data were gathered for 254 randomly selected cases of AD for comparison (approximately 10% of expected total cases). Of these, 222 were newly diagnosed between 2005-2012, and these were used as the comparator group.

Main results

In the DLB cohort there was an overall year-on-year increase in new diagnoses across the 8-year study period. An upward trend in annual diagnoses was also found in the AD group.

There were no differences between the DLB and AD groups in mean age at presentation with cognitive impairment or diagnosis, mean MMSE at diagnosis, physical comorbidity burden at diagnosis or antidementia drug prescribing. There was, however, a significantly higher proportion of females in the AD compared with the DLB group. The male/female ratio was almost equal in the DLB cohort. There were also significant differences between groups in antipsychotic prescribing and Parkinson's drug prescribing, both being higher in the DLB group (see Table 1).

Survival analysis

Median survival for DLB was significantly shorter in the DLB group compared with the AD group, both for males DLB: 1299 days (43.3 months) [95% CI 1186-1511] vs AD: 2360 days (78.7 months) [CI 1980-2967] and females DLB: 1391 days (46.4 months) [CI 1226-1643] vs AD:2566 days (85.5 months) [CI 2163-3190].

The difference in survival was not explained by any differences in sex, age, comorbidity burden, or antipsychotic prescribing. In the overall model, there was a large effect of diagnosis (hazard ratio [HR] 3.04 for DLB versus AD, $Z = 5.2$, $p = 2 \times 10^{-7}$). As expected, there was an effect of age (HR of 1.062 for every year older; $Z = 6.77$, $p = 1.3 \times 10^{-11}$), though ages were not different between the diagnostic groups (Table 1) and the effect of diagnosis was found over and above the effect of age.

There was no main effect of sex ($Z = 0.50$, NS) and no interaction between diagnosis and sex ($Z = 0.95$, NS). There was an effect of comorbidity that interacted with diagnosis ($Z = -2.17$, $p = 0.030$), but this effect was only seen in the AD group (sub-analysis for AD with sex, antipsychotic prescribing, comorbidity, and age as predictors: effect of comorbidity, HR 1.8291, $Z = 2.86$, $p = 0.0043$) and not in the DLB group (similar analysis; $Z = 0.18$, NS). The effect of antipsychotic prescribing did not reach significance, either as a main effect (HR 1.60, $Z = 1.94$, $p = 0.053$) or as an interaction with diagnosis

(Z = −1.85, p = 0.065), though the trend was for a numerically greater adverse effect of antipsychotics in AD (subgroup analysis as before, HR = 1.60, Z = 1.92, p = 0.055) than in DLB (HR = 0.94, Z = −0.37, p = 0.71).

Survival by diagnosis and sex is presented in Figure 2.

At global mean values for age at diagnosis (79.35 years), comorbidity (dichotomized frailty index 0.279), and antipsychotic prescribing (0.285), the model-predicted median survival for DLB was 1212 days (95% confidence interval [CI] 1052–1398 days) (3.3 years) for males and 1461 days (CI 1297–1826) (4.0 years) for females, while median survival for AD was 2436 days (CI 1924–3109) (6.7 years) for males and 2566 days (CI 2163–3190) (7.0 years) for females.

DISCUSSION

Key results

Survival was markedly poorer for the DLB cohort than the AD cohort. This difference was not explained by sex, stage of dementia or age at presentation, comorbidity burden or drug prescribing. There was a non-significant trend towards increased mortality rates in those with AD prescribed antipsychotics, with no suggestion of such an effect in DLB. It may be that antipsychotics are prescribed only to those with more severe behavioural or psychological symptoms in AD, and these symptoms themselves predict poorer outcomes, or there may be a differential impact of antipsychotics on mortality in the two dementias. This direction of effect was surprising given the increased sensitivity to neuroleptic medication in patients with DLB and Parkinson's disease dementia.

Comorbidity burden was specifically associated with mortality in the AD group only, raising the possibility that managing physical comorbidities may have a more pronounced impact on survival for people with AD than those with DLB.

This study further strengthens the findings from a number of studies that survival is poorer in DLB than AD, though in our cohort this finding was not accounted for by other factors measured, including physical comorbidity burden, suggesting that there may be an intrinsically higher rate of mortality in DLB than AD.

Further work is needed both to examine factors associated with this excess mortality in DLB in other cohorts, so that high risk subjects can be identified, and to elucidate potential mechanisms that may underpin this increase, to inform intervention studies.

Strengths

Clinical information was extracted from the electronic case records by experienced clinicians, to a clear protocol, using accepted diagnostic criteria. The advantage of identifying a large naturalistic sample is that the characteristics of the sample are reflective of a clinical population. The identification of a cohort of AD cases in the same service during the same time frame allowed for comparisons to be made under similar clinical conditions.

Limitations

Cases were primarily identified as DLB or AD in the study if they were assigned the diagnosis by the treating clinician. We attempted to minimise misclassification by removing diagnosed cases that, on

the basis of the clinical documentation, did not appear to fulfil diagnostic criteria for the dementia subtype. It is possible, though, that a small number of cases were misclassified and, if a prospective case identification strategy had been used these cases would have been assigned a different dementia subtype diagnosis. We were also not able to extract consistent data on the temporal onset of core DLB features. It is therefore possible that a subset of patients with more advanced AD were misclassified as having DLB based on core symptom profile. Using our methodological approach we were not able to identify patients who would have fulfilled criteria for DLB but had not been diagnosed with the condition as our search strategy relied upon text terms associated with the diagnostic descriptions.

The cohorts analysed in this study were selected based on their diagnoses being given within a specified time frame and were not more specifically matched, though every attempt was made to minimise bias in identification of the comparator cohort, and subsequent analysis found few significant differences in demographic and clinical characteristics. It is possible, though that the study outcome would have been different if a more robust matching strategy had been employed.

The study sample comprised two diagnostic groups over a specified time period in a secondary mental health care setting. It is possible that the findings of the study do not reflect the total populations with these diagnoses. Diagnosis in a secondary care setting may reflect greater symptom severity, for example, though in the UK the great majority of new diagnoses of dementia (and subsequent initiation of treatment) are currently made in secondary care following GP or specialist referral.

The mean MMSE at diagnosis for both groups was in the moderate range of severity of cognitive impairment, with similar standard deviations. The study findings may be limited by not identifying patients at earlier stages of disease, though patients referred into secondary care (especially to community mental health teams) are likely to be referred with functional decline or other related difficulty which will usually occur beyond the earliest stages of disease.

The retrospective nature of the study meant that accurate estimation of timing of symptom onset was not possible, limiting our ability to report duration of illness accurately. To minimise any bias introduced by differential timing of diagnoses between the groups (though there was no evidence in the baseline data to suggest this was the case) we based the survival analysis on date of first presentation with cognitive impairment, rather than date of diagnosis.

Interpretation

The underlying reason for the difference in mortality rates between the DLB and AD cohorts remains unclear, but this study adds to the existing evidence showing a higher mortality rate for DLB than AD, though not accounted for by other factors including comorbidity burden.

This study also adds to growing evidence that the male predominance of DLB shown in early epidemiological studies does not reflect the gender ratio in clinical populations: in our study, though the proportion of males was higher in DLB than AD, the male/female ratio was approximately equal within DLB.

Generalizability

The patient population served by CPFT comprises a wide range of geographical and socioeconomic environments. CPFT is a relatively small mental health Trust but because the methodology used identified a naturalistic clinical sample, it is likely that the cohorts identified are representative of a wider secondary care population with dementia. A number of other mental health Trusts are have or are developing the capability to use anonymised clinical records for research. The methodology used to identify the cohorts identified for this study could be repeated on these Trusts' clinical records and findings compared to determine whether our study's findings generalize across other clinical populations.

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CONTRIBUTORSHIP STATEMENT

JOB had the original idea for the study, AP and JOB designed the study. AP, RF, JMY and VM completed case identification and data extraction, AP and RC analysed the data. AP drafted the manuscript and all authors contributed to the finished manuscript. AP is guarantor.

COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

EXCLUSIVE LICENCE

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DATA SHARING STATEMENT

Data sharing: full dataset and statistical code [and/or] available from the corresponding author. Individual consent was not obtained but the presented data are anonymised and risk of identification is low.

TRANSPARENCY DECLARATION

The lead author AP affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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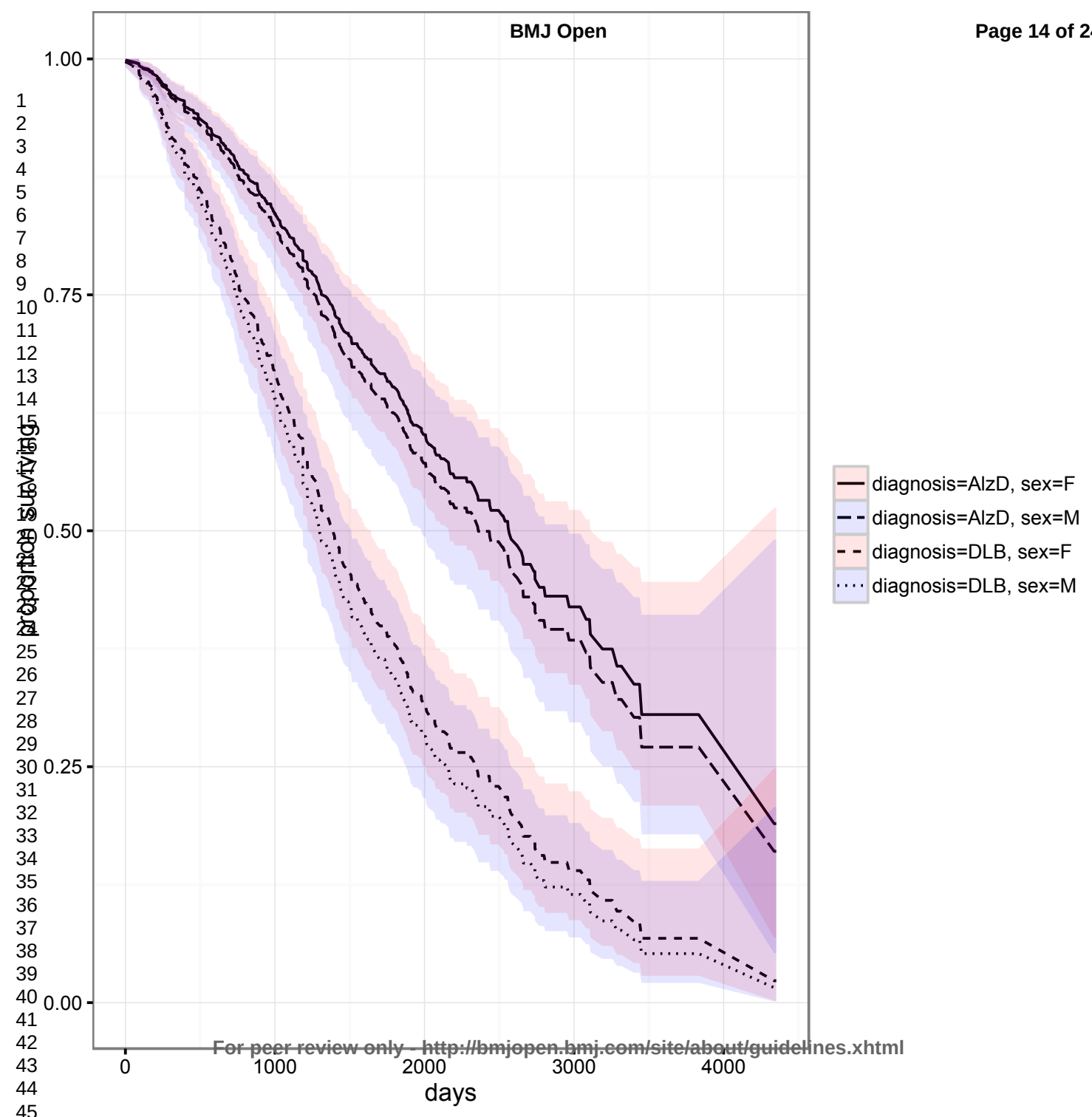
Table 1: Comparison of demographic and clinical data between DLB and AD cohorts

Characteristic	DLB (n=251)	AD (n=222)	χ^2 or *t* test statistic	*P* value
Gender				
Female	129 (51.4%)	139 (62.6%)	$\chi^2_1 = 6.037$	0.014
Male	122 (48.6%)	83 (37.4%)		
Age at first presentation with cognitive impairment (years)	78.3 (SD 7.7)	79.5 (SD 8.8)	$t = 1.575$	0.116
Age at diagnosis (years)	78.8 (SD 7.6)	80.2 (SD 8.8)	$t = 1.814$	0.07
MMSE score at diagnosis	20.2 (SD 5.4) (n=182)	19.7 (SD 5.8) (n=172)	$t = 0.84$	0.40
Charlson comorbidity index at diagnosis				
Low comorbidity (score ≤2)	183 (72.9%)	158 (71.2%)	$\chi^2_1 = 0.177$	0.67
High comorbidity (score >2)	68 (27.1%)	64 (28.8%)		
Medications prescribed				
Antipsychotic (neuroleptic) drugs	103 (41.0%)	32 (14.4%)	$\chi^2_1 = 39.6$	<0.0001
Parkinson's disease drugs	93 (37.1%)	0 (0%)	$\chi^2_1 = 102.386$	<0.0001
Anti-dementia drugs	152 (60.6%)	139 (62.6%)	$\chi^2_1 = 0.21$	0.65



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3+4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3+4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3+4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4+5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	4+5

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4+5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6+7
		(*b*) Report category boundaries when continuous variables were categorized	6+7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6+7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6+7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7+8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

We thank the two reviewers for their very constructive and helpful comments and have acted on all of them. Most importantly we have extracted further data including comorbidity and prescribing data and completed a survival analysis showing a significant difference in survival not accounted for by demographic or clinical differences between the two cohorts.

To help us to make sure we addressed all of the comments and because several of the comments were similar between the two reviewers we have ordered them by section rather than by reviewer. We hope this is acceptable.

Responses to the comments have been made in bold.

The corresponding manuscript has been substantially revised since the last submission.

Reviewer: 1

Reviewer Name Tanis J. Ferman, PhD
Institution and Country Mayo Clinic
Jacksonville, FL
USA
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
This study uses a retrospective sample with abstracted clinical data from medical charts to estimate survival differences within a specified period of time between DLB and AD. It has a nice large cohort, and a major strength is that it includes a wide geographical catchment area. The authors present the interesting finding of an increase in the diagnosis of AD and DLB over the 8 year study period, and cite an increased awareness of dementia and a move towards earlier identification and intervention. The findings of a shorter survival in DLB compared to AD, is consistent with reports using referral cohorts. This paper is nicely written, but there are several issues that need to be addressed.

Reviewer: 2

Reviewer Name Seyed-Mohammad Fereshtehnejad
Institution and Country Karolinska Institutet, Stockholm, Sweden
Please state any competing interests or state 'None declared': None declared

Manuscript editing

Please be consistent with abbreviations. DLB refers to clinical diagnosis of DLB, while LBD refers to Lewy body disease and should be reserved for pathologic group differentiation.

Many thanks for pointing out this inconsistency. This has been corrected to consistently use the acronym DLB.

Intro

It is unclear what 1/13 dementia diagnoses means.

The authors state that "DLB is poorly characterized", but this is an overstatement and misrepresents the gains that have been made over the years in improved diagnostic accuracy of DLB. This statement should be modified.

In many settings, vascular dementia has been found to be second most common type of dementia among the elderly after Alzheimer's disease, therefore, the statement on the importance of dementia with Lewy bodies (DLB) as the second most common subtype is better to be smoothed.

Thank you for the comments above-we have amended the manuscript introduction accordingly

There is at least another naturalistic cohort of a large number of patients with Lewy Body dementia or DLB, which is recommend being mentioned in both "Introduction" and "Discussion" sections. You can find the manuscript as described here:

Garcia-Ptacek S, Farahmand B, Kåreholt I, Religa D, Cuadrado ML, Eriksdotter M. Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15,209 patients based on the Swedish Dementia Registry. J Alzheimers Dis. 2014;41(2):467-77.

We apologise for this oversight and have duly cited this very relevant paper.

Methods

For readers who do not reside in the UK, it is not obvious what secondary care means or what the abbreviation NHS refers to. The authors need to better characterize the source of this sample. Does secondary care refer to hospital care or specialist clinic care? Along those lines, if the authors should identify who is doing the diagnosing and if possible, whether there is a difference in the medical specialty of who provides a diagnosis of DLB vs. AD.

We have attempted to clarify this point in the methods section

The most recently recorded diagnosis was used to identify cases, but the authors say that "manual case identification was carried out by experienced clinicians with knowledge of both diagnostic criteria and symptom presentation in dementia". Does this mean that those patients who did not have a diagnosis, were then reviewed manually and a diagnosis was given? This needs to be clarified.

We were only able to identify patients who had been given a clinician diagnosis already but were able to exclude cases where we judged the diagnosis to have been incorrect. We have amended the manuscript to clarify this.

More detailed information is needed to have a better picture of the database used in this research. Please describe comprehensively the answers to these questions in the revised "Methods" section:
We thank the reviewer for identifying these points of clarification and have sought to address each one in the methods section and also in the limitations section if relevant.

From which sources the data is entered into the Cambridge and Peterborough Foundation Mental Health Trust? Are all data collected from secondary specialist units or some were from primary care

units and/or even nursing homes?

Who have visited the patients referred to these settings? General physicians or specialists (either neurologists, geriatricians, psychiatrists)?

Which diagnostic criteria have been usually used for DLB and AD in each period of time in this database?

How is the cognitive status assessed in the cohort? How often is cognition reevaluated during the follow-ups?

Since the validity of diagnosis is of great importance in naturalistic databases, I wonder if there is any data available on the reassessment of DLB and AD diagnosis in the CPFT cohort? Is there any estimation on the validity of dementia diagnosis in this database?

Please clarify how often does the NHS Spine update mortality data for the selected participants?

It is necessary to explain how the matching procedure has been performed between the DLB and AD groups? Based on which variables were the two groups matched and how (baseline MMSE score, sex, age, date of diagnosis and disease duration are the necessary ones in my opinion)? Have you used the paired-matched method?

Please clarify in the "Methods" section that how the variable "time from presentation with cognitive impairment to diagnosis" has been defined? Is it the time lag between the first referral time to diagnosis or the date of first assessment? Or just a subjective question answered by the patients?

Results

Figure 2 is redundant and unnecessary.

Information in Figure 2 has been already mentioned in the text of the "Results" section and I recommend deletion of Figure 2.

This figure has been removed

Discussion

The authors should discuss the ascertainment bias inherent in this sample. In particular, a focus on how this secondary care sample is similar or different from specialty (dementia and movement disorder) referral samples and from community samples is needed. For example, referral samples tend

to include patients who are younger, more educated, and have greater access to health care, while community samples tend to include patients who are older, female and have a more advanced dementia at initial diagnosis.

A good proportion of patients were already in the middle to advanced stage of their dementia at initial diagnosis. Some discussion of this, in reference to your sample characterization and as a study limitation is needed.

Study limitations need to be better delineated. The potential for diagnostic misclassification given the retrospective nature of the study and reliance on clinician judgment instead of standardized assessment for dementia should be acknowledged. It may be worth noting that even if the DLB group has a subset of patients who are misclassified (and who really have AD), the results show that the presence of DLB core clinical features in dementia is associated with shorter survival time. Also, the authors briefly comment that physical comorbidity is one reason why physicians may avoid prescribing anti-dementia drugs. Another similar limitation that should be acknowledged is that frailty and other comorbidities associated with age (eg., vascular disease, medication side effects including anticholinergic load, etc.) were not assessed, but may also affect diagnosis and mortality.

Based on the above-mentioned recommendations, potential more relevant findings should be explained and interpreted in the revised "Discussion" section or the differences in survival time, survival rates and etc between the two groups.

The conclusion on the large difference in the mortality rate between DLB and AD groups could not be made prior to calculation and report of an appropriate effect size with 95% confidence interval (CI) such as odds' ratio, hazard ratio, mean difference in survival time, etc. Furthermore, any potential reason for the differences in outcome variables could be better interpreted and judged after multivariate analysis as mentioned previously. Please consider these issues to improve the "Discussion" and "Conclusion" sections.

As I mentioned in comment NO.2, there is at least another naturalistic cohort including quite a large number of DLB patients, which should be compared and discussed. Also I doubt if the statement on "To our knowledge this study has assembled the largest cohort of DLB cases to date" could be correct since the number of DLB patients in that cohort is >400 cases.

One potential reason for the worse mortality feature in DLB group might be the higher burden of comorbidities that have been recently shown (please see: Fereshtehnejad SM, Damangir S, Cermakova P, Aarsland D, Eriksdotter M, Religa D. Comorbidity profile in dementia with Lewy bodies versus Alzheimer's disease: a linkage study between the Swedish Dementia Registry and the Swedish National Patient Registry. Alzheimers Res Ther. 2014;6(5-8):65). I recommend adding some data on comorbidity profile from your own database if available and discuss this issue in the "Discussion" section, too.

Many thanks for these very helpful comments. The points raised have been incorporated into the discussion as suggested.

Data extraction

5. Education levels should be provided for each group. The presence of DLB core clinical features should also be provided for the AD group. If available, the temporal onset of the core DLB features should be included, since other studies have shown that VH, parkinsonism and fluctuations can occur in advanced AD. If this information is not attainable, then the caveat that a subset of AD patients with advanced dementia may have been misclassified as DLB if these core DLB symptoms occur later in the disease.

It was not possible to reliably extract education level from the dataset but this has been mentioned as a limitation, we have also stated as a limitation possible diagnostic misclassification.

The percentage of patients in each group (AD and DLB), taking cholinesterase inhibitors, anti-parkinson agents (levodopa-carbidopa, dopamine agonists), and neuroleptics would help to rule out the possibility that those patients taking neuroleptics, those exposed to dopamine agonists, or those who are treated for parkinsonism have a shorter survival time.

We have extracted this data and incorporated it into the analysis

Talking about the effect of medication in DLB patients, it is also necessary to report the features of dopaminergic treatments. Please provide information on this type of medication as well.
This has now been done

To make the data tables easier to read, I would suggest one column for the chi-square/t value, and one column for the p-value. In Table 1, the variable name "diagnosed 2005-2012", needs to be changed to a more descriptive term. Instead of gender ratio, provide females (%). Replace the "mean time presentation with cognitive impairment to diagnosis", with a duration of illness variable (death – estimated onset). Replace "died during study period" with death during study period (%), and just include the percentage without the whole number. There is no need to include the n for mean age of death and time to diagnosis of death, because you already have it listed in line above.

Table 1 has been updated with improved clarity in mind

Is there any data available on the comorbidity profile of the DLB and AD patients? There are some evidences showing that DLB patients have in general a higher burden of comorbidities, which might contribute in their higher mortality rate compared to the AD group.

Comorbidity data has been extracted and incorporated into the analysis

Data analysis

The estimated duration of illness (death – estimated dementia onset) should be calculated and used to compare groups. This may be used in lieu of the temporal interval of onset to diagnosis. because it theoretically removes the potential confound of differences in dementia stage at initial diagnosis.

We have used the date of first presentation with cognitive impairment as the most accurate time of onset we are able to gather from the database.

The statistical analysis used in this study does not seem to take advantage of the riches of this data. The sample is large enough to carry out a Kaplan Meier survival analysis which would allow the authors to directly compare the groups using time from diagnosis or time of estimated onset as the starting point, while co-varying age as a potential confound. This would provide a graph of the percentage survival for the two groups, which could be statistically compared. This would strengthen the impact of this paper. Consultation with a statistician to determine the best way to analyze this data may be helpful.

We have completed a survival analysis to May 2015 and include this in the manuscript. This should also address the further points made below.

I highly recommend using survival analysis, Kaplan-Meier method and Log Rank test to compare the time-to-death between the study groups. It provides more information comparing to just mortality rates. In addition, it is also recommended applying Cox regression model to calculate and report the hazard ratio (HR) for death in DLB patients compared to that of the AD group.

As I previously noted, it is necessary to perform time to death analysis by Kaplan-Meier and Cox regression method. Please perform these procedures and report the followings:

Tables 1 and 2 are just univariate comparisons that might have been influenced by many interactions and confounding biases. In addition, I recommend performing also multivariate comparisons with appropriate adjustments and calculation of hazard ratio (HR) for time to death and/or odd's ratio (OR) for mortality between the two subgroups in each table.

Other

Since the patients are not necessarily all the cases diagnosed during this period and especially the AD group has been randomly selected from a larger group, what is the usefulness of Figure 1? Instead, I recommend performing the matching procedure based on the year of diagnosis to reduce time bias between the two groups.

We have clarified how the cohorts were obtained in the methods section and discussed the lack of a more rigorous matching procedure in the limitations section.

BMJ Open

Mortality in dementia with Lewy bodies compared to Alzheimer's dementia: a retrospective naturalistic cohort study

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Mortality in dementia with Lewy bodies compared to Alzheimer's dementia: a retrospective naturalistic cohort study

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ABSTRACT

Objectives: To use routine clinical data to investigate survival in dementia with Lewy bodies (DLB) compared with Alzheimer's dementia (AD).

DLB is the second most common dementia subtype after AD accounting for around 7% dementia diagnoses in secondary care, though studies suggest that it is underdiagnosed by up to 50%. Most previous studies of DLB have been based on select research cohorts, so little is known about the outcome of the disease in routine healthcare settings.

Setting: Cambridgeshire & Peterborough NHS Foundation Trust, a mental health Trust providing secondary mental health care in England.

Sample: 251 DLB and 222 AD cases identified from an anonymised database derived from electronic clinical case records across an eight year period (2005-2012), with mortality data updated to May 2015.

Results:

Raw (uncorrected) median survival was 3.72 years for DLB [95%CI 3.33–4.14] and 6.95 years for AD [95%CI 5.78–8.12]

Controlling for age at diagnosis, comorbidity and antipsychotic prescribing the model-predicted median survival for DLB was 3.3 years [95% CI 2.88-3.83] for males and 4.0 years [95%CI 3.55-5.00] for females, while median survival for AD was 6.7 years [95%CI 5.27-8.51] for males and 7.0 years [95%CI 5.92-8.73] for females.

Conclusion: Survival from first presentation with cognitive impairment was markedly shorter in DLB compared with AD, independent of age, sex, physical comorbidity, or antipsychotic prescribing. This finding, in one of the largest clinical cohorts of DLB cases assembled to date, adds to existing evidence for poorer survival for DLB vs AD. There is an urgent need for further research to understand possible mechanisms accounting for this finding.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large clinical cohort of DLB cases
- Study design reflecting clinical conditions
- Cases identified by treating clinician diagnosis; therefore undiagnosed/wrongly diagnosed cases may have been missed
- Possibility of bias introduced by secondary care study setting

INTRODUCTION

Background/rationale

Dementia with Lewy bodies (DLB) accounts for around 7% of dementia cases in secondary care, according to clinic-based prevalence studies, (1) though other studies have suggested that DLB is underdiagnosed, with up to 50% of cases missed. (2)

Health services in the UK National Health Service (NHS) comprise primary care (provided in general practice settings), secondary care (specialist care including outpatient services such as memory clinics and inpatient services such as acute psychiatric wards), and tertiary care (subspecialist care provided in selected centres). In UK practice, new dementia diagnoses are usually made by clinicians working in secondary care, most commonly old-age psychiatrists and neurologists. There is no clear demarcation between which specialties diagnose which dementia subtypes, and new diagnoses are made in a range of secondary care settings.

Compared to Alzheimer's disease (AD), studies have suggested that DLB cases have accelerated cognitive decline, more comorbid conditions, a higher mortality rate, greater service use, and poorer quality of life. (3-8) Until recently it was generally accepted that DLB was more common in males than females, though recent studies have challenged this. (1)

Most previous studies of DLB have been based on select research cohorts, so less is known about the naturalistic patterns, characteristics and outcomes of the disease in routine clinical settings, though recent studies have used dementia registry and population data to examine subtype specific mortality and comorbidity patterns. (6, 8)

The emergence of electronic case records and the technology to make these records searchable gives the potential to bring together larger patient cohorts in order to study clinical populations that are otherwise difficult to identify. Routine clinical data can now be used to track referral and diagnostic patterns in order to characterise diagnostic trends better and to use these data to inform development of dementia services.

Objectives

This study aimed to identify a retrospective naturalistic cohort of patients with a diagnosis of DLB within a secondary care sample, describe their demographic and clinical characteristics, and measure survival, using as a comparator group a cohort of patients with AD diagnosed over the same time period.

METHODS

Study design

A retrospective cohort design was used. The cohort was identified from the electronic clinical records of Cambridge and Peterborough NHS Foundation Trust (CPFT), which provides secondary mental health care to a local population of approximately 900,000 people in the UK.

CPFT's electronic records from 2005-2012 were de-identified using Case Records Interactive Search (CRIS) software (9) into a research database. Ethical approval for this process was granted by the UK NHS National Research Ethics Service reference 12/EE/0407. There was also project specific NHS Institutional review. The de-identification process removes identifying information such as names

and addresses from the records and assigns an arbitrary patient-specific research identifier. Such anonymised electronic records methods have been successfully used in secondary mental health care to examine variables such as mortality (10, 11) and incidence of treatment complications.(12)

Data entered onto the system by CPFT clinicians (mental health specialists including doctors, nurses, allied health specialities and social workers) related only to patients currently under the care of secondary mental health services, though they may have been cared for in a number of settings (e.g. outpatient clinics, inpatient units, and in the community). Some data entered onto the clinical system were recorded in a systematic and structured way (e.g. date of birth), whilst others were recorded as required clinically and in free text (e.g. contemporaneous case records, cognitive scores, medical history). Frequency of data entry was guided by clinical necessity and not further specified. The corresponding research database therefore contains some structured data fields (including demographic variables and diagnosis if coded) but the majority of clinical information was found within free-text fields.

Population

All patients with electronic clinical records in CPFT between 2005 and 2012 (inclusive) were eligible for inclusion in the study. We chose not to include data prior to 2005 for reasons relating to implementation of electronic document storage.

Study sample

All patients with a clinician-recorded diagnosis of DLB within this timeframe were included, with a comparator cohort of patients with a clinician-recorded diagnosis of AD (sampled randomly from all possible such patients; see below).

Dementia diagnoses in CPFT were made by psychiatrists specialising in old-age psychiatry.

Case identification

Key word, phrase and acronym searches based on the diagnosis of DLB (e.g. ‘Lewy’, ‘LBD’, ‘DLB’) were applied to the full dataset. Unique document identifiers containing these key words were extracted, with surrounding text containing the key word, phrase or acronym. The same process was repeated for AD. Only records in which the key words or phrases appeared in the initial search were examined further.

An initial manual scan of the extracted text fragments excluded definite non-cases (e.g. ‘does not have Lewy body dementia’). For the remaining documents, a manual search of the anonymised patient record related to that document was performed.

Manual case identification was then carried out on the records identified by experienced clinicians (AP and VM), with knowledge of diagnostic criteria (13, 14) and symptom presentation in dementia. Cases were positively identified if a diagnosis had been given by a CPFT clinician and it was the most recently recorded diagnosis in the patient record (i.e. not later changed to another diagnosis that excluded the diagnosis of interest). Clinician-identified cases were then validated against diagnostic criteria for DLB and AD respectively.

Variables

Once cases had been positively identified, demographic, clinical and temporal data were extracted from the corresponding anonymised case record. Basic demographic data (e.g. date of birth and

gender) were extracted automatically using SQL (Structured Query Language) queries, and clinical data were extracted by clinicians manually by searching the anonymised case records.

Cognitive status was measured using the Mini-Mental State Examination (MMSE).(15) The MMSE score recorded closest to recorded diagnosis was taken as the MMSE score at diagnosis.

We recorded the date of the first consultation where cognitive impairment was recorded as a problem, and the date of diagnosis by month and year.

Physical comorbidy was measured using the Charlson comorbidity index. (16) This measure contains 19 categories of comorbidity and can be used to predict 10 year mortality for patients who have a range of comorbid conditions.(17) Each comorbid condition is assigned a score of 1, 2, 3 or 6 depending on the associated mortality risk, for example, metastatic cancer is assigned a score of 6. The Charlson score has been used in a previous study of comorbidity profile in DLB vs AD, though the scores used were not weighted by mortality risk. (6) We calculated the score that best reflected the physical comorbidities documented in the patient record at the time of diagnosis. All cases were assigned at least a score of 1 due to their dementia diagnosis as per the Charlson scoring algorithm.

Antipsychotic prescribing was recorded as present if any such drugs were documented as being prescribed at any time in the clinical record. Antidementia drug prescribing was recorded as present if the patient had received such a drug (cholinesterase inhibitor or memantine) and continued to take it beyond the initiation phase. Parkinson's disease drug prescribing (dopamine precursor or agonist) was recorded as present if documented at any time in the clinical record.

Mortality data in the database were derived from automatic updates of the source clinical records from the NHS Spine (18), providing mortality data including for patients who were discharged from the service before death. The study end date was May 2015.

Statistical methods

Baseline demographic and clinical data were analysed using Microsoft's Excel Analysis Toolpak. Within each diagnostic group, we calculated the sex ratio, mean age at diagnosis, mean MMSE at diagnosis, proportions of patients prescribed antipsychotic and antidementia medications, and proportions of those with high vs low comorbidity scores on the Charlson index. Continuous variables were compared between the two diagnostic groups using one way analysis of variance (ANOVA); binary variables were compared using χ^2 tests.

We analysed survival data using the Cox proportional hazards model, with R 3.3.0 (19) and the "survival" package. We defined each patient's start time as the date (month/year) that they presented with cognitive impairment. If this was not known then the date of diagnosis was used instead. The end time was either the date of death, or the study end time for surviving patients (May 2015, the data set's most recent update of NHS spine mortality data). Although dates of diagnosis were not included if before 2005, some records reported date of first presentation with cognitive impairment before 2005.

We tested for aseline differences in potential predictors between the AD and DLB groups using one-way ANOVA (for continuous variables) or χ^2 tests (for binary variables).

Survival was predicted using discrete factors of diagnosis (AD versus DLB), sex, physical comorbidity (dichotomized as: a "low" Charlson score of <=2 versus a "high" score of >2), and antipsychotic prescribing at any time (yes/no). The “diagnosis” predictor was allowed to interact with each of the other binary predictors (but interactions between sex, comorbidity, and antipsychotic prescribing were not included). Age was included as a continuous covariate (not interacting with other predictors). Data are displayed using survival (Kaplan-Meier) plots.

In addition to the full model (IC1 in Table 2), we tested a range of simpler models using the following predictors: (C1) diagnosis; (C2) diagnosis, age, and sex, with no interactions; (C3) diagnosis, age, sex, and frailty, with no interactions; (C4) diagnosis, age, sex, frailty, and antipsychotic prescribing, with no interactions. We compared sequential models using likelihood ratio tests to see if the addition of additional predictors was justified. We also tested an equivalent set of models (D1-D4 and ID1) using the time since diagnosis as the dependent variable, rather than the time since presentation with cognitive impairment, to see if the same pattern of results held.

Patient involvement

Patients were not involved directly in this study and patient level data was not identifiable due to the anonymisation process. The authors worked closely with a CPFT dementia patient and carer advisory group who advised on research priorities and agenda setting during the project.

RESULTS

Sample

The initial text word search in the DLB case identification process across the entire time period of the database yielded 2276 separate clinical documents (e.g. clinic letters) pertaining to 983 unique patient records. Manual searching of these records to exclude non-cases yielded a total of 304 individual cases in the database. Over the 8 year study period (2005-2012) there were 251 new diagnoses of DLB made within CPFT.

For the AD cohort the initial text search yielded 21,424 unique clinical documents pertaining to 7442 unique patient records. If a similar case-finding ratio is assumed then there would be approximately 2304 cases of AD in the database in total. Data were gathered for 254 randomly selected cases of AD for comparison (approximately 10% of expected total cases). Of these, 222 were newly diagnosed between 2005-2012, and these were used as the comparator group.

Main results

In the AD cohort 153 (69%) had been given a diagnosis of dementia in Alzheimer’s disease, 66 (30%) a diagnosis of atypical or mixed Alzheimer’s dementia and 3 (1%) a diagnosis of Alzheimer’s dementia with early onset. In the DLB cohort all the patients had been given a diagnosis of dementia with Lewy bodies (rather than a dementia in Parkinson’s disease or mixed DLB) diagnosis. We validated the clinician diagnosed DLB cases against standard diagnostic criteria and found that 244/251 (97%) had probable or possible DLB and of those 58% were probable and 39% were possible. All of the patients in the AD cohort met the diagnostic criteria for AD.

In the DLB cohort there was an overall year-on-year increase in new diagnoses across the 8-year study period. An upward trend in annual diagnoses was also found in the AD group.

There were no differences between the DLB and AD groups in mean age at presentation with cognitive impairment or diagnosis, mean MMSE at diagnosis, physical comorbidity burden at diagnosis or antidementia drug prescribing. There was, however, a significantly higher ratio of females to males in the AD compared with the DLB group. There were also significant differences between groups in antipsychotic prescribing and Parkinson's drug prescribing, both being higher in the DLB group (see Table 1).

Age at diagnosis did not differ significantly between groups (mean ± SD: AD 80.2 ± 8.8 years, n = 222; DLB 79.3 ± 7.6 years, n = 251) (one-way ANOVA, $F_{1,471} = 1.32$, $p = 0.25$). Age residuals deviated from a normal distribution (Shapiro–Wilk test, W = 0.968, $p = 1.33 \times 10^{-8}$) and a Q–Q plot showed that age exhibited some minor negative skew and was somewhat leptokurtic; ANOVA is robust to this situation .(20)

MMSE at diagnosis did not differ significantly between groups (mean ± SD: AD 20.6 ± 4.9, n = 172; DLB 20.1 ± 5.5, n = 183) (one-way ANOVA, $F < 1$, NS). MMSE residuals deviated from a normal distribution (Shapiro–Wilk test, W = 0.967, $p = 3.27 \times 10^{-7}$) and a Q–Q plot showed that MMSE also exhibited some minor negative skew, though the distribution was very close to mesokurtic (Pearson kurtosis 3.2); again, ANOVA is robust to this situation.(20)

Age at presentation with cognitive impairment was available for all DLB patients and 200/222 AD patients. There were no group differences (see Table 1). As for age at diagnosis, residuals for age at cognitive impairment deviated from a normal distribution (Shapiro–Wilk W = 0.969, $p < 0.001$) by being slightly negatively skewed (skew –0.77) and leptokurtic (Pearson kurtosis 4.29), to which ANOVA is robust. (20) In the survival analysis below, "age at presentation with cognitive impairment" is replaced with "age at diagnosis" for those subjects for which age at presentation with cognitive impairment was unavailable; see Methods.

Survival analysis

Median survival for DLB was significantly shorter in the DLB group compared with the AD group. Raw (uncorrected) median survival was 3.72 years for DLB [95%CI 3.33–4.14] and 6.95 years for AD [95%CI 5.78–8.12].For males, median survival in DLB was3.57 years [95% CI 3.24-4.14] and in AD 6.46 years [95% CI 5.42-8.12]. For females median survival in DLB was 3.81 years [95% CI 3.36-4.50] and in AD 7.03 years [95% CI 5.92-8.73].

The best fit model for survival from date of presentation with cognitive impairment included diagnosis, age, sex, frailty and neuroleptic prescribing with sex and diagnosis, frailty and diagnosis and neuroleptic prescribing and diagnosis included as interacting terms (see table 2) The difference in survival from time of presentation with cognitive impairment was not explained by any differences in sex, age, comorbidity burden, or antipsychotic prescribing. In the overall model, there was a large effect of diagnosis (hazard ratio [HR] 3.04 for DLB versus AD, $Z = 5.2$, $p < 0.001$). As expected, there was an effect of age (HR of 1.06 for every year older; $Z = 6.77$, $p < 0.001$), though ages were not different between the diagnostic groups (Table 1) and the effect of diagnosis was found over and above the effect of age.

There was no main effect of sex ($Z = 0.50$, NS) and no interaction between diagnosis and sex (Z = 0.95, NS). There was an effect of comorbidity that interacted with diagnosis ($Z = –2.17$, $p = 0.030$), but this effect was only seen in the AD group (sub-analysis for AD with sex, antipsychotic prescribing, comorbidity, and age as predictors: effect of comorbidity, HR 1.82, $Z = 2.86$, $p = 0.004$) and not in the

DLB group (similar analysis; $Z = 0.18$, NS). The effect of antipsychotic prescribing did not reach significance, either as a main effect (HR 1.60, $Z = 1.94$, $p = 0.053$) or as an interaction with diagnosis ($Z = -1.85$, $p = 0.065$), though the trend was for a numerically greater adverse effect of antipsychotics in AD (subgroup analysis as before, HR = 1.60, $Z = 1.92$, $p = 0.055$) than in DLB (HR = 0.94, $Z = -0.37$, $p = 0.71$).

Survival by diagnosis and sex is presented in Figure 1.

At the global mean values for age at diagnosis (79.4 years), comorbidity (dichotomized frailty index 0.279), and antipsychotic prescribing (0.285), the model-predicted median survival for DLB was 3.3 years [95% CI 2.88-3.83] for males and 4.0 years [95%CI 3.55-5.00] for females, while median survival for AD was 6.7 years [95%CI 5.27-8.51] for males and 7.0 years [95%CI 5.92-8.73] for females.

In order to ascertain if there was any bias introduced by choosing the start time as date of presentation with cognitive impairment rather than date of diagnosis, we repeated the survival analysis using date of diagnosis as the start time. We found few differences between the results of the two analyses (see table 2)

DISCUSSION

Key results

Survival was markedly poorer for the DLB cohort than the AD cohort. This difference was not explained by sex, stage of dementia or age at presentation, comorbidity burden or drug prescribing. Our study showed a differential survival between AD and DLB of around 3 years for both males and females with survival being shorter in males in both cohorts. In our study, men with DLB had the poorest survival numerically, followed by women with DLB, men with AD then women with AD ; however the sex differences were not significant in the full adjusted model (table 2). In contrast a previous study however a previous study (3) found women with DLB to have the poorest survival, followed by men with DLB, men with AD then women with AD. Previous studies have shown survival of 5.5-7.7 years from disease onset and 1.9-6.3 years from diagnosis. (7) Our findings are therefore in line with those from other mortality studies in DLB as the time of first presentation would be expected to be between symptom onset and diagnosis. Recent national data on dementia mortality in the Mental Health Minimum Data Set (MHMDS) shows a median survival of 3.5 years from diagnosis with cognitive impairment or dementia at 'moderate need' (not further defined) with shorter survival times when needs are high or very high . (21) This is somewhat surprising given that the mortality of the lowest needs group reported in the MHMDS sample is in line with the poorer surviving of our two cohorts. The MHMDS does not report the diagnostic breakdown of the population studied, nor does it report any adjustment for other potential confounders.

There was a non-significant trend towards increased mortality rates in those with AD prescribed antipsychotics, with no suggestion of such an effect in DLB. It may be that antipsychotics are prescribed only to those with more severe behavioural or psychological symptoms in AD, and these symptoms themselves predict poorer outcomes, or there may be a differential impact of antipsychotics on mortality in the two dementias. This direction of effect was surprising given the increased sensitivity to neuroleptic medication in patients with DLB and Parkinson's disease dementia. (22)

Comorbidity burden was specifically associated with mortality in the AD group only, which was surprising given that other studies have found that increased comorbidity burden is associated with increased risk of mortality in dementia including DLB in both a research cohort (3) and a whole population epidemiological study, (8) Three quarters of the patients in both of our cohorts had a Charlson comorbidity score of two or less, indicating dementia plus one other (lower risk) comorbidity. A previous study of comorbidity in DLB vs AD found a mean Charlson comorbidity score of 1.52 in DLB vs 1.33 in AD. (6) Although they did not count the dementia diagnosis in the scoring, the mean score was also quite low on average across the two study cohorts, though significantly higher in the DLB cohort. Unlike previous studies, our findings raise the possibility that managing physical comorbidities may have a more pronounced impact on survival for people with AD than those with DLB.

In our study we used a dichotomised comorbidy index of 'low' vs 'high' rather than the mean Charlson score, more detailed symptom profiles (3, 6) or number of prescribed medications. (8) Where finer grained physical comorbidity data have been included in analyses, resting tremor was the only single physical comorbidity related to survival and was found to be a protective factor. (3) When comorbidity profiles have been compared between DLB and AD cohorts, overall comorbidity burden has been shown to be higher in DLB with increased cerebrovascular comorbidity. (6)Unlike that study, where the DLB cohort had a worse overall health profile at diagnosis than the AD cohort, we found that at the time of diagnosis there was little difference between the two groups (though we were not able gather data to the same level of detail).

This study further strengthens the findings from a number of studies that survival is poorer in DLB than AD, though in our cohort this finding was not accounted for by other factors measured, including physical comorbidity burden, suggesting that there may be an intrinsically higher rate of mortality in DLB than AD.

Further work is needed both to examine factors associated with this excess mortality in DLB in this and other cohorts, so that high risk subjects can be identified, and to elucidate potential mechanisms that may underpin this increase, to inform intervention studies. A number of potential factors have been identified though often from small studies. These include clinical features such as the presence of autonomic symptoms and hallucinations, and pathological features such as increased cerebrospinal fluid (CSF) tau and apolipoprotein E4 (APOE4) .(7)

Strengths

Clinical information was extracted from the electronic case records by experienced clinicians, to a clear protocol, and validated against accepted diagnostic criteria. The advantage of identifying a large retrospective sample is that the characteristics of the sample are reflective of a clinical population. The identification of a cohort of AD cases in the same service during the same time frame allowed for comparisons to be made under similar clinical conditions.

Limitations

This study focused on identification of two clinically diagnosed dementia subtypes, dementia with Lewy bodies and a comparison group with Alzheimer's dementia, with a complete cohort of cases with DLB identified over an eight year period. Cases were primarily identified as DLB or AD in the study if they were assigned the diagnosis by the treating clinician and then validated against diagnostic criteria. It is possible, though, that a small number of cases were misclassified and, if a

prospective case identification strategy had been used these cases would have been assigned a different dementia subtype diagnosis. Low diagnostic accuracy (23) and comorbidity between DLB and AD in dementia (24) has previously been shown in pathological DLB cohorts. We were also not able to extract consistent data on the temporal onset of core DLB features. It is therefore possible that a subset of patients with more advanced AD were misclassified as having DLB based on the core symptom profile. Using our methodological approach, we were not able to identify patients who would have fulfilled criteria for DLB but had not been diagnosed with the condition as our search strategy relied upon text terms associated with the diagnostic descriptions. Given the limitations above, the difference between the two clinically diagnosed cohorts regarding survival is therefore more striking as one might expect the differences to be less marked given lower diagnostic accuracy in a clinical rather than pathologically diagnosed study sample.

The case note design meant that whilst we were able to capture data from a naturalistic cohort accessing secondary care, we were not able to ensure the completeness of data that might be acquired in a research sample. In particular we extracted the comorbidity data only from what we were able to gather from the patient record and we did not have a complete set of MMSE scores at diagnosis. In addition, we used MMSE as our primary measure of cognitive function, as this was the tool routinely used in clinical practice, but this would not have given a complete picture of cognitive dysfunction particularly in the DLB cohort.

The cohorts analysed in this study were selected based on their diagnoses being made within a specified time frame and were not more specifically matched, though every attempt was made to minimise bias in identification of the comparator cohort, and subsequent analysis found few significant differences in demographic and clinical characteristics. It is possible, though that the study outcome would have been different if a more robust matching strategy had been employed.

The study sample comprised two diagnostic groups over a specified time period in a secondary mental health care setting. It is possible that the findings of the study do not reflect the total populations with these diagnoses. Diagnosis in a secondary care setting may reflect greater symptom severity, for example, though in the UK the great majority of new diagnoses of dementia (and subsequent initiation of treatment) are currently made in secondary care following GP or specialist referral .(25)The mean MMSE at diagnosis for both groups was in the mild-to-moderate range of severity of cognitive impairment, with similar standard deviations. The study findings may be limited by not identifying patients at earlier stages of disease, though patients referred into secondary care (especially to community mental health teams) are likely to be referred with functional decline or other related difficulty which will usually occur beyond the earliest stages of disease. Previous studies of mortality in DLB have reported similar baseline mean MMSE scores. (6, 8)

The retrospective nature of the study meant that accurate estimation of timing of symptom onset was not possible, limiting our ability to report duration of illness accurately. To minimise any bias introduced by differential timing of diagnoses between the groups (though there was no evidence in the baseline data to suggest this was the case) we based the primary survival analysis on date of first presentation with cognitive impairment, rather than date of diagnosis, but reanalysis using date of diagnosis produced similar results.

Interpretation

The underlying reason for the difference in mortality rates between the DLB and AD cohorts remains unclear, but this study adds to the existing evidence showing a higher mortality rate for DLB than AD, though not accounted for by other factors including comorbidity burden.

Generalizability

CPFT is a relatively small mental health Trust but because the methodology used identified a naturalistic clinical sample, it is likely that the cohorts identified are representative of a wider secondary care population with dementia. A number of other mental health Trusts have or are developing the capability to use anonymised clinical records for research. The methodology used to identify the cohorts identified for this study could be repeated on these Trusts' clinical records and findings compared to determine whether our study's findings generalize across other clinical populations.

It was not possible to gather consistent or complete data on ethnicity, education level and level of deprivation. If we had been able to gather this data it may have been possible to discuss in more detail how the results of this study may be comparable with other dementia populations. Considering the CPFT patient population as a whole however, the Trust serves a fast growing, aging and diverse population with significant inequalities (26) which are likely to be reflected in our study cohort. FUNDING

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CONTRIBUTORSHIP STATEMENT

JOB had the original idea for the study. AP and JOB designed the study. AP, RF, JMY and VM completed case identification and data extraction. AP and RC analysed the data. AP drafted the manuscript and all authors contributed to the finished manuscript. AP is guarantor.

COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

EXCLUSIVE LICENCE

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DATA SHARING STATEMENT

Data sharing: full dataset and statistical code [and/or] available from the corresponding author. Individual consent was not obtained but the presented data are anonymised and aggregated.

TRANSPARENCY DECLARATION

The lead author AP affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Comparison of demographic and clinical data between DLB and AD cohorts

Characteristic	DLB (n=251)	AD (n=222)	χ^2 or *F* *test*statistic	*P* value
Gender				
Female	129 (51.4%)	139 (62.6%)	$\chi^2_1 = 6.04$	0.01
Male	122	83		
Age at first presentation with cognitive impairment (years)	78.8 (SD 7.7) (n=251)	79.5 (SD 8.8) (n=200)	$F_{1,449} = 2.51$	0.11
Age at diagnosis (years)	79.3 (SD 7.6)	80.2 (SD 8.8)	$F_{1,471} = 1.32$	0.25
MMSE score at diagnosis	20.1 (SD 5.5) (n=183)	20.6 (SD 4.9) (n=172)	$F_{1,353} < 1$	0.41
Charlson comorbidity index at diagnosis				
Low comorbidity (score ≤2)	183 (72.9%)	158 (71.2%)	$\chi^2_1 = 0.18$	0.67
High comorbidity (score >2)	68	64		
Medications prescribed				
Antipsychotic (neuroleptic) drugs	103 (41.0%)	32 (14.4%)	$\chi^2_1 = 39.6$	<0.0001
Parkinson's disease drugs	93 (37.1%)	0 (0%)	$\chi^2_1 = 102.39$	<0.0001
Anti-dementia drugs	152 (60.6%)	139 (62.6%)	$\chi^2_1 = 0.21$	0.65

Table 2: Survival Analysis Dementia in Lewy Bodies compared with Alzheimer's dementia.

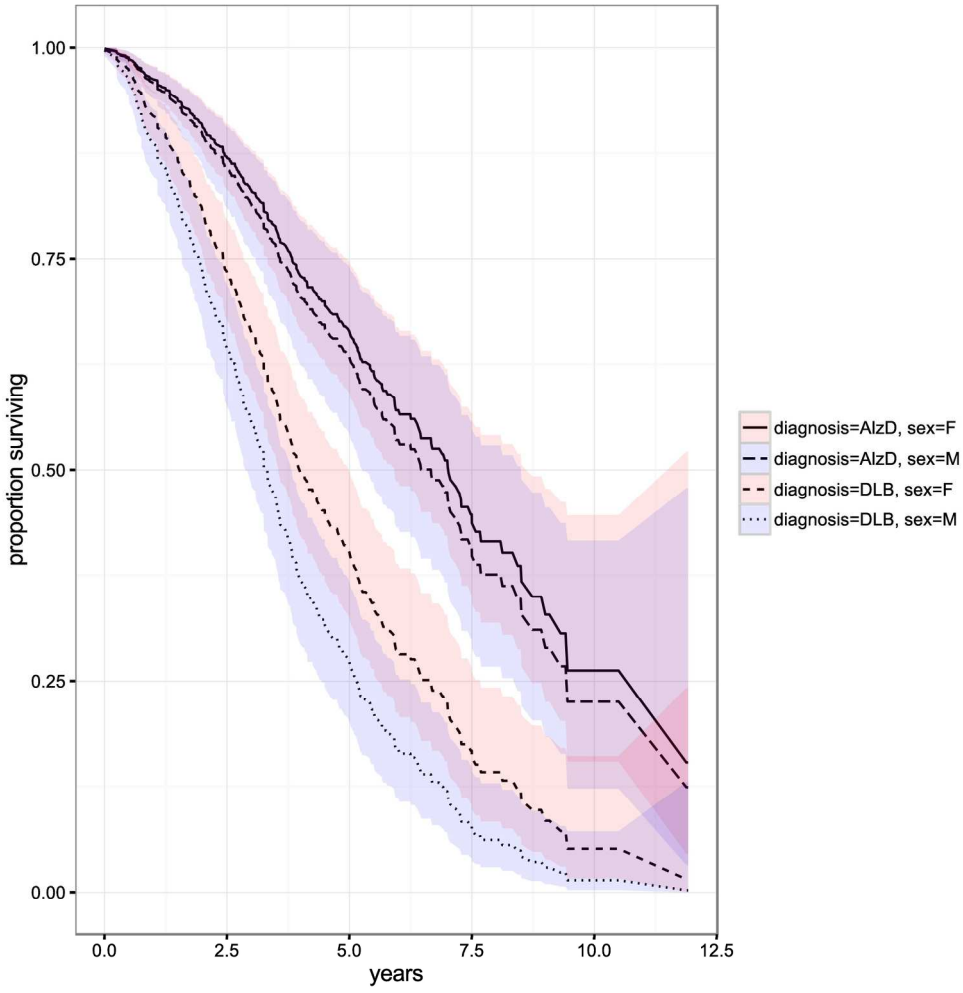
Family	Model	Dependent variable ~ Predictors	LL; LR test versus preceding model (unless stated)	HR with 95% CI for each predictor; corresponding *Z* test
		Group 1: using time since cognitive impairment		
C	C1	SCI ~ diagnosis	−1472.4; NA	diagnosis: HR 2.29 (1.78–2.94); $Z = 6.45$, $p = 1.1 \times 10^{-10}$ ***
	C2	SCI ~ diagnosis + age + sex	−1446.3; $\chi^2_2 = 52.3$, $p = 4.48 \times 10^{-12}$ ***	diagnosis: HR 2.48 (1.92–3.19); $Z = 7.01$, $p = 2.32 \times 10^{-12}$ *** age: HR 1.06 (1.04–1.08); $Z = 6.88$, $p = 5.85 \times 10^{-12}$ *** sex: HR 1.33 (1.04–1.70); $Z = 2.30$, $p = 0.0213$ *
	C3	SCI ~ diagnosis + age + sex + frailty	−1444.5; $\chi^2_1 = 3.58$, $p = 0.0585$; NS	–
	C4	SCI ~ diagnosis + age + sex + frailty + neuroleptics	−1444.3; $\chi^2_1 = 0.40$, $p = 0.526$; NS	–
IC	**IC1†**	**SCI ~ diagnosis + age + sex + sex×diagnosis + frailty + frailty×diagnosis + neuroleptics + neuroleptics×diagnosis**	**−1440.0; versus C2: $\chi^2_5 = 12.5$, $p = 0.0281$ ***	**diagnosis: HR 3.04 (2.00–4.63); $Z = 5.20$, $p = 2.04 \times 10^{-7}$ *** **age: HR 1.06 (1.04–1.08); $Z = 6.77$, $p = 1.33 \times 10^{-11}$ *** sex: HR 1.11 (0.73–1.69); $Z = 0.503$, $p = 0.615$; NS sex×diagnosis: HR 1.28 (0.769–2.14); $Z = 0.951$, $p = 0.341$ **frailty: HR 1.83 (1.21–2.75); $Z = 2.88$, $p = 0.00403$ **** **frailty×diagnosis: HR 0.558 (0.329–0.945); $Z = -2.17$, $p = 0.0301$ *** neuroleptics: HR 1.60 (0.994–2.58); $Z = 1.94$, $p = 0.0529$; NS neuroleptics×diagnosis: HR 0.587 (0.334–1.03); $Z = -1.85$, $p = 0.0646$; NS
		Group 2: using time since diagnosis		
D	D1	SDX ~ diagnosis	−1483.0; NA	diagnosis: HR 2.20 (1.71–2.82); $Z = 6.18$, $p = 6.59 \times 10^{-10}$ ***
	D2	SDX ~ diagnosis + age + sex	−1461.6; $\chi^2_2 = 42.8$, $p = 5.13 \times 10^{-10}$ ***	diagnosis: HR 2.31 (1.80–2.97); $Z = 6.54$, $p = 6.22 \times 10^{-11}$ *** age: HR 1.05 (1.04–1.07); $Z = 6.21$, $p = 5.34 \times 10^{-10}$ *** sex: HR 1.37 (1.07–1.75); $Z = 2.52$, $p = 0.0119$ *
	D3	SDX ~ diagnosis + age + sex + frailty	−1459.4; $\chi^2_1 = 4.47$, $p = 0.0346$ *	diagnosis: HR 2.30 (1.79–2.95); $Z = 6.49$, $p = 8.39 \times 10^{-11}$ *** age: HR 1.05 (1.03–1.07); $Z = 6.02$, $p = 1.73 \times 10^{-9}$ *** sex: HR 1.34 (1.05–1.72); $Z = 2.36$, $p = 0.0181$ * frailty: HR 1.32 (1.03–1.71); $Z = 2.15$, $p = 0.0316$ *
	D4	SDX ~ diagnosis + age + sex + frailty + neuroleptics	−1459.2; $\chi^2_1 = 0.34$, $p = 0.562$; NS	–
ID	ID1	SDX ~ diagnosis + age + sex + sex×diagnosis + frailty + frailty×diagnosis	−1453.5; versus D3: $\chi^2_4 = 11.8$, $p = 0.0186$ *	diagnosis: HR 2.93 (1.92–4.45); $Z = 5.01$, $p = 5.52 \times 10^{-7}$ *** age: HR 1.05 (1.04–1.07); $Z = 6.15$, $p = 7.92 \times 10^{-10}$ *** sex: HR 1.11 (0.73–1.69); $Z = 0.513$, $p = 0.608$; NS

		+ neuroleptics + neuroleptics×diagnosis		sex×diagnosis: HR 1.33 (0.799–2.21); $Z = 1.09$, $p = 0.274$; NS frailty: HR 1.87 (1.24–2.83); $Z = 2.98$, $p = 0.00287$ ** frailty×diagnosis: HR 0.559 (0.330–0.947); $Z = -2.16$, $p = 0.0307$ * neuroleptics: HR 1.82 (1.13–2.91); $Z = 2.48$, $p = 0.0133$ * neuroleptics×diagnosis: HR 0.492 (0.281–0.862); $Z = -2.48$, $p = 0.0131$ *

Table 2. Stepwise model comparisons. **SCI** survival time from presentation with cognitive impairment (or diagnosis if not known); **SDX** survival time from diagnosis; **LL** log-likelihood; **LR** likelihood ratio; **NA** not applicable; **NS** not significant; **HR** hazard ratio (exponentiated model coefficient); **CI** confidence interval; * $p < .05$; ** $p < .01$; *** $p < .001$; † overall preferred model. Times and ages are calculated in years. The effect for 'diagnosis' is that of Lewy body dementia (versus Alzheimer's disease); that for 'sex' is maleness (versus femaleness); 'frailty' is the dichotomized Charlson frailty index. 'Age' is, throughout, the age at presentation with cognitive impairment.

Figure 1: Survival in dementia with Lewy bodies versus Alzheimer's dementia

Bands indicate 95% confidence intervals for the cumulative hazard.



Survival in Dementia with Lewy bodies versus Alzheimer's dementia

200x200mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3+4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3+4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3+4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4+5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	4+5

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4+5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6+7
		(*b*) Report category boundaries when continuous variables were categorized	6+7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6+7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6+7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7+8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Mortality in dementia with Lewy bodies compared to Alzheimer's dementia: a retrospective naturalistic cohort study

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ABSTRACT

Objectives: To use routine clinical data to investigate survival in dementia with Lewy bodies (DLB) compared with Alzheimer's dementia (AD).

DLB is the second most common dementia subtype after AD, accounting for around 7% of dementia diagnoses in secondary care, though studies suggest that it is underdiagnosed by up to 50%. Most previous studies of DLB have been based on select research cohorts, so little is known about the outcome of the disease in routine healthcare settings.

Setting: Cambridgeshire & Peterborough NHS Foundation Trust, a mental health Trust providing secondary mental health care in England.

Sample: 251 DLB and 222 AD cases identified from an anonymised database derived from electronic clinical case records across an eight year period (2005-2012), with mortality data updated to May 2015.

Results:

Raw (uncorrected) median survival was 3.72 years for DLB [95%CI 3.33–4.14] and 6.95 years for AD [95%CI 5.78–8.12]

Controlling for age at diagnosis, comorbidity and antipsychotic prescribing the model-predicted median survival for DLB was 3.3 years [95% CI 2.88-3.83] for males and 4.0 years [95%CI 3.55-5.00] for females, while median survival for AD was 6.7 years [95%CI 5.27-8.51] for males and 7.0 years [95%CI 5.92-8.73] for females.

Conclusion: Survival from first presentation with cognitive impairment was markedly shorter in DLB compared with AD, independent of age, sex, physical comorbidity, or antipsychotic prescribing. This finding, in one of the largest clinical cohorts of DLB cases assembled to date, adds to existing evidence for poorer survival for DLB vs. AD. There is an urgent need for further research to understand possible mechanisms accounting for this finding.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Large clinical cohort of DLB cases
- Study design reflecting clinical conditions
- Cases identified by treating clinician diagnosis; therefore undiagnosed/wrongly diagnosed cases may have been missed
- Possibility of bias introduced by secondary care study setting

INTRODUCTION

Background/rationale

Dementia with Lewy bodies (DLB) accounts for around 7% of dementia cases in secondary care according to clinic-based prevalence studies, (1) though other studies have suggested that DLB is underdiagnosed, with up to 50% of cases missed. (2)

Health services in the UK National Health Service (NHS) comprise primary care (provided in general practice settings), secondary care (specialist care including outpatient services such as memory clinics and inpatient services such as acute psychiatric wards), and tertiary care (subspecialist care provided in selected centres). In UK practice new dementia diagnoses are usually made by clinicians working in secondary care, most commonly old-age psychiatrists and neurologists. There is no clear demarcation between which specialties diagnose which dementia subtypes, and new diagnoses are made in a range of secondary care settings.

Compared to Alzheimer's disease (AD), studies have suggested that DLB cases have accelerated cognitive decline, more comorbid conditions, a higher mortality rate, greater service use, and poorer quality of life. (3-8) Until recently it was generally accepted that DLB was more common in males than females, though recent studies have challenged this. (1)

Most previous studies of DLB have been based on select research cohorts, so less is known about the naturalistic patterns, characteristics and outcomes of the disease in routine clinical settings. More recent studies, however, have used dementia registry and population data to examine subtype specific mortality and comorbidity patterns. (6, 8)

The emergence of electronic case records and the technology to make these records searchable gives the potential to bring together larger patient cohorts in order to study clinical populations that are otherwise difficult to identify. Routine clinical data can now be used to track referral and diagnostic patterns in order to characterise diagnostic trends better and to use these data to inform development of dementia services.

Objectives

This study aimed to identify a retrospective naturalistic cohort of patients with a diagnosis of DLB within a secondary care sample, describe their demographic and clinical characteristics, and measure survival, using as a comparator group a cohort of patients with AD diagnosed over the same time period.

METHODS

Study design

A retrospective cohort design was used. The cohort was identified from the electronic clinical records of Cambridge and Peterborough NHS Foundation Trust (CPFT), which provides secondary mental health care to a local population of approximately 900,000 people in the UK.

CPFT's electronic records from 2005-2012 were de-identified using Case Records Interactive Search (CRIS) software (9) to create a research database. Ethical approval for this process was granted by the UK NHS National Research Ethics Service reference 12/EE/0407. There was also project specific NHS Institutional review. The de-identification process removes identifying information such as

names and addresses from the records and assigns an arbitrary patient-specific research identifier. Such anonymised electronic records methods have been successfully used in secondary mental health care to examine variables such as mortality (10, 11) and incidence of treatment complications.(12)

Data entered onto the system by CPFT clinicians (mental health specialists including doctors, nurses, allied health specialities and social workers) related only to patients currently under the care of secondary mental health services, though they may have been cared for in a number of settings (e.g. outpatient clinics, inpatient units, and in the community). Some data entered onto the clinical system were recorded in a systematic and structured way (e.g. date of birth), whilst others were recorded as required clinically and in free text (e.g. contemporaneous case records, cognitive scores, medical history). Frequency of data entry was guided by clinical necessity and not further specified. The corresponding research database therefore contains some structured data fields (including demographic variables and diagnosis if coded) but the majority of clinical information was found within free-text fields.

Population

All patients with electronic clinical records in CPFT between 2005 and 2012 (inclusive) were eligible for inclusion in the study. We chose not to include data prior to 2005 for reasons relating to implementation of electronic document storage.

Study sample

All patients with a clinician-recorded diagnosis of DLB within this timeframe were included, with a comparator cohort of patients with a clinician-recorded diagnosis of AD (sampled randomly from all possible such patients; see below).

Dementia diagnoses in CPFT were made by psychiatrists specialising in old-age psychiatry.

Case identification

Key word, phrase and acronym searches based on the diagnosis of DLB (e.g. 'Lewy', 'LBD', 'DLB') were applied to the full dataset. Unique document identifiers containing these key words were extracted, with surrounding text containing the key word, phrase or acronym. The same process was repeated for AD. Only records in which the key words or phrases appeared in the initial search were examined further.

An initial manual scan of the extracted text fragments excluded definite non-cases (e.g. 'does not have Lewy body dementia'). For the remaining documents, a manual search of the anonymised patient record related to that document was performed.

Manual case identification was then carried out on the records identified by experienced clinicians (AP and VM), with knowledge of diagnostic criteria (13, 14) and symptom presentation in dementia. Cases were positively identified if a diagnosis had been given by a CPFT clinician and it was the most recently recorded diagnosis in the patient record (i.e. not later changed to another diagnosis that excluded the diagnosis of interest). Clinician-identified cases were then validated against diagnostic criteria for DLB and AD respectively. (13, 14)

Variables

Once cases had been positively identified demographic, clinical and temporal data were extracted from the corresponding anonymised case record. Basic demographic data (e.g. date of birth and gender) were extracted automatically using SQL (Structured Query Language) queries, and clinical data were extracted by clinicians manually by searching the anonymised case records.

Cognitive status was measured using the Mini-Mental State Examination (MMSE).(15) The MMSE score closest to recorded diagnosis was taken as the MMSE score at diagnosis.

We recorded the date of the first consultation where cognitive impairment was recorded as a problem, and the date of diagnosis by month and year.

Physical comorbidy was measured using the Charlson comorbidity index. (16) This measure contains 19 categories of comorbidity and can be used to predict 10 year mortality for patients who have a range of comorbid conditions.(17) Each comorbid condition is assigned a score of 1, 2, 3 or 6 depending on the associated mortality risk; for example, metastatic cancer is assigned a score of 6. The Charlson score has been used in a previous study of comorbidity profile in DLB vs. AD, though the scores used were not weighted by mortality risk. (6) We calculated the score that best reflected the physical comorbidities documented in the patient record at the time of diagnosis. All cases were assigned at least a score of 1 due to their dementia diagnosis as per the Charlson scoring algorithm.

Antipsychotic prescribing was recorded as present if any such drugs were documented as being prescribed at any time in the clinical record. Antidementia drug prescribing was recorded as present if the patient had received such a drug (cholinesterase inhibitor or memantine) and continued to take it beyond the initiation phase. Parkinson's disease drug prescribing (dopamine precursor or agonist) was recorded as present if documented at any time in the clinical record.

Mortality data in the database were derived from automatic updates of the source clinical records from the NHS Spine (18), including data for patients who were discharged from the service before death. The study end date was May 2015.

Statistical methods

Baseline demographic and clinical data were analysed using Microsoft's Excel Analysis Toolpak. Within each diagnostic group, we calculated the sex ratio, mean age at diagnosis, mean MMSE at diagnosis, proportions of patients prescribed antipsychotic and antidementia medications, and proportions of those with high vs. low comorbidity scores on the Charlson index. Continuous variables were compared between the two diagnostic groups using one way analysis of variance (ANOVA); binary variables were compared using χ^2 tests. Results are presented in table 1.

We analysed survival data using the Cox proportional hazards model, with R 3.3.0 (19) and the "survival" package. We defined each patient's start time as the date (month/year) that they presented with cognitive impairment. If this was not known then the date of diagnosis was used instead. The end time was either the date of death, or the study end time for surviving patients (May 2015, the data set's most recent update of NHS spine mortality data). Although dates of diagnosis were not included if before 2005, some records reported date of first presentation with cognitive impairment before 2005.

We tested for baseline differences in potential predictors between the AD and DLB groups using one-way ANOVA (for continuous variables) or χ^2 tests (for binary variables).

Survival was predicted using discrete factors of diagnosis (AD versus DLB), sex, physical comorbidity (dichotomized as: a "low" Charlson score of <=2 versus a "high" score of >2), and antipsychotic prescribing at any time (yes/no). The “diagnosis” predictor was allowed to interact with each of the other binary predictors (but interactions between sex, comorbidity, and antipsychotic prescribing were not included). Age was included as a continuous covariate (not interacting with other predictors). Data are displayed using survival (Kaplan-Meier) plots.

In addition to the full model (IC1 in Table 2), we tested a range of simpler models using the following predictors: (C1) diagnosis; (C2) diagnosis, age, and sex, with no interactions; (C3) diagnosis, age, sex, and frailty, with no interactions; (C4) diagnosis, age, sex, frailty, and antipsychotic prescribing, with no interactions. We compared sequential models using likelihood ratio tests to see if the addition of additional predictors was justified. We also tested an equivalent set of models (D1-D4 and ID1) using the time since diagnosis as the dependent variable, rather than the time since presentation with cognitive impairment, to see if the same pattern of results held.

Patient involvement

Patients were not involved directly in this study and patient level data was not identifiable due to the anonymisation process. The authors worked closely with a CPFT dementia patient and carer advisory group who advised on research priorities and agenda setting during the project.

RESULTS

Sample

The initial text word search in the DLB case identification process across the entire time period of the database yielded 2276 separate clinical documents (e.g. clinic letters) pertaining to 983 unique patient records. Manual searching of these records to exclude non-cases yielded a total of 304 individual cases in the database. Over the 8 year study period (2005-2012) there were 251 new diagnoses of DLB made within CPFT.

For the AD cohort the initial text search yielded 21,424 unique clinical documents pertaining to 7442 unique patient records. If a similar case-finding ratio is assumed then there would be approximately 2304 cases of AD in the database in total. Data were gathered for 254 randomly selected cases of AD for comparison (approximately 10% of expected total cases). Of these, 222 were newly diagnosed between 2005-2012, and these were used as the comparator group.

Main results

In the AD cohort 153 (69%) had been given a diagnosis of dementia in Alzheimer’s disease, 66 (30%) a diagnosis of atypical or mixed Alzheimer’s dementia and 3 (1%) a diagnosis of Alzheimer’s dementia with early onset. In the DLB cohort all the patients had been given a diagnosis of dementia with Lewy bodies (rather than a dementia in Parkinson’s disease or mixed DLB) diagnosis. We validated the clinician diagnosed DLB cases against standard diagnostic criteria and found that 244/251 (97%) had probable or possible DLB and of those 58% were probable and 39% were possible. All of the patients in the AD cohort met the diagnostic criteria for AD.

In the DLB cohort there was an overall year-on-year increase in new diagnoses across the 8-year study period. An upward trend in annual diagnoses was also found in the AD group.

There were no differences between the DLB and AD groups in mean age at presentation with cognitive impairment or diagnosis, mean MMSE at diagnosis, physical comorbidity burden at diagnosis or antidementia drug prescribing. There was, however, a significantly higher ratio of females to males in the AD compared with the DLB group. There were also significant differences between groups in antipsychotic prescribing and Parkinson's drug prescribing, both being higher in the DLB group (see Table 1).

Age at diagnosis did not differ significantly between groups (mean ± SD: AD 80.2 ± 8.8 years, n = 222; DLB 79.3 ± 7.6 years, n = 251) (one-way ANOVA, $F_{1,471} = 1.32$, $p = 0.25$). Age residuals deviated from a normal distribution (Shapiro–Wilk test, W = 0.968, $p = 1.33 \times 10^{-8}$) and a Q–Q plot showed that age exhibited some minor negative skew and was somewhat leptokurtic; ANOVA is robust to this situation .(20)

MMSE at diagnosis did not differ significantly between groups (mean ± SD: AD 20.6 ± 4.9, n = 172; DLB 20.1 ± 5.5, n = 183) (one-way ANOVA, $F < 1$, NS). MMSE residuals deviated from a normal distribution (Shapiro–Wilk test, W = 0.967, $p = 3.27 \times 10^{-7}$) and a Q–Q plot showed that MMSE also exhibited some minor negative skew, though the distribution was very close to mesokurtic (Pearson kurtosis 3.2); again, ANOVA is robust to this situation.(20)

Age at presentation with cognitive impairment was available for all DLB patients and 200/222 AD patients. There were no group differences (see Table 1). As for age at diagnosis, residuals for age at cognitive impairment deviated from a normal distribution (Shapiro–Wilk W = 0.969, $p < 0.001$) by being slightly negatively skewed (skew –0.77) and leptokurtic (Pearson kurtosis 4.29), to which ANOVA is robust. (20) In the survival analysis below, "age at presentation with cognitive impairment" is replaced with "age at diagnosis" for those subjects for whom age at presentation with cognitive impairment was unavailable; see Methods.

Survival analysis

Median survival for DLB was significantly shorter in the DLB group compared with the AD group. Raw (uncorrected) median survival was 3.72 years for DLB [95%CI 3.33–4.14] and 6.95 years for AD [95%CI 5.78–8.12]. For males median survival in DLB was 3.57 years [95% CI 3.24-4.14] and in AD 6.46 years [95% CI 5.42-8.12]. For females median survival in DLB was 3.81 years [95% CI 3.36-4.50] and in AD 7.03 years [95% CI 5.92-8.73].

The best fit model for survival from date of presentation with cognitive impairment included diagnosis, age, sex, frailty and neuroleptic prescribing with sex and diagnosis, frailty and diagnosis and neuroleptic prescribing and diagnosis included as interacting terms (see table 2). The difference in survival from time of presentation with cognitive impairment was not explained by any differences in sex, age, comorbidity burden, or antipsychotic prescribing. In the overall model, there was a large effect of diagnosis (hazard ratio [HR] 3.04 for DLB versus AD, $Z = 5.2$, $p < 0.001$). As expected, there was an effect of age (HR of 1.06 for every year older; $Z = 6.77$, $p < 0.001$), though ages were not different between the diagnostic groups (Table 1) and the effect of diagnosis was found over and above the effect of age.

There was no main effect of sex (Z = 0.50, NS) and no interaction between diagnosis and sex (Z = 0.95, NS). There was an effect of comorbidity that interacted with diagnosis (Z = –2.17, p = 0.030), but this effect was only seen in the AD group (sub-analysis for AD with sex, antipsychotic prescribing, comorbidity, and age as predictors: effect of comorbidity, HR 1.82, Z = 2.86, p = 0.004) and not in the DLB group (similar analysis; Z = 0.18, NS). The effect of antipsychotic prescribing did not reach significance, either as a main effect (HR 1.60, Z = 1.94, p = 0.053) or as an interaction with diagnosis (Z = –1.85, p = 0.065), though the trend was for a numerically greater adverse effect of antipsychotics in AD (subgroup analysis as before, HR = 1.60, Z = 1.92, p = 0.055) than in DLB (HR = 0.94, Z = –0.37, p = 0.71).

Survival by diagnosis and sex is presented in Figure 1.

At the global mean values for age at diagnosis (79.4 years), comorbidity (dichotomized frailty index 0.279), and antipsychotic prescribing (0.285), the model-predicted median survival for DLB was 3.3 years [95% CI 2.88-3.83] for males and 4.0 years [95%CI 3.55-5.00] for females, while median survival for AD was 6.7 years [95%CI 5.27-8.51] for males and 7.0 years [95%CI 5.92-8.73] for females.

In order to ascertain if there was any bias introduced by choosing the start time as date of presentation with cognitive impairment rather than date of diagnosis, we repeated the survival analysis using date of diagnosis as the start time. We found few differences between the results of the two analyses (see table 2)

DISCUSSION

Key results

Survival was markedly poorer for the DLB cohort than the AD cohort. This difference was not explained by sex, stage of dementia or age at presentation, comorbidity burden or drug prescribing. Our study showed a differential survival between AD and DLB of around 3 years for both males and females with survival being shorter in males in both cohorts. In our study, men with DLB had the poorest survival numerically, followed by women with DLB, men with AD then women with AD; however the sex differences were not significant in the full adjusted model (table 2). In contrast a previous study (3) found women with DLB to have the poorest survival, followed by men with DLB, men with AD, then women with AD. Previous studies in DLB have shown survival of 5.5-7.7 years from disease onset and 1.9-6.3 years from diagnosis. (7) Our findings are therefore in line with those from other mortality studies in DLB as the time of first presentation would be expected to be between symptom onset and diagnosis. Recent national data on dementia mortality in the Mental Health Minimum Data Set (MHMDS) shows a median survival of 3.5 years from diagnosis with cognitive impairment or dementia at 'moderate need' (not further defined) with shorter survival times when needs are high or very high . (21) This is somewhat surprising given that the mortality of the lowest needs group reported in the MHMDS sample is in line with the poorer surviving of our two cohorts. The MHMDS does not report the diagnostic breakdown of the population studied, nor does it report any adjustment for other potential confounders.

We did not find a significant association between antipsychotic prescribing and mortality which was surprising especially in the DLB cohort where there is well characterised sensitivity to antipsychotic medication. (22)

Comorbidity burden was specifically associated with mortality in the AD group only, which was surprising given that other studies have found that increased comorbidity burden is associated with increased risk of mortality in dementia including DLB in both a research cohort (3) and a whole population epidemiological study. (8) In our study we used a dichotomised comorbidy index of 'low' vs. 'high' rather than the mean Charlson score, more detailed symptom profiles (3, 6) or number of prescribed medications. (8) Where finer grained physical comorbidity data have been included in analyses, resting tremor was the only single physical comorbidity related to survival and was found to be a protective factor. (3) When comorbidity profiles have been compared between DLB and AD cohorts, overall comorbidity burden has been shown to be higher in DLB, from the time of diagnosis, with increased cerebrovascular comorbidity. (6) In contrast we found that at the time of diagnosis there was little difference between the two groups (though we were not able gather data to the same level of detail).

This study further strengthens the findings from a number of studies that survival is poorer in DLB than AD, though in our cohort this finding was not accounted for by other factors measured, including physical comorbidity burden, suggesting that there may be an intrinsically higher rate of mortality in DLB than AD.

Further work is needed both to examine factors associated with this excess mortality in DLB in this and other cohorts, so that high risk subjects can be identified, and to elucidate potential mechanisms that may underpin this increase to inform intervention studies. A number of potential factors have been identified, though often from small studies. These include clinical features such as the presence of autonomic symptoms and hallucinations, and pathological features such as increased cerebrospinal fluid (CSF) tau and apolipoprotein E4 (APOE4).(7)

Strengths

Clinical information was extracted from the electronic case records by experienced clinicians, to a clear protocol, and validated against accepted diagnostic criteria. The advantage of identifying a large retrospective sample is that the characteristics of the sample are reflective of a clinical population. The identification of a cohort of AD cases in the same service during the same time frame allowed for comparisons to be made under similar clinical conditions.

Limitations

This study focused on identification of two clinically diagnosed dementia subtypes, dementia with Lewy bodies and a comparison group with Alzheimer's dementia, with a complete cohort of DLB cases identified over an eight year period. Cases were primarily identified as DLB or AD in the study if they were assigned the diagnosis by the treating clinician and then validated against diagnostic criteria. It is possible, though, that a small number of cases were misclassified and, if a prospective case identification strategy had been used these cases would have been assigned a different dementia subtype diagnosis. Low diagnostic accuracy (23) and comorbidity between DLB and AD in dementia (24) has previously been shown in pathological DLB cohorts. We were also not able to extract consistent data on the temporal onset of core DLB features. It is therefore possible that a subset of patients with more advanced AD were misclassified as having DLB based on the core symptom profile. Using our methodological approach, we were not able to identify patients who would have fulfilled criteria for DLB but had not been diagnosed with the condition as our search strategy relied upon text terms associated with the diagnostic descriptions. Given the limitations

above, the difference between the two clinically diagnosed cohorts regarding survival is therefore more striking as one might expect the differences to be less marked given lower diagnostic accuracy in a clinical rather than pathologically diagnosed study sample.

The case note design meant that whilst we were able to capture data from a naturalistic cohort accessing secondary care, we were not able to ensure the completeness of data that might be acquired in a research sample. In particular we extracted the comorbidity data only from what we were able to gather from the patient record and we did not have a complete set of MMSE scores at diagnosis. In addition, we used MMSE as our primary measure of cognitive function, as this was the tool routinely used in clinical practice, but this would not have given a complete picture of cognitive dysfunction particularly in the DLB cohort.

The cohorts analysed in this study were selected based on their diagnoses being made within a specified time frame and were not more specifically matched, though every attempt was made to minimise bias in identification of the comparator cohort, and subsequent analysis found few significant differences in demographic and clinical characteristics. It is possible, though that the study outcome would have been different if a more robust matching strategy had been employed.

The study sample comprised two diagnostic groups over a specified time period in a secondary mental health care setting. It is possible that the findings of the study do not reflect the total populations with these diagnoses. Diagnosis in a secondary care setting may reflect greater symptom severity, for example, though in the UK the great majority of new diagnoses of dementia (and subsequent initiation of treatment) are currently made in secondary care following GP or specialist referral.(25) The mean MMSE at diagnosis for both groups was in the mild-to-moderate range of severity of cognitive impairment, with similar standard deviations. The study findings may be limited by not identifying patients at earlier stages of disease, though patients referred into secondary care (especially to community mental health teams) are likely to be referred with functional decline or other related difficulty which will usually occur beyond the earliest stages of disease. Previous studies of mortality in DLB have reported similar baseline mean MMSE scores. (6, 8)

The retrospective nature of the study meant that accurate estimation of timing of symptom onset was not possible, limiting our ability to report duration of illness accurately. To minimise any bias introduced by differential timing of diagnoses between the groups (though there was no evidence in the baseline data to suggest this was the case) we based the primary survival analysis on date of first presentation with cognitive impairment, rather than date of diagnosis, but reanalysis using date of diagnosis produced similar results.

Interpretation

The underlying reason for the difference in mortality rates between the DLB and AD cohorts remains unclear, but this study adds to the existing evidence showing a higher mortality rate for DLB than AD, though not accounted for by other factors including comorbidity burden.

Generalizability

CPFT is a relatively small mental health Trust but because the methodology used identified a naturalistic clinical sample, it is likely that the cohorts identified are representative of a wider secondary care population with dementia. A number of other mental health Trusts have or are

developing the capability to use anonymised clinical records for research. The methodology used to identify the cohorts identified for this study could be repeated on these Trusts' clinical records and findings compared to determine whether our study's findings generalize across other clinical populations.

It was not possible to gather consistent or complete data on ethnicity, education level and level of deprivation. If we had been able to gather this data it may have been possible to discuss in more detail how the results of this study may be comparable with other dementia populations. Considering the CPFT patient population as a whole however, the Trust serves a fast growing, aging and diverse population with significant inequalities (26) which are likely to be reflected in our study cohort.

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CONTRIBUTORSHIP STATEMENT

JOB had the original idea for the study. AP and JOB designed the study. AP, RF, JMY and VM completed case identification and data extraction. AP and RC analysed the data. AP drafted the manuscript and all authors contributed to the finished manuscript. AP is guarantor.

COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work

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DATA SHARING STATEMENT

Data sharing: full dataset and statistical code available from the corresponding author. Individual consent was not obtained but the presented data are anonymised and aggregated.

TRANSPARENCY DECLARATION

The lead author AP affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Comparison of demographic and clinical data between DLB and AD cohorts

Characteristic	DLB (n=251)	AD (n=222)	χ^2 or *F test* statistic	*P* value
Gender				
Female	129 (51.4%)	139 (62.6%)	$\chi^2_1 = 6.04$	0.01
Male	122	83		
Age at first presentation with cognitive impairment (years)	78.8 (SD 7.7) (n=251)	79.5 (SD 8.8) (n=200)	$F_{1,449} = 2.51$	0.11
Age at diagnosis (years)	79.3 (SD 7.6)	80.2 (SD 8.8)	$F_{1,471} = 1.32$	0.25
MMSE score at diagnosis	20.1 (SD 5.5) (n=183)	20.6 (SD 4.9) (n=172)	$F_{1,353} < 1$	0.41
Charlson comorbidity index at diagnosis				
Low comorbidity (score ≤2)	183 (72.9%)	158 (71.2%)	$\chi^2_1 = 0.18$	0.67
High comorbidity (score >2)	68	64		
Medications prescribed				
Antipsychotic (neuroleptic) drugs	103 (41.0%)	32 (14.4%)	$\chi^2_1 = 39.6$	<0.0001
Parkinson's disease drugs	93 (37.1%)	0 (0%)	$\chi^2_1 = 102.39$	<0.0001
Anti-dementia drugs	152 (60.6%)	139 (62.6%)	$\chi^2_1 = 0.21$	0.65

Table 2: Survival Analysis Dementia in Lewy Bodies compared with Alzheimer's dementia.

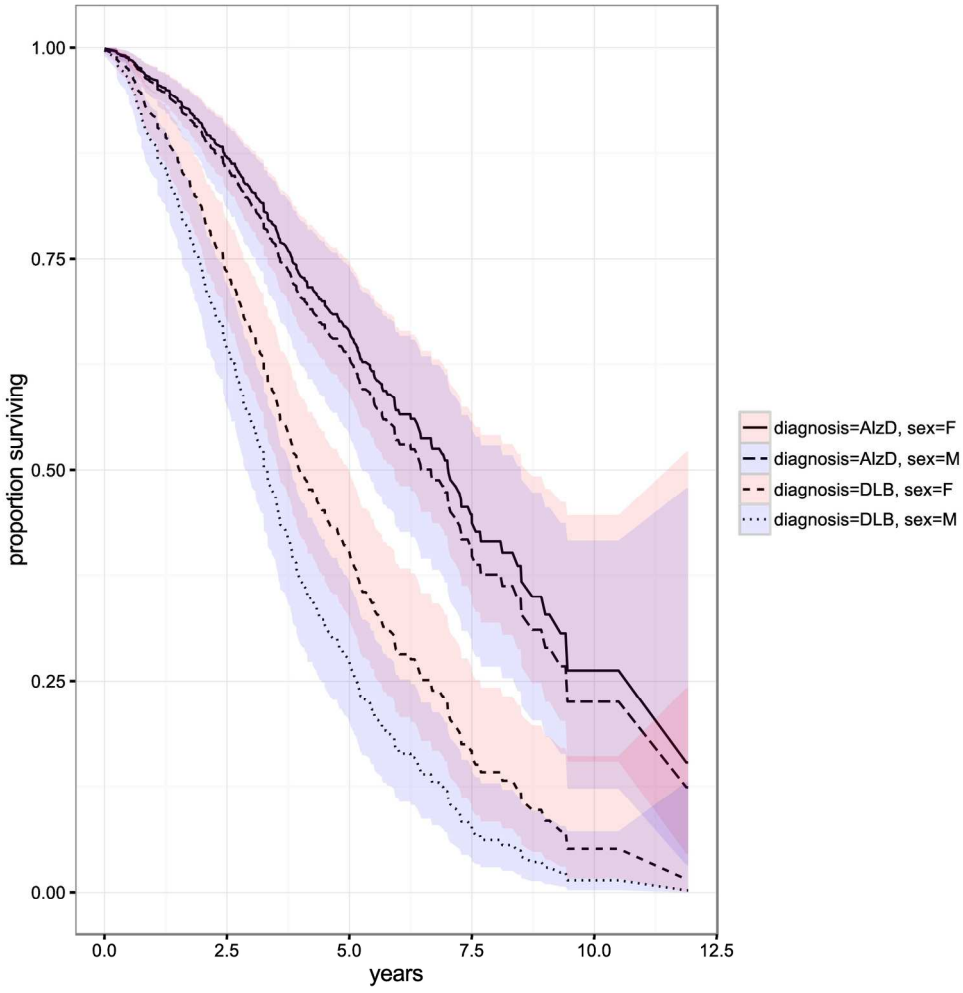
Family	Model	Dependent variable ~ Predictors	LL; LR test versus preceding model (unless stated)	HR with 95% CI for each predictor; corresponding *Z* test
		Group 1: using time since cognitive impairment		
C	C1	SCI ~ diagnosis	−1472.4; NA	diagnosis: HR 2.29 (1.78–2.94); $Z = 6.45$, $p = 1.1 \times 10^{-10}$ ***
	C2	SCI ~ diagnosis + age + sex	−1446.3; $\chi^2_2 = 52.3$, $p = 4.48 \times 10^{-12}$ ***	diagnosis: HR 2.48 (1.92–3.19); $Z = 7.01$, $p = 2.32 \times 10^{-12}$ *** age: HR 1.06 (1.04–1.08); $Z = 6.88$, $p = 5.85 \times 10^{-12}$ *** sex: HR 1.33 (1.04–1.70); $Z = 2.30$, $p = 0.0213$ *
	C3	SCI ~ diagnosis + age + sex + frailty	−1444.5; $\chi^2_1 = 3.58$, $p = 0.0585$; NS	–
	C4	SCI ~ diagnosis + age + sex + frailty + neuroleptics	−1444.3; $\chi^2_1 = 0.40$, $p = 0.526$; NS	–
IC	**IC1†**	**SCI ~ diagnosis + age + sex + sex×diagnosis + frailty + frailty×diagnosis + neuroleptics + neuroleptics×diagnosis**	**−1440.0; versus C2: $\chi^2_5 = 12.5$, $p = 0.0281$ ***	**diagnosis: HR 3.04 (2.00–4.63); $Z = 5.20$, $p = 2.04 \times 10^{-7}$ *** **age: HR 1.06 (1.04–1.08); $Z = 6.77$, $p = 1.33 \times 10^{-11}$ *** sex: HR 1.11 (0.73–1.69); $Z = 0.503$, $p = 0.615$; NS sex×diagnosis: HR 1.28 (0.769–2.14); $Z = 0.951$, $p = 0.341$ **frailty: HR 1.83 (1.21–2.75); $Z = 2.88$, $p = 0.00403$ **** **frailty×diagnosis: HR 0.558 (0.329–0.945); $Z = -2.17$, $p = 0.0301$ *** neuroleptics: HR 1.60 (0.994–2.58); $Z = 1.94$, $p = 0.0529$; NS neuroleptics×diagnosis: HR 0.587 (0.334–1.03); $Z = -1.85$, $p = 0.0646$; NS
		Group 2: using time since diagnosis		
D	D1	SDX ~ diagnosis	−1483.0; NA	diagnosis: HR 2.20 (1.71–2.82); $Z = 6.18$, $p = 6.59 \times 10^{-10}$ ***
	D2	SDX ~ diagnosis + age + sex	−1461.6; $\chi^2_2 = 42.8$, $p = 5.13 \times 10^{-10}$ ***	diagnosis: HR 2.31 (1.80–2.97); $Z = 6.54$, $p = 6.22 \times 10^{-11}$ *** age: HR 1.05 (1.04–1.07); $Z = 6.21$, $p = 5.34 \times 10^{-10}$ *** sex: HR 1.37 (1.07–1.75); $Z = 2.52$, $p = 0.0119$ *
	D3	SDX ~ diagnosis + age + sex + frailty	−1459.4; $\chi^2_1 = 4.47$, $p = 0.0346$ *	diagnosis: HR 2.30 (1.79–2.95); $Z = 6.49$, $p = 8.39 \times 10^{-11}$ *** age: HR 1.05 (1.03–1.07); $Z = 6.02$, $p = 1.73 \times 10^{-9}$ *** sex: HR 1.34 (1.05–1.72); $Z = 2.36$, $p = 0.0181$ * frailty: HR 1.32 (1.03–1.71); $Z = 2.15$, $p = 0.0316$ *
	D4	SDX ~ diagnosis + age + sex + frailty + neuroleptics	−1459.2; $\chi^2_1 = 0.34$, $p = 0.562$; NS	–
ID	ID1	SDX ~ diagnosis + age + sex + sex×diagnosis + frailty + frailty×diagnosis	−1453.5; versus D3: $\chi^2_4 = 11.8$, $p = 0.0186$ *	diagnosis: HR 2.93 (1.92–4.45); $Z = 5.01$, $p = 5.52 \times 10^{-7}$ *** age: HR 1.05 (1.04–1.07); $Z = 6.15$, $p = 7.92 \times 10^{-10}$ *** sex: HR 1.11 (0.73–1.69); $Z = 0.513$, $p = 0.608$; NS

		+ neuroleptics + neurolepticsxdiagnosis		sexxdiagnosis: HR 1.33 (0.799–2.21); Z = 1.09, p = 0.274; NS frailty: HR 1.87 (1.24–2.83); Z = 2.98, p = 0.00287 ** frailtyxdiagnosis: HR 0.559 (0.330–0.947); Z = –2.16, p = 0.0307 * neuroleptics: HR 1.82 (1.13–2.91); Z = 2.48, p = 0.0133 * neurolepticsxdiagnosis: HR 0.492 (0.281–0.862); Z = –2.48, p = 0.0131 *

Table 2. Stepwise model comparisons. **SCI** survival time from presentation with cognitive impairment (or diagnosis if not known); **SDX** survival time from diagnosis; **LL** log-likelihood; **LR** likelihood ratio; **NA** not applicable; **NS** not significant; **HR** hazard ratio (exponentiated model coefficient); **CI** confidence interval; * $p < .05$; ** $p < .01$; *** $p < .001$; † overall preferred model. Times and ages are calculated in years. The effect for 'diagnosis' is that of Lewy body dementia (versus Alzheimer's disease); that for 'sex' is maleness (versus femaleness); 'frailty' is the dichotomized Charlson frailty index. 'Age' is, throughout, the age at presentation with cognitive impairment.

Figure 1: Survival in dementia with Lewy bodies versus Alzheimer's dementia

Bands indicate 95% confidence intervals for the cumulative hazard.



Survival in Dementia with Lewy bodies versus Alzheimer's dementia

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