Review

Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies

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ABSTRACT

Objective: To synthesize the evidence across longitudinal studies comparing survival in dementia with Lewy bodies (DLB) and Alzheimer's disease (AD).
Methods: We conducted a systematic review and meta-analysis of studies comparing survival in clinically diagnosed DLB to AD. Longitudinal cohort studies were identified through a systematic search of major electronic databases from inception to May 2018. A random effects meta-analysis was performed to calculate survival time and relative risk of death.
Results: Overall, 11 studies were identified including 22,952 patients with dementia: 2029 with DLB (mean diagnosis age 76.3; 47% female) compared with 20,923 with AD (mean diagnosis age 77.2; 65.1% female). Average survival time in DLB from diagnosis was 4.11 years (SD ± 4.10) and in AD 5.66 (SD ± 5.32) years, equating to a 1.60 (95% CI: -2.44 to -0.77) years shorter survival in DLB (p < 0.01). Relative risk of death was increased by 1.35 (95%CI: 1.17–1.55) in DLB compared to AD (p < 0.01). Differences in survival were not explained by follow-up time, age at diagnosis, gender, or cognitive score.
Conclusions: There is consistent evidence for higher and earlier mortality in DLB compared to AD. This is important for all stakeholders and underlines the importance of expanding research into DLB.

1. Introduction

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia, accounting for up to a quarter of all diagnosed dementia cases (Vann Jones and O'Brien, 2014) and is estimated to be present in 1% of older adults (Ballard et al., 2013). Compared to Alzheimer's disease (AD), DLB has been reported to have a considerably poorer prognosis and is associated with higher caregiver burden, higher costs of care, as well as increased rates of admission to general hospitals and residential care (Mueller et al., 2017a, 2018).

Survival in DLB has been a matter of considerable clinical and academic debate (Mueller et al., 2017a). Initial post-mortem studies suggested a rapid mortality with survival times of less than two years (McKeith et al., 1992), but a later meta-analysis of neuropathologically confirmed cases of DLB published over 20 years ago suggested a longer mean survival time after diagnosis of 6.1 years (Cercy and Bylsma, 1997). Autopsy studies, which have provided most of the initial evidence, are prone to recruit biased cohorts, as post-mortems are usually carried out in selected samples of younger patients with uncertain diagnoses and atypical features (Walker et al., 2000). The advent of operationalized clinical criteria for DLB diagnosis (McKeith et al., 1996) paved the way for larger scale cohort studies to better understand prognosis and survival. Greater awareness amongst clinicians, further revisions of the diagnostic criteria (McKeith et al., 2017), the inclusion of DLB in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013), and the increased use of naturalistic data from electronic health records (Price et al., 2017) has led to an expanding number of publications on survival in DLB. The majority of observational studies, but not all, report shorter survival in DLB than AD (Mueller et al., 2017a). However, to the best of our knowledge, no systematic review or meta-analysis has synthesised this growing body of knowledge to describe and compare survival times from diagnosis.

Given the importance of understanding the prognosis of the DLB for patients, their families and service planners, we conducted a systematic review and meta-analysis of observational studies to determine survival times from diagnosis and differences between DLB and AD and relative risk of mortality (primary aim) and assessed via meta-regression which factors might account for these differences (secondary aim).

2. Methods

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement (Liberati et al., 2009; von Elm et al., 2007).

2.1. Search strategy

Two investigators (PS, NV) independently searched major databases (Pubmed, Medline, Scopus, Embase) without language restrictions, from inception until 01st May 2018. In Pubmed, the following controlled vocabulary terms and keywords were considered: (dementia lewy body or Lewy body OR Lewy bodies OR Lewy OR DLB OR LBD) and (mortality or death or survival). Similar searches were run in the other databases. Any inconsistencies were resolved by consensus with a third Author (CM). The reference lists of the articles included in the analysis were hand-searched to identify additional, potentially relevant publications. Conference abstracts were also considered. Authors were contacted at least two times in 1 month for obtaining additional information if needed.

2.2. Study selection

Two authors selected longitudinal cohort studies that reported survival time from dementia diagnosis (expressed in years) or in equivalents (e.g. months) in studies comparing people with DLB and AD.

2.3. Inclusion/exclusion criteria

We only considered studies that: (1) had a baseline and follow-up evaluation; (2) included patients with DLB, accepting all diagnostic criteria available (3) included a control group having a diagnosis of AD (accepting all diagnostic criteria available) (4) reported data on

survival/mortality parameters, expressed in years (from diagnosis of these conditions to death). Studies were excluded if they: (1) did not include patients with DLB; (2) conducted in vitro and on animal models; (3) were conducted in selected samples of autopsy cases; (4) evaluated co-morbid AD pathology in patients with DLB; (5) compared AD to the Lewy body variant of AD, or (6) were reviews, book chapters and single case reports.

2.4. Data extraction

Two authors (PS, NV) independently extracted data from the selected studies in a standardized Microsoft Excel spreadsheet. Any disagreement was resolved with a third author (BS). The following information was extracted: 1) characteristics of the study population (e.g. sample size, demographics, setting, country in which the study was performed); 2) mean age, gender distribution and baseline mean minimental state examination (MMSE) at dementia diagnosis; 3) diagnostic criteria of DLB and AD; 4) average age at diagnosis; 5) all data about survival. We planned to extract additional data (e.g. those regarding neuropsychiatric symptoms, disability, average age at the onset of symptoms), but since they were present in less than 4 studies (the minimum for running a meta-regression analysis), we did not include these data.

2.5. Assessment of study quality

Two independent reviewers (PS, NV) assessed the quality of studies, with a third available to resolve any discrepancies (BS). The Newcastle-Ottawa Scale (NOS) was used to assess study quality, which assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome (Luchini et al., 2017; Wells et al., 2012). Higher scores indicate better methodological quality.

2.6. Outcomes

The primary outcomes were survival data including mean survival time from diagnosis to death in DLB and AD. If expressed in other forms (e.g. median survival time, interquartile range survival time) these estimates were transformed in means and standard deviations (SDs). If the SD was not reported and was not possible to calculate from the data available in the full-text, a pooled SD was calculated, in agreement with the Cochrane guidelines (Higgins and Green, 2008). We further estimated the risk of death during the follow-up period between DLB and AD groups and performed meta-regression analyses to test whether differences in mean age, MMSE at diagnosis, follow-up time and gender explained outcome differences between the studied cohorts.

2.7. Statistical analysis

The meta-analysis was performed using the Comprehensive Meta-Analysis 2.0 (CMA) software.

The difference, in mean, of the years survived in DLB group and in the AD group was reported through a mean difference (MD) with the correspondent 95% confidence intervals (CIs). The random effects model was used to account for anticipated between-study heterogeneity (DerSimonian and Laird, 1986). This was assessed using the Chi-squared and I-squared statistics, assuming that a p < 0.10 for the former and a value ≥50% for the latter were indications of significant heterogeneity (Higgins and Thompson, 2002). For the primary outcome, whenever significant heterogeneity existed and ≥4 studies were available, a meta-regression analysis was performed examining the following pre-specified moderators: continent (categorized as Europe vs. America/Oceania); criteria used for DLB diagnosis (McKeith et al., 1992; McKeith et al., 1996; McKeith et al., 2005 or DSM-IV); year of publication (2000–2006, 2007–2012; 2013–2018); follow-up years (as continuous). Publication bias was assessed by visually inspecting funnel
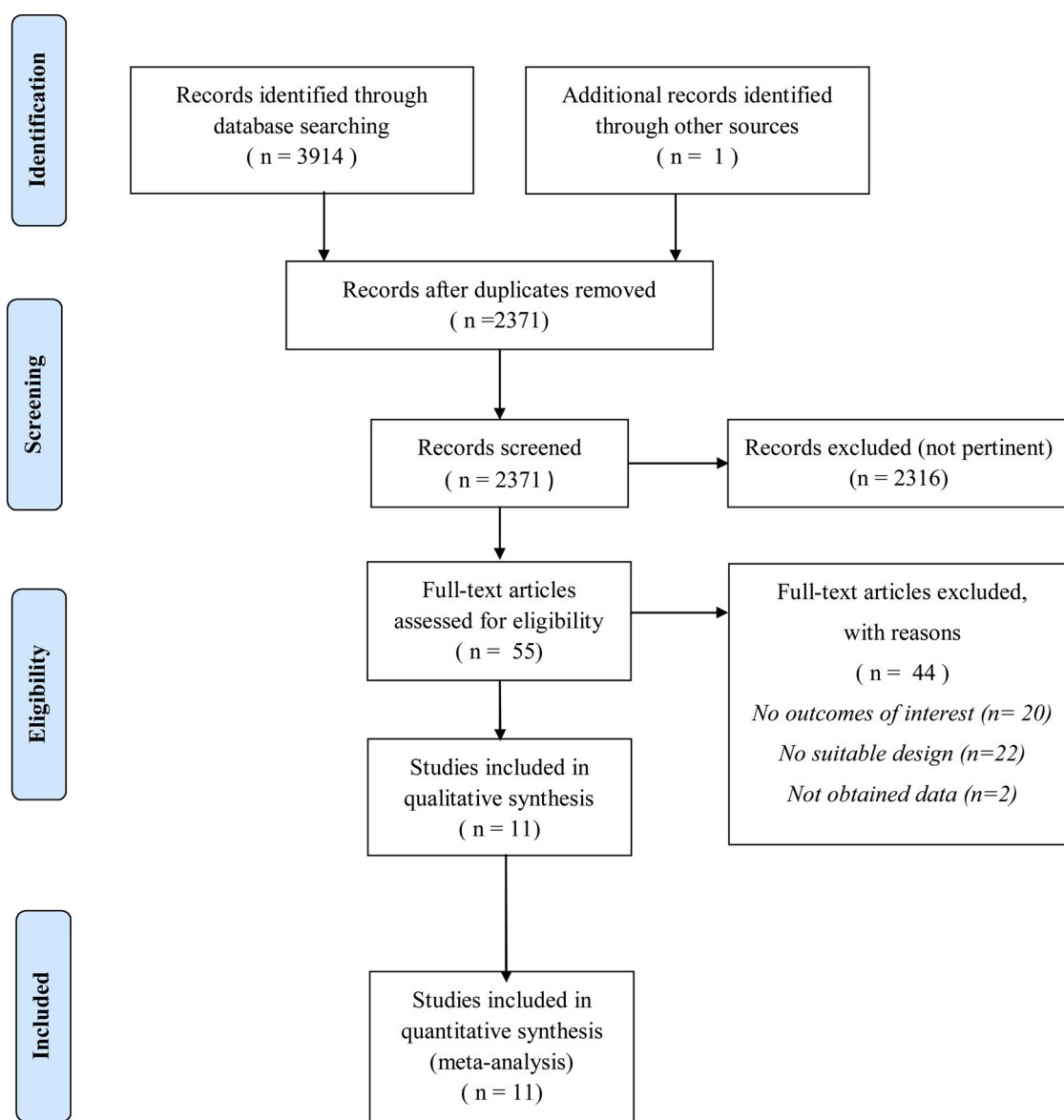
Fig. 1. PRISMA flow-chart.

plots and using the Egger bias test (Egger et al., 1997). Finally, to account for publication bias, we used the trim-and-fill method, which adjusts for the potential effect of unpublished (imputed) studies (Duval and Tweedie, 2000).

3. Results

The search identified 2371 non-duplicated potentially eligible studies. After excluding 2316 papers at title and abstract review, 55 full-text articles were examined, 11 of which (Bostrom et al., 2009; Connors et al., 2016; Garcia-Ptacek et al., 2016; Koedam et al., 2008; Magierski et al., 2010; Mueller et al., 2018; Oesterhus et al., 2014; Price et al., 2017; Stubendorff et al., 2011; Walker et al., 2000; Williams et al., 2006) were finally included in the systematic review and meta-analysis (Fig. 1). Additional or updated information was kindly provided by the authors of four of the studies (Garcia-Ptacek et al., 2016; Mueller et al., 2018; Oesterhus et al., 2014; Connors et al., 2016).

3.1. General characteristics

The 11 studies followed-up a total of 22,952 patients with dementia

(2029 with DLB compared with 20,923 with AD) for a median of 5.02 years (Table 1). Nine studies were conducted in Europe (10; = 81.8%). The quality of the studies was generally sufficient (median NOS = 7, range: 4–9) and the most common potential source of bias was short follow-up periods and limited inclusion of possible confounders in the final analyses (see Supplementary Table 1).

As reported in Table 1, the criteria suggested by McKeith, 2005 (McKeith et al., 2005) were the most commonly used for the diagnosis of DLB (4 studies; = 36.3%). The 2029 participants with DLB had a mean age of 76.3 (SD $\pm$ 7.0) years at the diagnosis and they were more frequently males (52.6%). They had a mean MMSE score of 21.1 ($\pm$ 5.1) at diagnosis. Of the comparison group with AD (N = 20,923) the mean age was 77.2 ($\pm$ 8.0) years, most were female (65.0%) and mean MMSE score at diagnosis was 20.2 ($\pm$ 4.9).

Overall, patients with DLB were younger at the time of diagnosis at a level close to statistical significance (p = 0.08) than patients with AD, and a higher proportion were male (p < 0.01). Mean MMSE at diagnosis was slightly higher in patients with DLB, but this difference was not statistically significant (p = 0.11).

Table 1
Descriptive characteristics of the studies included.

Author (year)	Country	Follow-up (years)	Diagnostic criteria	DLB N	Age at diagnosis (SD)	Survival from diagnosis to death (y; SD)	Female (%)	MMSE at diagnosis (SD)	AD N	Age at diagnosis (SD)	Survival from diagnosis to death (y)	Female (%)	MMSE at diagnosis (SD)
Bostrom et al., 2009	Sweden	7	McKeith criteria,2005	47		5.59 (5.7)	46.8	22.7 (5.3)	159		7.02 (7.16)	75.5	20.2 (4.9)
Connors et al., 2016[a]	Australia	3	DSM-IV	16	75.1 (5.7)	3.87 (1.46)	25	23.8 (4.2)	521	76.7 (7.9)	6.21 (2.89)	51.2	21.1 (5.3)
Garcia-Ptacek et al., 2016[a]	Sweden	2,03	McKeith criteria,2005	1054	76.52 (7.06)	2.06 (1.31)	39.7	21.41 (5.04)	9137	77.58 (8.27)	2.29 (1.39)	65.2	21.5 (5.01)
Koedam et al., 2008	Netherlands	2,5	McKeith criteria, 1996	52	75 (7)	1.9 (1.6)	33	22 (5)	589	71 (10)	3.4 (2.2)	57	20 (5)
Magierski et al., 2010	Poland	8	McKeith criteria,1996	47	76.6 (4.4)	6.3 (0.4)	70.2	19.9 (4)	103	78.1 (4.9)	8.3 (0.4)	68	20.3 (3.1)
Oesterhus et al., 2014[a]	Norway	6,7	McKeith criteria,2005	77	76.6 (7.3)	4.52	48.1	23.3 (3.2)	111	75.6 (7.4)	7.42	71.2	23.7 (2.3)
Mueller et al., 2018[a]	UK	10	McKeith criteria,2005[b]	341	78.6 (9.5)	3.44	50.2	19.5 (6.4)	9707	80.8 (9.3)	4.76	65.34	18.8 (6.4)
Price et al., 2017	UK	8	McKeith criteria,2005	251	79.3 (7.6)	4.40 (2.63)	51.4	20.1 (5.5)	222	80.2 (8.8)	6.99 (7.05)	62.6	20.6 (4.9)
Stubendorff et al., 2011	Sweden	5	McKeith criteria, 1996	49	75.8 (6)	4.7 (SE: 1.30)[c]	45	22 (8-29)	79	76 (6.0)	6.5 (SE: 1.03)[c]	73	21 (6-29)
Walker et al., 2000	UK	3	McKeith criteria 1992	32	75.8 (NA)	3.5 (mean)	71,8	16.7 (7.1)	43	78.1 (NA)	3.1 (mean)	65.1	15.8 (7.6)
Williams et al., 2006	USA		McKeith criteria, 1996	63	73.5 (8.7)	5.00 (SE: 1.54)	40.3		252	77.8 (9.5)	6.30 (SE: 0.81)	62.3	
Total		Median = 5.02 (range: 2-10)		2029	Mean= 76.3 (7.03)		47.4	Mean= 21.1 (4.7)	20,923	Mean= 77.2 (8.0)		65.1	Mean= 20.3 (4.9)

[a] Updated data acquired from author.
[b] 69 cases were examined according to McKeith criteria 2005, with a positive predictive value of 78% for DLB.
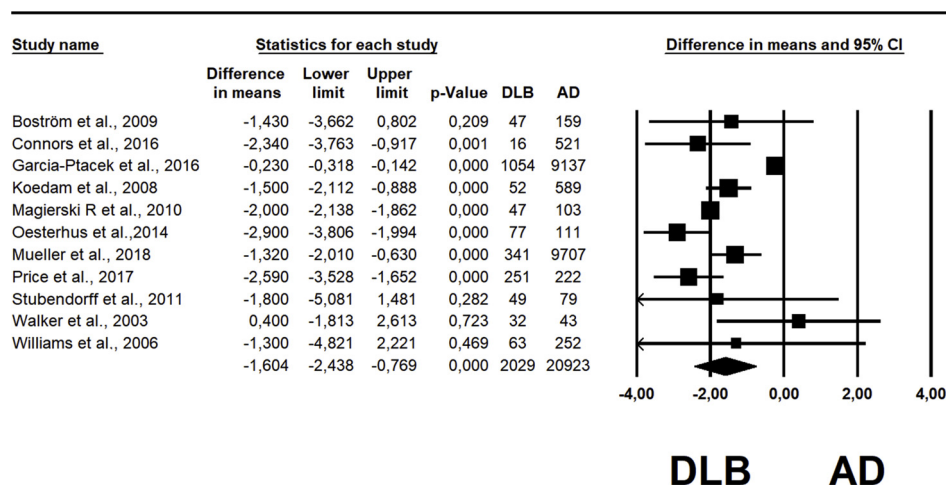[c] Only available for patients who died (80% in DLB group; 75% in AD group).

Study name	Statistics for each study						Difference in means and 95% CI
	Difference in means	Lower limit	Upper limit	p-Value	DLB	AD	
Boström et al., 2009	-1,430	-3,662	0,802	0,209	47	159	
Connors et al., 2016	-2,340	-3,763	-0,917	0,001	16	521	
Garcia-Ptacek et al., 2016	-0,230	-0,318	-0,142	0,000	1054	9137	
Koedam et al., 2008	-1,500	-2,112	-0,888	0,000	52	589	
Magierski R et al., 2010	-2,000	-2,138	-1,862	0,000	47	103	
Oesterhus et al.,2014	-2,900	-3,806	-1,994	0,000	77	111	
Mueller et al., 2018	-1,320	-2,010	-0,630	0,000	341	9707	
Price et al., 2017	-2,590	-3,528	-1,652	0,000	251	222	
Stubendorff et al., 2011	-1,800	-5,081	1,481	0,282	49	79	
Walker et al., 2003	0,400	-1,813	2,613	0,723	32	43	
Williams et al., 2006	-1,300	-4,821	2,221	0,469	63	252	
	-1,604	-2,438	-0,769	0,000	2029	20923	

Fig. 2. Comparison of survival time from dementia diagnosis in DLB and AD.

3.2. Differences in survival years between DLB and AD

Fig. 2 summarizes the differences in survival years between DLB and AD cohorts. Of the 11 included studies, 7 reported significantly shorter survival in DLB than in AD, while the other 4 studies did not detect any statistically significant difference. Mean survival time after diagnosis was 4.11 (SD ± 4.10) years in people with DLB compared to 5.66 (SD ± 5.32) years in patients with AD. Hence survival was 1.60 years shorter in patients with DLB than in patients with AD (95% CI: -2.44 to -0.77 years; p < 0.01), although between-study heterogeneity was high (I² = 99%). The Egger's test did not indicate significant publication bias (Egger's test: -2.61 ± 2.59; p = 0.33) and the trim and fill analysis did not meaningfully alter our findings. The fail-safe number for this outcome was high, needing 917 studies to nullify this finding. For those who died, the mean age at death was 80.8 (SD ± 7.0) for DLB and 83.7 (SD ± 7.2) for AD (p = 0.01).

Seven studies (Bostrom et al., 2009; Connors et al., 2016; Garcia-Ptacek et al., 2016; Koedam et al., 2008; Mueller et al., 2018; Oesterhus et al., 2014; Price et al., 2017) reported on the percentages of patients who died in the follow-up period. As shown in Fig. 3, in the DLB cohort 780/1,838 (42.4%) patients died during follow-up compared to 6,704/20,446 (32.8%) in the AD cohort. These estimates indicate a significantly higher risk of mortality in people with DLB compared to AD (relative risk = 1.35; 95%CI: 1.17–1.55; p < 0.01; I² = 80%). This

outcome was also not apparently influenced by publication bias (Egger's test: − 0.20 ± 2.05; p = 0.92) and the fail-safe number was 162.

3.3. Meta-regression and sensitivity analyses

Since our primary outcome had a high heterogeneity (I² = 99%), we investigated potential factors underpinning this using meta-regression and sensitivity analyses. Supplementary Table 2 shows the data on survival years stratified by continent, DLB diagnostic criteria applied (see Supplementary Table 3) and period of publication. Higher survival differences were observed in studies from outside Europe, and lower differences in older studies, but no significant interaction by stratum (p > 0.05) was detected in any of the three categories.

Meta-regression analyses reported in Supplementary Table 4 further demonstrate that none of the available moderators (i.e. follow-up period, differences in mean age, in mean MMSE, or in percentage of females) explained differences in survival time between AD and DLB.

4. Discussion

This meta-analysis of 11 longitudinal studies including more than 2000 people with a clinical diagnosis of DLB demonstrated that patients with DLB have a significantly shorter survival from dementia diagnosis than patients with AD. Survival time was almost 20 months shorter in

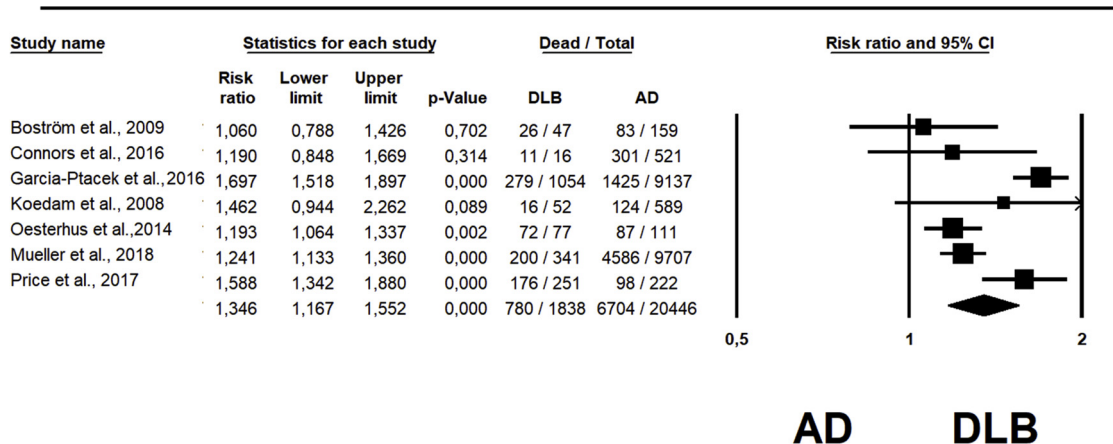| Study name	Statistics for each study				Dead / Total		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	p-Value	DLB	AD	
Boström et al., 2009	1,060	0,788	1,426	0,702	26 / 47	83 / 159	
Connors et al., 2016	1,190	0,848	1,669	0,314	11 / 16	301 / 521	
Garcia-Ptacek et al.,2016	1,697	1,518	1,897	0,000	279 / 1054	1425 / 9137	
Koedam et al., 2008	1,462	0,944	2,262	0,089	16 / 52	124 / 589	
Oesterhus et al.,2014	1,193	1,064	1,337	0,002	72 / 77	87 / 111	
Mueller et al., 2018	1,241	1,133	1,360	0,000	200 / 341	4586 / 9707	
Price et al., 2017	1,588	1,342	1,880	0,000	176 / 251	98 / 222	
	1,346	1,167	1,552	0,000	780 / 1838	6704 / 20446	

Fig. 3. Comparison of risk of death in DLB and AD.

patients with DLB and their average survival time was 4.1 years. Relative risk of death was 1.35 higher in DLB compared to AD, and although no significant difference was detected in age at diagnosis, patients with DLB had a significantly lower age at death. Neither gender difference, age at diagnosis, nor MMSE scores explained differences in survival time between DLB and AD.

Dementia is associated with a shortened life expectancy (Brodaty et al., 2012) and is increasingly recognised as a progressive, life-limiting condition without curative treatments, leading to a growing focus on advance care planning (Perera et al., 2016; van der Steen et al., 2014). With the expected rise in people affected with dementia (Prince et al., 2013), giving indicators for prognosis, specifically survival, is of considerable interest both for patients, their families, as well as providers of health and social care services, with the aim to enable suitable support through the various stages of the illness (Todd et al., 2013). Several risk factors for mortality have been evaluated in patients with Alzheimer's disease and all-cause dementia (Brodaty et al., 2012; Todd et al., 2013) but only recently there has been enquiry into non-Alzheimer's dementias such as DLB. DLB has been found to be associated with accelerated cognitive decline, higher rates of hospitalisation and residential care, higher health care costs and lower quality of life (Mueller et al., 2017a, 2018). Our results demonstrate that survival in DLB in clinically diagnosed samples is not as poor as expected from early autopsy studies (McKeith et al., 1992), although is significantly lower than in patients with AD.

Although the available data only allows a coarse comparison, demographic characteristics and MMSE scores in our AD cohort (age at diagnosis 77 years; 65% female; mean MMSE 20) were similar to what is reported in larger samples of patients with Alzheimer's disease. For instance the data with AD are broadly comparable with data from more than 26,000 patients diagnosed in Swedish memory clinics (age at diagnosis 80 years; 62% female; mean MMSE 21) (Cermakova et al., 2017) suggesting representability of our sample.

A number of factors might explain the increased mortality risk in DLB compared to AD. Previous literature suggested that male gender could be identified as risk factor for mortality in dementia (Brodaty et al., 2012). Although this has not been replicated in all prevalence studies (Vann Jones and O'Brien, 2014), DLB has been associated with a male preponderance both in autopsy studies (Klatka et al., 1996) and clinical samples (Kane et al., 2018). Our data confirms the latter by demonstrating a significantly higher percentage of males on meta-analysis of DLB cohorts. However, when compared to AD group, our meta-regression analysis did not suggest a role of differences in gender between the groups in explaining shorter time survival observed in DLB compared to AD patients. We can argue that, in agreement with the literature reporting a higher risk of death in older male subjects compared to females (Xu et al., 2010), also DLB males die more frequently than women, but this factor is not significant in explaining the differences in survival time between DLB and AD.

Although the difference only amounted to a trend (p < 0.1), DLB patients were also diagnosed at a slightly younger age. With age not explaining survival differences on meta-regression, despite being as strong risk factor for mortality (Todd et al., 2013), patients with DLB might be at a risk of a higher loss of life expectancy compared to those with other forms of dementia. This concurs with one Norwegian study finding that patients with DLB had a higher standardized mortality ratio compared to the general population than patients with AD (2.6 vs. 1.5) (Oesterhus et al., 2014) and is underlined by a significantly younger age of death in DLB than AD (81 vs. 84 years).

Dementia disease severity can be assessed from a global, functional or cognitive perspective. The only measure available for the included studies was MMSE, which is not consistently associated with mortality risk in dementia (Todd et al., 2013) and might be too coarse an instrument to assess severity in DLB (Mueller et al., 2018). On meta-analysis we did not find differences in MMSE at baseline between DLB and AD cohorts, underlining the need for more in-depth testing and

description of domains of cognitive decline between the conditions.

Although we cannot directly infer this from our data, other features of DLB and associated synucleinopathies, as motor, neuropsychiatric or autonomic symptoms, might contribute to the increased mortality risk. In patients with Alzheimer's disease, Parkinson-related symptoms as extrapyramidal signs, gait and postural instabilities and falls are related to increased mortality (Larson et al., 2004; Stern et al., 1997). Orthostatic hypotension is a specific risk factor for falls in patients with dementia (Allan et al., 2009) and is a predictor of mortality in DLB (Stubendorff et al., 2012). In addition to orthostatic hypotension, the effects of cardiovascular autonomic dysfunction, including neuro-cardiovascular instability, carotid sinus syndrome and abnormal sinus bradyarrhythmia, may cause a decrease in blood pressure and negatively affect disease progression and survival of patients with DLB (Fanciulli et al., 2013; Kenny et al., 2002, 2004). It is further possible that the neurodegenerative process in the synucleinopathy DLB is more rapid than in Alzheimer's disease, and a cell-to-cell alpha-synuclein spread has been hypothesized (George et al., 2013). Further AD-like pathological changes such as tau-inclusions and beta-amyloid are also likely to be present to some degree in DLB, and synergistic interactions between the three proteins have been suggested to yield a worse prognosis (Irwin et al., 2013).

Neuropsychiatric symptoms are more common in DLB than AD (Mueller et al., 2018), and in patients diagnosed with dementia these are independently associated with mortality, in particular the DLB core feature of visual hallucinations and the supportive feature of depression (Mehta et al., 2003; Okura et al., 2011; Scarmeas et al., 2005). Fluctuating cognition is a feature common to both DLB and delirium (Gore et al., 2015). As delirium frequently occurs in the months and weeks prior to a DLB diagnosis being established a delirium onset type of DLB has been postulated, whereby clinical misclassification being an alternative explanation (FitzGerald et al., 2018; McKeith et al., 2016; Morandi et al., 2017). Delirium is associated with increased mortality in older adults (Eeles et al., 2010) and this hazard might be increased in people diagnosed with delirium in the absence of a prior diagnosis of dementia, typical for DLB (Ward et al., 2015).

More than these features themselves, mortality risk in DLB may be further increased because of the medications prescribed to address them. The known increased mortality risk related to antipsychotic prescribing (e.g. for hallucinations or delirium) in people with dementia (Tampi et al., 2016) may be further amplified in those with DLB due to the pathognomonic feature of neuroleptic sensitivity (McKeith et al., 2005). However, although the majority of included studies report a higher proportion of these medications prescribed in DLB, antipsychotic prescription didn't emerge as significant modifier of survival differences in one study (Price et al., 2017). Although only demonstrated in Alzheimer's disease (Mueller et al., 2017b) and probably lower than antipsychotic risks (Maust et al., 2015), prescription of antidepressants in dementia might be associated with an increased mortality risk in patients with dementia.

Lastly, survival benefits of acetylcholinesterase inhibitors are well-demonstrated in AD (Mueller et al., 2017c) and these medications are in DLB associated with later transition to residential care and lower health care costs in DLB (Mueller et al., 2017a). Although no head-to-head comparisons are available, two studies reported level of antidementia drug use to be at a similar level in both cohorts (Price et al., 2017; Stubendorff et al., 2011) indicating that neither cohort is deprived of the benefits of these medications.

4.1. Limitations

Although our findings provide clinicians with helpful pointers to discuss prognosis with patients and carers, several caveats in assessing survival in patients with dementia need to be acknowledged.

First, we collated reported survival from the time of dementia diagnosis, as this is the point in time when questions about prognosis

often arise. This is an imprecise timepoint as it depends on various patient, physician and service related factors, as cultural background, readiness to refer to secondary service, or availability of diagnostic services which might change over time (Todd et al., 2013). Inaccuracies arise in particular in DLB since caregivers report that the diagnosis is established after more than one year in half of the cases, and more than three quarters of cases receiving a different diagnosis initially (Galvin et al., 2010). However, this appears superior to symptom onset, as this is determined by recall bias, and variations in ability and threshold to recognize symptoms (Brodaty et al., 2012).

Second, the majority of studies did not neuropathologically confirm the dementia subtype diagnosis. However, although not as accurate as neuropathologically confirmed diagnoses, the clinical diagnoses applied in the included studies are more likely to reflect the reality of day-to-day practice. Diagnostic criteria have evolved since the first consensus guideline were established in 1996 (McKeith et al., 1996), with the 2005 revision (McKeith et al., 2005) increasing detection by one quarter (Aarsland et al., 2008). A recent meta-analysis (Rizzo et al., 2018) demonstrated that the diagnostic criteria have become more sensitive, but less specific, over time, which appears desirable given that DLB remains underdiagnosed in clinical practice (Kane et al., 2018).

A third limitation of our study is high heterogeneity, which is common in meta analyses of observational data. We attempted to address this by utilizing a random effects meta-analysis and through meta-regression analyses. However, we were unable to explain large portions of the variability we encountered. To further reduce heterogeneity, we only included studies which followed newly-diagnosed patients and excluded prevalence studies or studies solely including patients on the basis of available autopsy samples. Heterogeneity was not explained by the continent where the study was conducted, the diagnostic criteria used for DLB, the time period of publication, follow-up time available or patient characteristics. The most important potential explanation of heterogeneity may be the above-mentioned variation in presentation in the patient group itself, as well as variations in diagnostic practice, both regionally and over time (Kane et al., 2018; McKeith et al., 2016; Rizzo et al., 2018). One scenario is the so-called Lewy-body variant of Alzheimer's disease, which relies on the presence of neuropathological criteria for AD and the additional presence of Lewy bodies. Under these conditions clinicians often do not make a diagnosis of DLB (McKeith et al., 2016; Thomas et al., 2018). However, when survival between the Lewy-body variant of AD was compared with pure AD in several post-mortem studies (Chung et al., 2015; Lopez et al., 2000; Olichney et al., 1998), only one out of four studies (Olichney et al., 1998) reported worse survival of Lewy-body variant AD. It has been postulated that Lewy-body pathology might be a feature of late-stage Alzheimer's disease, as 45% of 22 neuropathologically confirmed cases of AD had co-existing Lewy bodies on the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (Toledo et al., 2013). In contrast, studies evaluating the other scenario of mixed pathologies, the presence of AD pathology in patients with clinically diagnosed (Bostrom et al., 2009; Graff-Radford et al., 2016; Lemstra et al., 2017) and autopsy confirmed (Irwin et al., 2017; Jellinger et al., 2007) DLB have consistently demonstrated that co-morbid AD pathology increases mortality risk. We measured heterogeneity of the effect sizes using the I2 statistic as recommended by the Cochrane hand book (REF). However, it is important to also consider that the I2 metric may have some limitations when there are under than 20 studies (Langan et al., 2015).

Fourth, data available only allowed comparison of DLB to AD, with survival time for AD (5.7 years) being within the range previously reported (3.2–6.6 years) (Todd et al., 2013). Despite AD being the far most common type, future studies could attempt to elucidate survival differences in other dementia-causing disorders.

Fifth, we didn't have sufficient information to include ApoE4 status into the meta-analysis. However, a recent study in Alzheimer's disease has not implicated ApoE4 in survival (Rhodius-Meester et al., 2018) and

the one included study (Williams et al., 2006) applying ApoE4 as a potential effector of mortality differences between AD and DLB only detected a statistically significant effect from disease onset, not diagnosis, underlining its role as risk factor.

Lastly, changes in practice over time might affect survival, which could have improved over the studied period through greater awareness of public health measures (Livingston et al., 2017) and the availability of cholinesterase inhibitors which have been associated with survival benefits (Mueller et al., 2017c). However, period of study did not emerge as a moderator of the observed association on meta-regression.

4.2. Conclusions

Survival time after diagnosis of DLB is of growing clinical and research interest. A review conducted eight years ago (Brodaty et al., 2012) included less than 200 cases of DLB, and we are now able to report more than ten times the combined sample size. Although heterogeneity is pronounced in mortality and Lewy body disorder research, our findings suggest that patients diagnosed with DLB have shorter survival from dementia diagnosis than patients with AD. A mean survival time of 4.1 years was concluded from this review, but mean survival times from diagnosis in the included studies ranged from 1.9 to 6.3 years, so there is clearly substantial heterogeneity which limits what can be reasonably communicated to individuals at this stage. Higher mortality suggests a higher likelihood of morbidity and dependency, and while the demonstrating a shorter survival in DLB compared to AD is important for patients, their families and policy makers, important next steps are examining how this reduced life expectancy determines time spent at different levels of morbidity and the identification of specific risk factors of early mortality in this under-researched population.

Declarations of interest

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Appendix A. Supplementary data

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