Suicidal ideation in dementia: associations with neuropsychiatric symptoms and subtype diagnosis

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ABSTRACT

Objectives: To investigate factors associated with suicidal ideation (SI) around the time of dementia diagnosis. We hypothesised relatively preserved cognition, co-occurring physical and psychiatric disorders, functional impairments, and dementia diagnosis subtype would be associated with a higher risk of SI.

Design: Cross-sectional study using routinely collected electronic mental healthcare records.

Setting: National Health Service secondary mental healthcare services in South London, UK, serving a population of over 1.36 million residents.

Participants: Patients who received a diagnosis of dementia (Alzheimer's, vascular, mixed Alzheimer's/vascular, or dementia with Lewy bodies) between 1 Nov 2007–31 Oct 2021: 18,252 people were identified during the observation period.

Measurements: A natural language processing algorithm was used to identify recorded clinician recording of SI around the time of dementia diagnosis. Sociodemographic and clinical characteristics were also measured around the time of diagnosis. We compared people diagnosed with non-Alzheimer's dementia to those with Alzheimer's and used statistical models to adjust for putative confounders.

Results: 15.1% of patients had recorded SI, which was more common in dementia with Lewy bodies compared to other dementia diagnoses studied. After adjusting for sociodemographic and clinical factors, SI was more frequent in those with depression and dementia with Lewy bodies and less common in those with impaired activities of daily living and in vascular dementia. Agitated behavior and hallucinations were not associated with SI in the final model.

Conclusions: Our findings highlight the importance of identifying and treating depressive symptoms in people with dementia and the need for further research into under-researched dementia subtypes.

Key words epidemiology, suicide, suicidal ideation, dementia, dementia with Lewy bodies, Alzheimer's dementia, vascular dementia

Introduction

Around 50 million people worldwide have dementia and this number is predicted to triple by 2050 (Frankish and Horton, 2017; Livingston *et al.*, 2017). Disability, dependence, loss of personhood, and burden for family members associated with dementia are commonly feared (Haw *et al.*, 2009).

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Although people with dementia are generally at low risk of suicide compared to the age-matched general population, they may be at increased risk in the early period after diagnosis (Haw *et al.*, 2009). A recent Danish registry-based study found that whilst the incidence risk ratio in people with dementia was lower overall, risk was elevated in the 3 months following dementia diagnosis (Erlangsen *et al.*, 2020). The overall adjusted incidence risk ratio was 0.8 (95% CI, 0.7–0.9); during the first month after diagnosis it was 3.0 (95% CI, 1.9–4.6; P < .001) (Erlangsen *et al.*, 2020). Increased risk of suicide attempt has also been reported in patients

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with a recent diagnosis of dementia and mild cognitive impairment (Günak et al., 2021).

The reasons for these associations and temporal trends are not clear, but several explanations have been proposed. Patients with early dementia might have psychiatric comorbidities, such as depression, which increase suicide risk (Erlangsen *et al.*, 2020; Haw *et al.*, 2009). Another plausible mechanism for the elevated suicide risk immediately after diagnosis is the distress associated with receiving a diagnosis (Álvarez Muñoz *et al.*, 2020; Erlangsen *et al.*, 2020). Initial awareness of the implications of a diagnosis whilst cognition is relatively preserved, and while patients are in possession of the cognitive means to plan and effect suicide, may contribute to this period of increased risk (De Berardis *et al.*, 2018; Erlangsen *et al.*, 2020).

In light of these findings, we were interested in suicidal ideation (SI) in people with dementia around the time of diagnosis. Previous literature has identified that SI is observed in mild dementia and is strongly associated with depression (Haw et al., 2009). However, there are limitations of the current literature, including small sample sizes, unclear definitions of SI and insufficient investigation of the impact of diagnosis subtypes, particularly non-Alzheimer's dementias (Draper, 2015; Haw et al., 2009). We therefore specifically investigated diagnostic subtypes, including vascular dementia and dementia with Lewy Bodies (DLB). It is thought that patients with these disorders may be at increased risk due to the association of these subtypes with neuropsychiatric symptoms such as depression and, especially in the case of DLB, hallucinations, and delusions (Armstrong et al., 2020; Haw et al., 2009).

As the prevalence of dementia rises with increasing age, we were also interested in risk factors for suicidality in older adults, including physical illness, impairment in functioning, and activities of daily living and social isolation (Conwell *et al.*, 2011).

We hypothesised that preserved cognitive functioning, co-occurring neuropsychiatric symptoms, functional difficulties, and some dementia diagnosis subtypes (particularly DLB) would be associated with SI.

Methods

Data source

Data for this study were collected using the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) platform. SLaM is one of Europe's largest healthcare providers for dementia and mental illness and serves a population of over 1.36 million residents across four south London boroughs (Lambeth, Lewisham, Southwark, and Croydon). All services in SLaM have adopted fully electronic health records since 2006 and CRIS provides research access to over 400,000 anonymized health records within a robust governance framework (Fernandes *et al.*, 2013; Perera *et al.*, 2016). CRIS has received ethical approval as an anonymized data resource (Oxford Research Ethics Committee C, reference 18/SC/0372) and its functionality is enhanced through application of natural language processing to identified relevant information from free-text records (Mueller *et al.*, 2020; Perera *et al.*, 2016).

Study sample

We included patients who received a diagnosis of dementia in SLaM services between 1 Nov 2007 and 31 Oct 2021. The date of first dementia diagnosis served as index date for analysis. We included patients who received a diagnosis of Alzheimer's dementia (F00), vascular dementia (F01), a mixed-type dementia (including F00.2 or mentions of both F00 and F01 in the same record), or DLB according to the International Classification of Diseases, version 10 (World Health Organization, 2010). Diagnoses of dementia were ascertained from structured fields, supplemented by data from free-text records as previously described (Mueller et al., 2020). As there is no unique code for DLB used in mental health records, this diagnosis was identified through natural language processing, and the performance of this approach has previously been evaluated. Of 69 electronically identified cases of DLB, expert diagnoses were probable or possible DLB in 78.3% of cases and dementia in Parkinson's disease in 17.4% of cases. Only three case records (4.3%) contained false positives (Mueller et al., 2018).

Suicidality

A natural language processing application was used to identify clinician records referring to expressions of SI in a 1-year window around the index date of first dementia diagnosis (6 months before or after index date) (CRIS NLP SERVICE, 2020). The algorithm identified SI as the recorded thinking about considering or planning suicide from text fields in the record and was developed through expert annotation. In this process domain experts code whether the variable of interest is present in the current document having agreed pre-defined coding rules (Mueller *et al.*, 2020). Examples of positive annotations include: "Her main concerns were his low mood and 'the patient's suicidal ideation" and

"He has recently sent a letter (...) describing suicidal ideation", while examples of negative annotations are "There was no immediate risk in relation to self-harm or current suicidal ideation" and "She denies having self-harming or suicidal ideation". Interrater reliability (Cohen's k) from wider performance data (not limited to people with dementia), based on 50 documents (identified through the term ideat*), was 92%; precision, based on a random sample of 30 patients, was 97% (CRIS NLP SER-VICE, 2020).

Covariates

Sociodemographic factors as recorded at index date were ascertained as follows: age, gender, marital status, ethnicity (dichotomised to White and non-White) and a neighborhood-level index of deprivation (Noble et al., 2007). Cognitive performance was measured through the Mini-Mental State Examination (MMSE) score closest to the initial date of diagnosis (Folstein et al., 1975). Co-occurring mental and physical health problems, as well as functional difficulties, were established using the Health of the Nation Outcome Scales (HoNOS) (Burns et al., 1999). HoNOS is a well-established and validated measure of patient welfare, routinely used in UK dementia and mental services and encompassing 12 clinician-rated subscales. We included scales on difficulties due to neuropsychiatric symptoms, including agitated behavior, hallucinations and/or delusions or depressed mood, physical illness, or disability and activities of daily living. Each subscale is rated on a scale ranging from 0 (no problem) to 4 (severe or very severe problem). We dichotomized the scores to "minor or no problems" (scores 0 or 1) and "mild to severe problems" (scores 2-4) for easy interpretation (Burns et al., 1999).

Statistical Analyses

We used Stata version 15 (StataCorp. 2017, College Station, TX). Descriptive statistics were generated and presented for the full cohort, and whether or not the patient was recorded as displaying SI. We applied several logistic regression models to identify cross-sectional predictors of SI: first the crude/univariable analysis (model 1) and adjusted for age and gender (model 2), then for all sociodemographic variables and mean MMSE at diagnosis (model 3). Lastly, further adjustment was undertaken for physical illness and for problems with activities of daily living (model 4).

As 44% of the patients included in the final sample had missing data on at least one of the other covariates (whereby 25% of that missingness were attributable to missingness on HoNOS and MMSE

scores exclusively) and we judged missingness in this sample to be random, we imputed missing values using chained equations to maximize statistical power (Oudshoorn *et al.*, 1999). Applying the *mi* package in STATA, we created 22 imputed datasets through replacing missing values through simulated values assembled from potential covariates and outcome values. Rubin's rules were applied to combine coefficients in final analyses (Rubin, 2004).

Results

We identified 18,252 patients diagnosed with the specified dementia subtypes over the observation period. 15.1% had recorded SI around the time of dementia diagnosis. In relation to dementia subtype, 15.9% of patients with Alzheimer's dementia had SI recorded, 13.1% of patients with vascular dementia, 14.5% of patients with mixed-type dementia, and 19.9% of those with DLB.

Table 1 compares those with and without SI. Patients with SI were younger, more likely to be male and from less deprived areas. Those with SI had higher mean MMSE scores and were less likely to present with difficulties with activities of daily living. While a depressed mood was more frequently recorded in those with SI, agitated behavior and physical health problems were detected more frequently in those without SI. The proportion of patients with vascular dementia was lower in the SI group and the proportion of patients with DLB higher.

Table 2 presents logistic regression models for the association of patient characteristics and subtype diagnoses with SI. After adjustment for age and gender (model 2), a higher MMSE score, depressed mood, and a diagnosis of DLB were associated with SI. Conversely, higher deprivation, physical illness, impaired activities of daily living, agitated behaviors, as well as the diagnosis of vascular and mixed-type dementia were associated with lower odds of recorded SI.

Our final logistic regression model (adjusted for demographics, MMSE, physical illness, and problems with activities of daily living, model 4) identified male gender, not being married or cohabiting, and lower area-level deprivation to be associated with greater probability of recorded SI. Clinical factors associated with increased probability of SI included depressed mood and DLB subtype (odds ratio (OR): 1.35; 95% confidence interval (CI): 1.09–1.66; p-value = 0.005), while a diagnosis of vascular dementia yielded lower odds of SI compared to Alzheimer's disease. Of factors associated with dementia severity, the presence of impaired

Table 1. Sample characteristics for the whole cohort and by the presence of suicidality

| | | PATIENTS WITH | PATIENTS WITHOUT | | |
|---|-----------------------|-------------------|-------------------|--------------------|--|
| | FULL COHORT | SUICIDAL IDEATION | SUICIDAL IDEATION | P | |
| RISK FACTORS | (N = 18, 252) | (N = 2,756) | (N = 15,496) | VALUE ^A | |
| Sociodemographic status and cognitive | function ^b | | | | |
| Mean age at dementia diagnosis (SD) | 81.4 (8.3) | 81.1 (8.6) | 81.5 (8.2) | 0.031 | |
| Female gender (%) | 61.4% | 59.7% | 61.7% | 0.039 | |
| Non-White ethnicity (%) | 28.4% | 29.6% | 28.2% | 0.171 | |
| Married or cohabiting status (%) | 34.3% | 33.4% | 34.4% | 0.349 | |
| Mean index of deprivation (SD) | 27.2 (11.0) | 26.1 (11.2) | 27.3 (11.0) | < 0.001 | |
| Mean MMSE score at diagnosis (SD) | 18.4 (6.5) | 18.9 (6.4) | 18.4 (6.5) | 0.001 | |
| Dementia subtype | | | | | |
| Alzheimer's disease | 51.9% | 54.6% | 51.4% | < 0.001 | |
| Vascular dementia | 21.7% | 18.8% | 22.3% | | |
| Mixed-type dementia (including | 23.0% | 22.1% | 23.2% | | |
| Alzheimer's disease and Vascular | | | | | |
| dementia) | | | | | |
| Dementia with Lewy bodies | 3.4% | 4.5% | 3.2% | | |
| Neuropsychiatric symptoms (%) ^c | | | | | |
| Agitated behavior | 15.9% | 14.0% | 16.2% | 0.021 | |
| Hallucinations and/or delusions | 11.5% | 11.5% | 11.5% | 0.954 | |
| Depressed mood | 12.5% | 16.8% | 11.8% | < 0.001 | |
| Physical illness or disability (%) ^c | 48.7% | 45.6% | 49.2% | 0.005 | |
| Activities of daily living (%) ^c | 54.9% | 48.5% | 55.9% | < 0.001 | |

MMSE, Mini-Mental State Examination; SD, standard deviation.

activities of daily living remained associated with lower recording of SI, while a higher MMSE score predicted SI, but this association was no longer significant (OR: 1.01; 95% CI: 1.00–1.01; p-value = 0.059).

Discussion

In our study of more than 18,000 patients in routine health care, 15.1% of people with dementia had a record of SI around the time of diagnosis. After adjusting for sociodemographic and clinical factors, SI was more frequent in those with depression and a diagnosis of DLB and less common in those with impaired activities of daily living and a diagnosis of vascular dementia.

Few previous studies have reported the prevalence of SI in people with dementia (Draper, 2015). Nevertheless, our data can be compared to two outpatient studies, both of which used the Hamilton Depression Rating scale to identify SI over the preceding week. An Australian study reported the prevalence of different severities of SI: 5.4% of patients felt life was not worth living, 3.2% reported a "wish to die" and 0.9% reported SI or gestures (Draper *et al.*, 1998). Another outpatient study, conducted in America, reported 10% felt life was

not worth living, although the sample was small (Harwood and Sultzer, 2002). Compared to these studies, the prevalence of SI was higher in our study. This may reflect the longer period of observation: we observed patients for 1 year. Our study would also identify recorded SI in people with dementia reported by their carers to clinicians: it has been noted that prevalence of SI is higher in studies using caregiver-administered questionnaires compared to patient self-report (Draper *et al.*, 1998).

We found that younger age was associated with SI in a model adjusted for demographics and cognition (model 3), which is consistent with other studies of suicidality in people with dementia and may reflect difficulties in adjusting to the diagnosis (Álvarez Muñoz et al., 2020; Draper, 2015). Other predictors identified are also consistent with known risk factors in older adults without dementia. We found patients who were not married or cohabiting had a greater risk of SI; loneliness, low social support, and loss of a spouse have also been associated with increased risk in older adults (Conwell et al., 2011).

Less severe dementia at diagnosis was associated with higher odds of presenting with SI, which was reflected in both the MMSE score and our measurement of functional impairment. Previous studies of SI often lack information about the stage of dementia (Draper, 2015); nonetheless, our finding would

^at-test or Chi² test.

^bAt/around the time of dementia diagnosis.

^cPercentage with HoNOS scores of 2-4 at the time closest to dementia diagnosis.

Table 2. Associations between the characteristics of people with dementia with and without SI and the probability of SI in logistic regression models (presented as odds ratios and 95% confidence intervals)

| CLINICAL CHARACTERISTICS/RISK FACTORS | | MODEL 1 (CRUDE) | MODEL 2 (ADJUSTED FOR AGE AND GENDER) | MODEL 3 (ADJUSTED FOR A AND B) | MODEL 4 (ADJUSTED FOR A-D) |
|---|---|--------------------|---------------------------------------|--------------------------------|----------------------------|
| (A) Sociodemographic factors at time of | Age ^a | 0.99 (0.99-1.00) | 1.00 (0.99–1.00) | 0.99 (0.99-1.00) | 1.00 (0.99–1.00) |
| diagnosis | Female gender | 0.92 (0.84-1.00) | 0.93 (0.85–1.01) | 0.91 (0.83-0.99) | 0.90 (0.83-0.98) |
| | Non-White ethnicity | 1.06 (0.97–1.16) | 1.04 (0.95–1.14) | 1.09 (0.99–1.20) | 1.09 (0.99-1.20) |
| | Married or cohabiting | 0.96 (0.88–1.06) | 0.92 (0.84–1.02) | 0.89 (0.81-0.98) | 0.88 (0.80-0.97) |
| | Mean index of deprivation ^b | 0.91 (0.87-0.94) | 0.90 (0.87-0.94) | 0.90 (0.87-0.93) | 0.91 (0.88-0.95) |
| (B) Mean MMSE at time of diagnosis ^c | | 1.01 (1.01-1.02) | 1.01 (1.00-1.02) | 1.01 (1.01-1.02) | 1.01 (1.00-1.01) |
| (C) Physical illness or disability ^d | | 0.85 (0.77-0.94) | 0.86 (0.77-0.95) | 0.89 (0.80-0.99) | 0.96 (0.86-1.08) |
| (D) Problems with activities of daily living ^d | | 0.74 (0.68-0.82) | 0.75 (0.68-0.83) | 0.78 (0.71-0.87) | 0.79 (0.71-0.89) |
| Neuropsychiatric symptoms ^d | Agitated behavior | 0.83 (0.72-0.96) | 0.82 (0.72-0.95) | 0.88 (0.76-1.03) | 0.95 (0.81-1.10) |
| | Hallucinations and/or delusions | 0.98 (0.82–1.18) | 0.99 (0.83-1.18) | 1.02 (0.86-1.23) | 1.08 (0.90-1.29) |
| | Depressed mood | 1.47 (1.26–1.71) | 1.47 (1.26-1.71) | 1.50 (1.29-1.76) | 1.60 (1.37-1.88) |
| Dementia subtype | Alzheimer's dementia $(n = 9,468)$ | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| | Vascular dementia $(n = 3,968)$ | 0.79 (0.71-0.88) | 0.78 (0.70-0.87) | 0.80 (0.72-0.89) | 0.81 (0.73-0.90) |
| | Mixed-type dementia (including A lzheimer's and vascular) (n = 4,199) | 0.90 (0.81-0.99) | 0.89 (0.81-0.99) | 0.90 (0.81-1.00) | 0.92 (0.83–1.03) |
| | Dementia with Lewy bodies $(n = 617)$ | 1.32 (1.07-1.62) | 1.28 (1.04–1.57) | 1.28 (1.04–1.58) | 1.35 (1.09–1.66) |

MMSE, Mini-Mental State Examination.

^aPer 1-year increase in age.

bPer 10-point increase in deprivation score.
cPer one point increase in MMSE score.
dThose with HoNOS score 2–4 form the exposure group; bold denotes p value below the threshold for significance set at p < 0.05.

be consistent with research on suicide, in particular the Danish registry study described in our introduction (Erlangsen *et al.*, 2020). It would also be consistent with the theory that suicide risk may plausibly be elevated in the early stages of dementia when insight into the illness and its prognosis may be preserved (De Berardis *et al.*, 2018; Haw *et al.*, 2009).

The Danish registry study also showed the incidence risk ratio for suicide declined following a period of increased risk in the 3 months after diagnosis: this may be due to the reduced ability to consider and plan acts of suicide as cognitive impairment progresses (Erlangsen et al., 2020). Our study suggests that the pattern observed for SI may also be similar to that of suicide, with more advanced dementia being associated with lower risk. Agitated behavior (which is more common in moderate and severe stages of dementia (Livingston et al., 2017)) was only associated with a greater risk of SI in our first two models. In our more complex models, which include adjustment for other markers of dementia severity such as problems with activities of daily living, the association of agitated behaviour with SI was no longer significant.

Depressed mood was significantly associated with SI, which is in keeping with previous research showing depression is a risk factor for SI in dementia and also for suicide in later life (Conwell *et al.*, 2011). Depression is common in dementia and is associated with behavioral disturbance, poorer quality of life, and significant functional impairments even if the depressive symptoms are mild (Lyketsos *et al.*, 1997; Starkstein *et al.*, 2005).

After confounder adjustment, patients with DLB were at 1.35 higher odds of SI than those with Alzheimer's dementia. There are several possible explanations for this. First, patients with DLB might have a greater burden of non-cognitive symptoms, which significantly impact quality of life (van de Beek et al., 2019). These include delusions and hallucinations, behavioral disturbances, and sleep disorders (Armstrong et al., 2020; Galvin et al., 2010). Second, patients with DLB may have fluctuating insight into their cognitive limitations and times of greater insight and functioning could plausibly be associated with increased risk (Armstrong et al., 2020). Finally, patients and their carers report negative experiences of the diagnostic process with DLB: they may attend multiple consultations over years and receive a delayed diagnosis or an initial misdiagnosis (Armstrong et al., 2020; Galvin et al., 2010; Surendranathan et al., 2020). Reaching a diagnosis in DLB may be more challenging because of fluctuations in symptoms and use of different diagnostic criteria, which may lead to lower case detection rates (Hogan et al., 2016).

Vascular dementia subtype was associated with decreased risk for SI in our study. This is in keeping with previous research showing that, despite depression being more common in vascular dementia compared to Alzheimer's dementia, suicide may be less common (Haw *et al.*, 2009).

In addition to the differing symptom profiles of the dementia subtypes, underlying neurobiological changes might explain the variation in risk associated with different types of dementia. For example, amyloid deposits, which are observed in Alzheimer's disease, are a risk factor for suicide (De Berardis et al., 2018).

Strengths and limitations

Strengths of this study are the large sample size compared to previous studies: to our knowledge, this is the largest cross-sectional study of dementia and SI to date (Álvarez Muñoz et al., 2020). A further strength is the specific comparison of non-Alzheimer's dementias to Alzheimer's disease dementia. Our use of routinely collected data minimises response bias and we incorporated widely used and validated measures (MMSE and HONOS).

Limitations include a reliance on the accuracy of clinical data entries and on the natural language processing algorithm to bolster the detection of covariates. The algorithm for SI detection was not limited to people with dementia. As such, internal validity may be affected if people with dementia express SI differently to other patients in secondary mental healthcare settings and further investigation of this should be undertaken. We also acknowledge that we would not have detected SI if clinicians had not enquired, or patients declined to disclose it.

It is conceivable that clinicians, who are aware of the distressing neuropsychiatric symptoms in DLB, may enquire more frequently about SI in this patient group. This could plausibly have biased our results towards greater detection of SI in DLB compared to those with other dementia subtypes. However, we consider this unlikely because, in the UK, patients attending memory clinic are routinely asked about SI regardless of their dementia subtype.

Our findings for DLB also depend on the accurate detection and diagnosis of dementia subtype by clinicians. In our sample, 3.4% of all patients with dementia had the DLB subtype, which is in line with one previous estimated range of 3.2–7.1% from a previous systematic review (Hogan *et al.*, 2016). Due to being at the lower end of the expected DLB case detection rate, it is plausible that patients we included with DLB represent those with more

troubling neuropsychiatric symptoms who are more likely to come to medical attention.

Our study specifically focused on SI, but we were not able to investigate the related outcomes of selfharm and suicide, which might be expected to have similar associations. An NLP algorithm is not yet developed for the identification of self-harm in routinely collected data and suicide is challenging to study due to it being a comparatively rare outcome.

Conclusions and future research directions

The association of neuropsychiatric symptoms, physical illness, or disability and DLB subtype with a greater probability of SI highlights the need for further research to delineate potential causal relationships between the studied covariates and suicidality. This could be done using longitudinal designs and including more detailed measures of executive function in the months and years after diagnosis. Additional research in other locations would also inform the external validity of this study's findings.

Further study of the associations between SI, suicide attempt, and suicide would be of interest to clinicians in understanding the risk of these different outcomes. The potential effect of addressing modifiable risk factors such as depression and other neuropsychiatric symptoms should be undertaken. The potential for postdiagnostic support to reduce suicidality should also be investigated; the introduction of community support for people with dementia is one suggested explanation for a lower suicide rate in more recent cohorts of people with dementia in Denmark (Erlangsen *et al.*, 2020).

Efforts to reduce the estimated 4.8% of patients expressing SI after a dementia diagnosis may be served by further training memory clinic staff to ask about SI and addressing modifiable risk factors. Involving carers in medication safeguarding as part of means restriction may reduce risk as the suicide prevention intervention supported by the strongest evidence (Zalsman *et al.*, 2016).

Conflict of interest

R. Stewart has received funding from Janssen, GSK, and Takeda outside the submitted work. Other authors have nothing to disclose.

Description of authors' roles

C. Mueller, R. Howard, and H. Naismith formulated the research question; C. Mueller ran the CRIS data extraction and statistical analysis;

C. Mueller and H. Naismith wrote the first draft of the manuscript; C. Mueller, H. Naismith, and R. Howard made revisions to the manuscript in response to feedback from reviewers; all authors read, commented on, and contributed to the final manuscript.

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The data accessed by CRIS remain within a National Health Service firewall and governance is provided by a patient-led oversight committee. Subject to these conditions, data access is encouraged and those interested should contact R. Stewart (robert.stewart@kcl.ac.uk), CRIS academic lead.

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