Clinical Kidney Journal, 2025, vol. 19, no. 1, sfaf355

https://doi.org/10.1093/ckj/sfaf355
Advance Access Publication Date: 22 November 2025
Original Article

ORIGINAL ARTICLE

The electronic frailty index indicates mortality risk in end stage kidney disease patients on haemodialysis: retrospective survival analyses using linked data from two sources

Samuel D. Relton[1], Jenny Hewison[1], Zoe Rogers[1], Usha Appalsawmy[2], Kuldeep Sohal[3], John Birkinshaw[3], John Stoves[4], Robert West[1] and Andrew Mooney[1,2]

[1]Leeds Institute of Health Sciences, School of Medicine, University of Leeds, Leeds, UK, [2]Renal Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [3]Bradford Institute for Health Research, Bradford, UK and [4]Renal Unit, Bradford Royal Infirmary, Bradford, UK

Correspondence to: Andrew Mooney; E-mail: andrew.mooney2@nhs.net

ABSTRACT

Background. Over the last 30 years, with increasing comorbidity and frailty among people with end-stage kidney disease, there is recognition that dialysis may carry little benefit in some patient groups. We examined the utility of the electronic frailty index (eFI), modelling the survival time of patients starting dialysis at a single renal unit in northern England, hypothesising this would give useful prognostic survival information.

Methods. Two datasets describing the same population of patients receiving dialysis over a 226-month period (2000–2019) at a single dialysis unit were used ($n = 599$ and 553 participants). One dataset was derived from primary care (linked to UK Renal Registry submissions) and the other from the UK Renal Registry (linked with primary care data to facilitate eFI calculation). Retrospective survival analysis was undertaken with hazard ratios for the impact of eFI and other covariates on survival.

Results. The frailty score at dialysis start has a strong effect on subsequent survival time using either the primary care–derived or UK Renal Registry dataset, but there were differences in overall survival and the relation between eFI score and survival between datasets.

Conclusions. This represents the first study of eFI utility within tertiary renal care, demonstrating a strong association between frailty measured by eFI and survival time for patients on dialysis. However, significant differences between primary care–derived and UK Renal Registry–derived survival at different frailty scores were demonstrated. These differences indicate a need for greater understanding and analysis of large datasets before using them to discuss patient treatment choices, service planning and delivery.

Keywords: dialysis, eFI, electronic frailty index, survival modelling

Received: 28.1.2025; accepted: 13.11.2025

KEY LEARNING POINTS

What was known:

- Dialysis does not benefit some patients who are elderly, frail or comorbid.
- The electronic frailty index (eFI) derived from primary care records can predict outcomes in elderly community-dwelling people regarding hospitalisation, independence and survival.

This study adds:

- This is the first analysis of the utility of eFI in tertiary care, requiring linkage between primary and secondary care data.
- The study demonstrates the utility of the eFI in patients at dialysis start, indicating a strong correlation between eFI score and survival.
- Discrepancies exist depending on whether dialysis patients are identified from primary or secondary care sources.

Potential impact:

- Scores such as the eFI have strong potential to support patient decision-making about dialysis treatments, as well as service planning and delivery, and merit further evaluation.

INTRODUCTION

Over the last 30 years, the population of patients receiving dialysis has changed significantly [1]. In the UK, the median age of patients starting dialysis has risen to >65 years alongside increasing rates of comorbidity [1]. Dialysis is an invasive treatment associated with reduced quality of life [2], heavy symptom burden [3] and limited survival [1]. Increasingly, studies are suggesting there are patient groups for whom this treatment carries little, if any, benefit [4–8].

Thus there are now published guidelines advocating the consideration of conservative (non-dialysis) management for certain patient groups [9], making it increasingly important to identify those who would derive little or no survival benefit from dialysis. Factors shown to impact survival after commencing dialysis include comorbidity [4–8], functional status [4–8] and frailty [10, 11].

Frailty is the state of reduced resistance to adverse stressors. Recent conceptualisations based on a defined phenotype [12] or model of accumulated deficits [13] have allowed measurement and risk stratification in a variety of healthcare settings [14–16].

On this background, the electronic frailty index (eFI) was recently described [17]. Based on the Rockwood model of cumulative frailty, comprising 36 items, it is automatically calculated from 2171 primary care Read codes. Developed and validated in a population of 65- to 95-year-old community-dwelling people, it correlated with hospitalisation, institutionalisation and survival over a 5-year period [17]. The eFI has been made available to all general practices in England and Wales. It is also available in some secondary care settings but had not previously been validated in any tertiary renal practice.

We speculated that the eFI could give valuable prognostic information for people with advanced kidney disease approaching dialysis, with utility for commissioning and service planning, plus shared decision-making with patients for dialysis treatment and targeting of specific frailty-relevant interventions.

Therefore we sought to analyse data pertaining to people receiving dialysis at a single large renal unit in the north of England over a fixed time period, seeking correlation between outcomes on dialysis and eFI scores.

Typically such research would use the UK Renal Registry (UKRR) to decide who should be included within the cohort for analysis. The UKRR was established by the UK Renal Association in 1995, collating data originally limited to people on a renal replacement therapy, though more recently including data on advanced chronic kidney disease (CKD) in secondary care not on dialysis [1]. Recently Hole *et al.* [18] described several potential issues with this approach, which might lead to underestimation of mortality. To investigate this we used two approaches to define our study cohort that, in theory, should lead to the same study population.

The first study population was obtained in the standard fashion: using data submitted to the UKRR by the renal unit of the Bradford Teaching Hospitals Trust, which provides dialysis services to all patients in the region. This population receiving dialysis was augmented with the Connected Bradford (cBradford) database to obtain associated primary care data. The cBradford database covers >1 million citizens, 5 National Health Service (NHS) Trusts, 86 general practitioners and 200 schools and links pseudonymised health, education, social care, environmental and local government data.

The second study population was identified using primary care codes within the cBradford database: we selected all patients who were coded in their primary care record as receiving dialysis within the period of analysis (list of codes in Supplementary Table 1). These primary care records were augmented with information from the UKRR (e.g. date of transplant).

As these criteria both describe patients receiving long-term dialysis and this renal unit was the single dialysis provider for the entire catchment area of those in the cBradford population, both cohorts should theoretically have been identical; one was primary care derived with linked UKRR data and the other was UKRR derived with linked primary care data. However, discrepancies between the populations captured emphasise the need for careful consideration of selection biases when working with electronic healthcare records. Both datasets were subject to identical analysis.

MATERIALS AND METHODS

Study design, setting and patient identification

We analysed a cohort of patients beginning dialysis in a northern English hospital between 1 May 2000 and 6 March 2019 (the data extract date) using two cohort definitions as outlined above: first by augmenting the UKRR submission with primary care data and second by identifying dialysis within the primary care record and looking for the associated UKRR data. The cBradford database provided dialysis start dates, kidney transplant dates, basic demographics from the secondary care records linked to

the clinical codes from the primary care record for patients used to extract frailty scores and conditions within the Quality Outcomes Framework (QOF). The cBradford database ethical approval supports quality improvement and research purposes—primary care clinical data were recorded using the Read code CTV3 classification system. Data quality checks are performed centrally to assess data integrity, quality and representativeness of the population in England (https://tpp-uk.com/products/data-and-research/). The UKRR data were taken from the internal database that forms the basis of the unit submission to the registry.

The study was approved by the ResearchOne Project Committee and the University of Leeds, Medicine and Health University Ethics Review Committee (MREC-18-005) and the Connected Bradford Research Ethics Committee (IRAS ref: 227117 and REC ref: 17/EM/0254). No patients or members of the public were directly involved in this research.

Study participants

We identified all patients who began dialysis from the renal unit during the study period using two cohort definitions. First, the Bradford Renal Unit submissions to the UKRR were augmented with primary care data from the cBradford database, which we refer to as the UKRR-based cohort. Second, people were selected from within the cBradford database by searching for CTV3 codes indicating long-term dialysis and matched with their UKRR submission data—referred to as the CTV3-based cohort. The CTV3 codes used as inclusion criteria for the second cohort are shown in Supplementary Table 1. All individuals beginning dialysis within the study period with linked primary care records were eligible for inclusion. To determine frailty scores before treatment, patients whose primary care record began after the start of dialysis were removed from the dataset before analysis, which left 599 remaining in the UKRR data and 553 in the CTV3-based data. Eligibility for study inclusion ended on the earliest of the following: date of death or date of the last data item recorded from their general practitioner.

Study covariates and outcomes

Variables used for analysis were those collected within the UKRR database that we had access to (to ensure parity between both datasets) and the eFI of each patient extracted from the primary care record; UKRR comorbidity data were taken from secondary care records submitted for the period of time covered by this study. CTV3 codes for these covariates were taken from the QOF and the eFI. The full list of covariates can be seen in Table 3. All covariates are calculated based on the patient history at the time they started dialysis. The UKRR submission was used to determine the start date of dialysis and the date of transplant/death if applicable.

Mortality was extracted both from the date of death recorded in the primary care record and renal unit database of each patient (they matched in all cases), while the date of any kidney transplant was extracted from the renal unit database. Within the survival analysis, patients were right-censored after the earliest date when the following events occurred: death, a kidney transplant being recorded within the renal unit database or the last CTV3 code entered into their primary care record.

In terms of missing data, the non-appearance of a CTV3 code matching one of the conditions above was taken as an indication that the patient had not suffered from that specific condition. Basic demographics such as age at dialysis start and date of death did not have any missing values. The exception to this was for body mass index (BMI), where some patients had no matching events in their primary care record (see Table 1). Since BMI was treated as a categorical variable in our analyses, we encoded these cases with a specific 'Missing' category.

Table 1: Patient characteristics at the start of dialysis treatment for the UKRR cohort ($n = 599$) and the CTV3 cohort ($n = 553$).

	CTV3 cohort	UKRR cohort	P-value
Age (years), mean	57.7	59.4	.09
Female	41.8	39.4	.41
Male	58.2	60.6	.69
BMI			
Morbidly obese	4.3	3.2	.97
Obese	23.5	20.5	.22
Overweight	28.8	28.5	.91
Healthy	27.5	34.2	.01
Underweight	4.7	4.0	.56
Missing	11.2	34.2	<.001
Smoking			
Current	18.6	27.7	<.001
Former	27.7	5.3	<.001
Never	53.7	66.9	<.001
Angina	10.7	13.4	.16
Cancer	10.5	9.2	.13
Chronic vascular disease	17.7	21.4	.11
Chronic obstructive pulmonary disease	8.1	6.5	.30
Diabetes	44.1	46.6	.39
Ischaemic heart disease	17.7	26.4	<.001
Ischaemic neuropathic ulcer	0.5	0.8	.53
Myocardial infarction	4.3	6.7	.08
eFI	0.21	0.21	1.00

Values are presented as percentages unless stated otherwise.
Difference between the two datasets are expressed using *P*-values calculated via chi-squared or *t*-tests as appropriate.

Statistical analysis

Baseline patient characteristics are reported using either percentages or the median and interquartile range (IQR) for binary and continuous variables, respectively. We show the summary statistics where patients are split by eFI category (fit, mild, moderate and severe frailty) as defined in the original analysis [17] and look for any difference between the two cohort definitions using chi-squared tests.

Regarding statistical modelling, both cohort definitions were analysed in the same way as follows. First, a univariate analysis of all the dependent variables using the logrank test to compare the Kaplan–Meier curves of patients with various comorbidities. The continuous measures (age and eFI score) are categorised for the univariate testing: age is split into quartiles while the eFI is split into the standard fit, mild, moderate and severe frailty categories.

Second, we performed multivariate survival analysis to demonstrate the utility of primary care data and the eFI in dialysis survival modelling using only the information available at the beginning of dialysis treatment. Cox models were used throughout with the continuous variables (age and eFI) modelled using splines, where the number of knots is determined as explained below. Analyses were undertaken using Python for data cleaning (https://www.python.org/) and the R libraries splines, survival

and survminer for statistical modelling (https://www.r-project.org/).

We compare two survival models per cohort definition: a model using only the variables collected by the UKRR and a model adding the eFI score to the variables collected by the UKRR. The comparison of these models allows us to see the baseline performance using existing variables and discover the added impact of using the eFI to investigate the potential of linked primary and secondary care data in this patient group.

Models are compared using the concordance index, D-statistic and the Akaike information criterion (AIC). The number of knots used to model the effect of age and the eFI score are selected to minimise the AIC; in both cases this resulted in a linear term. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Model assumptions are checked by testing the Schoenfeld, Martingale and deviance residuals.

RESULTS

Overall mortality and patient characteristics

After data extraction and removing those whose available linked primary care record began after the start of dialysis treatment, there were 599 patients remaining in the UKRR-based cohort and 553 in the CTV3-based cohort. Overall, 46.1% of patients died over the study period within the UKRR-based cohort and 53.7% within the CTV3-based cohort. The median age at the start of dialysis was 60 years (IQR 40–75) in the UKRR and 60 years (IQR 37–76) in the CTV3. The proportion of patients who were male was 60.5% using UKRR data versus 58.2% using CTV3 data and the median survival time was 5.14 years (95% CI 4.27–6.18) in the UKRR and 5.6 (95% CI 4.8–6.7) in the CTV3. The median frailty score at the start of dialysis was 0.19 (IQR 0.11–0.31) in the UKRR and 0.19 (IQR 0.08–0.31) in the CTV3, equivalent to just under 7 of the 36 deficits.

A summary of the prevalence of our collected variables among all patients is shown in Table 1. This shows a number of differences between the two cohorts; for example, and most notably, in rates of ischaemic heart disease.

In Fig. 1 we show Kaplan–Meier curves for both cohort definitions. Fig. 2 shows Kaplan–Meier curves split by frailty category within each cohort definition, with the median survival of each group listed in Table 2. Of particular note is the large difference between median survival estimates in the severely frail group of 1.6 versus 2.7 years and that longer-term survival appears to be better in the cohort derived from the UKRR.

Univariate analysis

The logrank test results can be found in Table 3 for each cohort definition. We see that most of the recorded covariates are predictive and the strength of association is generally similar between the two cohorts despite the differences noted above.

Multivariate analysis

In Table 4 we show the HRs for fitting a survival model in each cohort without including the eFI. We see that HRs are comparable between cohorts, with the only major difference being in ischaemic neuropathic ulcers (CTV3 HR 7.1, UKRR HR 2.9); in the CTV3 cohort there were very few patients with this condition, leading to higher variability in the effect size and CI. The model metrics showed better concordance with the CTV3 cohort, but a lower AIC with the UKRR cohort: CTV3 concordance = 0.739, AIC = 3129.8, D = 1.593; UKRR concordance = 0.690, AIC = 3068.3, D = 1.258).

In Table 5 we add the eFI score as an additional predictor. As previously, we see that the models are largely comparable and the eFI is a hugely important predictor in both. Within the CTV3 cohort the HR is unfeasibly high [HR 34.4 (95% CI 8.7–136.3)], which we hypothesise to be related to performance bias: patients who are known to be highly frail receive closer attention, resulting in more thorough coding of their healthcare conditions and a more accurate frailty score. Similar to the models without the additional eFI, the CTV3 cohort had superior concordance, with the UKRR cohort having lower AIC (CTV3 concordance = 0.755, AIC = 3107.5, D = 1.727; UKRR concordance = 0.691, AIC = 3067.4, D = 1.291).

DISCUSSION

This study is the first validation of the eFI for its predictive utility in tertiary renal care and the first analysis of dialysis survival based on frailty scoring generated from routinely collected primary care data. It also provides the first analysis of dialysis survival among a cohort of people identified from their primary care record.

In keeping with other studies, frailty measured among dialysis patients by the eFI in the CTV3 dataset is more prevalent, more severe and occurring at an earlier age than similar groups who are not receiving dialysis [19–21]. The differences are particularly striking compared with the community-dwelling population in which the eFI was developed [17]; the median survival among this dialysis cohort is less than half of that in the eFI development cohort and this reduced survival is seen with a median age that is 15 years younger and a mean eFI score significantly higher. Other studies describing frailty and outcomes in people living with CKD and/or receiving dialysis show similar patterns [10, 11, 20–23].

However, although the datasets should have identified the same population cohort, comparative analysis of the outcomes using the two datasets under investigation revealed differences; although there was considerable overlap, there were different people included/excluded within the populations in each set. This was seen in demographic data, and also within some of the parameters within the datasets—e.g. there were more ‘fit’ patients in the CTV3 dataset (58% versus 42%) compared to the UKRR dataset; there were also differences in ischaemic heart disease and smoking prevalence. Discrepancies between cohorts of patients identified to be receiving dialysis depending on whether the identified patient dataset was derived from primary care, secondary care or the UKRR submissions have also been found by others [24].

Nevertheless, the survival curves for patients within each frail quartile (as described in the original eFI development paper) demonstrated that the eFI was a strong indicator of likely survival whether using the CTV3 or UKRR dataset. Such information could be highly valuable in pre-dialysis counselling, even though patients living with frailty value functional outcomes rather than just length of survival [25–27]; using an objective score to quantify the severity of frailty carries value, as physicians may underestimate the degree of frailty present [28].

Before their widespread use, however, the discrepancies between the outcomes viewed from primary or secondary care–derived datasets need to be properly understood. In the CTV3 dataset, between the least and most frail eFI groups, the survival curves separate early in the course after dialysis initiation but continue to widen so that ultimately the least frail quartile has

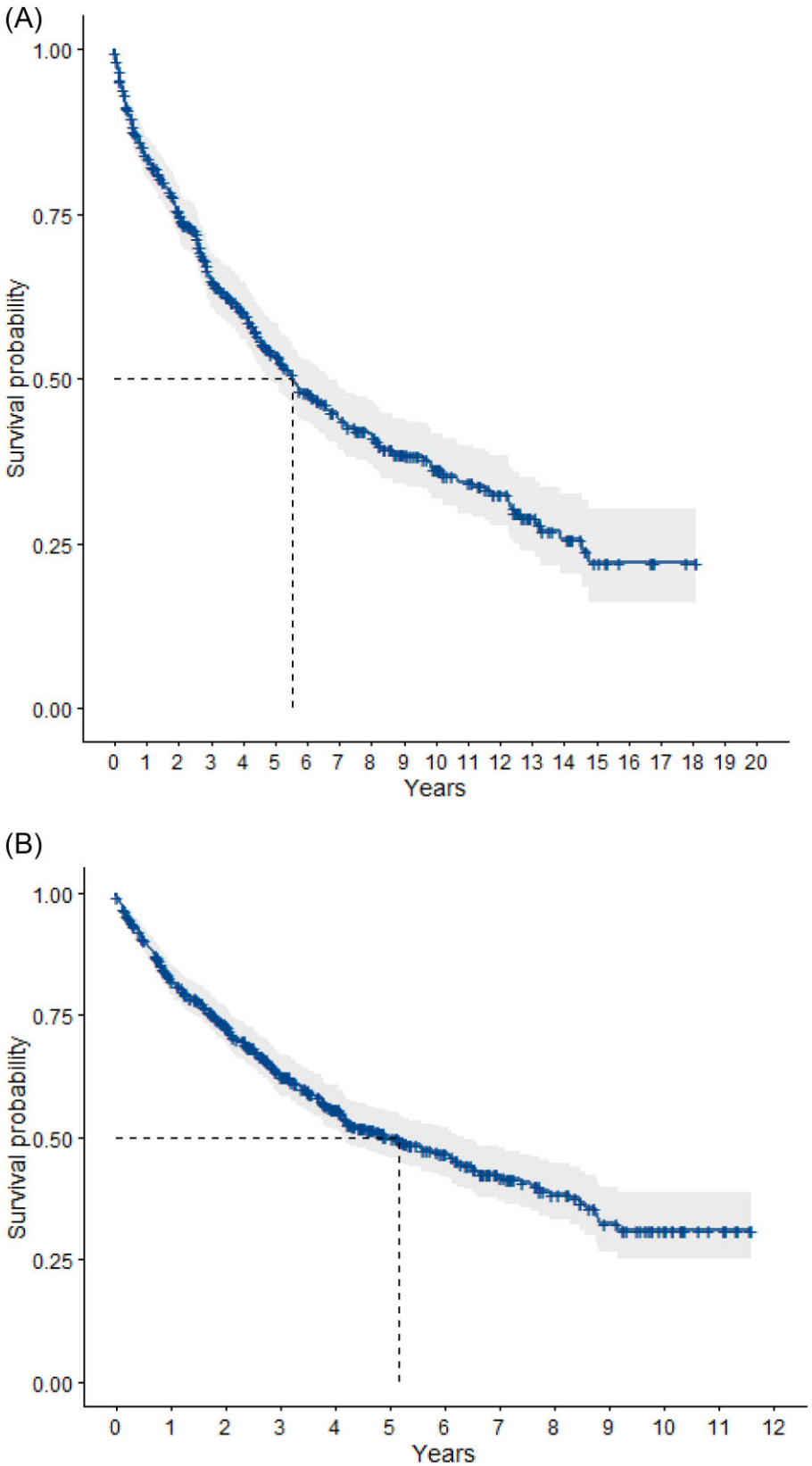

Figure 1: (A) Kaplan–Meier curve showing the survival function for all patients in the primary care–derived cohort and its 95% CI [median survival 5.55 years (95% CI 4.8–6.7)]. **(B)** Kaplan–Meier curve showing the survival function for all patients in the UKRR-derived cohort and its 95% CI [median survival 5.14 years (95% CI 4.1–6.4)].

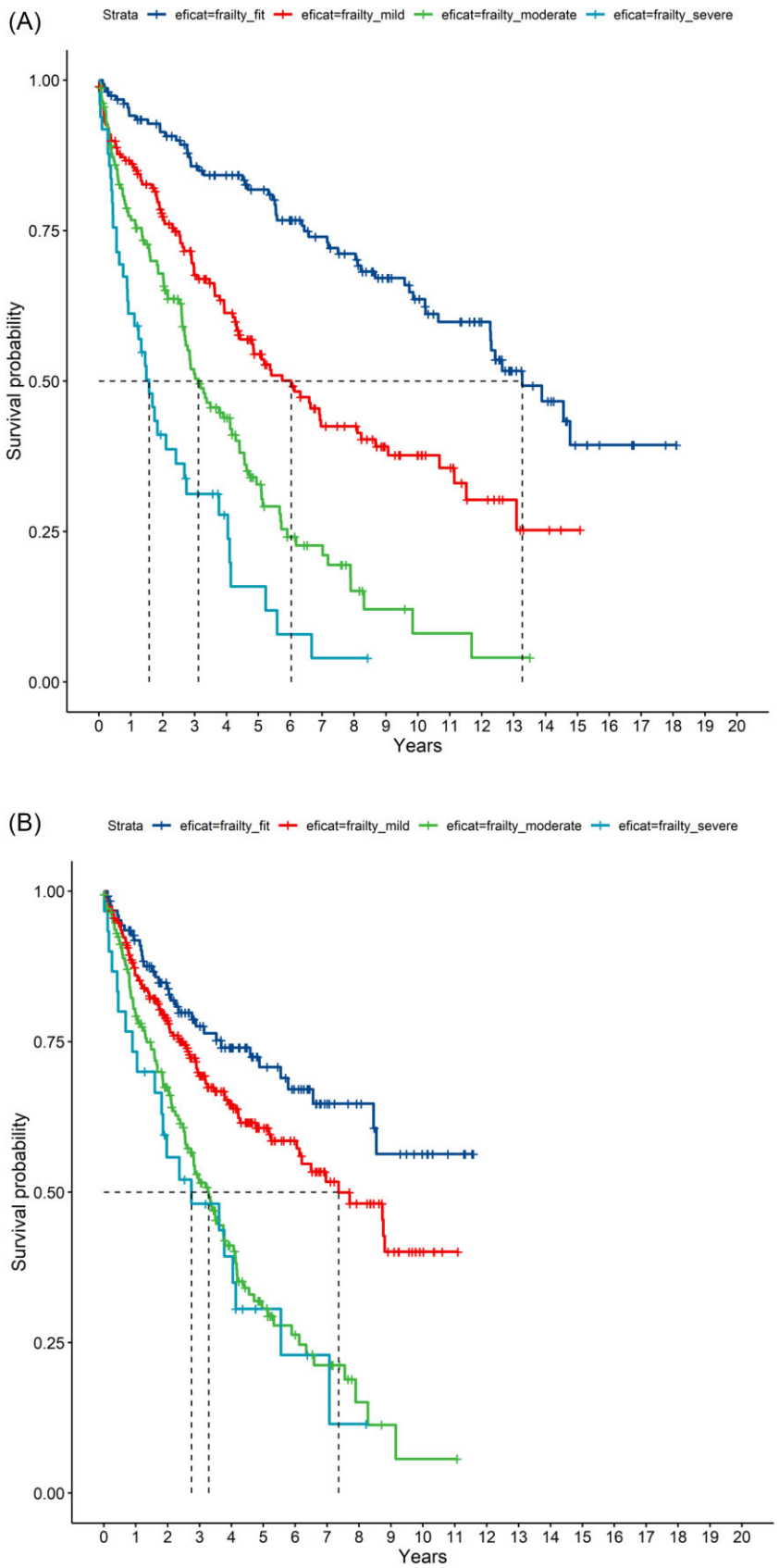

Figure 2: (A) Kaplan–Meier curve showing the survival function stratified by eFI category within the primary care–derived cohort. **(B)** Kaplan–Meier curve showing the survival function stratified by eFI category within the UKRR-derived cohort.

Table 2: Survival times and 95% CIs for each cohort definition when the population is stratified by frailty category.

CTV3-based cohort	*n*	Deaths	Survival (years), median (95% CI)
Fit	156	57	13.3 (12.3–NA)
Mild	189	95	6.0 (4.4–8.2)
Moderate	159	106	3.1 (2.7–4.3)
Severe	49	39	1.6 (0.9–2.8)
UKRR-based cohort	***n***	**Deaths**	**Survival (years), median (95% CI)**
Fit	125	35	NA (8.5–NA)
Mild	248	92	7.4 (6.1–NA)
Moderate	173	110	3.3 (2.7–4.1)
Severe	30	21	2.7 (1.8–NA)

NA: not available.
The Kaplan–Meier curves are shown in Fig. 2.

Table 3: Univariate survival analyses *P*-values using the logrank test.

Variables	CTV3 cohort	UKRR cohort
Age (quartiles)	<0.001	<0.001
Sex	0.1	0.08
BMI	<0.001	<0.001
Smoking	<0.001	0.05
Angina	0.005	0.03
Cancer	<0.001	<0.001
Chronic vascular disease	<0.001	<0.001
Chronic obstructive pulmonary disease	<0.001	<0.001
Diabetes	<0.001	<0.001
Ischaemic heart disease	0.004	<0.001
Ischaemic neuropathic ulcer	<0.001	0.004
Myocardial infarction	0.003	0.05
eFI (quartiles)	<0.001	<0.001

Kaplan–Meier curves for stratification by frailty category are shown in Fig. 2.

Table 4: HRs for the survival model variables collected by the UKRR with 95% CIs across both datasets.

Variables	CTV3 cohort	UKRR cohort
Age	1.05 (1.04–1.06)	1.04 (1.03–1.05)
Male	0.88 (0.67–1.15)	1.05 (0.81–1.36)
BMI		
Morbidly obese	0.98 (0.53–1.81)	0.86 (0.43–1.72)
Obese	0.86 (0.60–1.22)	1.03 (0.74–1.42)
Overweight	0.83 (0.60–1.15)	0.79 (0.78–1.08)
Underweight	1.38 (0.58–3.26)	0.27 (0.09–0.87)
Missing	1.58 (1.10–2.26)	1.50 (0.90–2.51)
Smoking		
Current	2.20 (1.58–3.06)	1.21 (0.91–1.60)
Former	1.16 (1.20–2.22)	1.40 (0.88–2.22)
Angina	0.54 (0.32–0.88)	0.67 (0.44–2.56)
Cancer	1.37 (0.97–1.93)	1.35 (0.92–1.97)
Chronic vascular disease	1.76 (1.09–2.83)	1.17 (0.76–1.79)
Chronic obstructive pulmonary disease	1.09 (0.73–1.63)	1.34 (0.88–2.04)
Diabetes	2.05 (1.56–2.68)	1.92 (1.44–2.56)
Ischaemic heart disease	0.95 (0.66–1.37)	1.09 (0.81–1.46)
Ischaemic neuropathic ulcer	7.11 (2.13–23.71)	2.94 (1.04–8.31)
Myocardial infarction	1.15 (0.66–2.00)	1.13 (0.70–1.83)

Table 5: HRs for the survival model using the eFI and UKRR variables with 95% CIs across both datasets.

Variables	CTV3 cohort	UKRR cohort
Age	1.04 (1.03–1.05)	1.04 (1.03–1.05)
Male	1.00 (0.76–1.31)	1.10 (0.84–1.43)
BMI		
Morbidly obese	0.84 (0.45–1.55)	0.82 (0.41–1.65)
Obese	0.81 (0.57–1.15)	1.00 (0.71–1.38)
Overweight	0.83 (0.60–1.16)	0.78 (0.57–1.06)
Underweight	1.27 (0.54–3.00)	0.27 (0.08–0.86)
Missing	1.57 (1.10–2.26)	1.54 (0.92–2.58)
Smoking		
Current	2.19 (1.57–3.06)	1.21 (0.91–1.61)
Former	1.54 (1.14–2.08)	1.39 (0.88–2.22)
Angina	0.48 (0.29–0.79)	0.67 (0.43–1.03)
Cancer	1.39 (0.99–1.96)	1.33 (0.91–1.94)
Chronic vascular disease	1.41 (0.87–2.28)	1.09 (0.71–1.68)
Chronic obstructive pulmonary disease	0.87 (0.87–1.32)	1.29 (0.85–1.96)
Diabetes	1.50 (1.12–2.01)	1.75 (1.29–2.38)
Ischaemic heart disease	0.95 (0.66–1.37)	1.08 (0.80–1.45)
Ischaemic neuropathic ulcer	5.78 (1.72–19.43)	2.89 (1.02–2.18)
Myocardial infarction	1.07 (0.62–1.85)	1.08 (0.67–1.76)
eFI	34.37 (8.67–136.25)	4.31 (0.81–22.81)

a median survival ≈3-fold superior or 10 years longer compared with that of the most frail.

However, whereas the less frail groups of the UKRR dataset have largely similar survival curves compared with the CTV3 dataset, outcomes in the 'severe' frailty group are most different, with even the most frail having a median survival twice that of the cBradford cohort. These results bear comparison with a recent analysis of survival undertaken as part of NHS Specialised Services [29]. In this report, the effect of the Hospital Frailty Risk Score (HFRS) [30] among patients >75 years of age found no patients free from frailty and overall a 30-month survival of nearly 60% among the most severely frail group [29]; deaths outside the hospital were not detected in the HFRS analysis and may have underestimated overall mortality rates.

The 'pseudonymisation' of the datasets prior to analysis precludes a complete examination of the reasons for these differences between datasets, however, the presence of greater numbers of dialysis patients in the CTV3 dataset missing a 'CKD' code suggests that patients with acute kidney injury may have been incorrectly coded (although there were also significant but fewer numbers with this anomaly in the UKRR cohort). Furthermore, the problem of accurately identifying early mortality among patients starting dialysis from end-stage kidney disease has been recognised and described by Hole *et al.* [18], whereby the UKRR may not contain these very early deaths in chronic dialysis patients.

It should be noted that we applied the eFI without modification, and the eFI has not been validated for use in populations younger than 65 years used in the eFI development, whereas in our dataset there was a wide IQR for our datasets (including as young as 37 years old); a separate analysis of performance in >65 and <65 year olds would be valuable but is beyond the scope of this study. Caution should be exercised when categorising frailty in younger people, given the risk of conflating multimorbidity (approximately half of eFI variables relate to health conditions)

and/or disability with frailty. Furthermore, eFI variables include 'anaemia and haematinic deficiency', 'polypharmacy' and other conditions that are likely to present at an earlier age in advanced CKD populations (and all included patients should have a deficit for the 'CKD' variable, although, as above, this was not always present). It is recommended that when developing frailty indices such as this, there should be exclusion of variables when coded deficits are too common and/or which are too highly correlated [31]. It is recognised that such steps are imperative before proposing prediction models for routine clinical use [32] and that survival data at the population level may be more difficult to utilise in individual patient management [33].

There are other potential limitations to the study presented. Significantly, the group under study all commenced dialysis, excluding those who chose not to receive this treatment. Further studies examining eFI scores in the pre-dialysis decision-making period may be helpful.

Nevertheless, we believe these results demonstrate that routinely collected patient primary care data such as those that contribute to calculation of the eFI have the potential to improve prognostication, clinical shared decision-making and service planning and are of sufficient interest to merit further investigation and analysis in patients with advanced CKD.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

Connected Bradford is a civic data cooperative that has been made possible by support from the people and professionals living and working in Bradford. We thank them for their enduring commitment. We also thank Andrew Clegg for advice and support on establishing and developing the project.

FUNDING

This research was funded by the Harry Summers Endowment Fund.

AUTHORS' CONTRIBUTIONS

S.R. and Z.R. had full access to the data in the study and were responsible for all the analyses. S.R., R.W., A.M., U.A., K.S., J.B., J.S. and A.C. were responsible for ethical approval and data acquisition. S.R., R.W., J.H. and A.M. were responsible for the study design. S.R., K.S., J.B., J.S. and A.C. were responsible for creation and validation of the diagnostic codes used to define conditions. S.R., K.S., J.B. and J.S. were responsible for creation of cohort and covariates. All authors approved the submission.

DATA AVAILABILITY STATEMENT

All data underlying this article are available in the article and in its online supplementary material. Further details about how to apply for Connected Bradford data are available at https://www.bradfordresearch.nhs.uk/our-researchteams/connected-bradford/.

CONFLICT OF INTEREST STATEMENT

All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work except for the Harry Summers Endowment Fund.

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Received: 28.1.2025; accepted: 13.11.2025