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ORIGINAL ARTICLE

Temporal trends in acute kidney injury across health care settings in the Irish health system: a cohort study

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ABSTRACT

Background. Complete ascertainment of the true rates of acute kidney injury (AKI) and emerging trends are essential for planning of preventive strategies within health systems.

Methods. We conducted a retrospective cohort study from 2005 to 2014 using data from regional laboratory information systems to determine incidence rates of AKI and severity Stages 1–3 in the Irish health system. Multivariable models were developed to explore annual trends and the contributions of demographic factors, clinical measures, geographic factors and location of medical supervision expressed as adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results. From 2005 to 2014, incidence rates of AKI increased from 6.1% (5.8–6.3) to 13.2% (12.7–13.8) per 100 patient-years in men and from 5.0% (4.8–5.2) to 11.5% (11.0–12.0) in women, $P < 0.001$. Stage 1 AKI accounted for the greatest growth in incidence, from 4.4% (95% CI 4.3–4.6) in 2005 to 10.1% (95% CI 9.8–10.5) in 2014 ($P < 0.001$ for trend). Compared with 2005, patients in 2014 were more likely to experience AKI [OR 4.53 (95% CI 4.02–5.1) for Stage 1, OR 5.22 (4.16–6.55) for Stage 2 and OR 4.11 (3.05–5.54) for Stage 3], adjusting for changing demographic and clinical profiles. Incidence rates of AKI increased in all locations of medical supervision during the period of observation, but were greatest for inpatient [OR 19.11 (95% CI 17.69–20.64)] and emergency room settings [OR 5.97 (95% CI 5.56–6.42)] compared with a general practice setting (referent).

Conclusion. Incidence rates of AKI have increased substantially in the Irish health system, which were not accounted for by changing demographic patterns, clinical profiles or location of medical supervision.

Keywords: acute kidney injury, acute renal failure, AKI, epidemiology, surveillance

INTRODUCTION

Acute kidney injury (AKI) is a global health issue, with severe episodes contributing to high rates of adverse clinical and economic outcomes [1–4]. The incidence of AKI varies widely in reported studies, from 486 to 2147 per million per year, which likely reflects differences in case ascertainment, changing definitions and the location of patient care [5–8]. The incidence of hospital-acquired AKI is ∼5–10 times higher than that of community-acquired cases [9]. AKI is a major independent predictor of both short- and long-term mortality in multiple settings and emerging evidence suggests that it also predicts long-term risk for cardiovascular events and end-stage kidney disease (ESKD) [4, 10–17].

Despite the public health importance of AKI, most published studies to-date have focused primarily on dialysis-requiring AKI (D-AKI) [18–20]. Evidence, mainly from the USA, has shown that the incidence of D-AKI has increased significantly in recent years, which may be related to the rising burden of acute and chronic medical illness [18, 20]. Non-dialysis-requiring AKI (ND-AKI) is a less well-studied entity and recent evidence suggests that the magnitude of this condition is substantially higher than D-AKI and may itself portend significant health risks [21]. Although great strides have been made in advancing the epidemiology of AKI, there remain several unanswered questions. First, there is residual doubt with regards to data validity, as most published studies on annual trends have relied mainly on clinical diagnosis codes rather than laboratory-based criteria for the identification and tracking of AKI events [22]. Second, clinical investigators have typically focused primarily on the most severe form of AKI that necessitates dialysis, with little or no data on less severe forms [23]. Third, there are limited data on the burden of AKI within health systems and the distribution of AKI events across the entire health system,

especially in key locations where preventive efforts may confer the greatest benefit [23].

To address these gaps in our knowledge, we determined temporal trends in the incidence and severity of AKI among new entrants to the Irish health system and further explored whether any observed variation in incidence rates over time might be explained by changes in demographic characteristics, markers of health status or changes in baseline kidney function prior to AKI.

MATERIALS AND METHODS

Data source

We utilized data from the National Kidney Disease Surveillance System, which serve to monitor trends and outcomes of chronic kidney disease (CKD) and AKI in the Irish health system [24]. Data sources included regional laboratory information systems, which capture all inpatient and outpatient laboratory tests within a designated region, dialysis registers that capture patients who progress to ESKD and mortality data files from the national Central Statistics Office (CSO).

Cohort participants

We identified all patients with measured serum creatinine values from two major health regions—Northwest region (from 2005 to 2014) and Midwest region (from 1999 to 2014)—and linked laboratory data records over time using an expectation-maximization (EM) algorithm-based probabilistic matching strategy [25]. We selected participants with calibrated serum creatinine measurements from 1 January 2005 to 31 December 2014. Individuals with kidney failure receiving dialysis or who had missing data on age, sex and unmatched mortality records were excluded. Cohort participants who did not experience AKI were included at the time of their first valid serum creatinine measurement recorded in the health system. Cohort participants who experienced an AKI were included at the time of their first episode.

Outcome: AKI

The primary outcome of interest was the incidence of AKI among new entrants into the health system. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria were used to identify all AKI events from 2005 to 2014 and subclassify each by severity grade [26]. The baseline serum creatinine was defined as the median creatinine value recorded within 3 months prior to the AKI event. Where creatinine values were unavailable prior to an AKI episode, we improvized by using median creatinine values recorded within 3 months following the AKI episode or the minimum creatinine value within 48 h following an AKI (Supplementary data, Figure S1). Per the KDIGO criteria, Stage 1 AKI was defined as an increase in creatinine by 50–100% within 7 days or $\geq$26.5 µmol/L above baseline within 48 h, Stage 2 as an increase of 100–200% above baseline creatinine and Stage 3 as a $\geq$200% increase or an increase $\geq$354 µmol/L.

Primary exposure variable

The primary exposure variable was calendar year from 2005 to 2014.

Covariates

Baseline data on all participants were measured at the time of study inclusion. Serum creatinine was measured using the modified kinetic Jaffe method and creatinine values were calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure to ensure standardization. Serum creatinine values were used to determine estimated glomerular filtration rate (eGFR; in mL/min/1.73 m^2) for patients using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) equation for sensitivity analysis [27, 28]. CKD was defined according to the kidney disease dialysis quality outcome initiative guidelines based on eGFR measurements [9]. Data were captured on an extensive list of laboratory measures including indicators of inflammation [C-reactive protein, erythrocyte sedimentation rate (ESR), white cell count and subtypes], nutrition (serum albumin and total protein) and bone biomarkers (serum calcium and phosphate). The location of medical supervision was defined as the location where the creatinine test was ordered by the supervising physician and categorized as inpatient facility (IP), outpatient facility (OP), general practice (GP) and emergency room (ER). The identification of these locations was considered important to explore relationships between the site of medical supervision and the frequency of AKI events. The county of residence was extracted from the patient administration system, which allowed us to classify patients by geography. The principal counties served by the Northwest region of Ireland included Donegal, Sligo and Leitrim while those served by the Midwest region included Clare, Limerick and Tipperary.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), as appropriate, while categorical variables are given as event numbers with percentages. Group comparisons for continuous variables were performed using the Kruskal–Wallis test while group comparisons were performed with the chi-squared test.

Poisson regression utilizing robust standard error estimated incident rates of AKI within the health system and rates were expressed as events per 100 person-years for the entire cohort and for selected subgroups across calendar years. Incidence rates of AKI were compared across calendar years using the 2005 year as the referent with the generation of incidence rate ratios (IRRs). Univariable and multivariable logistic regression models were developed to compare the likelihood of the first AKI across the years 2005–2014 with 2005 as the referent year. A purposeful selection process was employed in model development. Associations were expressed as odds ratios (ORs) and 95% confidence intervals (CIs); a cut-off point of $\alpha = 0.05$ was used to assess for statistical significance. We assessed whether the likelihood of an AKI differed by age, sex and eGFR across calendar years by including interaction terms. All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria) [26].

Sensitivity analysis

Sensitivity analyses were conducted to evaluate the robustness of our results. First, we restricted the definition of an AKI

event to incorporate creatinine values recorded prior to a potential AKI episode to remove possible bias introduced by the inclusion of post-AKI creatinine concentrations. Second, we examined to what extent AKI event rates and annual trends were influenced by the definition of baseline creatinine concentration prior to AKI. For this we substituted the median creatinine value with the mean creatinine concentration and repeated the entire analysis. Finally, we determined whether our definition of eGFR altered observed trends by replacing the CKD-EPI equation with the MDRD equation.

Ethics approval

The study was approved by the Ethics Committee at University Hospital Limerick.

RESULTS

Baseline characteristics of the study cohort

The construction of the final study cohort from the Northwest and Midwest regions of Ireland is shown in Figure 1. There were 40 786 (9%) laboratory-proven episodes of AKI among 451 646 patients from 2005 to 2014 (Table 1). Patients who experienced an AKI episode were on average older and male, had higher serum creatinine concentrations and lower eGFR values at baseline ($P < 0.001$) and had significantly higher levels of inflammatory markers and lower serum albumin levels. Most AKI episodes occurred in patients who were hospitalized as IP. Among all AKI episodes, Stage 1 occurred most frequently (81.3%), followed by Stage 2 (11.6%) and Stage 3 (7.1%). Patients who sustained a Stage 3 AKI event had baseline characteristics that reflected an older and sicker cohort (Table 2).

Temporal trends in incidence rates of AKI

Incidence rates of AKI increased by at least 2-fold, from 5.48 in 2005 to 12.39 per 100 patient-years in 2014. For both men and women, a trend of increasing incidence was observed between 2005 and 2014 (Figure 2a). Adjusting for age, sex and location of supervision, incidence rates peaked in 2011 [IRR 2.07 (95% CI 1.81–2.38)] and plateaued thereafter (Supplementary data, Table S1). Incidence rates were significantly higher for men than for women [IRR 1.13 (95% CI 1.07–1.18)] and increased significantly and substantially with advancing age. The adjusted IRR for patients >80 years of age was >11-fold higher than for patients ages 18–39 years (Supplementary data, Table S1). Within each age category, men experienced significantly higher rates than women, and this pattern persisted over time (Figure 2b). For men and women, a relative plateauing of AKI rates was observed from 2010 to 2012, and this was most pronounced for patients in the age categories 60–79 and >80 years.

Temporal trends in incident rates by stage of AKI

Temporal trends in the incidence of AKI by severity stage are presented in Table 3 and Figure 3. Overall, Stage 1 AKI accounted for the greatest proportion of all AKI events. The pattern of annual growth in incidence was similar for Stages 1 and 2 AKI, with adjusted IRRs that increased significantly from 1.44 (95% CI 1.28–1.62) to 2.62 (2.32–2.96) and from 1.58 (95% CI 1.33–1.88) to 2.83 (2.32–3.46), respectively ($P < 0.001$) (Supplementary data, Table S2). In contrast, incidence rates of Stage 3 AKI increased from 2006 until 2012 [peak IRR 2.27 (95% CI 2.01–2.57)] and plateaued thereafter. Across all stages of AKI, rates were significantly higher in men than in women and increased with advancing age.

AKI trends by location of supervision

Incidence rates of AKI increased significantly from 2005 to 2014 across all health care settings as shown in Table 3. Patients classified as IP recorded the highest incidence rates of AKI compared with patients observed in the ER, GP or OP settings. With adjustment for age, sex and calendar year, IP had incidence rates that were 15.5 times (13.66–17.63) greater than those in the GP setting (Supplementary data, Table S1).

Factors associated with first AKI

The results of univariate and multivariable associations of first AKI are shown in Table 4. In univariate analysis, the OR of AKI increased in a monotonic fashion with each successive year. With adjustment for demographic characteristics, illness indicators, county of residence and location of supervision, patients who entered the health system in 2014 were significantly more likely to experience an AKI compared with those in 2005 [OR 4.36 (95% CI 3.90–4.87), $P < 0.001$]. To determine whether this relationship varied by AKI stage, we repeated the analysis stratified by AKI stage in separate logistic models. In each of these additional analyses the pattern was similar with significantly higher ORs for AKI Stages 1–3 in 2014 compared with the referent 2005, as shown in Figure 4. Increasing age [OR 1.25 (95% CI 1.24–1.26)] and male gender [OR 1.28 (95% CI 1.22–1.35)] were significantly associated with AKI incidence in the multivariable model. Compared with patients in GP, patients managed as IP [OR 19.11 (95% CI 17.69–20.64)], attending the ER [OR 5.97 (95% CI 5.56–6.42)] or OP [OR 4.37 (95% CI 4.02–4.75)] were significantly more likely to experience an AKI event. Incidence rates of AKI also varied significantly by county of residence, which was not explained by patient-level factors or location of medical supervision, as shown in Table 4. The final model had excellent discrimination with a C-statistic of 0.93. Significant interactions were observed between age and sex ($P < 0.001$) and sex and calendar year ($P < 0.001$). Incorporating these interactions in the model indicated that the likelihood of AKI was significantly higher for men than for women in the earlier time periods but this difference had almost disappeared in later years (Supplementary data, Figure S2), particularly for those >50 years of age (Supplementary data, Figure S3).

SENSITIVITY ANALYSIS

We repeated the entire analysis, restricting the sample to patients who had creatinine values recorded prior to the AKI episode. This yielded a final cohort of 449 190 who experienced 30 836 (6.9%) AKI episodes and had similar demographic and clinical characteristics to those of the original cohort. Similar to before, we found that incidence rates increased with each successive year and that the patterns of association mirrored those of the primary analysis (Figure 5 and Supplementary data,

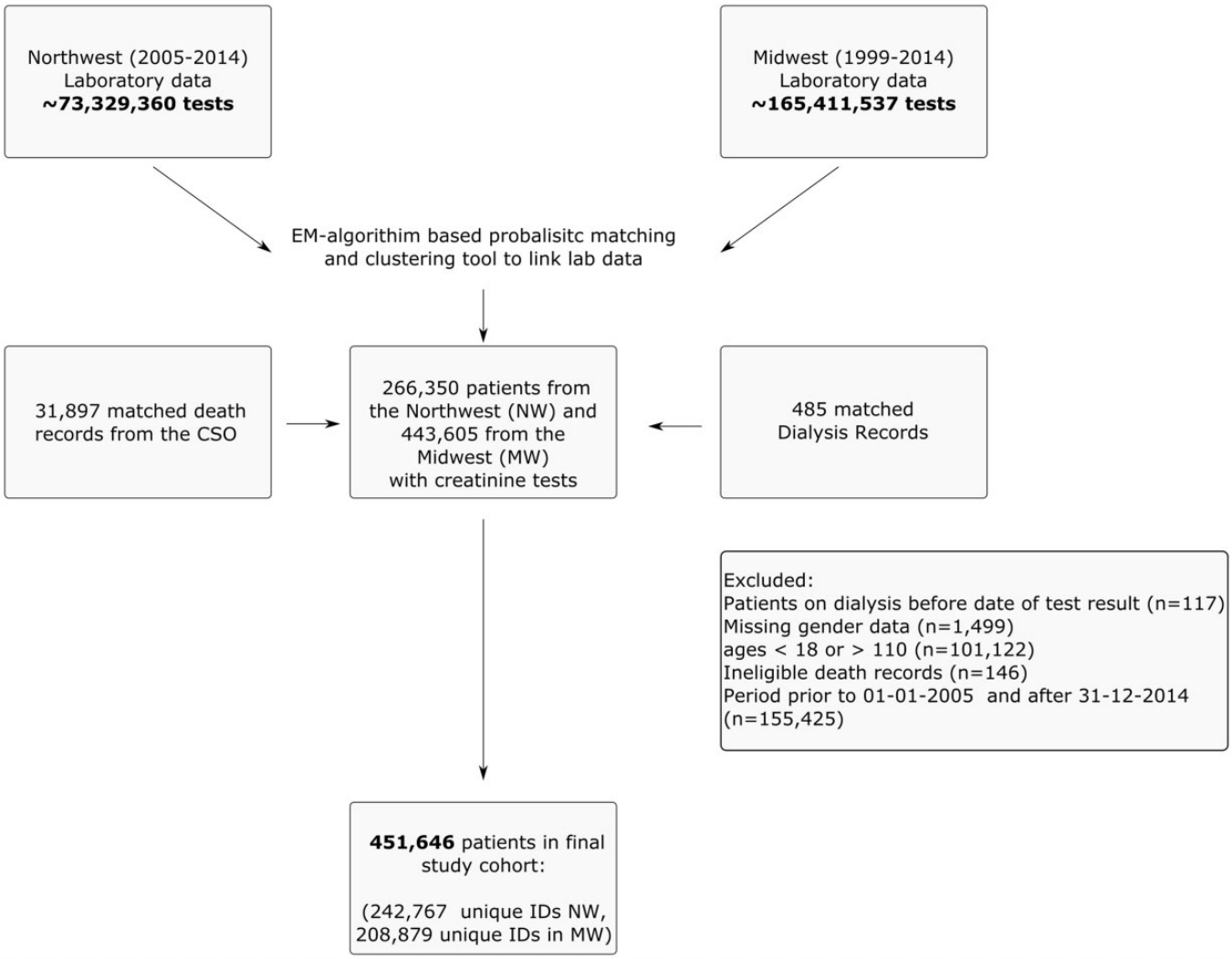

FIGURE 1: A Strengthening the Reporting of Observational Studies in Epidemiology flow diagram to illustrate cohort construction. The final data set ($n = 451\ 646$) captured information on demographic characteristics, county of residence, primary location of patient supervision, laboratory measures of health status, dialysis indicator variables and death.

Tables S3A and S3B). Similarly, substituting the mean for the median serum creatinine in the assessment of baseline creatinine or using the MDRD equation instead of the CKD-EPI equation in estimating baseline GFR, we found the same qualitative trends were observed and these are summarized in Supplementary data, Tables S3–S5.

DISCUSSION

To our knowledge, this is the first study to describe annual trends in the frequency of AKI by severity staging in the health system and to characterize differences across major health care settings. Using a laboratory-based definition of AKI, we demonstrated a trend of increasing incidence of AKI over the past decade, a pattern that was observed across all AKI Stages 1–3. The rising trend was observed for both men and women and across all age groups, although the greatest increases were observed in elderly patients. Moreover, we identified the IP setting as the most common location for AKI occurrence even though the rates were also common in other key locations such as the ER and OP settings. Several patient- and facility-levelcharacteristics were associated with the occurrence of a first AKI event, including older age, male gender, baseline kidney function, county of residence and location of medical supervision, although these did not sufficiently account for the rising annual trend in AKI incidence.

We highlight a pattern of increasing incidence of AKI in the Irish health system that was clearly manifested across several locations of patient supervision. Increases in the absolute rates of AKI were observed for men and women and in all age groups, accounting for a more than 2-fold increase in rates from 2005 to 2014. Given the mounting evidence that connects AKI with substantial adverse impact on both short- and long-term clinical outcomes [4, 10–17], it is imperative that we pay attention to these epidemiological trends. A fundamental challenge in all health systems is early detection of disease so that we can develop and implement effective prevention strategies [17, 29, 30]. In this

Table 1. Patient characteristics at baseline by the presence of AKI

Variable	*N*	No AKI	AKI	P-value
Patients, *n* (%)	451 646	410 860 (91)	40 786 (9)	
Demographic characteristics				
Age at baseline (years), mean (SD)	451 646	44.8 (17.5)	67.5 (18.1)	<0.001
Age group categories (years), %				
18–39	184 572	97.7	2.3	
40–59	148 651	95.3	4.7	
60–80	94 489	80.4	19.6	
>80	23 934	53.9	46.1	<0.001
Gender, %				
Women	241 696	91.7	8.3	
Men	209 950	90.1	9.9	<0.001
Geographic factors, %				
County of residence				
Donegal	119 025	90.9	9.1	
Sligo	56 521	91.2	8.8	
Leitrim	26 154	91.6	8.4	
Limerick	84 183	89.1	10.9	
Clare	50 622	88.3	11.7	
Tipperary	21 735	89.5	10.5	
Other counties	27 551	94.5	5.5	<0.001
Hospital region				
Midwest	208 879	89.9	10.1	
Northwest	242 767	91.9	8.1	<0.001
Location of medical supervision[a]				
ER	87 193	85.7	14.3	
GP	266 766	98.5	1.5	
IP	46 584	61.6	38.4	
OP	35 463	86.6	13.4	<0.001
Measures of kidney function				
Serum creatinine (μmol/L), median (IQR)	451 646	75.0 (22.0)	81.0 (43.0)	<0.001
eGFR[b] (mL/min/1.73 m^2), median (IQR)	451 646	95.1 (32.2)	73.7 (44.5)	<0.001
Plasma urea (mmol/L), median (IQR)	439 217	5.2 (2.2)	9.5 (8.6)	<0.001
Baseline eGFR category[c], %				
≥ 90	259 669	95.0	5.0	
60–89	148 223	90.7	9.3	
30–59	39 149	71.7	28.3	
15–29	3702	39.1	60.9	
<15	903	25.0	75.0	<0.001
Measures of inflammation				
C-reactive protein (SI), median (IQR)	48 474	3.4 (8.8)	37.0 (102.0)	<0.001
ESR, median (IQR)	141 905	9.5 (13.2)	32.0 (46.9)	<0.001
White blood count, median (IQR)	416 369	7.3 (3.6)	10.4 (6.6)	<0.001
Lymphocyte count, median (IQR)	401 969	1.9 (0.9)	1.3 (1.1)	<0.001
Neutrophil count, median (IQR)	409 435	4.3 (2.9)	7.6 (6.4)	<0.001
Measures of nutrition				
Serum albumin (g/L), mean (SD)	282 547	39.2 (5.1)	30.8 (7.6)	<0.001
Total protein (mmol/L), mean (SD)	255 996	68.4 (7.0)	61.1 (11.0)	<0.001
Measures of bone metabolism				
Serum calcium (mmol/L), mean (SD)	110 368	2.3 (0.1)	2.2 (0.2)	<0.001
Serum phosphorus (mmol/L), mean (SD)	107 723	1.2 (0.3)	1.3 (0.5)	<0.001
Other metabolic biomarkers				
Serum potassium (mmol/L), mean (SD)	393 599	4.4 (0.5)	4.4 (0.8)	<0.001
Serum uric acid (μmol/L), median (IQR)	46 992	308.0 (116.0)	347.7 (175.0)	<0.001
Haemoglobin A1c (%), median (IQR)	31 590	5.7 (1.3)	6.6 (2.0)	<0.001
Glucose (mmol/L), median (IQR)	103 517	5.0 (0.9)	6.2 (2.7)	<0.001
Haemoglobin (g/dl), mean (SD)	420 580	14.0 (1.6)	12.4 (2.3)	<0.001

[a]Location of medical supervision refers to the location of the patient when the test was conducted.
[b]eGFR was based on the CKD-EPI equation [19].
[c]Excluding patients who received dialysis at baseline.

study we identified key clinical locations in the health system where incidence rates of AKI were highest. By and large, the IP setting was the most common site of AKI occurrence, which is not surprising given that it accommodates the sickest patients. Patients within the health system and needing admission to an IP ward were almost 20-fold more likely to develop an AKI. The pattern of annual incidence increased to a peak in 2012 and appeared to plateau thereafter.

Table 2. Patient characteristics at baseline by stage of AKI

Variable	*N*	Stage 1	Stage 2	Stage 3	P-value
Patients, *n* (%)	40 786	33 155 (81.3)	4734 (11.6)	2897 (7.1)	
Age at baseline (years), mean (SD)	40 786	67.3 (18.3)	68.3 (17.5)	68.6 (16.7)	0.006
Age group categories (years), %					
18–39	4300	85.4	9.7	4.9	
40–59	6923	80.8	11.6	7.6	
60–80	18 526	80.6	11.9	7.5	
>80	11 037	81.1	11.9	7.0	<0.001
Gender, %					
Women	19 965	80.8	12.4	6.7	
Men	20 821	81.7	10.8	7.4	<0.001
County of residence, %					
Donegal	10 806	80.7	11.9	7.4	
Sligo	4970	80.3	12.8	6.9	
Leitrim	2209	79.7	12.4	7.9	
Limerick	9177	82.2	11.3	6.5	
Clare	5930	81.5	11.6	6.9	
Tipperary	2287	82.9	10.7	6.4	
All other counties	1524	82.4	9.6	8.0	0.002
Hospital region, %					
Midwest	21 155	82.0	11.1	6.9	
Northwest	19 631	80.6	12.1	7.3	0.001
Location of medical supervision[a], %					
ER	12 461	77.4	14.2	8.4	
GP	4084	83.3	11.4	5.2	
IP	17 897	83.7	10.0	6.3	
OP	4746	80.6	10.6	8.8	<0.001
Laboratory variables					
Measures of kidney function					
Serum creatinine (μmol/L), median (IQR)	40 786	81.5 (42.0)	73.0 (34.0)	117.0 (222.0)	<0.001
eGFR at baseline[b] (mL/min/1.73m^2), median (IQR)	40 786	73.8 (44.1)	82.0 (37.4)	46.2 (68.3)	<0.001
Urea (mmol/L), median (IQR)	39 641	8.7 (7.1)	12.2 (11.4)	23.8 (20.6)	<0.001
Baseline eGFR[c] (mL/min/1.73 m^2)					
≥90	12 911	81.7	13.7	4.5	
60–89	13 856	82.1	13.3	4.6	
30–59	11 088	85.3	9.8	4.9	
15–29	2254	75.8	1.3	22.8	
<15	677	8.1	0.0	91.9	<0.001
Measures of inflammation					
C-reactive protein (SI), median (IQR)	13 669	32.2 (93.0)	61.0 (134.2)	64.9 (147.0)	<0.001
ESR, median (IQR)	24 209	30.0 (45.2)	37.0 (54.0)	44.8 (54.6)	<0.001
White blood count, median (IQR)	40 272	10.2 (6.2)	11.7 (8.8)	11.4 (8.5)	<0.001
Lymphocyte count, median (IQR)	39 273	1.3 (1.1)	1.1 (1.0)	1.0 (0.9)	<0.001
Neutrophil count, median (IQR)	40 051	7.4 (6.0)	8.8 (8.2)	8.8 (7.9)	<0.001
Measures of nutrition					
Serum albumin (g/L), mean (SD)	36 359	31.3 (7.4)	29.1 (7.9)	28.4 (7.6)	<0.001
Total protein (mmol/L), mean (SD)	32 969	61.4 (10.7)	59.9 (12.1)	59.7 (11.9)	<0.001
Measures of bone metabolism					
Serum calcium (mmol/L), mean (SD)	26 748	2.2 (0.2)	2.2 (0.2)	2.1 (0.3)	<0.001
Serum phosphorus (mmol/L), mean (SD)	28 888	1.2 (0.4)	1.3 (0.5)	1.7 (0.8)	<0.001
Metabolic biomarkers					
Serum potassium (mmol/L), mean (SD)	40 472	4.3 (0.7)	4.4 (0.9)	4.7 (1.1)	<0.001
Serum uric acid (umol/L), median (IQR)	8036	343.0 (169.3)	338.0 (184.2)	412.4 (211.2)	<0.001
Haemoglobin A1c (%), median (IQR)	7538	6.6 (2.0)	6.7 (2.2)	6.5 (1.8)	0.007
Glucose (mmol/L), median (IQR)	13 590	6.2 (2.7)	6.3 (2.8)	6.3 (3.0)	0.367
Haemoglobin (g/dl), mean (SD)	39 854	12.5 (2.2)	12.4 (2.4)	11.8 (2.6)	<0.001

[a]Location of medical supervision refers to the location of the patient when the test was conducted.
[b]eGFR was based on the CKD-EPI equation [19].
[c]Excluding patients who received dialysis at baseline.

Our analysis would suggest that targeting of locations where AKI is most likely to occur would be a primary goal. Through early detection strategies including electronic alert systems and adoption of early treatment interventions, it is likely that many AKI events could be prevented and more effectively managed [30]. Our analysis also suggests that other locations should also be targeted, especially the ER and outpatient clinics. These are critical points where patients interact with their physicians and multidisciplinary teams to management acute and chronic conditions.

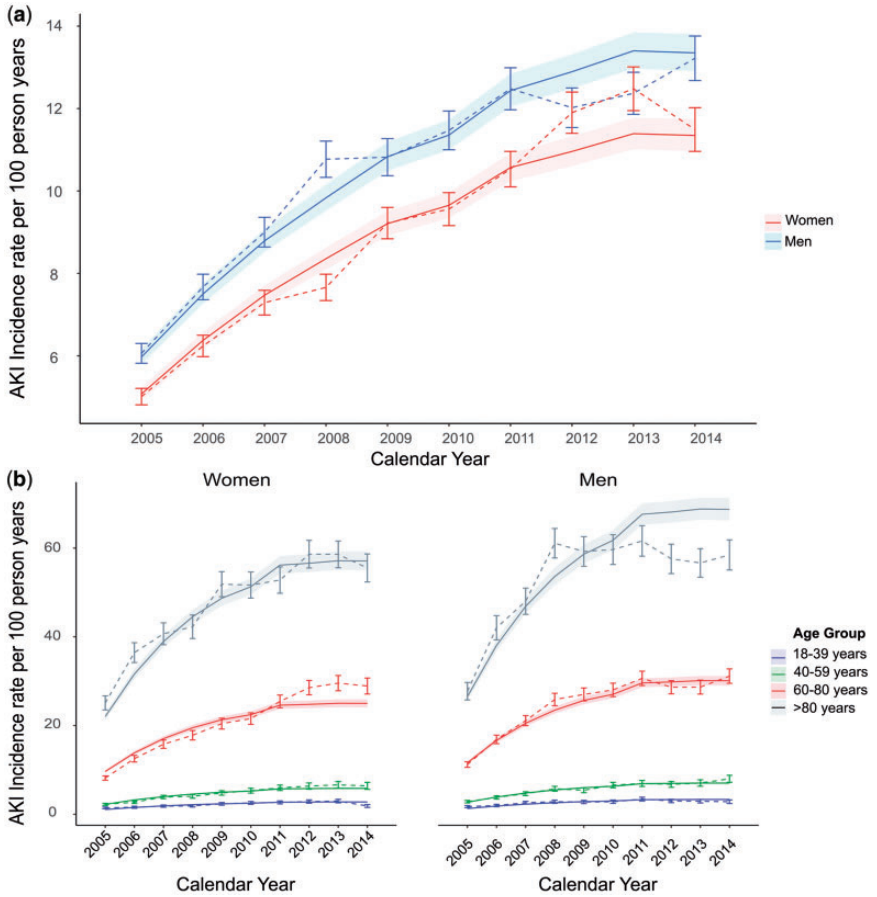

FIGURE 2: (**a**) Temporal trends in the incidence of AKI by sex in the health system. (**b**) Temporal trends in the incidence of AKI by age and sex in the health system. Dashed lines and error bars represent incidence rates with 95% CIs calculated from the direct method, whereas continuous lines and bands represent incident rates and 95% CIs calculated from Poisson regression.

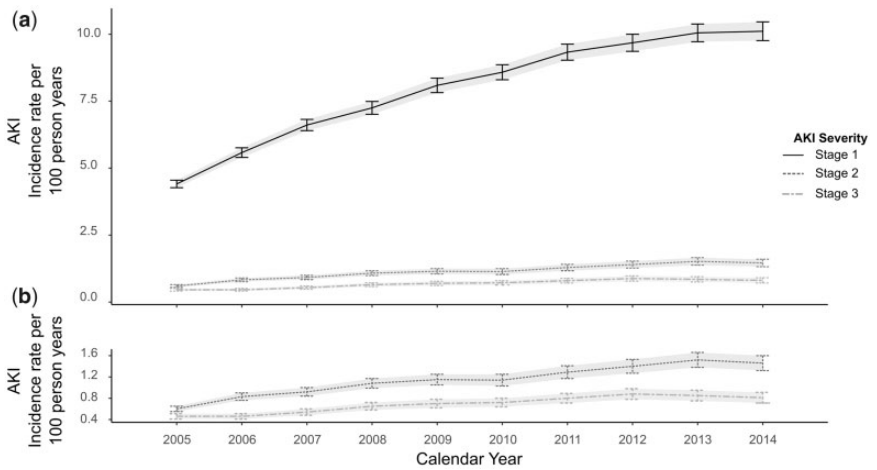

FIGURE 3: (a) Temporal trends in the incidence rates of AKI by severity stage in the Irish health system. (b) Temporal trends in incidence rates of Stage 2 and Stage 3 AKI (magnified).

Our study has shed new light not only on the overall pattern of AKI incidence over time but also on important trends according to the severity of AKI. Of particular interest is the finding that the greatest absolute increases in AKI incidence were accounted for by increases in AKI Stage 1. From 2005 to 2014, absolute rates of AKI Stage 1 increased from 4.4 to 11.1%, while the growth in Stage 2 (from 0.60 to 1.46%) and Stage 3 (from 0.46 to 0.81%) were less impressive. This would suggest that greater should attention be given to these 'minor' AKI events and their determinants. Equally important, the pattern of AKI incidence differed by severity stage over time. Indeed, on comparing IRR across calendar years, the IRR for Stage 3

Table 3. Temporal trends in incidence rates of AKI in the Irish health system from 2005 to 2014

Variable[a]	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P-value
All patients	82 657	60 869	53 962	45 713	40 595	38 540	35 817	33 644	31 020	28 829	
AKI events, *n*	4529	4189	4357	4108	4039	4023	4091	4025	3854	3571	
All patients	5.48 (5.32–5.64)	6.88 (6.68–7.08)	8.07 (7.84–8.3)	8.99 (8.73–9.25)	9.95 (9.66–10.24)	10.44 (10.13–10.75)	11.42 (11.09–11.75)	11.96 (11.61–12.31)	12.42 (12.05–12.79)	12.39 (12.01–12.77)	<0.001
Stage 1	4.41 (4.27–4.55)	5.58 (5.40–5.76)	6.61 (6.40–6.82)	7.25 (7.01–7.49)	8.09 (7.82–8.36)	8.58 (8.30–8.86)	9.33 (9.03–9.63)	9.68 (9.36–10.00)	10.05 (9.72–10.38)	10.11 (9.76–10.46)	<0.001
Stage 2	0.60 (0.55–0.65)	0.83 (0.76–0.90)	0.92 (0.84–1.00)	1.08 (0.99–1.17)	1.15 (1.05–1.25)	1.14 (1.03–1.25)	1.29 (1.17–1.41)	1.4 (1.27–1.53)	1.52 (1.38–1.66)	1.46 (1.32–1.60)	<0.001
Stage 3	0.46 (0.41–0.51)	0.46 (0.41–0.51)	0.54 (0.48–0.60)	0.65 (0.58–0.72)	0.70 (0.62–0.78)	0.72 (0.64–0.80)	0.80 (0.71–0.89)	0.88 (0.78–0.98)	0.85 (0.75–0.95)	0.81 (0.71–0.91)	<0.001
Men	6.06 (5.82–6.30)	7.67 (7.36–7.98)	9.00 (8.64–9.36)	10.77 (10.33–11.21)	10.82 (10.37–11.27)	11.47 (11.00–11.94)	12.48 (11.97–12.99)	12.02 (11.54–12.5)	12.37 (11.86–12.88)	13.22 (12.68–13.76)	<0.001
Stage 1	4.91 (4.69–5.13)	6.24 (5.95–6.53)	7.48 (7.15–7.81)	8.70 (8.30–9.10)	8.75 (8.34–9.16)	9.47 (9.04–9.9)	10.27 (9.80–10.74)	9.74 (9.30–10.18)	10.11 (9.64–10.58)	10.90 (10.40–11.40)	<0.001
Stage 2	0.62 (0.54–0.70)	0.87 (0.76–0.98)	0.94 (0.82–1.06)	1.26 (1.10–1.42)	1.21 (1.05–1.37)	1.15 (0.99–1.31)	1.35 (1.17–1.53)	1.32 (1.15–1.49)	1.34 (1.16–1.52)	1.42 (1.23–1.61)	<0.001
Stage 3	0.53 (0.46–0.60)	0.55 (0.46–0.64)	0.58 (0.49–0.67)	0.81 (0.68–0.94)	0.86 (0.73–0.99)	0.86 (0.72–1.00)	0.86 (0.72–1.00)	0.96 (0.82–1.10)	0.91 (0.76–1.06)	0.90 (0.75–1.05)	<0.001
Women	5.01 (4.81–5.21)	6.24 (5.98–6.50)	7.29 (6.99–7.59)	7.66 (7.34–7.98)	9.22 (8.84–9.6)	9.56 (9.16–9.96)	10.53 (10.10–10.96)	11.90 (11.40–12.40)	12.48 (11.95–13.01)	11.49 (10.96–12.02)	<0.001
Stage 1	4.01 (3.83–4.19)	5.04 (4.81–5.27)	5.88 (5.61–6.15)	6.18 (5.89–6.47)	7.54 (7.19–7.89)	7.82 (7.45–8.19)	8.54 (8.15–8.93)	9.61 (9.16–10.06)	9.99 (9.51–10.47)	9.27 (8.79–9.75)	<0.001
Stage 2	0.59 (0.52–0.66)	0.80 (0.70–0.90)	0.91 (0.80–1.02)	0.95 (0.83–1.07)	1.11 (0.97–1.25)	1.14 (1.00–1.28)	1.23 (1.08–1.38)	1.49 (1.30–1.68)	1.71 (1.50–1.92)	1.51 (1.31–1.71)	<0.001
Stage 3	0.41 (0.35–0.47)	0.39 (0.32–0.46)	0.51 (0.43–0.59)	0.53 (0.44–0.62)	0.58 (0.48–0.68)	0.60 (0.49–0.71)	0.76 (0.64–0.88)	0.80 (0.66–0.94)	0.78 (0.64–0.92)	0.71 (0.57–0.85)	<0.001
Age group (years)											
18–39	1.55 (1.40–1.70)	1.74 (1.57–1.91)	2.18 (1.99–2.37)	2.26 (2.05–2.47)	2.53 (2.30–2.76)	2.67 (2.43–2.91)	3.00 (2.74–3.26)	2.92 (2.65–3.19)	2.95 (2.67–3.23)	2.33 (2.07–2.59)	<0.001
40–59	2.50 (2.32–2.68)	3.21 (2.97–3.45)	4.24 (3.95–4.53)	4.81 (4.47–5.15)	5.09 (4.71–5.47)	5.93 (5.51–6.35)	6.43 (5.97–6.89)	6.55 (6.07–7.03)	6.84 (6.32–7.36)	7.28 (6.72–7.84)	<0.001
60–80	9.53 (9.14–9.92)	14.45 (13.85–15.05)	18.23 (17.5–18.96)	21.25 (20.40–22.10)	23.45 (22.51–24.39)	24.56 (23.57–25.55)	27.9 (26.82–28.98)	28.59 (27.49–29.69)	29.08 (27.92–30.24)	30.16 (28.95–31.37)	<0.001
>80	26.19 (24.95–27.43)	38.76 (37.02–40.5)	43.76 (41.85–45.67)	49.49 (47.38–51.6)	54.88 (52.72–57.04)	55.07 (52.85–57.29)	56.44 (54.18–58.7)	58.14 (55.86–60.42)	57.68 (55.47–59.89)	56.88 (54.56–59.20)	<0.001
Men (years)											
18–39	1.72 (1.48–1.96)	1.96 (1.69–2.23)	2.60 (2.29–2.91)	2.81 (2.45–3.17)	2.76 (2.40–3.12)	2.82 (2.44–3.20)	3.41 (2.99–3.83)	3.00 (2.62–3.38)	2.94 (2.54–3.34)	2.82 (2.42–3.22)	<0.001
40–59	2.83 (2.55–3.11)	3.79 (3.42–4.16)	4.63 (4.19–5.07)	5.74 (5.19–6.29)	5.41 (4.85–5.97)	6.56 (5.94–7.18)	6.94 (6.26–7.62)	6.73 (6.07–7.39)	7.04 (6.32–7.76)	7.99 (7.20–8.78)	<0.001
60–80	11.20 (10.58–11.82)	16.87 (15.91–17.83)	21.11 (19.97–22.25)	25.87 (24.47–27.27)	27.01 (25.55–28.47)	28.04 (26.52–29.56)	30.64 (29.02–32.26)	28.64 (27.15–30.13)	28.67 (27.10–30.24)	31.15 (29.52–32.78)	<0.001
>80	27.74 (25.77–29.71)	42.04 (39.31–44.77)	48.03 (45.07–50.99)	61.11 (57.79–64.43)	59.25 (55.91–62.59)	59.68 (56.32–63.04)	61.62 (58.180–65.06)	57.58 (54.26–60.90)	56.66 (53.44–59.88)	58.47 (55.07–61.87)	<0.001
Women (years)											
18–39	1.42 (1.23–1.61)	1.57 (1.35–1.79)	1.83 (1.59–2.07)	1.88 (1.63–2.13)	2.34 (2.04–2.64)	2.55 (2.23–2.87)	2.67 (2.34–3.00)	2.85 (2.48–3.22)	2.97 (2.58–3.36)	1.86 (1.54–2.18)	<0.001
40–59	2.22 (1.99–2.45)	2.71 (2.41–3.01)	3.89 (3.51–4.27)	4.03 (3.60–4.46)	4.80 (4.29–5.31)	5.31 (4.75–5.87)	5.96 (5.35–6.57)	6.35 (5.65–7.05)	6.61 (5.85–7.37)	6.40 (5.61–7.19)	<0.001
60–80	8.16 (7.68–8.64)	12.53 (11.78–13.28)	15.79 (14.85–16.73)	17.81 (16.75–18.87)	20.43 (19.21–21.65)	21.56 (20.26–22.86)	25.44 (24–26.88)	28.54 (26.92–30.16)	29.56 (27.84–31.28)	28.91 (27.11–30.71)	<0.001
>80	25.11 (23.52–26.70)	36.44 (34.20–38.68)	40.69 (38.22–43.16)	42.27 (39.62–44.92)	51.87 (49.05–54.69)	51.67 (48.73–54.61)	52.8 (49.83–55.77)	58.64 (55.52–61.76)	58.59 (55.57–61.61)	55.53 (52.37–58.69)	<0.001
Location of medical supervision[b]											
GP	0.71 (0.64–0.78)	1.04 (0.94–1.14)	1.38 (1.25–1.51)	1.33 (1.19–1.47)	1.64 (1.48–1.80)	1.74 (1.57–1.91)	2.20 (2.00–2.40)	2.28 (2.07–2.49)	2.72 (2.48–2.96)	2.36 (2.13–2.59)	<0.001
ER	8.21 (7.75–8.67)	10.85 (10.26–11.44)	12.25 (11.6–12.9)	13.84 (13.1–14.58)	15.01 (14.23–15.79)	15.60 (14.79–16.41)	17.77 (16.9–18.64)	18.73 (17.84–19.62)	18.82 (17.91–19.73)	19.79 (18.85–20.73)	<0.001
IP	28.76 (27.80–29.72)	32.85 (31.71–33.99)	34.3 (33.13–35.47)	39.58 (38.21–40.95)	40.78 (39.31–42.25)	44.64 (43.09–46.19)	46.28 (44.64–47.92)	49.30 (47.57–51.03)	46.44 (44.57–48.31)	46.17 (44.24–48.10)	<0.001
OP	6.46 (5.84–7.08)	7.54 (6.73–8.35)	10.32 (9.31–11.33)	14.05 (12.93–15.17)	17.3 (16.04–18.56)	18.37 (17.04–19.70)	17.44 (16.16–18.72)	16.62 (15.27–17.97)	16.83 (15.42–18.24)	17.73 (16.25–19.21)	<0.001
Hospital region											
Northwest region	4.18 (4.02–4.34)	6.14 (5.89–6.39)	7.47 (7.16–7.78)	8.14 (7.79–8.49)	9.77 (9.36–10.18)	9.51 (9.08–9.94)	10.94 (10.47–11.41)	11.71 (11.22–12.2)	12.79 (12.24–13.34)	13.73 (13.14–14.32)	<0.001
Midwest region	8.30 (7.97–8.63)	7.97 (7.63–8.31)	8.74 (8.39–9.09)	9.85 (9.46–10.24)	10.12 (9.71–10.53)	11.25 (10.82–11.68)	11.87 (11.41–12.33)	12.20 (11.71–12.69)	12.11 (11.62–12.60)	11.28 (10.79–11.77)	<0.001
County of residence											
Donegal	4.80 (4.55–5.05)	7.15 (6.77–7.53)	8.39 (7.93–8.85)	9.10 (8.58–9.62)	10.98 (10.36–11.6)	10.93 (10.28–11.58)	11.55 (10.88–12.22)	13.55 (12.80–14.30)	13.17 (12.39–13.95)	14.68 (13.82–15.54)	<0.001
Sligo	3.97 (3.67–4.27)	6.25 (5.76–6.74)	8.38 (7.71–9.05)	9.19 (8.4–9.98)	11.05 (10.11–11.99)	10.91 (9.91–11.91)	14.26 (13.09–15.43)	13.83 (12.61–15.05)	17.56 (16.14–18.98)	18.24 (16.75–19.73)	<0.001
Limerick	8.97 (8.42–9.52)	8.61 (8.04–9.18)	9.02 (8.47–9.57)	10.74 (10.11–11.37)	10.54 (9.89–11.19)	11.55 (10.87–12.23)	12.69 (11.94–13.44)	13.57 (12.78–14.36)	13.20 (12.39–14.01)	12.78 (11.96–13.60)	<0.001
Leitrim	3.83 (3.36–4.30)	6.10 (5.35–6.85)	6.84 (5.95–7.73)	8.98 (7.86–10.10)	12.00 (10.60–13.40)	9.62 (8.33–10.91)	13.38 (11.80–14.96)	11.19 (9.75–12.63)	14.45 (12.63–16.27)	16.21 (14.18–18.24)	<0.001
Clare	8.13 (7.49–8.77)	8.02 (7.37–8.67)	9.46 (8.75–10.17)	11.83 (10.97–12.69)	11.84 (10.94–12.74)	14.29 (13.3–15.28)	15.31 (14.23–16.39)	15.22 (14.09–16.35)	16.11 (14.94–17.28)	13.21 (12.08–14.34)	<0.001
Tipperary	10.39 (9.25–11.53)	9.07 (7.99–10.15)	10.03 (8.89–11.17)	8.72 (7.60–9.84)	11.44 (10.08–12.80)	11.7 (10.33–13.07)	11.21 (9.81–12.61)	10.43 (8.99–11.87)	12.20 (10.64–13.76)	11.54 (9.95–13.13)	0.001
All other counties	3.68 (3.10–4.26)	4.96 (4.20–5.72)	5.42 (4.59–6.25)	5.07 (4.24–5.90)	6.04 (5.07–7.01)	6.19 (5.24–7.14)	5.73 (4.82–6.64)	5.82 (4.92–6.72)	6.65 (5.67–7.63)	7.29 (6.23–8.35)	<0.001

[a]Incidence rates expressed at events per 100 patients at risk with 95% CIs.
[b]Location of medical supervision refers to the location of the patient when the test was conducted.

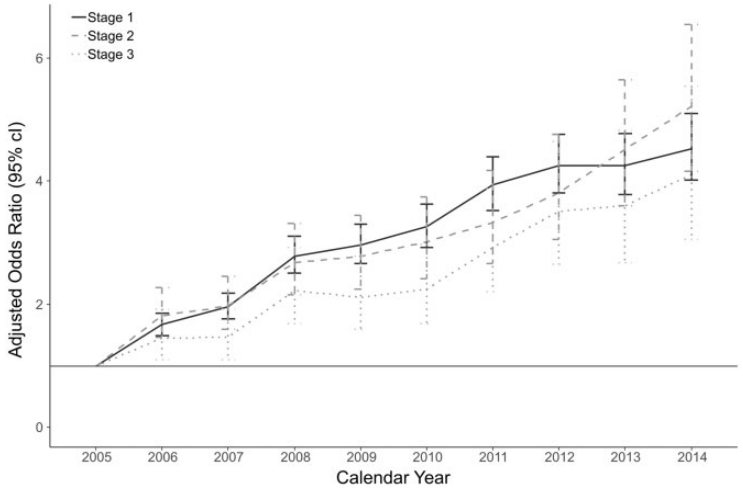

FIGURE 4: Adjusted OR for the first AKI event by the stage of AKI across calendar years in the Irish health system. The relationship between calendar year and the OR of AKI is modelled separately for AKI Stages 1–3 with year 2005 as the referent. In each model, covariates for adjustment include age, sex, baseline GFR estimated using the CKD-EPI equation, county of residence, location of medical supervision, laboratory measures of illness (haemoglobin, serum albumin, white blood cell count, serum potassium, serum calcium and serum phosphorus concentration) and calendar year. $P < 0.001$ for each year compared with referent 2005.

Table 4. Factors associated with the first AKI in the Irish health system

Variable	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)[a]	P-value
Age (per 5 years)	1.41 (1.40–1.41)	<0.001	1.25 (1.24–1.26)	<0.001
Men (versus women)	1.22 (1.20–1.25)	<0.001	1.28 (1.22–1.35)	<0.001
Baseline eGFR[b] (per 5 unit decrease)	1.17 (1.17–1.17	<0.001	1.01 (1.01–1.02)	<0.001
County of residence				
Donegal (reference)	1.00	–	1.00	–
Sligo	0.97 (0.93–1.00)	0.050	1.09 (1.00–1.18)	0.040
Leitrim	0.92 (0.88–0.97)	<0.001	0.88 (0.79–0.98)	0.020
Limerick	1.23 (1.19–1.26)	<0.001	1.70 (1.60–1.81)	<0.001
Clare	1.33 (1.28–1.37)	<0.001	1.91 (1.74–2.08)	<0.001
Tipperary	1.18 (1.12–1.24)	<0.001	0.89 (0.78–1.01)	0.080
All other counties	0.59 (0.55–0.62)	<0.001	0.34 (0.31–0.38)	<0.001
Location of medical supervision[c]				
GP (reference)	1.00	–	1.00	–
ER	10.72 (10.34–11.12)	<0.001	5.97 (5.56–6.42)	<0.001
IP	40.13 (38.70–41.60)	<0.001	19.11 (17.69–20.64)	<0.001
OP	9.94 (9.52–10.38)	<0.001	4.37 (4.02–4.75)	<0.001
Calendar year				
2005 (reference)	1.00	–	1.00	–
2006	1.27 (1.22–1.33)	<0.001	1.65 (1.49–1.83)	<0.001
2007	1.52 (1.45–1.58)	<0.001	1.93 (1.74–2.13)	<0.001
2008	1.70 (1.63–1.78)	<0.001	2.66 (2.40–2.95)	<0.001
2009	1.91 (1.82–1.99)	<0.001	2.81 (2.54–3.11)	<0.001
2010	2.01 (1.92–2.10)	<0.001	3.09 (2.78–3.42)	<0.001
2011	2.22 (2.13–2.33)	<0.001	3.70 (3.33–4.10)	<0.001
2012	2.34 (2.24–2.45)	<0.001	4.05 (3.64–4.50)	<0.001
2013	2.45 (2.34–2.56)	<0.001	4.09 (3.67–4.56)	<0.001
2014	2.44 (2.33–2.55)	<0.001	4.36 (3.90–4.87)	<0.001

[a]Multivariable models show adjusted ORs and corresponding 95% CIs. Model is adjusted for the following measures assessed at baseline: age, sex, baseline GFR estimated using CKD-EPI equation, county of residence, location of medical supervision, laboratory measures of illness (haemoglobin, serum albumin, white blood cell count, serum potassium and serum urea concentration) and calendar year; C-statistic = 0.95.
[b]eGFR was based on the CKD-EPI equation [19].
[c]Location of medical supervision refers to the location of the patient when the laboratory test was conducted.

AKI appears to peak in 2012 at 2.27 (95% CI 2.01–2.57) and declined thereafter to 2.03 (95% CI 1.75–2.36) compared with AKI Stages 1 and 2. This might suggest that the driving forces for Stage 3 AKI are better managed, including earlier recognition and management of AKI Stages 1 and 2 and thereby less transition to Stage 3.

Our study has several strengths that merit comment. Our analysis depended solely on a laboratory-based approach. The measurement of serum creatinine was based on assays that are traceable to IDMS. The diagnosis of AKI using KDIGO criteria was determined based solely on serum creatinine concentrations from regional laboratory systems, thereby avoiding the

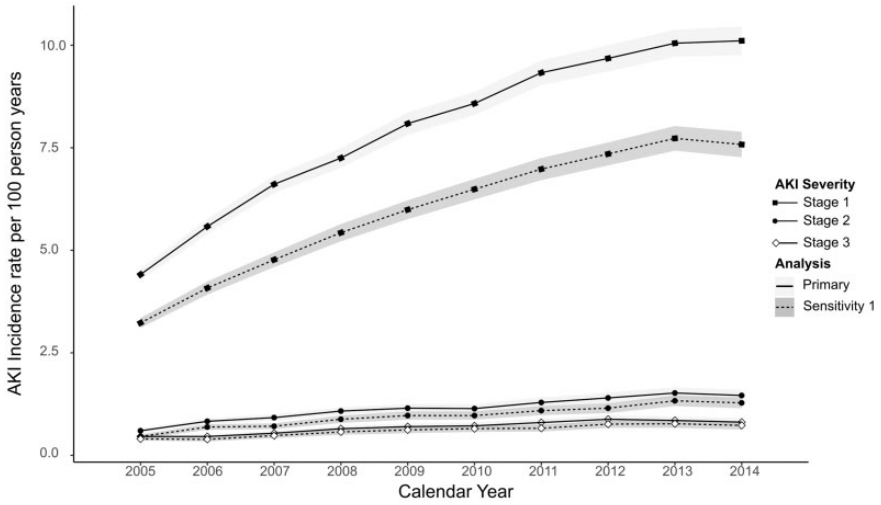

FIGURE 5: Temporal trends in the incidence of AKI by severity stage in the Irish health system. The solid line represents data from primary analysis and the dashed line represents data from the first sensitivity analysis.

need for hospital-based coding. Therefore our analysis provides a more accurate reflection of the true event rate of AKI in the health system [22]. An equally important advantage of our study was the availability of serum creatinine measurements measured prior to the AKI event in 87% of all patients. Accordingly we were able to ascertain the baseline stage of CKD and baseline creatinine to define the presence and severity of AKI. Finally, our study was strengthened by the use of large regional samples that included 451 646 patients with extensive demographic, laboratory and facility-level data captured over time. Despite these strengths, some weaknesses were apparent. First, we did not have available data on comorbidity and medical procedures, and therefore adjustment for case mix depended on laboratory parameters to reflect the presence and severity of illness. Nevertheless, the final set of demographic characteristics and clinical and geographic variables included in our model were important enough to yield a C-statistic of 0.93. Second, our analysis lacked data on hospital admission and length of stay, information that would have further clarified our understanding of community and hospital-based AKI events. Instead, we were able to pinpoint with certainty the exact location of medical supervision from blood request forms completed by the supervisory physicians. Third, it is possible that underreporting of Stage 3 AKI events may have occurred, as our analysis did not capture acute dialysis-requiring AKI. Similarly, underreporting of Stages 2 and 3 events may have resulted from our dependence on creatinine values near the initiation of an AKI episode rather than on maximal values. Fourth, longitudinal tracking of patients in the Irish health system was based on a probabilistic matching strategy rather than a unique identifier [25]. Finally, we readily acknowledge the limitations of serum creatinine as a diagnostic marker of AKI, as it has been shown to be affected by factors independent of GFR such age, sex, race, body size, diet and certain drugs [31].

Within the Irish health system, we demonstrate patterns of increasing incidence of AKI from 2005 to 2014. For men and women from all age groups, incident rates of AKI increased over time. Increasing incidence was observed for all stages of AKI, but most of the increase was accounted for by accelerated growth of Stage 1 AKI. AKI events were more common in the key areas of medical supervision and physical locations that could potentially be targeted for early detection and prevention programmes. Changes in patient- and facility-level characteristics were significantly associated with an increasing incidence of AKI, however, adjustment for these did not fully account for the observed growth. Effective management of AKI in health systems requires robust surveillance systems embedded within the health system to track the frequency and impact of AKI events over time as well as monitor the effectiveness of preventive strategies in high-risk clinical settings. The goal of the National Kidney Disease Surveillance System in Ireland is to better understand the evolving landscape of AKI in the Irish health system, its determinants and outcomes, resource utilization and costs in order to improve both patient outcomes and health system performance.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

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AUTHORS' CONTRIBUTIONS

X.L., L.D.B. and A.G.S. had full access to the study data and the analyses. All authors reviewed the manuscript and signed off on its accuracy.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests. The results presented in this article have not been published previously in whole or part, except in abstract format.

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