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Original Article

Hyponatraemia during an emergency medical admission as a marker of illness severity & case complexity

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ABSTRACT

Background: Altered sodium balance at time of an emergency medical admission adversely impacts on outcome; whether hyponatraemia is independently associated with outcomes or a surrogate of acute illness severity has been debated.

Methods: All emergency medical admissions between 2002 and 2017 were studied and a risk score calculated. We compared univarate deciles of admission sodium using a multivariable model, adjusting for risk score.

Results: There were 106,586 admissions in 54,928 patients. Patients with lower sodium at admission were older at 66.7 years (IQR 46.7–79.5) compared with 63.3 years (IQR 42.9–78.2) with a longer length of stay (LOS) of 6.8 days (IQR 3.0–14.7) versus 4.9 days (IQR 1.8–10.9). They had a higher 30-day in-hospital mortality at 6.4% vs 4.4% ($p < 0.001$). Admission sodium predicted survival – OR 0.89 (95%CI 0.88–0.90). We adjusted the model with a Risk Score that is predictive and exponentially related to 30-day in-hospital mortality. When adjusted for Risk Score, the admission sodium value was less predictive – OR 0.95 (95%CI 0.92–0.97). The cumulative percentages within the lowest five deciles fell from 63.3% between 2002 and 2009 to 48.1% from 2010 to 2017. The slope of the prediction line relating admission sodium to mortality did not change over time but a lower mortality rate was predicted at any given sodium level.

Conclusion: Hyponatraemia at the time of an emergency medical admission is predictive and probably a marker of Acuity Illness Severity and Case Complexity. Both the frequency of abnormality in admission sodium and mortality have fallen over time.

1. Introduction

The discipline of Acute Medicine investigates and treats urgent clinical conditions that require immediate and specialist management [1]; it is a high risk period that over the past two decades has undergone restructuring of operational systems and improved patient flow [2, 3]. These together with the establishment of acute medical admissions units (AMAU) [4–6] have contributed to an improvement in clinical outcomes with continuing falls over time of 30-day in-hospital mortality [5, 7]. Risk management of critical admissions requires reliable measures that predict clinical outcomes, enabling patient profiling; laboratory risk predictors have been investigated including hypoalbuminaemia [8, 9], hyperglycaemia [10–13], renal insufficiency [14–16] or combinations to develop predictive laboratory score systems [17, 18]. The importance of disturbance of sodium has been debated [16, 19–21].

Hyponatraemia at clinical presentation is indicative of a disruption in the body's water balance with appreciable clinical manifestations including convulsions, coma and even death [22]. Abnormal sodium levels below the normal limits of the laboratory range are said to occur in about 15% of hospitalized patients [20]; however such estimates may be less reliable than direct biochemical estimates as clinical coding tend to greatly underestimate its prevalence [23]. Major morbidity and mortality have been demonstrated at the extremes of serum sodium in many patient groups including general internal medicine patients [24–26]. Hyponatraemia has been shown to be prognostic for specific groups of patients with cardiovascular disease, such as congestive heart failure [27, 28] but also for patients with pulmonary hypertension [29]. How the risk of an adverse outcome is impacted by small shifts in sodium levels is unknown.

There is still debate as to whether outcomes are causally related to the presence and extent of hyponatraemia, or merely a proxy for

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mortality due to the underlying condition [30]. We have developed a Risk Score that is related exponentially to 30-day in-hospital mortality; this sums an Acute Illness Severity Score (AISS) (laboratory multivariable fractional polynomial method) [15, 31] with additional clinical risk estimate from discharge codes (ICD9/ICD10) to calculate the Charlson Comorbidity index [32], the Chronic Disabling Score [33] and data on a blood culture request (yes/no whether negative or positive) to assess Sepsis Status [34]. It allows us to examine the important question, using a database of over 100,000 emergency medical admissions between 2002 and 2017, as to whether hyponatraemia is independently associated with acute hospital mortality outcomes (30-day in-hospital mortality and length of stay) or an epiphenomenon reflecting acute illness severity and case complexity.

2. Methods

2.1. Background

St James's Hospital, Dublin serves as a secondary care centre for emergency admissions in a catchment area with a population of 270,000 adults. All emergency medical admissions were admitted from the Emergency Department to an AMAU, the operation and outcome of which have been described elsewhere [5, 7]. As a city centre hospital St James's admits persons resident elsewhere but working in the capital in addition to visitors to Dublin who became acutely ill. The number of emergency medical admissions resident in the catchment area was 74.5%; this compares with a figure of 59% for ED presentations where the social influences on emergency department visitations on two London hospitals have been examined [35].

2.2. Data collection

An anonymous patient database was employed, collating core information of clinical episodes from the Patient Administration System (PAS), the national hospital in-patient enquiry (HIPE) scheme, the patient electronic record, the emergency room and laboratory systems. HIPE is a national database of coded discharge summaries from acute public hospitals in Ireland [36, 37]. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) has been used for both diagnosis and procedure coding from 1990 to 2005 with ICD-10-CM used since then. Data included parameters such as the unique hospital number, admitting consultant, date of birth, gender, area of residence, principal and up to nine additional secondary diagnoses, principal and up to nine additional secondary procedures, and admission and discharge dates. Additional information cross-linked and automatically uploaded to the database includes physiological, haematological and biochemical parameters.

2.3. Acute illness severity score

Derangement of biochemical parameters may be utilised to predict clinical outcome. We derived an AISS based on laboratory data – this is an age adjusted 30-day in-hospital mortality risk estimator, representing an aggregrate laboratory score based on the admission serum sodium, serum potassium, serum urea, red cell distribution width, white blood cell count, serum albumin and troponin values at admission [15, 38]; the score predicts 30-day in-hospital mortality from the biochemical parameters recorded in the Emergency Department [39]. The AISS can be enhanced with data from the ICD9/10 discharge codes to compute Co-Morbidity (as per the Charlson Index [32]) and chronic disabling disease [33] status. This Risk Score is exponentially related to the 30-day mortality outcome with a range of mortality outcomes from 0.5% (0.40%–0.53%) to 39% (37.8%–40.2%). We have demonstrated using a nomogram that this laboratory models derives most of its predictive power from the values of albumin, urea and haemoglobin recorded at the time of admission [40].

2.4. Statistical methods

Descriptive statistics were calculated for background demographic data, including means/standard deviations (SD), medians/interquartile ranges (IQR), or percentages. Comparisons between categorical variables and mortality were made using chi-square tests.

We employed a logistic model with robust estimate to allow for repeated admissions; the correlation matrix thereby reflected the average dependence among the specified correlated observations [15]. Logistic regression analysis identified potential mortality predictors and then tested those that proved to be significant univariate predictors ($p < 0.01$ by Wald test). We used the margins command in Stata 13.1 to estimate and interpret adjusted predictions for sub-groups, while controlling for other variables such as time, using computations of average marginal effects. Margins are statistics calculated from predictions of a previously fitted model at fixed values of some covariates and averaging or otherwise over the remaining covariates. In the multiple variable model (logistic), we adjusted univariate estimates of effect, using the previously described outcome predictor variables. The model parameters were stored; post-estimation intra-model and cross-model hypotheses could thereby be tested.

Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for those predictors that significantly entered the model ($p < 0.10$). Statistical significance at $P < 0.05$ was assumed throughout. Stata v.13.1 (Stata Corporation, College Station, Texas) statistical software was used for analysis.

3. Results

3.1. Patient demographics

During the over the 16-year study period (2002–2017), there were a total of 106,586 episodes of medical emergencies in 54,928 unique patients admitted through the Emergency Department. This represented all emergency medical admissions, including patients admitted directly into the Intensive Care Unit or High Dependency Unit. The proportion of males was 48.5%. The median (IQR) length of stay (LOS) was 4.3 days (1.7–8.9). The median (IQR) age was 58.9 years (38.2–76.3) with the upper 10% boundary at 85.0 years.

The demographic characteristics (Table 1) is outlined with a cut point at the median admission sodium level of 138 mEq/l and tabulated (to allow group comparisons) by AISS [15, 38], Charlson Co-Morbidity Index [32], Chronic Disabling Disease Score [33] and Sepsis status [34]. Admissions with a lower sodium were older over time 66.7 years (IQR 46.7–79.5) compared with 63.3 years (IQR 42.9–78.2) and had a longer hospital LOS – 6.8 days (IQR 3.0–14.7) versus 4.9 days (IQR 1.8–10.9). The per episode 30-day in-hospital mortality rate was higher for those with an admission sodium below the median – 6.4% vs 4.4% ($p < 0.001$). In terms of the AISS, Chronic Disabling Disease and Sepsis Rates these were all significantly worse for those admitted with lower sodium values (e.g. Illness Severity Groups V & VI – 69.7% vs 55.5%, Charlson CoMorbidity Group II – 33.0% vs 23.7%, Chronic Disabling Disease 4+ 18.4% vs 13.7% and Sepsis culture positive – 5.6% vs 3.2%).

3.2. Mortality related to admission sodium level

The 30-day per patient (one admission only per patient – last admission if > 1) mortality declined between 2002 and 2017 – from 12.4% to 4.8%. This represented a relative risk reduction (RRR) of 61.3% with a numbers to treat (NNT) of 13.1. We calculated the same mortality data related to the presenting sodium level; a higher presenting value predicted survival – OR 0.89 (95% CI 0.88–0.90). A falling sodium level was associated with an decreasing mortality rate across the deciles; from decile 1 (lowest sodium) – 16.9% (95% CI 16.0%–17.8%) to decile 5–11.4% (95% CI 11.0%–11.8%) and decile

Table 1
Characteristics of Emergency Medical Admission Episodes by initial Sodium Level.

Factor	Level	< 138	≥ 138	p-Value
N		56,180	50,388	
Gender	Male	28,046 (49.9%)	23,848 (47.3%)	< 0.001
	Female	28,134 (50.1%)	26,540 (52.7%)	
Outcome	Alive	52,580 (93.6%)	48,170 (95.6%)	< 0.001
	Died	3600 (6.4%)	2218 (4.4%)	
Age, median (IQR)		66.7 (46.7, 79.5)	63.3 (42.9, 78.2)	< 0.001
Length of stay (days)		6.8 (3.0, 14.7)	4.9 (1.8, 10.9)	< 0.001
Acute illness severity	1	870 (1.7%)	2098 (4.7%)	< 0.001
	2	2607 (5.0%)	3990 (8.9%)	
	3	5029 (9.6%)	6089 (13.6%)	
	4	7436 (14.2%)	7808 (17.4%)	
	5	10,127 (19.3%)	8509 (19.0%)	
	6	26,450 (50.4%)	16,373 (36.5%)	
Charlson index	0	26,450 (50.4%)	24,928 (49.6%)	< 0.001
	1	15,435 (27.5%)	13,420 (26.7%)	
	2	18,476 (33.0%)	11,941 (23.7%)	
Disabling disease	0	4070 (7.2%)	6659 (13.2%)	< 0.001
	1	11,579 (20.6%)	12,567 (24.9%)	
	2	16,319 (29.0%)	14,020 (27.8%)	
	3	13,901 (24.7%)	10,239 (20.3%)	
	4	10,311 (18.4%)	6903 (13.7%)	
Sepsis status	0	38,287 (68.2%)	40,446 (80.3%)	< 0.001
	1	14,727 (26.2%)	8339 (16.5%)	
	2	3166 (5.6%)	1603 (3.2%)	

LOS: length of stay, MDC: Major disease category, IQR: Inter-Quartile Range.

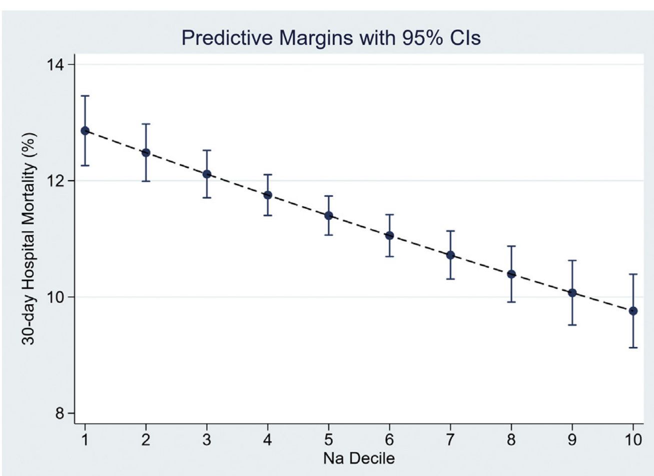

Fig. 1. The relationship between the admission sodium level and the 30-day in-hospital mortality. For each decile of sodium, the 30-day in-hospital mortality rate was derived from the logistic regression model and adjusted for the Charlson Co-Morbidity, Chronic Disabling Disease, Sepsis Scores and Deprivation Index. The decile cut-offs for sodium were at 131, 134, 136, 137, 138, 139, 140, 141 and 142 mEq/l; there was a linear relationship between admission sodium and 30-day in-hospital mortality.

10–6.7% (95% CI 6.2%–7.2%). However, adjusted for the other predictor variables the influence of the presenting sodium level was somewhat less – OR 0.96 (95% CI 0.95–0.97) with mortality ranges over the deciles from decile 1 (lowest sodium) of 12.8% (95% CI 12.3%–13.4%) to decile 10 (highest) – 9.8% (95% CI 9.1%–10.4%), Fig. 1.

We adjusted the model with a Risk Score that is predictive of 30-day hospital mortality – OR 1.80 (95% CI 1.76–1.84) with an AUROC of 0.86 (95% CI 0.85–0.86). The Risk Score has an exponential relationship to 30-day hospital mortality rate and is constructed from admission laboratory data [15, 34] and hospital codings data [37]; the range of predicted mortality is considerable ranging from 0.1% (95% CI 0.08–0.12) to 54.0% (95% CI 52.3–55.7). When adjusted for Risk Score and other small area predictive variable (educational level, single parent families, elderly dependency rate) across quintiles of sodium (same for deciles) the initial admission sodium value was less predictive – OR 0.95 (95% CI 0.92–0.97) unlike the Risk Score that was the most powerful predictor – OR 1.80 (95% CI 1.76–1.84). The effect of age did not influence the predictive value of the admission sodium but older persons had a greater absolute risk.

3.3. Improved hyponatraemia outcome with time

We compared the 30-day in-hospital mortality rates for two time periods – 2002-2009 versus 2010–2017. For both periods the sodium decile was inversely related to mortality outcomes with lower admission values predicting worse outcomes. However mortality outcomes were consistently worse from 2002 to 2009 with 30-day predicted mortality of 16.2% (95% CI 15.2%–17.2%) at lowest sodium decile versus 7.3% (95% CI 6.6%–8.1%) at highest sodium decile. In contrast, the data on model predicted mortality outcomes from 2010 to 2017 were 10.6% (95% CI 9.8%–11.3%) and 5.0% (95% CI 4.5%–5.4%) for the same deciles.

This might imply that the frequency of abnormal sodium by decile was lower in the second 8 year period compared with the first. Indeed comparison of the frequency of occurrence of the five lowest sodium deciles (2002–2009 12.6%, 13.0%, 15.0%, 9.5% and 10.3% vs 2010–2017 9.1%, 9.0%, 11.3%, 7.6% and 9.1%) showed a marked reduction over time, Fig. 2. Thus, the cumulative percentages within the lowest five deciles fell from 63.3% between 2002 and 2009 to 48.1% between 2010 and 2017 – the reason for such a striking change in admission sodium profile is unclear. Therefore, as the distribution of sodium by decile might have been different across the two time periods, we estimated the outcome risk against the absolute level of admission

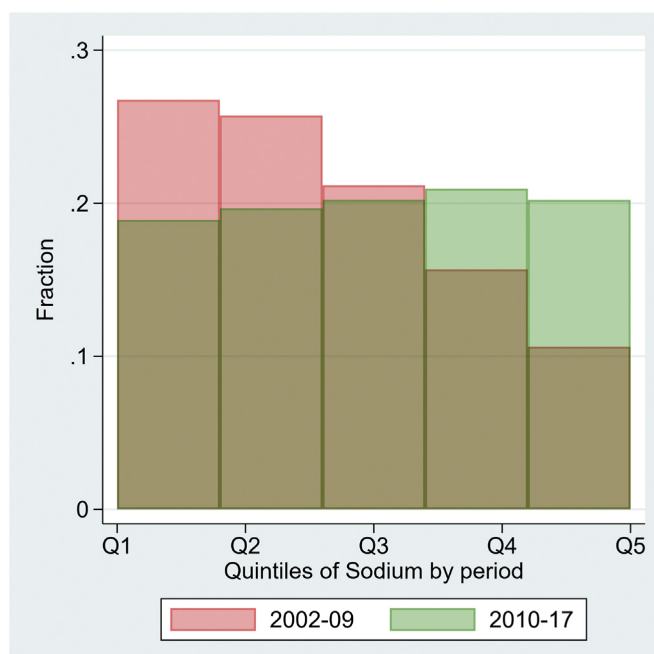

Fig. 2. The relationship between the admission sodium comparing the years 2002–09 and 2010–17 (two consecutive 8 year periods). Pink represents 2002–09, green represents 2010–17, brown represents were the datasets for both time periods overlap. The hypothesis was of no difference in distribution over time. However, between 2002 and 09, lower admission values (pink: Q1, Q2) were more common compared with 2010–17 brown). The respective frequencies in the bottom three deciles were 12.6%, 13.0% and 15.0% for 2002–09 and 9.1%, 9.0% and 11.2% between 2010 and 17. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

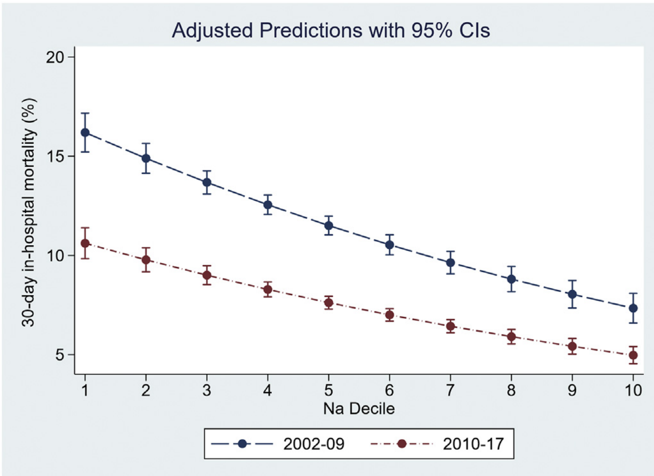

Fig. 3. The relationship between the admission sodium level and the 30-day in hospital mortality. At each level of admission sodium, the 30-day mortality rate was derived from the logistic regression model and was the sum of the Illness Severity, Charlson Co-Morbidity, Chronic Disabling Disease and Sepsis Scores. Data was analysed for two consecutive periods 2002–2009 and 2010–2017. At sodium admission level, the 30-day hospital mortality was lower for the second period.

sodium (Fig. 3). Although the calculated mortality rates were higher at the absolute sodium level, the overall trends between the two periods were very similar. Thus the relationship between outcome and predictive variable did alter over time – it was not the case that the explanation for the mortality reduction was solely due to a reduction in frequency of hyponatraemia over time.

4. Discussion

Our data shows that over a period of 16 years a substantial change has occurred in the level of sodium at the time of an emergency medical admission. To those engaged in daily clinical practice this would not have been evident but the frequency of patients in the lowest decile of sodium at admission declined from 63.3% between 2002 and 09 to 48.1% between 2010 and 17. The overall medians (IQR) for the two 8 year periods were 137 mmol/l (134–140) and 139 mmol/l (136–141) and although one might on superficial inspection conclude no difference, the statistics would not agree (one anova with Scheffe's ‘t’ - F 1821, $p < 0.00$). Over the same time span, the 30-day in-hospital mortality for admissions with hyponatraemia fell, with mortality per patient from 2002 to 2009 of 11.2% declining to 7.4% from 2010 to 2017. For the top risk (Deciles I—V) comparing 2002 with 2016, this represents a model adjusted fall in per patient mortality from 13.6% to 9.0% translating into a RRR of 33.0% and a calculated NNT of 22.2. The slope of the relationship between the admission sodium value was very similar over the two 8 year periods, however the predicted mortality outcome was substantially lower for the 2010–2017 period. The population between the two time periods 2002–09 and 2010–17 was significantly older (median 66.7 vs 63.3 years) and therefore one might have expected more patients with lower levels of sodium as increasing age is a strong independent risk factor for both hypo- and hypernatremia [41]. This illustrates the problem with risk scores and their generalizability – if the underlying relationship can be different not alone between populations but can evolve from one state to another over time within the same hospital population. It is not clear from our data why there has been such a decrease in the incidence of hyponatraemia. There was no intervention, either within the hospital or within the community in that time frame which may have resulted in this decrease. This may be a result of improved awareness and management of hyponatraemia within primary care. It may also be due to a reduction in the use of medications which may cause hyponatraemia, such as thiazide diuretics, due to increased availability of alternative agents. This question will require further studies to answer.

Our analyses suggested that the admission sodium value in part was a proxy for AISS and case co-morbidity/complexity but that there had been a significant shift over time both in the frequency of admissions below the sodium median as well as a change in the relationship between baseline value and the predicted 30-day in-hospital mortality. We conclude that like the AISS that increases with age the alterations in biochemical markers run in tandem with the integrity of the homeostatic functions. Abnormality in sodium then cannot be considered truly an independent entity; although predictive of mortality outcomes and hospital length of stay when measured alone, abnormal sodium values at presentation point to wider issues, conveying increased risk of an adverse outcome rather than being limited to a highly specific impairment of sodium homeostasis.

For the practicing physician the focus is often on clinical outcomes at the extremes with the high mortality rates reported [42] and the intervention and rate of correction of the disorder [43]. There is no evidence of recognition that the level of sodium at the time of presentation is predictive right across the range of values. However disturbed biochemistry has been recognised to predict hospital mortality outcomes and incorporated into laboratory score systems [18, 44, 45]. Broadly speaking, clinical outcomes for the entire population of hospital admissions can be predicted using admission laboratory data [17, 18] with an underlying assumption that adjusted (for age) the degree of biochemical disturbance reflects illness severity and is predictive of outcome. This prediction extends across many different conditions including stroke [46], congestive heart failure [28], and pulmonary hypertension [29]. The question that has not been conclusively addressed is as to whether patients die with or as a consequence of hyponatraemia [30]; in one series with severe hyponatremia, the mortality rate was 8%, but the view was that most deaths were caused by underlying diseases [42]. Gheorghiade et al. demonstrated a marked correlation between serum sodium < 135 mEq/l and both hospital LOS and mortality and an apparent “U shaped’ curve with increased mortality if serum sodium was > 140 mEq/l [27]. Our data illustrates that the relationship between admission sodium and clinical outcomes is essentially linear but sodium levels at the upper limit of those typically encountered in clinical practice are predicted to be strongly associated with a low risk of adverse outcomes. That does not preclude the possibility that values well beyond the range encountered in typical medical emergency admissions, may have poorer outcome. There are no studies showing the benefit of the correction of abnormal sodium values in the absence of severe symptoms on mortality. However some studies have shown benefits in terms of other endpoints such as gait [47].

While this study uses a comprehensive dataset gathered over a long period of time, it has limitations; it is based at a single centre, analysing a retrospective cohort and therefore relying on accurate and consistent coding and documentation over a period of 16 years. The results will need to be verified in other centres to establish external validity. Hyponatraemia was based on absolute lab values at time of admission and did not differentiate volume status with Cuesta et al. showing a difference in mortality rates between SIADH and hypervolaemic or hypovolaemic hyponatraemia [48]. The criteria ‘defining’ hyponatraemia also varies among the literature which makes comparison challenging; this study termed any sodium reading below the median as hyponatraemia which would include readings within normal limits. We do not hold information on the specific treatment of individual patients and there were no hospital wide pathways for hyponatraemia; therapy was at the discretion of the admitting consultant physician. Finally, while we have identified an independent association between serum sodium and 30 day in-hospital mortality, this does not imply causation; such a question would require a randomised controlled trial intervening in sodium homeostasis to answer.

In conclusion this study demonstrates that in unselected emergency medical admissions hyponatraemia more frequently affects an older population with a worse AISS and case complexity. It is a strong independent predictor of both mortality and hospital LOS and at a minimum should arouse concern in clinicians that affected patients are at higher risk of adverse outcomes. The frequency of hyponatraemia has fallen with a reduction in mortality over this timeframe which may be explained by concurrent operational improvements for acute medical admissions.

Conflict of interest

The authors declare that they have no conflict of interest regarding this publication.

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