

The Problems with Risk Prediction during an Emergency Medical Admission Using Laboratory Data – Evidence from Potassium

R Conway, D Byrne, S Cournane, D O’Riordan & B Silke

Abstract

Background: The prediction of clinical outcomes using biochemical markers is an important tool.

Methods: We calculated a risk score for all emergency admissions 2002-2017. We related potassium and mortality in a multivariable fractional polynomial model. We investigated the potassium distribution and relationship of potassium to mortality over time.

Results: There were 106,586 admissions in 54,928 patients. Mortality was higher for those with an admission potassium above the median – 6.1% vs 4.6% ($p < 0.001$), OR 1.07 (95%CI: 1.06, 1.09). There was a progressive increase in mortality from the lowest – 8.9% (95%CI: 8.3%, 9.4%) to highest potassium decile – 14.2% (95%CI: 13.5%, 14.8%). The frequency of admission hypokalaemia and the mortality at any given potassium decreased over time.

Conclusion: Admission potassium predicts mortality.

Key Words

Emergency Medical Admission, Mortality prediction, Potassium.

Introduction

The discipline of Acute Medicine investigates and treats conditions that require immediate and specialist management.¹ The outcomes for emergency medical admissions appear to have improved over time;² the restructuring of operational systems^{3, 4} and the establishment of acute medical admissions units (AMAU)^{5, 6} have contributed to these improvements. The USA National Hospital Discharge Survey (NHDS) data from 2000 through 2010 reported that inpatient hospital mortality decreased 8% from 2000 to 2010⁷ – an effect size comparable with the outcome improvement we have witnessed.²

Risk management of critically ill admissions requires reliable measures that predict clinical outcomes enabling patient profiling; risk score systems have been developed in an attempt to quantify risk and predict outcomes, particularly in the Intensive Care Unit (ICU).⁸⁻¹⁰ Laboratory score systems predict the outcome of hospitalized patients¹¹ and been investigated for acute medical admissions.¹²⁻¹⁴ They may be allied with clinical data to predict short and longer-term outcomes.^{15, 16} Despite this the art of prognostication seems elusive.¹⁷

We therefore were interested to examine the stability and reliability of laboratory predictors of outcome over time. We previously validated a complex laboratory score prediction system to estimate, from laboratory data collected at time of

admission, the 30-day in-hospital mortality.¹⁸ One of the components used in this computation of risk is the admission serum potassium; we have previously described the relationship of admission potassium to mortality.¹⁹ Although the effect of potassium on risk for specific subsets such as patients with chronic kidney disease or coronary artery disease has been described in detail, the relationship to mortality in the general population has been less frequently studied.²⁰ During risk score development, the predicting parameters are typically entered into a multivariable logistic regression model, and a score computed weighted to the regression coefficients.²¹ This is usually validated against a 20% independent sample, although frequently this may be a subset of the same population. Thus, the generalizability to other populations cannot be assumed. In this work we explore the stability of potassium distribution across hospital admissions over time, using as comparison two consecutive 8 year periods. We further evaluate the relationship of admission mortality to 30-day in-hospital mortality. The hypothesis being tested was that the distribution of admission potassium over a large population of emergency medical admissions should be stable and that even if outcomes have improved over time, the slope of the regression line relating deciles of admitted potassium values to mortality outcomes, should have remained constant.

Richard Conway¹
PhD

Declan Byrne¹
MD

Seán Cournane²
PhD

Deirdre O’Riordan¹
MD

Bernard Silke¹
MD DSc

¹ Department of Internal Medicine

² Medical Physics and Bioengineering Department, St James’s Hospital, Dublin 8, Ireland.

Correspondence

Bernard Silke
Department of Internal Medicine, St James’s Hospital, Dublin 8, Ireland
Email: bernardsilke@physicians.ie

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Methods

Background

Our institution, 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 are admitted from the Emergency Department (ED) to an AMAU, the operation and outcome of which have been described elsewhere.^{2, 5, 22} 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.²³

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.^{24, 25} 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.

Acute Illness Severity Score

Derangement of biochemical parameters may be utilised to predict clinical outcome. We derived an Acute Illness Severity Score (AISS) based on laboratory data – this is an age adjusted 30-day in-hospital mortality risk estimator, representing an aggregate laboratory score based on the admission serum sodium, serum potassium (potassium), serum urea, red cell distribution width, white blood cell count, serum albumin and troponin values at admission;^{14, 18} the score predicts 30-day in-hospital mortality.²⁶ The AISS can be enhanced with data from the ICD9/10 discharge codes to compute co-morbidity (as per the Charlson Index²⁷) and

chronic disabling disease²⁸ status. This Risk Score is exponentially related to the 30-day in-hospital mortality 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 model derives most of its predictive power from the values of albumin, urea, and haemoglobin recorded at the time of admission.²⁹

Statistical methods

Descriptive statistics were calculated for background demographic data, including means/standard deviations (SD), medians/inter-quartile 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.¹⁸ 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 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 multivariable logistic model, 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.15 (Stata Corporation, College Station, Texas) statistical software was used for analysis.

Results

Patient Demographics

During the 16-year study period (2002–2017), there were a total of 106,586 emergency medical admissions in 54,928 patients admitted through the ED. This represented all emergency medical admissions, including patients admitted directly into the ICU and 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.

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Table 1. Characteristics of Emergency Medical Admissions by Potassium Level

Factor	Level	< 4.0	≥4.0	p-value
N		43190	63598	
Gender	Male	19292 (44.7%)	32602 (51.4%)	<0.001
	Female	23898 (55.3%)	30776 (48.6%)	
Outcome	Alive	41216 (95.4%)	59531 (93.9%)	<0.001
	Died	1974 (4.6%)	3847 (6.1%)	
Age, median (IQR)		61.1 (41.5, 76.9)	67.7 (48.0, 80.0)	<0.001
Length of Stay (days)		6.0 (2.7, 13.0)	5.8 (2.2, 12.9)	<0.001
Acute Illness Severity	1	1546 (3.8%)	1422 (2.5%)	<0.001
	2	3328 (8.1%)	3270 (5.8%)	
	3	5411 (13.2%)	5706 (10.1%)	
	4	7088 (17.3%)	8157 (14.4%)	
	5	8278 (20.3%)	10358 (18.3%)	
	6	15227 (37.2%)	27594 (48.8%)	
Charlson Index	0	20497 (47.5%)	26604 (42.0%)	<0.001
	1	11602 (26.9%)	17252 (27.3%)	
	2	11015 (25.5%)	19414 (30.7%)	
Disabling Disease	0	4516 (10.5%)	6214 (9.8%)	<0.001
	1	10253 (23.7%)	13893 (21.9%)	
	2	12825 (29.7%)	17519 (27.6%)	
	3	9603 (22.2%)	14542 (22.9%)	
	4	5993 (13.9%)	11210 (17.7%)	
Sepsis Status	0	30830 (71.4%)	47903 (75.6%)	<0.001
	1	10282 (23.8%)	12784 (20.2%)	
	2	2078 (4.8%)	2691 (4.2%)	

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

Demographic characteristics are outlined in Table 1, with a cut point at the median admission potassium level of 4.0 mEq/l and tabulated (to allow group comparisons) by AISS,^{14, 18} Charlson Co-Morbidity Index (27), Chronic Disabling Disease Score²⁸ and Sepsis status.³⁰ Admissions with a lower potassium were younger at 61.1 years (IQR: 41.5, 76.9) compared with 67.7 years (IQR: 48.0, 80.0) and had a longer LOS – 6.0 days (IQR: 2.7, 13.0) versus 5.8 days (2.2, 12.9). The 30-day hospital mortality rate per admission was higher for those with an admission potassium above the median – 6.1% vs 4.6% ($p<0.001$). AISS, Chronic Disabling Disease but not sepsis rates were significantly higher in those with a higher admission potassium (AISS Groups V & VI – 67.1% vs 57.5%, Charlson Co-Morbidity Group II – 30.7% vs 25.5%, Chronic Disabling Disease Score 4+ 17.7% vs 13.9% but not for Sepsis (culture positive – 4.2% vs 4.8%).

Mortality related to admission potassium

The 30-day in-hospital mortality per patient (one admission only per patient – i.e. sole or final admission if >1) declined from 12.4% to 4.8% between 2002 and 2017. This represented a relative risk reduction (RRR) of 61.3% with a number needed to treat (NNT) of 13.1. Higher admission potassium level predicted mortality – OR 1.07 (95%CI: 1.06, 1.09) and there was a progressive increase in 30-day in-hospital mortality across all deciles (Figure 1) from decile 1 (lowest) – 8.9% (95%CI: 8.3%, 9.4%) to decile 5 – 11.0% (95%CI: 10.6%, 11.3%) and decile 10 – 14.2% (95%CI: 13.5%, 14.8%). When adjusted for Risk Score, the initial admission potassium value was less predictive – OR 1.03 (95%CI: 1.02, 1.05).

Relationship between admission Potassium and Mortality outcome over time

We examined the admission potassium by decile between the two 8 year periods 2002–09 and 2010–

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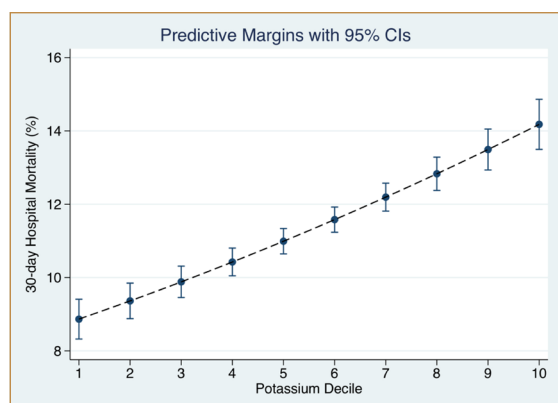


Figure 1. The relationship between the admission potassium level and the 30-day in hospital mortality. For each decile of admission potassium, the 30-day mortality rate was derived from the logistic regression model and adjusted for the Charlson Co-Morbidity, Chronic Disabling Disease, Sepsis Score and Deprivation Quintile. The decile cut-offs for potassium were at 3.4, 3.6, 3.8, 3.9, 4.0, 4.2, 4.3, 4.5 and 4.8 mEq/l; there was a linear relationship between presentation Na⁺ and 30-day mortality outcome.

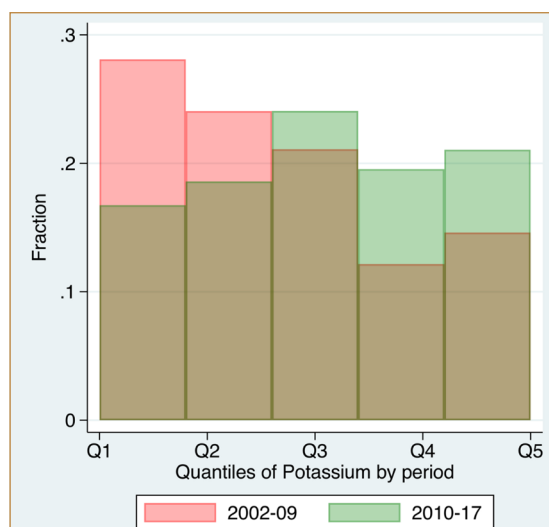


Figure 2. The relationship between the potassium at time of admission comparing the years 2002-09 and 2010-17 (two consecutive 8 yr.). Pink represents 2002-09, green represents 2010-17, brown represents were the datasets for both time periods overlap. The hypothesis was of no difference in distribution 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 15.1%, 11.6% and 15.2% for 2002-09 and 8.3%, 7.1% and 10.7% between 2010-17.

17 (Figure 2). Hypokalaemia at admission was less frequent during the second period. The frequency of the bottom three potassium deciles was 15.1%, 11.6% and 15.2% for 2002-09 and 8.3%, 7.1% and 10.7% between 2010-17. Potassium below the median 4.0 mEq/L was seen in 60.4% and 43.1% respectively during the two periods. For both periods admission potassium was linearly related to mortality outcomes – higher levels predicted increased mortality. Mortality was consistently higher between 2002-2009 with model predicted rates ranging from 10.2 % (95%CI: 9.5%, 10.9%) in the lowest deciles of potassium to 15.4 % (95%CI: 14.5%, 16.2%) in the highest deciles of potassium. In contrast, the data on model predicted mortality outcomes between 2010-2017 were 6.8% (95%CI: 6.3%, 7.4%) and 7.8% (95%CI: 7.3%, 8.3%) for the same deciles. Thus, not only did the population potassium distribution alter over time, the strength of the prediction reduced over time – the absolute mortality outcome and the slope of the regression line were altered (Figure 3).

Discussion

Most studies relating potassium to mortality have described a U shaped curve for potassium levels outside the normal laboratory range (higher rates for hypo- or hyperkalaemia).³¹ This contrasted with a general population study that found a positive association between elevated potassium levels and mortality risk – each 1-mmol/L increase in potassium being associated with a 40% increase in the adjusted hazard ratio for death.²⁰ Our data is different in certain respects

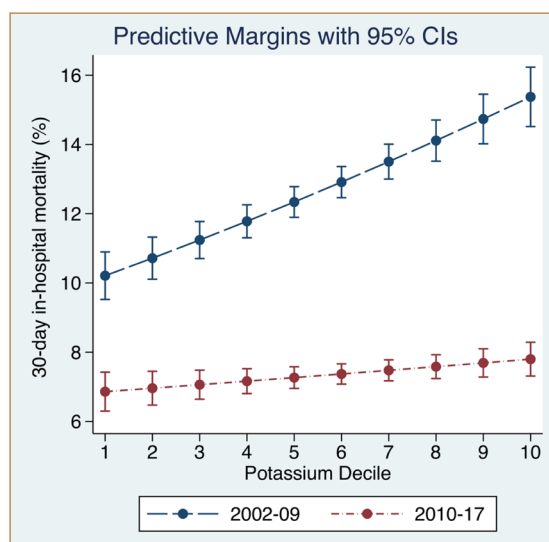


Figure 3. The relationship between the admission potassium level and the 30-day in hospital mortality. At each level of admission potassium, the 30-day mortality rate was derived from the logistic regression model and was the sum of the Illness Severity, Charlson Co-Morbidity, Chronic Disabling Disease and Sepsis Scores. Data was analysed for two consecutive periods 2002-2009 and 2010-2017. For the second period both the absolute level of risk predicted and the slope of the relationship were significantly different.

from previously published studies. Firstly, there was no selection bias – all admitted medical emergencies over 16 years were included – from a catchment area

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population that represents approximately 5% of the Irish population. Secondly, we made no assumptions or applied arbitrary potassium quantiles – we simply divided the total population into deciles and related these to 30-day in-hospital mortality outcomes. Third as approximately 5% of admissions could be expected to die by day 30, there were a large number of end-points to quantitate the risk relationship to the admitted potassium quantile. We adjusted the data related to other predictive laboratory outcome predictors using an AISS^{14, 18} and ICD9/10 discharge codes to adjust for the independent risks of comorbidity (Charlson Index²⁷), Chronic Disabling Disease Score²⁸ and sepsis status.³⁰ Unlike previous studies, our data clearly demonstrate that the risk of an adverse outcome progressively increased with a rising admission potassium level across the entire range of measured values. The OR of 1.39 above or below the populations median was virtually identical to the general population risk estimate reported by Loprinzi and Hall²⁰ with our model adjusted 30-day mortality rates increasing from 9.7% to 12.3% related to the median. In the same model but examining outcomes against admission Na⁺ there is the opposite relationship; lower admission Na⁺ deciles demonstrated a progressively increasing mortality risk across the entire range of values. Therefore, although there are many factors that will impact on the serum potassium level, we would propose that the most likely hypothesis explaining these fundamental relationships of the linear relationship between the levels of admission cation and mortality outcomes, may be as a proxy of the ability of the homeostatic control mechanisms to maintain these cations within their respective intra- or extracellular compartments. Impaired function in homeostatic mechanisms as the organism ages or is subject to disease process will cause Na⁺ ingress or K⁺ outflow across cellular membranes.

Disturbed biochemistry has of course been recognised to predict hospital mortality outcomes and incorporated into laboratory score systems.^{11, 12, 32} The laboratory data is typically recorded at time of admission to establish baseline status and to estimate risk status;^{11, 13} these parameters may predict outcomes for specific disorders including stroke,³³ congestive heart failure,³⁴ and pulmonary hypertension.³⁵ A number of assumptions would need to be present to allow widespread generalizability of individual studies that appear not to be confirmed by our data. The first is that in a large sample of the general population the distribution of the predictor variable would be stable over time and that the relationship to the outcome should in absolute terms be clear cut – a certain level or quantile of the predictor variable would have a particular specific mortality rate. In

this work, we demonstrate that lower decile values for admission potassium became less frequent over time. Mortality outcomes improved over time but although the absolute outcome predictions also fell, the slope of the relationship was very much attenuated. Thus, over time, higher admission levels of potassium had a proportionally lower mortality rate than would have been expected, based on the data from earlier experience.

Risk stratification methods have been developed based on aggregated clinical scoring systems such as the Modified Early Warning Score (MEWS),³⁶ the Rapid Acute Physiology Score (RAPS)³⁷ and the Rapid Emergency Medicine Score (REMS).³⁸ Mortality may be predicted based on the specific derangement of certain laboratory parameters at time of emergency presentation.^{11, 13} Laboratory values including hypo- or hypernatraemia,^{39–42} hypoalbuminaemia^{43, 44} and hyperglycaemia^{45–48} have predicted individually outcomes. An elevated serum urea had also been shown to be of prognostic significance.^{41, 49} We aggregated different laboratory tests as an AISS¹⁸ for predicting in-hospital mortality from admission laboratory tests employing a multivariate fractional polynomial method.⁵⁰ However, derivation and validation of a Risk Score is complex;²¹ a weighting of each category proportionate to the coefficients from the multiple variable logistic regression might be required. The accuracy of prediction is predicated on the presumption that there is a fixed relationship between the absolute score and the ensuing outcome having correctly weighted the relative contributions of the individual predictors. It does not however allow for the complex biological interaction possibility that the total score might depend on the specific construction – or that higher scores might have lower outcome risks depending on the underlying risk factors. As we now show, one cannot take for granted that the population distribution may not be different at different times within a population never mind differences that might exist between populations, or that the relationship between baseline values and outcomes might differ. A way forward might be to try to identify those variables that appear, based on the population distribution, to be stable over time and to incorporate only those variables into the prediction algorithms.

As with any study, there are a number of limitations to our work. The findings we have demonstrated are confined to a single centre, the external validity of the results will require confirmation in other studies. We have analysed all emergency medical admissions, while other categories of emergency admission such as cardiology or surgery may be expected to have similar outcomes, our results are not directly

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generalisable to these populations and will require further assessment. Our study included a large number of patients and therefore was able to identify small absolute differences in outcomes; while one may question the relevance of these incremental aggregate differences to the individual patient it must be remembered that when dealing with outcomes such as mortality, even small changes are important.

In conclusion, we have demonstrated that admission serum potassium level independently

predicts mortality in emergency medical admissions, hyperkalaemia appears to be more deleterious in this regard. The population distribution and the relationship of the admission potassium level to mortality have however altered over time, and this must be born in mind when modelling outcome.

Conflict of interest

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

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