

How much does hyperkalemia lengthen inpatient stays? About methodological issues in analyzing time-dependant events

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Abstract. Adverse events may increase the hospital length of stay (LOS). As a consequence, computing the mean difference of LOS between two inpatient groups, with or without event, is a convenient way to evaluate their severity. Conversely, some adverse events are time-dependent: this leads to overestimate the consequences of the adverse event when statistical tests are performed. In this paper, we interest on hyperkalemia in the inpatient database of a community hospital (2% of the inpatient stays). The cumulated risk of hyperkalemia appears to be a linear function of the LOS. We compute the LOS difference associated with hyperkalemia by using 17 statistical methods. The raw LOS difference is 8.8 days, but the simulation finds a difference of 2.3 days, while the regressions (with linear or log link, with or without pairing, with or without propensity score) find a difference of 4.4 to 4.6 days. The characteristics of the methods are discussed, but it is not possible to know which one is true. However the raw difference seems to overestimate the truth. This methodological bias is quite frequent and is a challenge in public health, as it participates in false knowledge discovery, which could lead decision makers to focus on wrong issues and make wrong decisions.

Keywords. Hyperkalemia, Length of stay, Statistical tests, Adverse events.

Introduction

Potassium ion (K^+) is a mostly extracellular cation that takes a fundamental place in muscular and neurological functioning. The normal plasmatic K^+ concentration ranges from 3.5 to 5.5 mmol/l. It is regulated by the renal excretion of K^+ , which adapts function of the dietary intake. Hyperkalemia consists of an increase of the K^+ concentration above 5.5 mmol/l. It can be caused by several diseases, notably renal failure, and drugs [1], notably potassium supplementation, potassium-sparing diuretics, beta blockers, etc. As the transmission of the electric signal along cells membranes relies on the K^+ gradient, hyperkalemia increases the neuromuscular excitability and can induce heart rhythm troubles. These troubles are inconstant and may range from isolated electric abnormalities to ventricular fibrillation and death [2,3].

Hyperkalemia that occur during inpatient stays are often the consequence of an adverse drug event (ADE). ADEs are the most common type of iatrogenic injury [4] and can be defined as “injur(ies) due to medication management rather than the underlying condition of the patient” [5].

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The excess length of stay (LOS) plays an important role in adverse events (AE) evaluation. For instance, severe ADEs can be defined as ADEs that result in death, disability or added hospitalization days, and each ADE is estimated to increase the hospital LOS by 2.2 days [6,7]. More generally speaking, an excess LOS is a convenient criteria to evaluate the severity of an AE, such as in [8,9]. In those studies, an excess LOS is the consequence of the AE.

Conversely, some AE are time-dependent, which means that the cumulated probability grows significantly with the total LOS. The daily probability may be constant, or even growing over time. High LOS has been identified as an important risk factor of AE or ADE [10,11]. Each extra day in hospital may increase the cumulated risk of ADE by 5% [11]. Similarly, a study showed that the daily incidence of AEs was similar in Japan and in the USA, but the incidence per stay was much higher in Japan due to a higher average LOS [12]. In those studies, the excess LOS is a risk factor of AE.

There is a complex relationship between AEs and excess LOS: AEs may increase the LOS, but also inpatients with high LOS are more likely to have an AE. As a consequence, when a difference of LOS is observed between two inpatient groups, one with AE and the other without AE, only part of this difference might be the consequence of the AE. However, many researchers consider that this raw difference enables to evaluate the severity of the AE, which probably leads to overestimate this severity. Indeed, the output of the statistical test is interpreted as if the null hypothesis was “ H_{0a} : the AE does not increase the LOS”, but most often the null hypothesis that is actually tested is “ H_{0b} : the LOS means are identical”, due to the statistical design of the study. This methodological error is quite frequent to our knowledge.

The objective of this work is to test different statistical methods to evaluate the excess LOS due to hyperkalemia, as a specific example of hospital AE.

1. Methods

1.1. Database, descriptive analysis

A database of 10,244 inpatient stays from a community hospital of the North of France is used. The database contains notably demographic and administrative data, diagnostic codes in ICD10 [13], and exhaustive laboratory results with parameter name, value, unit and date of the sample. The patients who finally died (1.9%) are excluded, because a preliminary chart review showed that before the death, a hyperkalemia and an increased LOS were both more likely to occur, in a context of palliative care: in fact the hyperkalemia was not an adverse event. The inpatient stays without any laboratory sample are also excluded (31.6%). Then 6,808 cases are analyzed.

A descriptive analysis of potassium values measured in blood samples is performed. A hyperkalemia (the “event”) is defined as $K^+ > 5.5$ mmol/l. The “HyperK” group is made of all the inpatient stays with at least one event. The “NormoK” group is made of all the other stays. The analyses are performed using R statistical software [14], and 95% confidence intervals of proportions are computed using a binomial law.

1.2. Estimation of the LOS difference using classical statistical methods

Various statistical methods are tested to compare the groups “HyperK” and “NormoK”.

We first compute the raw difference of the average LOS of both groups.

Then we perform a linear regression, trying to explain the LOS by the event, the age, the gender, and the number of diagnoses (which is a proxy for the patients' severity). Then the same model is tested by adding significant interactions (presently the event and the number of diagnoses). Finally a logarithmic transformation of the LOS is used.

Similarly, the same 3 models are over-adjusted using a propensity score, which estimates the probability of having the event by mean of a logistic regression.

Finally, each stay of the group HyperK is paired with 3 stays of the group NormoK, using the values of the propensity score (step=0.05). The raw difference is computed, as well as a linear and log-linear regression, using the age, gender and number of diagnoses as explanatory variables.

Except for the paired regressions, all the models are tested with and without removing the 10 most influent outliers according to Cook's distance.

In each regression described above, the difference of LOS is estimated as follows. For each patient of the database, the actual LOS is ignored, the event is set to "absent", and the LOS predicted by the model function of the explanatory variables is computed. Then the event is set to "present" and the predicted LOS is computed again. Each individual has then a LOS variation, and the mean of this variation is considered to be the excess LOS estimated by the model in this specific population.

1.3. Estimation of the LOS difference using simulations

The simulation is performed under the null hypothesis " H_{0a} : the event does not increase the LOS". The empirical cumulated probability of event during an inpatient stay is first estimated as a function of the total LOS using the Kaplan Meier estimator from the database.

Then a sample of 1,000 LOS is drawn from the total database. The presence or absence of hyperkalemia is randomly simulated taking into account the LOS, using the empirical law defined above, which gives us a "HyperK" and a "NormoK" group. The difference of LOS of those 2 groups is stored. This step is iterated 10,000 times.

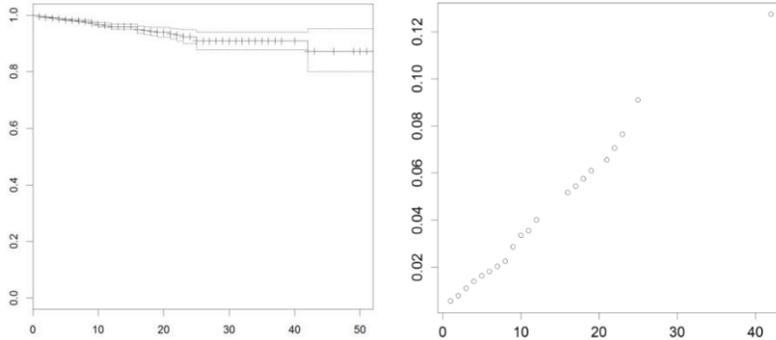
The distribution of the LOS difference is then plotted, and the mean is computed (a). Let (b) be the raw LOS difference that was observed in the actual database in the previous section. We assume that $b=a+c$, where (a) is the part of observed LOS difference due to the relation {excess LOS \rightarrow event} and (c) is the part due to the relation {event \rightarrow excess LOS}. We then consider that (c) is the number of interest.

2. Results

Two percent of the inpatient stays present at least one hyperkalemia, and 2.2% of the potassium measurements are over the threshold (Table I). Figure 1 (right part) shows the cumulated risk of hyperkalemia as a function of the total LOS (in days). This risk appears to be linear, which emphasizes the hypothesis that longer inpatient stays have a higher probability of event. Table II is the main result of the study. It shows the excess LOS that is imputable to the event, according to different methods.

Table I. Classification of the blood samples (left) and inpatient stays (right) with threshold: $K^+ > 5.5$ mmol/l

Blood sample	n	Frequency	Inpatient stays	n	Frequency
No hyperkalemia	13,431	97.8% [97.5;98.0]	NormoK	6,678	98% [97.7;98.4]
Hyperkalemia	310	2.2% [2.0;2.5]	HyperK	130	2.0% [1.6;2.3]
Total	13,741	100%	Total	6,808	100%

**Figure 1.** Left part: Kaplan-Meier estimator of the occurrence of a first hyperkalemia as a function of time in days. Right part: estimated cumulated probability of the event as a function of the total LOS.**Table II.** Estimated excess LOS (in days) related to the hyperkalemia, according to different methods

Method		LOS difference (days)	LOS difference after outliers deletion (days)
Group comparison	(raw difference)	8.78	
Simulation		2.28	
Linear regression	Basic model	6.01	4.45
	Model with interaction	4.19	4.35
	Loglinear model	4.45	4.60
Over-adjusted model	Basic model	5.74	4.48
	Model with interaction	4.58	4.61
	Loglinear model	3.83	4.38
Paired analysis	Group comparison	6.01	
	Linear model	5.98	
	Loglinear model	5.43	

3. Discussion

In this study, we attempt to evaluate the excess LOS related to hyperkalemia. Although the raw difference of inpatients groups with or without the event is 8.8 days, the part of the difference that is imputable to hyperkalemia ranges from 2.3 to 6.0 days, and most of the methods tested here evaluate this difference around 4.4 days after outliers' deletion. The excessive estimation of 8.8 days is due to an artifact: a high LOS exposes the patient to various time-dependent adverse events, including hyperkalemia. We can surely say that the raw difference overestimates the LOS difference, but this study does not allow for deciding which method is true. The real difference is probably in the interval [2.3; 4.6]. On one hand, the regression methods may still overestimate the real LOS difference because the coefficient of determination is still low (less than 35% in every case). On the other hand, the simulation may underestimate the real LOS

difference because the null hypothesis was too simple, as the daily risk of hyperkalemia could be dependent from other covariates (e.g. age, renal failure, drugs, comorbidities, etc.). The issue raised by this work might be extended to other kinds of events, but the results cannot be directly extrapolated: similar studies should be performed ad hoc.

This work highlights the difficulty to analyze the excess LOS imputable to an adverse event, especially when the event is time-dependent, such as bedsores, phlebitis, infections, etc. This difficulty often leads to overestimate the LOS, which participates more generally in the risk of false knowledge discovery, which is not only due to type I error inflation. False knowledge discovery is a challenge, as it could lead decision-makers to focus on wrong issues and make inappropriate decisions.

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