Alan B. Solinger and Steven I. Rothman*

Risks of mortality associated with common laboratory tests: a novel, simple and meaningful way to set decision limits from data available in the Electronic Medical Record

Abstract

Background: Laboratory tests provide objective measurements of physiologic functions, but are usually evaluated by demographic reference-intervals (RI), instead of risk-based decision-limits (DL). We show that hospital electronic medical record (EMR) data can be utilized to associate all-cause mortality risks with analyte test values, thereby providing more information than RIs and defining new DLs.

Methods: Our cohort was 39,964 patients admitted for any reason and discharged alive, during two 1-year periods, at Sarasota Memorial Hospital, Florida, USA. We studied five routinely-performed in-hospital laboratory tests: serum creatinine, blood urea nitrogen, serum sodium, serum potassium, and serum chloride. By associating a mortality odds ratio with small intervals of values for each analyte, we calculated relative risk of all-cause mortality as a function of test values.

Results: We found mortality risks below the population average within these proposed DLs: potassium 3.4–4.3 mmol/L; sodium 136–142 mmol/L; chloride 100–108 mmol/L; creatinine 0.6–1.1 mg/dL; blood urea nitrogen (BUN) 5–20 mg/dL. The DLs correspond roughly to the usually-quoted RIs, with a notable narrowing for electrolytes. Potassium and sodium have reduced upper limits, avoiding a "high-normal" area where the odds ratio rises 2 to 3 times the population average.

Conclusions: Any clinical laboratory test can be transformed into a mortality odds ratio function, associating mortality risk with each value of the analyte. This provides a DL determined by mortality risk, instead of RI assumptions about distribution in a "healthy" population. The odds ratio function also provides important risk information for analyte values outside the interval.

Keywords: blood chemical analysis/standards; blood urea nitrogen (BUN); chloride; clinical chemistry tests; creatinine; decision limits; potassium; reference standards; reference values; sodium.

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Introduction

Laboratory tests are utilized to provide objective measurements of vital physiologic functions of patients in many clinical settings. Every test used to assess patient condition has an associated reference interval (RI) or decision limit (DL), determined either demographically by population samples, or by medical evidence [1]. According to Horn and Pesce, "the reference interval is the most widely used medical decision-making tool" [2]. Deviations from standard clinical values of normal ranges are generally taken to indicate dysregulated organ system function and/or pathophysiology, and are considered indicative of loss of protective homeostatic mechanisms, as well as possible markers of specific diseases [3]. Additionally, some tests are regarded as critical laboratory values that may be indicative of life-threatening conditions requiring rapid clinical intervention. Designation of critical values by clinical laboratories is required by the Clinical Laboratory Improvement Amendments and regulatory agencies [4].

There are two types of intervals that may be reported by laboratories [1]. The most common is a RI, usually termed health-associated or population-based [5, 6], derived from a sample of individuals who are in "good health". The other type is a DL, based on specific limits that national and international expert clinicians decide are helpful to diagnose and/or manage patients [7]. Usually a DL is the result of extensive medical research. Here, we describe a simple method for deriving risk-based DLs from data available in the Electronic Medical Record (EMR).

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The underlying assumption in RIs is that the population mean represents optimal health, i.e., good functionality of the corresponding physiologic system(s). This is not necessarily true (e.g., cholesterol) [8–10]. While demographic-based definitions are clearly attempts to establish objective, quantitative estimates of the values of analytes for minimal risk, they are not based on any direct measurements of risk. When the assumption that a "healthy" population is optimum at its average test value is shown by medical research to be false, i.e., when actual associated risks become known, the RI is replaced by a DL, conforming to the data.

Attempts to establish the risks associated with deviations from the norm of some clinical measures are usually very narrowly defined [11–16]. One recent study pointed out that abnormal routine laboratory analyte test results can be utilized to stratify mortality risk in patients hospitalized with acute decompensated heart failure [16]. Their interest was in predicting the mortality consequences associated with specific ranges of values of the analyte for these specific patients.

We propose that population-based RIs be replaced by risk-based DLs for all analytes, utilizing the methodology demonstrated below, which associates mortality risk with laboratory test data in the EMR of any hospital. By this, we do not mean to apply statistical methods to cull "healthy" data from in-hospital patients, as advocated by some investigators [17]. On the contrary, it is our hypothesis that by calculating the all-cause mortality odds associated with laboratory test value data for in-hospital patients, independent of diagnoses and medical histories, we can discover the lowest risk and optimal value ranges of those analytes, as well as the specific risks of deviations from those optimal values. In other words, analyte test result values can be put on a scale that reflects the health consequences of each test result in terms of the relative risks of all-cause mortality associated with the value. Defining the mortality odds ratio (OR) as 1 for the cohort average for an analyte, there is minimal risk when the OR is one or less, and any value of the analyte associated with an OR greater than one reflects an increase in risk above the cohort average for that value. Thus this becomes a new and simple methodology to determine risk-based DLs for analytes, being those values of each test that have less than average associated risk of mortality from any cause. The purpose of this study is to illustrate the methodology, show that it provides information more meaningful and useful than RIs, and for several example analytes, provide preliminary (single-site) results in the form of risk functions and new proposed DLs.

Materials and methods

This is a retrospective (historical) cohort study based on data extracted from the EMR at sarasota memorial hospital (SMH) in Sarasota, Florida, USA. The data had been extracted for a different investigation, which excluded gender and patients in obstetrics, pediatric and psychiatric units. Laboratory test data associated with the last test result before each patient's discharge was extracted for all patients discharged alive admitted for any reason during two 1-year periods, calendar year 2004, and July 2005 – June 2006, which determined the study size of 39,964. Demographic data was not extracted; however, the age data was obtained for 1 year and shows a bimodal distribution, with peaks at 35 and 79 years, and median age of 69. The general description of the Sarasota population, according to the census bureau [18], is 84% white, 8% Hispanic, and 5% Black, with 52% female. Persons 65 year and older make up 32% of the population, while those under 18 constitute 16%.

The SMH Institutional Review Board granted approval for this work.

Tests

We have studied for five commonly available, in-hospital laboratory tests: serum creatinine, blood urea nitrogen (BUN), serum potassium, serum sodium, and serum chloride. The test samples were collected routinely, analyzed by the SMH laboratory utilizing the Siemens Dimension Vista® System and its prescribed procedures, and results entered into the EMR. A single result was used for each patient's visit: the last test before discharge.

Calculation of the analyte mortality odds risk function

The primary outcome was 1-year mortality, which was utilized to calculate mortality odds within intervals of analyte values. For each analyte, the number of patients living and the number dead within a year of discharge were found by comparison with the Social Security Master Death file. ORs were computed for intervals of each analyte by calculating the mortality odds for patients with results within each interval, and comparing their odds with the mortality odds for all patients with results outside the interval. The 95% confidence intervals (CIs) for each OR were calculated by standard statistical methods [19].

To obtain smooth and statistically powerful functions, the data was subjected to a "moving-average" type of analysis, where a set of three to five adjacent test results was used in each calculation. The intervals were established by choosing sufficient adjacent results to achieve $p<0.05$ statistical significance for the calculated OR for the interval under consideration, or ORs whose 95% CIs did not overlap 1, where possible. The population-weighted mean for the analyte value was calculated for each interval, and considered to be the moving-average OR for that interval, and for the next interval, the adjacent set of test results were used, overlapping the prior set. An example of the data and the OR calculation is given in Table 1. This procedure associates a mortality OR with each mean test value, which we interpret as the relative risk of 1-year post-discharge

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Table 1 Example of odds ratio calculation for potassium.

Test result, mmol/L	Live	Died	Odds ratio table			Potassium test OR results			
4.5	1138	237		Live	Died	Average Potassium in Interval	OR	Lower 95% CI	Upper 95% CI
4.6	829	214	Within interval	2602	608	4.58, mmol/L	1.23	1.13	1.35
4.7	635	157	Not within	23,209	4397				
Total in Interval	2602	608							
Total Tested	25,811	5005							

The left-most column gives the test result values for the interval considered, followed by the numbers of living and dead subjects with that result in the next two columns, respectively. At the bottom of these columns are the total numbers of living and dead subjects in the cohort who were tested for serum potassium. These numbers allow calculation of the OR Table for this interval, with live and dead subjects within and without the interval, and the weighted average test result for the interval. The results to the right are a standard calculation. All OR values in the results have been calculated similarly. The average mortality for the population studied was 16.2%, and the average odds for dying were approximately 1:5. The OR calculation for the next higher interval includes the points 4.6, 4.7, and 4.8 mmol/L, and so on.

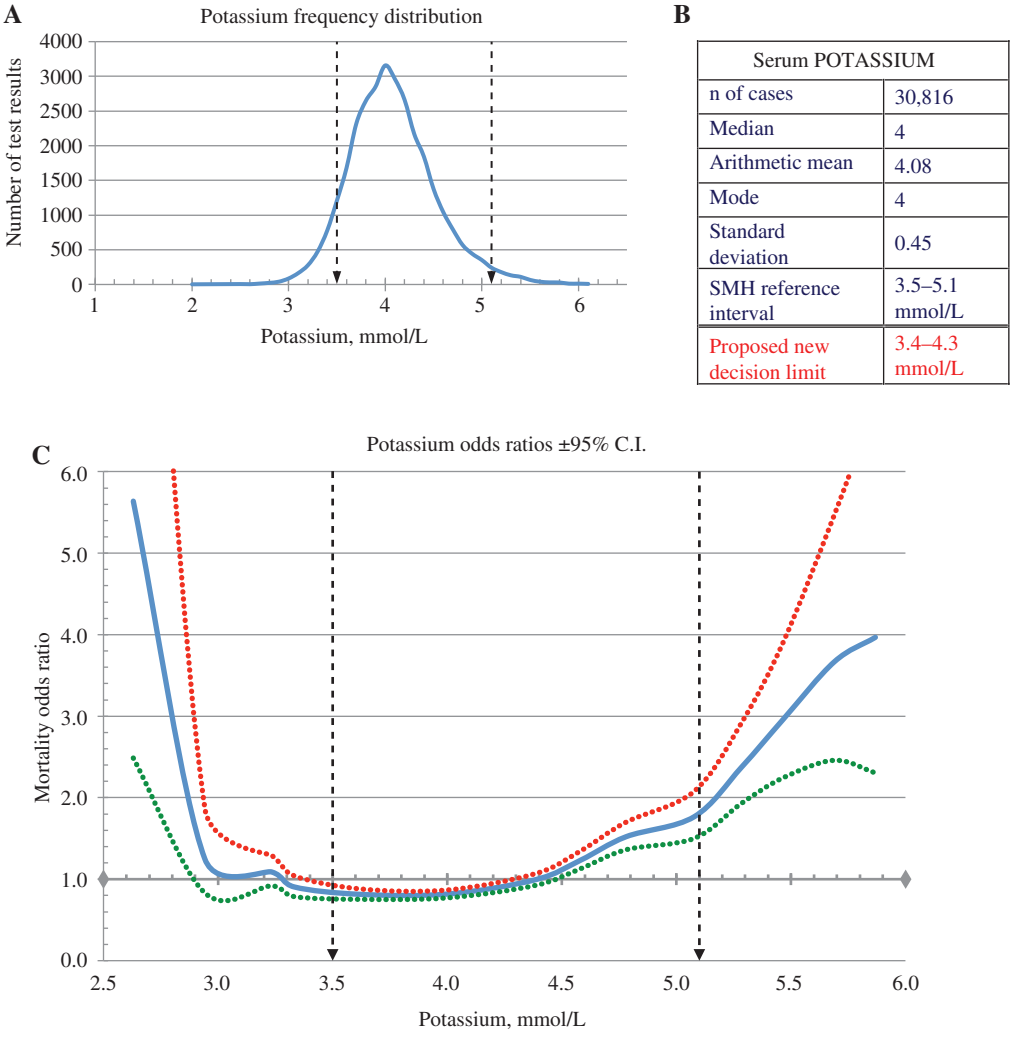

Figure 1 (A) Distribution of serum potassium test results. (B) Cohort statistics. (C) Mortality odds ratios as a smoothed function of potassium test values.
The usual laboratory reference interval is indicated by vertical dashed lines, with upper and lower 95% CI indicated by dotted lines. The upper CI at OR=1 defines a proposed new risk-based decision limit.

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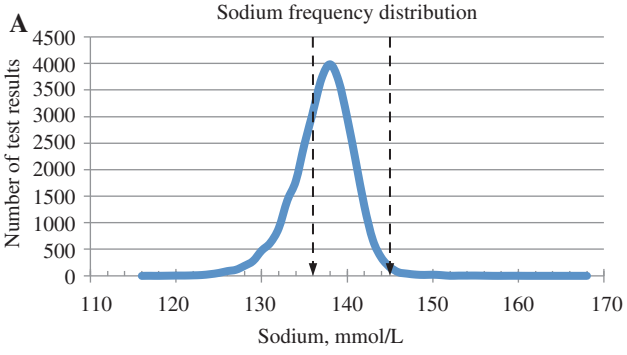
all-cause mortality as a function of the test value. The results represent relative risks for the entire population studied, with no attempt to stratify by demographics, disease, seriousness of illness, or any other co-morbidity. However, we also investigated age as a confounder of our results by dividing the approximately 20,000 cases for which we have age data into quartiles and comparing them. Since not all tests were administered to every patient, the exact numbers of test results varied; each test result represents one patient (the last test before discharge).

Results

OR functions of mortality risks per interval versus weighted mean test values in the interval, with 95% CIs for each OR, were calculated for all studied analytes. Note that here the OR reflects the odds of death within a small interval around each value divided by the odds outside that interval (which is approximately the average odds for the population). This is in contrast to OR calculated for disease, where minimum risk is often used as a baseline. Thus, the OR=1 line represents an all-cause mortality risk equivalent to the average over the entire test sample. The OR function defining all-cause mortality risk associated with each test analyte is graphed in Figures 1–5, along with frequency distributions of test results and their associated statistics. The resulting functions all have some test values for which the OR is below 1, where the mortality risk is lower than average (which we consider to be the desirable limits), and some values of the analyte for which the risk is higher than average.



B

Serum SODIUM	
n of cases	30,756
Median	138
Arithmetic mean	137.24
Mode	138
Standard deviation	3.58
SMH Reference interval	136–145 mmol/L
Proposed New decision limit	136–142 mmol/L

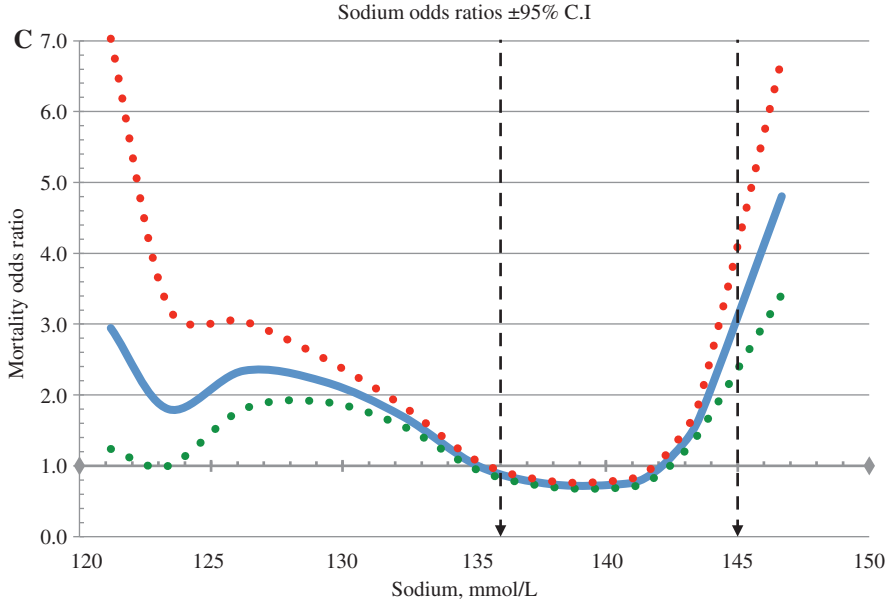


Figure 2 (A) Distribution of serum sodium test results. (B) Cohort statistics. (C) Mortality odds ratios as a smoothed function of sodium test values.
The usual laboratory reference interval is indicated by vertical dashed lines, with upper and lower 95% CI indicated by dotted lines. The upper CI at OR=1 defines a proposed new risk-based decision limit.

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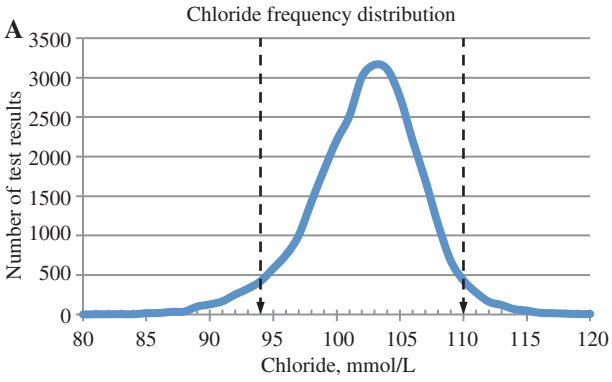

B

Serum CHLORIDE	
n of cases	30,754
Median	103.0
Arithmetic mean	102.4
Mode	103
Standard deviation	4.462
SMH reference interval	94–110 mmol/L
Proposed new decision limit	100–108 mmol/L

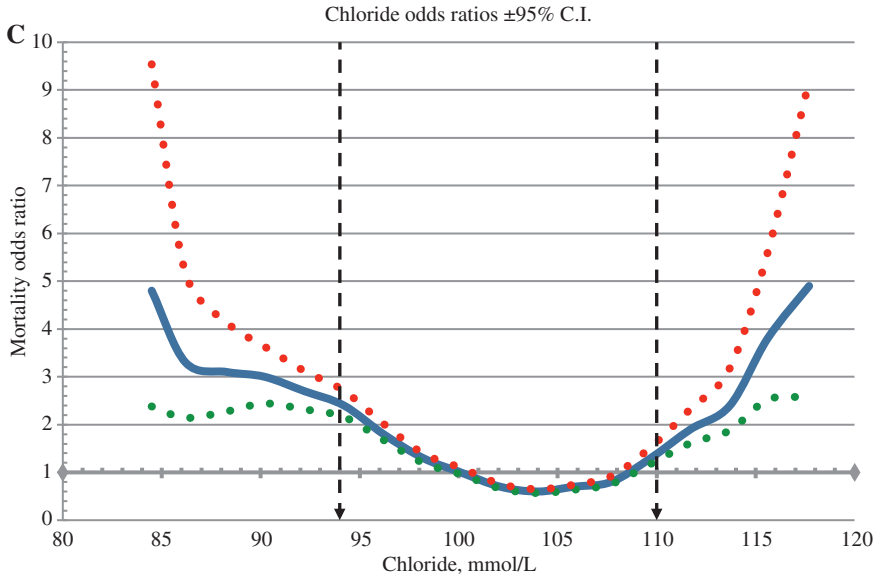

Figure 3 (A) Distribution of serum chloride test results. (B) Cohort statistics. (C) mortality odds ratios as a smoothed function of chloride test values.
The usual laboratory reference interval is indicated by vertical dashed lines, with upper and lower 95% CI indicated by dotted lines. The upper CI at OR=1 defines a proposed new risk-based decision limit.

There are three distinct kinds of areas of the functions defined by their relation to the OR=1 line (refer to Figure 1 as an example): a) the analyte values for which the upper 95% CI is below the OR=1 line; b) the values between the points where the lower and upper 95% CI lines cross the OR=1 line, and c) the values where the lower 95% CI is above the OR=1 line. The interpretation of these areas is straightforward: values of the test result for which the lower limit of the 95% CI is above the OR=1 line ("c") clearly represent above average risk to the patient, while the transition area ("b") marks values which are not certain to be of minimal risk, and could be called "borderline" results. Where the upper 95% CI is below the OR=1 line ("a"), the risk is below the population average; thus these values can be taken as a risk-based DL for that analyte. We describe the graphs of the mortality OR functions individually for each analyte below. All standard RIs cited for comparison were provided by the SMH laboratory at the time of the tests. These RIs and our proposed new risk-based DLs are listed in Table 2.

Results for the potassium test

For potassium, the OR is below 1 within the interval 3.3(−0.4, +0.1) through 4.4(±0.1) mmol/L. Referring to Figure 1C, note that using the upper CI as a limit (where it crosses the OR=1 line) suggests that the risk-based DL ought to be 3.4–4.3 mmol/L. The central 95% of our population frequency distribution lies between 3.1 and 5.3 mmol/L.

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Results for the sodium and chloride tests

The OR for sodium is below 1 for the interval 135(−0.2, +0.7) to 142(±0.1) mmol/L. Using the upper CI as a limit suggests that the risk-based DL ought to be 136–142 mmol/L. The central 95% of our population frequency distribution lies between 131 and 144 mmol/L.

The OR for chloride is below 1 for the interval 100 (±0.1) to 109(−0.8, +0.2) mmol/L. Using the upper CI as a limit suggests that the risk-based DL ought to be 100–108 mmol/L. The central 95% of our population frequency distribution lies between 92 and 110 mmol/L.

Results for the creatinine test

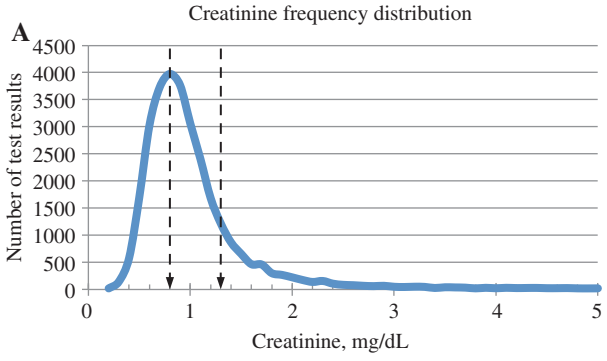
The OR for creatinine is below 1 for the interval 0.6 (±0.03) to 1.2 (−0.1, +0.2) mg/dL. Using the upper CI as a limit suggests that the risk-based DL ought to be 0.6–1.1 mg/dL. The central 95% of our population frequency distribution lies between 0.2 and 2.2 mg/dL.

Results for the BUN test

As indicated in Figure 5C, the OR is below 1 at values <20 mg/dL, and increases steadily for higher values of BUN. Using the upper CI as a limit suggests that the risk-based DL ought to be 5–20 mg/dL (we have insufficient data below 5 mg/dL).

Results of age analysis

Although the data that we have available is not sufficient for the kind of regression analysis that may be required



B

Serum CREATININE	
n of cases	30,760
Median	0.9
Arithmetic mean	1.17
Mode	0.8
Standard deviation	1.10
SMH reference interval	0.8–1.3 mg/dL
Proposed new decision limit	0.6–1.1 mg/dL

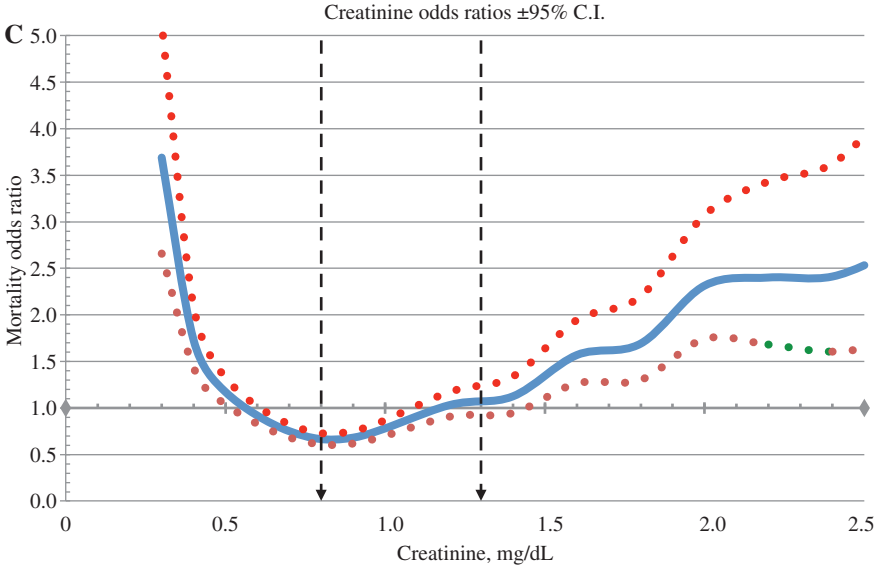


Figure 4 (A) Distribution of serum creatinine test results. (B) Cohort statistics. (C) Mortality odds ratios as a smoothed function of creatinine test values.
The usual laboratory reference interval is indicated by vertical dashed lines, with upper and lower 95% CI indicated by dotted lines. The upper CI at OR=1 defines a proposed new risk-based decision limit.

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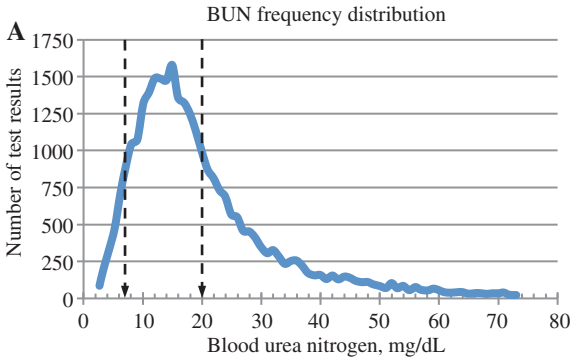

B

Blood urea nitrogen	
n of cases	30,746
Median	17
Arithmetic mean	21.07
Mode	15
Standard deviation	15.52
SMH reference interval	7–20 mg/dL
Proposed new decision limit	5–20 mg/dL

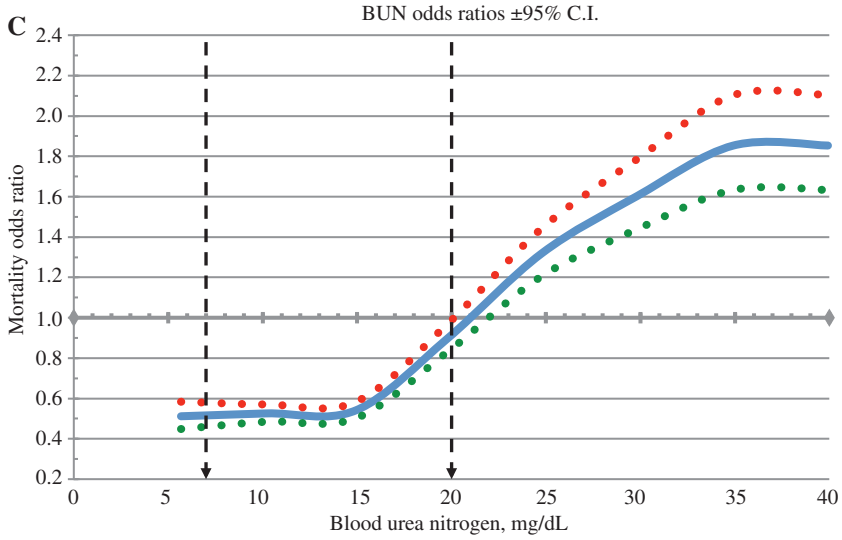

Figure 5 (A) Distribution of blood urea nitrogen test results. (B) Cohort statistics. (C) Mortality odds ratios as a smoothed function of BUN test values.
The usual laboratory reference interval is indicated by vertical dashed lines, with upper and lower 95% CI indicated by dotted lines. The upper CI at OR=1 defines a proposed new risk-based decision limit.

to quantify dependency on confounding factors, we have been able to establish a few facts about the dependence of the data on age. The age distribution breaks down into quartiles at 48, 69, and 80 years, making this population definitely older than a standard US urban population (median 37 years). For the electrolytes, the distribution of test results does not shift with quartile, and all the limits at which the OR functions for each quartile cross the OR=1 line are within the 95% CIs of each other, and within the 95% CIs of the OR function for cohort as a whole. For BUN, both the distribution and the OR functions shift slightly to higher values (i.e., by from 1 to 4 mg/dL) with increasing age quartile, while for creatinine, the distribution modes shift to higher values by about the same amount without a corresponding shift in the OR functions. In all cases, the fundamental shapes of the OR functions do not change with age quartile. Also, when we examine the ORs for each analyte outside the intervals using the

Table 2 Proposed risk-based decision limits, compared with reference intervals.

Analyte, units	Standard reference interval in use at SMH	Risk-based decision intervals (with 95% C.I.)	Proposed new decision limit
Potassium, mmol/L	3.5–5.1	3.3 (−0.4,+0.1) – 4.4 (±0.1)	3.4–4.3
Sodium, mmol/L	136–145	135 (−0.2,+0.7) – 142 (±0.1)	136–142
Chloride, mmol/L	94–110	100 (±0.1) – 109 (−0.8,+0.2)	100–108
Creatinine, mg/dL	0.8–1.3	0.6 (±0.03) – 1.2 (−0.1,+0.2)	0.6–1.1
BUN [Urea], mg/dL	7–20	Lower limit not detected – 21 (±1.0)	5–20

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decision-based interval as baseline, there are no significant differences among the age quartiles. Quantitatively, looking at the ORs for patients with results above and below our intervals, the results are consistent across quartile age groups, with an intra-class correlation coefficient of 0.6, indicating good reproducibility [20], which would not be the case if the results were directly related to age. Thus, although we cannot eliminate age as a confounding factor, and future studies with more extensive data are necessary to establish the exact relationships between age and decision limits for creatinine and BUN, it is clear that age cannot account for the mortality observed.

Discussion

Potassium, sodium and chloride tests

For potassium, we find that the risk-based DL ought to be 3.4–4.3 mmol/L. This is significantly lower than the 3.5–5.1 RI usually quoted [21–24]. Although the test result distribution is slightly lower than expected, the main factor driving our OR interval result is association with mortality. Our results indicate that patients with test values between 4.8 and 5.1 mmol/L, usually considered within the normal RI, have an OR as high as 2.1 (95% CI) compared to patients with lower "normal" test values. A recent study found similar results, but the population studied was limited to AMI patients [25]. Since our population sample is not so limited, the increased risk at "high-normal" values must apply to the general population, not just to cardiac patients. As potassium is a critical value analyte, these results can have an immediate impact on patient mortality. The standard error in the test result is 0.1 mmol/L according to the SMH laboratory, so it cannot be the source of the difference. A detailed study of this analyte is in progress, and will be published in a separate article.

We note that our upper DL for sodium at 142 mmol/L is lower than the usual RI upper limit of 145 mmol/L, where the OR has risen to 4.1 (95% CI).

Our DL for chloride is 100–108 mmol/L, and the OR has risen to 2.8 (95% CI) at the usual RI lower limit of 94 mmol/L.

Creatinine and BUN tests

Our DL for creatinine is 0.6–1.1 mg/dL, which differs negligibly from the usual population-based RI, and confirms it as a good estimate. Since we had no gender identifiers for our cohort, we could not establish any gender-related differences.

Our DL for BUN at 5–20 mg/dL is in agreement with the usual RI. A surprising result is that there seems to be no reason to ascribe risk for low values of BUN, which accords well with anecdotal experience in the ICU (pers. comm. GD Finlay). Our data at the lower values do not present the usual U-shaped curve. In proposing a lower limit, we use the lowest values for which statistically sufficient data is available.

Commentary

It is hard to underestimate the importance of analyte test RIs and DLs. Nearly 80% of physicians' medical decisions are based on information provided by laboratory reports [26], most of which are framed in the context of RIs. Thus it is important to understand exactly what a test result means in relation to a patient's health. Clearly, a test result by itself is of little value unless the appropriate information for its interpretation is available. Typically, this information is provided in the form of a RI. The majority of RIs in use today refer to the central 95% of the reference population of subjects. Thus, 5% of all results from "healthy" people will fall outside of the reported RI by definition and will be flagged as being "abnormal." There are many problems associated with this type of calculation of RI. Methods for estimating them are expensive, difficult to perform, often inaccurate, and non-reproducible [27].

Many studies have noted that current RI determination methodology suffers from various problems, but almost all cite purely practical issues: e.g., deciding on inclusion and exclusion criteria, or assembling suitable numbers of cohorts, or deciding on the specific statistical procedures, or the expense involved, or laboratory methodology [17, 27–32].

By contrast, we suggest using DLs established by the simple methodology herein described because RIs do not specify what a test result means in relation to a patient's health: RIs are based on the twin assumptions: 1) that a healthy cohort can be defined and assembled; and 2) that values within the central statistical limits represent optimal values for health. Neither of these assumptions is necessarily valid, and both have been shown to be problematic in specific cases [8, 17].

The methodology utilized here eliminates these issues, and allows the potential for DLs to be determined from unlimited data mining of any EMR or a variety of

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other sources without consideration of selecting and maintaining a healthy cohort. As the study can be done retrospectively at any hospital or laboratory with extant data, the statistical sample sizes are just about unlimited, meaning that 95% confidence intervals can be as small as desired.

One might question our methodology because we include patients of all types, irrespective of whether they are sick or well. On the contrary, this is a strength of our approach, our cohort is completely randomly mixed, including all patients from accidents and elective surgeries through terminal illnesses with almost any conceivable diagnosis. This provides a robust mixture that reflects a huge spectrum of possibilities. We seek not to establish an interval of health, but to find the risk of dying associated with varying values of the analyte. Thus we want to include every imaginable type of patient, healthy and sick, in order to sample all possible physiologic variations that result in any test value, and find their associated risks. We look at patients after their laboratory test was administered, and ask whether they lived or died without concern for cause of mortality. The only thing that our patients have in common (besides having been in SMH) is that they had the test administered. What differentiates them is simply where they are within the test values, and whether they survived 1-year post-discharge. Since there are more than 30,000 cases from a general hospital, no diagnosis or demographic feature can possibly dominate our results. What we have then are the odds of dying within each small test interval, compared to the mortality odds when not within that interval; the mix of patients is random in both samples. This provides a natural cut-off for the DL: the interval of test values with OR ≤ 1, being the values with less than average risk.

Clearly, it is possible to choose data bases or limit cases by stratification along demographic lines if and when desirable. In this preliminary study, we have chosen a nearly random mix of cases. However, it is obvious that one could stratify the data along gender, race, age, diagnosis, or any other category or line of interest. It would also be of interest to compare different geographical areas and different laboratories with similar demographic populations.

By and large, the methodology utilized here confirms, at least approximately, the usual RIs. What our methodology also does is extend our understanding by providing specific risks for test results outside the DLs found, affording physicians the information necessary to deliver the best possible care to their patients. There is no way to provide this information by studies of a healthy population. Thus, we think that our proposed methodology is superior, allowing researchers to determine risk-based DLs. Subject to confirmation in other populations (ours being skewed older and racially), our proposed DLs could replace the demographically-determined RIs.

A limitation of this study is the data utilized. It omits some patient categories (psychiatric, obstetric, maternity) and lacks certain demographic information (preventing an analysis of gender dependence). The data is from of a cohort older than the US population; however we did examine quartile subsets of our data and found the test results for each age group have virtually identical normal distributions with the same mean analyte values. Since the distribution of most laboratory tests was normal (which is the expected distribution in a general population), we think it likely that this in-hospital population is representative of the general population of the area.

Another limitation is that our methodology uses a period of 1 year after discharge to examine risk of mortality; this time period was chosen simply to provide the numbers necessary for reasonable statistics. Clearly, another possible methodology would be to study the first test results after admission compared with risk of in-hospital mortality. We have shown these two methods, 1-year post-discharge versus in-hospital mortality, to be highly correlated [33, 34], but in our dataset the latter provides insufficient statistical significance for our purpose in defining DLs. This will be the subject of further study on the authors' part, and others are certainly encouraged to initiate similar investigations. A mix of in-hospital and post-discharge studies may provide interesting insights.

The most notable example of our DLs differing from usual RIs is for the electrolytes, which is the reason we have used several as our examples. Specifically, for serum potassium and for serum sodium, we find that patients within the upper third of the standard RI are at increased risk compared to the average risk of the population tested; laboratories are currently reporting as "normal" test results that have an OR of 1.8 for potassium and 3 for sodium. This has to be considered a preliminary result, and needs to be confirmed by a similar analysis at other sites.

Conclusion

By utilizing extant electronic data from any clinical laboratory, combined with the necessary mortality data, the methodology presented here provides both a novel utilization of the EMR and a means to transform any database of specific test results into a mortality OR function for that test. One then takes the DL as the interval of the function

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for which the mortality OR is less than or equal to one. This provides an interval determined by actual mortality risk instead of by assumptions about the distribution in a "healthy" population. The risk-based DLs presented here are illustrations of the methodology. While we have shown that these limits may be generally valid, they are limited by the stated inadequacies of the data utilized, and need to be confirmed by further similar investigations.

The mortality OR function provides more information than any demographic reference interval, since it specifies the mortality risk for any value of the test result. We believe the approach here presented opens the door to a way of exploring and resolving many issues in patient assessment. Clearly, researchers with access to the database of a laboratory or a hospital EMR can perform retrospective research on risk associated with various clinical and physiological variables and stratified by age, gender, race, etc., and we encourage others to pursue these avenues of inquiry.

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Conflict of interest statement

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