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The zlog value as a basis for the standardization of laboratory results

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Abstract

Background: With regard to the German E-Health Law of 2016, the German Society for Clinical Chemistry and Laboratory Medicine (DGKL) has been invited to develop a standard procedure for the storage and transmission of laboratory results. We suggest the commonly used z-transformation.

Methods: This method evaluates by how many standard deviations (SDs) a given result deviates from the mean of the respective reference population. We confirm with real data that laboratory results of healthy individuals can be adjusted to a normal distribution by logarithmic transformation.

Results: Thus, knowing the lower and upper reference limits LL and UL, one can transform any result x into a zlog value using the following equation:

$$\text{zlog} = (\log(x) - (\log(LL) + \log(UL))/2) \cdot 3.92 / (\log(UL) - \log(LL))$$

The result can easily be interpreted, as its reference interval (RI) is -1.96 to $+1.96$ by default, and very low or high results yield zlog values around -5 and $+5$, respectively. For intuitive data presentation, the zlog values may be transformed into a continuous color scale, e.g. from blue via white to orange.

Using the inverse function, any zlog value can then be translated into the theoretical result of an analytical method with another RI:

$$x = LL^{0.5 - \text{zlog}/3.92} \cdot UL^{0.5 + \text{zlog}/3.92} \quad (1)$$

Conclusions: Our standardization proposal can easily be put into practice and may effectively contribute to data quality and patient safety in the frame of the German E-health law. We suggest for the future that laboratories should provide the zlog value in addition to the original result, and that the data transmission protocols (e.g. HL7, LDT) should contain a special field for this additional value.

Keywords: laboratory results; lognormal distribution; standardization; z-transformation; z-value; zlog value.

Introduction

As digitalization of medicine increases, so does the need for standardized laboratory results for long-term storage in electronic health and patient files [1]. At its core, it is mainly about the medical interpretability of quantitative measured results against the background of analytical and biological variability – and all that in the most diverse context possible: from the one-time intake status in an emergency room to the long-term monitoring of the chronically ill, as well as from simple lifestyle counseling at the gym to assessing the critical situation of an intensive-care patient.

The call for standardized results has become more urgent as a result of the 2016 E-Health Act, which requires that medical data be stored on an electronic health card by January 1, 2018, and in electronic patient files as well as in the electronic patient portal by December 31, 2018 (www.bmg.bund.de >> E-Health-Gesetz). In the event of non-compliance, the contract partners may be penalized, which means that their budgets will be cut considerably.

Laboratory medicine, too, is obligated to present appropriate proposals. The immediate focus is on verifying medication safety (AMTS): The “Action Plan AMTS 2016–2018” of the German Federal Ministry of Health (BMG) calls for electronic support of physicians and pharmacists with respect to the identification and prevention of risks in medication-based treatment (www.akdae.de/AMTS/Aktionsplan/index.html), such as allergies or impaired kidney or liver function.

It was against this background that the Medicines Committee of the German Medical Association (AkDÄ)

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addressed an inquiry to the German Society for Clinical Chemistry and Laboratory Medicine (DGKL) in March 2016. According to this, the BMG would welcome it if the DGKL were to take the lead on the measure mentioned under item 10 of the Action Plan AMTS 2016–2018 together with the AkdÄ. This involves working out recommendations for the electronic mapping of standardized lab results.

The Department of Laboratory Management of the DGKL is happy to comply with this request, as laboratory medicine has always supplied the bulk of digitized healthcare data and, among all medical disciplines, has the longest tradition in electronic data storage and communication [2, 3]. Various proposals have been generated over decades, and they fall into two categories: the technical standardization of measurement methods, units, quality criteria, etc. [4–6] as well as the selection of suitable reference populations and calculation of reference intervals (RIs) necessary for medical interpretation [7–9]. That technical and medical components are connected is not in dispute: for example, RIs can be standardized only if the traceability of all analytical methods used to one binding reference method is ensured [10, 11]. This is true, for instance, of electrolytes or enzymes, but not of many other analytes.

Our proposal may serve as a basis for discussion. It is submitted in support of standardized electronic storage and communication of laboratory results regardless of the methodology and unit employed in the respective case. The proposal is based on published work done by various working groups of the DGKL [1, 9, 12–15].

Materials and methods

The proposed method has been developed from real data contained in a study that was approved by the Ethics Committee of the Hannover Medical School (MHH) and published in 2013 [16]. The original data set comprised nearly 10,000 measured values in the area of liver diagnostics, collected from over 600 persons. From that group, 200 healthy male and 200 female blood donors as well as 20 male and 20 female hepatitis C patients were selected randomly. In total, 3520 measured values were available for the eight analytes shown in Figure 1.

The calculations presented here were done in the programming environment R and the graphical user interface R-Commander (www.r-project.org).

The proposed standardization is based on the so-called z-transformation, a statistical method widely used since Pierre-Simon Laplace (1749–1827), which renders multivariate data sets comparable: from each measured value, the mean μ is subtracted, which is then divided by the standard deviation (SD) σ . The z-value obtained indicates the number of SDs by which a measured value differs from the mean of the respective data set. The z-transformed data set has the mean 0 and SD 1. This method is also called scaling or normalization.

For illustration purposes, Figure 1 shows the box plots of all available values. As for the original data on the left, the position of the “normal” and “pathological” values is difficult to assess visually: for example, an absolute value of 20 means a reduction for albumin, normal for transaminases and an increase for cholinesterase (CHE). On the right, the main group of values (>50%) is now between -1 and $+1$ SDs as a result of the z-transformation, while the diagnostically significant reductions in albumin, CHE and total protein in hepatitis patients are now easier to see.

However, this simple form of z-transformation is not sufficiently robust for standardizing lab results, because μ and σ are influenced substantially by random outliers in the data set. This is why we recommend a modified form of z-transformation that does not refer to

Figure 1: Distribution of laboratory results for a mixed population, consisting of 400 healthy blood donors and 40 hepatitis-C patients. A, absolute values; B, z-transformed values with the mean 0 and standard deviation 1. According to the box plot method of Tukey [17], the boxes comprise 50% of the values measured, the horizontal lines within the boxes indicate the medians and the circles outside the areas marked by vertical “whiskers” represent potential outliers.

the μ and σ of the entire data set, but instead only to the results of healthy reference subjects (for an overview of relevant methods, see Ref. [12]).

If one knows the respective lower and upper limits (LL and UL) of the RI, the mean values and SDs of a normally distributed reference population, and from this the z-value, can be calculated as follows:

$$\mu = (LL + UL)/2 \quad (1)$$

$$\sigma = (UL - LL)/3.92 \quad (2)$$

$$z = (x - (LL + UL)/2) \cdot 3.92 / (UL - LL) \quad (3)$$

According to Haeckel et al. [13], we recommend assuming a log-normal distribution for the measured values of the reference population. In other words, a normal distribution is assumed for the logarithms of the measured values, and the above equations can be applied as follows:

$$\mu \log = (\log(LL) + \log(UL))/2 \quad (4)$$

$$\sigma \log = (\log(UL) - \log(LL))/3.92 \quad (5)$$

$$z \log = (\log(x) - (\log(LL) + \log(UL))/2) \cdot 3.92 / (\log(UL) - \log(LL)) \quad (6)$$

This modification takes into account the fact that the laboratory results of healthy subjects frequently exhibit an asymmetrical right-skewed distribution (e.g. transaminases). Logarithmation renders the distribution in these cases approximately symmetrical [13]. Distributions that are symmetrical from the start (e.g. sodium, potassium) tend to become left-skewed when logarithmized, but this shift has only negligible, minor effects on the result in practice (see the Results section).

The RI of the zlog values calculated according to equation 6 is always between -1.96 and $+1.96$, regardless of the method and unit used. This range covers about 95% of the results in a healthy reference population. Using the inverse function of equation 6, it is also possible to calculate from the zlog value secondary results for any other RI if its LL and UL are entered:

$$x = LL^{0.5 - z \log / 3.92} \cdot UL^{0.5 + z \log / 3.92} \quad (7)$$

Thus, equation 7 allows for method A (with RI A) to be rescaled to method B (with RI B). For example, if a bilirubin level of $35 \mu\text{mol/l}$ has been measured, equation 8, with the assumption of a RI from 2 to $21 \mu\text{mol/l}$, will yield a zlog value of 2.81, somewhat above the upper RI limit of $+1.96$. If this zlog value is now inserted in equation 8, while assuming a RI from 0.1 to 1.2 mg/dL , the above inverse function will produce a value of 2.06 mg/dL , which is as slightly elevated as the initial value of 35 mmol/L .

For the purposes of an intuitive representation of the findings, the measured values can be placed against a continuous color scale derived from the zlog value (Figure 2). Out of consideration for people with red-green color blindness, a color scale should be used that ranges from blue for strongly reduced ($z \log = -10$) and white ($z \log = 0$) to orange ($z \log = +10$), for example. The color gradients

in this paper were generated by means of logistic equations of the following basic form:

$$F = D / (1 + e^{-z \log}) \quad (8)$$

F represents the color value in the red-green-blue scheme (RGB), and D the variation of each individual color (maximum 255). For example, to achieve the continuously increasing orange color for zlog values from 0 to 10, as seen in Figure 2, the values for blue and green can be set to 255 and moved toward 0 and/or 120, with a constantly high red value. The gradations have been selected in such a way that the center of the distribution of normal measured values ($0 \pm \sigma$) appears almost pure white. Slightly elevated or decreased values in the range between 2 and 3 σ are slightly tinted; significant differences can be seen in the clinically relevant range up to around 6 σ , while extremely elevated or decreased values differ only slightly.

Results

Figures 3 and 4 are based on the subgroup of blood donors in the Figure 1 data set, following the elimination of any outliers using the QQ-plot method [15]. Some significantly elevated values were found in the transaminases and γ -glutamyltransferase (GGT), for example, likely due to clinically silent liver diseases. The data thus adjusted yielded nearly symmetrical (Figure 3) distributions for four analytes and significantly right-skewed distributions for another four analytes (Figure 4).

Figure 5 shows for albumin and bilirubin that symmetrical distributions with good approximation can be described by means of a normal distribution (Figure 5A), and right-skewed distributions by way of a log-normal distribution (Figure 5B). After logarithmation, both approach normal distribution (Figure 5C and D).

As the mean values of all eight analytes differ significantly in men and women (t-test: $p < 0.05$), the RIs were calculated separately for the two sexes. The resulting limit values were a good match for the benchmarks used by MHH, except for the UL of transaminases in men and the LL for creatinine (CREA) in women. These deviations might be explained by subpopulations on the margins of the respective distributions, a visual hint of which can also be seen in Figure 4 [alanine aminotransferase (ALT), aspartate aminotransferase (AST)]. For ALT, AST and GGT, in addition to the MHH information, it was also possible to calculate the LL of the RIs necessary for equation 8.

Figure 2: Proposal for a standardized color scale for zlog values in the range of -10 to $+10$.

Figure 3: Approximately symmetrical density curve for healthy blood donors. Continuous lines: men; dashed lines: women.

Figure 6 shows that the zlog transformation proposed here is a better representation of the physiological variation shown in Table 1 compared to the traditional z-transformation. This becomes clear from the boxes of approximately equal size that include 50% of the respective measured values and from the fairly symmetrical whiskers. Reduced values for albumin, ALT, CHE and protein, which are characteristic of severe liver damage, are more significant in this representation than in Figure 1.

To test the robustness of the method presented here for reference intervals, we look at the analytes with the largest downward and/or upward deviations (see Table 1) separately: for women, the LL for CREA was around a

quarter above the MHH reference value, while the men's UL for ALT was about a third above the MHH value.

Figure 7A–C show that the zlog values for CREA are affected only to a minor extent by these considerable fluctuations. By contrast, the differences in ALT for men, for which MHH does not provide a LL in accordance with an International Federation of Clinical Chemistry (IFCC) recommendation [6], are more significant. According to Figure 7D, this missing limit affects the zlog values in terms of an upward shift and toward a smaller variance if 0 is inserted, erroneously, for $\log(LL)$ in equation 6.

Using albumin and bilirubin as examples, Table 2 illustrates that the zlog values of healthy blood donors are between around -2 and $+2$, as expected. A moderately

Figure 4: Significantly right-skewed density curve for healthy blood donors. Continuous lines: men; dashed lines: women.

elevated bilirubin level with a zlog value of just above 3 is detected in the case of hepatitis without liver cirrhosis. Cirrhosis patients, however, exhibit drastically reduced albumin and substantially elevated bilirubin levels with zlog values around -5 and/or $+5$. In the result output, it is the colors derived from the zlog values that allow for a more intuitive classification of the values in terms of “normal” and “pathological”.

Discussion

The zlog transformation method presented herein offers a possible pragmatic solution for a difficult problem that has so far been underestimated, because it becomes evident only when laboratory results are stored in electronic patient records over the long term. Traditionally, most laboratory data are collected, like “snapshots”, over

short periods of time and shared directly between the submitter and the laboratory service provider. This is why both parties have been able to assume that key boundary conditions, such as method, unit or patient age, do not change throughout the investigation period.

Where long-term electronic storage is concerned, these assumptions do not apply unreservedly, because many RIs change over the course of a patient’s life, and methods, units, etc., too, may differ greatly from one laboratory or device to the next – such as between a central laboratory and self-test devices. Thus, to map all conceivable eventualities in order to ensure lifelong interpretability, it would be necessary to store for each measured value a lot of additional information – ranging from ethnicity to the antibody or calibrator batches for specific critical assays.

Even more prominent is the fact that the results in the E-Health scenario described are no longer sent

Figure 5: Actual and theoretical density curves under the assumption of a normal and/or log-normal distribution (upper part).

The bottom part shows the logarithmized values.

Continuous line: core density estimate for the actual measured values. Dashed line: theoretical density functions using the calculated values for μ and σ .

only to the requesting physician, who is familiar with the work of “his or her” laboratory. Instead, laboratory results in electronic files will be available to physicians and non-medical healthcare service providers all over the world, as well as the patients themselves. Even if all that additional information were to be stored as well, it would be unlikely that such a large, heterogeneous group of users would be in a position to interpret the original results correctly. For example, what use is it to a pharmacist who is to stop dispensing a specific drug in the event of deteriorating kidney function to know that the current CREA value of 1.4 mg/dL was measured by means of the kinetic Jaffé method on serum, while the

previous value of 111 μmol/L was determined enzymatically in the plasma (Table 3).

The pharmacist would require the zlog values or, alternatively, the color tints derived from them to know intuitively, and without detailed knowledge of the methodology, that the CREA level has increased substantially in the last few months, despite an absolute value of 1.8 that is 2 decimal powers lower: the first zlog value of 1.08 indicates that the CREA level of 111 μmol/L is within the 2 SD range of the healthy population; the last zlog value of 4.75, however, signals a substantial difference by more than 4 SD increases for the CREA level of 1.8 mg/dL. Furthermore, for a layperson who is

Figure 6: Distribution of the measured values shown in Figure 1 after the z-transformation.

not familiar with statistics, the color shift from white to orange illustrates the gradual increase in the CREA level over time very well. In short, before dispensing the drug in question, the pharmacist should consult a physician.

It is, of course, crucial that the respective RIs be correct. For example, the LL must not simply be set to 0 if only the UL is specified (cf. Figure 7). The age and sex of the patient as well as the higher specificity of the enzymatic method must also be taken into account. To cover all these factors, IFCC, Clinical and Laboratory Standards Institute (CLSI), DGKL and many other organizations require that every laboratory develop and determine its own method- and population-specific RIs on the basis of at least 120 reference subjects [8].

Table 1: Reference intervals of healthy blood donors.

Analyte	Unit	Reference interval		MHH benchmarks	
		Men	Women	Men	Women
Albumin	g/L	35–53	34–50	35–52	35–52
Alanine aminotransferase	U/L	13–60	10–31	<45	<34
Aspartate aminotransferase	U/L	18–41	14–34	<35	<31
Bilirubin	mmol/L	3–19	2–18	2–21	2–21
Cholinesterase	kU/L	6–13	5–12	5–13	4–11
Creatinine	mmol/L	66–112	56–85	59–104	45–84
γ-Glutamyl transferase	U/L	10–52	6–41	<55	<38
Total protein	g/L	65–81	66–79	65–80	65–80

Figure 7: Influence of different limit values on the results of the zlog transformation (cf. Table 1). The following reference intervals (in $\mu\text{mol/L}$) have been assumed for creatinine in women: A = 45–84, B = 56–84, C = 56–85. The following reference intervals (in U/L) have been assumed for ALT in men: D = 1–45, E = 13–45, F = 13–60.

Table 2: Sample calculations for zlog values and resulting quotients.

Category	Albumin	zlog	Bilirubin	zlog
Blood donor	42	-0.15	11	0.85
Blood donor	34	-2.25	9	0.57
Blood donor	38	-1.15	2	-1.66
Hepatitis without cirrhosis	43	0.08	5	-0.43
Hepatitis without cirrhosis	50	1.57	22	2.04
Hepatitis without cirrhosis	42	-0.15	42	3.12
Hepatitis with cirrhosis	27	-4.53	37	2.90
Hepatitis with cirrhosis	31	-3.16	200	5.72
Hepatitis with cirrhosis	24	-5.70	20	1.88

The MHH data in Table 1 was used as reference intervals (albumin 35–52 g/L, bilirubin 2–21 µmol/L).

But given the organizational and financial expenditure involved, this guideline is generally not observed. An informal, non-representative survey among laboratories at universities, municipal hospitals and in the private sector in Germany, Austria and Switzerland has shown that around 80% of the reference values are obtained from manufacturer's package leaflets and 20% from textbooks (unpublished data). The use of such data is generally permissible if the information has been verified on the basis of at least 20 healthy reference subjects [8]. Verification via routine values from the laboratory information system is easier and also statistically more valid [9, 15].

So-called “common RIs” obtained from large-scale multicenter studies should be taken into account, particularly where children [18] and seniors [19] are concerned. In the case of highly age-dependent lab results, such as alkaline phosphatase in childhood [20], the zlog value's advantage is that it adapts to the development of the reference limits virtually automatically, which means that one can do without complex graphics and space-consuming reference value lists. Similarly beneficial is the effect

of standardization on long-term follow-ups for highly method-dependent results, such as prostate specific antigen (PSA) testing on devices of different manufacturers [21]. Thus, if these measures are implemented by every laboratory with critical acumen, the user of electronic health files will be able to rely on the zlog values and variables derived therefrom when interpreting lab results. A corresponding guideline has been planned.

Despite all the advantages of zlog transformation, however, the communication of absolute values cannot be dispensed with entirely if for nothing else than legal reasons. Under Chapter 6.3 of the directive of the German Medical Association (for quality assurance of quantitative medical laboratory tests – RiliBÄK), a minimum data set consisting of the test, result, unit and test material, including sampling date and RI, is required [22]. The same requirements are found in DIN EN ISO 15189, paragraph 5.8.3 regarding laboratory accreditation; another provision, in paragraph 5.5.2 since 2014, stipulates that the recipient of the results must be informed of the source of the RIs [23].

In other words, the recommended standardization of laboratory results, as proposed herein, does not cause the mandatory data set to decrease in its scope, but rather adds the zlog value. In view of the alternative, having to communicate considerably larger data sets to ensure life-long and global interpretability, this added effort seems negligible by comparison. Without the zlog value, users would have to communicate and consider within the context of interpretation a veritable flood of RIs for each age group, ethnic background information, methodological details on measurement equipment, calibrators, etc.

This is why all laboratories are expected to provide not only the original value, but also the zlog value in future. To render this value useful in electronic patient files, the protocols for the electronic transmission of laboratory data, such as HL7 Clinical Document Architecture (CDA) [24] and LDT 3.0 [25], should be expanded to include a separate field for this additional value. The additional

Table 3: Usefulness of zlog transformation in connection with method change, with the serum creatinine level as an example.

Date	Creatinine	zlog	Method	Unit	Reference interval	
					Lower limit	Upper limit
03.04.2015	87	1.08	Enzymatic	µmol/L	44	106
20.10.2015	111	2.17	Enzymatic	µmol/L	44	106
15.12.2015	1.8	4.75	Jaffé	mg/dL	0.55	1.10

The color shift from almost white to clearly orange indicates the deterioration of the kidney function; the zlog values quantify this intuitive estimation by indicating the number of SDs increases by which the respective measured value differs.

information thus gained represents an easy-to-implement and effective contribution to improved data quality, intuitive assessment of laboratory results and, thus, better patient security in connection with the E-Health Act.

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