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Quantity quotient reporting versus z-value for standardizing quantitative laboratory results

Ergebnisquotient versus z-Wert zur Standardisierung quantitativer Laborergebnisse

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Abstract: The rapid increase to digitalize whatever is possible in human lives will lead to electronic storage of medical data probably during the whole life of most individuals. This requires standardization and condensation of an enormous amount of data. Most laboratory data are already reported in digitalized form, but they are far from being sufficiently standardized. Several attempts for standardization have been suggested. The most common standardizing approach is the z-transformation of laboratory data. It is proposed to modify the z-value to a quantity quotient in analogy to the intelligence quotient well known even to laymen.

Keywords: biological variation; report standardizing; z-transformation.

Zusammenfassung: Die rasch zunehmende Digitalisierung des menschlichen Lebens, wo immer es möglich ist, wird zur elektronischen Speicherung medizinischer Daten während des ganzen Lebens der meisten Individuen führen. Das erfordert die Standardisierung und Kondensation enormer Datenmengen. Die meisten Daten aus Laboratorien werden bereits in digitalisierter Form bereit gestellt, sind allerdings noch weit von einer Standardisierung entfernt. Verschiedene Versuche wurden bereits vorgeschlagen, beispielsweise die z-Transformation. Der z-Wert kann als Ergebnis-Quotient modifiziert werden, in Analogie zu dem als Laien bekannten Intelligenz-Quotienten.

Schlüsselwörter: biologische Variation; Ergebnisquotient; z-Transformation.

Introduction

The increasing trend to digitalize the whole human life as much as possible, requires a sufficient standardization especially if the digitalized data shall not only be stored but transferred between health care providers. Thus, the German e-Health law of 2016 requires that medical data must be stored on an electronic health card from the 1st January 2018 on. This health card will contain digitalized information which should not only be understandable to medical staff, but also to pharmacists, insurance companies and especially to the owner of the card – the patient – usually a layperson. Although many regulatory questions are still open, a consensus on the standardization of laboratory results should be obtained.

Several concepts for the standardization of laboratory results have been developed which have been summarized by Dybkaer and Solberg [1]. These authors mentioned in their approved recommendation (1987) as a common concept: observed value minus the arithmetic mean divided by the standard deviation. The general equation has been used frequently as [2–6]:

$$z = (x_i - \text{mean})/s_B \quad (1)$$

In this equation x_i means the observed value, mean is the arithmetic mean (location of the distribution) and s_B

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means the biological standard deviation (as a measure of the dispersion). Several possibilities to define the biological variation s_B exist, one common approach is to derive s_B from the reference interval, defined by a lower reference limit RL_1 to an upper reference limit RL_2 (s_E, empirical biological standard deviation) [7]:

$$s_E = (RL_2 - RL_1) / 3.92 \quad (2)$$

Inserting s_E in equation 1:

$$z = (x_i - \text{mean}) \cdot 3.92/(RL_2 - RL_1) \quad (3)$$

$$\text{Mean} = (RL_1 + RL_2)/2 \quad (4)$$

The results may be misleading if the reference distribution is non-Gaussian [1]. Two attempts tried to circumvent this problem: the z(log)-value of Hoffmann et al. [8] and the quantity quotient of Haeckel et al. [9–11].

z(log)-Value

Most quantities in clinical chemistry, however, are not normally distributed. If the distribution type is not known, the assumption of a log-normal transformation was recommended [12] and equation 3 can correspondingly be modified:

$$z(\log) = [\log x_i - (\log RL_1 + \log RL_2/2)] \cdot 3.92/ (\log RL_2 - \log RL_1) \quad (5)$$

The z(log) can easily be interpreted, as its reference interval is –1.96 to +1.96 by default, and very low or high results yield z(log) values around –5 and +5, respectively [8]. The z(log) value is compressed above the upper reference limit (Table 1), especially if high measured values are observed. This effect becomes more distinct with wider reference intervals [increasing biological variation, e.g. thyroid stimulating hormone (TSH), aspartate aminotransferase (AST)] and can be neglected for measurands of a low biological variation (e.g. sodium with an empirical biological variation $CV_E = 1.82$). The examples in Table 1 were chosen to cover the entire range of biological variations encountered in laboratory medicine.

Quantity quotient reporting

The concept of quotient reporting is well known from the intelligence quotient which was developed to make intelligence tests comparable. The result of such a test is compared with the mean of all test results of a reference population, and expressed as a quotient. The term intelligence quotient was coined 1912 by William Stern [13]. An intelligence quotient of 100 is supposed to represent the mean of the general population and 70–130 is the 95% interval. This interval implicates a normal distribution with a standard deviation of 15 quotient units.

The concept of the intelligence quotient can be transferred to laboratory results as proposed by Lo and Kellen [14] who called the quotient "clinical unit". A reference range of 40 is suggested. Then, the conventional result is transformed to a quotient which we termed quantity quotient (QQ) by equation 6 [9–11]:

$$QQ = 100 + 10.2\ (x_i - M)/s_E \quad (6)$$

In this equation, x_i means the conventional result, M is the mean value of the reference interval, and s_E the observed standard deviation of the biological variability (in the case of a Gaussian distribution). The factor 10.2 is the result of the division 40/3.92.

Equation 6 represents a transformed z-value: $QQ = 100 + 10.2 \cdot z$.

If the reference range is used to estimate s_E, equation 6 can be modified to

$$QQ = 100 + 40\ (x_i - M)/(RL_{97.5} - RL_{2.5}) \quad (7)$$

Most quantities in clinical chemistry, however, are not Gaussian distributed. Therefore, a log-normal transformation was proposed [12]. As with z-transformation, equation 7 leads to compression of the QQ value below RL_1 (Table 1, e.g. 0.005–0.1 mU/L TSH), whereas, log-transformation compresses QQ values above RL_2 (Table 1, e.g. >100 mU/L TSH). Therefore, above $x_i = RL_2$ a linear relation was suggested to avoid the compression effect mentioned above [11].

A well-known approach for transforming non-symmetrical distribution to a symmetrical one is the power transformation in which the asymmetry of the distribution can be corrected by a λ-value. With a normal distribution λ equals 1, with a log-normal distribution λ is 0. As a compromise, a $\lambda = 0.5$ may be chosen for the purpose of standardizing laboratory reports ($x_i^{\lambda} = x_i^{0.5} = \sqrt{x_i}$). Then, equation 7 becomes

$$QQ = 100 + 40 \cdot (x_i^{0.5} - m)/(RL_2^{0.5} - RL_1^{0.5}) \quad (8)$$

$$m = (RL_1^{0.5} + RL_2^{0.5})/2 \quad (9)$$

Equation 8 leads to QQ values which are only slightly and acceptably compressed below RL_1 and above RL_2 (model II in Table 1).

Table 1: Three models for standardizing measurement values demonstrated with four examples representing extreme biological variations: plasma sodium with a relatively small reference interval (small biological variation), creatinine with a medium reference interval, aspartate aminotransferase (AST) and thyrotropin (TSH) with larger reference intervals (larger biological variation).

Quantity	Unit	Mean/median/mode	Measured value	Quantity quotient		z(log)-value
						Model III
			x_i	Model I QQ x_i[a]	Model II QQ $\sqrt{x_i}$	
Sodium	mmol/L	140/140/140	100	−60	−73	−18.42
RI[b] = 135–145			117	8	4	−9.81
CV_E = 1.82[c]			118	12	8	−9.34
			135	80	80	−1.96
			140	100	100	0.04
			145	120	120	1.96
			150	140	139	3.82
Creatinine	µmol/L	84/81.6/80.3	25	41	25	−9.55
RI = 64–104			30	46	34	−8.08
CV_E = 17.6			64	80	80	−1.96
			80.3	96.3	97	−0.13
			81.6	97.6	99	0.00
			84	100	101	0.24
			104	120	120	1.96
			140	156	150	4.36
			200	216	192	7.24
AST	U/L	22.5/18.7/16.9	2	67.2	55	−7.00
RI = 10–35			10	80	80	−1.96
CV_E = 32.8			16.9	91.04	94	−0.32
			18.7	93.92	97	0.00
			22.5	100	103	0.58
			35	120	120	1.96
			50	144	137	3.08
			100	224	179	5.24
			1000	1664	493	12.45
			2000	3264	684	14.62
			10,000	16,064	1487	19.65
TSH	mU/L	1.5/1.12/0.94	0.005[d]	≤70.1	≤51	≤−13.18
RI = 0.5–2.5			0.03	70.6	56	−8.81
CV_E = 42.9			0.05	71	58	−7.57
			0.1	72	62	−5.88
			0.5	80	80	−1.96
			0.94	88.8	92	−0.42
			1.12	92.4	96	0.00
			1.5	100	104	0.72
			2.5	120	120	1.96
			10	270	192	5.34
			100	2070	505	10.94
			1000	20,070	1495	16.55

[a]Model I, based on symmetrical distribution. [b]RI, reference interval; reference limits taken from ref. [7]. [c]CV_E, empirical biological coefficient of variation, taken from ref. [7]. [d]Detection limit declared by Roche for their Cobas Bio test kit.

Graphical presentation of QQ reporting

The example shown in Figure 1 (model II) provides a helpful tool for physicians and patients to recognize any laboratory result outside the reference interval with one glance (Figure 1). This is particularly useful if a large number of tests are presented. Other examples have been reported elsewhere [9–11].

Advantages of the quotient reporting

Benefits of the new proposal are [11]:

1. Reference limits are always the same for all quantities (80 and 120). All persons interested in laboratory results, especially the patients, can interpret results without knowledge of reference limits. The results can also be easily transferred to other institutions, even

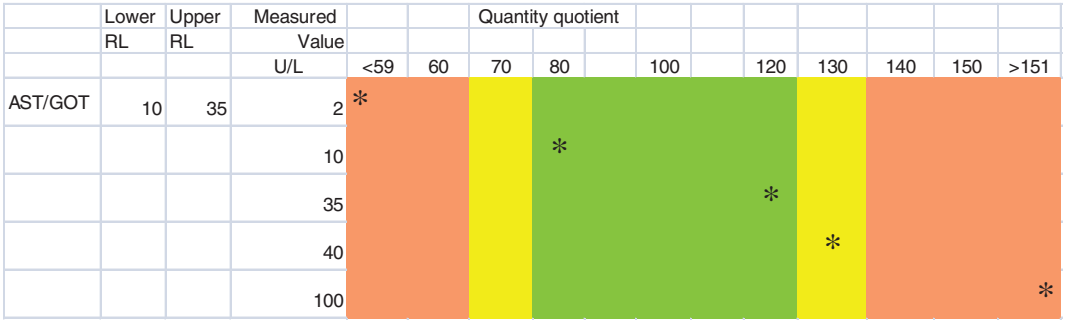

Figure 1: Quantity quotient (model II) of aspartate aminotransferase (AST,GOT).
80, lower reference limit (RL); 120, upper reference limit. Green cells represent the reference interval, yellow cells the intermediate interval between 70 and 80 or between 120 and 130, and red cells contain pathological quotients outside the 99% reference interval (QQ < 70 or >130).

after decades when the knowledge on the former RLs may not be available anymore.

2. For many quantities, several reference limits exist. In Europe for instance, laboratories presently use at least three different procedures for the determination of plasma creatinine. Therefore, at least 18 different reference intervals (stratified for gender and age of adults) are reported in the same unit system [9]. Considering SI and conventional systems, there exist 36 reference intervals. This number would be even higher if children and the elderly are considered. In all cases the reference interval is 80–120 in the QQ-model.
3. The "gray zone" between ±2 SD and ±3 SD is always 10.
4. All results have automatically the same number of digits and reference intervals always have 41 distinct values if only integer values are reported.
5. A general adaption of the proposal would avoid future confusions between SI units and conventional units and the need for transformations. The problem of unit presentation would remain an intra-laboratory problem which would not bother the requesting physicians.

The same benefits analogously can be attributed to the z(log)-value. However, the concept of the QQ reporting may be more easily understandable due to its analogy to the intelligence quotient. Interpretation of multiples of a standard deviation (z-value) may be more difficult for laymen. All QQ values are positive in the reference interval (between 80 and 120), whereas the z(log) model leads always to negative values in about 50% of all results. This phenomenon may be unusual to laymen. Furthermore, high concentrations of measurands with large measurement ranges are less compressed in the present QQ model than in the z(log) approach.

According to Lo and Kellen [14], the concept of QQ reporting may also be applied if "+"-systems are used (assuming from "negative" to "2" to represent the normal range). Quotient units can then be arbitrarily assigned as follows: negative: 80, 1+: 100, 2+: 120, 3+: 140, 4+: 160.

Limitations of the present proposal

1. Although the present proposal may be generally applicable to many (if not all) quantitative measurands in laboratory medicine, it is especially recommended for the classical quantities in clinical chemistry with well known reference intervals. It may need special rules if applied to large measuring scales covering more than three decimals (e.g. human chorionic gonadotropin).
2. QQ reporting is not suited for quantities which physicians are accustomed to using in diagnostic nomograms (e.g. pO_2, pCO_2, pH) and for quantities already reported as ratios [9].
3. Action limits (11) cannot be used to derive QQ. Action limits (e.g. 4.0 µg/L PSA or 7 mmol/L plasma glucose) should be marked as such [11]. The velocity of PSA increase (e.g. >0.75 µg/L per year) has been recommended as an indicator for prostatic cancer and can also be included in the QQR as outlined elsewhere [11].
4. In extreme cases, a negative QQ value is observed (e.g. –73 with 100 mmol/L plasma sodium, Table 1). Negative values always indicate that the original value is also extremely pathological. The advantage of the QQ reporting is that in over 99% positive values are obtained whereas the z(log) value in about 50% is negative.
5. In the case that a lower RL is not available, a lower reference limits of $0.15 \cdot RL_2$ has been suggested [7]. "For one-tail distributions, that is, tests in which a positive deviation is abnormal but a negative deviation is not,

then the lower clinical limit will naturally be 80 (e.g. absence of detectable protein in urine)"[14].

Discussion

The present situation is that quantitative laboratory results in most cases are sent to the requester without information on bias, imprecision and transferability of reference limits taken from external sources. In the future, it can be expected that biochemical profiles of all individuals are stored on individual small data chips or cards. Thus, patients' data on biochemical quantities may be easily available over decades. But it will probably be difficult to get the necessary analytical data required for correct interpretation (as analytical procedure, bias, adequate reference limits) over a long-time period. Dybkaer and Solberg (1) claim that the original value of a given quantity must be reported – irrespective of the way in which it is related to reference values – to allow, e.g. comparisons with other types of quantities and metabolic calculations.

In conclusion, the modified QQ value proposed above, appears to fulfill all minimal requirements for standardizing quantitative measurement values in laboratory medicine: easy to calculate and easy to understand and to interpret by all parties involved, especially by the end user of the data (usually the patient).

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