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A study of blood glucose determination by means of an interlaboratory test

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Abstract

Through inter-laboratory comparison, based on the measurement process and measuring equipment conducted according to predetermined criteria, it is possible to evaluate the performance of the participants, which is known as qualification testing and is regulated in accordance with ISO 17043:2017/2018.

In the medical field, the term “external quality assessment” is used for qualification testing schemes or wider programs where samples (standard, certified, attested), products, artefacts, pieces of equipment, measurement standards, data sets or other information are used for qualification testing. The processing of measurement data, which in many cases includes a random error detector along with a systematic error detector, is carried out using mathematical statistics methods, including statistical methods that are less sensitive to small deviations from the basic assumptions surrounding the probabilistic model, which are known as robust methods. Robust methods are a powerful tool for demonstrating competence in performing tests and measurements related to qualification testing schemes.

Keywords: Interlaboratory test, robust method

Introduction

9 clinics and hospitals with different material capabilities, different technical equipment, different medical training, qualifications, and profile medical licenses were selected for inter-laboratory tests.

The venous blood of a 42-year-old man, practically healthy, was used as a control sample, so that the glucose content in his blood was not known to the observers in advance. 300 ml of venous blood was taken from the patient, which was divided into 9 closed test tubes with a volume of 30-33 ml using measuring pipettes and sent to the analytical laboratory for conducting ten parallel experiments. The time of transportation and analysis did not exceed 3 hours due to the requirements of homogeneity of the samples.

The standard deviation of the obtained results of the analysis was carried out depending on the specific, normative, and legal requirements of data processing. An advantage of such an approach should be considered the direct connection and dependence of the standard deviation of competence with the measurement method.

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Media laboratories and their measuring devices are estimated to be able to determine blood glucose levels with an accuracy of ±10% of the established norm [(Zedginidze, 2000)], although a deviation of ±6 mg/dL is allowed for very low concentrations (<60 mg/dL). This information can be used to calculate the standard deviation of the proficiency:

- For the given value X<60 mg/dL, for its standard deviation we will have σˆ_ref=60⁄3.0=2mg/dL;
- For the given value X>60 mg/dL, for its standard deviation we have σˆ_ref=(0,1∂·X)⁄3.0=0.033·X mg/dL;

where coefficient 3 is the critical value of the permissible standard deviation.

The results of multiple measurements of the inter-laboratory test conducted in clinics with the above-mentioned approach are given in Table No. 1.

Among the measurement data (meaning arithmetic mean values) we have the smallest doubtful data, which can be considered as a gross error and can be ignored. To check the data for gross error, using the Q criterion,

$$Q_{mc} = \frac{y_2 - y_1}{y_n - y_1} = \frac{121-110}{135-110} = 0.44$$

Because the calculated value Q_mts=0.44=Q_txh=0.44 indicates [1] (p. 9. Tk. 1) that X ̅=110 can be considered both a gross error and a basic value, that is, it was possible to leave it, therefore We decided to keep these data, but to analyze the results using the robust method. That is, we should group the results not with respect to the arithmetic mean, but with respect to the median of the measurement results. Such an approach allows us to use all the research data in the data analysis without deteriorating the quality of the research.

A robust method is a method dependent on the results of participating laboratories that is not sensitive to small deviations from the basic assumptions surrounding the underlying probabilistic model. Its use is appropriate in cases where the possibility of using a certified control sample is complicated due to various conditions. Among such reasons can be the difficulty of making a control sample, in our case we are talking about the use of natural certified blood, for which the determination of the certified value is not always available. In addition, combining data due to their inhomogeneity is not allowed, as was shown [(ISO 13528:2015, Statistical methods for use in proficiency testing by interlaboratory comparison)], where the results of laboratory research are not uniform with respect to the arithmetic mean and standard deviation, so combining them for a single series of measurement process is not appropriate (Chkheidze, Otkhohzoria, & Narchemashvili, 2021).

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Table 1. test results

Laboratories									
№ x_i	№1	№2	№3	№4	№5	№6	№7	№8	№9
1	136	120	136	106	119	132	129	127	121
2	133	118	138	108	118	133	128	128	125
3	133	126	142	112	124	136	134	130	123
4	126	125	131	111	122	134	132	125	124
5	127	128	137	114	124	136	134	126	128
6	125	123	133	108	118	132	128	131	125
7	128	122	130	109	119	135	129	132	127
8	130	129	130	112	122	134	132	129	128
9	125	121	135	107	119	131	129	128	126
10	127	124	138	103	125	137	135	124	124
$\overline{X}$	**129**	**124**	**135**	**110**	**121**	**134**	**131**	**128**	**125**
u_A	3.83	2.98	3.97	2.75	2.7	2.0	2.71	2.51	2.1
u_B	4.85	6.32	5.03	5.27	4.78	5.45	6.25	5.45	7.5
u_Σ	6.18	6.99	6.41	5.94	5.49	5.8	6.81	6.03	7.79
U_{095}	13.39	15.1	13.90	10.84	10.02	12.58	12.42	13.07	16.9

Considering all of the above, we should use a robust method of data analysis for the results of the research of multiple measurement data (arithmetic averages).

As it is known, the use of the robust method is based on the process of determining not the arithmetic mean of the data, but the results are considered with respect to the median of the data. To find the median (X*) of the existing data, arrange the data in non-decreasing form.

110; 121; 124; 125; 128; 129; 131; 134; 135 (1)

The middle member of the data arranged in such a form is the median of the given sample. Calculate the initial values of the robust mean and the robust standard deviation and . for this group. That being said, the median is the middle point of the data in ascending order, in our case

$X_0^*=128$

And the robust standard deviation of this data is the product of the median of the new data group created by the difference between the median and each data point (mean modulus) by the empirical factor of 1.483. [3]

$S_0^*=1.483$ median $|X_1-X^*|, |X_2-X^*|, \dots |X_P-X^*|)=1,483[(|110-128|,|121-128|,\dots |135-128|)]=1,483[18,7,4,3,0,1,3,6,7]$ (2)

To find a new median for the newly obtained sequence of data, we need to sort these data again in non-decreasing form and limit the middle term.

med= [0; 1; 3; 3; 4; 6; 7; 7; 18] =4

Accordingly, we will have a robust standard deviation of zero iteration:

$S_0^*=1,483\cdot 4=5,932$

Calculate the standard deviation of the experiment:

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δ=1,5S*=1,5·5,932=8,898≈8,9 (3)

For each Xı (i=1,2,...p) will be calculated

$$X_i^* = \begin{cases} X^* - \delta & \text{if} \quad X_i < X^* - \delta \\ X^* + \delta & \text{if} \quad X_i > X^* + \delta \\ X_l & \text{if} \quad X^* - \delta \le X \le X^* + \delta \end{cases}$$

The value of calculated for member will be:

Since X*-δ=128-8,898>X_1=110, therefore, by virtue of the previous image for X_1 we have that X_1=X*-δ=128-8,898=119,102.

The calculated X_2* value for the second X_2 term will be:

because X*-δ=128-8,898=119,102<X_2=121 (the condition is not fulfilled);

Let's check X*+ δ=128+8,898=136,898 >121 (the condition was not fulfilled);

Let's check X*-δ≤X≤X^*+ δ, which is fully satisfied, so the second term will keep its value, i.e. X_2*=X_i=X_2=121;

Let's check X*-δ≤X≤X*+ δ, which is fully satisfied, so the second term will keep its value, i.e. X_2*=X_i=X_2=121;

The other members will also keep their values because their values X*-δ≤X≤X*+ δ =119.1....136 are in the middle and we will get new values for the data group

119; 121; 124; 125; 128; 129;
131; 134; 135;

The next step in robust estimation calculation is to calculate the robust mean and robust standard deviation for the new set of data, which is the first step in specifying these quantities and is known as the first iteration. The process of iterations is terminated when the robust averages and standard deviation values obtained in two subsequent iterations become so close to each other that the values of the third position after the comma become identical, this indicates the basis for stopping the process.

The robust mean - Xi* and the robust standard deviation value – S_i* of the first iteration are calculated this time with the following formulas:

$$X_I^* = \sum_{i=1}^{p} X_i^*/_p \ \text{and} \ S_I^* = 1{,}134\sqrt{\sum_{i=1}^{p}\left(X_i^* - X^*\right)^2/(p-1)} \qquad (5)$$

It will give us the calculation of the robust average

$$X_I^* = \sum_{i=1}^{p} X_i^*/_p = {}^{119{,}102}/_9 + {}^{121}/_9 + {}^{124}/_9 + {}^{125}/_9 + {}^{128}/_9 + {}^{129}/_9 + {}^{131}/_9 + {}^{134}/_9 + {}^{135}/_9$$
$$= 13{,}234 + 13{,}44 + 13.78 + 13{,}89 + 14{,}22 + 14{,}33 + 14{,}55 + 14{,}89 + 1 = 127{,}344$$

For robust standard deviation, data and intermediate results are presented in tabular form (Table 2.) For the robust standard deviation, we have:

$$S_I^* = 1{,}134\sqrt{\sum_{i=1}^{p}\left(X_i^* - X^*\right)^2/(p-1)} = 1{,}134\sqrt{{}^{244{,}31}/_8} = 6{,}269 \qquad (6)$$

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Table 2. Intermediate calculation results

№ In row	X_I^*	$\lvert X_I^*-X^*\rvert$	$(X_I^*-X^*)^2$
1	119,102	127,34119,102=8,242	67.93
2	121	127,346,33	40,07
3	124	127,343,33	11,09
4	125	127,342,33	5,43
5	128	127,340,67	0,45
6	129	127,34-129=1,67	2,79
7	131	127,34-131=3,67	13,47
8	134	127.34-134=6,67-	44,45
9	135	127,34-135=7,67	58,83
Σ			244.51

The difference of the robust averages for the last two results of the iterations is

$$|X_0^*-X_I^*|=0.667$$

Such a difference between the quantities is unacceptable, so the calculations continue until the next approximation of the robust averages. We move to the second iteration level. 119.1 for the new data group; 121; 124; 125; 128; 129; 131; 134; 135 The new value of the median is equal to the calculated value of iteration I X_i^*=127,344. and the standard deviation of the robust value

$$S_{II}^* = \sum_{i=1}^{p} X_i^*/_p \cdot S_I^* = 1{,}483[(|119{,}1-127{,}344|,|121-127{,}34|,\dots|135-127{,}34|)] = 1{,}483$$

Median [8,24 2; 6,34; 3,34; 2,34; 0,67; 1,67 ; 3,67; 6,67; 7,67]=1,483· 3,67=5,442 and the standard deviation of the experiment

$$\delta_I=1{,}5\cdot S_{II}^*=8{,}163$$

For each X_i (i=1, 2, p) will be calculated

$$X_i^* = \begin{cases} X^*-\delta & \text{if } X_i < X^*-\delta \\ X^*+\delta & \text{if } X_i > X^*+\delta \\ X_l & \text{if } X^*-\delta \le X \le X^*+\delta \end{cases}$$

For the first i=1 and other members of the second iteration, let's introduce the notation calculated $X_{2(I)}^*$i.e. the i-th member of the second iteration, and its value:

Because $X_1^*-\delta$=127,344-8,163=119,181 which is >119.1 value, therefore by virtue of the previous image for the first term we have that the first term of the second iteration is .=119,181.

For member i=2, the value of $X^*_{2(2)}$ will be:

The calculated $X^*_{2(2)}$ value for the secondX_2^* term will be:

Because of $X^*-\delta$=127,344-8, 163=119, 181 < X_2=121 (the condition is not fulfilled)

Check $X^{\wedge *}+\delta$=128+8,898=136,898 >121 (the condition is not fulfilled)

Check $X^*-\delta \le X \le X^*+\delta$ which is fully satisfied; therefore, the second term will retain its value, i.e.

The rest of the members will also retain their values because of their values is located in the middle and we get new values for the data group 119,181; 121; 124; 125; 128; 129; 131; 134; 135;

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Calculating the robust mean for a new set of data will give us:

$$X_{II}^{*} = \sum_{i=1}^{p} X_i^{*}/_p = {}^{119.181}/_9 + {}^{121}/_9 + {}^{124}/_9 + {}^{125}/_9 + {}^{128}/_9 + {}^{129}/_9 + {}^{131}/_9 + {}^{134}/_9 + {}^{135}/_9 = 13{,}242 + 13{,}444 + 13{,}667 + 13{,}889 + 14{,}222 + 14{,}333 + 14{,}555 + 14{,}889 + 15 = 127{,}241$$

The second iteration robust mean estimation

$X_{II}^{*}=127{,}241$

The difference of the robust averages for the last two results of the iterations is

$|X_I^{*}-X_{II}^{*}| = |127{,}181-127{,}241| = 0.060$

Such a difference between the quantities is unacceptable, so the calculations continue until the next approximation of the robust averages. We move to the third iteration level.

119,181 for the new data group; 121; 124; 125; 128; 129; 131; 134; 135 The new value of the median is equal to the calculated value of iteration II $X_{II}^{*}=127{,}241$.

The standard deviation of the robust value

$$S_{II}^{*} = \sum_{i=1}^{p} X_i^{*}/_p \cdot S_I^{*} = 1{,}483[(|119{,}181 - 127{,}241|, |121 - 127{,}241|, \dots |135 - 127{,}241|)] = 1{,}483$$

Median [8,06; 6,241; 3,241; 2,241; 0,759; 1,759 ; 3,759; 6,759; 7,759] = 1,483· 3,759=5,575

and the standard deviation of the experiment

$\delta_{II}=1{,}5 \cdot S^{*}_{II}=1.5 \cdot 5.575=8{,}361$

For each X_i (i=1,2,...p) will be calculate

$$X_i^{*} = \begin{cases} X^{*} - \delta & \text{if } X_i < X^{*} - \delta \\ X^{*} + \delta & \text{if } X_i > X^{*} + \delta \\ X_l & \text{if } X^{*} - \delta \le X \le X^{*} + \delta \end{cases}$$

For the first i=1 and other members of the third iteration, let's introduce the notation calculated $X^{*}_{3}(I)$ i.e. the i-th member of the third iteration, and the value of its first member will be:

Because of $X_1^{*}-\delta=127{,}241-8{,}361=118{,}88$ which is <119.181 on the value, therefore by virtue of the previous image (the condition is not fulfilled) for the first term we have that the first term of the second iteration $X^{*}_{2}(1)=119{,}181$

Check $X^{*}+\delta=127{,}241+8{,}361=135{,}602$ (the condition is not fulfilled)

The third condition comes into effect when all members retain their value.

For member i=2, the value of $X^{*}_{2}(2)$ will be:

The calculated X_2^{*} value for the second $X^{*}_{2}(2)$ term will be:

Because of $X^{*} - \delta = 127{,}344 - 8{,}163 = 119{,}181 < X_2=121$ (the condition is not fulfilled)

Check $X^{*}-\delta \le X \le X^{*}+\delta$ which is fully satisfied; therefore, the second term will retain its value, i.e. $X_2^{*}=X_L=X_2=121$;

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The rest of the members will also retain their values because of their values X*- δ ≤ X ≤ X*+ δ =119,1....136, It is located in the middle, and we will get new values for the data group

119,181; 121; 124; 125; 128; 129; 131; 134; 135;

$$X_{III}^{*} = \sum_{i=1}^{p} X_i^{*}/_{p} = 119.186/_{9} + 121/_{9} + 124/_{9} + 125/_{9} + 128/_{9} + 129/_{9} + 131/_{9} + 134/_{9} + 135/_{9} = 13{,}242 + 13{,}444 + 13{,}667 + 13{,}889 + 14{,}222 + 14{,}333 + 14{,}555 + 14{,}889 + 15 = 127{,}246$$

The Third iteration robust mean estimation

Xɪɪ*=127,246

The difference of the robust averages for the last two results of the iterations is

|X*ɪɪ-X*ɪɪɪ|=|127,241-127,246|=0.005

Such a difference between the values is acceptable because it is important for us to estimate the measurement results with an accuracy of one hundredth, so we can stop the calculations and finally determine the value of the robust average estimate.

X*ɪɪɪ=127,246

Unlike the arithmetic mean, which is equal to X̅= 126.33 units.

For the standard deviation of the robust value, we will have:

$$S_{III}^{*} = \sum_{i=1}^{p} X_i^{*}/_{p} \cdot S_I^{*} = 1{,}483[(|119{,}181 - 127{,}241|, |121 - 127{,}241|, \dots |135 - 127{,}241|)] = 1{,}483 \text{ მედიანა } [\mathbf{8,06};\ \mathbf{6,241};\ \mathbf{3,241};\ \mathbf{2,241};\ \mathbf{0,759};\ 1{,}759;\ 3{,}759;\ 6{,}759;\ 7{,}759\ ] = 1{,}483 \cdot\ 3{,}759 = 5{,}575$$

and the standard deviation of the experiment

δɪɪɪ=1,5·S*ɪɪɪ=1.5·5.575=8,361

Comparing the value of the z score criterion of the robust average X*ɪɪɪ=127,246 obtained by the third iteration and the standard deviation of the robust experiment δɪɪɪ=8.361 with the result obtained z score by the arithmetic mean for the result of the fourth laboratory gives us

Evaluation criterion obtained by robust averaging:

$$\bar{z}_{score} = \frac{x_1 - X_{III}^{*}}{\delta_{III}} = \frac{119{,}181 - 127{,}246}{8{,}361} = 0.96$$

Criterion of assessment obtained by means of arithmetic:

$$\bar{z}_{score} = \frac{\bar{x}_1 - x_{ref}}{\hat{\sigma}} = \frac{110 - 126{,}33}{7{,}64} = 2{,}13$$

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The results of all other laboratories, calculated in a similar manner, are given in Table 3.

Table 3. The results of all other laboratories

<table>
<tr><td colspan="2">Laboratories</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td></tr>
<tr><td colspan="2">data</td><td>129</td><td>124</td><td>135</td><td>110</td><td>121</td><td>134</td><td>131</td><td>128</td><td>125</td></tr>
<tr><td rowspan="4">Evaluation criteria</td><td>$X_{robust.}$</td><td>0,21</td><td>-0,38</td><td>0,93</td><td>0,96</td><td>-0,74</td><td>0,81</td><td>0,45</td><td>0,09</td><td>-0,27</td></tr>
<tr><td>Robust standard deviation δııı</td><td colspan="9">8,361</td></tr>
<tr><td>X_{mean}</td><td>0,35</td><td>-0,31</td><td>1,13</td><td>-2,13</td><td>0,7</td><td>1,0</td><td>0,61</td><td>0,22</td><td>-0,17</td></tr>
<tr><td>X_{mean} standard deviation $\hat{\sigma}$</td><td colspan="9">7,64</td></tr>
</table>

According to the data in the table, the results of all laboratories calculated by the robust evaluation method meet the evaluation criterion determined by the z criterion at the level of 1 standard deviation, while the norm of 1 standard deviation of the evaluation criterion calculated according to the arithmetic mean is violated for laboratory № 4, whose result was classified as a gross error in the preliminary evaluation.

Conclusion

A complex inter-laboratory experiment of blood glucose determination was conducted, where the possibility of using the biological mass of a volunteer patient as a control sample was simultaneously investigated among the participating laboratories, their equipment, and personnel.

Among the methods of processing data results, it is recommended to use a robust evaluation method, which allows us to use the obtained results more fully, thereby ultimately increasing the reliability and accuracy of the research.

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