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Assessment of the rate of glomerular filtration by a non-invasive method

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Abstract

Background. Existing methods for assessing glomerular filtration rate (GF) are invasive. Therefore, we set ourselves the goal of evaluating the rate of glomerular filtration by a non-invasive method.

Materials and Methods. The object of observations were 10 men aged 37-69 years without clinical diagnosis tested twice with 7-days interval. The rate of glomerular filtration was calculated according to endogenous creatinine clearance and the Cockcroft & Gault formula. Systolic and

diastolic blood pressure was measured three times in a row. The state of the autonomic nervous system was assessed by the HRV method.
Results. We confirmed the significant correlation of GF with age and weight. The screening revealed a significant correlation of GF with a number of blood pressure and HRV parameters.
If in the classic formula we replace creatinineemia with systolic blood pressure and HRV-markers of sympathetic tone, we get a formula for estimating the GF with a standard error of 10,9 mL/min vs 2,7 mL/min, but without blood sampling. The regression model, which includes HRV and blood pressure parameters, as well as urinary creatinine concentration, allows estimating GF with a standard error of 12 mL/min.
Conclusion. The balneotherapy has a significant effect not only on blood creatinine level, but also on HRV and blood pressure parameters, and even more pronounced. Therefore, the estimation of GF based only on the Cockcroft & Gault formula is at least not much more accurate than the one proposed by us, besides, our method is completely non-invasive.
Keywords: glomerular filtration rate, HRV, blood pressure, relationships.

INTRODUCTION

It is known that the most common method of assessing the rate of glomerular filtration is the determination of endogenous creatinine clearance. Cockcroft DW & Gault MH [2] showed that the rate of creatinine excretion, the determination of which is rather inconvenient due to the need to collect urine, can be replaced by the age and weight of the patient without significant loss of accuracy. However, the method remains invasive with all its drawbacks. Therefore, we set ourselves the goal of evaluating the rate of glomerular filtration by a non-invasive method.

MATERIALS AND METHODS

The object of observations were 10 men aged 37-69 years and weight 75-100 kg without clinical diagnosis, tested twice with 7-days interval. Daily urine was collected on the eve, in which determined the concentration of creatinine (by Jaffe's color reaction by Popper's method [3]). Next day creatinine determined in serum. The rate of glomerular filtration was calculated according to endogenous creatinine clearance and the Cockcroft DW & Gault MH [2] formula.

Systolic (Ps) and diastolic (Pd) blood pressure was measured (tonometer “Omron M4-I”, Netherlands) in a sitting position three times in a row followed by the calculation of Ps2/Ps1, Ps3/Ps1, Pd2/Pd1, and Pd3/Pd2 rations [8].

To assess the parameters of heart rate variability (HRV), recorded electrocardiogram during 7 min in II lead (hardware-software complex "CardioLab+HRV" produced by "KhAI-Medica", Kharkiv, Ukraine). For further analysis the following parameters HRV were selected. Temporal parameters (Time Domain Methods): heart rate (HR), the standard deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 ms (pNN_{50}), triangular index (TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV: high-frequency (HF, range 0,4÷0,15 Hz), low-frequency (LF, range 0,15÷0,04 Hz), very low-frequency (VLF, range 0,04÷0,015 Hz) and ultralow-frequency (ULF, range 0,015÷0,003 Hz). We calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (VLF+LF)/HF [1,5].

For statistical analysis used the software package “Microsoft Excell” and "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA).

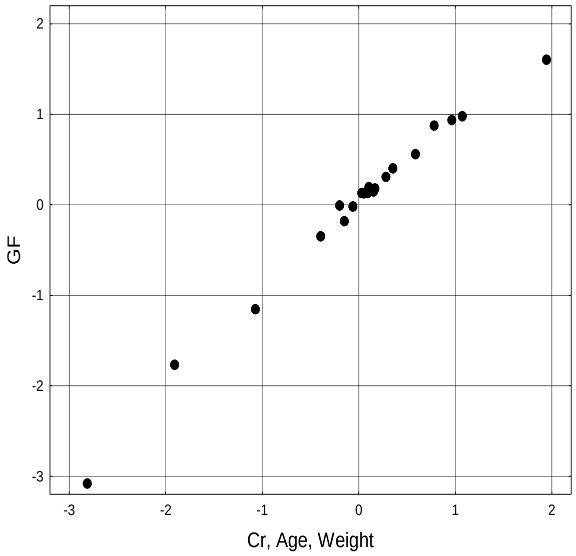
RESULTS

First of all, we confirmed the significant correlation of GF with age and weight on our own material (Table 1 and Fig. 1).

Table 1. Regression Summary for GF and classical parameters

$R=0,992$; $R^2=0,985$; Adjusted $R^2=0,982$; $F_{(3,2)}=348$; $p<10^{-6}$; SE of estimate: 2,7 mL/min

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(16)}$	p-level
Variables	r		Intercpt	179,5	10,3	17,4	10^{-6}
Creatinineemia, µM/L	**-0,58**	-0,575	0,031	-1,485	0,080	-18,6	10^{-6}
Age, years	**-0,54**	-0,721	0,032	-1,421	0,062	-22,8	10^{-6}
Weight, kg	**0,46**	0,561	0,032	1,519	0,086	17,7	10^{-6}



R=0,992; R^2=0,985; $\chi^2_{(3)}$=69; p<10^{-6}; Λ Prime=0,015

Fig. 1. Scatterplot of canonical correlation between creatinineemia, age and weight (X-line) and glomerular filtration rate (Y-line)

The table shows the results of a multiple linear regression analysis. This is a statistical method used to model the relationship between a dependent variable (in this case, GF - Glomerular Filtration Rate) and multiple independent variables (Creatinineemia, Age, and Weight).

Here's a breakdown of how the method works based on the information in the table:

1. Model Fitting: The regression analysis fits a mathematical equation that best explains how the independent variables (Creatinineemia, Age, and Weight) influence the dependent variable (GF).

2. R-squared and Adjusted R-squared:

· R-squared (0.985): This value indicates a very strong positive correlation between the predicted GF values and the actual GF values.

· Adjusted R-squared (0.982): This value adjusts for the number of independent variables and provides a more accurate estimate of the model's explanatory power.

1. Regression Coefficients (Beta): These coefficients represent the impact of each independent variable on the dependent variable, holding all other independent variables constant.

· Creatinineemia and Age: Negative coefficients indicate a negative association with GF. In other words, higher Creatinineemia and Age are associated with lower GF.

· Weight: Positive coefficient suggests a positive association with GF. Higher Weight might be associated with higher GF in this model.

1. Standard Errors and t-statistics: These values help assess the significance of each coefficient.

· A low standard error indicates a more precise estimate of the coefficient.

· The t-statistic and p-value together tell us if the coefficient is statistically significant (meaning it's likely not due to chance). In this case, all p-values are less than 0.00001, suggesting all coefficients are statistically significant.

1. F-statistic and p-value: This test assesses the overall significance of the model. The high F-statistic (348) and very low p-value (<10^-6) indicate the model is statistically significant, meaning the independent variables together explain a significant portion of the variation in GF.

Overall, this table shows the results of a multiple linear regression analysis that successfully models the relationship between GF and Creatinineemia, Age, and Weight.

At the same time, the screening revealed a significant correlation with a number of blood pressure (Fig. 2) and HRV (Fig. 3) parameters.

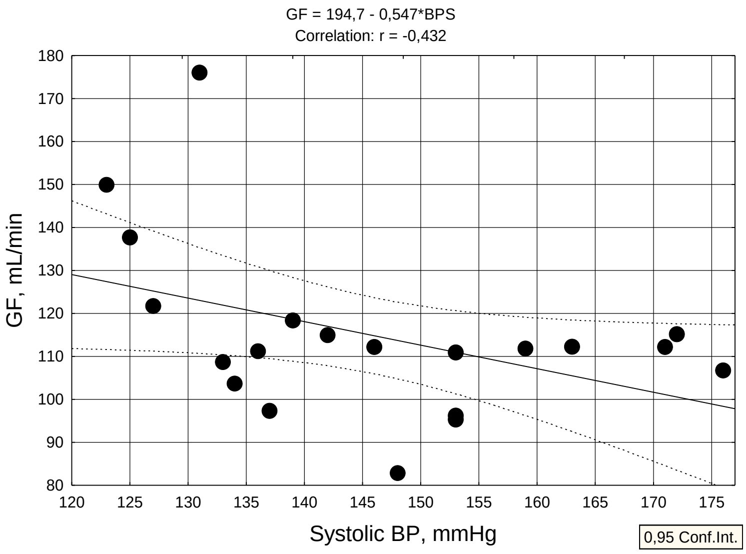


Fig. 2. Scatterplot of correlation between systolic blood pressure (X-line) and glomerular filtration rate (Y-line)

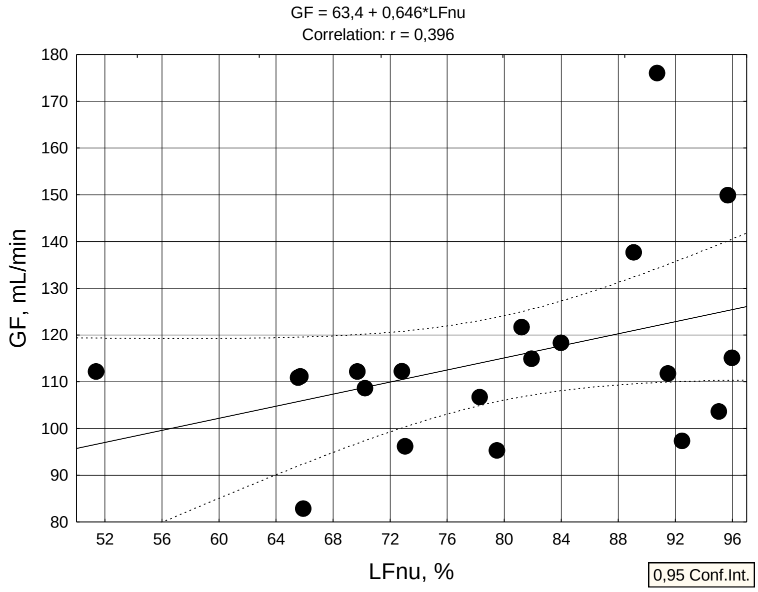
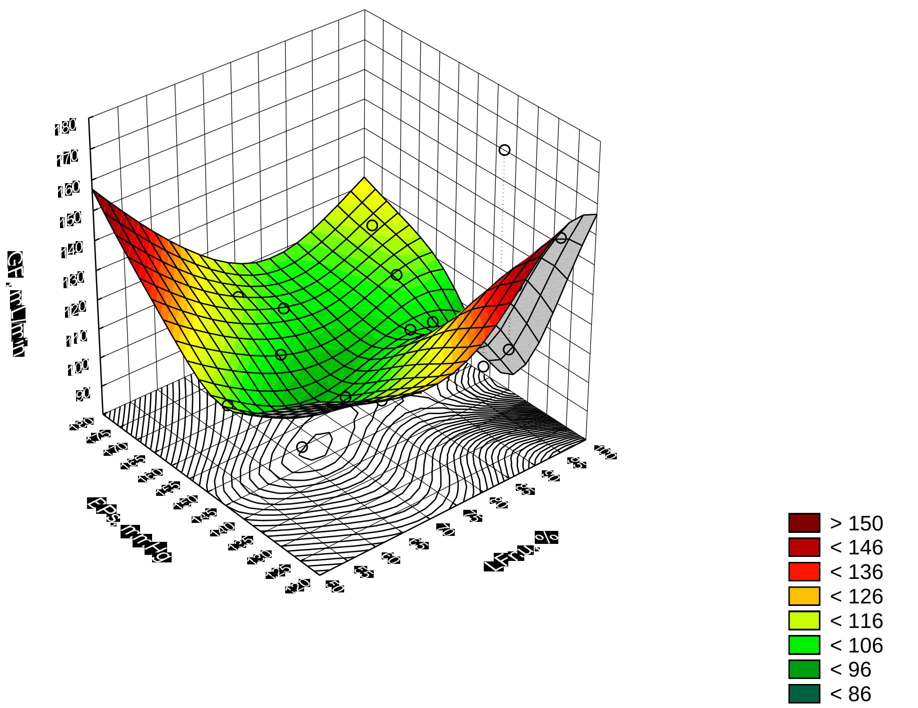


Fig. 3. Scatterplot of correlation between LFnu HRV (X-line) and glomerular filtration rate (Y-line)

However, the coefficient of multiple correlation appeared on the border of significance, and accordingly the SE of estimate 18 mL/min (Fig. 4).



$Z(\pm 18) = 141(\pm 52) + 0{,}516(\pm 0{,}344)\bullet X - 0{,}459(\pm 0{,}267)\bullet Y$

$R=0{,}531$; $R^2=0{,}282$; Adj $R^2=0{,}197$; $F_{(2,2)}=3{,}3$; $p=0{,}060$

Fig. 4. Quadratic surface of relationship between LFnu HRV (X-line), systolic BP (Y-line) and glomerular filtration (Z-line)

However, if in the classic formula we replace creatininemia with systolic blood pressure and HRV-markers of sympathetic tone, we get a formula for estimating the rate of glomerular filtration with an SE of 10,9 mL/min (Table 2 and Fig. 5).

Table 2. Regression Summary for GF

$R=0{,}889$; $R^2=0{,}791$; Adjusted $R^2=0{,}716$; $F_{(5,1)}=10{,}6$; $p<10^{-3}$; SE of estimate: 10,9 mL/min

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(14)}$	p-level
Variables	r		Intercpt	103,7	45,8	2,26	0,040
Age, years	**-0,54**	-0,930	0,187	-1,834	0,369	-4,97	10^{-3}
Weight, kg	**0,46**	0,466	0,140	1,262	0,379	3,33	0,005
Systolic BP, mmHg	**-0,43**	-0,172	0,145	-0,218	0,184	-1,18	0,256
LFnu HRV, %	**0,40**	0,424	0,163	0,692	0,267	2,59	0,021
LF HRV, %	**0,37**	-0,461	0,207	-0,732	0,329	-2,23	0,043

The table you provided shows the results of another multiple linear regression analysis, similar to the one you saw in Table 1. Here's a breakdown of the information:

1. Model Fit: This analysis examines the relationship between the dependent variable, GF (Glomerular Filtration Rate), and this time, five independent variables: Age, Weight, Systolic BP (Systolic Blood Pressure), LFnu HRV (Low Frequency component of heart rate variability in normalized units), and LF HRV (presumably the raw value of the Low Frequency component of heart rate variability).
2. R-squared and Adjusted R-squared:

· R-squared (0.791): This value indicates a strong positive correlation between the predicted GF values and the actual GF values, but it's weaker than the model in Table 1 (R-squared = 0.985).

· Adjusted R-squared (0.716): This value is lower than R-squared because it accounts for the number of independent variables (5 in this case) and suggests a still good, but moderately strong explanatory power of the model.

1. Regression Coefficients (Beta): These coefficients represent the impact of each independent variable on GF, holding all other independent variables constant.

· Age: Negative coefficient suggests a negative association with GF. Higher Age is associated with lower GF in this model.

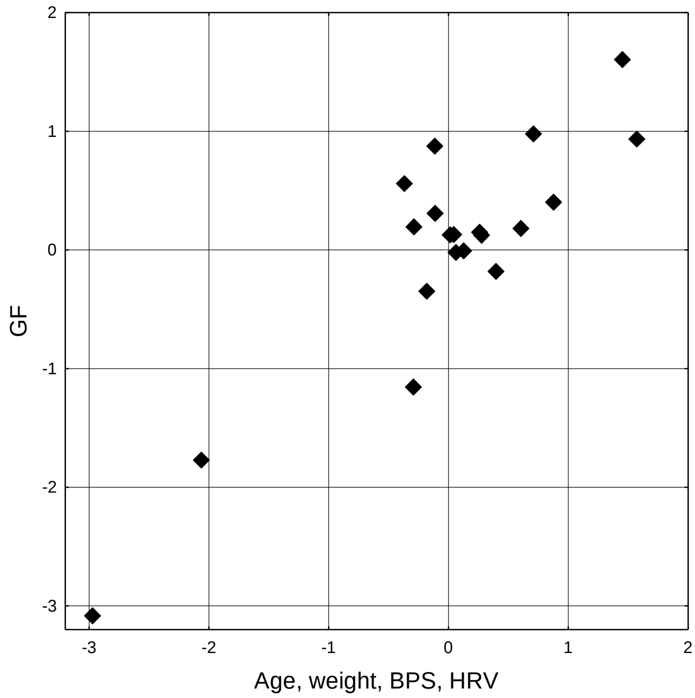
· Weight: Positive coefficient suggests a positive association with GF, similar to Table 1.

· Systolic BP, LFnu HRV, and LF HRV: Interpretations of these coefficients depend on their signs. A negative sign indicates a negative association (higher values lead to lower GF) and vice versa. However, some p-values are higher than 0.05, which means the association with GF might be due to chance.

1. Standard Errors and t-statistics: Similar to Table 1, these values help assess the significance of each coefficient. A lower standard error indicates a more precise estimate, and a significant p-value suggests the coefficient is unlikely due to chance. Here, Age and Weight have significant p-values, while the significance of others is less clear.

2. F-statistic and p-value: This test assesses the overall significance of the model. The F-statistic (10.6) and p-value (< 0.001) indicate the model is statistically significant, meaning the five independent variables together explain a significant portion of the variation in GF.

Overall, this table shows a multiple linear regression model that finds a significant relationship between GF and a combination of Age, Weight, and potentially some heart rate variability measures. However, the explanatory power (adjusted R-squared) is lower compared to the model in Table 1, suggesting that the model in Table 1 might be a better fit for predicting GF based on the available data.



R=0,889; R^2=0,791; $\chi^2_{(5)}$=24,2; p=0,0002; Λ Prime=0,209

Fig. 5. Scatterplot of canonical correlation between Age&Weight and HRV&BP parameters (X-line) and glomerular filtration rate (Y-line)

An attempt to estimate the rate of glomerular filtration using only the blood pressure and HRV parameters was not successful enough, judging by the values of p and SE (Table 3 and Fig. 6).

Table 3. Regression Summary for GF

R=0,717; R^2=0,514; Adjusted R^2=0,290; $F_{(6,1)}$=2,3; p=0,099; SE of estimate: 17 mL/min

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(13)}$	p-level
Variables	r		Intercpt	-448	416	-1,08	0,301
Heart Rate, beats/min	**0,37**	2,948	1,525	6,352	3,287	1,93	0,075
ULF HRV, %	**0,28**	1,122	0,726	3,968	2,565	1,55	0,146
ULF HRV, $msec^2$	**0,24**	-1,246	0,760	-0,224	0,136	-1,64	0,125
Systolic BP, mmHg	**-0,43**	-0,461	0,244	-0,585	0,308	-1,89	0,081
Mode HRV, msec	**-0,35**	2,566	1,523	0,426	0,253	1,68	0,116
BPd2/BPd1 ratio	**-0,25**	-0,456	0,240	-165,8	87,31	-1,90	0,080

The table you provided shows the results of another multiple linear regression analysis, similar to the ones you saw in Tables 1 and 2. Here's a breakdown of how this method is used based on the information in Table 3:

1. Model Fit: This analysis investigates the relationship between the dependent variable, GF (Glomerular Filtration Rate), and this time, six independent variables: Heart Rate, ULF HRV (Ultra-Low Frequency component of heart rate variability in two forms: percentage and milliseconds squared), Systolic BP (Systolic Blood Pressure), Mode HRV (Mode of heart rate variability in milliseconds), and BPd2/BPd1 ratio (possibly a ratio of blood pressure values).
2. R-squared and Adjusted R-squared:

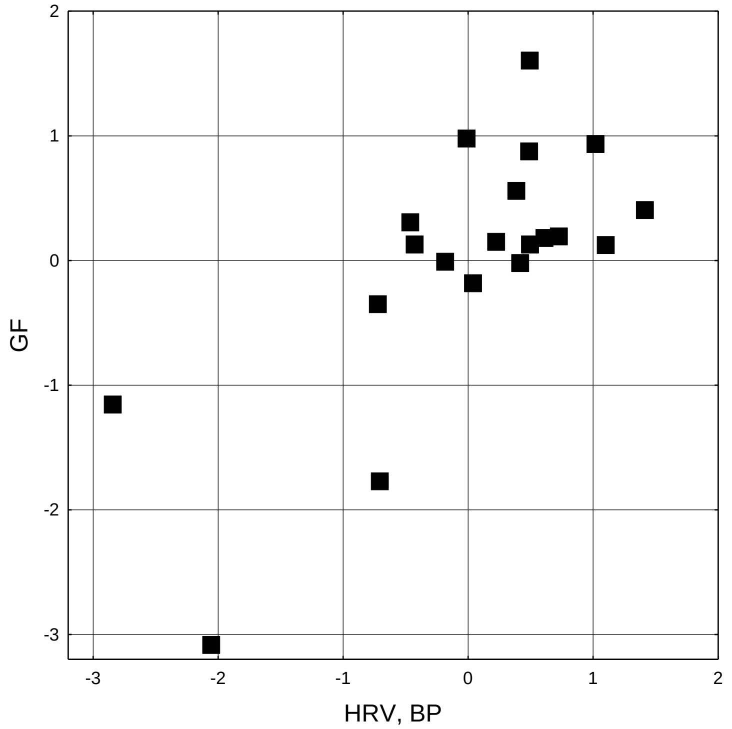
· R-squared (0.514): This value indicates a moderate positive correlation between the predicted GF values and the actual GF values. It's weaker than the models in Tables 1 (R-squared = 0.985) and 2 (R-squared = 0.791).

· Adjusted R-squared (0.290): This is considerably lower than R-squared, likely due to the higher number of independent variables (6 in this case). It suggests a weak to moderate explanatory power of the model.

1. Regression Coefficients (Beta): These coefficients represent the impact of each independent variable on GF, holding all other independent variables constant. Interpretations depend on the signs: positive for a positive association and negative for an inverse association. However, due to some high p-values (> 0.05), some associations might be due to chance.
2. Standard Errors and t-statistics: Similar to previous tables, these values assess the significance of each coefficient. A lower standard error indicates a more precise estimate, and a significant p-value (less than 0.05) suggests the coefficient is unlikely due to chance. Here, none of the p-values are definitively significant, so we cannot be confident about the individual effects of these variables on GF.

3. F-statistic and p-value: This test assesses the overall significance of the model. The F-statistic (2.3) and p-value (0.099) are not statistically significant (p-value is close to 0.10). This suggests the model, in its current form, does not explain a statistically significant portion of the variation in GF.

Overall, this table shows a multiple linear regression analysis where the model with six independent variables does not statistically explain the variation in GF. This might be due to weak individual effects of the included variables or because other relevant variables are missing from the model.



R=0,717; R^2=0,514; $\chi^2_{(6)}$=10,8; p=0,094; Λ Prime=0,486

Fig. 6. Scatterplot of canonical correlation between HRV and blood pressure parameters (X-line) and glomerular filtration rate (Y-line)

At the same time, we found that the rate of glomerular filtration correlates with the concentration of creatinine in daily urine to the same extent as with weight (Fig. 7).

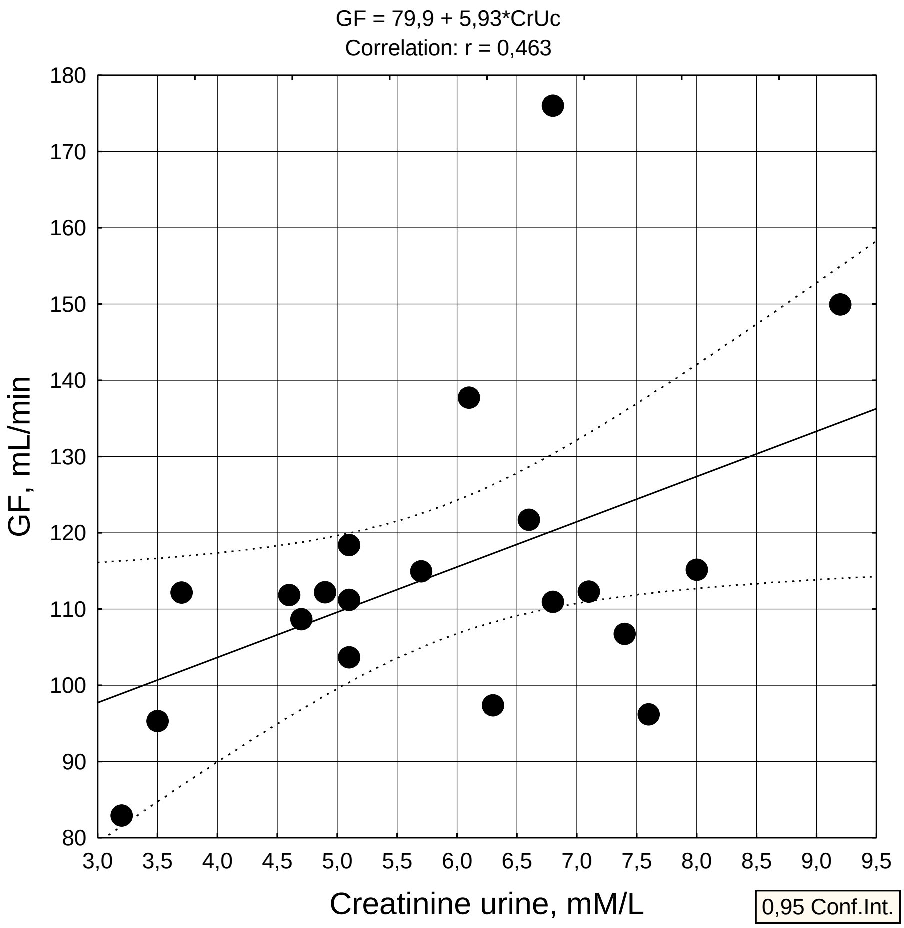


Fig. 7. Scatterplot of correlation between creatinine urine (X-line) and glomerular filtration rate (Y-line)

By including the last parameter in the regression model, we get the opportunity to estimate the rate of glomerular filtration with an error of only 12 mL/min (Table 4 and Fig. 8).

Table 4. Regression Summary for GF

R=0,909; R^2=0,837; Adjusted R^2=0,635; $F_{(10,9)}$=4,3; p=0,019; SE of estimate: 12 mL/min

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(9)}$	p-level
Variables	r		Intercpt	-465	307	-1,52	0,164
Creatinine urine, mM/L	**0,46**	0,713	0,181	9,136	2,323	3,93	0,003
Systolic BP, mmHg	**-0,43**	-0,639	0,202	-0,810	0,255	-3,17	0,011
LFnu HRV, %	**0,40**	0,955	0,398	1,560	0,650	2,40	0,040
LF HRV, %	**0,37**	-2,296	0,788	-3,650	1,252	-2,91	0,017
Heart Rate, beats/min	**0,37**	2,676	1,159	5,765	2,497	2,31	0,046
Mode HRV, msec	**-0,35**	2,199	1,173	0,365	0,195	1,88	0,093
BPs2/BPs1 ratio	**0,31**	0,741	0,254	304,9	104,6	2,91	0,017
VLF HRV, %	**-0,30**	-2,089	0,779	-2,628	0,979	-2,68	0,025
BPs3/BPs1 ratio	**0,28**	-0,635	0,276	-229,9	99,98	-2,30	0,047
ULF HRV, $msec^2$	**0,24**	-0,801	0,336	-0,144	0,060	-2,38	0,041

The table you provided shows the results of another multiple linear regression analysis, similar to the ones you saw in previous tables. Here's a breakdown of the method used based on the information in Table 4:

1. Model Fit: This analysis examines the relationship between the dependent variable, GF (Glomerular Filtration Rate), and this time, eleven independent variables:

· Physiological measurements: Creatinine urine, Systolic BP, LFnu HRV (Low Frequency component of heart rate variability, normalized unit), LF HRV (raw value), Heart Rate, Mode HRV (Mode of heart rate variability in milliseconds), Blood Pressure ratios (BPs2/BPs1, BPs3/BPs1), VLF HRV (Very Low Frequency component of heart rate variability), and ULF HRV (Ultra-Low Frequency component of heart rate variability in milliseconds squared).

1. R-squared and Adjusted R-squared:

· R-squared (0.837): This value indicates a strong positive correlation between the predicted GF values and the actual GF values. It's stronger than the model in Table 3 (R-squared = 0.514) but weaker than the models in Tables 1 (R-squared = 0.985) and 2 (R-squared = 0.791).

· Adjusted R-squared (0.635): This value is considerably lower than R-squared due to the high number of independent variables (11 in this case). It suggests a moderate explanatory power of the model.

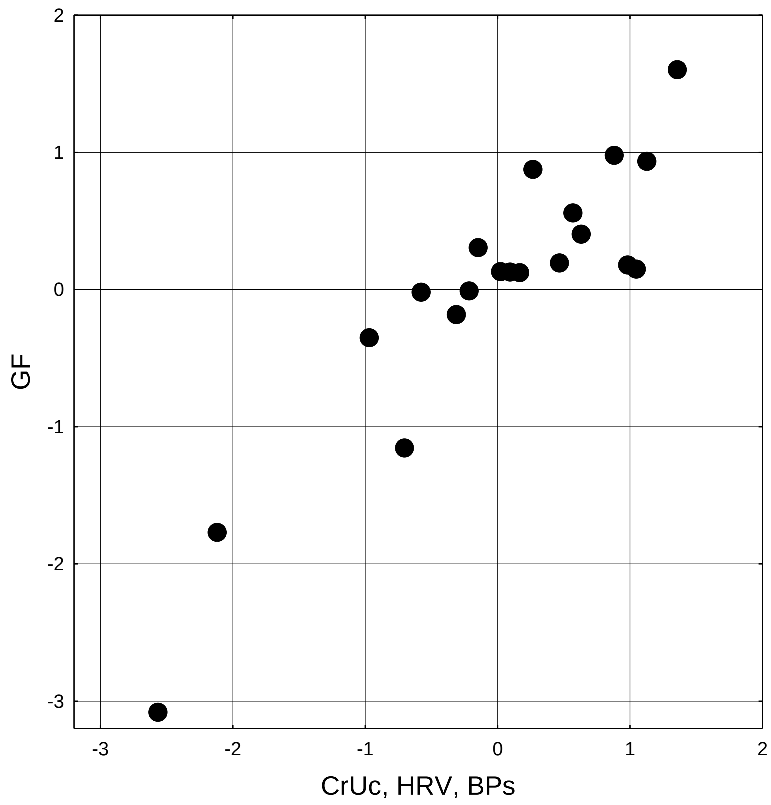
1. Regression Coefficients (Beta): These coefficients represent the impact of each independent variable on GF, holding all other independent variables constant. Interpretations depend on the signs: positive for a positive association and negative for an inverse association. However, some p-values are higher than 0.05, so some associations might be due to chance.

2. Standard Errors and t-statistics: Similar to previous tables, these values assess the significance of each coefficient. Here, several variables have significant p-values (less than 0.05), including Creatinine urine, Systolic BP, LFnu HRV, LF HRV, Heart Rate, BPs2/BPs1 ratio, VLF HRV, and BPs3/BPs1 ratio. This suggests these variables have a statistically significant influence on GF after accounting for the other variables in the model.

3. F-statistic and p-value: This test assesses the overall significance of the model. The F-statistic (4.3) and p-value (0.019) indicate the model is statistically significant (p-value is less than 0.05). This suggests the model, with all eleven variables, explains a statistically significant portion of the variation in GF.

Overall, this table shows a multiple linear regression analysis where the model with eleven independent variables explains a significant portion of the variation in GF. Several variables, including Creatinine urine, blood pressure measures, and heart rate variability components, have statistically significant relationships with GF.

However, it's important to note that a high number of independent variables can increase the risk of overfitting. This means the model might be too specific to this dataset and might not generalize well to unseen data. It would be helpful to compare this model with simpler models (e.g., the one in Table 1) to see if similar explanatory power can be achieved with fewer variables.



R=0,909; R^2=0,827; $\chi^2_{(10)}$=22,8; p=0,011; Λ Prime=0,173

Fig. 8. Scatterplot of canonical correlation between creatinine urine and HRV/blood pressure parameters (X-line) and glomerular filtration rate (Y-line)

CONCLUSION

Determination of glomerular filtration is used to assess the functional reserve of the kidneys [4,6] and the effectiveness of treatment of patients with kidney diseases [7]. In particular, balneotherapy has a significant effect not only on blood creatinine level, but also on HRV and blood pressure parameters, and even more pronounced [7]. Therefore, the estimation of glomerular filtration rate based only on the Cockcroft & Gault formula, with all due respect to the classics, is at least not much more accurate than the one proposed by us, besides, our method is completely non-invasive.

This study investigated non-invasive methods for estimating GFR, focusing on the relationship between GFR and various physiological parameters. Here are the key findings:

1. Creatinine Urine is a Strong Predictor of GFR:

· The analysis revealed a strong correlation between GFR and creatinine concentration in daily urine.

· Including creatinine urine in the regression model significantly improved the accuracy of GFR estimation, with an error of only 12 mL/min.

2. Age and Weight Influence GFR:

· The study confirms a previously known correlation between GFR and age and weight.

· Higher age was associated with lower GFR, while higher weight showed a positive association with GFR in this study.

3. Blood Pressure and HRV Parameters Show Potential:

· While not as strong as creatinine urine, some blood pressure (Systolic BP) and heart rate variability (HRV) parameters (LFnu HRV, LF HRV) showed a significant correlation with GFR.

· However, a model using only these parameters for GFR estimation was not statistically significant.

4. Complex Model with Multiple Variables Requires Caution:

· A model including multiple physiological measures (creatinine urine, blood pressure, HRV components) achieved a moderately strong explanation of GFR variation.

· Including many variables increases the risk of overfitting, where the model might not be generalizable to new data.

Overall, the study highlights the potential of using creatinine urine concentration in daily urine samples for non-invasive GFR estimation. Blood pressure and HRV parameters might also be informative, but further research is needed to optimize their use in GFR prediction models.

ACKNOWLEDGMENT

We express sincere gratitude to colleagues from sanatorium "Moldova" for help in conducting this investigation.

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all parent of participants the informed consent is got and used all measures for providing of anonymity of participants.

For all authors any conflict of interests is absent.

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