ORIGINAL ARTICLE

The ABC of linear regression analysis: What every author and editor should know

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Abstract

Regression analysis is a widely used statistical technique to build a model from a set of data on two or more variables. Linear regression is based on linear correlation, and assumes that change in one variable is accompanied by a proportional change in another variable. Simple linear regression, or bivariate regression, is used for predicting the value of one variable from another variable (predictor); however, multiple linear regression, which enables us to analyse more than one predictor or variable, is more commonly used. This paper explains both simple and multiple linear regressions illustrated with an example of analysis and also discusses some common errors in presenting the results of regression, including inappropriate titles, causal language, inappropriate conclusions, and misinterpretation.

Keywords: Causal language, linear models, prediction, regression analysis, reporting, residuals, statistics

Introduction

Linear regression analysis is a widely used statistical technique that can be applied in different fields, such as the natural sciences, biomedicine, engineering, and social sciences for building a model from a set of data on variables[1] and is based on correlation, which estimates the linear relationship between continuous variables,[2] most often by Pearson's or Spearman's coefficient, while the significance of the coefficient is expressed by *P* value. The coefficient of correlation shows the extent to which changes in the value of one variable correlate to changes in the value of the other. It is usually performed either to build a prediction equation, that is to predict the value of a variable, referred to as the dependent variable, from the value(s) of other variables, referred to as the independent variable(s), or to estimate the contributions of different independent variables to predicting the dependent variable.[1–5]

The first author of the present paper (KB) was recently asked to assist with statistics in an international medical project and to analyse a large sample of data. To better understand what was expected, the investigator sent several similar articles published in public-health journals, some of them highly rated. While reading these articles (especially the way the results had been presented and interpreted) several statistical errors in using regression analysis with large data sets were noticed—errors that could have been avoided if the authors, reviewers, and editors of those papers followed the existing guidelines on reporting statistical results.[3] This experience prompted us to write this article, which focuses solely on data analysis and does not discuss errors related to sampling and measuring, and seeks to guide researchers in using simple and multiple linear regressions and in reporting the results by explaining the techniques with suitable examples.

Simple linear regression

A simple linear regression, or bivariate regression, is used for predicting the value of one variable from only one other variable. The equation for a simple linear regression is as follows:[4]

Y' = A + BX

where *Y'* is the outcome variable (often called the criterion, the value of which is to be predicted), *A* is a constant (intercept), and *B* is the slope (regression coefficient) of *X*, which is the independent variable (predictor). Because regression is a model and therefore only an approximation of values, the predicted value (*Y'*) and the observed (*Y*) data values differ, and the difference constitutes the errors of prediction, or residuals.[4] The best-fitting regression line is the one in which the sum of squared errors of prediction (differences between the observed and mean value - residuals) is minimized. [1,4] The coefficient of determination (R^2) is the proportion of the variation in *Y* explained by the regression equation.[6] The proportion corresponds to the squared coefficient of correlation between the variables *X* and *Y* in simple linear regressions and to the squared coefficient of multiple correlation (R^2) in multiple regression and describes the extent(proportion) of the explained variation in the outcome variable *Y* (*Y'*).[5]

To illustrate a simple linear regression, we use a published data set (n = 974), interpret the results, and present the data. The example involves predicting the quality of renal function in patients with atrial fibrillation. [6]bleeding and mortality risks of mrEF in comparison to pEF and rEF in a cohort of 1000 non-valvular AF patients presenting in our institution during the period 2013-2018. Patients with mrEF presented with older age (P < 0.001 Renal function is usually expressed in terms of the estimated glomerular filtration rate (eGFR) using either MDRD (short for modification of diet in renal disease) or other similar formulas.[7]but this concentration is affected by factors other than glomerular filtration rate (GFR (The analyses and figures presented here have not been published before.)

To calculate a simple linear regression, such multipurpose programs as MS Excel can be used. Unfortunately, although the programs can calculate a regression, they cannot carry out the following steps that are necessary to evaluate the appropriateness of the method. Therefore, we used the statistical program MedCalc (https://www.medcalc.org/, ver. 19.4.0; MedCalc Software Ltd, Ostend, Belgium), because it is adapted for biomedical sciences and has a very good manual (https://www.medcalc.org/manual/); however, other open-source software packages, such as JASP (https://jasp-stats.org/), can also be helpful.

We started by evaluating the relationship between eGFR and haemoglobin (Figure 1, data file available online as supplementary material). Several conditions had to be met to arrive at meaningful and precise conclusions using linear regression. Both variables needed to be numerical rather than categorical, recorded on an interval or ratio scale, and have a linear relationship.[8] Linearity can be judged by observing the scatter plot of two variables. Figure 1 shows the linear relationship between eGFR and haemoglobin (correlation, or r=0.31, P<0.001) as the values on the *Y* axis rise proportionally to the values on the *X* axis. The continuous straight line in Figure 1 is called the *regression line* and is defined by the regression equation that goes through the means of *X* and *Y* and helps in visualizing this relationship, which may be difficult to perceive from the scatter plot alone. If the investigated relationship is linear, residuals should have a normal distribution and be randomly dispersed when evaluated on the scatter plot against the independent value. MedCalc software requires residuals to be saved as a new variable for them to be analysed further. By evaluating a histogram of the residual distribution (Figure 2A) and plotting the residuals against an independent variable (Figure 2B), we observed that these assumptions were fulfilled. Although no linearity exists between the numerical and binary variable, categorical variable is often included as independent variable into the analysis and usually is coded as either '1' and '0' if it has only two levels or as dummy variables if more than two. If coded as dummy variables, their differences from the reference level (usually the first subgroup in an alphanumerical order) are presented for each level of the variable. If a categorical variable with a large number of levels in ordinal order is used, the obtained results actually represent the trend of increase in the dependent variable over the levels of the independent variable used.

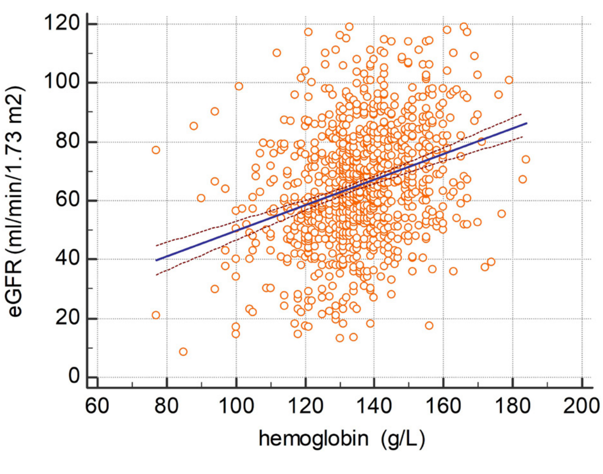


Figure 1. Scatterplot of estimated glomerular filtration rate (eGFR, mL/min/1.73 m²) and haemoglobin (g/L) with regression line and corresponding 95% confidence intervals (r = 0.31; P<0.001).

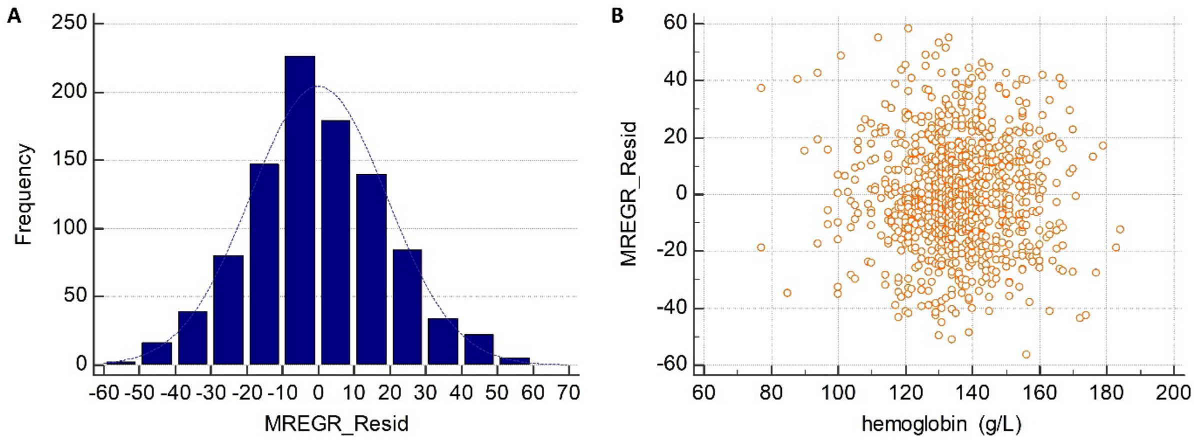


Figure 2: A) Histogram of distribution of residuals of linear regression investigating estimated glomerular filtration rate (eGFR) and haemoglobin relationship and B) scatter plot of residuals and haemoglobin values.

The output of the program is shown in Figure 3. First, we should look at the *P* value to ensure that the model fits (number 1 in Figure 3). In our example, the *P* value for the overall model was <0.001, which shows the analysis to be significant and that the model fitted and could have been interpreted; had *P* been >0.05, the regression is usually not interpreted. The next step is to look for the coefficient of determination (R^2) (number 2 in Figure 3). The closer the value of the coefficient to 1, the better the prediction. In our example, R^2 was 0.099, which enabled us to simply calculate the percentage of explained variation by multiplying the proportion with 100; therefore, 0.099 × 100 = 9.9%, which is the proportion of the variation in eGFR that can be explained by the haemoglobin value. Individual values of eGFR can then be predicted with the regression equation. In Figure 3, the regression equation is formed by using regression coefficients (number 3 in Figure 3). The regression coefficient represents the amount of change in the dependent variable per unit increase in the predictor variable. For example, if a patient has a haemoglobin level of 130 g/L, the eGFR can be calculated as follows: eGFR = 6.556 + 0.433 × 130 = 62.8. Note that the regression line with a 95% confidence interval is narrower in the middle and wider at the ends of data set, which means that the estimations are close to the actual values had they been measured and can be interpreted with more confidence if the input data correspond to the average values used in the study. Using values outside the range used in the study is called extrapolation and can yield unrealistic estimates and therefore should be avoided.

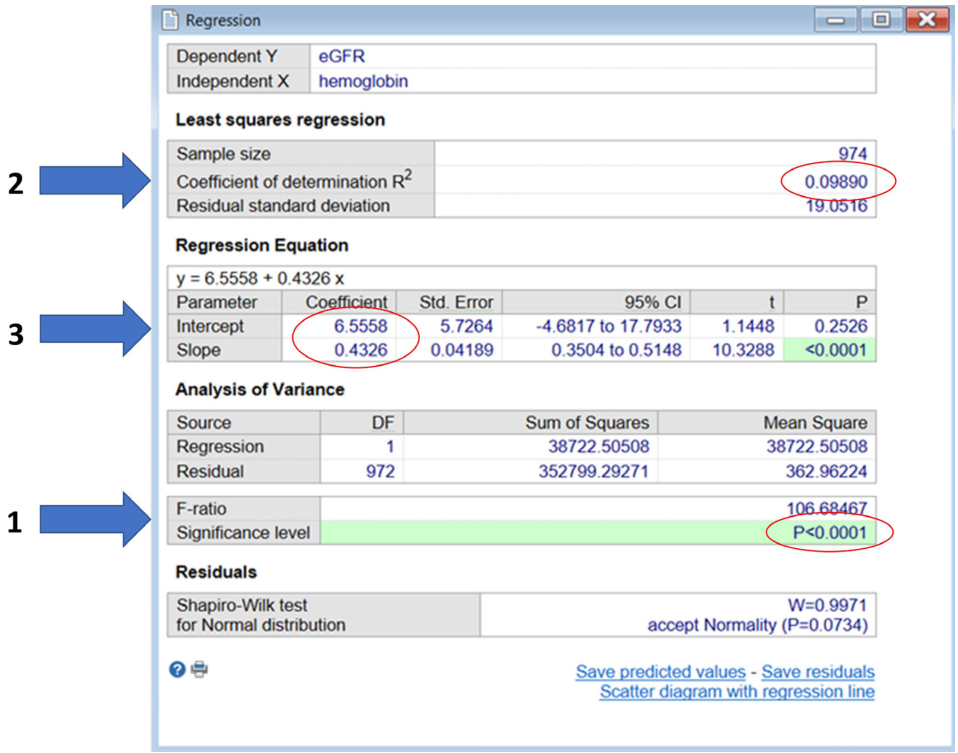


Figure 3. Output of 'multiple' (but actually simple) linear regression provided by MedCalc, a statistical program.

Multiple regression analysis

Multiple linear regression is a statistical method similar to linear regression, the difference being that a multiple linear regression uses more than one predictor or variable.[4,5]

When building a model, the investigator has to be aware of the assumptions behind multiple regression analysis.

Assumptions in multiple regression analysis

Multiple regression analysis is a parametrical statistical method: it requires that the dependent variable be numerical (continuous) on an interval or ratio scale, that the relationship between variables be linear, and that some other assumptions also be satisfied (Table 1).[9,10] The linearity is usually checked by correlating the variables using Pearson product moment correlation coefficient and looking at the scatter plot.[11–13] However, the linearity could be even better estimated by looking at the graph of residuals.[10] Normality and homoscedasticity presume identical and independent distribution of residuals with a zero mean and constant variance. The residual plot against the independent variable should show a random pattern (equally scattered and not forming a U-shaped curve) and the variability of residuals should be relatively constant across all values of the independent variable. Also, the residuals should be approximately normally distributed.[11] Formal statistical testing of distribution normality is more likely to yield significant results implying non-normal distribution in a large data set (as all statistical tests in large data sets tend to do), automatically invalidating the assumptions behind the analysis. It is thus acceptable to check the histograms of distribution of independent variables and residuals visually to ascertain whether we are dealing with unimodal and not highly skewed distributions (especially if dealing with larger data sets comprising, for example, a few hundred or more cases). With large samples, the requirement for normal distribution of residuals is less stringent because of the central limit theorem. Also, assumptions for multiple regression are not met if any two variables are highly correlated, that is the condition of multicolinearity is not satisfied.

Regarding the required sample size, when choosing a number of independent variables, keep in mind that a minimum of 10 (or even up to 20) subjects are needed for each variable.[11] Therefore, if a criterion is explained by three predictors, at least 30–60 subjects should be included (a free A-priori sample size calculator for multiple regression available at https://www.danielsoper.com/statcalc/calculator.aspx?id=1).[11]

Table 1. Assumptions of multiple regression analysis

Assumption	Assumption met if
Dependent variable (criterion)	Dependent variable has to be on a continuous, interval, or ratio scale.
Independent variables (predictors)	Multiple regression presumes including more than two independent variables as predictors. Predictors are mostly continuous, dichotomous, or binary variables (coded with '0' and '1').
Linearity, normality, and homoscedasticity	For checking linearity, normality, and homoscedascity, use a residuals plot. Residuals have to be distributed with a zero mean and constant variance.
Multicollinearity	Only those predictors that are not highly correlated are to be included in the analysis.
Number of predictors	The number of predictors included in the analysis is dependent on the sample size. Online tools are available to ascertain the minimum sample size required.

Multiple linear regression

The formula for multiple regression is similar to that for simple linear regression; moreover, the value of the criterion is a linear combination of predictors. The formula for multiple linear regression is as follows:

$$Y' = B_1X_1 + B_2X_2 + ... + B_nX_n + A$$

where Y' is the criterion, X_1 to X_n are the predictor scores (X_1, score of the first variable; X_2, score of the second; etc.), B_1 to B_n are regression coefficients (similar to the slope in simple regression), and A is the intercept. [1]

Each predictor has its own weight that depends on the size of the regression coefficient (B) or standardized standardized beta (β) coefficients.[4,14] The regression coefficient represents the amount of change in the dependent variable for each unit increase in the predictor variable.[11,14] The result of a multiple regression is the optimal prediction of the criterion from two or more continuous (or dichotomous or binary) predictors. The coefficient of multiple correlation 'R' is the correlation of all predictors with the criterion, whereas the coefficient of multiple determination 'R^2' describes the proportion of variance explained by predictors varying from 0 to 1 (0% to 100%). The closer the value to 1, the better the prediction. [1,5,14]

Contributions of the independent variables to predict the criterion can be interpreted by using the multiple correlation coefficient and standardized beta (β) coefficients. The contribution of a predictor (effect size of a variable) has to be presented with a standardized β coefficient to be comparable between variables. B coefficients that are routinely obtained by MedCalc are not standardized and are scale dependent and therefore unsuitable for this purpose. To obtain standardized β coefficients in MedCalc, you need to standardize input data first in MS Excel. Despite the name, you do not standardize the coefficients after the analysis is done; you standardize input variables by subtracting the mean from every observation and dividing it by the standard deviation and thus obtain standardized variables with a mean of 0 and standard deviation of 1. To calculate the individual contribution of a variable as a percentage, we use squared semi-partial coefficients of correlation (sr^2), which are provided by MedCalc. Semi-partial r^2 provides information on what proportion of the criterion variable can be explained with this particular predictor while the rest of the correlations are excluded.

To continue with the example with regard to predicting renal function quality in the multivariable context. In addition to haemoglobin, we included in the model other clinical variables with potential associations with eGFR, such as body mass index, left ventricle ejection fraction, age, and presence of coronary artery disease. All these parameters can either reflect on renal function, be affected by it, or share some common risk factors and pathophysiologic mechanisms—we cannot judge *causal* relationships between investigated variables; we can only assess whether *significant* relationships exist. The variable eGFR is the criterion, whereas the other variables are considered predictors and entered as independent variables into the statistical program. The program output is shown in Figure 4 and, as explained in the text below, two outputs are given: one with existing data set (Figure 4A) and one with standardized input data (Figure 4B). The non-standardized data allow us to calculate eGFR from raw data, whereas standardized data allow us to compare effect sizes.

The residuals in the above example were normally distributed, suggesting that the assumptions were met. Also, a correlation matrix between continuous variables is part of the program output (Figure 4) and helps us to understand the level of mutual correlations that exist between used predictors, that is to assess multicolinearity. We were unable to put all the variables into a linear correlation (presence of coronary artery disease (CAD = 1) is a binary variable and has to be coded in the program as '0' if absent and '1' if present) and some of the investigated variables had low coefficients of correlation, implying that a linear relationship actually does not exist (correlation coefficients between eGFR and body mass index and between eGFR and left ventricle ejection). However, there are scientifically plausible reasons to include those variables into the analysis, so we decided to keep them.

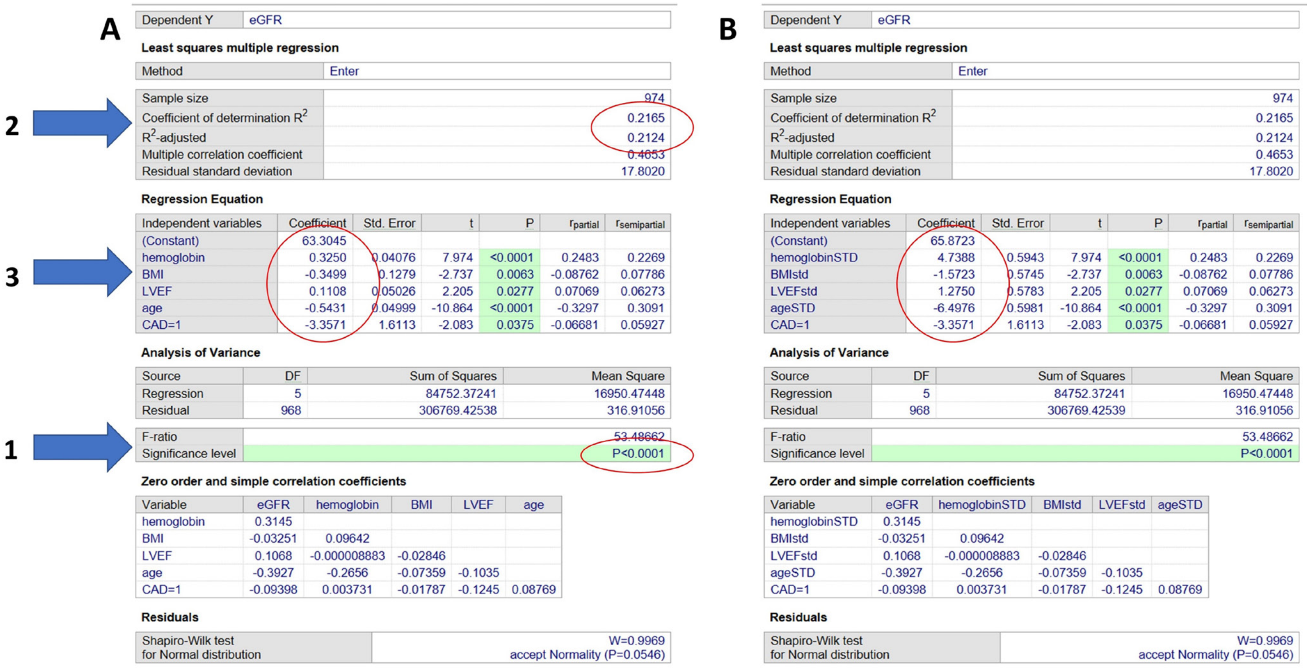
As in simple linear regression, first you have to check if the model fits (number 1 in Figure 4). Because the overall *P* value for the regression is significant, we can proceed with interpreting the results. The second step is to look at the coefficient of determination (R^2, number 2 in Figure 4). In our example, R^2 is 0.217, meaning that 21.7% of the eGFR is explained with this model. Because this coefficient increases with the number of variables included in the model, it is advisable to present the adjusted coefficient of multiple determination (adjusted for the number of variables included in the model). $R^2_{adjusted}$ was 0.212, that is 21.2% of the eGFR is explained.

We further considered which variables explain, or are associated with, eGFR. We can search for the answer to that question under number 3 in Figure 4. As can be observed, all of the included variables had statistically significant independent relationships with eGFR. We can speculate that these variables might have different independent biological mechanisms behind the mathematical relationship. Thereby, all variables should probably be considered separately if we wish to understand eGFR in patients with atrial fibrillation. Individual contributions of particular predictors differ in the standardized β coefficients (Figure 4B), and semi-partial correlation coefficients (Figure 4A and 4B) provide the same output, because the data were not standardized for the first analyses but were standardized for the second one. Age and haemoglobin seem to explain the highest proportion of the eGFR. Furthermore, different directions of predictors with dependent variables are present, indicating that patients who experienced higher haemoglobin and left ventricle ejection fraction were more likely to have higher eGFR (positive B and β coefficients), whereas patients with higher body mass index, older patients, and those with coronary artery disease were more likely to have lower eGFR (negative B and β coefficients). The variable CAD = 1 beta coefficient is the adjusted mean difference in eGFR between the two groups, meaning that the group in which coronary artery disease was present had lower eGFR (−3.35 points, or 3.35%).

From the data (number 3 in Figure 4A), we can construct a regression equation for predicting the eGFR from the given data. For example, if we have a 65-year-old patient with atrial fibrillation but without coronary artery disease, with a haemoglobin level of 130 g/L, a body mass index of 30, and left ventricle ejection fraction of 60%, the patient's eGFR can be easily calculated as follows: $eGFR = 63.3045 + 0.325 \times 130 - 0.3499 \times 30 + 0.1108 \times 60 - 0.5431 \times 65 - 3.3571 \times 0 = 66.4$.

One can consider the obtained adjusted R^2 to be modest, because our model explained only 21% of the eGFR variance. However, that small percentage does not invalidate the observations, which may have important clinical repercussions and can help in planning future studies on the topic. As shown, all the investigated variables seem to contribute independently to eGFR prediction. We did not recognize or could not measure major predictors of eGFR that would result in higher R^2 (we deliberately chose not to consider such parameters of renal excretion function as urea and creatinine, because that would have resulted in a 'self-fulfilling prophecy' of little real interpretation value). It was also possible that some variables have no statistical significance if analysed in a multivariable context. Such variables either truly do not have independent predictive properties or our sample might have been too small for such analysis. Anyhow, such variable can yet be considered in a model if its inclusion increases the adjusted R^2 substantially. If the analysis is repeated with and without such additional predictor(s) and if the variable is not considered as a mandatory adjustment, then it should probably be excluded from the equation.

Further exploratory analyses investigating whether interactions between different independent variables and the dependent variable exist can be undertaken to better understand the given data set. Interaction is present when the degree of association between two variables changes depending on the value of the third one, that is when one variable moderates the relationship between two other variables. The present article does not deal with this issue in more detail because the complexity of the theme and the lack of space do not permit a more detailed discussion; however, we plan to do so in future.



A

Dependent Y	eGFR

Least squares multiple regression

Method	Enter

Sample size	974
Coefficient of determination R^2	0.2165
R^2-adjusted	0.2124
Multiple correlation coefficient	0.4653
Residual standard deviation	17.8020

Regression Equation

Independent variables	Coefficient	Std. Error	t	P	$r_{partial}$	$r_{semipartial}$
(Constant)	63.3045					
hemoglobin	0.3250	0.04076	7.974	<0.0001	0.2483	0.2269
BMI	-0.3499	0.1279	-2.737	0.0063	-0.08762	0.07786
LVEF	0.1108	0.05026	2.205	0.0277	0.07069	0.06273
age	-0.5431	0.04999	-10.864	<0.0001	-0.3297	0.3091
CAD=1	-3.3571	1.6113	-2.083	0.0375	-0.06681	0.05927

Analysis of Variance

Source	DF	Sum of Squares	Mean Square
Regression	5	84752.37241	16950.47448
Residual	968	306769.42538	316.91056

F-ratio	53.48662
Significance level	P<0.0001

Zero order and simple correlation coefficients

Variable	eGFR	hemoglobin	BMI	LVEF	age
hemoglobin	0.3145				
BMI	-0.03251	0.09642			
LVEF	0.1068	-0.000008883	-0.02846		
age	-0.3927	-0.2656	-0.07359	-0.1035	
CAD=1	-0.09398	0.003731	-0.01787	-0.1245	0.08769

Residuals

Shapiro-Wilk test for Normal distribution	W=0.9969 accept Normality (P=0.0546)

B

Dependent Y	eGFR

Least squares multiple regression

Method	Enter

Sample size	974
Coefficient of determination R^2	0.2165
R^2-adjusted	0.2124
Multiple correlation coefficient	0.4653
Residual standard deviation	17.8020

Regression Equation

Independent variables	Coefficient	Std. Error	t	P	$r_{partial}$	$r_{semipartial}$
(Constant)	65.8723					
hemoglobinSTD	4.7388	0.5943	7.974	<0.0001	0.2483	0.2269
BMIstd	-1.5723	0.5745	-2.737	0.0063	-0.08762	0.07786
LVEFstd	1.2750	0.5783	2.205	0.0277	0.07069	0.06273
ageSTD	-6.4976	0.5981	-10.864	<0.0001	-0.3297	0.3091
CAD=1	-3.3571	1.6113	-2.083	0.0375	-0.06681	0.05927

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Variable	eGFR	hemoglobinSTD	BMIstd	LVEFstd	ageSTD
hemoglobinSTD	0.3145				
BMIstd	-0.03251	0.09642			
LVEFstd	0.1068	-0.000008883	-0.02846		
ageSTD	-0.3927	-0.2656	-0.07359	-0.1035	
CAD=1	-0.09398	0.003731	-0.01787	-0.1245	0.08769

Residuals

Shapiro-Wilk test for Normal distribution	W=0.9969 accept Normality (P=0.0546)

std = standardized

Figure 4: Results of multiple regression using MedCalc. A) data as originally recorded and B) data standardized to obtain standardized β coefficients. eGFR, estimated glomerular filtration rate; BMI, body mass index; LVEF, left ventricular ejection fraction; CAD, coronary artery disease.

Some common areas of errors in presenting regression analysis

Adequate guidelines are available from the EQUATOR network for almost every type of article. These include guidelines for reporting statistics, for example the 'SAMPL Guidelines for Biomedical Journals' written by Tom Lang and Doug Altman, which also discuss the reporting of regression analysis in detail.[15] We propose a quick checklist that can help authors and editors in evaluating multiple regression analyses.

Table 2. A checklist for multiple regression analysis

Question	Answer
Does the title or main text use causal language appropriately?	The title of an article in which simple or multiple regression is used contains words such as 'correlation', 'relation' and 'association' but avoids words such as 'influence' or 'cause'.
Are statistical assumptions for multiple regression satisfied?	See Table 1.
Are variable transformations used sensibly?	Check whether the assumptions are met after carrying out a variable transformation: If the relationship between variables needs to be linear, a graph of the transformed variable should reflect that.
Is the analysis significant?	If the analysis is not significant (*P*<0.05), the regression cannot be interpreted.
Is the interpretation of regression correct?	Depends on the R^2 size where higher values indicate better model fit and prediction.

Area 1: Titles of the articles with multiple regression analysis and the use of causal language in the manuscripts

Titles are supposed to attract readers and clearly represent the paper's content.[16] Most of the clinical data obtained and analysed by common contributors are observational and not interventional. Such studies (either retrospective, cross-sectional, or prospective) cannot *prove* causality of the investigated relationships but only assess whether variables are related to each other. One should bear in mind that even if two variables have a statistically significant relationship, neither of the two variables needs to be the cause of the change in the other: a third variable that can affect both may be unrecognized and not measured in the study. One such example is the discovery of the mechanism behind the tendency to bleed seen in patients with myeloprofliferative neoplasms and high platelet counts that are a direct consequence of tumour production. Although this relationship seems to be counterintuitive, it is well described in the literature and it was not easy to understand before the discovery that secondary depletion of von Willebrand factor (glicoprotein crucial for platelet adhesion to damaged sites in the vasculature) occurs because of the high number of circulating platelets.[17]

Therefore, the title of an article in which simple or multiple regression is used should contain words such as 'correlation', 'relation', and 'association' but avoid words such as 'influence' or 'cause' because they imply, possibly incorrectly, a causal relationships between variables.[18,19] Some authors consider the term 'correlation' more appropriate than the term 'association' because the latter is usually used for expressing the relationship between categorical variables.[20] The distinction, however, is debatable. The terms 'multivariate' and 'multivariable' are often used: a multivariable model refers to an analysis with one dependent and two or more (multiple) independent variables whereas a multivariate analysis refers to an analysis with more than one outcomes (for example repeated measures) and multiple independent variables.[21]

JAMA editors strongly suggest avoiding causal language except in randomized controlled trials (https://jamanetwork.com/journals/jama/pages/instructions-for-authors#SecReportsofSurveyResearch). Furthermore, they also advise describing methods and results using the words 'association' and 'correlation' and to avoid avoiding words that imply a 'cause-and-effect' relationship. The same principle can be applied to studies where regression analysis is used as a statistical method.

Area 2: Assumptions for calculating multiple regression

A long time ago, the medical editor and writer Tom Lang wrote that "every scientific article that includes statistical analysis should contain a sentence confirming that the assumptions on which the analysis is based were met."[10] It is important to notice that violating the assumptions (or ignoring them) makes the estimates obtained by regression analysis less reliable, possibly unreliable, or even false. Real-life clinical data rarely meet all the assumptions that multiple regression requires. However, if authors decide to use this method, it is fair to make attempts to limit the violations and to recognize the limitations of their work so that readers (and editors) can judge the work objectively. Furthermore, other statistical analyses may be chosen instead, if the main assumptions are not met.

It should be noted that linearity cannot be checked for binary variables and that non-linearly correlated variables might be significant predictors of the criterion of interest, as described in our example. Authors should be guided by logic and scientific plausibility. If the relationship between the dependent and the independent variables is not linear, variables can be transformed,[9] and authors are advised to consider categorizing the predictors if they believe there is a non-linear relationship to overcome the breach of linearity. By transforming either the dependent or the independent variable we can obtain better coefficients of determination and better linearity. Possible transformation options include creating an exponential model (testing different logarithms of dependent variables), a quadratic model (taking the square root, the 3rd root, etc of an independent variable), a reciprocal model (1/dependent variable), a logarithmic model (different logarithms of the independent variable), or a combination of models (combining different types of transformations for both dependent and independent variables). We would like to point out that a simple one-time transformation of the dependent variable (using logarithmic transformation, for example), without assessing whether assumptions are improved by the process, does not make sense and does not suddenly make the regression unbiased and acceptable. However, this is a phenomenon often encountered in medical journals because many authors consider this to be a great move to checkmate the reviewers. If authors, editors, or reviewers realize that the assumptions have not been met and therefore ask for solutions, other methods of regression can be suggested or other statistical methods can be used. In such cases, a logistic regression (if authors wish to base their conclusions on the prediction that the dependent variable odds are higher or lower than something else) or a Poisson regression (in dealing with numerical data that are usually highly skewed) can be used for the same purpose and can yield similar conclusions. Authors can still insist on using a multiple regression and choose to ignore the above-mentioned points; however, in that case, they are concerned mainly with describing their data set and not in making inferential conclusions on the population in general.

The point is not to include all measured variables in the model but only those clinically meaningful that fit well.[5] It is a common practice that it is appropriate to include variables in the multivariable model. It is recommended that recognized predictors described in the literature be used, as well as variables that show significant univariate associations or that have clinically meaningful biological relationships despite not being significantly related in the current data set. Furthermore, variables such as age and sex can be considered mandatory adjustments if the sample size permits it. It is possible that the number of variables that need to be considered is much higher than the possibilities afforded by sample size. In that case, the authors must consciously limit their analyses or perform automatic stepwise model building, letting the computer chose the best predictors. However, this does not absolve authors of the responsibility of interpreting how and why the variables in the final model were chosen.

Area 3: Significance of regression

A common and frequent mistake is to interpret regression models that are not significant. The results of regression can be interpreted by the strength of the evidence: a small P value suggests stronger evidence for rejecting the null hypothesis. An arbitrary value of P, namely 0.05, is very common in the literature, and $P<0.01$ is considered as strong evidence and $P<0.001$ very strong evidence whereas $P<0.1$ can suggest only a possibility or weak evidence (check assumptions for the analysis).

Area 4: Interpretation of regression: coefficient of determination 'R^2' and beta coefficients

There are different models of regression and sometimes investigators or authors think that if they choose a bunch of variables, at least some of them will eventually prove significant. The same applies to choosing a different approach to model building (backward or forward stepwise regression), which can yield different results. This practice is called *P*-hacking and it is definitely something to be avoided.[22] The analysis could even be statistically significant because of the sample size or the number of variables without having a real interpretation value.

When using multiple regression to derive the prediction equation, to ensure that the regression is not only significant ($P<0.05$) but also interpretable, the coefficient of multiple regression 'R' and the coefficient of determination 'R^2' (preferably adjusted for sample size) should be presented along with significance. If R^2 is 0.10, this means that 10% of the measured variance can be explained with the independent variables (predictors). Moreover, if there are 15 predictors and $R^2 = 0.10$, the individual contribution of the predictor could be around 0.1%–2%, which is probably not clinically significant.

When using multiple regression to determine if specific predictors remain mutually independent contributors to the dependent variable, significance of particular predictors is assessed in the same manner as the regression model ($P<0.05$) and only independent variables that remain statistically significant can be interpreted as mutually independent predictors. Often, only one variable remains statistically significant in the model. It is then erroneous to claim that this variable bears statistically independent predictive properties in comparison to others that were analysed: it is more likely that collinearity exists, and the predictive properties of other variables were nullified by the variable that remained significant in the model. It is possible that the model was controlled for variables that did not have predictive properties in the first place but were included in the model were included in the model to satisfy some standard requirements (for example age and sex). It is also possible that the sample was too small and there is not enough statistical power to demonstrate a truthful relationship that perhaps occurs in nature. If a model was created through automatic stepwise building, conclusions regarding independent contributions can be based only on variables that remained significant and remained in the final model. Thus, a commonly encountered claim, namely that a variable is independently associated in comparison to other variables that did not make it to the final model or did not remain statistically significant, is faulty.

Conclusion

The purpose of multiple regression is to explore a set of predictors (independent variables) and either find their best combination to predict the value of a criterion (dependent variable) or to evaluate the independent contributions of each predictor. Although referred to as dependent and independent, these variables are in fact in relation, and explanations of causality should be avoided.[5] If and only if the analysis is significant ($P<0.05$), squared multiple correlation coefficient and other coefficients can be explained.

Journal editors should offer better guidance on statistical methods in their instructions to authors. We are aware that not every journal has a statistical editor, although this is advised. Statistical peer review should be part of the peer-review process to reduce waste in research[23] and to enhance the quality of articles in biomedical publications.

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