RESEARCH LETTER

blood advances

TO THE EDITOR:

Correcting the record on anemia of aging: a statistical reanalysis

Geoffrey G. Fell,[1] David G. Nathan,[2-4] and Donna S. Neuberg[1]

[1]Data Science and [2]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA; [3]Division of Hematology/Oncology, Boston Children's Hospital, Boston, MA; and [4]Department of Pediatrics, Harvard Medical School, Boston, MA

In older patients, anemia identified based on the measurement of circulating hemoglobin concentration is of unknown causes in nearly half of the reported cases.[1] It is known as the anemia of aging. Concerned that such a diagnosis was likely illusory in the 1960s, D.G.N. measured the total red blood cell volume (TRBCV) related to the body weight, total body water (TBW), and total exchangeable potassium (the latter 2 measurements are functions of lean body mass [LBM]) in 2 groups of volunteers of very disparate ages.[2] The study was based on the widely held understanding that the metabolism and oxygen consumption of the LBM are the central drivers of erythropoiesis. Thus, the TRBCV may be a direct function of the size and oxygen consumption of the LBM. It is well established that the LBM declines with age, whereas the ratio of visceral to skeletal LBM increases.[3]

The young subjects were novitiate residents in a monastery. The same data were also obtained from a group of older Spanish American War veterans. Data for TRBCV, body weight, TBW, and intracellular water (ICW) were assessed using simple linear regression, examining each pair of measured variables separately for younger and older subjects. Comparisons of the slope between groups were performed only if the variability of the 2 groups did not differ significantly. These results were striking. The older patients were, if anything, polycythemic when the TRBCV was related to LBM. However, variances were disparate between the 2 groups. Although the paper was published in *Blood*, it was not sufficiently definitive. The illusion persists and is reinforced by the fact that the frequency of clonal hematopoiesis is age dependent.[4] Concerned that the term anemia of aging should be abandoned and replaced with anemia in aging and to assess the robustness of this finding from 1962, we reanalyzed the data using relatively modern methodology and computational resources.

Although the original paper data files were no longer available, G.G.F. was able to reconstruct the data with acceptable precision using the method of Guyot[5] applied to the excellent graphics included in the original publication. Data for TRBCV, body weight, ICW, and TBW were obtained for all 19 seminarians and for a subset of 49 veterans who participated in the intracellular water assessment. Multiple logistic regression models were fit using the lm package in R (version 4.2.2) to predict TRBCV using these variables, with the addition of an indicator variable for older veterans to enable us to assess the impact of age on the predictive model.

Inclusion of TBW in our models led to a statistically significant model for TRBCV but excluded body weight and ICW as significant components of the model. The model with TBW explained the variability in the TRBCV significantly more than the model with ICW alone. This was likely because of the use of bromide dilution, which is an inexact methodology, to measure extracellular water. The addition of a binary variable for age group was retained in our final model, which appears in Table 1, to demonstrate the absence of a significant effect. The point estimate of the slope for TBW was 52.5 ($P = 5.0e{-}10$). Older age, as a factor, did not contribute significantly to the model, with a point estimate of shift of 101.1 ($P = .348$). This model demonstrated 58% variability in the TRBCV in this group of 68 subjects.

In summary, the original analyses of these data were constrained by the absence of computational resources that would readily permit multivariable modeling and by the inability to address differential

Submitted 27 March 2023; accepted 31 March 2023; prepublished online on *Blood Advances* First Edition 4 April 2023; final version published online 17 July 2023. https://doi.org/10.1182/bloodadvances.2023010311.

Data are available on request from the corresponding author, David G. Nathan (david_nathan@dfci.harvard.edu).

Table 1. Multiple regression model for TRBCV as a function of extracellular water, intracellular water, and age group

	Coefficient	SE	t	*P* (>|t|)
Intercept	−271.70	348.03	−0.781	.438
TBW	52.50	7.18	7.307	5.0e−10
Older age	101.10	107.00	0.945	.348

Residual SE: 273.1 on 65 DF.
Multiple R^2: 0.5889 and adjusted R^2: 0.5762.
F-statistic: 46.55 on 2 and 65 DF; *P*-value 2.85e-13.
DF, degrees of freedom; SE, standard error; t, t-statistic.

variability between seminarians and veterans. We resolved these issues by using multiple logistic regression modeling. We found that a single model fit both younger and older patients. Our results do not suggest that the TRBCV is the same in the 2 groups of subjects but that the relationship between the TRBCV and TBW is similar for the 2 groups of subjects. Figure 1 shows that the measurements of both TRBCV and TBW in the older subjects are indeed lower than those in the younger subjects, but this does not alter the relationship between TRBCV and TBW. LBM and its dependent TRBCV decrease simultaneously in older patients. The higher variance in the older subjects suggests that many of the older individuals actually produce more than the expected number of red blood cells, presumably because of low oxygenation, and some produce fewer, likely because of occult renal atrophy. However, the broad relationship between the red blood cell production and LBM is preserved even in older patients.

This reanalysis helps confirm that the anemia of aging is indeed an illusory terminology. The TRBCV remains governed by LBM throughout the human lifespan. Erythrocyte indices measured in clinical laboratories vary more widely in older patients than in younger patients, likely because of variations in the plasma volume, oxygenation, and renal function. However, age does not influence the fundamental basis of human erythropoiesis.

Contribution: G.G.F. and D.S.N. were the biostatisticians who retrieved the data from the original manuscript and applied both regression and modeling methods to the data; and D.G.N. wrote the manuscript.

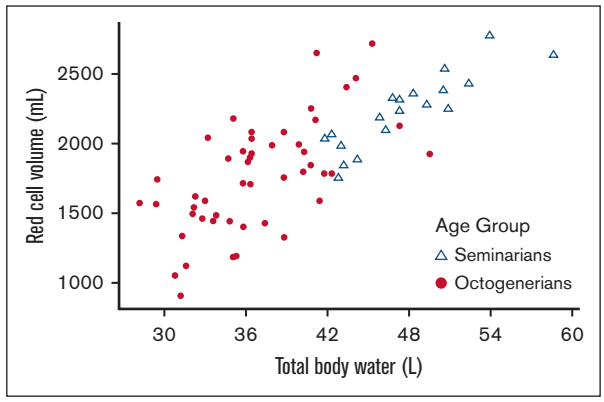

Figure 1. TBW and TRBCV in younger and older patients.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: David G. Nathan, Harvard Medical School, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215; email: david_nathan@dfci.harvard.edu.

References

1. Guralnik J, Ershler W, Artz A, et al. Unexplained anemia of aging: etiology, health consequences, and diagnostic criteria. *J Am Geriatr Soc*. 2022;70(3):891-899.
2. Piomelli S, Nathan DG, Cummins JF, Gardner FH. The relationship of total red cell volume to total body water in octogenarian males. *Blood*. 1962;19(1):89-98.
3. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging, and body composition study. *J Gerontol A Biol Sci Med Sci*. 2006;61(10):1059-1064.
4. Jaiswal S, Ebert BL. Clonal hematopoiesis in human aging and disease. *Science*. 2019;366(6465):eaan4673.
5. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12(12):9.