Clinica Chimica Acta 510 (2020) 26–27

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

On the use of lymphocyte to neutrophil ratios in laboratory medicine

In recent years, clinical laboratory medicine has been confronted with a new hype: the use of the lymphocyte to neutrophil ratios (LNR) in peripheral blood as a diagnostic and a prognostic basic test for almost any disease. The clinical use of such ratios per se is a bit remarkable: the relative error of a ratio is approximately the sum of the relative errors of the nominator and the denominator. Moreover, both neutrophil and neutrophil counts are characterized by an important intra- and inter-individual variation. For lymphocytes, the within–individual variation (CVw) is 10.4%, the between-individual variation (CVb) 27.8%, for neutrophils, CVw and CVb are even 16.1% and 32.8% [1]. Ingestion of a meal can be followed by a post-prandial increase in granulocyte count of ± 1500/mm^3. Smoking affects leukocyte counts [2]. Air travelling has a long lasting effect on neutrophil count [3]. Reference ranges for neutrophil and lymphocyte counts are therefore broad. Ethnicity is a major additional confounder: e.g. people from African descent typically have a higher granulocyte count than Caucasians [4,5]. In areas with peoples of African descent, race-specific white blood cell and white blood cell differentiation reference intervals must be provided for proper diagnosis and clinical research. Results from a well-defined population are not always expandable to a wider universe.

Despite the fact that basic characteristics of the analyte are far from ideal to be considered as a clinically useful biomarker, the popularity of the topic is rapidly rising: from 871 papers in 2015 to 1819 papers in 2019 (Table 1) [6]. Many paper suggest LNR for monitoring and diagnosis in all kinds of cancer and infections (e.g. COVID-19). Remarkably, most diagnostic studies report excellent values for sensitivity and specificity for a broad variety of conditions, which would mean a violation of Bayes' law. In many studies, receiver operating characteristics curves are derived from a rather artifical comparison between a specific disease group versus a healthy control group, which yields an optimistic view which differs from clinical reality. Such approach may ultimately increase the probability of unwarranted conclusions.

The reasons for this rapid growth are a combination of the low threshold of the technology (LNR often being a part of a patient's routine laboratory examination) and the apparently endless list of potential clinical applications, which has created an eldorado for less priviliged authors. It is clear that the common denominator for the observed alterations in the LNR ratio in disease is inflammation. But as an inflammation marker, LNR (characterized by a broad reference range, and a relatively small dynamic range) is by far inferior to class I acute phase reactants like C-reactive protein or procalcitonin (with a shorter response time and a dynamic range spanning multiple orders of magnitude).

As conventional hemograms generated by modern hematological analyzers contain a lot of basic parameters and derived indices, similarly the platelet-to-lymphocyte ratio, and the lymphocyte-to-monocyte ratio have been proposed. This evolution even paves the way for future exploration of all kinds of diagnostic and prognostic ratios [7]. The scientific community should be critical about this evolution in low-threshold science and consider the potential consequences of spreading this type of study results to a broader public.

Table 1
Number of publications dealing with neutrophil: lymphocyte ratio in Web of Knowledge.

Year	Number of publications in Web of Science® core collection
2015	871
2016	1066
2017	1289
2018	1471
2019	1819

https://doi.org/10.1016/j.cca.2020.07.008
Received 3 July 2020; Accepted 3 July 2020
Available online 08 July 2020
0009-8981/

References

[1] C. Ricos, V. Alvarez, F. Cava, et al., Current databases on biological variation: pros, cons and progress, Scand. J. Clin. Lab. Investig. 59 (1999) 491–500.
[2] F. Corre, J. Lellouch, D. Schwartz, Smoking and leukocyte counts, Lancet 2 (1971) 632.
[3] H. Ohkoshi, I. Asukata, N. Tajima, K. Yamamoto, M. Sasaki, M. Hokari, et al., The influence of transmeridian flight on human circulating lymphocytes, Aviat. Space Environ. Med. 62 (1991) 14–18.
[4] G. Karayalcin, F. Rosner, A. Sawitsky, Pseudo-neutropenia in American negroes, Lancet 1 (1972) 387.
[5] E.-M. Lim, G. Cembrowski, M. Cembrowski, G. Clarke, Race-specific WBC and neutrophil count reference intervals, Int. J. Lab. Hematol. 32 (2010) 590–597.
[6] Web of science (accessed July 1st 2020).
[7] H. Luo, L. He, G. Zhang, J. Yu, Y. Chen, H. Yin, et al., Normal reference intervals of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and systemic immune inflammation index in healthy adults: a large multi-center study from Western China, Clin. Lab. 65 (2019) 10.7754.

Joris R. Delanghe*
Dept. of Diagnostic Sciences, Ghent University, Belgium
E-mail address: joris.delanghe@ugent.be.

Marijn M. Speeckaert
Dept. of Internal Medicine, Ghent University, Belgium

Marc L. De Buyzere
Dept. of Internal Medicine, Ghent University, Belgium

* Corresponding author at: Dept of Clinical Chemistry, Ghent University, C. Heymanslaan 10, B-9000 Gent, Belgium.