TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

LETTER TO THE EDITORS

Reply to: Cancer inflammation and inflammatory biomarkers: Can neutrophil, lymphocyte, and platelet counts represent the complexity of the immune system?

doi:10.1111/tri.12259

Dear Sirs,

With great interest, we read the paper by Sideras *et al.* [1], in which the authors report the recent discoveries related to the connection between inflammation and hepatocellular cancer (HCC).

However, we are not fully in agreement with the conclusions of the paper. Sideras *et al.,* in fact, report the fact that inflammatory markers such as absolute lymphocyte count (ALC), C-reactive protein and neutrophil-to-lymphocyte ratio (NLR) cannot completely capture the complexity of cancer inflammation and cancer immune responses or accurately represent tumor biology. However, this obvious statement represents the limit of every surrogate marker: Similarly, morphological features such as tumor size and number tell only a partial tale of the HCC characteristics and one size (or number) does not always fit all, as efficaciously observed in a recent editorial by Mehta and Yao [2].

On the other side, it is intriguing to note that only in the last year, not <7 papers have been published focusing their attention on the prognostic role of NLR in patients with HCC waiting for liver transplantation (LT) [3–9].

Sideras *et al.* correctly observed that no full agreement still exists on the threshold value to adopt, the used different cutoffs ranging from ≥3 to ≥5: However, in our recent study, the cutoff value was accurately investigated adopting a c-statistics analysis, and the found value of 5.4 was substantially superimposable to the previously reported ones [9]: Obviously, the main limit for the detection of a valid threshold value is related to the investigated sample size, and, as a consequence, the limit of the nowadays used values derives from the fact that they have been investigated only in relatively small monocentric series.

Another potential limit reported by Sideras *et al.* is represented by the scarce utility of this marker in the clinical routine, mainly in a scenario of wait-list patients, because of its late availability. However, we are not in agreement with this consideration: On the opposite, NLR is a cheap and rapidly available marker, potentially obtainable in every laboratory worldwide. Its introduction in the clinical practice and its prospective collection in regular measurements during the waiting list period can potentially increase our information about the tumor, driving the physician to a more aggressive approach with locoregional treatments despite an apparently good morphological condition of the tumor and, finally, to a more refined selection of patients with HCC waiting for LT.

Obviously, as observed by the colleagues from Rotterdam, a prospective study focused on this aspect should be performed to confirm our retrospective results.

The authors finally underline that the composition of the inflammatory milieu at the site of the tumor microenvironment may be more informative in relation to tumor biology than peripheral blood markers. Indeed several interesting studies reported that peri- and intratumor immune infiltrates are superior to morphological aspects in relation to predicting tumor behavior and clinical evolution [10]. Although we agree with the authors that these data might be superior to the 'simple' peripheral blood tests, we feel that it is quite impossible to obtain such information without a large biopsy (with inherent risk of seeding to be kept in mind) or, even better, a complete excision of the tumor. This can be realized only in resected patients which are afterward undergoing salvage LT. Large tissue availability will allow us to study not only inflammation but also microvascular invasion, grading, and even genetic mutations, increasing thereby substantially the information about the potential aggressiveness of the tumor.

In conclusion, NLR and the other inflammatory markers are cheap, rapidly available, worldwide obtainable, noninvasive, and safe for the patient. If combined with other 'dynamic' biological markers such as radiological progression and alpha-fetoprotein slope [11], they indeed can effectively improve our ability in select patients waiting for LT.

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None.

Funding sources

No funding.

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