



# A Review on the Synthetic and Less Expensive Biomarkers to Monitor the Clinical Course of Cancer Autoimmune Diseases and Cardiovascular Disorders

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## Abstract

The evolution of the medical Sciences corresponded to the discovery of new classes of molecules, firstly the vitamins, then the hormones, then again the neurotransmitters, and finally the cytokines, and each discovery of new molecules allowed the possibility to definitively cure some human diseases. Unfortunately, the last discovery that of cytokines, has still substantially excluded from the common clinical practice. Therefore, it becomes essential to clinically introduce the new science of cytokines, that we could call as cytokinology, before from either a diagnostic, or a prognostic point of view, and after from a therapeutic one. This statement is justified by the fact that the cytokines produced by the activated immune cells do not regulate the only immune system, but all biological functions, being the main responsible for host biological response. The most synthetic and less expensive biomarker could be the same lymphocyte-to-monocyte (LMR), since the evidence of a progressive decline in LMR has been proven to predict a negative prognosis in both metastatic cancer and cardiovascular disorders, as well as to be related to the exacerbation phase of the autoimmune diseases. The occurrence of high blood levels of TNF-alpha, IL-6 and IL-17A has a negative prognostic significance in both advanced cancer and autoimmunity. On the contrary, the evidence of high concentrations of TGF-beta and IL-10 is associated with a negative prognosis in metastatic cancer and with a disease control in the autoimmune disorders.

**Keywords:** Autoimmunity; Biomarkers; Cancer; Cardiovascular diseases; Cytokines; Lymphocyte-to-monocyte ratio

## Introduction

Despite its great complexity, the immune functionless is the end-results of the interactions occurring between lymphocyte and monocyte-macrophage functions, with the dendritic cells as the link between old innate and new acquired immunity. Moreover, within the lymphocyte system, the immune regulation is mainly determined by three major subsets of T lymphocytes, consisting of TH1 lymphocytes (CD4+CD25-CD17-), regulatory T lymphocytes (T reg) (CD4+CD25+), and TH17 lymphocytes (CD4+CD17+) [1-3]. All lymphocyte subpopulations may release several proteins, the so-called cytokines, but from a clinical point of view it is important to remember the main factors involved in

the regulation of the whole immune system, which are represented by IL-2 for TH1 cells, IL-17A for TH17 cells, and IL-10 and TGF-beta for T reg cells. On the other side, the differentiation of the monocyte-macrophage system into different sub-sets is more controversial [4-8]. However, it has been shown that monocyte count may reflect the functional status of the macrophage system [9]. Therefore, because of the great number of potential immune biomarkers and their different economic cost, it is fundamental to distinguish the most important ones from a clinical point of view to monitor the clinical course of the various systemic diseases from those useful for the only experimental researches. At this proposal and by taking into consideration that the immune status is depending on the

**Received date:** 31 October 2020; **Accepted date:** 18 November 2020; **Published date:** 27 November 2020

**Citation:** Lissoni P, Rovelli F, Pelizzoni F, Zanandrea G, Galli C, Merli N, et al. (2020). A Review on the Synthetic and Less Expensive Biomarkers to Monitor the Clinical Course of Cancer Autoimmune Diseases and Cardiovascular Disorders. *SunText Rev Biotechnol* 1(3): 114.

**DOI:** <https://doi.org/10.51737/2766-5097.2020.014>

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lymphocyte-macrophage relationships the most simple and less expensive biomarker from a clinical point of view may be considered the lymphocyte-to-monocyte ratio (LMR) which has appeared to play a prognostic significance in all severe human systemic diseases, including cancer autoimmune diseases and cardiovascular disorders [10-13]. Finally, as far as systemic disease-related symptomatology is concerned, IL-1 beta would be the main responsible for fever TNF-alpha for cachexia and anorexia IL-6 for sepsis-related hypotension and multi-organ failure and IL-31 for pruritus. Unfortunately, most Clinicians do not seem to be interested in the investigation of the physiopathology of cytokines [14-17].

### **The Clinical Significance of Th1/T Reg, Th17/T Reg, Th1/Th17**

Since the pathogenesis of human systemic diseases may be reinterpreted as depending at least in part on an altered relation among the different T lymphocyte subsets, it becomes clinically important to quantify T cell subpopulations. In fact, the alterations in cytokine secretions occurring in the different systemic diseases would be the simple consequence of those involving the various T cell subsets. The progressive decline in TH1 cell count in association with an increase in T reg cell number and activity is the main advanced cancer-related immune alteration which would be due to macrophage-mediated chronic inflammatory status. Then, the progressive decline in TH1/T reg cell ratio occurring during cancer progression depends either on a diminished TH1 cell count, or an increased T reg cell number. Moreover, it has been shown that the decline in TH1/ T reg cell ratio positively correlates with a decline in LMR values. Then, LMR values could represent an adequate and less expensive biomarker to monitor the evolution of advanced cancer patents. As far as the autoimmune diseases are concerned, until few years ago the increased activity of TH1 cells was considered the main event responsible for the onset of autoimmune processes. In contrast, it has been demonstrated that the autoimmune diseases are namely characterized by an increase in TH17 cell activity in association with a decline in T reg cell count since the main action of TH17 cells is the inhibition of T reg cell generation and function. Then, the evidence of an abnormally high values of TH17/T reg cell ratio, which is due to both TH17 cell increase and T reg cell decline, may be considered as the main biomarker with negative prognostic significance to monitor the clinical course of the autoimmune diseases. LMR values have also appeared to have a prognostic significance in the autoimmune pathologies, since it has been shown to be normal or a little increased during the remission phase of disease and abnormally low during the exacerbation phase in any case not due to a diminished lymphocyte production as well as in the metastatic

neoplasms but probably to lymphocyte exit from the blood to infiltrate organ tissues. In addition, at least some autoimmune diseases may be also characterized by a decline in TH1/TH17 cell ratio, since the increase in TH17 cell count would be superior to TH1 enhancement. The occurrence of a diminished TH1/TH17 could also characterized the advanced neoplastic pathologies, because of cancer-related decline in TH1 count, as well as a probable increase in TH17 cell number, even though the TH17 profile in cancer patients has been less investigated up to now [18,19]. In any case, according to the data available up to now, cancer progression would be characterized not only by an increased T reg cell function, but also by an enhanced TH17 cell activation. Moreover, IL-17, despite its potential favourable effect due to an inhibition of T reg cell system, may directly stimulate cancer cell proliferation, and IL-17-expression by cancer cells would enhance their malignant aggressiveness. Finally, a marked increase in TH17/T reg cell ratio has been shown to predict a risk of acute respiratory distress syndrome (ARDS) in patients with lung injury, or viral infections, including coronavirus infection.

### **Main Alterations of Cytokine Secretions in Human Systemic Diseases**

In non-metastatic cancer patients, the immune profile is substantially within the normal range. On the contrary, the metastatic disease is characterized by an increase in IL-6, TNF-alpha and TGF-beta blood concentrations in association with a progressive decline in LMR values and in TH1/T reg cell ratio [20]. On the contrary, IL-17 secretion in cancer needs to be furtherly investigated and understood. The common immune profile of the autoimmune disorders is depending on the phase of disease, since the remission phase tends to present LMR values within the normal range in association with normal blood levels of the main inflammatory cytokines. On the other hand, the exacerbation phase of disease is characterized by abnormally high concentrations of IL-17A, IL-6, and TNF-alpha, in association with a rapid decline in LMR and with an abnormal increase in TH17/T reg cell ratio while the evidence of high levels of IL-10 and TGF-beta may reflect a disease control because of their anti-inflammatory action [21-29]. Finally, the cardiovascular disorders, including myocardial infarction and brain stroke, are substantially characterized by a decline in LMR values. Two other important biomarkers for the cardiovascular diseases are represented by atrial natriuretic peptide-to-endothelin-1 ratio (ANP/ET-1), and by vasopressin-to-oxytocin ratio (ADH/OT). The evidence of an abnormal decline in ANP/ET-1 ratio as well as an abnormal increase in ADH/OT ratio would predict a less favourable prognosis [30]. The occurrence of an abnormal increase in the blood concentrations of inflammatory cytokines, such as TNF-alpha, has been proven to be also associated with a

more severe prognosis in the myocardial infarction [31]. These findings would confirm that the functionless of the cytokine network is not involved only in the regulation of the immune system, but also of the overall biological systems. On the contrary, the profile of TGF-beta secretion and lymphocyte and monocyte subsets in the myocardial infarction, as well as in the other cardiovascular disorders, needs to be furtherly established. In addition, it seems that the concomitant occurrence of an

abnormally enhanced secretion of IL-18 may furtherly worsen the severity of systemic disease-related exaggerated host inflammatory response [32]. Finally, the loss of the physiological light/dark rhythm of the pineal hormone melatonin, whose fundamental immunoregulatory role has been well demonstrated, would also be associated with a more negative prognosis either in the metastatic cancer, or in cardiovascular ischemic diseases [33].

**Table 1:** The main immune and neuroendocrine pathological and prognostic biomarkers to monitor the clinical course of the main systemic human diseases.

Pathology Significance	Biomarkers	Prognostic
Metastatic Cancer	Low LMR	Negative
	Low TH1/T reg ratio, low TH1/TH17 ratio	Negative
	High TNF-alpha and IL-6 levels	Negative
	High TGF-beta and IL-10 levels	Negative
	Lack of light/dark MLT rhythm	Negative
Autoimmune Diseases	Low LMR	Negative
	High TH17/T reg ratio, low TH1/TH17 ratio	Negative
	High IL-17A, TNF-alpha and IL-6 levels	Negative
	High IL-10 and TGF-beta levels	Positive
Cardiovascular Diseases	Low LMR	Negative
	High TNF-alpha, IL-6, IL-18 levels	Negative
	Low ANP/ET-1 ratio	Negative
	High ADH/OT ratio	Negative
	Lack of light/dark MLT rhythm	Negative
Ards	Low LMR	Negative
	High TH17/ T reg ratio	Negative
	High IL-17A, TNF-alpha and IL-6 levels	Negative
	High IL-10 levels	Probably positive

### How to Monitor Adequately and In a Less Expensive Way Host Immunity in Systemic Diseases?

The two extreme mistakes are the almost complete lack of immune evaluation in patients with systemic diseases, including cancer and autoimmunity, and on the other side the detection of an excessive number of laboratory immune parameters, including cytokine blood levels and lymphocyte subsets. Then, the correct clinical behaviour would have to consist of the measurement of the only essential and synthetic immune biomarkers to establish the immune status of patients, in particular by avoiding the measurement of cytokines provided by the same pathological

significance, such as the concomitant detection of IL-1 beta and IL-6, because of their positive correlation. Obviously, the choice of the fundamental immune parameters to be clinically detected requires a perfect knowledge of the physiopathology of the different human systemic diseases. In addition, the synthetic group of biomarkers to monitor the clinical course of the systemic diseases must include both parameters provided by physiopathologic and prognostic significance. The main cytokine levels and T lymphocyte subsets provided by pathological or prognostic significance in the most important human systemic diseases are summarized in (Table 1). LMR: Lymphocyte/monocyte ratio; ANP: Atrial natriuretic peptide; ET-1: Endothelin-1; MLT: Melatonin, ADH: Vasopressin; OT: Oxytocin.

## Conclusions

A further future evolution of the medical Sciences will be achieved and realized only when the evaluation of the functionless of the cytokine network will be included within the commonly laboratory examinations to monitor the clinical course of the most important severe human systemic disease.

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