# Searching for Easy Reliable Prognostic Parametres in Colorectal Cancer Patients Evaluation

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## Abstract

Tumor node metastasis (TNM) staging system is the most useful method in predicting prognosis of colorectal cancer (CRC), the third most common cause of death worldwide, even if other biological markers are currently under evaluation to assess their role in affecting CRC outcome and planning the best tailored therapeutic approach. Several molecular factors are being demonstrated to be effective in influencing both overall survival (OS) and disease-free survival (DFS) in CRC, acting on different aspects of tumor promoting and progression.

Patient inflammatory and nutritional status evaluation, strictly correlated with immune-surveillance system, plays a crucial role in affecting CRC outcome.

The Authors, analyzing data of 562 consecutives CRC patients, suggest a new prognostic model, called Naples Prognostic Score (NPS), for an exhaustive assessment of both inflammatory and nutritional status through the determination of several routine blood parameters. NPS is an independent factor in affecting outcome of CRC patients undergoing surgery with a power almost similar to TNM pathological system.

NPS results by albumin and total cholesterol serum levels, neutrophils to lymphocyte ratio (NRL) and lymphocyte to monocytes ratio (LMR); the score stratifies CRC patients in three homogeneous groups that are significantly different in terms of advanced stages, postoperative complication rate, DFS and OS.

Further studies with higher numbers of patients are necessary to standardize NPS routine use to become a reference model to modified management and integrated treatment of CRC patients.

**Keywords:** Tumor node metastasis (TNM), Overall survival (OS), Disease-free survival (DFS), Colorectal cancer (CRC)

## Main Body

Despite the advances in diagnostic and therapeutic field [1], colorectal cancer (CRC) still remains the third most common cause of death worldwide, with more than 600,000 cancer-related deaths per year [2].

TNM system is currently the most useful method both in evaluating CRC prognosis and in planning its treatment [3.] Nevertheless, a different outcome in the same TNM stage is commonly observed [4], moreover in early-stage cancers [5], in which no other treatment than surgery is required, so that some other factors could affect the clinical history of CRC.

The assessment of further categories of high-risk patients, other than advanced TNM stages, is a major challenge nowadays in improving the outcome of the disease, moreover in such cases where adjuvant therapy is not currently indicated (I and II stages) [6].

Due to the molecular heterogeneity of CRC [7,8], many biomarkers are now being investigated [9], even if a wide accepted consensus about them is not reached yet.

Further studies will be necessary to set a standardized panel of these prognostic factors and their own cut-off values for the evaluation of the best therapeutic

choice for each CRC patient. In the meantime, it could be useful to adopt simpler indicators that are currently effective in planning follow-up controls and therapeutic determinations, in the future.

There is a growing evidence that inflammatory and nutritional status, since they are strictly related with the immuno-surveillance system, affect the outcome of several tumors [10]. In the past decade, the strong relation between peripheral lymphocytes/monocyte count and prognosis of several tumors, including CRC, has been investigated11,12. Cell-mediated immunoresponse against tumors, mostly related to lymphocytes activity, is associated with a good prognosis in terms of OS and DFS, and a consistent lymphocyte infiltration in tumoral tissue is predictive of a better outcome.

Tumoral microenvironment is one of the most interesting topics in this field, since promoting and suppressing factors may affect tumor behavior [10,11,13]. Particularly the host reaction against the tumor growth, via the systemic inflammation, seems to affect the CRC prognosis [14].

The neutrophil to lymphocyte ratio (NLR) an easy to achieve inexpensive biomarker, expresses the balance between systemic (neutrophils) and cell-mediated (lymphocytes) immunity: the higher its value the more the host immune response is shifted towards a systemic not effective reaction against the tumor. A significant NLR increase is commonly observed in advanced stages of the diseases, elderly patients, non-curative surgery, and postoperative complicated cases. Furthermore, among early (node negative) CRC, a high NLR is significantly associated with a worse DFS and a higher recurrence rate (RR). In conclusion, NLR is useful in identifying a high-risk subgroup that should be considered for a further tailored therapy. Similarly, LMR is independently related to CRC prognosis, since monocytes, by differentiating into macrophages, promote tumor progression and metastases.

Controversial data are reported about the macrophage role in determining a favorable microenvironment for the tumor: it seems that specific subsets of these cells are involved in DFS rather than in OS [13]. Also, platelet count seems to be related to progression of malignant tumors [15] and many reports indicate Systemic Immune-Inflammation Index (SII), the proportion between peripheral platelet, neutrophil and lymphocyte count, as effective in predicting malignant tumors outcome [16-18].

In addition, the evaluation of patient nutritional status [19-21], through albumin and cholesterol serum levels, might offer a further help in achieving a better patient setting, showing its importance in affecting CRC outcome.

These parameters, organized in several score systems [22-24], are currently used in peroperative settings in order to predict the patient outcome. Score systems as CONUT, PNI and SIS are easy to achieve, based on data normally drawn by a simple blood sample, and easy to fit each patient. Nevertheless, nutritional and immunological status are evaluated separately in each of these scores.

NPS [25], the combined contemporary evaluation both of inflammatory and nutritional status, is able to better predict the long-term outcome of patients undergoing surgery for gastrointestinal malignancies [26].

NPS (Figure 1) is a widely applicable prognostic model, using routinely detection values, such as albumin and total cholesterol serum levels, NLR and LMR; in this way, NPS simultaneously investigates nutritional and immunological status. It is noteworthy that hypoalbuminemia, due to a low assumption and a low hepatic production, is a significative malnutrition sign; in neoplastic patients, it may be also linked to increased cytokine levels, that represent the systemic inflammatory state. On the other hand, hypocholesterolemia, often present in CRC patient, by changing cell membrane composition, reduces the ability of the immune system to detect the cancer. Likewise, lymphocytopenia indicates the lack of cell mediated response in fighting cancer and macrophages seem to be involved in tumoral microenvironment by promoting neoangiogenesis and tumor progression.

Authors investigated the role of NPS in 562 consecutive CRC patients and found that NPS positively related to other nutritional and inflammatory score systems, such as CONUT and SIS, and inversely related to PNI; moreover, NPS worsened with advanced TNM stage and postoperative complication rate. NPS was significantly related with OS: among patients with all parameters within the normal range (score 0), five-year OS was 88%; in score 1 (1-2 altered values) 68%; in score 2 (3 -4 altered values) 34%, respectively. Also, DFS was strictly related to NPS showing a progressive worsening from score 0 to score 3.

Compared with other immunologic or nutritional score systems, such as SIS [16,17], PNI [19-21] and CONUT [22,23], NPS represents the best model to achieve homogeneity among groups with similar overall survival rate; moreover, in each group the five-year prognostic power is comparable to that of TNM staging system, currently considered the best one [26].

Furthermore, NPS can be useful also in analyzing patients outcome because it is independently correlated with DFS, risk of recurrence and post-operative complications. In addition, while TNM system analyzes only pathological stage, NPS intersects both the tumor stage and the patient's state of competence in responding to the disease. In this way, the peroperative study of the patient, according to NPS, may help the physician to predict the risks of recurrence and early complications,
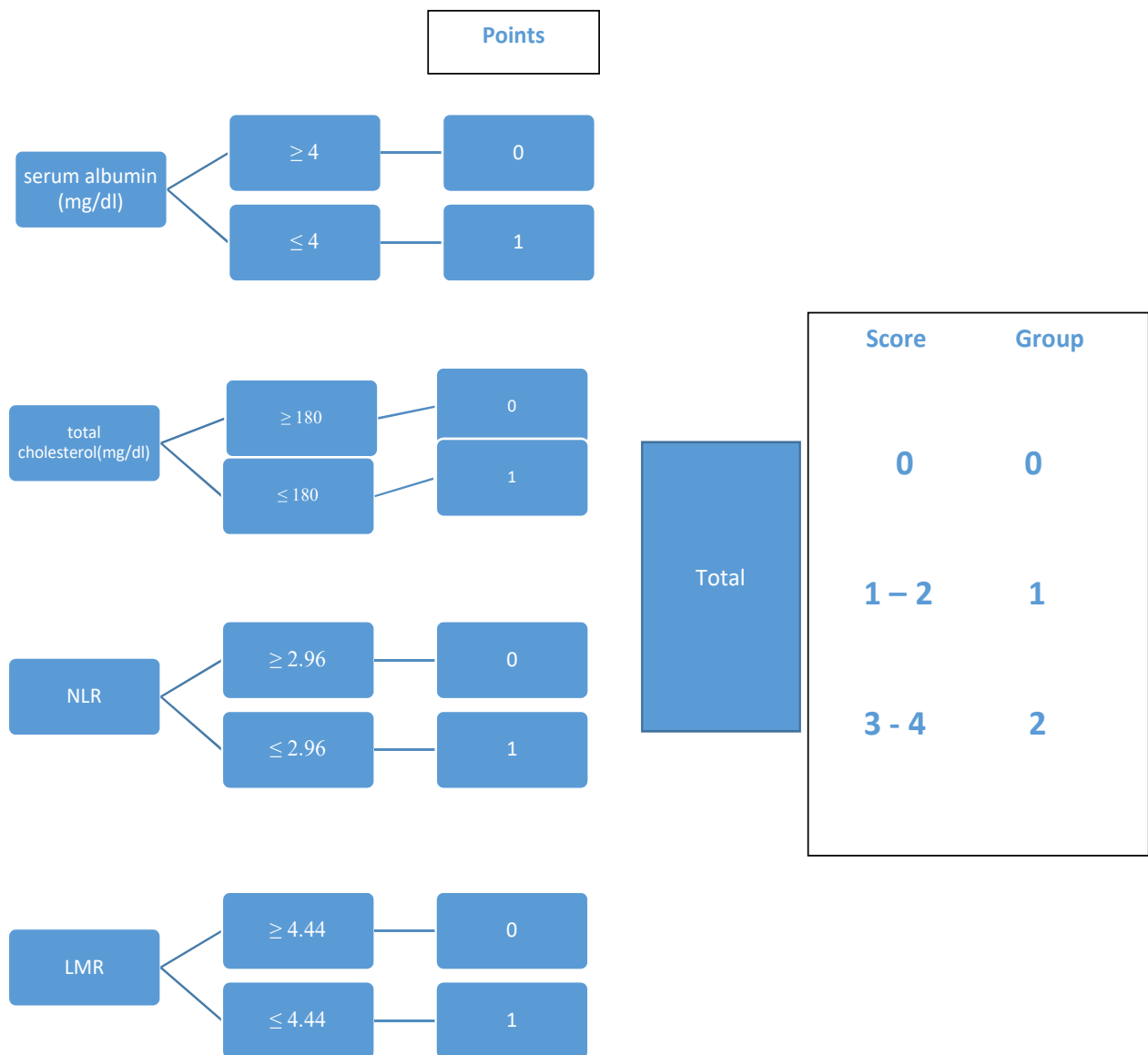
**Figure 1:** Calculating NPS.

and gives useful suggestions in terms of therapeutic regimen, as well as in the long-term prognostic judgment.

In conclusion, although NPS, as far as others, needs further validations in larger groups of patients. Nevertheless, it might allow an easy classification of CRC patients in order to better decide about their management and surgical treatment.

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