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# Absolute Monocyte Count and Lymphocyte-Monocyte Ratio Predict Outcome in Nodular Sclerosis Hodgkin Lymphoma: Evaluation Based on Data From 1450 Patients

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## Abstract

**Objective:** To verify whether absolute monocyte count (AMC) and lymphocyte- monocyte ratio (LMR) at diagnosis are valid prognostic parameters in classical Hodgkin lymphoma (cHL).

**Patients and Methods:** Data were collected from 1450 patients with cHL treated in Israel and Italy from January 1, 1988, through December 31, 2007.

**Results:** The median age of the patients was 33 years (range, 17-72 years), and 70% (1017) of the patients had nodular sclerosis (NS); the median follow-up duration was 87 months. The best cutoff value for AMC was 750 cells/mm$^3$, and the best ratio for LMR was 2.1. The adverse prognostic impact of an AMC of more than 750 cells/mm$^3$ was confirmed for the entire cohort, and its clinical significance was particularly evident in patients with NS histology. The progression-free survival (PFS) at 10 years for an AMC of more than 750 cells/mm$^3$ was 65% (56%-72%), and the PFS at 10 years for an AMC of 750 cells/mm$^3$ or less was 81% (76%-84%; $P<.001$). The overall survival (OS) at 10 years for an AMC of more than 750 cells/mm$^3$ was 78% (70%-85%), and the OS at 10 years for an AMC of 750 cells/mm$^3$ or less was 88% (84%-90%; $P=.01$). In multivariate analysis, both AMC and LMR maintained prognostic significance for PFS (hazard ratio [HR], 1.54, $P=.006$, and HR, 1.50, $P=.006$) after adjusting for the international prognostic score, whereas the impact on OS was confirmed (HR, 1.56; $P=.04$) only in patients with NS and an AMC of more than 750 cells/mm$^3$.

**Conclusion:** This study confirms that AMC has prognostic value in cHL that is particularly significant in patients with NS subtype histology. This finding links the known impact of macrophages and monocytes in Hodgkin lymphoma with routine clinical practice.

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Current therapy for classical Hodgkin lymphoma (cHL) cures about 80% of the patients with this disease, whereas the rest relapse or are refractory to therapy. Major efforts have been made to avoid possible overtreatment and potential long-term toxicity in younger patients and to identify patients requiring more aggressive therapy in order to avoid the development of refractory disease. In this regard, to define a scoring system that could stratify patients, and possibly even predict outcome, would be both helpful and practical to apply in daily practice. The international prognostic score (IPS) proposed in 1998[1] uses a model that incorporates 7 prognostic factors at initial diagnosis to predict outcome in patients with cHL. The major limitation of the IPS relates to the fact that it was first proposed for advanced cHL in an attempt to avoid overtreatment in some patients and identify others in whom standard therapy would be inadequate. However, its role in both favorable and unfavorable early stage disease is limited.

 

**TABLE 1. Clinical and Laboratory Characteristics of the 1450 Patients Included in the Study**

| Variable | Median (2.5th-97.5th percentile) |
|---|---|
| Age (y) | 33 (17-72) |
| Hemoglobin (g/dL) | 12.4 (7.9-16.1) |
| WBC (cells/mm$^3$) | 8600 (3200-20,000) |
| AMC (cells/mm$^3$) | 550 (82-1527) |
| ALC (cells/mm$^3$) | 1543 (334-3981) |
| LMR | 2.8 (0.7-17) |
| Albumin (g/dL) | 4.0 (2.4-5.0) |
| **Variable** | **n (%)** |
| Age >45 y | 402 (28) |
| Sex: male | 728 (50) |
| Stage IV disease | 234 (16) |
| Hemoglobin <10.5 g/dL | 253 (17) |
| Albumin <4 g/dL | 846 (58) |
| WBC >15,000 cells/mm$^3$ | 157 (11) |
| ALC <600 cells/mm$^3$ | 90 (6) |
| Histology, NS | 1017 (70) |
| Systemic symptoms | 640 (44) |
| IPS | |
| 0-2 | 1054 (73) |
| 3-7 | 396 (27) |

ALC = absolute lymphocyte count; AMC = absolute monocyte count; IPS = international prognostic score; LMR = lymphocyte-monocyte ratio; NS = nodular sclerosis; WBC = white blood cell.

An absolute lymphocyte count (ALC) of less than 600 cells/mm$^3$ or less than 8% of the total white blood cell (WBC) count is one of the factors included in the IPS and is regarded as an important prognostic parameter influencing the interval of freedom from progression.[1] Indeed, ALC is considered a surrogate biomarker of tumor-infiltrating lymphocytes and reflects the general status of host immunity. Recently, however, several studies have reported that absolute monocyte count (AMC) at diagnosis also has prognostic value in lymphomas.[2-7] The rationale for using AMC as a prognostic parameter in cHL is even more relevant than in other malignancies because of the immunohistochemical and molecular data, including gene expression profile, which identify a key role for monocytes and macrophages in the biology of cHL, particularly in patients with nodular sclerosis (NS) histology.[8-12]

Combining AMC and ALC as a lymphocyte-monocyte ratio (LMR) has been proposed and shown to have prognostic potential in both non-Hodgkin lymphoma (NHL) and cHL.[13,14] Each of the above studies has used different cutoff values for AMC and LMR, which are easily accessible and simple to apply, but an agreed standard value has as yet not been defined.

The aim of the present study was to verify, using a large cohort of patients from 2 countries and continents, whether AMC and LMR represent valid prognostic parameters in cHL and at the same time identify the best cutoff value for AMC and LMR.

## PATIENTS AND METHODS

This study is a retrospective analysis of previously untreated patients with cHL. We reviewed clinical and laboratory data of "therapy-naive" patients, treated in different centers from January 1, 1988, to December 31, 2007, in Israel and Italy. Italian cases were retrieved from 38 centers belonging to the Gruppo Italiano Studio Linfomi archive. Data from Israeli patients were collected from 2 medical centers after approval by local institutional review boards. All studies were performed in accordance with the principles of the Declaration of Helsinki.

Patients were accepted into this study if the following criteria were fulfilled: histopathological diagnosis of cHL, no previous therapy, age more than 18 years, no human immunodeficiency virus infection, availability of data on all clinical and laboratory features and treatments given, as well as outcome, and follow-up. The database contained a total of 1848 patients who had received combination chemotherapy with or without radiotherapy. Analysis was performed on a final cohort of 1450 patients after the exclusion of those with missing data relating to IPS (n=166), or monocyte count (n=137), or missing reports (n=95). Definition of response was based on guidelines revised by Cheson et al.[15]

Primary end points of the study were to assess the impact of AMC, ALC, and LMR on progression-free survival (PFS) and overall survival (OS). The secondary end point was to establish the best cutoff value for AMC and LMR on the basis of different values reported in the literature.

### AMC and ALC Adjusted to the IPS

Absolute monocyte count and ALC were adjusted to the IPS[1] used to predict survival in patients with advanced cHL. The IPS is based on 7 adverse clinical and laboratory parameters: age more than 45 years, albumin less than 4 g/dL, ALC of less than 600 cells/mm$^3$ or