Psoas muscle index at the time of diagnosis might reflect the prognosis of classical Hodgkin's lymphoma patients

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Title: Psoas muscle index at the time of diagnosis might reflect on prognosis of classical Hodgkin lymphoma patients

Abstract:

We retrospectively investigated clinical and prognostic significance of psoas muscle index (PMI) calculated as total psoas muscle area at L3 vertebra level obtained from baseline CT scans in 49 newly diagnosed classic Hodgkin lymphoma (cHL) patients prior to specific therapy. Median PMI was 572.5 mm^2/m^2 and was significantly higher in males (P<0.001), patients with higher BMI (P<0.001), absence of extranodal disease (P=0.037), higher absolute lymphocyte count (P=0.037), higher hemoglobin (P=0.010) and lower LDH (P=0.050). There were no significant associations with age, disease subtype, presence of constitutional symptoms, Ann Arbor disease stage, presence of advanced disease or International Prognostic Score. Patients with lower PMI had significantly worse PFS (HR 4.91; P=0.009). This phenomenon persisted in the multivariate model (HR=5.09; P=0.042) adjusted for IPS and chemotherapy type.

Keywords: Hodgkin lymphoma; sarcopenia; psoas muscle; prognostication; survival; progression

Dear Editor,

Classical Hodgkin lymphoma (cHL) is a B-cell lymphoid malignancy affecting predominantly young adults [1]. Disease usually presents with asymptomatic lymphadenopathy but can be accompanied by presence of constitutional symptoms as a result of cytokine activity (fever, night sweats, unintended weight loss). Multimodal treatment approach made cHL highly curable cancer, however, 15%-20% of patients experience relapsing or refractory disease [2]. International Prognostic Score (IPS) which includes information on albumin, hemoglobin, white blood cell count (WBC), lymphocyte count, age, sex and clinical stage is the most robust and widely used baseline prognostication model reflecting both disease burden and metabolic alterations that might lead to cachexia. However, interim positron emission tomography (PET) scan assessing early response to therapy became the most sensitive predictor of long term outcomes [3]. Sarcopenia, i.e. loss of skeletal muscle mass, is recognized as a negative prognostic factor in a variety of chronic and malignant diseases. Sarcopenia assessed by measurement of psoas muscle index (PMI) was recently shown to be prognostic in aggressive non-Hodgkin lymphoma (NHL) patients [4]. Role of PMI and its clinical correlations in cHL have not been investigated so far. Thus, we aimed to investigate clinical associations and potential prognostic properties of PMI in a cohort of newly diagnosed cHL patients.

We retrospectively analyzed a single institution cohort of newly diagnosed cHL patients that presented to our institution in the period from November 2003 to December 2018. There were a total of 49 patients with available data to calculate baseline PMI. PMI was calculated as total psoas-muscle area at L3 vertebra

level in mm^2 obtained from baseline CT scans prior to specific therapy, divided by squared height of patients in m^2. Patients were treated with either ABVD (38 patients) or eBEACOPP (11 patients) chemotherapy regimens with subsequent radiotherapy in a subset of patients. Baseline clinical and laboratory characteristics were obtained through analysis of electronic and paper medical records and were correlated with PMI. The study was approved by the Institutional Review Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All patients provided informed consent for diagnostics and treatment. Normality of distribution of numerical variables was tested using the Shapiro-Wilk test. Neither of assessed numerical variables had normal distribution and they were analyzed using the non-parametric statistical procedures. The Mann Whitney U test, the Spearman rank correlation, the χ^2 test, the log rank test and the Cox regression analysis were used. P values <0.05 were considered statistically significant. Statistical program MedCalc ver. 19.6 was used for all analyses.

Median follow-up of our cohort was 51 months. Median age was 36 years, with similar proportion of male (51%) and female patients (49%). Majority of patients had nodular sclerosis histologic subtype (77%). Median PMI was 572.5 mm^2/m^2. PMI was significantly higher in male patients (median 667 vs 443 mm^2/m^2 for males and females; P<0.001) and in patients with higher BMI (Rho=0.49; P<0.001), but was not associated with age (P=0.774), nor with histologic subtype (P=0.136).

Regarding disease specific features, PMI did not show significant association with neither Ann-Arbor clinical stage, presence of constitutional symptoms, number of affected regions, bulky disease status, erythrocyte sedimentation rate, albumin, CRP, WBC, nor ECOG status (P>0.05 for all analyses). However, lower PMI was observed in patients presenting with extranodal disease (P=0.037), lower absolute lymphocyte count (P=0.037), lower hemoglobin (P=0.010) and higher LDH (P=0.050). There was no significant difference in PMI among patients with early, intermediate and advanced disease stage as defined by GHSG criteria (median 650 vs 472 vs 594 mm^2/m^2; P=0.321). PMI did not correlate with IPS neither in the whole cohort (P=0.854), nor among advanced stage patients (P=0.843). PMI was not predictive of response rates at the end of treatment (P=0.969).

Using the ROC curve analysis we determined optimal cut-off level for progression free survival (PFS) discrimination (<582 mm^2/m^2). Patients with lower PMI had significantly worse PFS (HR 4.91; P=0.009) in comparison to higher PMI as shown in Figure 1. This phenomenon persisted in the multivariate model (HR=4.55; P=0.050) adjusted for IPS (P=0.248). There was no significant difference in PFS between ABVD-only and eBEACOPP treated patients (P=0.696). Also, lower PMI remained significantly associated with shorter PFS (HR=5.09; P=0.042) after additionally adjusting the model for chemotherapy type. PMI was not prognostic for overall survival.

We would like to point out several interesting observations that emerge from our findings. In line with observations in aggressive NHL patients [4], PMI assessed at baseline seems to bear prognostic relevance

in patients with cHL as well and might indicate the severity of the disease. We did not establish relationship with prognostic score IPS, nor clinical stage of the disease. Association of PMI with PFS remained statistically significant in the multivariate model adjusted for IPS suggesting that baseline PMI indeed has good prognostic potential. However, prognostic features of PMI might be partially overlapping with IPS score as it correlates with hemoglobin, sex and lymphocyte count which are all included in the IPS score. It is interesting to note that positive correlations of psoas muscle size and its dynamics with hemoglobin level were reported by several studies analyzing different hematologic malignancies [4, 5]. However, mechanisms behind clinical associations still remain elusive. PMI seems to have good prognostic potential in cHL at baseline prior to therapy exposure and is easily accessible from routinely obtained radiographic data. Question remains how would PMI perform and whether it can improve current standard of prognostication – interim PET-CT scans from which it can be easily reconstructed. Unfortunately, we were not able to investigate this issue at the moment.

In conclusion, psoas muscle mass adjusted for patient height might aid in prognostication of patients with cHL. Future research is warranted.

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Figure 1: Progression free survival (PFS) in newly diagnosed classical Hodgkin lymphoma patients stratified by psoas muscle index (PMI) assessed at the time of diagnosis.