

LABORATORIO E FATTORI PREDITTIVI

THE PREDICTIVE VALUE OF HIGH-SENSITIVITY C-REACTIVE PROTEIN FOR ASSESSING THROMBOSIS RISK IN NON-SMALL CELL LUNG CANCER.

P. Gomez-Rosas^{1,2}, M. Marchetti^{1,3}, L. Russo¹, C. J. Tartari¹, S. Bolognini¹, C. Ticozzi¹, F. Schieppati¹, A. D'alesio⁴, R. Labianca⁵, A. Falanga^{1,3}.

All on behalf of the Hypercan Investigators.

¹Hospital Papa Giovanni XXIII, Bergamo; ²Cardiovascular Research Institute Maastricht, CARIM, Maastricht University, Maastricht, the Netherlands; ³School of Medicine and Surgery, University of Milan Bicocca; ⁴University Vita-Salute San Raffaele, Milan; ⁵Fondazione ARTEF Onlus, Bergamo.

Background Patients with non-small cell lung cancer (NSCLC) are often diagnosed at advanced stages, which makes treatment significantly more challenging. Additionally, NSCLC is commonly associated with a high incidence of venous thromboembolic events (VTE), which further worsen the prognosis. Contributing factors from the host's inflammatory response in cancer align with the prothrombotic state of cancer patients. Thromboinflammation is correlated not only with VTE but also with a more aggressive cancer phenotype.

Aims In a large, prospective, multinational, observational study involving newly diagnosed NSCLC patients, we evaluated a panel of hypercoagulable biomarkers, along with high-sensitivity C-reactive protein (hs-CRP), to determine their predictive significance for the occurrence of VTE within 6 months of initiating chemotherapy. Additionally, we aimed to assess whether the occurrence of VTE is associated with increased disease progression (DP) after one year.

Methods A cohort of advanced-stage NSCLC patients was enrolled before starting chemotherapy. Serum and platelet-free plasma samples were collected at enrollment and tested for hs-CRP, D-dimer, and prothrombin fragment 1+2 (F1+2) levels. The primary outcome was the occurrence of VTE within 6 months of enrollment. DP was also monitored within 1 year after enrollment.

Results 719 patients with NSCLC (489 men and 230 women, median age of 65 years) were evaluated. Among these patients, 79% presented metastatic disease and 21% locally advanced disease. The cumulative incidence of VTE within 6

months was 11% (95% CI 7-13). Patients who experienced VTE during the follow-up period exhibited significantly ($p < 0.05$) higher baseline levels of hs-CRP, F1+2, and D-dimer compared to those who remained VTE-free. Following adjustments for cardiovascular risk factors, age, and sex, multivariable analysis conducted using the Fine and Gray method, with mortality as competing risk, revealed that VTE was significantly associated with increased levels of hs-CRP (SHR 1.08, $p = 0.016$), while F1+2, and D-dimer did not reach statistical significance ($p > 0.05$). Cut-off values derived from the 75th percentile of predictive hs-CRPs were established to assess the risk of VTE. Levels of hs-CRP above the 75th percentile effectively stratified patients into a high-risk category (14%), whereas those below this threshold presented a risk level of 8% (SHR 1.3, $p = 0.039$). Additionally, the disease-free survival rate after one year of treatment initiation was 27.8%. Among the 68 patients who developed VTE within the first six months, 42 subsequently experienced DP in the ensuing six months, whereas 26 remained free of DP ($\chi^2 = 0.028$). The incidence of VTE within six months of enrollment was significantly correlated with an increased likelihood of developing DP at the 12-month (HR, 1.352; 95% confidence interval, 1.018-1.794; $p = 0.037$).

Conclusions In patients with NSCLC, the pre-chemotherapy levels of hs-CRP, an easily quantifiable marker, predicted the occurrence of VTE. This is critically important, as the presence of VTE is associated with an unfavorable prognosis, as shown by its correlation with an increased risk of disease progression.

Email: patmlhs@hotmail.com