The non-invasive fibrosis biomarker measuring type III collagen synthesis (PRO-C3) is elevated in patients with myeloproliferative neoplasms and associate with disease severity and allele burden – lessons learned from the DALIAH trial

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the extracellular matrix pharmacology congress

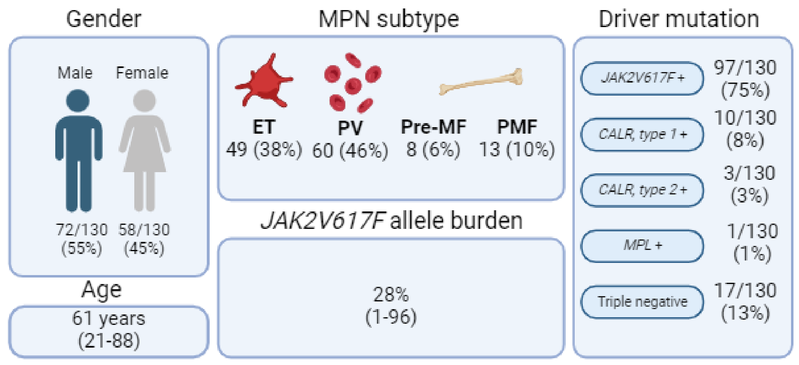
BACKGROUND

Myeloproliferative neoplasms (MPNs) are chronic blood cancers characterized by elevated blood cell counts. MPNs arise due to acquired somatic driver mutations in stem cells (*JAK2V617F, CALR and MPL*) and develop over decades from the earliest stages of essential thrombocythemia (ET) and polycythemia vera (PV) towards advanced primary myelofibrosis (PMF) with bone marrow failure. MPNs are driven by chronic inflammation and characterized by persistent connective tissue remodeling leading to organ dysfunction due to excessive accumulation of collagens (fibrosis) in the bone marrow. Reduction or stabilization of bone marrow fibrosis is considered a significant therapeutic goal in MPNs, hence monitoring and quantitating fibrosis non-invasively is ideally suited for patients with MPNs.

The aim of this study was to investigate the relevance of non-invasive serological biomarkers of type I collagen synthesis (PRO-C1) and type III collagen synthesis (PRO-C3) In patients with MPNs.

METHODS

PRO-C3 and PRO-C1 were measured by ELISAs in pre-treatment serum from 130 patients enrolled in the DALIAH trial (NCT01387763) - a randomized phase III trial of hydroxyurea (HU) vs. interferon-α (IFN-α) in newly diagnosed or untreated patients with MPNs (n, subtypes: ET=49, PV=60, pre-PMF=8, PMF=13), and compared to age- and gender-matched healthy individuals (n=32). Biomarker levels in patients with MPNs were assessed according to disease stage, somatic driver mutation status, and *JAK2V617F* allele burden.

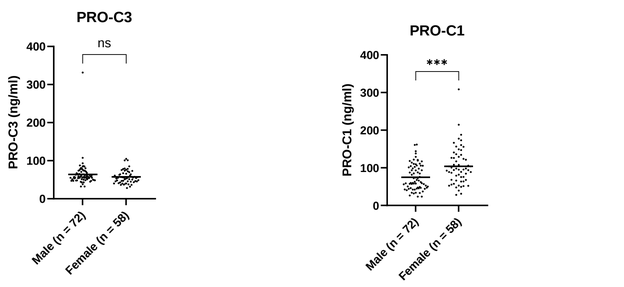


RESULTS

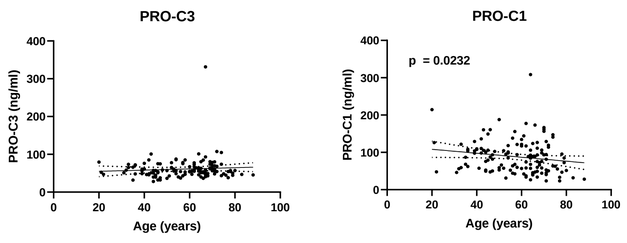
Only PRO-C3 was significantly elevated in patients with MPNs compared to healthy individuals (p=0.033, 95% CI=0.9343-21.93). Separating into MPN subtypes, PRO-C3 was significantly elevated in patients with PMF compared to patients with ET or PV, respectively (p=0.0012, 95% CI=-54.51- -10.33 and p=0.0024, 95% CI=-51.70 - -8.387). By contrast, no significant differences were observed concerning PRO-C1. Neither PRO-C3 nor PRO-C1 differed between patients according to different somatic driver mutations. However, patients with high *JAK2V617F* allele burden (>40%) had a significantly higher level of PRO-C3 (p=0.0397, 95% CI=0.4996-20.35).

Patient characteristics

Gender correlation

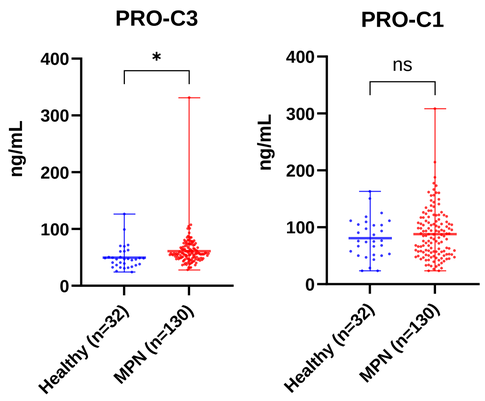


Age correlation

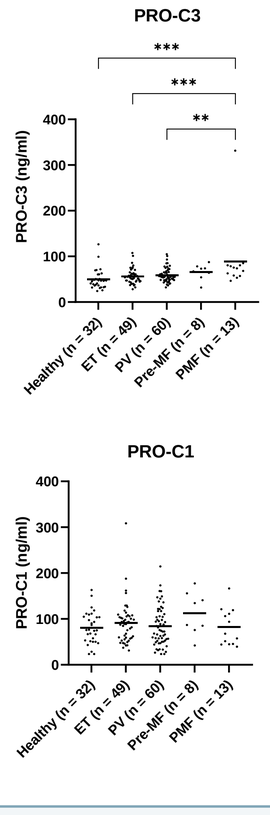


Disease severity

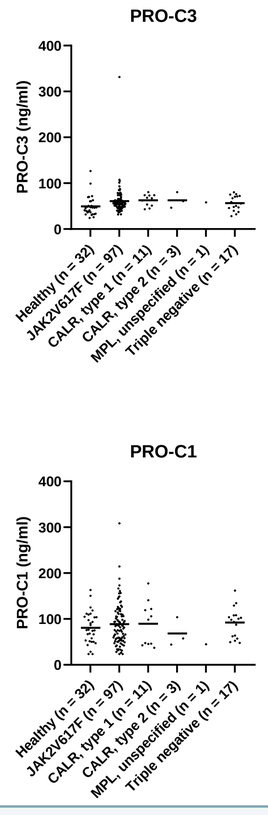
Healthy individuals vs. MPN patients



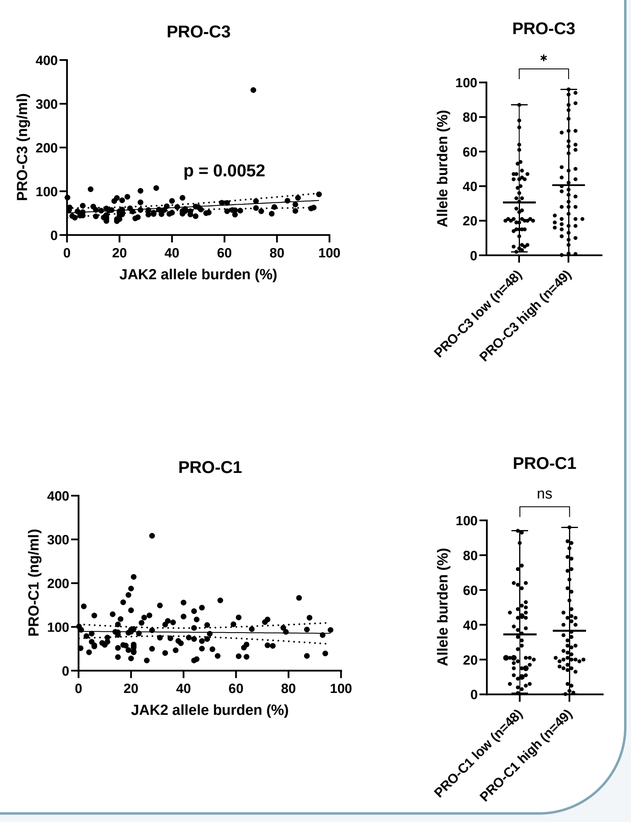
Diagnosis



Driver mutation



Allele burden



* p<0.05 ; ** p<0.01; *** p<0.001; **** p<0.0001

NORDIC BIOSCIENCE

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Disclosures: MK and NWI are employed at Nordic Bioscience and may be shareholders.

CONCLUSION

The non-invasive fibrosis associated biomarker PRO-C3, that reflects type III collagen synthesis, is elevated in MPN patients and associate with the severity of the disease and with the JAK2V617F allele burden. PRO-C3 has potential as a non-invasive bone marrow fibrosis biomarker to stratify and monitor patients with MPNs.