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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Clinical and Genetic Features By Next-Generation Sequencing and RNA Sequencing in Pre-Fibrotic Primary Myelofibrosis Patients

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The 2016 WHO classification recognized pre-fibrotic primary myelofibrosis (pre-PMF) as a distinct entity. Such knowledge is essential to depict the landscape of pre-PMF and develop mechanism-based approaches to slow the progression of pre-PMF. Here, we conducted a retrospective study of 234 pre-PMF patients defined by 2016 WHO diagnostic criteria in 13 hematoon-cology centers between 01 January 2015 and 31 July 2023 (ChiCTR2200061208). We evaluated clinical characteristics, risk factors and genetic features of progression to overt-PMF in pre-PMF patients.

Among 234 pre-PMF patients, 135 (57.7%) harbored *JAK2V617F*, 36 (15.4%) *CALR* and 3 (1.3%) *MPL* mutations; 60 (25.6%) patients were negative for all three mutations. *JAK2V617F*-mutated patients were older (P=0.036), had more constitutional symptoms (P=0.027) and cardiovascular risk factors (P=0.045), higher white blood cell count (WBC) (P<0.001), hemoglobin level (HB) (P<0.001), neutrophile granulocyte (NEU) (P<0.001), eosinophilic granulocyte (EOS) (P<0.001), basophilic gran-ulocyte (BAS) (P<0.001), hematocrit (HCT) (P=0.002) and red blood cell distribution width (RDW) (P<0.001) (Figure A). *CALR*-mutated cases had higher platelet hematocrit (PCT) (P=0.043) and lactic dehydrogenase (LDH) (P=0.008). Besides, *CALR* group had a higher proportion of 25.0% to progress to overt-PMF than *JAK2V617F* group (9.6%) and *TN* group (6.7%) (P=0.025) (Figure A).

As for risk factors of progression to overt-PMF, univariable analysis found it was associated with mean platelet volume (MPV) (P=0.019), HB (P=0.027), WBC (P=0.008), LDH (P=0.004) and *CALR* mutations (P=0.007). Multivariable analysis revealed that lower HB value (P=0.041; HR 0.981, 95% CI 0.962-0.999) and *CALR* mutation (P=0.001; HR 3.716, 95% CI 1.331-10.069) had negative impact on the progression to overt-PMF (Figure B). When divided by HB with cut-off point of 128 g/L, patients with HB value ≤128 g/L were more likely to progress to overt-PMF compared to >128 g/L groups (P=0.007) (Figure C). And patients carried *CALR* mutation were also more likely to progress to overt-PMF (P<0.001) (Figure D).

We performed next-generation sequencing (NGS) in 18 pre-PMF patients, including 9 *JAK2V617F*, 3 *CALR* and 6 *TN*, 3 of which progressed to overt-PMF and 15 stayed in pre-PMF until the end of the follow-up. *JAK2V617F* was the most frequently mutated gene (9/38, 23.7%), followed by *TET2* (7/38, 18.4%), *RELN* (4/38, 10.5%) and *ASXL1* (3/38, 7.9%). *JAK2V617F*-mutated patients possessed more mutations related to activation signaling pathway (P=0.025) and DNA methylation (P=0.033) (Figure F). *TN* patients possessed more mutations related to transcription factor (P=0.048) (Figure F). Patients who progressed to overt-PMF possessed more mutations associated with myeloid related transcription factor (P=0.025) (Figure H). We further performed RNA-Seq analysis in 6 pre-PMF samples and 14 overt-PMF samples. Compared to pre-PMF, overt-PMF showed 49 up-regulated and 13 down-regulated differentially expressed genes (DEGs), of which CSCF3 and CXCL13 were significantly up-regulated (Figure I,J). Gene ontology (GO) functional enrichment analysis showed that DEGs were enriched in cell-cell signaling, cytokine activity, monocyte chemotaxis and chemokine activity (Figure K). KEGG biofunctional analysis showed that DEGs were significantly enriched in cytokine-cytokine receptor interaction, chemokine signaling pathway, IL-17 signaling pathway and NF-kappa B signaling pathway (Figure L).

In conclusion, *CALR*-mutated pre-PMF patients with HB value ≤128 g/L were more likely to progress to overt-PMF. Genetic analysis found patients with high proportion of progress to overt-PMF tended to possess mutations associated with myeloid related transcription factor. And the upregulation of CSCF3 and CXCL13 may potentially drive the progression of overt-PMF in pre-PMF patients through inflammatory and cytokine related pathways.

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Disclosures No relevant conflicts of interest to declare.

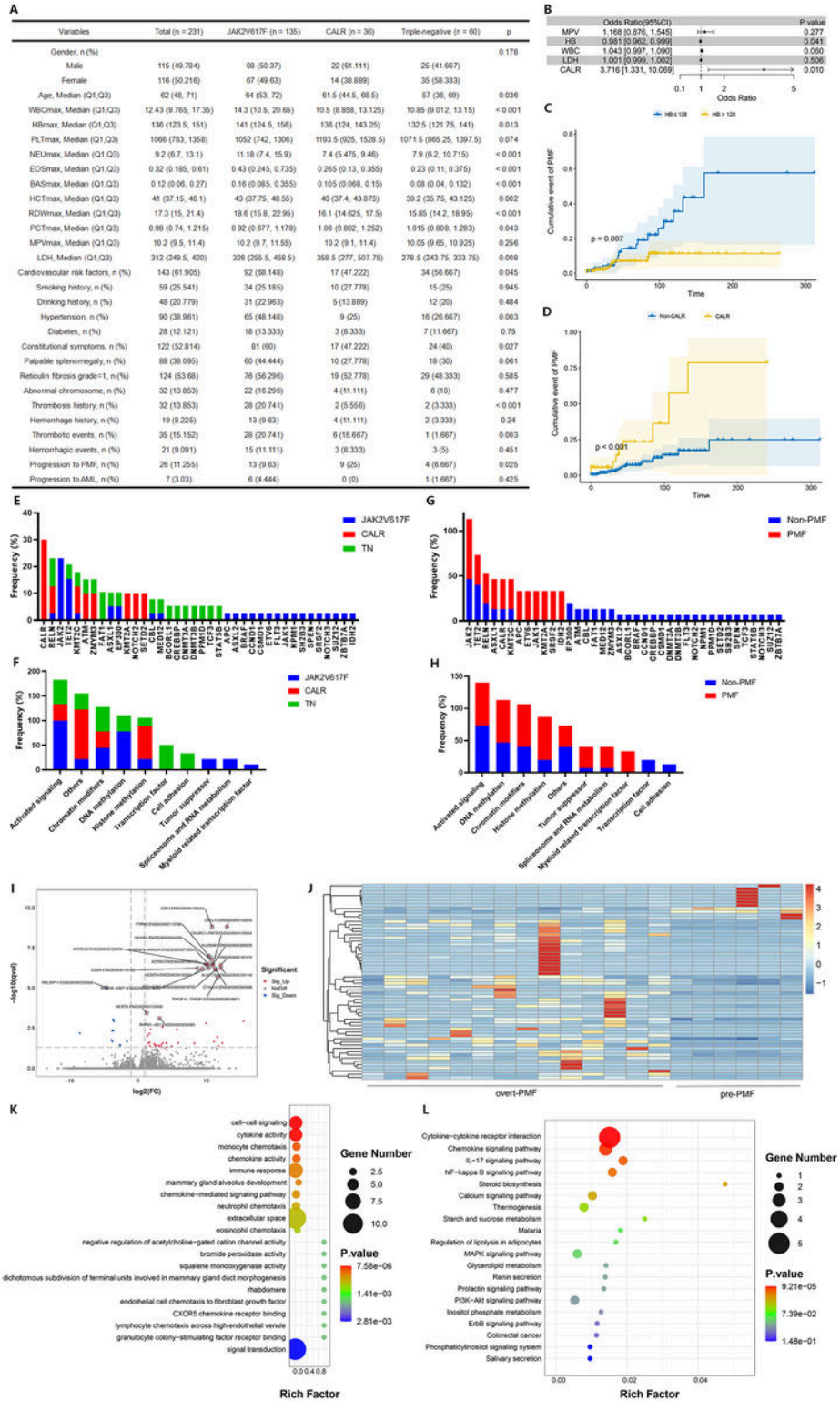

Figure 1

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