P1019 A PREDICTION RULE TO GUIDE JAK2 MUTATION TESTING IN PATIENTS WITH SUSPECTED POLYCYTHEMIA VERA: RESULTS FROM THE JAK2 PREDICTION COHORT (JAKPOT) STUDY

**Topic:** 16. Myeloproliferative neoplasms - Clinical

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**Background:** The widespread availability of molecular testing for JAK2 mutations in patients referred for elevated hemoglobin has facilitated the diagnosis of polycythemia vera (PV) but also raises concerns of test overuse. A prediction rule could be useful to improve test utilization.

**Aims:** In this study, we aimed to derive and validate a simple rule using complete blood count and white blood cell differential (CBC) parameters to predict the likelihood of having a JAK2 mutation in patients referred for elevated hemoglobin.

**Methods:**

We examined all adult patients with elevated hemoglobin (≥160 g/L for women, or ≥165 g/L for men) who underwent JAK2 mutation testing using either quantitative polymerase chain reaction (qPCR), single nucleotide polymorphism (SNP) allelotyping or Next Generation Sequencing (NGS) panel between 2015 and 2021 at London Health Sciences Centre in Ontario, Canada. We extracted data on age, sex, and complete blood count and white blood cell differential (CBC) at the time of testing. All CBCs were performed on a Sysmex XN Analyzer. Patients were randomly divided into derivation and validation cohorts including all methods of JAK2 mutation testing. JAK2-positive and -negative groups were compared using Student’s t-tests or χ² tests, as appropriate. Continuous variables were dichotomized at optimal cut-off points using receiving operating characteristic curves. Potentially significant predictors were evaluated using multiple variable stepwise logistic regression analysis with JAK2 positivity as the dependent variable. A score was derived and internally validated using non-parametric bootstrapping. The model was tested in the validation cohort and sub-analyses for each method were conducted in a similar fashion. Test accuracy for the score was evaluated in all cohorts.

**Results:**

The total study cohort included 901 patients (derivation n=616, validation n=285). Population characteristics are shown in Table 1A. The final model included 1-point for any of the following: erythrocytes >6.45 × 10¹²/L, platelets >350 × 10⁹/L, and neutrophils >6.2 × 10⁹/L. Patients with a score of 0 were considered low-risk; all others were classified as high-risk. The percentage of JAK2 positive patients in patients with a score of 1-3 was 24% versus 0.8% in patients with a score of 0. The model had a sensitivity of 94.7% and a negative predictive value of 98.8% in the derivation cohort; both sensitivity and negative predictive value were 100% in the validation cohort. The percent of false negatives was 0.6% and 0% in the derivation and validation cohorts, respectively (Table 1B). The results were consistent for each testing method.
We developed and validated a simple rule using CBC parameters to predict the likelihood of JAK2 mutation positivity in patients with elevated hemoglobin with demonstrated high sensitivity and negative predictive value across different JAK2 mutation testing platforms. In our cohort, the use of this rule to guide molecular testing would have resulted in over 50% fewer tests. Further studies to prospectively validate this prediction rule in different populations are planned.

**Summary/Conclusion:**

We developed and validated a simple rule using CBC parameters to predict the likelihood of JAK2 mutation positivity in patients with elevated hemoglobin with demonstrated high sensitivity and negative predictive value across different JAK2 mutation testing platforms. In our cohort, the use of this rule to guide molecular testing would have resulted in over 50% fewer tests. Further studies to prospectively validate this prediction rule in different populations are planned.

**Table 1.**

| Characteristic          | Derivation cohort (n = 616) | Validation cohort (n = 285) |
|-------------------------|-----------------------------|-----------------------------|
| Age, mean (SD) (years)  | 58 (15)                     | 58 (15)                     |
| Male sex, number (%)   | 409 (72.0)                  | 265 (71.9)                  |
| Hemoglobin, mean (SD) (g/L) | 177 (11)                   | 177 (11)                   |
| Hematocrit, mean (SD) (L/L) | 9.53 (0.04)               | 9.53 (0.04)               |
| Erythrocytes, mean (SD) (× 10¹²/L) | 6.11 (0.997)           | 5.90 (0.607)           |
| Platelets, mean (SD) (× 10¹²/L) | 266 (162)                 | 281 (187)                 |
| Leukocytes, mean (SD) (× 10⁹/L) | 9.2 (4.0)                | 9.1 (3.3)                |
| Neutrophils, mean (SD) (× 10⁹/L) | 6.0 (3.7)               | 5.7 (2.5)               |
| JAK2 mutation, positive, number (%) | 35 (12.2)             | 31 (10.9)               |

| Testing method, number (%) | 359 (58.1) | 173 (60.7) |
|-----------------------------|------------|------------|
| Next Generation Sequencing  | 59 (8.0)   | 13 (4.3)   |
| Polymerase Chain Reaction   | 252 (39.2) | 70 (24.6)  |
| SNP Allelotyping             | 163 (26.7) | 42 (14.7)  |

**R. JAK2 prediction rule contingency tables for derivation and validation cohorts.**

| Cohort | Prediction rule score | JAK2 mutation |
|--------|-----------------------|---------------|
|        | Positive | Negative |
| Derivation (n = 616) | 0 | 4 (0.6%) | 326 (52.9%) |
|        | 1-3 | 71 (11.5%) | 215 (34.9%) |
| Validation (n = 285) | 0 | 0 (0%) | 155 (53.7%) |
|        | 1-3 | 31 (10.9%) | 101 (35.4%) |
| Total (n = 901) | 0 | 4 (0.4%) | 479 (53.2%) |
|        | 1-3 | 162 (13.3%) | 316 (35.1%) |

**Abbreviations:** standard deviation (SD); single nucleotide polymorphism (SNP).