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# Association of red blood cell distribution width and lactate dehydrogenase with disease transformation in essential thrombocythaemia and polycythaemia vera patients: a UK cohort study using electronic health records

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## Introduction

Patients living with essential thrombocythaemia (ET) or polycythaemia vera (PV) are at risk of disease transformation to secondary myelofibrosis (SMF) and/or acute myeloid leukaemia (AML), which results in poorer outcomes for these patients[1].

Prognostic markers for disease transformation are pivotal in ensuring earlier and potentially more successful therapeutic management[2].

While the role of haemoglobin, platelets, and white blood cells (WBC) for prognosis has repeatedly been described in the literature[3], the importance of other biomarkers, such as red blood cell distribution width (RDW) and lactate dehydrogenase (LDH) for prognosis is less certain[4].

## Objective

To investigate whether RDW and LDH are associated with disease progression in patients diagnosed with ET or PV.

## Methods

Electronic health records for patients diagnosed with either ET or PV were collected from two UK NHS trusts (Chelsea & Westminster Hospital NHS Foundation Trust and Oxford University Hospitals NHS Foundation Trust) between 2008 and 2020.

Patients entered the cohort on the day of their earliest recorded ET or PV diagnosis (index date) and were observed until transformation to SMF or AML, death, loss to follow-up, or 5 years after index event.

Any laboratory tests recorded within ±30 days of index date were included to account for potential time differences between investigations and diagnosis.

Analysis adjusted for age, sex, Charlson Comorbidity Index (CCI), and laboratory measurements at index date, including blood counts (haemoglobin, platelets, WBC, % neutrophils, % lymphocytes, % monocytes).

Missing laboratory data was imputed using multiple imputation (M=100), where predictive mean matching was used to impute likely values.

Competing-risks survival regression was used to determine the adjusted hazard ratio (HR) of increased RDW and LDH with the risk of transformation to SMF or AML, where death was considered a competing risk.

An independent patient cohort from the NHS Greater Glasgow and Clyde health board in Scotland using medical records collected between 2000 and 2020 was used as a validation cohort.

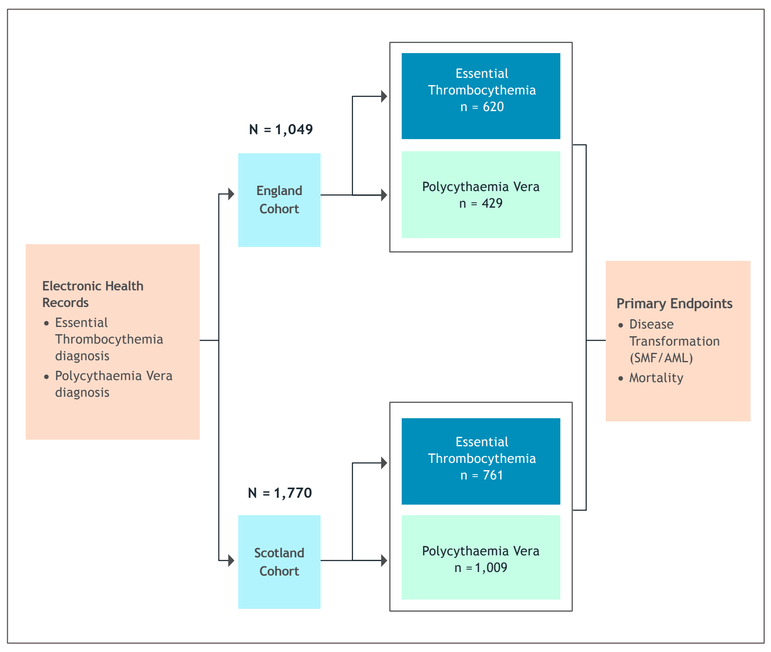
## Results

### Summary Statistics

A total of 1,049 patients were identified from the two English NHS trusts, 620 ET patients and 429 PV patients **(Figure 1 and Table 1)**.

- Age at first presentation was 66.7 years, where PV patients were marginally younger on average (65.6 years) relative to ET patients (67.4 years).
- A greater proportion of ET patients were female (59.5%), whereas a greater proportion of PV patients were male (68.1%).
- ET patients were on average more comorbid, with a greater proportion with a CCI ≥3 (25.8%) relative to PV patients (14.9%).
- As expected, ET patients had higher levels of platelets on average, whilst PV patients had higher levels of haemoglobin, haematocrit and RBC on average.

Figure 1. Patient cohorts for the England and Scotland datasets




### Transformation to SMF or AML

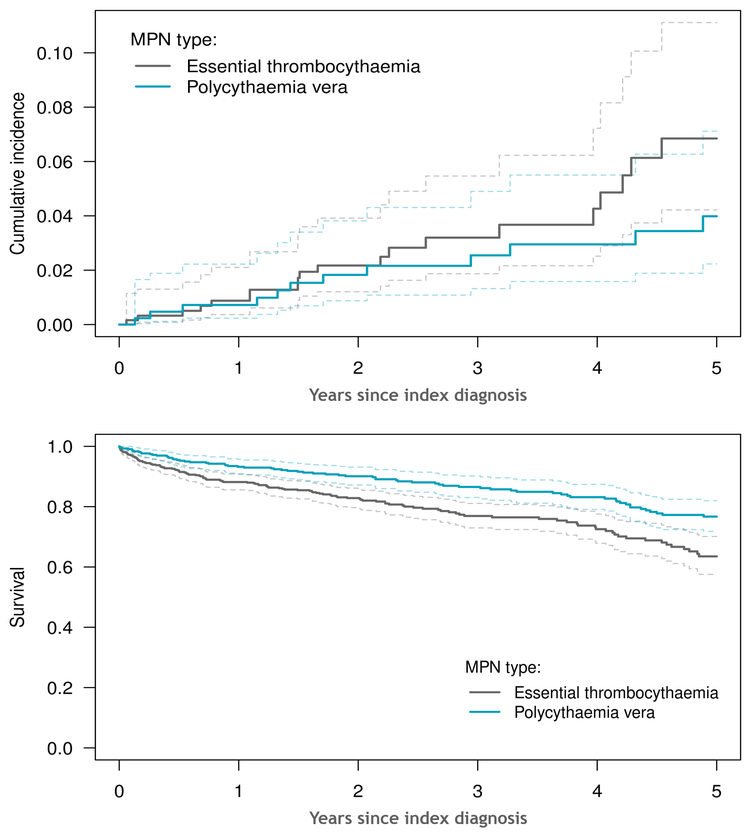
The cumulative incidence of transformation to MF or AML was comparable between ET and PV patients **(Figure 2A)**.

- After 5 years of follow-up an estimated 6.8% (95% CI 4.2-11.1) of ET patients and 4.0% (95% 2.2-7.1) PV patients had undergone transformation.

Adjusted survival rates were lower for ET patients relative to PV patients **(Figure 2B)**.

- After 5 years of follow-up, an estimated 63.5% (95% CI 57.5-70.1) of ET patients had survived, whereas 76.7% (95% 71.8-82.0) of PV patients survived.

Figure 2. Cumulative incidence of transformation to MF or AML (A) and proportion of ET and PV patients still alive (B) over the course of follow-up.




### Association of RDW and LDH on risk of transformation

After adjusting for demographic, CCI and other blood markers,

- An increase in RDW by one standard deviation (SD) (19.1% vs 15.5%) was associated with a 2.6-fold increase in the risk of transformation for patients (HR=2.56; 95% CI 1.20-5.47, p=0.019).
- An increase in LDH by one SD (411.5 U/L vs 268.8 U/L) was associated with a 2.2-fold increase in risk of transformation (HR=2.21; 95% CI 1.37-3.55, p=0.002).

Analysis of an independent cohort of 761 ET and 1,009 PV patients from Scotland resulted in very similar estimates:

- An increase in RDW by one SD (19.1% vs 15.5%) was associated with a 2.5-fold increase in the risk of transformation for patients (HR=2.47; 95% CI 1.30-4.72, p=0.014).
- An increase in LDH by one SD (411.5 U/L vs 268.8 U/L) was associated with a 2.2-fold increase in risk of transformation (HR=2.23; 95% CI 1.38-3.61, p=0.003) **(Figure 3)**.

Figure 3. Estimated crude and multivariably adjusted hazard ratios for the association of RDW and LDH and transformation to SMF or AML among patients with ET or PV in England and Scotland.

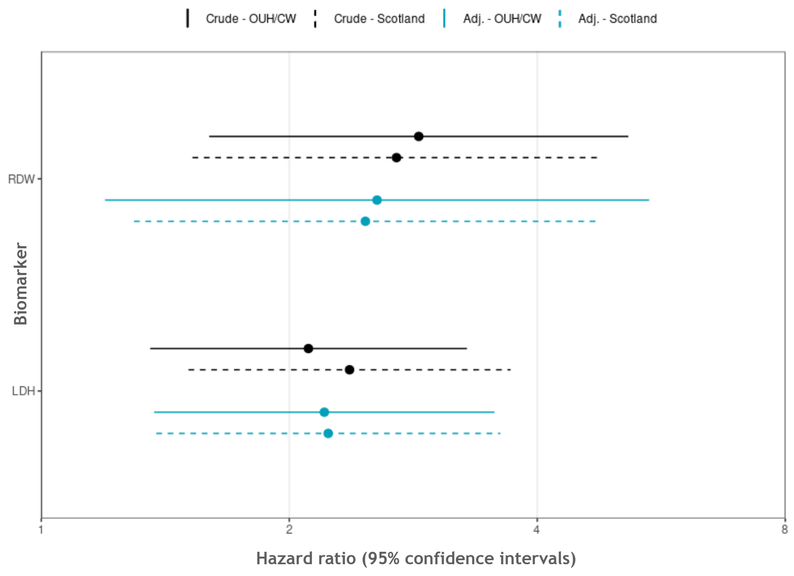



Table 1. Summary characteristics

| | Total (N = 1,049) | | ET (N = 620) | | PV (N = 429) | |
|---|---|---|---|---|---|---|
| | N (%) or median (IQR) | Missing % | N (%) or median (IQR | Missing % | N (%) or median (IQR) | Missing % |
| **Demography** | | | | | | |
| Age at cohort entry | 66.7 (53.2, 77.7) | 0.0% | 67.4 (51.2, 79.0) | 0.0% | 65.6 (54.2, 75.4) | 0.0% |
| Sex | | 0.0% | | 0.0% | | 0.0% |
| Male | 543 (51.8%) | | 251 (40.5%) | | 292 (68.1%) | |
| Female | 506 (48.2%) | | 369 (59.5%) | | 137 (31.9%) | |
| CCI | | 14.1% | | 5.5% | | 26.6% |
| 0 | 377 (41.8%) | | 224 (38.2%) | | 153 (48.6%) | |
| 1-2 | 326 (36.2%) | | 211 (36.0%) | | 115 (36.5%) | |
| ≥3 | 198 (22.0%) | | 151 (25.8%) | | 47 (14.9%) | |
| **Blood measurements** | | | | | | |
| Haemoglobin (g/dL) | 12.9 (10.7, 15.1) | 15.1% | 11.6 (9.8, 13.1) | 14.2% | 15.6 (13.7, 17.2) | 15.9% |
| Haematocrit (%) | 39.5 (33.3, 46.7) | 15.1% | 35.1 (30.3, 39.7) | 14.2% | 47.5 (43.4, 51.6) | 15.9% |
| RBC count (x $10^{12}$/L) | 4.3 (3.5, 5.3) | 15.1% | 3.8 (3.3, 4.4) | 14.4% | 5.5 (4.8, 6.1) | 15.9% |
| Platelet count (x $10^9$/L) | 456.4 (300.6, 625.9) | 15.1% | 524.0 (382.3, 681.9) | 14.4% | 328.7 (222.1, 496.0) | 15.9% |
| WBC count (x $10^9$/L) | 9.8 (7.3, 12.7) | 15.1% | 10.3 (7.8, 12.8) | 14.4% | 8.9 (7.0, 12.3) | 15.9% |
| Neutrophils (%) | 72.0 (63.8, 78.7) | 15.1% | 73.1 (65.0, 79.1) | 14.4% | 70.4 (61.4, 77.8) | 15.9% |
| Lymphocytes (%) | 16.2 (11.4, 23.9) | 15.1% | 15.3 (11.0, 22.5) | 14.4% | 18.3 (12.2, 25.0) | 15.9% |
| Monocytes (%) | 7.3 (5.9, 9.3) | 15.1% | 7.6 (6.1, 9.5) | 14.4% | 7.0 (5.5, 9.2) | 15.9% |
| RDW (%) | 15.3 (13.8, 17.8) | 56.3% | 15.6 (14.0, 18.1) | 54.4% | 15.0 (13.6, 17.5) | 59.2% |
| LDH (u/L) | 268.5 (220.5, 350.0) | 78.8% | 273.0 (222.0, 341.0) | 82.4% | 267.0 (219.0, 350.0) | 73.7% |
| **Outcomes** | | | | | | |
| Transformation to MF or AML | 32 (3.1%) | 0.0% | 20 (3.2%) | 0.0% | 12 (2.8%) | 0.0% |
| Death from any cause | 201 (19.2%) | 0.0% | 131 (21.1%) | 0.0% | 70 (16.3%) | 0.0% |

## Conclusions

- Increased levels of RWD and LDH were found to be associated with increased risk of disease transformation whilst controlling for established prognostic factors in two independent patient cohorts in England and Scotland.
- These are novel markers not yet described in the literature.
- Integration of these markers in the development of prognostic scores of disease transformation in both ET and PV should be considered.

## References

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