

Avoid getting hot under the collar: Indices to guide Bone Marrow Examination in Pyrexia of Unknown Origin

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Introduction

Pyrexia of unknown origin (PUO) is defined as a persistent temperature $>38.3^{\circ}\text{C}$ over a period of three or more weeks, for which a cause has not been identified despite one week of inpatient hospital investigations.

Over 200 underlying aetiologies described including infective, neoplastic and inflammatory pathologies, although for a considerable proportion of patients, no diagnosis is made.

Following initial work-up of detailed history, clinical examination and investigations including blood cultures, serological tests, autoimmune screen and imaging, **second-line investigations may be considered, including bone marrow examination (BME).**

As an invasive test that may be uncomfortable for the patient, it is important to maximise pre-test probability. **Previous work has suggested that the use of a bone marrow 'score', including haemoglobin, platelet and neutrophil counts, LDH, ferritin, blood film appearances and presence of splenomegaly, may aid patient selection.**

Methods

Retrospective review of patients presenting to Newcastle-upon-Tyne Hospitals NHS Foundation Trust between 2012 and 2017 with PUO who underwent BME.

Collected following patient characteristics:

- Age
- Sex
- Immune status (including HIV)
- FBC indices
- CRP
- Ferritin
- LDH
- Ferritin
- Blood film appearances
- Presence/ absence splenomegaly
- Final known outcome

Differences in variables according to bone marrow outcome (positive or negative diagnosis) were assessed using Chi-square or Fisher's exact tests (categorical variables) or Wilcoxon rank sum tests (continuous variables).

Effects of different variables on having a positive bone marrow result were estimated using age- and sex-adjusted odds ratios.

Results

Patient Demographics:

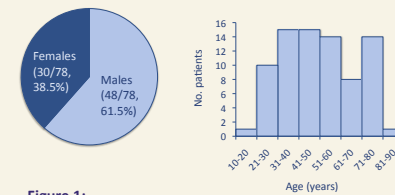


Figure 1: Sex and age demographics of the patient cohort.

Patient Characteristics:

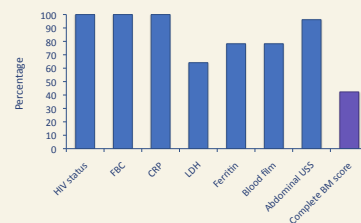


Figure 2: Percentage of characteristics available for each patient. Complete bone marrow score could only be calculated for 33/78 patients due to incomplete data availability.

Characteristics as predictors of positive diagnosis following BME:

Indice	Negative BM (n=62)	Positive BM (n=16)	p-value
Age (years)	49	59	0.091
Male (%)	56.5	81.3	0.060
HIV +ve (%)	21.0	12.5	0.45
Hb (g/L)	102	97	0.69
Neut count ($\times 10^9/\text{L}$)	5.34	3.96	0.32
Plt count ($\times 10^9/\text{L}$)	265	174	0.13
CRP (mg/L)	49	115	0.028
Ferritin (ng/ml)	533	1037	0.007
LDH (U/L)	395	1107*	0.077
Splenomegaly (%)	23.7	37.5	0.27
BM score ≥ 6 (%)	29.0	63.5	0.017
Alive at final follow-up (%)	87.3	57.1	0.004

Figure 3: Summary of average blood indices, or percentage of cohort with certain characteristic. *Value influenced by single outlier with LDH 11,295 U/L.

Indice	adj.OR	95% CI	p-value
CRP >40	5.90	1.19-29.1	0.029
Ferritin >750	4.88	1.26-18.9	0.022
BM score ≥ 6	11.0	1.30-93.7	0.028
Alive at final follow-up	0.24	0.031-0.065	0.031

Figure 4: Age- and sex-adjusted odds ratios with statistically significant association for positive diagnosis being made as a result of BME.

Discussion

• Strong evidence of higher ferritin in patients with positive diagnosis made on BME, with all having a ferritin ≥ 500 .

• Five patients with no diagnosis made on BME had a ferritin $>10,000$, the ultimate diagnosis in these patients was HLH (2 patients), undifferentiated connective tissue disease (1 patient), Still's disease (1 patient), and Multiple Organ Failure in context of advanced HIV (1 patient).

• Weak evidence that positive bone marrows more likely in older, male patients.

• No evidence of significant difference in haemoglobin, platelet or neutrophil count, or LDH according to positive or negative result on BME in this series.

• Good evidence of higher median CRP in patients who had positive diagnosis made following BME - no patients in this series had normal CRP.

• Strong evidence that larger proportion of survivors had no diagnosis made on bone marrow examination.

Conclusion

Bone marrow 'score' ≥ 6 , and CRP and ferritin independently, appear to be predictors of a positive diagnosis being made on bone marrow examination.

Recommendations

Collection of the parameters making up the bone marrow 'score' should form part of the standardized work-up of PUO.

Prospective evaluation of complete data, and collaborative study across different sites to increase statistical power.

Prospective evaluation of ferritin <500 as rule-out test for proceeding to bone marrow examination.

References

Wang HY, Yang CF, Chiou TJ, Yang SH, Gau JP, Yu YB, et al. A "bone marrow score" for predicting hematological disease in immunocompetent patients with fevers of unknown origin. *Medicine*. 2014 Dec;93(27):e243.