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International, Multicentre Evaluation of AI Augmented Fibrosis Grading in a Real-World, Clinical Cohort of 1000 Patients

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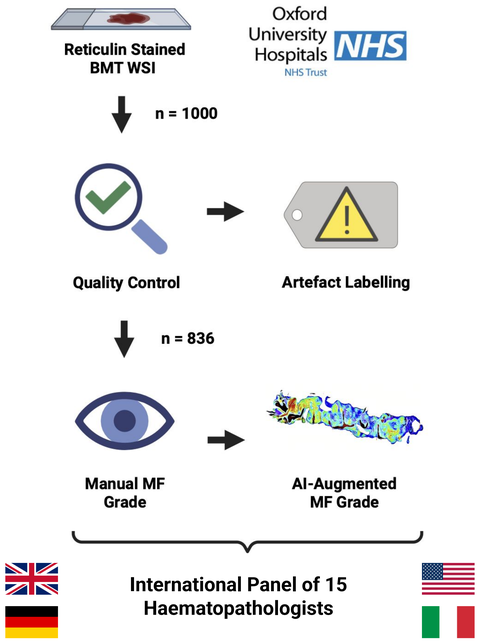
INTRODUCTION

Fibrosis grading is critical to the classification, prognostication and monitoring of myeloproliferative neoplasms (MPN). Manual estimation of fibrosis is subjective and only semi-quantitative. AI-augmented evaluation of fibrosis using *continuous indexing of fibrosis* (CIF) improves accuracy of fibrosis grading in clinical trials.[1] Here we evaluate its performance to support deployment in clinical practice.

AIMS

- Determine the quality of digital whole slide images (WSI) of reticulin-stained bone marrow trephines (BMT) from a large, tertiary referral laboratory.
- Measure the concordance of reticulin quality control (QC) assessments between expert Haematopathologists.
- Evaluate the performance of an AI fibrosis algorithm (CIF v1.5.3) on a large cohort of routine clinical BMT samples.

METHOD



MODEL TRAINING

CIF v1.5.3 is a ranking convolutional neural network, trained using a pairwise ranking strategy (*RankNet*), incorporating human-in-the-loop manual image ranking.

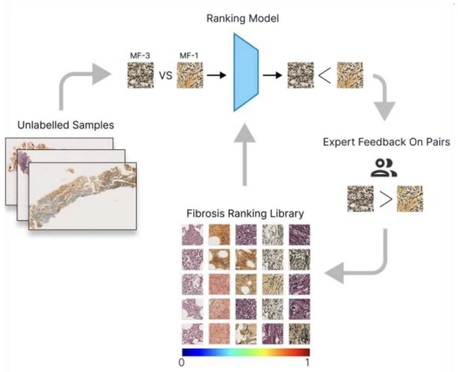
WSIs are divided into uniform tiles then segmented to exclude non-haematopoeitic areas. The model output is the CIF score for each tile: 0 (no fibrosis) to 1 (maximal fibrosis).

Training: 476 BMTs (23,504 tiles)

Independent Testing: 105 BMTs (6,090 tiles)

Accuracy 0.891 | Precision 0.904 | Recall 0.885 | F1 0.895

Performance based on pairwise ranking agreement vs. human annotations.



Overview of the computational steps for detection and quantification of reticulin fibrosis from WSIs of BMTs. From Ryou, H et al Leukaemia (2023.)

VALIDATION DATASET

Digital WSIs of 1,000 sequential BMTs were identified from Oxford University Hospitals pathology archive (April 2023-July 2024.)

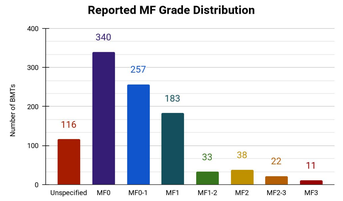
Inclusion: H&E + reticulin WSIs available

Exclusion: patient registered for NHS data opt out

Age (mean): 60.6 years

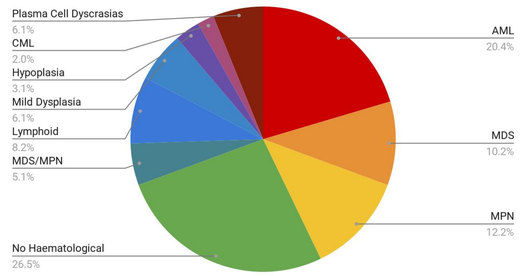
Age (range): 1-95 years

Sex: ♂ 56%, ♀ 43%



Histogram of reported MF-grades for sample BMTs

Ethnicity: White 50%, Not Stated 41%, Asian 6%, Black 1%, Other 1%



Pie chart of histological diagnoses for sample BMTs as reported by Oxford University Hospitals NHSFT Pathology Department

PRELIMINARY ANALYSIS I

On viewing the same sample on separate occasions, pathologists assigned a different MF-grade in 1/3 cases (intraobserver agreement 66.26%)

Access to heatmaps significantly reduced interobserver variability:

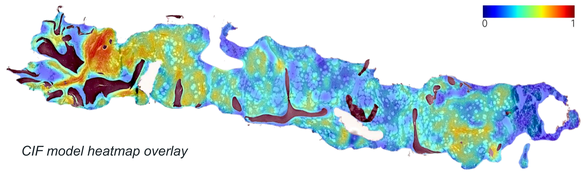
Manual Read: 0.51-0.84 (weighted kappa range)
CIF Assisted Read 0.60-0.84
} p=0.0017*

Access to heatmaps significantly improved MF-grade consensus:

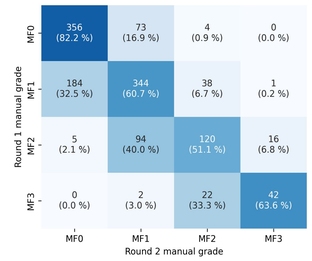
CIF Sequential Read OR 1.43 (1.19-1.71), p=0.0001*

CIF Concurrent Read OR 2.41 (1.93-3.02), p<0.0001*

(Odds ratio of consensus agreement relative to manual read, based on generalised linear modelling)



CIF model heatmap overlay



LEFT: confusion matrix for overall intraobserver variation: manual MF-grade round 1 vs. manual MF-grade round 2 (identical slide sets.)

Weighted kappa = 0.746 (95% CI: 0.720-0.772)

PRELIMINARY ANALYSIS II

Interpretation of CIF heatmaps was in agreement with ground truth*:

Round	Agree (n)	Disagree (n)	Agreement with ground truth*
Manual Read	771	384	66.8%
CIF Assisted Sequential Read	798	384	69.1%
CIF Assisted Concurrent Read	719	342	67.8%

*ground truth was the manual consensus MF-grade due to conventional acceptability.

CONCLUSIONS

Access to a CIF generated heatmap significantly improved interobserver agreement and MF-grading consensus, whilst remaining in agreement with our ground truth (manual consensus).

The variability we have described in human assigned MF-grades supports the need to pursue a more objective approach to quantifying reticulin fibrosis.

REFERENCES

1. Ryou, H., Sirinukunwattana, K., Aberdeen, A. *et al.* Continuous Indexing of Fibrosis (CIF): improving the assessment and classification of MPN patients. *Leukemia* 37, 348–358 (2023). https://doi.org/10.1038/s41375-022-01773-0

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