

Clonal Hematopoiesis Risk Score

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Abstract

The Clonal Hematopoiesis Risk Score (CHRS) stratifies patients with clonal hematopoiesis of indeterminate potential (CHIP) or clonal cytopenia of undetermined significance (CCUS) into three different risk categories: low-risk (88.4%), intermediate-risk (10.5%), and high-risk (1.1%). These risk categories correspond to 10-year cumulative incidence of myeloid neoplasm of 0.7%, 7.8%, and 52.2%.

I. HOW TO USE

When to Use: This risk score is relevant for patients with CHIP or CCUS.

Pearls / Pitfalls: This CHRS was developed based on a cohort of participants ages 40-70 years of age. CHIP and CCUS were defined as somatic mutations with a variant allele frequency (VAF) of at least 0.02. CHRS does not take into account malignancy history and previous exposure to antineoplastic therapy, which was shown by Bolton et al. and Coombs et al. as enriching for certain high-risk mutations. Additionally, Nead et al. and Chien et al. showed clonal evolution and myeloid neoplasm development with these external stressors.

Why Use: This risk score defines three unique risk groups for patients with CHIP or CCUS based on age, red blood cell indices, and mutational profiles. It might help health systems triage which patients could be followed in an early cancer detection program given elevated risk of developing myeloid neoplasm.

II. NEXT STEPS

Advice: The tool should not be the sole basis for care, and clinicians should use judgment and a full clinical evaluation when advising patients. NCCN Guidelines for Myelodysplastic Syndromes, Version 3.2026 recommend considering using CHRS to risk categorize patients with CHIP or CCUS, but CHRS efficacy confirmatory studies are needed to help determine the role of CHRS in clinical decision-making.

Management: The creators of CHRS recommend possible malignancy risk mitigation strategies by risk level, outlined below.

For high-risk CHRS score, patients could have a complete blood count with differential every 3-6 months, next generation sequencing annually, bone marrow biopsy if any clinical changes, and considering the risks and benefits of participating in a clinical trial.

For intermediate-risk or low-risk CHRS scores, patients could have a complete blood count with differential annually, as well as next generation sequencing and bone marrow biopsy if any clinical changes.

Critical Actions: Given patients with a CHRS score should have CHIP or CCUS, the creators of CHRS also recommend non-malignant disease risk management for all patients. First, risk factors or symptoms of ischemic cardiovascular disease should be assessed. Additionally, patients should be referred to a primary care physician or preventive cardiologist for guideline-based prevention strategies of cardiovascular disease. Finally, depending on patients' symptoms, exam findings, and personal risk, other specialties such as rheumatology, endocrinology, or hepatology may be engaged.

Saadatagah et al. also recommended cardiovascular screening, especially for those with higher CHRS scores given associations with cardiovascular disease-related mortality.

III. EVIDENCE

Evidence Appraisal: Patel et al. evaluated CHRS in a real-world sample of 94 patients with clonal hematopoiesis and compared 27 patients solely with canonical *DNMT3A/TET2/ASXL1* mutations to 67 patients without these sole mutations. They identified that 0% of those with sole canonical mutations progressed to myeloid neoplasm without acquiring other mutations

while 20% of those without these sole mutations progressed. This analysis was done to account for CHRS being developed with data from healthy adults.

Galli et al. determined that CHRS predicted therapy-related myeloid neoplasms after CAR T-cell therapy with good specificity. Only patients with intermediate-high CHRS developed therapy-related myeloid neoplasms (OR 2.89).

Saadatagah et al. demonstrated that CHRS was associated with all-cause mortality, hematologic malignancy-related mortality, and cardiovascular disease-related mortality in older adults with clonal hematopoiesis.

The accompanying editorial by Xie & DeZern (*NEJM Evid*, 2023) highlights important limitations about the United Kingdom biobank database used to develop CHRS. These include concerns about lead-time and length bias from the younger median age of those in the biobank and potentially missed dysplasias in those labeled “normal at entry” due to the absence of a bone marrow biopsy at enrollment. These limitations were addressed through robust validation in 1 internal and 2 external cohorts. Of note, most of the patients in the training and validation cohorts were White, so CHRS may not be applicable to patients of other races.

The creators of CHRS (Weeks & Ebert, *Blood*, 2023) also note that there are potentially missing predictive features in CHRS, such as body mass index and serum chemistries (included in MN-Predict) or cytogenetic abnormalities. The creators of MN-Predict note that CHRS groups all types of myeloid neoplasms into a single category and has heterogeneity in the likelihood of progression within each of the 3 risk groups.

FORMULA

1. Cytopenia - select whether the diagnosis is CCUS (1.5) or CHIP (1), where CCUS is defined as anemia (hemoglobin < 12 g/dL for females or < 13 g/dL for males), thrombocytopenia (platelet count < 150K/uL), or neutropenia (absolute neutrophil count < 1.8K/uL)
2. Mutation Number - select whether the number of pathogenic somatic variants (mutations) detected by peripheral blood or bone marrow sequencing is 2+ (2) or 1 (1)
3. Single *DNMT3A* – if a patient has only one mutation, indicate whether the mutated gene is *DNMT3A* (0.5) or not (1) – this should default to absent (1) for those with multiple mutations
4. High Risk Mutation – indicate whether mutations in high risk genes (*SF3B1*, *SRSF2*, *ZRSR2*, *JAK2*, *TP53*, *RUNX1*, *FLT3*, *IDH1* or *IDH2*) are present (2.5) or absent (1)

5. VAF – indicate if the maximum variant allele fraction (VAF) for any mutation is $\geq 20\%$ (2) or if all are < 20% (1)
6. MCV – indicate whether the mean corpuscular volume (MCV) is ≥ 100 (2.5) or < 100 (1)
7. RDW – indicate whether the red cell distribution width (RDW) is $\geq 15\%$ (2.5) or < 15% (1)
8. Age – indicate if the age is ≥ 65 (1.5) or < 65 (1)

Sum the number of points to stratify risk into low (≤ 9.5), intermediate (10-12), or high (≥ 12.5).

Facts & Figures: Patients in the low-risk group have a 10-year cumulative incidence of myeloid neoplasm of 0.7%. Their 10-year survival is 93.7% of those without CHIP/CCUS.

Patients in the intermediate-risk group have a 10-year cumulative incidence of myeloid neoplasm of 7.8%. Their 10-year survival is 84.0% of those without CHIP/CCUS.

Patients in the high-risk group have a 10-year cumulative incidence of myeloid neoplasm of 52.2%. Their 10-year survival is 51.2% of those without CHIP/CCUS.

LITERATURE

Original/Primary & Validation

Weeks LD et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. *NEJM Evid*. 2023;2(5):10.1056/evidoa2200310. PMID 37483562.

Other References (including meta-analyses, CPGs, and impact analyses):

Patel SA et al. Natural history of clonal haematopoiesis seen in real-world haematology settings. *Br J Haematol*. 2024;204(5):1844-1855. PMID 38522849.

Galli E et al. Predicting therapy-related myeloid neoplasms after CAR-T with Clonal Haematopoiesis Risk Score (CHRS). *Br J Haematol*. 2025;206(1):372-374. PMID 39539012.

Saadatagah S et al. Clonal Hematopoiesis Risk Score and All-Cause and Cardiovascular Mortality in Older Adults. 2024;7(1):e2351927. PMID 38231513.

Greenberg PL et al. Myelodysplastic Syndromes. NCCN Guidelines Version 3.2026 – January 12, 2026.

Xie Z & DeZern AE. How Great Is The Threat of Clonal Hematopoiesis? Let This New Risk Score Be Your Guide. *NEJM Evid*. 2023;2(5):EVIDe2300053. PMID. 38320009.

Weeks LD & Ebert BL. Causes and consequences of clonal hematopoiesis. *Blood*. 2023;142(26):2235-2246. PMID 37931207.

Gu M et al. Multiparameter prediction of myeloid neoplasia risk. *Nat Genet*. 2023;55(9):1523-1530. PMID 37620601.