Drivers of Inflammation; Clonal Hematopoiesis: Clinical Implications

Tuğcan Alp Kırkızlar[1], Mutlu Arat[2]

[1]Department of Hematology, Trakya University Faculty of Medicine, Edirne, Türkiye
[2]Clinic of Hematology, Memorial Şişli Hospital, İstanbul, Türkiye

In recent years, growing evidence linking clonal hematopoiesis (CH) to aging, inflammation, inflammation-driven systemic diseases, cardiovascular risk, and cancer has increased interest in its role in disease evolution and somatic variation. In parallel, advances in next-generation and single-cell sequencing technologies, combined with computational modeling, have significantly improved our understanding of CH biology.[1-3]

CH was initially identified through age-related skewing of X-chromosome inactivation and later associated with somatic TET2 mutations. It is now recognized as a fundamental age-related process characterized by the expansion of hematopoietic stem and progenitor cells carrying somatic variants and mosaic chromosomal alterations (mCAs), with prevalence increasing sharply with age.[2,4]

CH is most commonly driven by mutations in epigenetic regulators such as DNMT3A, TET2, and ASXL1. However, a substantial proportion of cases lack identifiable driver mutations despite being associated with increased mortality, which challenges a purely mutation-centric model. Increasingly, CH is viewed as a dynamic and multifactorial process influenced not only by genetic alterations but also by inflammatory signaling, stochastic processes, epigenetic variability, and bone marrow niche interactions.[2,5] CH likely originates early in life, whereas its expansion is shaped by mutation-specific fitness in the context of germline predisposition and cumulative environmental and inflammatory pressures, including inflammaging and cytotoxic exposures.[1,6] The bidirectional interaction between CH and inflammation further promotes clonal expansion, particularly in DNMT3A- and TET2-mutant clones.[7-9] Together, these findings support a shift from a static genomic framework toward an integrated model of clonal fitness driven by both intrinsic and microenvironmental factors.

CH is increasingly recognized as a clinically relevant condition extending beyond the hematopoietic compartment and is associated with malignancy, cardiovascular disease, and overall mortality.[5,9] Notably, CH has emerged as an independent cardiovascular risk factor, challenging traditional paradigms.[1,9] Its role in oncogenesis is supported by its presence as an early event in both myeloid and lymphoid malignancies, as well as its detection in a substantial proportion of patients with solid tumors. In these cases, tumor-infiltrating CH may remodel the microenvironment, contributing to treatment resistance and late complications such as cardiotoxicity. Furthermore, the selective expansion of preexisting CH clones under therapeutic pressure highlights its contribution to treatment response and the development of therapy-related myeloid neoplasms.[1,3,9]

In transplantation settings, CH has important implications for both recipient and donor selection. High-dose chemotherapy and hematopoietic stem cell transplantation (HSCT) exert selective pressure that promotes clonal expansion, impairs hematopoietic recovery, and increases the risk of secondary malignancies. While donor-engrafted CH in allogeneic HSCT may reduce relapse without affecting overall survival, pretransplant CH in autologous HSCT is associated with inferior outcomes. In solid organ transplantation, CH has also been linked to adverse outcomes, including donor-derived leukemia, although its clinical relevance remains investigational.[5,10,11]

Collectively, these findings position CH as a potentially actionable biomarker with emerging relevance for risk stratification, donor selection, and therapeutic decision-making across both hematologic and solid malignancies. However, its dual and context-dependent effects underscore the need for prospective validation before routine screening can be broadly implemented.

Corresponding author: Tuğcan Alp Kırkızlar, Department of Hematology, Trakya University Faculty of Medicine, Edirne, Türkiye
e-mail: tugcanalp82@hotmail.com
Available Online Date: xxxxxx • **DOI:** 10.4274/balkanmedj.galenos.2026.2026.240426
Available at www.balkanmedicaljournal.org
ORCID iDs of the authors: T.A.K. 0000-0002-1361-6213; M.A. 0000-0003-2039-8557.
Cite this article as: Alp Kırkızlar T, Arat M. Drivers of Inflammation; Clonal Hematopoiesis: Clinical Implications. Balkan Med J. 2026;43:

Beyond cancer, CH is associated with a broad spectrum of non-malignant conditions, including inflammation-driven diseases such as cardiovascular disorders (e.g., atherosclerosis, heart failure, stroke, and arrhythmias), chronic kidney and liver disease, chronic obstructive pulmonary disease, osteoporosis, gout, and diabetes. In addition, CH has been linked to immune-mediated disorders, including anti-neutrophil cytoplasmic antibodies-associated vasculitis, autoimmune diseases, VEXAS syndrome, multiple sclerosis, and chronic infections, collectively highlighting its systemic impact. Emerging and sometimes paradoxical associations, such as a potential protective effect in Alzheimer's disease, further reflect the biological complexity of CH.[1,3,12]

Collectively, these observations support a paradigm shift in which CH is viewed not merely as a biomarker of aging but as a pleiotropic and potentially actionable driver of disease with implications across multiple medical disciplines. This broadened perspective extends beyond hematology and underscores the need for integrated approaches such as cardio-immunology and cardio-oncology.

As understanding of the clinical, genetic, and bone marrow microenvironmental determinants of CH has expanded, its definitions and classifications have been progressively refined. Classification based on variant allele frequency (VAF) and hematologic parameters remains central to prognostic assessment. CH encompasses a spectrum of entities, including clonal hematopoiesis of indeterminate potential (CHIP) (VAF ≥ 2% in the absence of cytopenia), age-related CH, and micro-CH (VAF < 2%). Lineage-based subclassification further distinguishes myeloid CHIP (e.g., DNMT3A, TET2, ASXL1) from lymphoid CHIP (e.g., PAX5, NOTCH1). Clonal cytopenia of undetermined significance (CCUS) is defined by the presence of somatic mutations accompanied by persistent cytopenia, whereas therapy-related CCUS reflects prior cytotoxic exposure. In addition, mCAs and the concept of context-relevant CH highlight the contribution of structural genomic changes and environmental or germline factors to CH biology and clinical risk.[1,5]

Given the strong associations of CH with both malignant and non-malignant conditions, as well as increased morbidity and mortality, identifying high-risk individuals has become a clinical priority. Although current classification frameworks and prediction models, such as CH and Clonal Cytopenia Risk Scores and MN-Predict, enable risk stratification, they remain incomplete, as they do not fully incorporate key determinants such as structural alterations and germline variation.[1,13,14] This gap highlights the need for more integrative, biology-driven models to improve risk prediction and support truly personalized clinical decision-making.

The growing clinical relevance of CH has led to the emergence of specialized "CHIP clinics" in cancer centers, reflecting an increasing need for multidisciplinary and individualized management in the absence of standardized guidelines. In current practice, CH is most often identified incidentally during evaluation of cytopenias, solid malignancies, germline predisposition syndromes, transplant and cellular therapy settings, and in patients with unexplained atherosclerotic vascular disease or ischemic cardiomyopathy. This pattern reflects a shift from targeted testing to opportunistic detection, raising important questions regarding whom to test and how to act on these findings.[1,3,5] While prospective evidence supporting routine screening remains limited, accumulating retrospective data and clinical experience support a risk-adapted approach to testing.

CH assessment appears particularly informative in selected contexts, including unexplained cytopenias, pretransplant evaluation, and treatment planning in patients exposed to genotoxic therapies, where it may influence prognostication and therapeutic decision-making. At the same time, clinical management remains centered on risk-based surveillance and counseling, with emphasis on avoiding overtreatment in low-risk individuals while identifying those who may benefit from closer monitoring or enrollment in clinical trials. The systemic implications of CH further necessitate multidisciplinary care, particularly for cardiovascular risk assessment and prevention.

However, the current evidence base is largely derived from large-scale biobanks and integrated genomic datasets rather than prospective, clinically driven studies, highlighting a critical gap between discovery and clinical implementation. Moving forward, addressing this gap will be essential to define the true clinical utility of CH testing and guide its integration into routine practice.

VAF thresholds in CH reflect a fundamental tension between clinical applicability and technological sensitivity, as increasingly sensitive sequencing approaches identify low-burden clones of uncertain significance. This underscores the need for harmonized standards across VAF thresholds, gene panels, and analytical pipelines. Ultimately, the clinical relevance of CH depends not on its presence alone but on the biological context, including driver mutation, timing of clonal emergence, clone size, and growth dynamics, highlighting the need for more refined, biology-informed risk stratification.[2,15]

As CH testing becomes increasingly widespread, its integration into clinical workflows will require not only technical standardization but also careful consideration of patient preferences, informed consent, and psychosocial impact.[2] CH is rapidly transitioning from a descriptive biomarker to a potentially actionable clinical entity and therapeutic target, necessitating biomarker-driven trials, refined risk prediction tools, and truly multidisciplinary care models (Figure 1). However, this evolution must proceed cautiously, balancing identification of high-risk individuals against the risks of overmedicalization, while addressing persistent uncertainties regarding clinical benefit, context-dependent effects, and cost-effectiveness.

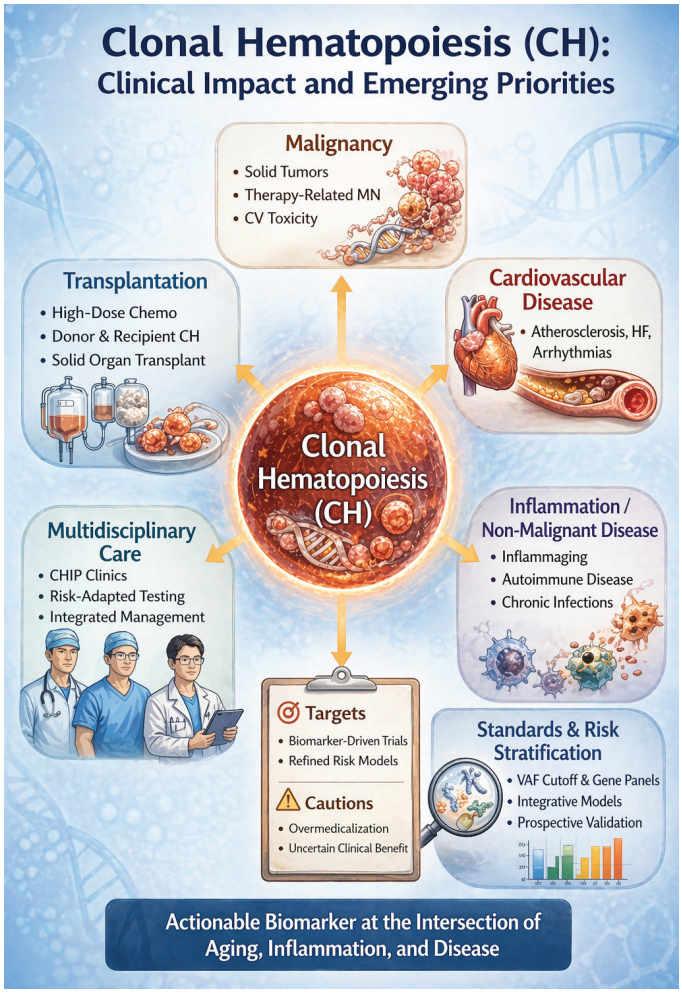

FIG. 1. Clinical impact and emerging priorities (this figure was created with the assistance of ChatGPT/OpenAI for visual/illustrative purposes). *CHIP, clonal hematopoiesis of indeterminate potential; MN, myeloid neoplasm; CV, cardiovascular; HF, heart failure; VAF, variant allele frequency.*

Authorship Contributions: Concept- M.A., T.A.K.; Data Collection or Processing- T.A.K.; Analysis and/or Interpretation- M.A., T.A.K.; Literature Review- M.A., T.A.K.; Writing- T.A.K.; Critical Review- M.A.

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Mangaonkar AA, Bolton KL, Patnaik MM. Clonal hematopoiesis of ındeterminate potential and clonal cytopenias of undetermined significance: 2026 update on clinical associations and management recommendations. *American J Hematol.* 2026;101:550-565. [CrossRef]
2. Wong CK, McDonald A, Buttigieg MM, Rauh MJ. CHIP ahoy: charting a decade of discovery in clonal hematopoiesis. *Haematologica.* 2026;111:457-469. [CrossRef]
3. Weeks LD, Ebert BL. Causes and consequences of clonal hematopoiesis. *Blood.* 2023;142:2235-2246. [CrossRef]
4. Busque L, Mio R, Mattioli J, et al. Nonrandom X-inactivation patterns in normal females: lyonization ratios vary with age. *Blood.* 1996;88:59-65. [CrossRef]
5. Vanner RJ, Zeng AGX, Kim RH, Chan S, Bankar A. Clinical decisions in clonal hematopoiesis: a contemporary review for clinicians. *Haematologica*. 2026;111:1584-1609. [CrossRef]
6. Joo L, Bradley CC, Lin SH, Scheet PA, Nead KT. Causes of clonal hematopoiesis: a review. *Curr Oncol Rep*. 2023;25:211-220. [CrossRef]
7. Winter S, Götze KS, Hecker JS, et al. Clonal hematopoiesis and its impact on the aging osteo-hematopoietic niche. *Leukemia.* 2024;38:936-946. [CrossRef]
8. Cook EK, Luo M, Rauh MJ. Clonal hematopoiesis and inflammation: partners in leukemogenesis and comorbidity. *Exp Hematol.* 2020;83:85-94. [CrossRef]
9. Jaiswal S, Libby P. Clonal haematopoiesis: connecting ageing and inflammation in cardiovascular disease. *Nat Rev Cardiol.* 2020;17:137-144. [CrossRef]
10. Xie Y, Kazakova V, Weeks LD, et al. Effects of donor-engrafted clonal hematopoiesis in allogeneic and autologous stem cell transplantation: a systematic review and meta-analysis. *Bone Marrow Transplant.* 2024;59:1585-1593. [CrossRef]
11. Gillis N, Ebied A, Thompson ZJ, Pidala JA. Clinical impact of clonal hematopoiesis in hematopoietic cell transplantation: a review, meta-analysis, and call to action. *Haematologica*. 2024;109:3952-3964. [CrossRef]
12. Uğurlu S, Kılıç B. VEXAS syndrome: an overlooked threat. *Balkan Med J.* 2025;42:185-187. [CrossRef]
13. Weeks LD, Niroula A, Neuberg D, et al. Prediction of risk for myeloid malignancy in clonal hematopoiesis. *NEJM Evidence.* 2023;2:10. [CrossRef]
14. Xie Z, Komrokji R, Al Ali N, et al. Risk prediction for clonal cytopenia: multicenter real-world evidence. *Blood.* 2024;144:2033-2044. [CrossRef]
15. Marzban S, Stiehl T, Xie Z, et al. Modeling the evolutionary dynamics of clonal hematopoiesis. *Nat Genet.* 2026;58:481-491. [CrossRef]