Inherited DNA repair variants are associated with clonal hematopoiesis and cardiovascular risk in men with metastatic prostate cancer

Myeloid clonal hematopoiesis (CH) arises from somatic mutations in myeloid genes within hematopoietic stem and progenitor cells.[1,2] These mutations confer a proliferative advantage, leading to clonal expansion, increased risk of myeloid neoplasms (MN), and reduced survival in patients with solid tumors.[1,2] While CH is most commonly associated with aging and involves mutations in *DNMT3A, TET2*, and *ASXL1* (collectively referred to as DTA mutations), it is also highly prevalent in solid tumors such as metastatic prostate cancer (mPC), with reported rates up to 57%.[3] In mPC, secondary to genotoxic therapeutic exposures, there is a marked shift toward DNA damage response (DDR) gene mutations such as *TP53, PPM1D*, and *CHEK2*.[3-5] Importantly, in addition to CH, mPC is also characterized by frequent tumor-derived somatic alterations and pathogenic germline variants (PGV), all of which may influence therapy selection and complicate genomic interpretation.[6]

The increasing use of therapeutic modalities such as poly ADP ribose polymerase (PARP) inhibitors and radiopharmaceuticals (e.g., 177Lu-PSMA) raises concerns about further clonal selection.[7] Moreover, CH may influence disease trajectory and treatment tolerance.[8,9] As these therapies move earlier in the disease course, understanding the complex interactions between therapeutic exposures, germline predisposition, and somatic evolution becomes increasingly important for anticipating long-term hematologic and cardiovascular risks. However, despite increasing awareness of CH in prostate cancer, the extent to which inherited genetic variation contributes to CH acquisition and the effects of sequential therapies on clonal evolution remain poorly understood.

This study characterized the somatic mutational landscape of CH in men with metastatic castration-resistant prostate cancer (mCRPC) and examined the association between PGV in DDR genes and somatic CH. Secondary objectives included evaluating major adverse cardiovascular events (MACE), cytopenias, MN, and overall survival (OS).

Following institutional review board approval, we identified participants from the Prostate Cancer Medically Optimized Genome Enhanced Therapy (PROMOTE) study (*clinicaltrials gov. Identifier: NCT01953640*) (see *Online Supplementary Figure S1*). All patients had histologically confirmed prostate adenocarcinoma and met criteria for mCRPC. Peripheral blood samples collected at enrollment were analyzed for somatic mutations using error-corrected next-generation sequencing (340 CH-related genes). Concurrent whole-exome sequencing of matched tumor and blood samples identified germline alterations. Somatic variants with a variant allele fraction (VAF) ≥0.5% were classified as CH, consistent with prior error-corrected sequencing studies.[10] Variants with VAF ≥0.5% were included to capture low-frequency somatic clones with potential for clinical impact.[4] Outcomes of interest, determined retrospectively, included MACE-defined as a composite of acute coronary syndrome (ACS) and stroke/transient ischemic attack. Additional outcomes included persistent cytopenias, incident MN, and OS. Associations between genomic and clinical variables were analyzed using Fisher exact test and multivariable logistic regression. Survival was evaluated using the log-rank test.

The final cohort consisted of 67 men with mCRPC (median age 74.4 years, interquartile range [IQR], 58-79). Thirty-one percent had *de novo* metastatic disease. All received androgen deprivation therapy (ADT) with or without androgen receptor pathway inhibitors (ARPI) for a median of 2.6 years (IQR, 1.3-4.6) prior to enrollment. Sixty-seven percent had received prior radiotherapy (pelvic N=35, palliative N=10), while only 3% (N=2) had received prior chemotherapy, both with docetaxel (Table 1). None had prior PARP inhibitor, 177-lutetium-PSMA-617, or radium-223. Median intervals from the first treatment to blood sampling was 4.1 years for radiotherapy and 2.3 years for chemotherapy. At CH testing, 52% of patients were anemic (94% grade 1, 3% grade 2, 2% as grade 3), 6% had grade 1 thrombocytopenia, and 1% had grade 3 neutropenia (Table 1). Somatic CH mutations with a VAF of ≥2% were identified in 30 of 67 participants (53%). Including exploratory lower-frequency clones (0.5-2%), overall CH prevalence increased to 88% (59/67), totaling 108 mutations (*Online Supplementary Table S1*). Among CH-positive individuals, 39% of mutations occurred in DTA genes, 16% in DDR genes, including *PPM1D* which accounted for 11% of all mutations. The most frequent mutations involved *TET2* (16%), *DNMT3A* (14%), and *PPM1D* (11%). Median number of mutations per individual was two (range, 1-6), and the median VAF was 1.8 % (range, 0.5-50.2) (Figure 1A). Variants were categorized by VAF into micro-CH (VAF <2.0%, N=65), CH with low VAF (2.0-<5.0%, N=28), intermediate (5.0-<10.0%, N=5), and high (≥10.0%, N=10) VAF groups (Figure 1B). Most mutations fell into micro-CH and CH with low VAF categories, comprising approximately 60% and 30% of variants, respectively. Two likely germline *ATM* variants and one likely tumor-derived *TP53* variant were excluded from analysis.

Likely pathogenic and PGV were identified in 13 men (19%), including *ATM* (6%), *BRCA2* (6%), and *TP53* (6%) (Figure 1C;

Online Supplementary Table S2). On multivariable logistic regression, while there was no association between overall CH prevalence and PGV status, PGV carriers had significantly increased odds of harboring DDR-associated CH (odds ratio =8.03, 95% confidence interval: 1.90-34.04; *P*=0.0047) (Figure 1D), suggesting a germline contribution to somatic DDR mutation acquisition.

At a median follow-up of 2.2 years from CH testing, MACE was significantly more common in CH-positive individuals compared to CH-negative individuals (39% [23/59] *vs*. 0 % [0/8]; *P*=0.04) (Figure 2A). The proportion of MACE events did not differ between individuals with higher (VAF ≥10%) and lower (VAF <10%) CH clones. During the same period, 17 patients (25 %) developed persistent cytopenias (>3 months). Among four who underwent bone marrow biopsy, three had marrow involvement by metastatic prostate cancer, and one patient met criteria for clonal cytopenia of undetermined significance, demonstrating a somatic *CHEK2* mutation. No cases of MN were observed.

In two patients with serially collected blood samples, longitudinal sequencing demonstrated dynamic clonal behavior. Low-frequency CH clones identified at enrollment (VAF <5%) expanded substantially over time, including an *ATM*-mutated clone increasing from 3.9% to 37.7% after 8 years, with others, such as *KMT2D* and *TET2*, potentially regressing to undetectable limits (Figure 2B). These findings highlight the potential for even small, initially subclinical clones to evolve under therapeutic pressure.

Median overall survival (OS) from prostate cancer diagnosis was 8.6 years. At last follow-up, two patients remained alive. Most deaths were attributed to progressive metastatic disease. While CH status was not independently associated with OS (Figure 2C), baseline cytopenias correlated with poorer survival (median OS 1.2 years *vs*. 2.5 years; *P*=0.025).

In this prospective cohort of men with pretreated mCRPC, we observed a high prevalence of CH (53%), with numerous low-frequency clones that may represent early clonal events capable of expansion under therapeutic pressure. Serial sampling in two individuals confirmed this trend, as low-frequency clones at baseline expanded after years of ongoing systemic therapy. These findings reinforce the hypothesis that even micro-CH clones may possess latent fitness advantages that become clinically relevant with cumulative genotoxic exposure.[4] Although prior studies have emphasized cardiovascular risk primarily among high-VAF clones, emerging data suggest a more complex, potentially

Table 1. Baseline clinical and laboratory characteristics of the cohort stratified by clonal hematopoiesis status.

Characteristic	Total N=67	CH N=59	No CH N=8	*P*
Age, years, median (IQR)	74 (58-79)	75 (70-79)	73 (71-79)	0.43
History of prior chemotherapy, N (%)	2 (3)	2 (3)	0	1.00
History of prior radiation, N (%)	45 (67)	38 (64)	7 (88)	0.30
Pelvic irradiation, N (%)	35 (52)	28 (47)	7 (88)	0.06
Gleason score, N (%) ≤6 7 ≥8 Missing	 8 (12) 20 (30) 34 (51) 5 (7)	 6 (10) 18 (31) 32 (54) 3 (5)	 2 (25) 2 (25) 2 (25) 2 (25)	 0.20 1.00 0.10 0.10
Baseline PSA, median (IQR)	11 (6-27)	11 (6-27)	11 (3-22)	0.40
Hemoglobin, g/dL, median (IQR)	12.5 (11.8-13.3)	12.5 (11.8-13.3)	12.7 (11.5-13.75)	0.95
Platelets, x10^9/L, median (IQR)	200 (162-230)	200 (161-233)	198 (173-219)	0.73
WBC, x10^9/L, median (IQR)	5.8 (5.1-7.6)	5.8 (5.2-7.8)	5.3 (4.7-6.12)	0.25
Anemia, N (%) Any grade Grade 1 Grade 2 Grade 3	 35 (52) 33 (49) 1 (1) 1 (1)	 31 (53) 29 (49) 1 (2) 1 (2)	 4 (50) 4 (50) 0 0	 1 - - -
Thrombocytopenia, N (%) Any grade Grade 1	 6 (9) 6 (9)	 6 (10) 6 (10)	 0 0	 0.57 -
Neutropenia, N (%) Any grade Grade 3	 1 (1) 1 (1)	 1 (1) 1 (1)	 0 -	 1 -

CH: clonal hematopoiesis; IQR: interquartile range; PSA: prostate-specific antigen; WBC: white blood cell.

non-linear relationship in which smaller clones may still exert biological effects depending on context and inflammatory milieu.[11]

We did not observe a significant association between the presence of PGV and overall CH prevalence. However, individuals with PGV had more than an 8-fold increased likelihood of harboring DDR-associated CH. Although exploratory, this finding suggests that germline variation may influence the somatic mutational profile of the hematopoietic compartment, particularly in DDR pathway genes. Notably, a recent population-based analysis did not observe a comparable association, suggesting that germline-somatic interactions may be context-dependent.[12]

In prostate cancer, PGV in genes such as *BRCA2, ATM*, and *TP53* are established drivers of tumorigenesis. Our results extend this paradigm to the hematopoietic system, demonstrating that inherited DDR defects may shape somatic mutational patterns in non-malignant tissues. We found that 19% of men in our cohort with mCRPC carried DDR PGV and had a higher prevalence of DDR-associated CH, suggesting susceptibility to treatment-induced hematologic toxicity. DDR CH confers a selective advantage under genotoxic stress, potentially driving more aggressive clonal dynamics, particularly during therapies such as PARP inhibitors.[13,14] We observed a significantly higher incidence of MACE in CH-positive individuals, which was primarily driven by ACS, aligning with emerging data linking CH to cardiovascular risk.[15] Given the cardiometabolic side effects of ARPI, CH may interact with these therapies to amplify cardiovascular toxicity. While CH status was not independently associated with overall mortality, baseline cytopenias remained the strongest predictor of poorer outcomes. Prospective longitudinal studies tracking CH evolution, cytopenias, and other adverse outcomes could enable earlier intervention, refined risk stratification, and more personalized treatment strategies in this high-risk population.

A key limitation of our study is the relatively small sample

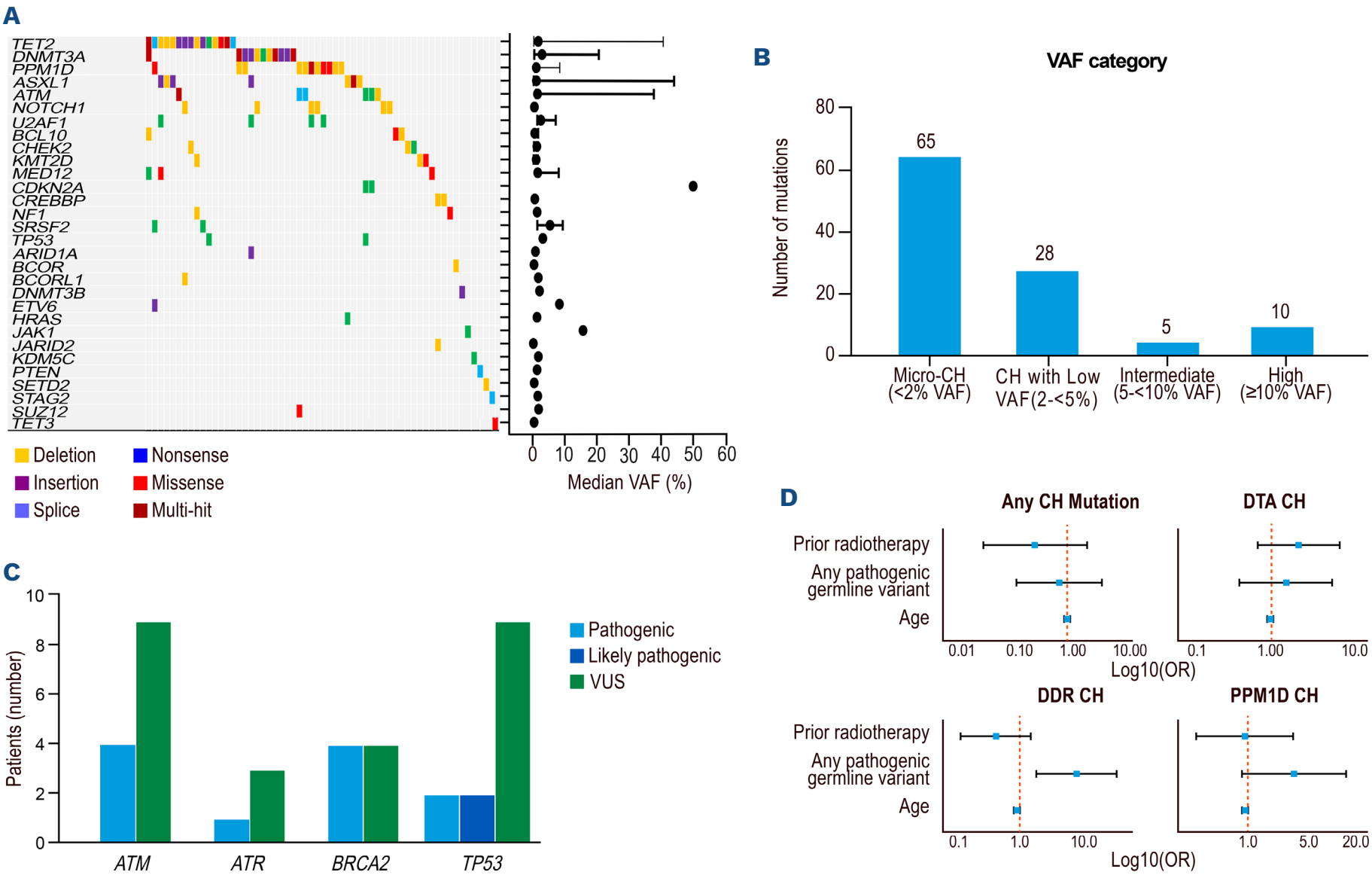

Figure 1. Somatic and germline mutational landscape in metastatic prostate cancer. (A) Somatic clonal hematopoiesis (CH) landscape in metastatic prostate cancer. Oncoplot depicting all somatic CH variants identified in the cohort. Variant classes are color-coded: yellow= deletion, red= nonsense, purple= insertion, blue= splice site, green= missense, deep red= multihit. Median variant allele fraction (VAF) per gene is shown. (B) Distribution of somatic mutations by VAF categories. (C) Germline variants in the cohort. Variant classes are color coded: red= pathogenic, blue= likely pathogenic, black= variant of unknown significance (VUS). (D) Multivariable logistic regression of factors associated with clonal hematopoiesis. Forest plot displaying odds ratios from logistic regression models evaluating the association between clonal hematopoiesis and prior radiotherapy, pathogenic/likely pathogenic germline variants, and age at testing.

size, which may limit the power to detect modest associations and reduce generalizability.

In summary, this study defines the interplay between germline predisposition and somatic CH mutations in men with mPC treated primarily with ADT, ARPI, and radiation. We report a high prevalence of subclonal CH mutations and

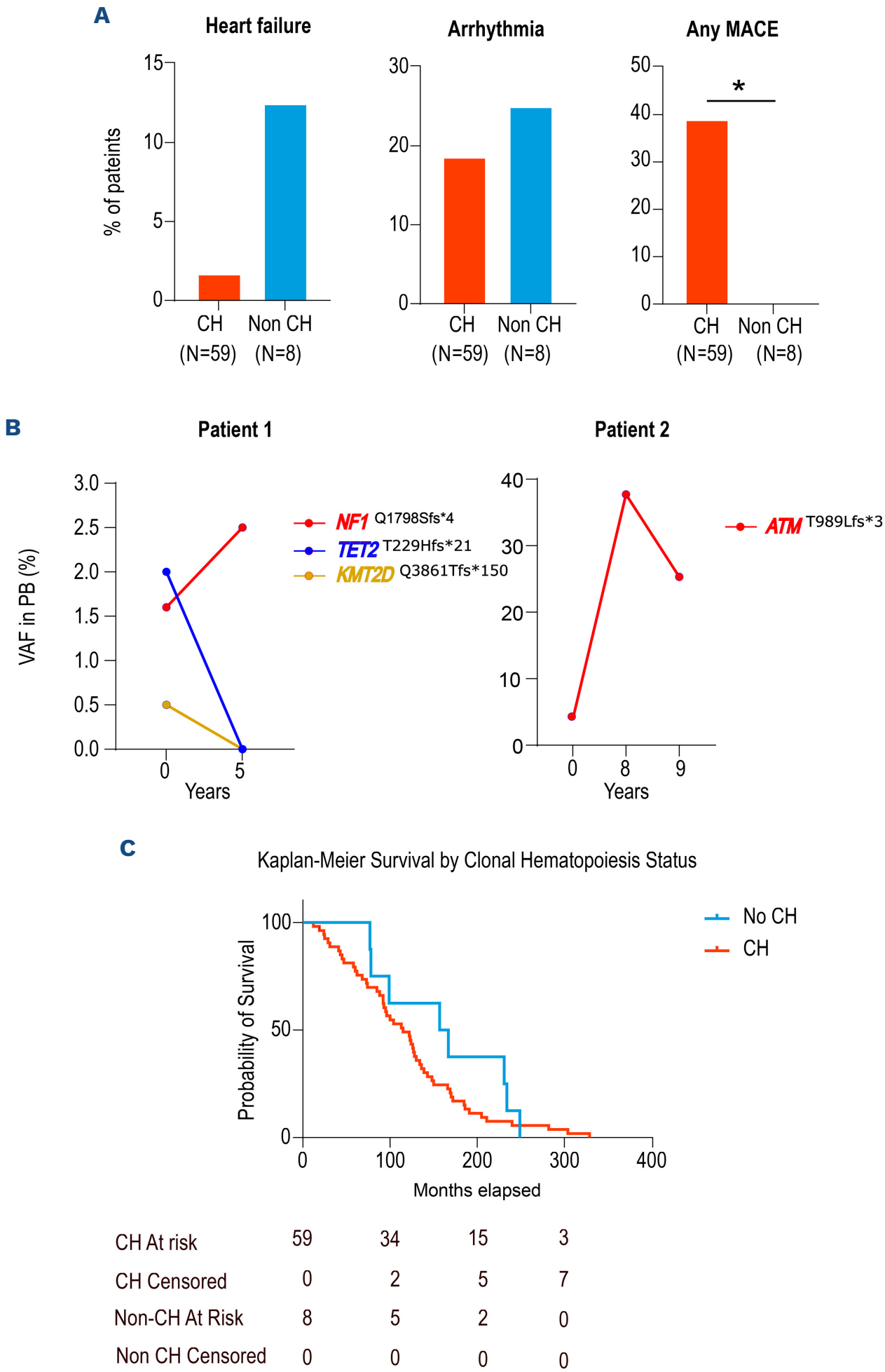

Figure 2. Cardiovascular risk, clonal progression, and survival associated with clonal hematopoiesis. (A) Cardiovascular outcomes in patients with metastatic prostate cancer. Assessment of cardiovascular events including major adverse cardiovascular events (MACE) in patients with and without clonal hematopoiesis (CH). (B) Clonal evolution over time in 2 patients with metastatic castration-resistant prostate cancer demonstrating expansion of an ATM-mutated clone. (C) Kaplan-Meier survival analysis comparing overall survival between patients with and without CH. VAF: variant allele frequency; PB: peripheral blood.

demonstrate that PGV in DDR genes might be associated with increased risk of DDR CH. Given the increasing use of genotoxic therapies in mPC and the emerging links between CH and adverse outcomes, future studies integrating serial genomic profiling, treatment exposure data, and functional validation will be essential to confirm these observations and define the biological and therapeutic implications of CH in mCRPC.

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https://doi.org/10.3324/haematol.2025.288975

Received: August 18, 2025.
Accepted: November 25, 2025.
Early view: December 4, 2025.

Disclosures

No conflicts of interest to disclose.

Contributions

OO and YK conceived and designed the study, analyzed data, and drafted the manuscript. OM, KT, AF, KK, WT, and LAJ contributed to data acquisition and analysis. BAC, DC, AAM, JAF, CF, TLL, RW, and LW provided critical review and intellectual input. MMP supervised the study and provided overall guidance. All authors reviewed and approved the final manuscript.

Data-sharing statement

De-identified genomic and clinical data underlying this study are available upon reasonable request to the corresponding author, subject to Mayo Clinic institutional policies and data-sharing agreements.

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