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ORIGINAL RESEARCH

Clonal Hematopoiesis Is Associated With Long-Term Adverse Outcomes Following Cardiac Surgery

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BACKGROUND: Cardiac surgery triggers sterile innate immune responses leading to postoperative complications. Clonal hematopoiesis (CH) is associated with short-term inflammation-mediated outcomes after cardiac surgery. The impact of CH on long-term postoperative outcomes remains unknown.

METHODS AND RESULTS: In this cohort study, patients undergoing elective cardiac surgery were included from January 2017 to September 2019. Patients were screened for CH using a predefined gene panel of 19 genes. Recorded clinical events were all-cause death, major adverse cardiac and cerebral events including cardiovascular death, myocardial infarction or non-scheduled coronary revascularization, stroke, and hospitalization for acute heart failure. The primary study outcome was time to a composite criterion including all-cause mortality and major adverse cardiac and cerebral events. Among 314 genotyped patients (median age: 67 years; interquartile range 59–74 years), 139 (44%) presented with CH, based on a variant allelic frequency $\geq 1\%$. Carriers of CH had a higher proportion of patients with a history of atrial fibrillation (26% for CH versus 17% for non-CH carriers, $P=0.022$). The most frequently mutated genes were *DNMT3A*, *TET2*, and *ASXL1*. After a median follow-up of 1203 [813–1435] days, the primary outcome occurred in 50 patients. After multivariable adjustment, CH was independently associated with a higher risk for the primary outcome (hazard ratio, 1.88 [95% CI, 1.05–3.41], $P=0.035$). Most adverse events occurred in patients carrying *TET2* variants.

CONCLUSIONS: In patients undergoing cardiac surgery, CH is frequent and associated with a 2-fold increased long-term risk for major adverse clinical outcomes. CH is a novel risk factor for long-term postcardiac surgery complications and might be useful to personalize management decisions.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03376165.

Key Words: cardiac surgery ■ clonal hematopoiesis ■ heart failure ■ inflammation ■ survival

Despite major improvements in nonsurgical techniques (eg, percutaneous aortic valve replacement or edge-to-edge mitral repair), cardiac

surgery is still among the most frequent major surgical procedures worldwide. However, the proportion of patients at high risk for postoperative complications

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CLINICAL PERSPECTIVE

What Is New?

- Clonal hematopoiesis is frequent in a population of patients undergoing cardiac surgery, with an overall prevalence of 44% based on variant allelic frequency $\geq 1\%$.
- Clonal hematopoiesis is associated with a 2-fold increased risk for major adverse clinical outcomes following cardiac surgery.
- Clone size is a determinant of outcome, with patients with the largest clone size presenting with a 2.4-fold increased risk for adverse clinical outcomes. Most events occurred in patients carrying *TET2* mutation.

What Are the Clinical Implications?

- Clonal hematopoiesis is a novel risk factor for long-term postcardiac surgery complications and might be useful to personalize management decisions.
- Targeting clonal hematopoiesis may be beneficial to prevent adverse outcomes following surgery.

Nonstandard Abbreviations and Acronyms

| | |
|--------------|---|
| CH | clonal hematopoiesis |
| MACCE | major adverse cardiac and cerebral events |
| VAF | variant allelic frequency |

remains significant and raises issues in terms of perioperative management.¹ Identifying markers of long-term postoperative outcomes following cardiac surgery is a major topic of interest to provide tailored personalized medicine that improves therapeutic choices and perioperative management.

Cardiac surgery triggers a sterile systemic inflammatory response to which release of damage-associated molecular patterns is a major contributor.² Immune responses induced by damage-associated molecular patterns enhance myocardial recruitment of leukocytes that promote wound healing. On the other hand, postoperative inflammation is associated with postoperative complications like postoperative atrial fibrillation (AF) and acute kidney injury.^{3–5} As such, the identification of factors involved in the postoperative inflammatory response and predictive of postoperative outcomes is of great importance.

During aging somatic mutations occur in hematopoietic stem cells and provide a selective growth advantage when occurring in driver genes such as

DNMT3A, *TET2*, *ASXL1*, *TP53*, and *JAK2*.⁶ This results in a fraction of circulating leukocytes carrying these mutations, a state referred to as clonal hematopoiesis (CH). CH was first associated with an increased risk for hematological malignancies.⁷ However, several studies associated CH with adverse cardiovascular outcomes such as coronary artery disease, heart failure (HF), or atrial fibrillation.^{8–13} The mechanistic link between CH and adverse cardiovascular outcomes is not fully understood but involves a shift of leukocytes toward a proinflammatory phenotype leading to chronic inflammation.^{14–17} We recently demonstrated that CH is associated with increased risk for postoperative AF after cardiac surgery.⁵ Moreover, we found a transcriptomic signature indicative of an activated preoperative phenotype in circulating classical monocytes from patients with CH and an accumulation of proinflammatory monocyte-derived macrophages in the myocardium. Because CH was found to affect early postoperative outcomes, we hypothesize that CH might be associated with adverse long-term postoperative clinical outcomes following cardiac surgery. Therefore, we here assessed long-term risk for all-cause death and major adverse cardiac and cerebral events (MACCE) after cardiac surgery according to CH status.

METHODS

Patient Cohort

The data that support the findings of this study are available from the corresponding author upon reasonable request. The clinical cohort is part of the POMI-AF (Post-Operative Myocardial Incident and Atrial Fibrillation) study (NCT#03376165), approved by the institutional ethics committee (Comité de Protection des Personnes Ile de France V). Written informed consent was obtained from all patients before inclusion. Patients (aged ≥ 18 years) referred to the cardiovascular surgery department at the Lille University Hospital (Lille, France) for cardiac surgery were included. The medical history of each patient was collected, transthoracic echocardiography and an ECG recorded to detect preexisting AF at baseline. Valvular surgery was defined as any surgery including aortic valve replacement, mitral valve replacement, or any valve repair. Exclusion criteria were pregnancy, emergency surgery, and patients unable to give their consent.

Postoperative Outcomes

Patients underwent clinical follow-up after surgery. Data were obtained from medical records and interviews with the cardiologist or general practitioner of the patients. Recorded clinical events were all-cause death, MACCE including cardiovascular death, myocardial infarction or nonscheduled coronary revascularization,

stroke, and hospitalization for acute HF. Each end point was centrally reviewed by 2 independent cardiologists who were blinded to patient CH status. In case of discrepancy, the end point was decided after discussion with a third cardiologist.

Cardiovascular death was defined according to the *International Classification of Diseases, Tenth Revision (ICD-10 codes I00–I78)*. Hospitalization for HF was defined as hospitalization for symptoms of dyspnea or edema associated with bilateral rales, elevated venous pressure, interstitial or alveolar edema on chest X-ray, with the addition of intravenous diuretics or inotropic medications. Stroke was defined as a focal neurologic deficit, from a nontraumatic cause, associated with evidence of a cerebral lesion on brain imaging (computed tomography or magnetic resonance imaging).

The primary end point of the study was a composite criterion including all-cause mortality and MACCE. MACCE alone and variant allelic frequency (VAF) quartiles were examined in secondary analyses.

DNA Extraction, Library Preparation, and Sequencing

DNA from buffy coat samples was extracted with QIAamp DNA Micro Kit (Qiagen) following the manufacturer's instructions and submitted to the Integrated Genomics Operation at the Memorial Sloan-Kettering Cancer Center for quality and quantity analysis, library preparation, and sequencing. DNA quality was measured with TapeStation 2200 and all samples had a DNA Integrity Number >6. DNA quantity was measured with PicoGreen. For each sample, ~200 ng of genomic DNA were used for library construction using the KAPA Hyper Prep Kit (Kapa Biosystems KK8504) with 8 cycles of polymerase chain reaction. After sample barcoding, 2.5 ng to 1 µg of each library were pooled and captured by hybridization with baits specific to 19 genes previously involved in hematological malignancies¹⁸ (Table S1). Capture pools were sequenced on the HiSeq 4000 sequencer, using the HiSeq 3000/4000 SBS Kit (Illumina) for PE100 reads. Samples were sequenced to a mean depth of coverage of 1175×. For detailed information on the sample quality control checks used to avoid potential sample or barcode mixups and contamination from external DNA, see.¹⁸

Mutation Data Analysis

For the analysis, FASTQ files were trimmed using trimmomatic(v0.36) and aligned using Bowtie2(v2.3.5) to GRCh37. Unique molecular identifiers were collected to generate consensus collapsed FASTQs using fgbio(v0.8.0). These sequences were realigned using Bowtie2 and variant calling was performed using veridict (v1.5.8). Common variants and single-nucleotide

variants were annotated using SnpEff (v4.3), dbSNP common (v9606_b151), gnomAD (r2.1.1), and Clinvar (v20190408) and final variant calls reported. Each variant call was assigned a confidence score using a logistic regression model which estimates likelihood of reproducibility adjusting for variant depth, mutant allele fraction, mutation type, and the background error rate in the sample. A minimum confidence score of >25 was required for reporting.

Classification of Variants

Classification of somatic variants according to their pathogenicity was performed as follows: variants were classified as “deleterious” when the single-nucleotide variant is (1) predicted to affect protein function as determined by polymorphism phenotyping v2 (possibly and probably damaging) and sorting intolerant from tolerant (deleterious), or (2) reported as pathogenic/likely pathogenic by ClinVar,¹⁹ or (3) oncogenic/predicted oncogenic/likely oncogenic by OncoKb.²⁰ Variants were classified as “pathogenic” if reported as (1) pathogenic/likely pathogenic by ClinVar or (2) oncogenic/predicted oncogenic/likely oncogenic by OncoKb. These 2 databases report pathogenicity in cancer and other diseases, based on supporting evidence from curated literature. For patients presenting multiple mutations, the highest VAF was considered for association between clone size and clinical outcomes. Germline variants were defined as variants presenting VAF ≥35% and defined as common variants in dbSNP (v9606_b151) or presenting at least 500 observations in gnomAD (r2.1.1).

Sample Size Calculation

We aimed at testing the potential association between the primary end point and 4 predefined predictors: CH, left ventricular (LV) dysfunction, age, and diabetes, meaning that at least 40 events were needed according to Concato and Peduzzi rules.²¹ Based on our previous publications,^{22,23} we expected an incidence of MACCE of 10% to 15% after a 4-year follow-up. As the primary end point was expected to be more frequent than MACCE, we thus needed to include at least 300 patients.

Statistical Analysis

Continuous variables were tested for normality with the Shapiro test. Continuous variables with Gaussian distribution are given as mean±SD. Continuous variables with non-Gaussian distribution are given as median (interquartile range). Categorical variables are given as percentages of individuals. Bivariate comparisons were performed using the *t* test for normally distributed continuous variables or the Mann–Whitney *U* test

for not normally distributed variables. Bivariate comparisons of categorical variables were done with the χ^2 test.

To assess the impact of CH on long-term postoperative outcomes, a log-rank test was performed as a first step and unadjusted hazard ratios (HRs; 95% CIs) were computed. Univariate Cox analysis was performed to identify variables of interest for multivariable adjustment. A multivariable Cox model was then performed and included CH status, age, LV dysfunction (defined as LV ejection fraction [EF] $\leq 40\%$), hypertension, history of AF, and preoperative estimated glomerular filtration rate as competing variables and adjusted HRs (95% [CIs]) were computed. A value of $P < 0.05$ was judged to be statistically significant. All analyses were done using MedCalc v16.4 (Olstead, Belgium). The assumptions of Cox proportional model were verified from phreg procedure in SAS STAT software (SAS version 9.4; SAS Institute, Inc., Cary, NC) including Schoenfeld residuals, Martingale residuals, and the symmetric transformation of the Martingale residuals.

RESULTS

A flow chart is provided in [Figure S1](#). A total of 342 patients with available buffy coat samples were included between January 2017 and September 2019. DNA sequencing, CH screening, and clinical follow-up were performed in 314 patients ([Figure 1A](#); [Figure S1](#)). Median age was 67 (59–74), the median body mass index was 27 kg/m² (24–31). The most frequent surgeries were isolated coronary artery bypass graft (46%) and lone valvular surgeries (33%). Ten percent of patients underwent coronary artery bypass graft combined with valvular surgery. Twenty-one percent ($n=63$) had a history of AF ([Table 1](#)).

Characterization of CH in the Cohort

Out of 314 patients, 139 (44%) presented with CH, based on a VAF $\geq 1\%$. Out of 314, 95 (30%) presented with a VAF $\geq 2\%$ and 49/314 (16%) presented with a VAF $\geq 5\%$. In line with previous publications,⁷ carriers of CH were older (carriers: 70 [61–76] versus noncarriers: 66 [57–72], $P=0.0013$) ([Table 1](#)), with a prevalence of CH in patients >80 years old reaching 60% ([Figure 1C](#)). The VAF ranged from 1.02% to 31.6%; the mutations were mostly found in *DNMT3A* and *TET2* ([Figure 1E](#) and [1F](#)) and represented single-nucleotide variants. Among carriers of CH, 29% presented with multiple mutations ([Figure 1G](#)). The prevalence of multiple mutations did not increase with age ([Figure 1D](#)). We noticed a significant variability in the distribution of VAF among individuals, regardless of the mutated gene, as reported in earlier studies,⁷ ([Figure 1H](#)). A higher proportion of patients with a history of AF was observed in carriers of

CH (carriers: 26% versus noncarriers: 17%, $P=0.022$). There was no significant difference regarding surgery subtypes according to CH status. The complete list of variants found in the cohort is provided in [Table S2](#).

Long-Term Outcomes Following Cardiac Surgery According to CH Status

After a median follow-up of 1203 (813–1435) days, the primary end point (all-cause mortality and MACCE) occurred in 50 patients, with 34 MACCEs and 16 noncardiovascular deaths. MACCEs comprised 16 cardiovascular deaths, 8 myocardial infarctions or unscheduled coronary revascularizations, 6 strokes, and 16 hospitalizations for HF. The overall rate of in-hospital death following cardiac surgery was 2.9% (1.7% for non-CH and 4.3% for carriers of CH, P value=0.17). The primary end point and MACCEs occurred in 17.6% and 12.4% of patients respectively. Furthermore, carriers of CH presented a 2-fold higher risk for the primary end point (unadjusted HR, 2.17 [95% CI, 1.24–3.82], $P=0.0079$) ([Figure 2A](#); [Table 2](#); [Table S3](#)) and also for MACCE (unadjusted HR, 2.15 [95% CI, 1.09–4.3], $P=0.03$) ([Figure 2B](#); [Table 2](#)). At 90 days after surgery, the primary outcome occurred in 3.4% (95% CI, 2.02%–4.78%) of non-CH carriers and 7.2% (95% CI, 5.01%–9.39%) of carriers of CH (log rank, $P=0.07$). At 6 months, the primary outcome occurred in 4.6% (3.02%–6.18%) of non-CH carriers and 8.6% (95% CI, 6.21%–11%) of carriers of CH (log rank, $P=0.075$). Univariate analysis revealed that age, hypertension, history of AF, LV dysfunction (defined as LVEF $\leq 40\%$) and preoperative estimated glomerular filtration rate were associated with the primary outcome ([Table S3](#)). CH remained associated with the primary end point and MACCE across the 2 applied multivariate models. For model 2, including age, hypertension, preoperative estimated glomerular filtration rate, LVEF, and history of AF as covariates, CH was associated with a higher risk for the primary end point (HR, 1.88 [95% CI, 1.05–3.41], $P=0.035$) and MACCE (HR, 2.14 [95% CI, 1.05–4.39], $P=0.038$) ([Table 2](#); [Tables S4](#) and [S5](#)). Schoenfeld residuals are provided in [Tables S6](#) through [S9](#). Among the primary end point events, hospitalization for HF was the most frequent event occurring in carriers of CH, whereas noncardiovascular death was the most frequent event occurring in non-CH carriers ([Figure 2D](#) and [2E](#)).

Further Characterization of CH According to Postoperative Outcomes

To better characterize the association between CH and postoperative outcomes, we next assessed the association between clone size (VAF%) and long-term postoperative outcomes. Carriers of CH with the

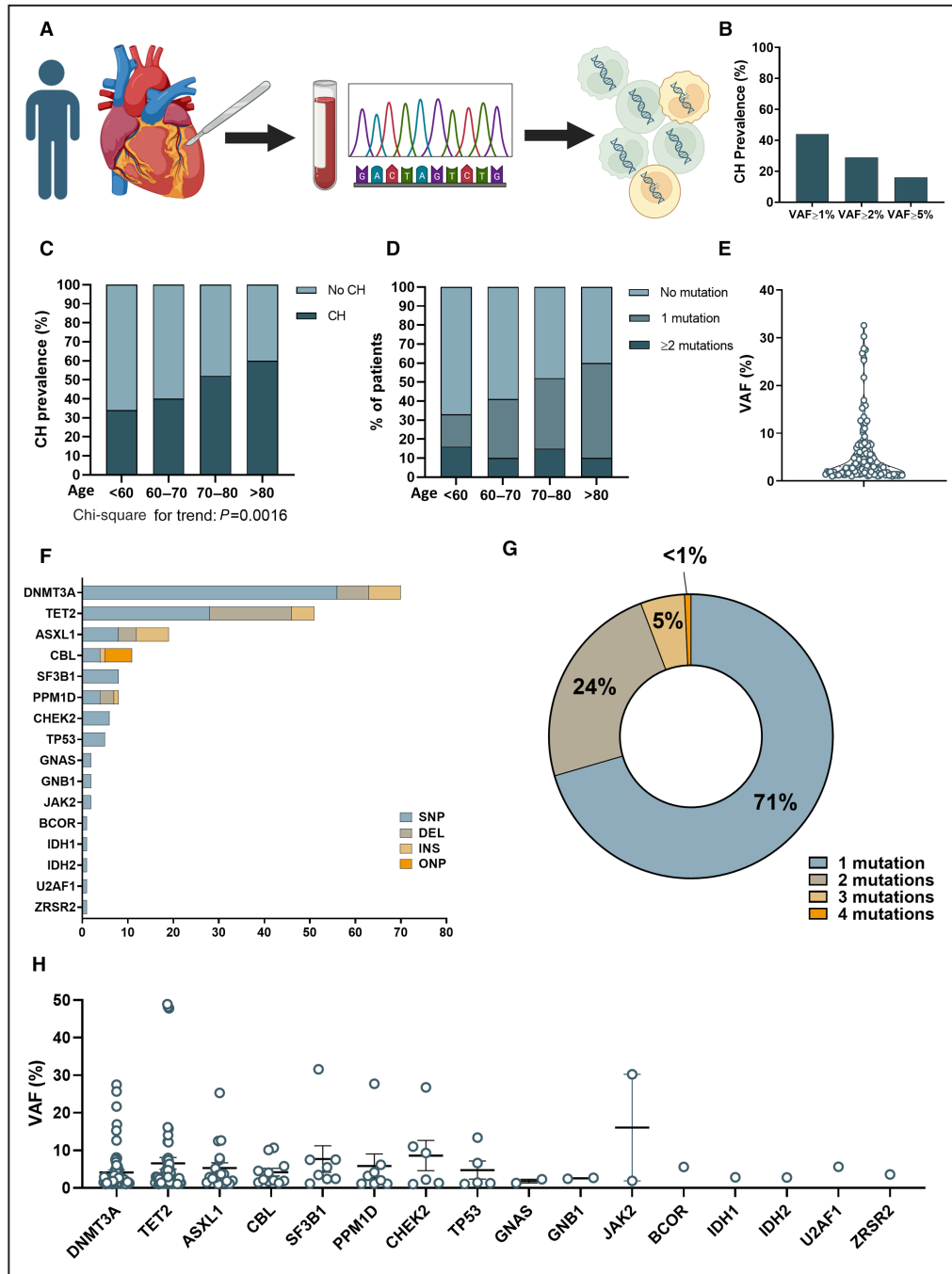


Figure 1. CH prevalence and characteristics in the cohort.

A, Preoperative buffy coat DNA samples were sequenced for 19 genes commonly implicated in hematological malignancies in 314 patients undergoing cardiac surgery. **B**, Prevalence of CH according to VAF threshold. **C**, Prevalence of CH based on VAF \geq 1% according to age category. **D**, Prevalence of single or multiple variants according to age category. **E**, Distribution of VAF in the cohort. **F**, Most mutated genes and mutations subtypes. **G**, Prevalence of multiple mutations in the entire cohort. **H**, Distribution of VAF according to mutated gene. CH indicates clonal hematopoiesis; DEL, deletion; INS, insertion; ONP, oligonucleotide polymorphism; SNP, single nucleotide polymorphism; and VAF, variant allelic frequency.

lowest clone sizes (VAF <1st quartile, ie, VAF <1.7%) did not present a higher risk for the primary outcome nor MACCE. However, the risk for the primary end point consistently increased for the highest clone sizes

(for VAF \geq 4th quartile, ie, VAF \geq 6.6%, HR, 2.55 [95% CI, 1.56–5.64], $P=0.02$) (Table 3). Furthermore, the risk for the primary end point remained significantly higher in patients presenting the highest clone sizes, even after

Table 1. Baseline Characteristics According to CH Status

| | Total (n=314) | No CH (n=175) | CH (n=139) | P value |
|--|---------------|---------------|------------|---------|
| Age, y | 67 (59–74) | 65 (57–72) | 70 (61–76) | 0.0013* |
| Women, n (%) | 98 (31) | 55 (31) | 43 (31) | 0.92 |
| Body mass index, kg/m ² | 27 (24–31) | 27 (24–31) | 27 (24–30) | 0.91 |
| History of diabetes, n (%) | 102 (32) | 49 (28) | 53 (38) | 0.057 |
| Hypertension, n (%) | 194 (62) | 107 (61) | 87 (63) | 0.79 |
| Current smoker, n (%) | 84 (27) | 48 (27) | 36 (26) | 0.76 |
| History of atrial fibrillation, n (%) | 63 (21) | 27 (17) | 36 (26) | 0.022* |
| LVEF, % | 60 (54–65) | 60 (54–65) | 60 (55–66) | 0.65 |
| LV dysfunction (LVEF≤40%), n (%) | 22 (7) | 15 (9) | 7 (5) | 0.22 |
| Left atrial area, cm ² | 24 (20–27) | 24 (20–27) | 23 (20–28) | 0.88 |
| Preoperative creatinine, mg/L | 9 (7–11) | 9 (8–11) | 9 (8–11) | 0.30 |
| Preoperative eGFR, mL/min per 1.73m ² | 85.5 (70–97) | 86 (70–100) | 81 (69–93) | 0.017* |
| Type of surgery | | | | |
| Isolated valvular surgery, n (%) | 103 (33) | 63 (36) | 40 (29) | 0.09 |
| Isolated CABG, n (%) | 144 (46) | 83 (47) | 61 (44) | |
| Combined valvular surgery and CABG, n (%) | 33 (10) | 10 (6) | 23 (17) | |
| Other surgery, n (%) | 34 (11) | 19 (11) | 15 (11) | |
| Overall valvular surgery, n (%) | 136 (43) | 73 (42) | 63 (45) | 0.52 |
| Overall CABG, n (%) | 178 (57) | 94 (54) | 84 (60) | 0.23 |

Variables are given as median [first quartile–third quartile], mean±SD or number (percentage). eGFR is based on Chronic Kidney Disease Epidemiology Collaboration equation (2021). CABG indicates coronary artery bypass graft; CH, clonal hematopoiesis; eGFR, estimated glomerular filtration rate; and LVEF, left ventricular ejection fraction.

*p value < 0.05.

adjustment for covariates (age, hypertension, preoperative estimated glomerular filtration rate, history of AF and LV dysfunction) (for VAF ≥4th quartile HR, 2.36 [95% CI, 1.05–5.32], $P=0.037$). Midrange clone sizes were also associated with a higher risk for MACCE (for second–third VAF quartiles, adjusted HR for model 2, 2.71 [95% CI, 1.25–5.89], $P=0.012$).

Interestingly, most adverse events occurred in patients carrying *TET2* variants (Figure 2F and 2H). Furthermore, the proportion of patients developing adverse outcomes was highest in *TET2* carriers compared with *DNMT3A* and *ASXL1* (Figure 2G and 2I).

DISCUSSION

To the best of our knowledge, ours is the first report of an association between CH and long-term postoperative outcomes following cardiac surgery. Our study demonstrates that (1) CH is frequent in a population of patients undergoing cardiac surgery, with an overall prevalence of 44% based on VAF ≥1%, increasing to 60% in elderly patients; (2) CH is associated with a 2-fold increased risk for major adverse clinical outcomes including all-cause mortality and MACCEs; and (3) clone size is a determinant of outcome, with patients presenting with the largest clone size presenting a 2.4-fold increased risk for primary outcome.

Furthermore, most events occurred in patients carrying *TET2* mutation(s). These data suggest that CH assessment might improve the prediction of postoperative outcomes following surgery.

The prevalence reported in each CH study critically depends on screening methods applied and the studied population. The sensitivity of detecting driver mutations is highly dependent on sequencing depth. Both whole genome²⁴ and whole exome sequencing⁸ are effective for identifying larger clones, whereas deeper coverage and error-corrected targeted sequencing techniques enable the detection of very small clones. When screening 74 predefined genes, Jaiswal et al. reported a prevalence of CH mutations of 17% and 10% in a cohort of elderly patients (median age of 70 years) with and without coronary artery disease, respectively.⁹ Using a gene panel including 54 genes, Pascual-Figal et al. reported a prevalence of CH of 39% in a cohort of 62 patients presenting HF with reduced EF.²⁵ In contrast, recent data from the UK Biobank highlighted a lower CH prevalence of 5.45% in a lower cardiovascular risk population upon screening 43 genes.¹⁰ Thus, a high prevalence of CH is expected in populations at high cardiovascular risk, especially when using large gene panels. The high burden of cardiovascular comorbidities in our population is in line with the relatively high CH prevalence. A VAF threshold of 1% was applied to define CH status. A recent study

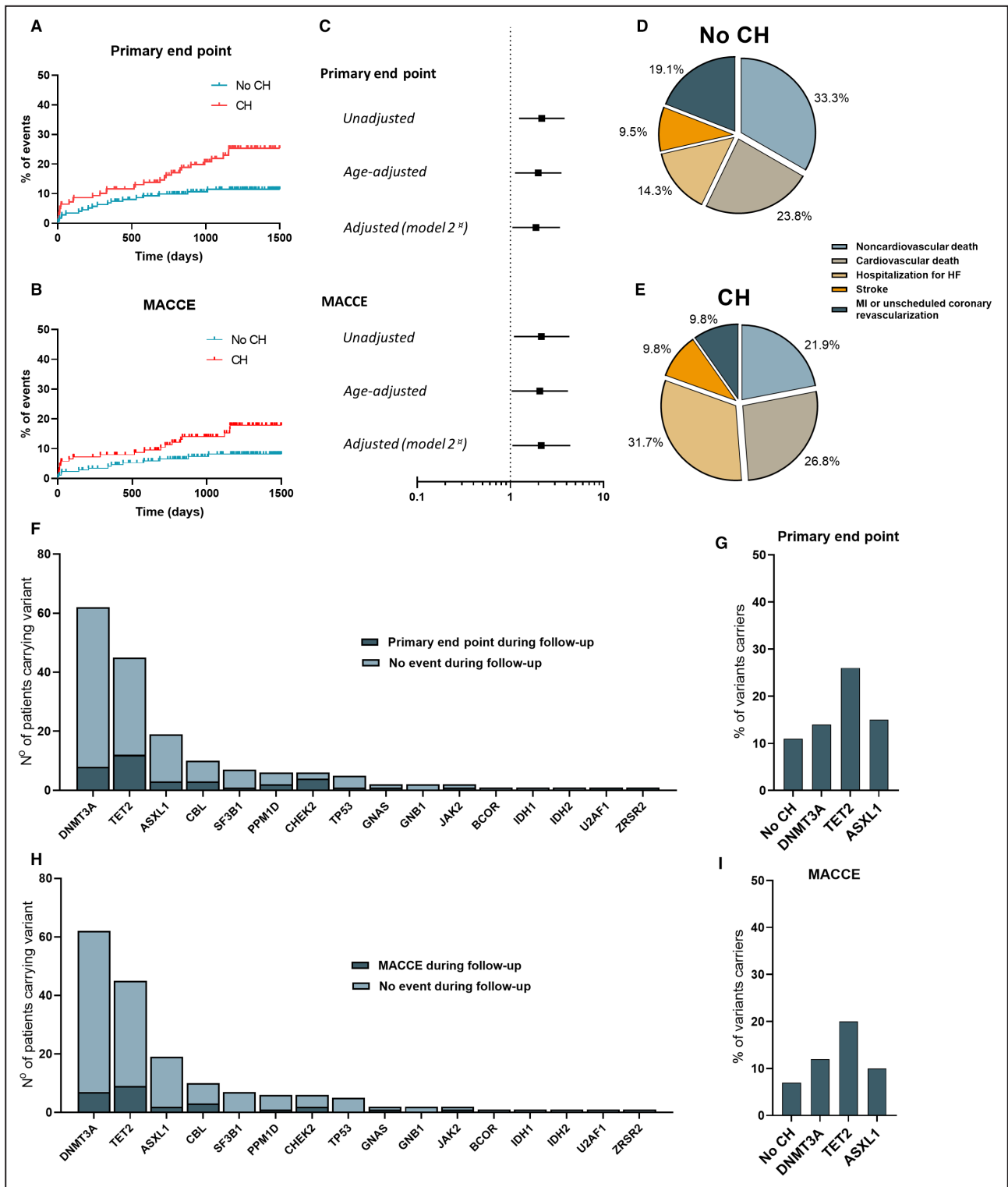


Figure 2. Long-term prognostic impact of CH after cardiac surgery.

A, Kaplan–Meier curves according to CH status (based on VAF $\geq 1\%$) for the primary end point. **B**, Kaplan–Meier curves according to CH status (based on VAF $\geq 1\%$) for MACCE. **C**, Forrest plot providing unadjusted and age-adjusted hazard ratio for each clinical outcome. **D**, Proportion of primary end point events subtypes in non-CH carriers. **E**, Proportion of primary end point events subtypes in carriers of CH. **F**, Number of primary outcome events occurring for each mutated gene. **G**, Proportion of patients presenting primary end point events among patients carrying at least 1 mutation in the top 3 mutated genes (*DNMT3A*, *TET2*, and *ASXL1*). **H**, Number of MACCE events occurring for each mutated gene. **I**, Proportion of patients presenting MACCE events among patients carrying at least 1 mutation in the top 3 mutated genes (*DNMT3A*, *TET2*, and *ASXL1*). CH indicates clonal hematopoiesis; HF, heart failure; MACCE, major adverse cardiac and cerebral events; MI, myocardial infarction; and VAF, variant allelic frequency.

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Table 2. Adjusted Cox Model for CH vs Major Adverse Cardiovascular Outcomes

| | Primary end point | | MACCE* | |
|------------------------------------|-------------------|---------|------------------|---------|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| No CH, reference | ... | ... | ... | ... |
| CH (variant allelic frequency ≥1%) | | | | |
| Unadjusted | 2.17 (1.24–3.82) | 0.0079 | 2.15 (1.09–4.3) | 0.030 |
| Adjusted (model 1) | 1.99 (1.12–3.55) | 0.019 | 2.07 (1.03–4.29) | 0.042 |
| Adjusted (model 2) | 1.88 (1.05–3.41) | 0.035 | 2.14 (1.05–4.39) | 0.038 |

Primary end point includes all-cause mortality and MACCEs. Model 1: CH and age were included. Model 2: CH, age, hypertension, history of atrial fibrillation, left ventricular dysfunction (defined as left ventricular ejection fraction ≤40%) and preoperative estimated glomerular filtration rate were included. CH indicates clonal hematopoiesis; HR, hazard ratio; and MACCE, major adverse cardiac and cerebral events.

*MACCE included stroke, unexpected coronary revascularization, hospitalization for heart failure, and cardiovascular death.

highlighted the potential relevance of lower threshold that may be linked to adverse clinical outcomes²⁶ and raised questions about the clinically pertinent threshold for assessing CH. Thus, this threshold was used to characterize the full spectrum of detectable CH and its clinical relevance for risk stratification. We identified a notable correlation between CH and adverse cardiovascular outcomes for clone sizes ranging from midrange to large, with VAF >1.7%. This finding further supports the notion of the negligible impact of small clone sizes, consistent with earlier research. The most frequently mutated genes in our study are in agreement with previous studies highlighting *TET2* and *DNMT3A* as the most commonly mutated genes. Accumulating evidence suggests that, in addition to being highly prevalent, *TET2* and *DNMT3A* mutations are highly relevant for prediction of cardiovascular outcomes. Mas-Peiro et al. screened for *TET2* and *DNMT3A* variants

in a cohort of 279 patients undergoing transfemoral aortic valve replacement. In this high-risk population, *TET2* and *DNMT3A* CH variants were found in 33.3% of patients and were associated with increased risk for all-cause mortality.²⁷

In our study, CH was associated with a 2-fold higher risk for the primary major adverse-event end point, including all-cause mortality and major cardiovascular outcomes. The prognostic impact of CH has been previously assessed in various clinical settings. A recent phenome-wide association study, including >200 000 individuals from the UK Biobank, revealed a strong association between CH and HF, AF, and a composite of all cardiovascular disease for large clones in multivariable regression models.¹⁰ In a study of patients with HF and reduced EF, CH increased the risk of several HF-related outcomes including HF-related hospitalization and mortality.²⁵ In a recent study assessing the

Table 3. Cox Model for the Effect of Clone Size (VAF%) vs Major Adverse Cardiovascular Outcomes

| | Primary end point | | MACCE* | |
|--------------------|-------------------|---------|------------------|---------|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| No CH, reference | ... | ... | ... | ... |
| CH, VAF<Q1 | | | | |
| Unadjusted | 1.43 (0.53–3.82) | 0.48 | 1.25 (0.36–4.39) | 0.73 |
| Adjusted (model 1) | 1.33 (0.49–3.57) | 0.58 | 1.21 (0.34–4.27) | 0.77 |
| Adjusted (model 2) | 1.2 (0.44–3.26) | 0.72 | 1.25 (0.35–4.48) | 0.73 |
| CH, Q1≤VAF<Q4 | | | | |
| Unadjusted | 2.34 (1.22–4.49) | 0.011† | 2.81 (1.32–5.98) | 0.007† |
| Adjusted (model 1) | 2.15 (1.11–4.16) | 0.02† | 2.71 (1.26–5.82) | 0.011† |
| Adjusted (model 2) | 2 (1.02–3.92) | 0.043† | 2.71 (1.25–5.89) | 0.012† |
| CH, VAF≥Q4 | | | | |
| Unadjusted | 2.55 (1.56–5.64) | 0.02† | 1.66 (0.54–5.09) | 0.37 |
| Adjusted (model 1) | 2.34 (1.05–5.21) | 0.038† | 1.60 (0.52–4.95) | 0.41 |
| Adjusted (model 2) | 2.36 (1.05–5.32) | 0.037† | 1.74 (0.55–5.47) | 0.34 |

Primary end point includes all-cause mortality and MACCEs. Q1: first VAF quartile among CH carriers (VAF <1.7%). Q4: fourth VAF quartile among carriers of CH (VAF ≥6.6%). Model 1: CH and age were included. Model 2: CH, age, hypertension, history of atrial fibrillation, left ventricular dysfunction (defined as left ventricular ejection fraction ≤40%), and preoperative estimated glomerular filtration rate were included. CH indicates clonal hematopoiesis; HR, hazard ratio; MACCE, major adverse cardiac and cerebral events; and VAF, variant allelic frequency.

*MACCE included stroke, unexpected coronary revascularization, hospitalization for heart failure, and cardiovascular death.

†p value < 0.05.

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prognostic impact of CH in patients presenting cardiogenic shock, carriers of CH had worse short-term outcomes, measured either as mortality or as a combined clinical end point of mortality or severe 30-day renal failure.²⁸

The primary end point and MACCEs occurred in 17.6% and 12.4% of patients respectively after a median follow-up of 1203 (813–1435) estimated glomerular filtration rate days. The intrahospital mortality was 2.9%. These incidences are in line with previous studies. For instance, in a Danish nationwide cohort, the 30-day mortality following coronary artery bypass graft was 3.2%.²⁹ A post hoc analysis of the SYNTAX (Synergy Between PCI [Percutaneous Coronary Intervention] With Taxus and Cardiac Surgery) and the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trials revealed that a composite of all-cause death, myocardial infarction, stroke, or ischemia-driven revascularization occurred in 14.0% and 20.9% of patients undergoing coronary artery bypass graft at 3 years, respectively.³⁰ Higher rates of adverse events are also reported following aortic valve replacement surgery. In a multicenter study including consecutive patients with severe aortic stenosis and complex coronary artery disease undergoing aortic valve replacement, the rate of MACCE was 38.2% at 5 years for patients with surgical valve replacement.³¹

The prognostic impact of CH after cardiac surgery has not been assessed previously. The mechanisms leading to adverse cardiovascular outcomes in carriers of CH are not well understood, but the relatively high proportion of events related to HF suggests a potential role of CH in ventricular remodeling. Such a mechanistic link was previously shown in animal studies. Indeed, mice with *Tet2*-deficiency in hematopoietic cells displayed greater maladaptive cardiac remodeling and dysfunction in models of pressure overload hypertrophy and permanent coronary artery ligation, due to the activation of the inflammasome complex.³² In line, a recent study demonstrated in a mice model of HF with preserved EF that adoptive transfer of *Tet2*-deficient bone marrow exacerbated hallmarks of ventricular remodeling.³³ Moreover, our group recently highlighted a preoperative immune shift in the human myocardium from carriers of CH, illustrated by the accumulation of proinflammatory monocyte-derived macrophages.⁵ As cardiac surgery triggers inflammatory responses and the recruitment of leukocytes that are involved in scar formation and the remodeling process, CH might be a major actor in adverse postoperative remodeling and HF-related outcomes.

Of note, most events occurred in patients carrying *TET2* mutations, with a relatively high proportion of HF-related events. In contrast, *DNMT3A* mutations were associated with lower event rates. In a previous study

based on 5 cardiovascular cohorts that analyzed CH in relation to incident HF in >50 000 patients, a significant association was found between *TET2*, *ASXL1*, and *JAK2* mutations and risk for HF, whereas no significant association was found for *DNMT3A* mutations.¹¹ In line, a recent study suggests that non-*DNMT3A* CH is associated with incident coronary artery disease.³⁴ The heterogeneity of association between clinical outcomes and mutation subtypes highlights the complexity of CH pathophysiology. A better understanding of the mutation-specific effects is a major area of interest in the field of CH that might be relevant to improving personalized therapeutic strategies. A recent post hoc analysis of the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial investigated the response to canakinumab in patients carrying CH variants³⁵ and reported that patients harboring *TET2* variants had numerically fewer major adverse cardiovascular events while taking canakinumab compared with patients without CH.

Limitations

Our study has several limitations. First, because the sample size calculation was performed to assess the primary composite outcome and MACCEs as a secondary end point, additional analyses are hypothesis generating. Variables suitable for multivariable adjustment were selected based on univariate analysis results. However, given that previous research has identified additional variables associated with CH, further investigation with larger sample sizes would be necessary to explore the potential impact of these covariates. The individual components of the primary outcome were not examined separately due to the constraint imposed by the limited number of events, which restricts statistical adjustments. The current study was not designed to assess the effect of specific mutations on adverse clinical outcomes, which requires further investigation. Most genes screened in the gene panel were genes involved in myeloid malignancies, which constitute the most common set of genes identified with CH to date. Therefore, the association found between CH and adverse outcomes is currently restricted to myeloid CH, the most frequent CH subtype. The exclusion of germline variants was based on a combined approach that used a 35% VAF threshold and variant frequency assessment. This approach did not include additional sequencing from tissue biopsies, which might lead to the exclusion of potentially pathogenic variants.

CONCLUSIONS

In patients undergoing cardiac surgery, CH is common and associated with a 2-fold increased long-term risk for major adverse clinical outcomes, including

all-cause mortality and MACCEs. Low clone size was not associated with adverse outcomes. CH screening might be a useful tool in patients undergoing cardiac surgery to assess the risk for long-term postoperative outcomes.

ARTICLE INFORMATION

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Disclosures

James Robert White is founder and owner of Resphera Biosciences. Frederic Geissmann has performed consulting for Third Rock venture. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S9
Figure S1

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