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ORIGINAL RESEARCH

Clonal Hematopoiesis Is Associated With Adverse Clinical Outcomes and Left Ventricular Remodeling in Aortic Stenosis

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ABSTRACT

BACKGROUND Clonal hematopoiesis of indeterminate potential (CHIP) has been linked to intensified systemic inflammation and represents a novel risk factor for atherosclerotic cardiovascular diseases, including aortic stenosis (AS).

OBJECTIVES This study aimed to assess the clinical impact of CHIP in a cohort of severe AS patients undergoing transcatheter aortic valve implantation (TAVI).

METHODS We enrolled 110 severe AS patients in this retrospective study. Targeted next-generation sequencing was employed to detect somatic mutations with a variant allele frequency >2% in 16 genes most frequently associated with CHIP. Correlative analyses on clinical, laboratory, and echocardiographic parameters were also performed. The primary endpoint was post-TAVI heart failure hospitalization. Multivariate Cox regression model was used to account for confounding effects of relevant clinical factors.

RESULTS CHIP was detected in 40 (36.4%) patients in our cohort. The most commonly mutated genes were *DNMT3A*, *TET2*, and *ASXL1*. With a median follow-up of 55.2 months, patients carrying CHIP had a significantly higher heart failure hospitalization rate (adjusted HR: 3.060; 95% CI: 1.090-8.589; $P = 0.034$) than those without CHIP. Additionally, patients harboring CHIP had higher serum ferritin levels, as well as echocardiographic evidence of left ventricular hypertrophy and diastolic dysfunction.

CONCLUSIONS Our study supports the adverse clinical impact of CHIP in AS patients undergoing TAVI, which could be attributed to systemic inflammation and maladaptive LV remodeling. Prospective trials are anticipated to validate our findings and provide further evidence that CHIP holds the potential of being an actionable therapeutic target in AS. (JACC Adv. 2025;4:101532) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AV = aortic valve

CHIP = clonal hematopoiesis of indeterminate potential

CRP = C-reactive protein

CV = cardiovascular

HF = heart failure

HFH = heart failure hospitalization

IL = interleukin

LV = left ventricle

MDCT = multi-detector computed tomography

NGS = next generation sequencing

NT-proBNP = N-terminal pro-brain natriuretic peptide

NTUH = National Taiwan University Hospital

PB = peripheral blood

PH = proportional hazard

STS = Society of Thoracic Surgery

TAVI = transcatheter aortic valve implantation

VAF = variant allele frequency

As individuals age, somatic mutations inevitably accumulate in the hematopoietic system, leading to survival advantage of some hematopoietic stem cells and their clonal expansion. This process is currently known as clonal hematopoiesis or clonal hematopoiesis of indeterminate potential (CHIP),[1,2] because these mutational events can be detected even in the general population. CHIP is clinically defined as the presence of myeloid disease-associated mutations in the peripheral blood (PB) or bone marrow at a variant allele frequency (VAF) of >2% in individuals without a formal diagnosis of hematological malignancies.[3,4] CHIP mainly occurs in the following 3 transcriptional regulators, namely *DNMT3A*, *TET2*, and *ASXL1* (aka. DTA mutations), accounting for more than 80% of the CHIP events. However, other commonly affected genes in CHIP include those involved in the intracellular signaling cascade (eg, *JAK2*, *GNAS*, *GNB1*, *CBL*), DNA damage response (eg, *TP53*, *PPM1D*), and splicing factors (eg, *SF3B1*, *SRSF2*).[1,2,5]

With accumulating evidence in the past decade, we now realize that CHIP is associated with not only hematological malignancies but also an increased risk of several inflammatory diseases,[6,7] as well as atherosclerotic cardiovascular (CV) diseases, such as coronary artery disease (CAD), myocardial infarction, and ischemic heart failure (HF).[4,8-14] In a previous single cell transcriptomics study examining the peripheral blood mononuclear cells derived from *DNMT3A*-mutated HF patients, elevated expressions of several interleukins (IL) and cytokines, such as *IL1B*, *IL6*, *IL8*, and *CCL3*, were observed in the circulating monocytes.[15] In another experimental study, *Tet2* deficiency in the mouse model aggravated atherosclerosis and accelerated HF through an augmented inflammatory chemokine milieu resulting from NLRP3 inflammasome-mediated overproduction of IL-1β by the *Tet2*-deficient macrophages.[16]

Aortic stenosis (AS) is the most common degenerative valvular heart disease in the elderly,[17] characterized by progressive restriction of the aortic valve (AV) leaflets and left ventricular (LV) outflow obstruction, which eventually becomes fatal if left untreated.[18] Of note, when AS patients become symptomatic, clinical deterioration can be rapid and the 2-year mortality rate may exceed 60%.[19] Although the conventional surgical AV replacement was shown to improve the survival and LV systolic function in patients with severe AS,[20,21] the minimally invasive transcatheter aortic valve implantation (TAVI) procedure has recently revolutionized the treatment of severe AS and has now become the most common treatment modality.[22-25] In terms of pathogenesis, the etiology of AS has historically been attributed to age-related calcium deposition on the AV leaflets; however, recent evidence suggests that chronic inflammation is actually the more fundamental driving force underlying degenerative fibrocalcific AS.[26,27] In a recent report, the researchers examined the prognostic relevance of *DNMT3A* or *TET2* mutations, the 2 most frequently mutated genes in CHIP, in a cohort of severe AS patients, and found that patients having *DNMT3A* or *TET2* mutations had inferior medium-term overall survival post-TAVI. They also observed a higher Th17/Treg ratio and increased nonclassical monocytes in the AS patients carrying CHIP compared with those without.[28] Although the current mainstream knowledge indicates that CHIP is linked to worse prognosis in atherosclerotic CV diseases through an enhanced inflammatory response, how CHIP contributes to compromised outcomes in AS remains to be further elucidated. Therefore, in line with the contemporary recognition of the link between CHIP and systemic inflammation,[29] we hypothesized that CHIP may potentiate the progressive atherosclerotic degeneration of the AV, leading to accelerated functional decline of the valve leaflets, LV outflow obstruction, and inferior patient outcomes. In this study, we aimed to characterize the prevalence of CHIP in an Asian cohort of severe AS patients undergoing TAVI, examine how CHIP may impact postprocedural clinical outcomes, and provide additional insights into the underlying pathophysiologic mechanisms.

MATERIALS AND METHODS

STUDY POPULATION AND OUTCOMES. Between March 2016 and July 2021, a total of 114 consecutive patients who had been diagnosed with severe AS according to the 2020 American College of Cardiology/American Heart Association Guideline for the Management of Patients With Valvular Heart Disease[30] and received TAVI at the National Taiwan University Hospital (NTUH) were recruited. None of these patients had been previously diagnosed with hematological malignancies; patients who had a prior diagnosis of solid cancer and were actively receiving anti-cancer treatments (N = 4) were excluded. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the NTUH. (IRB approval

number: 202207051RINB) Written informed consent was obtained from each study participant.

All study participants were prospectively enrolled in the Asian TAVR registry and were clinically followed up in accordance with the study protocol.[31] Baseline clinical characteristics including demographics, body mass index, stage of AS (D1, D2, and D3 for symptomatic severe AS),[30] Society of Thoracic Surgery (STS) risk score, NYHA functional classification, associated comorbidities, laboratory data, multidetector computed tomography (MDCT), and echocardiographic parameters were systematically collected at the pre-TAVI evaluation (within 1 month before the TAVI procedure). The electrocardiogram-gated MDCT was performed with a 256-slice scanner (Revolution, GE Healthcare). The calcium deposition was quantified with the Agatston score method.[32] All the transthoracic echocardiographic examinations were performed by board-certified sonographers using commercially available cardiac ultrasound machines (iE33/EPIQ 7G, Philips Healthcare) in compliance with contemporary guidelines[30] and reviewed by experienced cardiologists with level III training. The echocardiographic parameters were measured from an average of 3 heartbeats for patients in sinus rhythm and 5 heartbeats for patients with atrial fibrillation, except for peak aortic velocity and mean aortic valve pressure gradient, which were recorded with the highest value to avoid underestimation of AS severity.

OUTCOMES. The primary outcome was time to heart failure hospitalization (HFH), defined as the duration from the date of TAVI to the first hospitalization due to HF exacerbation. Secondary outcomes included CV mortality (defined as death attributed to end-stage HF, fatal thromboembolic events, or sudden cardiac death) and all-cause mortality.

SAMPLE PROCESSING AND NEXT GENERATION SEQUENCING. DNA was extracted with the QIAamp DNA Blood Mini Kit (Qiagen) from PB mononuclear cells of study participants after lysis of erythrocytes. To detect CHIP mutations in patient samples, a customized amplicon-based next generation sequencing (NGS) gene panel, the iNA CHIP NGS kit (Instant NanoBiosensors), was designed to detect the presence of somatic mutations in 16 genes previously identified as candidate drivers of CHIP (Supplemental Table 1). A total of 20 ng of DNA from each patient was used for library preparation. The quantity and quality of DNA libraries were confirmed with the Qubit Fluorimeter (Thermo Fisher Scientific) and Qsep 100 Analyzer (BiOptic Inc). The libraries were then sequenced on the NovaSeq 6,000 sequencer (Illumina) at the 150 bp pair-end mode. Mean coverage across all samples was about 2,500X, with a minimal coverage of 300X.

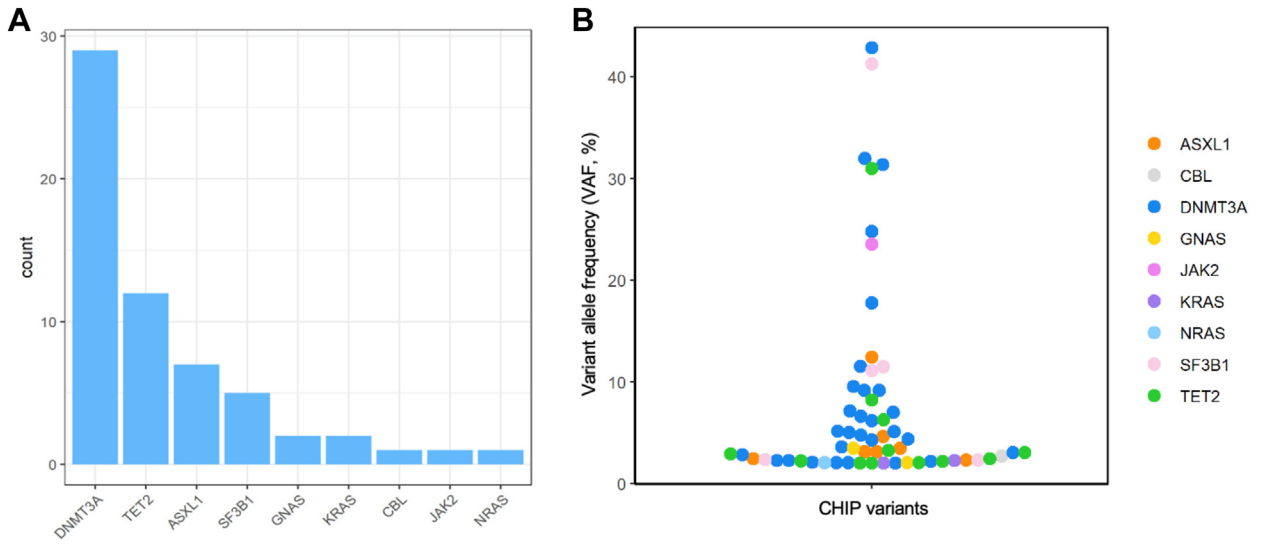
The FASTQ files were mapped to the GRCh37 human genome with Burrows-Wheeler Alignment-MEM. Somatic mutations were identified using Varscan 2 (version 2.4.4).[33] The variants were annotated with SnpEff (version 4.3 t),[34] with information from the following databases:1,000 Genome Project (phase 3), Genome Aggregation Database (release 2.1),[35] Catalogue Of Somatic Mutations In Cancer (v92),[36] and dbSNP (version 154).[37] The variant calls were further filtered by the following criteria: 1) protein coding region variants with a VAF $\geq$ 2.0%; 2) total depth of coverage $\geq$250; 3) number of reads supporting the alternate allele $\geq$10; and 4) documented in the Catalogue Of Somatic Mutations In Cancer database or with minor allele frequency $\leq$ 0.01 in 1,000 Genome Project and Genome Aggregation Database.

STATISTICAL ANALYSIS. Continuous variables were expressed as median (IQR), and categorical variables as numbers and frequencies, unless otherwise specified. For the comparison of continuous variables between 2 groups, Wilcoxon rank-sum test was used. For the comparison of categorical variables between 2 groups, Chi-square test and Fisher exact test were used. Time-to-event data were plotted with the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards (PH) model was used to estimate the adjusted HR and 95% CI in the multivariate analysis, with additional clinically relevant factors included as covariates. In addition, we used overlap propensity score-weighting to account for potential confounding associated with baseline clinical characteristics.[38-40] A propensity score for having CHIP was estimated from a multivariable logistic regression model including the demographic, clinical, laboratory, and echocardiographic parameters collected in this study. All tests were two-sided and were considered statistically significant if $P < 0.05$. All analyses were conducted in the R statistical computing environment (version 4.0.3).

RESULTS

PATIENT CHARACTERISTICS. In this study, we analyzed 110 consecutive severe AS patients, without a prior diagnosis of hematological or solid cancers that required active anti-cancer treatments, who had undergone the TAVR procedure at NTUH. The baseline demographic and clinical characteristics of the 110 patients were summarized in Supplemental Table 2. The median age of this cohort was 82.5

FIGURE 1 Characterization of the Clonal Hematopoiesis of Indeterminate Potential (CHIP) Variants Identified in the Patients With Severe Aortic Stenosis



(A) Number of genetic variants identified across various genes included in our sequencing panel. (B) Distribution of variant allele frequency of the genetic variants identified in this study.

(78.0-86.0) years, and 41 (37.3%) were male. About 42.7% of the patients had an AS stage greater or equal to D2, the median STS score was 4.12 (2.66-8.00). Nearly all (99.1%) of the patients had clinical symptoms of congestive heart failure, and 80.9% of them presented with NYHA functional classes 3 or 4. Upon preprocedural echocardiographic examination, the median AV area was 0.76 (0.62-0.89) cm^2, and the median AV peak pressure gradient was 73.10 (51.10-91.72) mm Hg. On preprocedural MDCT scans, the median Agatston calcification score was 1771.45 (1,090.57-2,554.00) for the AV and 778.04 (160.05-1,561.36) for the coronary arteries, reflecting the heavy calcium deposition and severity of AS in our patient cohort.

PREVALENCE OF CHIP AND ITS CLINICAL ASSOCIATION IN PATIENTS WITH AS. In our cohort consisting of 110 patients with severe AS, we identified 60 CHIP variants in 40 (36.4%) patients (**Figure 1A**, Supplemental Table 3, Supplemental Figure 1A); this prevalence is comparable with previous reports in cardiovascular patients.[8-10,13,28,41] We also observed that the prevalence of CHIP increased with age (Supplemental Figure 1B), in accordance with our knowledge derived from previously reported large population-based cohorts.[1,2,42,43] Among the 60 CHIP variants detected in our AS cohort, 29 (in 24 patients, 21.8% of the cohort) affected *DNMT3A*, 12 (in 12 patients, 10.9% of the cohort) affected *TET2*, 7 (in 7 patients, 6.4% of the cohort) affected *ASXL1*, while 12 (in 9 patients, 8.2% of the cohort) affected other myeloid disease-related genes. Among the 40 AS patients who harbored CHIP, 24 (60.0%) harbored only one variant, 12 (30.0%) harbored 2 variants, while only 4 (10.0%) harbored 3 variants. As shown in **Figure 1B**, the median VAF of the CHIP variants was 3.49% (range, 2.01-42.86), approximately equivalent to the presence of 6.98% mutated nucleated cells in the PB, if the variants were heterozygous. The median VAF for the 3 most prevalent mutated genes, namely *DNMT3A*, *TET2*, and *ASXL1*, were 5.11%, 2.67%, and 3.16%, respectively. On the other hand, 48 (80.0%) of the variants detected had a VAF less than 10%, indicating that most of the CHIP carriers had rather small clones.

The baseline clinical characteristics in AS patients with or without CHIP are summarized in **Table 1**. Overall, we observed that AS patients with CHIP had a higher proportion of the D3 stage, while there were no statistically significant differences in terms of age, gender, NYHA functional classes, Agatston calcification scores, or comorbidities.

THE IMPACT OF CHIP ON PATIENT OUTCOMES POST TAVI. With a median follow-up period of 55.2 months, AS patients carrying CHIP had significantly increased HFH rate than those without CHIP ($P = 0.026$) (**Figure 2**). In subgroup analyses (Supplemental Figure 2), we noted that the HFH rates were consistently higher in the patients carrying CHIP compared

with those without CHIP, whether we examined the patients with or without the DTA (*DNMT3A*, *TET2*, *ASXL1*) mutations, the DT (*DNMT3A*, *TET2*) mutations, or CHIP mutations >10% VAF. Further, in the multivariate Cox PH analysis (Table 2), after adjusting for age, NYHA functional class, STS risk score, LVEF, and N-terminal pro-brain natriuretic peptide (NT-proBNP) level, the presence of CHIP remained a significant risk factor for HFH (adjusted HR: 3.060; 95% CI: 1.090-8.589; $P = 0.034$). On the other hand, we observed that none of all-cause mortality, CV-related mortality, or non-CV mortality was significantly modulated by the presence of CHIP, likely because of the overall low postprocedural complication rates in this cohort (Supplemental Figure 3).

We implemented the overlap weighting method to adjust for potential confounding derived from baseline differences between patients with or without CHIP. Supplemental Tables 4 and 5 reported the standardized mean differences of all patient characteristics before and after overlap weighting analysis, respectively. We could observe that in the overlap propensity score-weighted Cox proportional hazards analysis, CHIP was significantly associated with a higher risk of HFH post-TAVI ($P = 0.013$) (Supplemental Figure 4).

MECHANISTIC INSIGHTS INTO THE INFERIOR CLINICAL OUTCOMES OF CHIP CARRIERS. To derive potential mechanistic insights into how CHIP may adversely affect patient outcomes, we first examined the preprocedural laboratory parameters of our AS patients, including complete blood counts, cardiac troponin, NT-proBNP, and inflammatory markers such as C-reactive protein (CRP), IL-6, and ferritin (Table 3). We noted that the serum ferritin level was significantly higher in the patients harboring CHIP than those without CHIP (median 285.00 vs 153.53, $P = 0.045$). There were no significant differences in other laboratory parameters between patients with or without CHIP. We then analyzed the preprocedural echocardiographic findings of the patients (Table 3). We observed that patients harboring CHIP, as compared with those without CHIP, had significantly smaller LV end diastolic diameter (median 45.50 vs 48.50 mm, $P = 0.029$), LV end systolic diameter (median 27.00 vs 30.00 mm, $P = 0.028$), LV end diastolic volume (median 99.50 vs 110.85 mL, $P = 0.030$), and LV end systolic volume (median 27.75 vs 36.50 mL, $P = 0.006$). We also noted that patients harboring CHIP had thicker interventricular septum (median 13.50 vs 12.00 mm, $P = 0.011$) and LV posterior wall (median 13.00 vs 12.00 mm, $P = 0.017$), compared to those without CHIP. In addition, patients with CHIP demonstrated a trend toward an increased E/e' ratio (median 20.3 vs 18.3, $P = 0.069$) and a higher percentage of grade 2 and 3 diastolic dysfunction (45.0% vs 28.6%, $P = 0.081$) suggesting more severe diastolic dysfunction. Overall, our exploratory data analysis revealed that in severe AS patients carrying CHIP, systemic inflammation, LV hypertrophy, and diastolic dysfunction may jointly contribute to the worse clinical outcome.

TABLE 1 Baseline Clinical Characteristics in Aortic Stenosis Patients With or Without Clonal Hematopoiesis of Indeterminate Potential

	No CHIP (N = 70)	CHIP (N = 40)	*P* Value
Age, y	80.5 (76.0-85.0)	83.0 (80.8-86.0)	0.085
Male	24 (34.3)	17 (42.5)	0.514
BMI (kg/m^2)	24.29 (21.24-26.73)	23.79 (20.89-26.86)	0.965
Stage of AS			**0.026**
D1	39 (55.7)	24 (60.0)	
D2	14 (20.0)	1 (2.5)	
D3	17 (24.3)	15 (37.5)	
NYHA functional class III/IV	57 (81.4)	32 (80.0)	>0.999
STS score	4.12 (2.81-7.13)	4.16 (2.60-8.03)	0.842
MDCT calcium scan			
Agatston score: AV	1771.45 (1,089.00-2,717.00)	1710.64 (1,199.49-2,177.31)	0.390
Agatston score: coronary	810.08 (140.46-1771.60)	764.12 (469.21-1,457.78)	0.881
Associated conditions			
CAD	34 (48.6)	14 (35.0)	0.238
Previous MI	4 (5.7)	0 (0.0)	0.312
CHF	70 (100.0)	39 (97.5)	0.776
A-fib	15 (21.4)	9 (22.5)	>0.999
DM	26 (37.1)	13 (32.5)	0.778
HTN	44 (62.9)	29 (72.5)	0.412
Stroke	4 (5.7)	4 (10.0)	0.652
HLP	24 (34.3)	7 (17.5)	0.096
COPD	4 (5.7)	3 (7.5)	>0.999
Pulmonary HTN	10 (14.3)	3 (7.5)	0.451
CKD	49 (70.0)	29 (72.5)	0.953

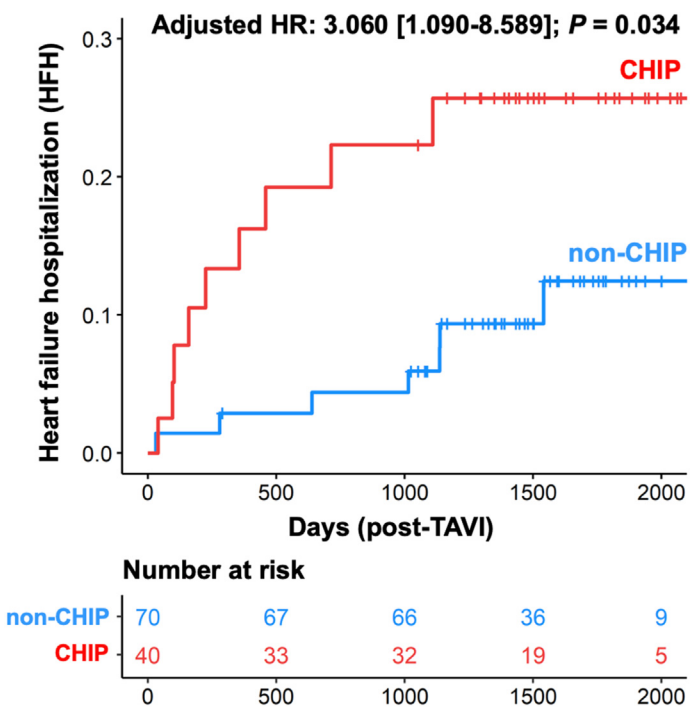
Values are median (IQR) or n (%). **Bold** values indicate *P* values <0.05.

A-fib = atrial fibrillation; AS = aortic stenosis; AV = aortic valve; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; HLP = hyperlipidemia; HTN = hypertension; MDCT = multi-detector computed tomography; MI = myocardial infarction; STS = Society of Thoracic Surgeons.

DISCUSSION

In this study, we demonstrated that CHIP can be frequently detected in an Asian cohort of severe AS patients and provided evidence that the AS patients harboring CHIP had higher serum ferritin levels indicating a hyperinflammatory status, echocardiographic evidence of LV hypertrophy and maladaptive

FIGURE 2 Kaplan-Meier Analysis of Heart Failure Hospitalization in the AS Patients of this Study



AS patients harboring CHIP had significantly higher HFH rate than those without. (5-year HFH rate: 22.7% vs 11.7%; adjusted HR: 3.060; 95% CI: 1.090-8.589; $P = 0.034$).

TABLE 2 Multivariate Cox Proportional Hazards Regression Analysis of Heart Failure Hospitalization

	HR	95% CI Lower	95% CI Upper	*P* Value
Age[a]	1.016	0.949	1.087	0.650
NYHA functional class	0.847	0.359	2.002	0.706
STS score	1.116	0.978	1.273	0.103
LVEF[b]	4.113	0.868	19.483	0.075
NT-proBNP[c]	0.816	0.194	3.437	0.782
Presence of CHIP	3.060	1.090	8.589	**0.034**

Bold values indicate *P* values <0.05. [a]As continuous variable. [b]LVEF <40% vs >40%. [c]NT-proBNP >400 pg/mL vs <400 pg/mL.

CHIP = clonal hematopoiesis of indeterminate potential; LVEF = LV ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

LV remodeling, and a trend toward more severe diastolic dysfunction. Importantly, we found that CHIP was associated with an increased HFH rate even following successful TAVI procedures (**Central Illustration**). We acknowledge that in the literature, the presence of CHIP has been correlated with an increased risk of incident severe AS[44] and both mid-term and long-term mortality rates in AS patients undergoing TAVI[28,45]; however, our study provides additional insights by investigating potential pathophysiological mechanisms contributing to the compromised clinical outcome beyond the analysis of inflammation-associated biomarkers.

In our cohort, 36.4% of the AS patients harbored CHIP mutations. In a recent study examining the prevalence of CHIP in a cohort of Asian AS patients, the researchers reported that the prevalence was 39.2% or 20.0%, when the VAF cutoff was selected at 1% or 2%, respectively, which was deemed higher than age- and gender-matched controls.[46] In another seminal study looking into the prognostic value of CHIP in severe AS patients undergoing TAVI, the researchers used targeted sequencing to examine somatic mutations in *DNMT3A* and *TET2*, the 2 most commonly affected genes in CHIP, and reported a prevalence of CHIP at 33.3%.[28] We reason that the slightly higher prevalence of CHIP in this study, as compared with the aforementioned studies, may be secondary to differences in the age distributions, ethnic groups, or AS severities among different studies and because of the additional CHIP-associated genes included in our targeted NGS panel.

In terms of clinical outcomes of severe AS patients, in the aforementioned study by Mas-Peiro et al., the researchers reported that the patients with *DNMT3A* or *TET2* mutations had increased medium-term all-cause mortality in the first 8 months following TAVI.[28] In this study, 8 out of 279 (2.9%) AS patients died due to procedure-related complications during the first 1 month post-TAVI, and these patients were excluded in the survival analysis to avoid confounding effects directly associated with the TAVI procedure. In a follow-up study, the researchers found that CHIP was also associated with a significantly higher all-cause mortality up to 4 years post-TAVI.[45] In contrary, we did not observe such differences in the all-cause mortality or CV-related mortality in our study, even after a rather prolonged follow-up period of 55.2 months (Supplemental Figure 3). We reason that the overall low immediate procedure-related complication rates (no patient died or experienced major bleeding, stroke, or other vascular complications within 30 days post-TAVI) and postprocedural CV-related mortality in our cohort may be the major reason why we did not observe a discernible survival difference in AS patients with or without CHIP. Nevertheless, we found that AS patients carrying CHIP had indeed a higher rate of postprocedural HFH (**Figure 2**) and that CHIP remained an independent

TABLE 3 Baseline Laboratory and Echocardiographic Parameters in Aortic Stenosis Patients With or Without Clonal Hematopoiesis of Indeterminate Potential

	No CHIP (n = 70)	CHIP (n = 40)	*P* Value
Laboratory tests			
WBC ($\times 10^9$/L)	6.32 (5.18-7.64)	6.27 (5.17-7.94)	0.958
Hb (g/dL)	12.15 (10.53-13.40)	12.45 (10.52-13.50)	0.770
MCV (fL)	92.00 (88.32-96.27)	91.85 (88.95-94.58)	0.591
Platelet ($\times 10^9$/L)	178.50 (147.25-219.75)	198.00 (142.00-235.00)	0.792
LDH (U/L)	200.00 (175.00-247.00)	198.00 (168.25-220.50)	0.370
Troponin I (ng/mL)	112.00 (0.00-5,145.00)	78.00 (0.00-3,926.00)	0.411
C-reactive protein (mg/dL)	0.22 (0.08-0.54)	0.17 (0.09-0.52)	0.891
Interleukin 6 (pg/mL)	6.36 (2.80-10.74)	5.65 (2.25-10.88)	0.477
NT-proBNP (pg/mL)	1,316.00 (464.68-7,333.75)	1,627.50 (467.40-8,186.50)	0.878
Ferritin (ng/mL)	153.53 (72.10-372.72)	285.00 (143.59-522.40)	**0.045**
Echocardiography			
AV peak PG (mm Hg)	74.60 (51.00-95.37)	71.35 (54.27-87.83)	0.869
AV mean PG (mm Hg)	40.50 (29.70-57.00)	41.00 (30.15-52.17)	0.671
AVA (cm^2)	0.75 (0.63-0.88)	0.78 (0.62-0.92)	0.548
LVEF <40%	6 (8.57%)	1 (2.50%)	0.419
LVEDD (mm)	48.50 (44.00-52.75)	45.50 (41.00-49.00)	**0.029**
LVESD (mm)	30.00 (26.00-36.75)	27.00 (24.00-31.00)	**0.028**
LVEDV (mL)	110.85 (87.73-133.32)	99.50 (74.38-115.02)	**0.030**
LVESV (mL)	36.50 (25.00-60.43)	27.75 (19.78-37.42)	**0.006**
LV mass (gram)	220.35 (170.02-265.35)	214.00 (183.30-269.80)	0.697
LVOTd (mm)	2.00 (2.00-2.20)	2.00 (1.95-2.15)	0.309
LA (mm)	42.00 (37.00-46.00)	43.00 (38.00-47.00)	0.345
LA volume (mL)	74 (61.0-94.0)	70 (52.0-93.0)	0.342
IVS (mm)	12.00 (10.25-14.00)	13.50 (12.00-15.00)	**0.011**
PW (mm)	12.00 (10.00-13.00)	13.00 (11.00-14.00)	**0.017**
Mitral-E (cm/s)	88.90 (67.80-107.80)	91.70 (75.05-109.35)	0.245
Mitral-A (cm/s)	111.50 (92.42-132.45)	126.20 (97.80-142.65)	0.286
E/e'	18.3 (14.0-22.5)	20.3 (16.9-25.1)	0.069
TR velocity (cm/s)	2.85 (2.4-3.2)	2.91 (2.58-3.1)	0.872
Grade of diastolic dysfunction			0.081
Normal + Grade 1	50 (71.4)	22 (55.0)	
Grade 2 + Grade 3	20 (28.6)	18 (45.0)	

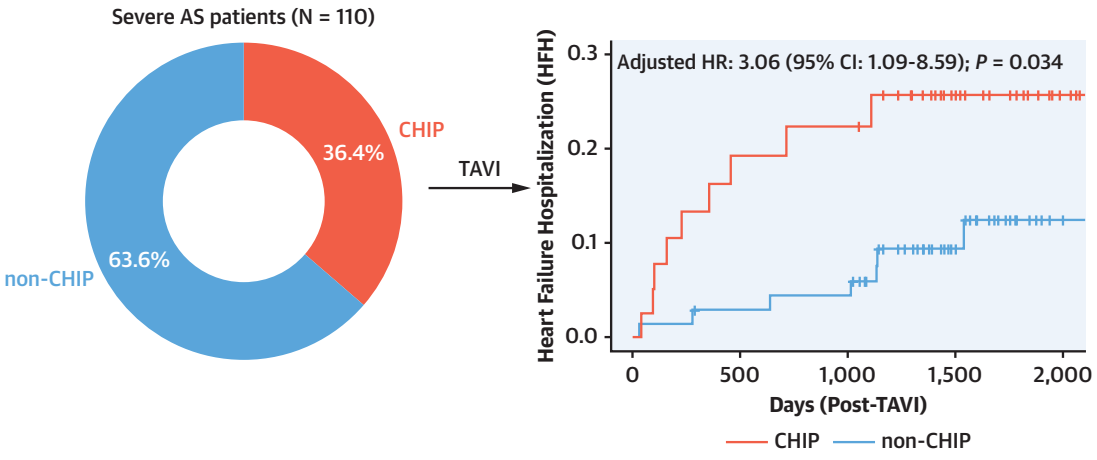
Values are median (IQR). **Bold** values indicate *P* values <0.05.

AV = aortic valve; AVA = aortic valve area; Hb = Hemoglobin; IL = interleukin; IVS = interventricular septum; LA = left atrium; LDH = lactate dehydrogenase; LV = left ventricle; LVEDD = LV end-diastolic diameter; LVEDV = LV end diastolic volume; LVEF = LV ejection fraction; LVESD = LV end-systolic diameter; LVESV = LV end systolic volume; LVOTd = LV outflow tract diameter; MCV = mean corpuscular volume; NT-proBNP = N-terminal pro-brain natriuretic peptide; PG = pressure gradient; PW = posterior wall; TR = tricuspid regurgitation; WBC = white blood cell.

poor prognostic factor in the multivariate Cox PH analysis taking into account other important confounding factors such as age, NYHA functional class, STS risk score, LVEF, and NT-proBNP level (Table 2). The finding that CHIP represents as yet another important poor prognostic factor in AS and other atherosclerotic CV diseases could be corroborated by previous reports conducted in CAD, chronic ischemic HF, or HF with reduced LV ejection fraction.[8-10,41]

Furthermore, we sought to search for underlying pathophysiological mechanisms that could explain the worse clinical outcomes in AS patients harboring CHIP. In previous studies exploring the causal relationship between CHIP and atherosclerotic CV disease development in mouse models, C-X-C motif chemokines including Cxcl1, Cxcl2, Cxcl3, as well as Pf4, Il1b, Il6, and NLRP3 inflammasome components were found to be overexpressed in the macrophages derived from mice carrying CHIP.[8,16] In the previous clinical study examining the clinical implications of CHIP in AS, although inflammatory markers such as CRP and IL-6 were not significantly different between carriers or noncarriers of CHIP, the researchers noted that CHIP carriers had increased pro-inflammatory

CENTRAL ILLUSTRATION **The Prevalence and Clinical Impact of CHIP in Patients With Severe AS**



Yao C-Y, et al. JACC Adv. 2025;4(2):101532.

In this study, 36.4% of the 110 severe AS patients undergoing transcatheter aortic valve implantation (TAVI) were found to harbor CHIP. The presence of CHIP is a strong predictor for a higher HFH rate post-TAVI.

Th17 cells and nonclassical monocytes.[28] In the current study, we observed that most of the patients' baseline clinical characteristics, comorbidities, PB blood counts, CRP, and IL-6 levels were not significantly different between AS patients with or without CHIP, similar to previous reports.[28,45] Nevertheless, we did note that patients carrying CHIP had higher circulating ferritin levels indicating a hyperinflammatory status and a higher proportion of stage D3 AS, which is often linked to LV hypertrophy, small ventricular size, diastolic dysfunction, and poor prognosis in the literature.[47,48] In our echocardiographic data analysis, AS patients harboring CHIP indeed demonstrated evidence of maladaptive LV remodeling, such as thicker interventricular septum and posterior wall, smaller LV chamber volumes either at end diastole or end systole, and increased E/e' ratio (**Table 3**). These findings indicated that AS patients with CHIP had more pronounced LV hypertrophy and more severe diastolic dysfunction than those without CHIP. As diastolic dysfunction has been associated with increased mortality and adverse events in AS,[49] we reason that it may be one of the main mechanisms contributing to the compromised postprocedural outcome in severe AS patients with CHIP. Furthermore, a recent study reported that *Tet2*-mediated clonal hematopoiesis in mice would lead to upregulation of IL-1β and maladaptive cardiac remodeling following LAD ligation (to model myocardial infarction in mice). In this model, the observed cardiac remodeling included increased LV systolic and LV diastolic volumes and decreased LVEF.[50] Although in our AS patient cohort we actually observed thicker myocardium and smaller LV chamber sizes in those harboring CHIP, we reason this mainly reflects the unique pathophysiology of AS, which is dominated by pressure overload secondary to valve malfunction and LV outflow tract obstruction, instead of loss of viable myocardium and pumping failure. It is thus plausible that in AS, CHIP may activate proinflammatory pathways and aggravate atherosclerotic fibrosis of the AV and myocardium.[50] The worsening pressure overload, maladaptive LV remodeling, and diastolic dysfunction then collectively make AS patients more susceptible to HF exacerbations and HFH events, even though TAVI has successfully relieved the hemodynamic obstruction.

This study features the following merits. First, this is the first study characterizing the prevalence and landscape of CHIP in an Asian AS patient cohort, using the high throughput sequencing technique. Second, although the patents in our study had a low immediate procedure-related complication rate and a low CV-related mortality rate during long-term follow-up, we were able to demonstrate that AS

patients with CHIP still had a higher risk of HFH even following successful TAVI, and therefore in these patents, a higher degree of clinical vigilance and more intensive monitoring schedule should be exercised to improve postprocedural patient outcomes. The characterization of CHIP in AS patients may represent a new dimension that we can leverage to refine patient management, which is currently an unmet need in most clinical settings. Third, we performed detailed echocardiographic surveillance in our patients and provided evidence that systemic hyperinflammation and maladaptive LV remodeling may be underlying pathophysiology for worse patient outcomes. To counteract the negative clinical impact of CHIP on AS patients, the following leads could be thoughtfully evaluated. CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) first demonstrated that IL-1β blockade with canakinumab could reduce major adverse cardiovascular events in patients with stable coronary artery disease and elevated levels of CRP, predominantly by reducing the incidence of repeated myocardial infarction.[51] Moreover, in a later follow-up study, the researchers found that actually those patients with *TET2* variants may respond better to canakinumab than other patients without detectable CHIP mutations.[52] Therefore, the presence of CHIP seems to be a strong predictor in terms of selecting patients with AS or other atherosclerotic CV diseases for anti-inflammatory therapy to improve clinical outcomes.

STUDY LIMITATIONS. We acknowledge the following limitations in our study, including the retrospective study design and single-center, small patient number; therefore, the findings of this study served to establish the association of CHIP and inferior clinical outcomes in severe AS patients, but whether there is a causal relationship warrants further investigations. In addition, to address the issue of potential confounding secondary to selection bias commonly present in retrospective studies, we performed overlap propensity score-weighting analysis based on baseline characteristics of the patients in our cohort. Although after overlap weighting analysis (Supplemental Table 5), the number of patients in each group was substantially reduced (6 in non-CHIP and 8 in CHIP subgroup), the overlap propensity score-weighted Cox proportional hazards model still demonstrated that CHIP was a significant risk factor for HFH post-TAVI. We also lack laboratory data on a wider array of inflammatory cytokines or PB immune cell subsets for more extensive correlative analysis.

CONCLUSIONS

Our study supports the clinical relevance of CHIP in modulating the clinical outcomes of severe AS patients undergoing TAVI. The negative prognostic impact of CHIP in AS patients is most likely driven by systemic inflammation, maladaptive LV remodeling, and diastolic dysfunction. Larger prospective trials are anticipated to validate our findings and provide further evidence whether the characterization of CHIP in AS patients would go beyond merely being a novel molecular risk factor and become an actionable therapeutic target in the foreseeable future.

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AUTHOR CONTRIBUTIONS C-YY and T-YK were responsible for data collection and management, statistical and bioinformatic analysis, result interpretation, literature research, and manuscript writing; L-TY supervised the cardiac echocardiography data analysis; Takeuchi-M supervised and performed the propensity score analysis; C-FY, M-SL, Y-HC were responsible for data collection and management; C-YK supervised the variant curation procedure; C-LH supervised the sequencing experiments and bioinformatic analysis; H-LK and W-CC planned, designed, and coordinated the study over the entire period and wrote the manuscript. All authors read and approved the final manuscript.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the study, we integrated the clinical, sequencing, and echocardiographic data from 110 severe AS patients undergoing TAVI and identified CHIP in up to 36.4% of this cohort, with the most frequently mutated genes being *DNMT3A*, *TET2*, and *ASXL1*. We also provided evidence for the adverse prognostic impact of CHIP on postprocedural patient outcomes, which could be attributed to systemic inflammation, maladaptive LV remodeling, and diastolic dysfunction. CHIP therefore represents a novel adverse prognostic factor in patients with severe AS.

TRANSLATIONAL OUTLOOK: Our study serves as an important step toward personalized management of AS. As accumulating evidence suggests that anti-inflammatory agents can improve CV outcomes in patients with atherosclerosis, we speculate that CHIP may represent a novel molecular biomarker that can help clinicians more appropriately select the subset of patients that would derive direct benefits from anti-inflammatory therapy. Further prospective studies are warranted to validate our findings and investigate whether CHIP holds the potential of being an actionable therapeutic target in AS.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.