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Journal

American Journal of Transplantation, 23(8)

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Publication Date

2023-08-01

DOI

10.1016/j.ajt.2023.04.028

Peer reviewed

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Am J Transplant. Author manuscript; available in PMC 2024 August 01.

Published in final edited form as:

Am J Transplant. 2023 August ; 23(8): 1256–1263. doi:10.1016/j.ajt.2023.04.028.

Clonal hematopoiesis of indeterminate potential and outcomes after heart transplantation: A multi-center study

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Abstract

Cardiac allograft vasculopathy (CAV) is a leading cause of late graft failure and mortality after heart transplantation (HT). Sharing some features with atherosclerosis, CAV results in diffuse

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Conflicts of interest disclosures: Dr. Bick is on the scientific advisory board of TenSixteen Bio. Dr. Moslehi has severed on advisory boards for Bristol Myers Squibb, AstraZeneca, Myovant, Cytokinetics, Takeda, BeiGene, Kiniksa, Kurome Therapeutics, and Pfizer. All other authors declare no relevant conflicts of interest.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Alexander G Bick reports a relationship with TenSixteen Bio that includes: consulting or advisory. Javid Moslehi reports a relationship with Bristol Myers Squibb, AstraZeneca, Myovant, Cytokinetics, Takeda, BeiGene, Kiniksa, Kurome Therapeutics, and Pfizer that includes: consulting or advisory.

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narrowing of the epicardial coronaries and microvasculature with consequent graft ischemia. Recently, clonal hematopoiesis of indeterminate potential (CHIP) has emerged as a risk factor for cardiovascular disease and mortality. We aimed to investigate the relationship between CHIP and post-transplant outcomes, including CAV. We analyzed 479 HT recipients with stored DNA samples at two high-volume transplant centers, Vanderbilt University Medical Center and Columbia University Irving Medical Center. We explored the association between the presence of CHIP mutations with CAV and mortality after HT. In this case-control analysis, carriers of CHIP mutations were not at increased risk of CAV or mortality after HT. In a large multicenter genomics study of the heart transplant population, the presence of CHIP mutations was not associated with increased risk of CAV or post-transplant mortality.

INTRODUCTION

Heart transplantation (HT) remains the definitive treatment for end-stage heart failure. Despite substantial improvement over time in early survival after HT, long-term survival remains unchanged.[1] Cardiac allograft vasculopathy (CAV) represents the leading cause of late graft failure and mortality beyond the first-year post-HT.[1, 2] While it shares overlapping features with traditional atherosclerotic cardiovascular disease (ASCVD), CAV is a distinct entity that represents chronic vascular rejection. An alloreactive process involving recognition of graft vasculature by recipient immune cells causes endothelial dysfunction, vascular smooth muscle cell and fibroblast activation, and ultimately leads to diffuse narrowing of the epicardial coronaries and microvasculature.[3] Identifying patients at high-risk for CAV may offer an opportunity to interrupt CAV pathogenesis early in its course. Clonal hematopoiesis of indeterminate potential (CHIP) has been recognized as an independent risk factor for the development of ASCVD through the skewing of immune cells toward a highly-inflamed phenotype.[4] As CAV shares risk factors with ASCVD and is driven by an immune response against the allograft, we sought to characterize the relationship between CHIP and post-HT outcomes.

METHODS

We performed a multicenter retrospective study comprising patients aged ≥18 years that underwent HT at Vanderbilt University Medical Center (VUMC) via its BioVU DNA Biobank and Columbia University Irving Medical Center (CUIMC). This study was approved by each institution's review boards. DNA samples from BioVU are linked to the Synthetic Derivative (SD), a deidentified database containing clinical information from Vanderbilt's electronic health record. All donor data were available in the CUIMC cohort, whereas these data were not available in BioVU due to the deidentified nature of the data. The following data dictionary was used to generate a list of heart transplant recipients in the SD, followed by manual curation:

In both cohorts, data collected included demographic data, co-morbidities, and transplant-related outcomes: occurrence and degree of cellular rejection, antibody-mediated rejection, presence of donor-specific antibodies (DSAs), CAV, and death. CAV was defined according to the International Society for Heart and Lung Transplantation (ISHLT).[2] Moderate-to-

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severe CAV refers to ISHLT CAV grade 2 and 3. In the VUMC cohort, only class II DSAs are reported while the CUIMC cohort include both class I and class II DSAs. As only the presence of class II DSAs is associated with increased risk of CAV, we do not anticipate that this difference influenced results. In both VUMC and Columbia cohorts, patient underwent coronary angiography for the assessment of CAV on an annual or bi-annual basis, alternating with non-invasive imaging in the latter. Only coronary angiogram data were used to define CAV in this study.

DNA samples from HT recipients underwent targeted sequencing at >500x depth to identify somatic mutations with variant allele fraction (VAF) ≥ 2% in 24 of the most common CHIP genes which account for >95% of CHIP observed in the general population. Targeted genes include: *GNB1, MPL, NRAS, DNMT3A, ASXL2, SF3B1, IDH1, KIT, TET2, ZNF318, JAK2, CBL, ETNK1, KRAS, IDH2, TP53, PPM1D, SRSF2, SETBP1, ASXL1, GNAS, U2AF1, ZBTB33,* and *BRCC3*. Briefly, 100–200 ng of DNA was obtained per patient. Library preparation and capture was performed using an exome library prep and custom capture kit. Sequencing was performed at paired-end 150 bp on the Illumina NovaSeq 6000, targeting an average of 1 million reads/sample. In the VUMC cohort, patients were defined as CHIP-positive or CHIP-negative if: 1) they had DNA collected within 3-years of diagnosis of CAV, as established literature suggest stable CHIP clonal dynamics over a 3–5 years period;[5, 6] 2) had a sample collected >3 years prior to CAV diagnosis or last follow-up, but were CHIP-positive at that time; or 3) had a sample collected >3 years after CAV diagnosis or last follow-up but were CHIP-negative at that time. The median time between sample collection and CAV assessment was 0.1 years after coronary angiography for the first group described above in the VUMC cohort. For the entirety of the VUMC cohort included in downstream analyses, samples were collected at a median of 2.3 years prior to OHT. All patients in the Columbia cohort had their samples drawn just prior to heart transplantation.

Continuous variables are summarized as median ± interquartile range (IQR) and categorical variables are reported as frequencies and percentages. Logistic regression models were used to test the effects of CHIP on CAV and mortality after transplantation. Multiple imputation was performed in the VUMC cohort, as a small percentage of patients had unknown information regarding one variable, DSAs. The *mice* package was used for multiple imputations with $m = 16$. Logistic regression models were performed, adjusted for the following pre-specified variables based on known literature: age of transplant, ischemic etiology of heart failure, hypertension, diabetes, and immunologic events. Models derived from complete cases analyses and from the imputed model were consistent. Thus, the Tables in the manuscript and Supplemental Material show results using the imputed model. The cumulative incidence of CAV was estimated using the Kaplan-Meier method. We performed statistical tests for association with CAV using a Cox proportional hazard model, stratified by the presence of CHIP mutations. Cox proportional hazard models were adjusted for age at transplant, hypertension, diabetes, and presence of CAV. We also performed a meta-analysis of the two cohorts using a fixed-effects model. In the CUIMC cohort, the analyses were also adjusted for donor age, gender, and smoking status with no meaningful changes. All analyses were performed using R (version 4.1.0) and SAS (version 9.4). The fixed-effect meta-analyses had 80% power to detect an effect size of 1.41 or higher. This study was approved by the individual institutional review boards at Vanderbilt University Medical

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Center (VUMC) and Columbia University Irving Medical Center (CUIMC). All code used in these analyses is deposited on https://github.com/learning-MD/CHIP.

RESULTS

A total of 787 patients were identified, including 609 patients at VUMC and 178 patients at CUIMC (Table 1). Eighty-two patients (13.5%) in the VUMC cohort had at least one CHIP mutation, as compared to 35 patients (19.7%) in the CUIMC cohort. The prevalence of CHIP mutations in the combined cohorts was 14.9%. The mean VAF was 3.9% in the VUMC cohort and 3.7% in the CUIMC cohort. Using the criteria listed above, filtering of patients in the VUMC cohort resulted in 301 patients suitable for downstream analyses. Thus, 479 patients spanning both cohorts were studied. In both groups, median recipient age at the time of transplant was higher in CHIP carriers. Those with CHIP mutations in the VUMC cohort were more likely to have an ischemic etiology for their heart failure (62% vs 40%, p = 0.007). In the full cohort of 787 patients, *DNMT3A* mutations were the most common, followed by *PPM1D*, *TET2*, and *ASXL1* mutations (Figure 1). The distribution of CHIP mutations in each individual cohort is shown in Supplemental Figure 1.

The presence of CHIP mutations was not associated with increased risk of the composite outcome of CAV and/or mortality in the VUMC (OR 1.92, 95% CI 0.89–4.17) or CUIMC cohorts (OR 1.54, 95% CI 0.69–3.46; Table 2). In secondary analyses, the presence of CHIP mutations was not associated with any CAV at VUMC (OR 1.72, 95% CI 0.83–3.56) or CUIMC (OR 1.86, 95% CI 0.83–4.19; Table 3), or with increased risk of moderate-severe CAV (Supplemental Table 1). This held true even in patients carrying large CHIP clones, defined as those harboring clones with variant allele fraction (VAF) ≥10%, in the VUMC cohort (Supplemental Table 2). There was a significantly increased risk of CAV with large CHIP clones in the CUIMC cohort, but this was representative of only six patients. In an exploratory sub-analysis, the presence of mutations in *DNMT3A*, the most common CHIP mutation, was associated not with an increased risk of the composite of CAV and/or mortality in both cohorts (Supplemental Table 3).

Over a median follow-up of approximately 18 years in the VUMC cohort, Kaplan-Meier and Cox proportional hazards analysis did not show any difference in post-transplant mortality between CHIP carriers and non-carriers (hazard ratio 0.80, 95% CI 0.41–1.57; log-rank p = 0.51; Figure 2). The same was true in the CUIMC cohort, over a median follow-up time of 5.1 years (log-rank p = 0.15; Supplemental Figure 2). The presence of CHIP was not associated with mortality in the VUMC cohort or the CUIMC cohort (no deaths in the CHIP group; Supplemental Figure 2). In the VUMC cohort, presence of CAV alone was associated with increased mortality (OR 4.70, 95% CI 2.62–8.42). A fixed-effect meta-analysis of the two combined cohorts showed that CHIP carriers did not have increased risk of CAV (OR 1.42, 95% CI 0.86–2.34) or mortality after transplant (OR 0.62, 95% CI 0.31–1.22; Table 4).

DISCUSSION

To our knowledge, this is the largest study to date in the heart transplant population that explores the association of CHIP mutations and post-transplant outcomes. Our primary

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finding is that among heart transplant recipients harboring CHIP mutations, there was not a significantly increased risk of CAV and/or mortality. Additionally, we found that CHIP mutations were not associated with increased risk of moderate-to-severe CAV and that the presence of large CHIP clones (VAF ≥10%) was not associated with increased risk of CAV.

While minimal data exist regarding CHIP and solid-organ transplantation, our results are in contrast to the only other study relating CHIP to post-heart transplant outcomes. Comprising 127 patients,[7] investigators identified an association between CHIP and increased risk of CAV and post-HT mortality. However, the study was confounded by incomplete coronary angiography data for a third of the patients and only four total patients in the cohort had identifiable CAV. CHIP carriers also had longer follow-up periods and the risk of CAV is known to increase with time. Lastly, the majority of mortality in CHIP carriers in that study occurred early after transplant when mortality due to CAV is low. In contrast, our study involves a larger cohort from two high-volume transplant centers, comprises a longer follow-up, and all patients underwent coronary angiography as the primary method of CAV diagnosis. Regardless, that study was important as it opened a new field of research in an understudied area in solid-organ transplantation.

Our data exclude large effect sizes of CHIP in HT recipients and suggest that CHIP may not be a significant driver of CAV. However, our study is not powered to detect smaller effect sizes. The results of our study still leave many questions unanswered. CAV pathogenesis is thought to be coordinated in part by T-lymphocytes while most CHIP analyses in non-transplant patients have focused on the role of myeloid cells.[3, 8, 9] It may be that the presence of CHIP does not influence lymphocytes in the same manner that it affects monocytes and macrophages,[9] thus explaining the results of our study. Since CHIP exerts its effects through inflammation, it is also possible that the use of immunosuppressive therapies after HT attenuates the inflammation associated with CHIP mutations and “evens the playing field” between CHIP carriers and non-carriers. Biologically, this appears plausible as exploratory interventional studies in CHIP and cardiovascular disease are focused on reducing inflammation.[10] Interestingly, we found that *PPM1D* mutations were the second-most common mutation in our combined cohort. Mutations in this gene are particularly associated with prior chemotherapy exposure and it may be that immunosuppressive therapies impose similar clonal selective pressures.[11, 12] Finally, during heart transplantation, passenger immune cells from the donor are transferred to the recipient and may persist for long periods of time.[13–16] With the persistence of donor immune cells and recent data implicating donor-derived macrophages playing an important role in the pathogenesis of acute cellular rejection after HT,[14] it may be important to define the interaction between donor and recipient CHIP. The strengths of our study include 1) the relative sample size, as only a few thousand heart transplants are performed annually; and 2) the multicenter nature of this study. Some of the differences between the VUMC and CUIMC cohorts may be due to the differing follow-up lengths between the two groups.

LIMITATIONS

Several limitations exist in our study, including its retrospective nature and the presence of missing variables. It is possible that, with a larger sample size, we may see a statistically

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significant association between CHIP and post-HT outcomes as our study is only powered to exclude large effect sizes. Additionally, the VUMC cohort contains deidentified patient data; thus, donor variables could not be accessed. While this is a limitation, adjusting for donor variables in the CUIMC cohort did not impact results.

CONCLUSIONS

In a multicenter case-control study, we did not find an association between CHIP mutations and increased risk of CAV or mortality after heart transplantation. However, there remain many unanswered questions in the context of solid-organ transplantation and further studies are warranted to better understand contributions of CHIP to post-transplant outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Dr. Amancherla is supported by an American Heart Association Career Development Award (#929347). This work was supported by NIH grant DP5 OD029586, a Burroughs Wellcome Fund Career Award for Medical Scientists and the Vanderbilt University Medical Center Brock Family Endowment to Dr. Bick. Dr. Clerkin is supported by the National Heart, Lung, and Blood Institute (K23HL148528). Dr. Moslehi is suppported by the NIH (R01HL141466, R01HL155990, R01HL156021, R01HL160688). The dataset(s) used for the analyses described were obtained from Vanderbilt University Medical Center's BioVU which is supported by numerous sources: institutional funding, private agencies, and federal grants. These include the NIH funded Shared Instrumentation Grant S10RR025141, S10OD025092, and S10OD017985; and CTSA grants UL1TR002243, UL1TR000445, and UL1RR024975. Genomic data are also supported by investigator-led projects that include U01HG004798, R01NS032830, RC2GM092618, P50GM115305, U01HG006378, U19HL065962, R01HD074711; and additional funding sources listed at https://victr.vumc.org/biovu-funding/.

ABBREVIATIONS AND ACRONYMS

ACR	Acute cellular rejection
AMR	Antibody-mediated rejection
ASCVD	Atherosclerotic cardiovascular disease
CAV	Cardiac allograft vasculopathy
CHIP	Clonal hematopoiesis of indeterminate potential
CUIMC	Columbia University Irving Medical Center
DNA	Deoxyribonucleic acid
DSA	Donor-specific antibodies
HT	Heart transplantation
ISHLT	International Society for Heart and Lung Transplantation
IQR	Interquartile range
SD	Synthetic Derivative

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VAF	Varian allele frequency
VUMC	Vanderbilt University Medical Center

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Data Dictionary (Synthetic Derivative)

- Age ≥ 18 years
- ICD-9 codes: 37.51 (heart transplantation), V42.1 (heart replaced by transplant)
- ICD-10 codes: Z94.1 (heart transplant status), 02YA0Z0 (transplantation of heart, allogeneic), 02YA0Z1 (transplantation of heart, syngeneic)
- CPT codes: 33944 (backbench preparation of donor heart), 00580 (anesthesia for heart or heart/lung transplant), 33940 (donor cardiectomy), 33945 (heart transplant, with or without recipient cardiectomy), 93505 (endomyocardial biopsy)
- Text: “orthotopic heart transplant”, “orthotopic heart transplantation”, “s/p OHT” in all except Family History
- Medications: everolimus, sirolimus, tacrolimus, cyclosporine, azathioprine, mycophenolate mofetil

INCLUDE:

- ICD-9 codes: 996.83 (complications of transplanted heart)
- ICD-10 codes: T86.290 (CAV), T86.22 (heart transplant failure), T86.21 (heart transplant rejection), T86.20 (unspecific complication of heart transplant)
- CPT codes: 92978 (IVUS, initial vessel), 92979 (IVUS, each additional vessel)
- Text: “CAV1”, “CAV-1”, “CAV2”, “CAV-2”, “CAV3”, “CAV-3”, “allograft arteriopathy”, “microvascular ischemia” in all except Family History
- Manual review of all charts for presence and severity of CAV

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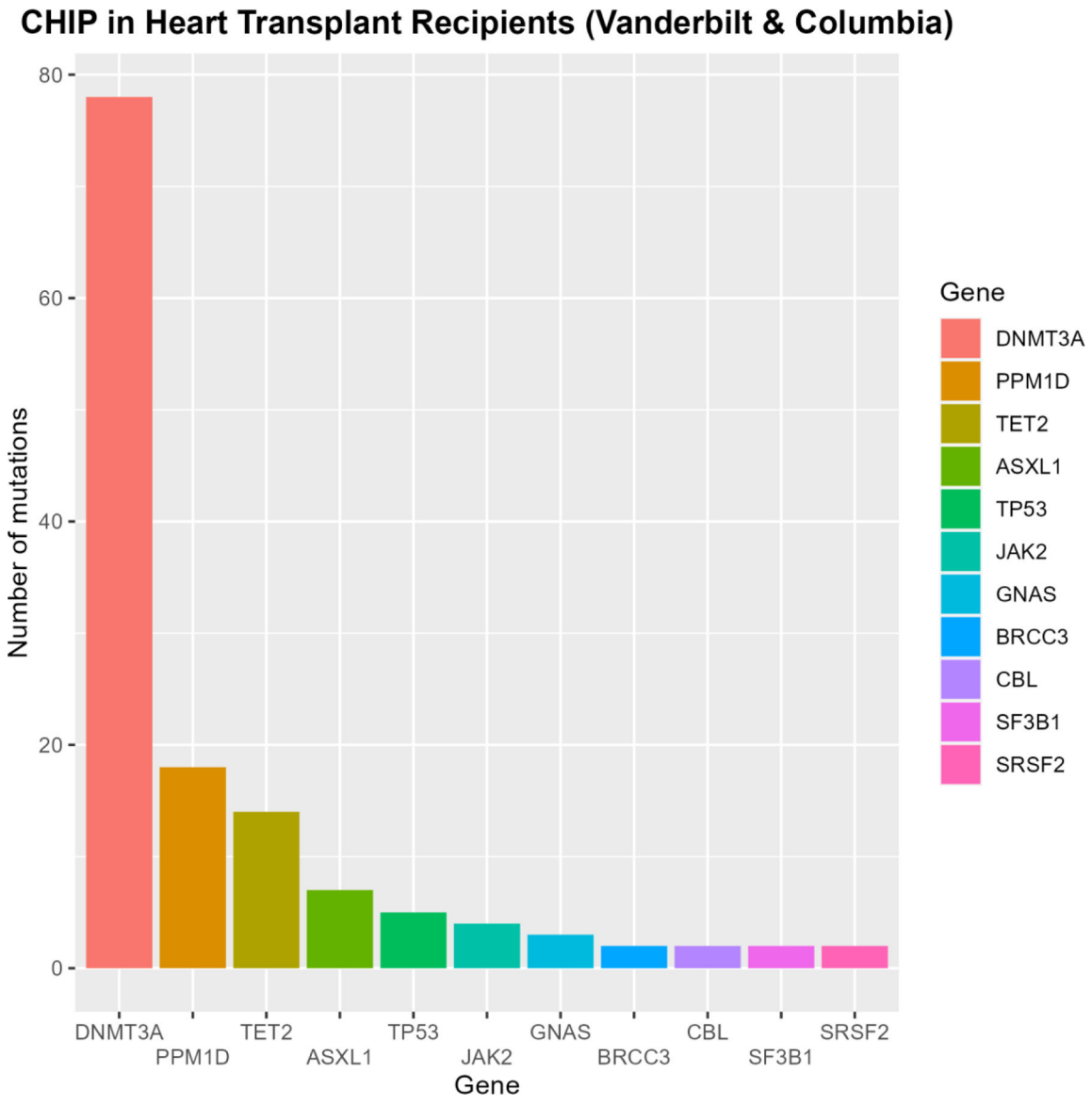

Figure 1.
The distribution of CHIP mutations across both VUMC and CUIMC cohorts.

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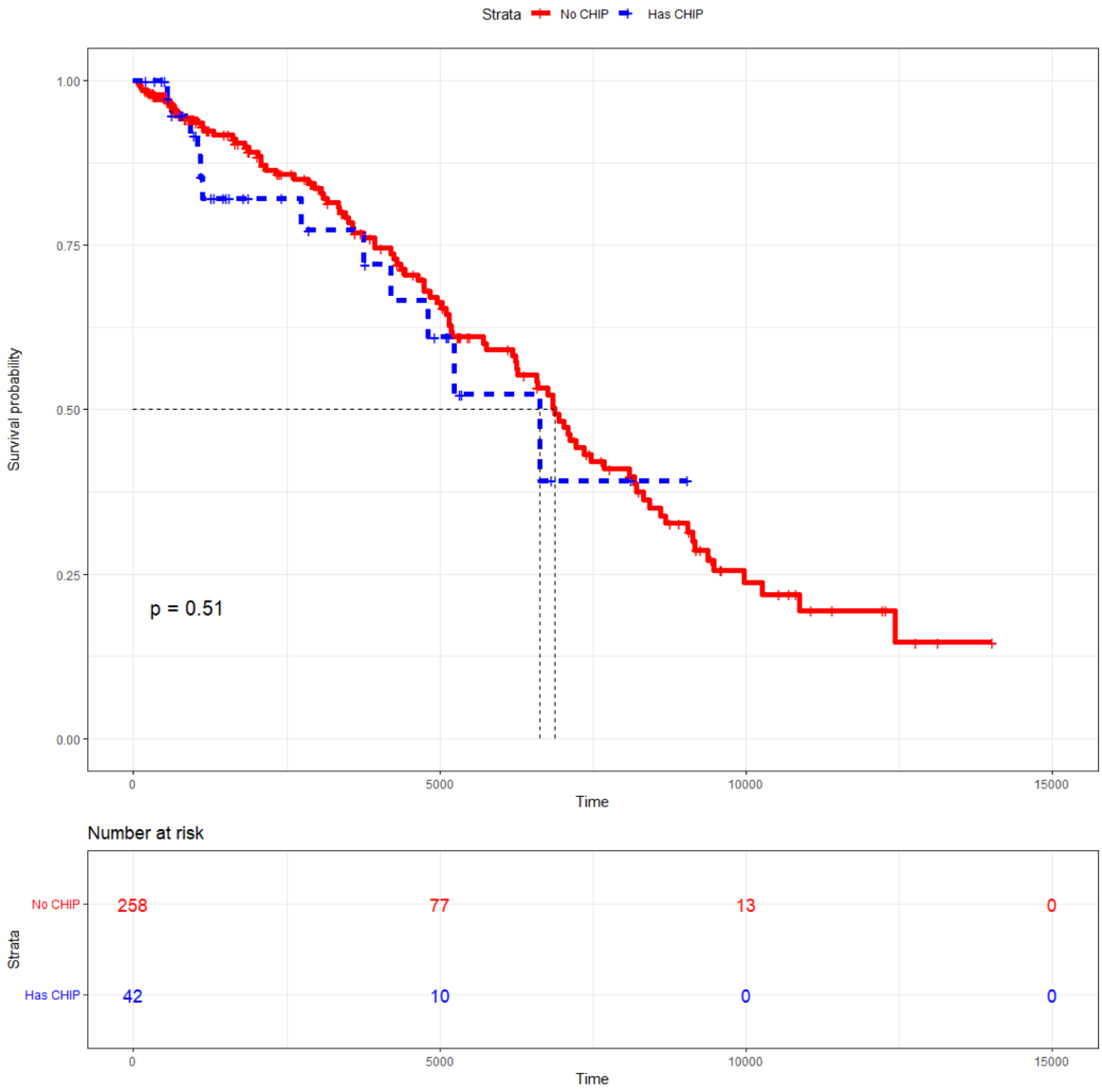

Figure 2.

Kaplan-Meier survival estimates by CHIP status in the VUMC cohort. Time is defined in days post-transplant.

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Table 1.

Baseline cohort characteristics.

	Vanderbilt University			Columbia University		
Demographics by CHIP status	**No CHIP (N = 259)[1]**	**Has CHIP (N = 42)[1]**	**p-value[2]**	**No CHIP (N = 143)[1]**	**Has CHIP (N = 35)[1]**	**p-value[2]**
Age at transplant (years)	49 (36, 59)	59 (52, 65)	<0.001	54 (44, 62)	60 (52, 66)	0.032
Gender (male)	189 (73%)	33 (79%)	0.4	99 (69%)	24 (69%)	>0.9
Ischemic etiology	103 (40%)	26 (62%)	0.007	33 (23%)	10 (29%)	0.5
Hypertension	232 (90%)	38 (90%)	>0.9	86 (60%)	18 (51%)	0.3
Diabetes mellitus	129 (50%)	25 (60%)	0.2	51 (36%)	11 (31%)	0.6
Statin use	247 (95%)	41 (98%)	>0.9	140 (98%)	35 (100%)	>0.9
Acute cellular rejection	99 (38%)	17 (40%)	0.8	19 (13%)	3 (8.6%)	0.6
Antibody-mediated rejection	40 (15%)	5 (12%)	0.6	15 (10%)	4 (11%)	>0.9
Donor specific antibodies	67 (26%)	11 (26%)	>0.9	41 (29%)	10 (29%)	>0.9
Cardiac allograft vasculopathy	151 (58%)	27 (64%)	0.5	61 (43%)	19 (54%)	0.2
Deceased	93 (36%)	12 (29%)	0.4	10 (7.0%)	0 (0%)	0.2

[1] Median (IQR); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

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Table 2.

Multivariable logistic regression analyses relating the presence of CHIP mutations with CAV and/or mortality.

	VUMC		Columbia	
CAV and/or Mortality	**OR[1]**	**95% CI[1]**	**OR[1]**	**95% CI[1]**
Presence of CHIP	1.92	0.89, 4.17	1.54	0.69, 3.46
Age at transplant	0.96	0.94, 0.98	0.99	0.97, 1.02
Ischemic etiology	1.55	0.87, 2.75	1.00	0.47, 2.16
Hypertension	1.20	0.50, 2.87	0.84	0.43, 1.62
Diabetes mellitus	1.03	0.60, 1.78	1.30	0.66, 2.56
History of ACR	1.45	0.82, 2.56	1.72	0.85, 3.50
History of AMR	1.24	0.51, 3.05	0.56	0.18, 1.76
Presence of DSAs	1.78	0.85, 3.73	3.98	1.83, 9.17

[1]OR = Odds Ratio, CI = Confidence Interval

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Table 3.

Multivariable logistic regression analyses relating the presence of CHIP mutations with CAV.

	VUMC		Columbia	
CAV	**OR[1]**	**95% CI[1]**	**OR[1]**	**95% CI[1]**
Presence of CHIP	1.72	0.83, 3.56	1.86	0.83, 4.19
Age at transplant	0.97	0.95, 0.99	0.99	0.97, 1.02
Ischemic etiology	1.44	0.83, 2.51	0.93	0.43, 2.01
Hypertension	1.16	0.50, 2.67	0.70	0.36, 1.37
Diabetes mellitus	0.95	0.56, 1.61	1.57	0.80, 3.13
History of ACR	1.53	0.89, 2.63	1.59	0.79, 3.23
History of AMR	1.11	0.49, 2.53	0.40	0.12, 1.23
Presence of DSAs	1.88	0.89, 3.95	3.87	1.79, 8.85

[1]OR = Odds Ratio, CI = Confidence Interval

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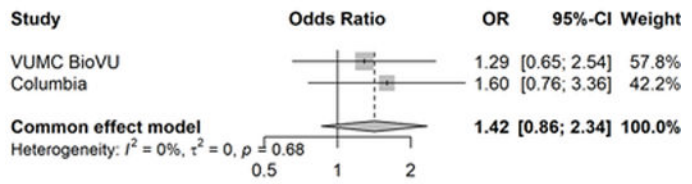
Table 4.

Fixed-effects meta-analysis associating the relationship between CHIP and CAV (**Panel A**) and CHIP and mortality (**Panel B**) in the VUMC and CUIMC cohorts.

A.



B.