Clinical impact of clonal hematopoiesis in hematopoietic cell transplantation: a review, meta-analysis, and call to action

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SUPPLEMENTARY INFORMATION

Methods

Search Strategy

We systemically searched for articles indexed in PubMed, Scopus, Embase (Elsevier), and Web of Science (Clarivate). The general search terms used to search for the articles were ("clonal hematopoiesis" OR "clonal haematopoiesis" OR "clonal hematopoiesis of indeterminate potential" OR "age-related clonal hematopoiesis" OR "age-related clonal hematopoiesis" OR “CHIP” OR “ARCH”) AND (“stem cell transplantation” OR “hematopoietic stem cell transplantation” OR “haematopoietic stem cell transplantation” OR “bone marrow transplant*” OR “stem cell transplant*” OR “hematopoietic stem cell transplant*” OR “haematopoietic stem cell transplant*” OR “hematopoietic cell transplant*” OR “haematopoietic cell transplant*”). For Scopus, Embase, and Web of Science, a language filter was used to specify documents written in English, and a document type filter was used to specify articles or articles in press. For PubMed, language (English) and species (human) filters were applied.

Our search strategy within the four selected databases yielded 1,245 articles (280 from PubMed, 456 from Scopus, 248 from Embase, and 261 from the Web of Science. EndNote 20 (Clarivate Analytics LLC, USA) was used to remove any duplicates and select eligible studies from the database findings and other sources. After removal of 491 duplicate articles, we performed title and abstract screening for 754 articles.

Search Results

The process of selection of the final studies included is outlined using a PRISMA flow diagram (**Figure 1**). Out of the articles screened, 32 articles were included in this review. Among the 699 excluded articles, 179 (26%) were non-human studies, 158 (23%) were reviews, 121 (17%) were not CH papers, 88 (13%) were neither CH nor HCT papers, 72 (10%) were not HCT papers, 57 (8%) were case reports or series, 13 (2%) were letters with no new data, 5 (1%) were clinical guides, 4 (1%) were conference

proceedings, and 2 (0.3%) were commentaries. The 32 included studies are summarized in **Table S1**; the CH-related results are summarized in **Table S2**.

Results

Auto-HCT

Clonal Expansion and Evolution

In this article, we define clonal expansion as an increase in the VAF of pre-existing CH mutations; clonal evolution is acquisition of new CH mutations. Both scenarios represent progression of CH and, theoretically, increased CH-related risk.

Evidence largely suggests that CH mutations increase in number and VAF after auto-HCT, but longer-term may become stable. In mantle cell lymphoma patients, 98% (53/54) of post-treatment CH mutations were present before starting chemotherapy.[42] The median VAF of CH mutations increased after induction and after HCT (1.5% to 2.8%, p=0.001), but stabilized to an age-related rate during follow-up (growth rate 5.1% per year). A small cohort study found that, from the time of auto-HCT to tMN, VAFs of *DNMT3A* clones did not increase significantly (0.8% to 2.1%, p=0.63), whereas non-*DNMT3A* clones did (1% to 37%, p=0.002).[39] Most CH mutations (86%) were at VAFs < 2% before auto-HCT. A study in patients with post-HCT CH (n=18) showed that there was a mean 6.3-fold increase in VAF from auto-HCT to first follow-up.[23] Of the 28 CH mutations detected after auto-HCT, 9 (32%) had a VAF ≥ 2% and 7 (25%) had a VAF between 0.5% and 2% before auto-HCT. Evidence of clonal evolution was found with 12 CH mutations detected after but not before auto-HCT, which either arose from HCT or were below the level of detection (i.e., VAF < 0.5%).[23] As with other studies, longer-term, mutations became stable over time.

Relapse: Lymphoid Malignancies

No studies (0/3) reported an association between CH status and relapse after auto-HCT. In lymphoma, CH was not associated with time to relapse or PFS.[24] In MM, cumulative incidence of relapse

(CIR) did not significantly differ between patients with versus without CH (73.9% vs 64.9%, p=0.67).[36] Although the incidence of NRM was higher in patients with CH (4.3% vs 1.2% if no CH), this difference did not meet statistical significance (p=0.08).

Relapse and Survival: Myeloid Malignancies

One retrospective study in patients with AML who received auto-HCT investigated persistence of *DNMT3A, TET2*, and *ASXL1* (DTA) mutations.[16] Patients were considered to have CH if DTA mutations persisted despite complete remission (CR) and clearance of other pathogenic variants; if the DTA mutation was not detected at CR it was classified as a leukemia mutation. With these classifications, there was no association between CH status after auto-HCT and OS (HR 0.79, 95% CI 0.41-1.51, p=0.44) or PFS (HR 0.75, 95% CI 0.42-1.33, p=0.287). Relapse rate was also similar between patients with and without CH-like mutations (51.6% vs 41.7%, respectively, p=0.04).[16] Caution should be noted before weighing these findings as evidence of the impact of CH in HCT, since it is unclear whether persistence of DTA mutations at CR in AML patients is truly CH versus measurable residual disease.

Other Adverse Events: Lymphoid Malignancies

Several less frequently investigated outcomes were reported. In lymphoma, pre-HCT DRP mutations (not CH in general) were associated with more inpatient days during years 2 to 5 after auto-HCT (median 20 vs. 2 days; p=0.0025) and intensive care unit admissions.[34] Other adverse events investigated in lymphoma that did not meet statistical significance were risk for severe infections, cardiovascular events, and transfusions.[34] However, in patients with MM, pre-HCT CH was associated with risk for cardiovascular events (including heart failure, coronary artery disease, and stroke)[37, 65] and recurrent bacterial infections.[37] In another study of MM patients, although CH was not associated with overall risk for venous thromboembolism, there was evidence that incidence > 3 months after discontinuing lenalidomide was higher in patients with CH than those without CH.[36]

Allo-HCT

CH Engraftment: Heterogenous Groups

Data consistently show that donor CH successfully engrafts in recipients via HCT regardless of donor type. In a study of MRD HCTs, all donor CH mutations engrafted in the recipients except for one *SF3B1* mutation.[47] This was in line with another study in that detected all (7/7) matched sibling donor (MSD) CH mutations in recipients at day 56 or 90 post-HCT[53] and a third study that detected 84.3% (86/102) of donor CH mutations in recipients 12 months after allo-HCT.[44] When looking at *DNMT3A*-CH specifically, all *R882* mutations engrafted (10/10, 100% vs. 46/54, 85.2% for non-*R882*) and the VAF was significantly higher in recipients than non-*R882* mutations (**Table S2**).[44] Additional evidence of CH engraftment was presented in a study of young MUDs, where 19 CH mutations were identified in 44% (11/25) of donors, all of which engrafted in recipients.[43] A study that assessed long-term engraftment of CH mutations identified donor-engrafted CH in 50% (5/10) of donor CH cases.[48]

Clonal Expansion and Evolution: Myeloid Malignancies, Young Unrelated Donors

Two studies investigated rates of clonal expansion and evolution in HCTs with young MUDs but had differing methods and results. In one study (median donor age 26 years, range 20-58), most (74%) of the CH mutations persisted a year after allo-HCT, despite low VAFs (median 0.25%) in donors.[43] Of engrafted mutations, 3 (16%) expanded in recipients beyond VAF ≥2% at days 100 and 365. Moreover, within the first 100 days after allo-HCT, the mutational burden in recipients increased from 19 to 33 CH mutations (p=0.048). Some of these new mutations were present in MUDs at low levels (< 0.1%) and others were *de novo* mutations that arose after HCT. The second study included elderly individuals (n=22) at a median follow-up of 9.8 years after allo-HCT from young MUDs (<41 years old), and found a single *BCORL1* CH mutation in a recipient; however, the mutation was not detected in the donor or recipient pre-HCT at a VAF ≥0.05%.[46]

Clonal Expansion and Evolution: Heterogenous Groups

Other studies provide additional insight into the relationship between CH expansion and evolution with outcomes. In MRDs, engrafted CH mutations expanded after HCT and decreases in VAF paralleled decreases in donor chimerism and relapse.[47] Similarly in MSDs, donor CH mutations expanded most rapidly until day +56 then stabilized.[53] Furthermore, CH mutations expanded more rapidly than germline mutations, and non-donor-derived pathogenic mutations expanded most rapidly. In long-term allo-HCT survivors, CH mutations expanded more rapidly in recipients than MRDs (p=0.03).[48] Gene-specific differences in clonal expansion have also been reported (**Table S2**) and a study found that patients with the largest expansion of *DNMT3A*-CH died from HCT-related complications within a year.[51]

CH Persistence: Myeloid Malignancies

Multiple studies investigated the persistence of CH-related mutations throughout treatment, including HCT, for myeloid malignancies. In a study of AML patients who achieved CR after induction, post-CR CH persisted in 91% (39/43) of patients during and after post-CR treatment; however, 95% (20/21) of the patients who received allo-HCT had clearance of the post-CR CH.[55] In another study of AML patients who received allo-HCT, persistence of CH-related mutations from diagnosis to CR only occurred in 28% (21/75) of patients and did not affect 4-year cumulative instance of relapse or OS; post-HCT persistence of these mutations was not studied.[50]

Peripheral Blood Stem Cell Mobilization: Related Donors

One study reported results on differences in PBSC mobilization by CH status and found that in MRDs, CH status was not associated with the amount of harvested $CD34^+$ cells.[47]

Engraftment: Leukocytes, Neutrophils, Platelets, and Donor Cells

In MRD HCTs, the cumulative incidence of leukocyte engraftment at 15 days was higher in patients with CH+ donors.[47] Three studies found no difference in time to neutrophil or platelet

engraftment by donor CH status[45, 51, 52] and one study reported no difference in time to full donor chimerism by donor CH status.[51]

Other Adverse Events

Additional adverse outcomes reported in the allo-HCT studies include atrial fibrillation in-hospital, prolonged neutropenia, second primary malignancies, and telomere shortening. Although incidence of atrial fibrillation in-hospital was not statistically different between patients with and without pre-HCT DTA CH mutations, incidence was notably higher in patients with *DNMT3A*-CH (53% vs. 27% if no *DNMT3A*-CH).[66] Prolongation of neutropenia was associated with *TET2*-CH in AML HCT recipients.[55] Incidence of second malignancies (median follow-up: 13 years) was 6% and 14.8% in HCT recipients with CH+ and CH- donors, respectively; however, the two cases of second malignancy in recipients with CH+ donors were non-melanoma skin cancers.[43] Finally, one study investigated telomere shortening, a measure of aging, between donors and recipients of allo-HCT and found that the difference was equivalent to approximately 20 years of proliferative life history in the hematopoietic system of recipients; however, telomere shortening was not different between individuals with and without CH.[48]

Table S1. Summary of original studies investigating the association between clonal hematopoiesis (CH) and outcomes in hematopoietic cell transplantation (HCT).

Study	Study design	Donor type	Cancer type(s)	Sample size	Follow-up (median)	Outcome[a]	Effect
AUTOLOGOUS HCT							
Heini et al.[16]	RC	Self	AML	110	51.3 m	OS	No difference by CH status
							Early mortality (100 d) higher in CH (12.9 vs 1.3% if no CH, p=0.022)
						PFS	No difference by CH status (16.7 vs 26.9 mo if no CH, p=0.29)
						Relapse	No difference by CH status
Gifford et al.[18]	CS	Self	Lymphoid	96	NA	PBSC mobilization	CH more common in poor CD34+ mobilizers than normal mobilizers (28% vs 3.4%, p=0.018)
Gibson et al.[19]	PC	Self	Lymphoma	413 (401 PC)	10 y	NRM	Higher in CH (26.2%) than non-CH (11.1%), p<0.01
						OS	Lower in patients with vs without CH (30.4% and 60.9%, respectively)
						PBSC mobilization	Patients with CH more likely to fail peripheral mobilization and required more days to collect sufficient stem cells
						tMN	14.1% (CH) vs 4.3% (no CH), p=0.002
							25.3% (multiple mutations) vs 9.9% (single mutation), p<0.001
Mouhieddine et al.[20]	RC	Self	MM	629	9.7 y	Cardiovascular events	No difference by CH status
						Clonal expansion/tMN	8/10 tMN cases had mutation present prior to HCT (4 with VAF < 1%)
						OS	Lower in patients with CH (5.3 vs 7.5 y if no CH; HR 1.34, p=0.02)
						OS (by treatment)	No IMiD maintenance group: CH worse OS (3.6 vs 6.6 y if no CH, p=0.013)
							Yes IMiD maintenance group: No difference by CH status
						PBSC mobilization	CH decreased efficiency compared to no CH (5.8 vs 8.3 cells/kg/day, p=0.03)
						PFS	Lower in patients with CH (2.2 vs 2.6 y if no CH; HR 1.45, p<0.001)

						PFS (by treatment)	No IMiD maintenance group: CH worse PFS (1.1 vs 1.8 y if no CH, p<0.001) Yes IMiD maintenance group: No difference by CH status
						tMN	CH prior to HCT not associated with increased risk (p=0.6)
Hazenberg et al.[21]	NCC	Self	Lymphoid	179 (for CH analysis)	43.6 m	OS	No difference by CH status in cases or controls
						PBSC mobilization	No difference in CH prevalence in poor mobilizers (31% vs 22% of controls, p=0.24)
						tMN	All patients who developed tMN (3/3) had CH at mobilization
Stelmach et al.[22]	PC	Self	MM	457	NA	OS	Gene-specific effects in patients not treated with maintenance (*Table S2*)
						PBSC mobilization	Gene-specific effects (*Table S2*)
						Platelet engraftment	Gene-specific effects (*Table S2*)
Ortmann et al.[23]	PC	Self	Lymphoid	81	2 y	Clonal evolution	12 new CH mutations detected post-HCT
						Clonal expansion	Increase in mean VAF from ~2% to ~9% at first follow-up, p=0.0002
						Neutrophil engraftment	Longer for patients with post-HCT CH (8.1 vs 6.7 d if no CH, p=0.008)
						PBSC mobilization	No difference by post-HCT CH status
Lackraj et al.[24]	RC	Self	Lymphoma	420	4.5 y	Baseline blood counts at HCT	No difference by CH status
						Neutropenia	Longer in CH (11.0 vs 10.7 d in no CH, p=0.01)
						OS (5-y)	Worse in CH (51.8 vs 59.3% in no CH, p=0.018)
						PBSC mobilization	No difference by CH status
						Platelet recovery	Longer in CH (15.3 vs 13.7 d in no CH, p=0.016)
						PFS	No difference by CH status
						Relapse	No difference by CH status
						tMN	No difference by CH status (3.3 vs 3.0% in no CH, p=0.45)
Li et al.[28]	RC	Self	MM	41	100 d	Neutrophil engraftment	No difference by CH status (20 vs 17 days in no CH, p=0.12)
						NRM	No difference by CH status (data NR)
						Platelet engraftment	Delayed in patients with CH (42 vs 19 days if no CH, p<0.0001)
						Severe infections	No difference by CH status (data NR)

						Survival	No difference by CH status (data NR)
						tMN	No difference by CH status (data NR)
Husby et al.[34]	PC	Self	Lymphoma	440	9.1 y	Cardiovascular events	No difference by CH status overall
						EFS	No difference by CH status overall
						ICU admission	No difference by CH status overall
						In-patient days	No difference by CH status overall
						OS	<1 y: AdjHR 1.12, 95% CI 0.73-1.73, p=0.6 ≥1 y: AdjHR 1.36, 95% CI 0.93-1.99, p=0.11
						Severe infections	No difference by CH status overall
						tMN	Increased risk if CH, AdjHR 6.5, 95% CI 2.34-18.03, p=0.0003
						Transfusions	No difference by CH status overall
Yan et al.[35]	RC	Self	Hodgkin lymphoma	321	6.5 y	NRM	No difference by CH status; gene-specific effects
						OS, relapse-related mortality	No difference by CH status
						tMN	Increased risk (AdjHR 4.5, CI 1.54-13.19)
Wudhikarn et al.[36]	CC	Self	MM	101	11 y	NRM & relapse	No difference by CH status
						OS	No difference by CH status (100.2 vs 135.6 mo if no CH, p=0.24)
						PFS	No difference by CH status
						tMN & SPM	No difference by CH status
						VTE	No difference by CH status (30% vs 24% if no CH, p=0.4) Time to VTE: CH more likely to have VTE > 3 mo after stopping IMiD (p=0.04)
Mouhieddine et al.[37]	RC	Self	MM	986 (529 received HCT)	5.5 y (HCT patients)	Bacterial infections	Increased in CH (p=0.01)
						Cardiovascular disease	Increased in CH (p=0.003)
						Cerebrovascular accidents, Coagulopathies	No difference by CH status
						OS	No difference by CH status (in HCT cohort: HR 1.06, CI 0.54-2.11, p=0.86)
						PFS	No difference by CH status (in HCT cohort: HR 0.92, CI 0.59-1.46, p=0.74)
						SPM (hematologic or solid)	No difference by CH status
Gramegna et al.[38]	CC	Self	Lymphoid	45	6 y	Clonal evolution (at tMN diagnosis)	Increase in the number of CH mutations from 16 to 46 from HCT to tMN

						Clonal expansion (at tMN diagnosis)	Increase in VAF from 13.2% at HCT to 33.2% at tMN, p<0.05; attributable to new mutations
						tMN	Pre-HCT CH more common in tMN cases than controls (58% vs 23%, p=0.029); VAF similar in cases and controls
Soerensen et al.[39]	PC	Self	Lymphoid who developed tMN	12	4 y	tMN	75% of patients had CH at HCT that persisted at tMN; 8/14 (57%) of CH mutations were <2% VAF at HCT
Soerensen et al.[40]	CC	Self	Lymphoid	72	3.5 y	Clonal expansion	1/5 pre-HCT CH mutations expanded at tMN (4/5 were no longer present at tMN)
						tMN	When excluding *DNMT3A* and *TET2*, increased in CH (OR 5.9, 95% CI 1.8-19.1, p=0.03)
Slavin et al.[41]	CC	Self	Lymphoid	39	2 y	NRM	NRM cases more likely to have pre-HCT CH (70% vs 24% of controls, p=0.002)
Eskelund et al.[42]	PC	Self	Mantle cell lymphoma	149	8 y	Clonal expansion	VAF increased after induction (median relative increase 44%) and after HCT (median relative increase 42%) but remained constant during follow-up (median relative increase 5%)
						OS	No difference by CH status (HR 0.92, CI 0.48-1.8, p=0.82)
Rhee et al.[65]	RC	Self	MM	1,036	5 y	Cardiovascular disease	Incidence higher in CH (21.1% vs 8.4%; HR 2.72, CI 1.69-4.39); also significant for individual outcomes (i.e., heart failure, coronary artery disease, and stroke)
ALLOGENEIC HCT							
Wong et al.[43]	RC	Matched unrelated	AML	25 donor-recipient pairs, young donors	1 y	Clonal evolution	Mutation burden increased at 100 d (from 19 pre-HCT to 33, p=0.048)
						Chronic GVHD	No difference by CH status (1-yr post-HCT, p=0.17); *Note:* limited sample size
						Engraftment	100% of donor CH (19/19) engrafted in recipients; 74% persisted through 1 y
Gibson et al.[44]	PC	Mixed donor types	Mixed	1,727 donors	5 y	Acute GVHD, NRM Chronic GVHD, Relapse, OS	No difference by CH status Effects only in *DNMT3A*-CH (*Table S2*)

						DCL	Difference by CH status not reported; 83% of recipient DCL mutations were detected in donors
						PFS	Improved PFS if donor CH VAF ≥1% (HR 0.79, 95%CI 0.66-0.95, p=0.011)
Kim et al.[45]	PC	Mixed donor types	Mixed	744 (372 donor-recipient pairs)	13 y	Acute GVHD (100-d)	No difference by donor CH status (80% vs 77% if no CH, p=0.49)
						Chronic GVHD (3-y)	No statistical difference by donor CH status (48% vs 64% if no CH, p=0.22)
						Neutrophil/platelet engraftment	No difference by donor CH status
						NRM (10-y)	No difference by donor CH status
						OS (10-y)	No difference by donor CH status (48% vs 41% in no CH, p=0.97)
						Relapse (10-y)	No difference by donor CH status
						SPM	No difference by donor CH status
Heumuller et al.[46]	CS	Mixed donor types	Myeloid	22 recipients who had young donors	9.8 y	Post-HCT CH	4.5% (1/22) patients had CH after HCT; not detectable in donor or recipient at HCT
Frick et al.[47]	RC	Related donors	Mixed	500 donors	3.3 y	Acute GVHD	Incidence not different by donor CH status
						Chronic GVHD	5-y incidence: higher if CH+ donor (53% vs 36% if CH- donor, p=0.008)
						Clonal expansion	21/22 donor CH mutations expanded linearly or disproportionately (i.e., doubling) over time in recipients
						DCL	More common if CH+ donor (2/82 vs 0/426 if CH- donor, p=0.026)
						Leukocyte engraftment	Faster if CH+ donor (15-day incidence 64% vs 51% if CH- donor, p=0.023)
						OS	No difference by donor CH status (AdjHR 0.88, 95% CI 0.65-1.32, p=0.43)
						NRM	No difference by CH status
						PBSC mobilization	No difference by CH status
						Relapse	5-y CIR/P: lower if CH+ donor (p=0.027)
Boettcher et al.[48]	CS	Related donors	Mixed	84	16 y	Clonal expansion	VAF increased in recipients relative to donors (p=0.03)

				(42 donor-recipient pairs)		DCL/MDS	1/5 donor-engrafted CH cases progressed to MDS in donor and recipient; no inherited predisposition
						Telomere length	T/S greater in recipients than donors (~20-y premature aging, p <0.0001) T/S not different by CH status in donors (0.6 vs 0.75 if no CH) or recipients (0.45 vs 0.55 if no CH)
Grimm et al.[50]	PC	Mixed donor types	AML	113 recipients	4.4 y	Clonal persistence	35.4% of CH mutations in 28.0% of patients persisted from diagnosis to CR; not associated with OS or relapse
						OS	71.7% (CH) vs 55.1% (No CH), p=0.06
						Relapse	CIR: No difference by CH status (35.3% vs 38.7% if no CH, p=0.41)
Newell et al.[51]	CC	Mixed donor types	Mixed	290 recipients (confirmed in donors)	25.8 m (CH cases); 37.2 m (controls)	Acute GVHD	No difference by donor CH status (53% vs 57.8% in no CH, p=0.74)
						Chronic GVHD	Higher incidence of chronic GVHD requiring immunosuppressive therapy if CH+ donor (73% vs 56% if CH- donor, p=0.045)
						Donor chimerism	No difference in time to full donor chimerism by CH status
						GVHD-free relapse-free survival	No difference by donor CH status
						Neutrophil/platelet engraftment	No difference by donor CH status
						OS	No difference by donor CH status
						Relapse	No difference by donor CH status
Oran et al.[52]	PC	Matched sibling	AML/MDS	363 donors	5.3 y	Acute GVHD	6-m cumulative incidence higher in CH (e.g., grade II-IV 53% vs 28% in no CH, HR 2.4, p < 0.001)
						Chronic GVHD	No difference by CH status (5-y incidence 23% vs 35% if no CH, p=0.2)
						Neutrophil/platelet engraftment	No difference by donor CH status
						PFS	No difference by donor CH status
						Relapse	No difference by donor CH status
						Treatment-related mortality	No difference by donor CH status
Gillis et al.[53]	RC	Matched sibling	Myeloid	299 donors; 13 recipients	48.4 m	Acute GVHD	Higher incidence if CH+ donor (37.5% vs 25.1%), but cumulative incidence ns (HR 1.35, p=0.47)

						Chronic GVHD	No difference by CH status (HR 0.75, 95% CI 0.51-1.1, p=0.14)
						CRFS, DFS, NRM	No difference by donor CH status; suggestive decreased risk for early-stage patients (p<0.05), but small numbers
						GRFS	No difference by donor CH status
						OS	No difference by donor CH status
Imus et al.[54]	RC	Mixed donor types	Lymphoid	97 recipients	32 m	aGVHD	No difference by CH status
						Cytokine release syndrome	No difference by CH status
						NRM	Higher if recipient had pre-HCT CH (35% vs 11%, HR 3.4)
						OS	Worse if recipient had pre-HCT CH (3-y OS 47% vs 78% if no CH, HR 3.1)
						PFS	Worse if recipient had pre-HCT CH (3-y PFS 39% vs 60% if no CH)
						Relapse	No difference by CH status
Tanaka et al.[55]	PC	Donor types NR	AML	43 recipients (longitudinal)	467 d	Clonal persistence	91% of post-CR CH mutations persisted until HCT; 95% of post-CR CH mutations were eradicated by HCT
						Relapse	CIR: No difference by CH status (p=0.17)
Lueck et al.[66]	CC	Mixed donor types	Myeloid only for CH analysis	52 recipients for CH analysis	NA	AFiH	No statistical difference by CH status (46 vs 21% in no CH, p=0.08)

[a]Clonal expansion is defined here as an increase in the VAF of pre-existing CH mutations; clonal evolution is acquisition of new CH mutations.

AdjHR, adjusted hazard ratio; **AFiH**, atrial fibrillation in-hospital; **Allo**, allogeneic; **AML**, acute myeloid leukemia; **CC**, case-control; **CH**, clonal hematopoiesis; **95% CI**, 95% confidence interval; **CIR**, cumulative incidence of relapse; **CIR/P**, cumulative incidence of relapse or progression; **CR**, complete response; **CRFS**, cGVHD relapse-free survival; **CS**, cross-sectional; **d**, days; **DCL**, donor cell leukemia; **DFS**, disease-free survival; **EFS**, event-free survival; **GRFS**, GVHD-free relapse-free survival; **GVHD**, graft-versus-host disease; **HCT**, hematopoietic cell transplantation; **HR**, hazards ratio; **ICU**, intensive care unit; **IMiD**, immunomodulatory imide drugs; **m**, months; **MDS**, myelodysplastic syndromes; **MM**, multiple myeloma; **NA**, not applicable/available; **NCC**, nested case-control; **NRM**, non-relapse mortality; **OS**, overall survival; **OR**, odds ratio; **PBSC**, peripheral blood stem cells; **PC**, prospective cohort; **PFS**, progression-free survival; **RC**, retrospective cohort; **SPM**, second primary malignancy; **tMN**, therapy-related myeloid neoplasm; **T/S**, telomere to single copy ratio, a measure of telomere length; **VAF**, variant allele frequency; **VTE**, venous thromboembolism; **y**, years

Table S2. Summary of clonal hematopoiesis (CH) results in original studies investigating the association between CH and outcomes in hematopoietic cell transplantation (HCT).

Study	Samples used	Sample collection timepoint	Age, median (range)	Genes (n)	Sequencing depth	VAF included/ median	CH prevalence	Gene-specific effects: Outcome[a]	Gene-specific effects: Results
AUTOLOGOUS HCT									
Heini et al.[16]	BM, PB, or cell apheresis product (2.8%)	Post-HCT (2.8% pre-HCT)	54 (40-61)	3, persistence of DTA mutations after HCT	NR	≥2% NR	28.2%	OS PFS	DTA: No difference (54.4 vs 80.9 if no DTA, p=0.44) DTA: No difference (16.7 vs 26.9 if no DTA, p=0.29)
Gifford et al.[18]	Cell apheresis products	Pre-HCT	63 (19-72)	6	1209 (median)	≥2% 3.3%	13.5%	NR	NR
Gibson et al.[19]	Cell apheresis products	Pre-HCT + pre/post-HCT (n=12)	NR	86	NR	≥2%	29.9%	OS (10-y)	*PPM1D* 20.8% vs 39.9% if no *PPM1D* (p=0.02)
Mouhieddine et al.[20]	Cell apheresis products	Pre-HCT	58 (24-83)	224	978x	≥1% 2.7%	21.6%	OS PFS	*DNMT3A R882*: 1 y if no IMiD maintenance (p=0.008 vs no CH) *DNMT3A R882*: 0.9 y if no IMiD maintenance (p=0.007 vs no CH)
Hazenberg et al.[21]	PB	Pre-HCT	59 (51-64)	28	5619x (mean)	≥1% 2.6%	26.8%	PBSC mobilization CD34+ yield	*PPM1D* mutations more common in poor mobilizers (20 vs 1 control, p=0.005) *TP53* mutations only in poor mobilizers (p=0.06) Lower in *PPM1D*- or *TP53*-CH (4.26 vs 8.2 x10^6/kg if no CH, p=0.007)
Stelmach et al.[22]	Cell apheresis products	Pre-HCT	59 (28-72)	56	NR	≥1% NR	33.3%	CD34+ yield OS Platelet engraftment	*DNMT3A* and/or *PPM1D*: lower yield (4.65 vs 7.5 x10^6/kg if no CH, p=0.009) *DNMT3A* and/or *PPM1D*: in patients not treated with maintenance, decreased OS compared to no CH (p=0.048) *DNMT3A* and/or *PPM1D*: Delayed platelet engraftment compared to no CH (p=0.02)

								Platelet transfusions	*DNMT3A* and/or *PPM1D*: 1.41x more platelet transfusions 20 days after HCT than non-CH patients (p=0.02)
Ortmann et al.[23]	Cell apheresis products or PB	Pre- and post-HCT	60 (IQR 51-68)	55	14,572 (median)	>0.5% 10.7%	22% (post-HCT)	Neutrophil engraftment	DRP: longest time to neutrophil engraftment (10.5 vs 7.38 if non-DRP CH and 6.66 d if no CH, p=0.001)
Lackraj et al.[24]	Cell apheresis products	Pre-HCT	53 (18-70)	36	NR	Not set 2.9%	43.1%	Platelet recovery OS	*PPM1D*: longer time, HR 1.92 (FDR p=0.0005) DTA: HR 1.56 (p=0.017) *PPM1D* in DLBCL: HR 2.41 (FDR p=0.02)
Li et al.[28]	BM MNC minus CD38/CD138+	Pre-HCT	57 (43-62) (IQR 61-62)	7	>1500x	≥2% NR 3.2%	NR (CH identified in 6 and matched to patients without CH)	NR	NR
Husby et al.[34]	Cell apheresis products	Pre-HCT	57 (47-63)	21	~4000x (median)	≥2% 4.9%	26%	Cardiovascular events ICU admission In-patient days OS (median) Severe infection tMN Transfusions	DRP: ns DRP: AdjHR 1.85 (p=0.035) DRP: 20 vs 2 d if no DRP (p=0.003) DRP: 2.2 vs 9.0 y if no DRP (p=0.0005) ≥1 y OS AdjHR 2.37 (p=0.0007) DRP: AdjHR 1.48 (ns) DRP: AdjHR 5.63 (p=0.003) DRP: RR 1.46 (ns)
Yan et al.[35]	PB	Pre-HCT	34 (18-71)	91	>1000x	≥1%	14.3%	NRM tMN	*TP53* and/or *PPM1D* associated with 4.17-fold hazard compared to no CH *TP53*: All patients with *TP53*-CH developed tMN *TP53* and/or *PPM1D* associated with 7.29-fold risk compared to no CH

									DNMT3A: No patients with *DNMT3A*-only CH developed tMN Cumulative incidence increased with number of CH mutations and VAF
Wudhikarn et al.[36]	BM MNC minus CD38/CD138+	Pre-HCT	61 (54-67)	42	NR	NR 6.0%	23%	NR	NR
Mouhieddine et al.[37]	PB	Newly diagnosed (pre-HCT)	63 (27-93)	110	113x (mean)	≥2% 7%	10% (7.6% in HCT patients)	OS, PFS Clonal evolution (n=52 w/ serial samples)	DTA: No difference by CH status No difference by CH clone size CH prevalence increased following initiation of therapy (5.8% to 25%); most common emergent mutation was *DNMT3A*
Gramegna et al.[38]	Cryopreserved HSCs	Pre-HCT and tMN (for cases)	63 (34-71)	45	≥ 500x	≥1% 13.2%	23% (controls) and 58% (tMN cases)	tMN	*TP53* mutations most common at tMN; *RUNX1, NRAS, KRAS* mutations only detected at tMN (not prior to HCT)
Soerensen et al.[39]	Cell apheresis products and BM MNCs (at tMN)	Pre-HCT and tMN	63 (37-69)	30	≥ 3000x	≥0.3% 1.1%	75% (pre-HCT)	Clonal expansion	*DNMT3A* low-level expansion from HCT to tMN (0.8-2.1%, ns)
Soerensen et al.[40]	Cell apheresis products	Pre-HCT		30, excluded *DNMT3A* and *TET2* from primary analysis	~8800x (median)	≥0.3% NR	NR	tMN	*Non-DNMT3A* high-level expansion from HCT to tMN (1-37%, p=0.002)
Slavin et al.[41]	Mobilized PB HSCs	Pre-HCT	65 (39-75)	79	560x (mean)	>2% NR	35.9%	NR	NR
Eskelund et al.[42]	BM or PB	MRD-negative post-HCT + paired pre-HCT (n=59)	58 (IQR 61-62)	21	> 5000x (mean)	≥1% 3.2%	30%	Clonal expansion	DRP genes (*PPM1D, RAD21, BRCC3*): greater increase in VAF than non-DRP (1.7 vs 0.48, p=0.008) after induction

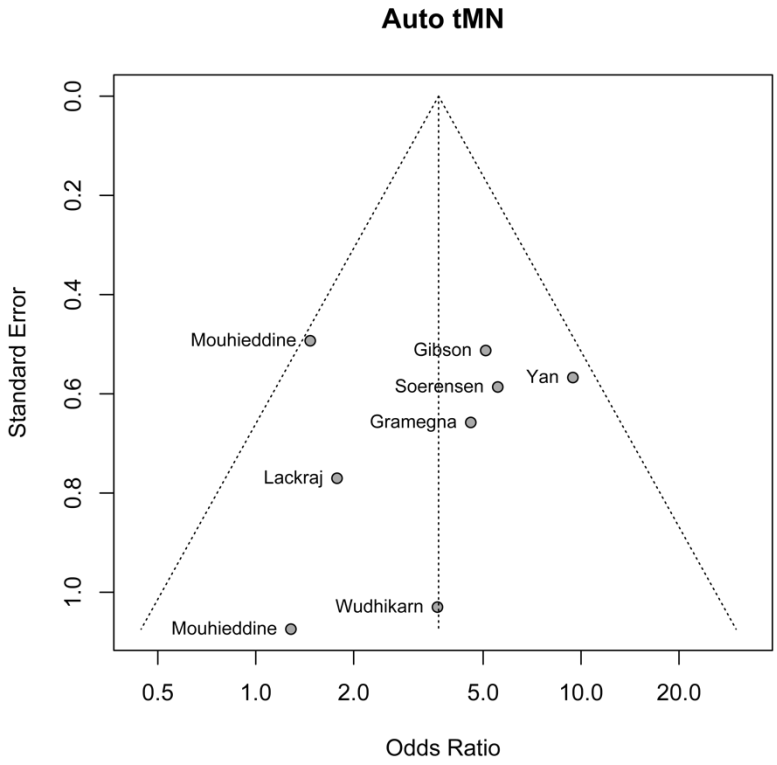
Rhee et al.[65]	PB	Pre-HCT	60 (35-77)	108	560x (mean)	≥2% NR	19.4%	Cardiovascular disease	Incidence increased with increasing number of CH mutations No difference in risk by VAF *ASXL1*: Strongest risk for cardiovascular disease; also risk for heart failure and stroke
ALLOGENEIC HCT									
Wong et al.[43]	BM or PB	Pre- and post-HCT; donors only pre-HCT	26 (20-58) for donors	80	9200x (mean)	≥0.1% 0.25%	at > 2% VAF: 4% at ≥ 0.1% VAF: 44% (donors)	NR	NR
Gibson et al.[44]	PB or BM	Pre-HCT	51 (40-80)	46	≥ 1000x	≥0.5% NR	22.5% (donors)	Death/OS PFS Relapse Chronic GVHD Clonal expansion	No PTCy, *DNMT3A*: HR 0.65 (p=0.01) *DNMT3A*: HR 0.72 (p=0.003) No PTCy, *DNMT3A*: HR 0.59 (p=0.014) No PTCy, *DNMT3A*: HR 1.37 (p=0.04) *DNMT3A R882:* 10/10 engrafted and had higher VAF at 12-months than non-*R882* (VAF 5% vs 2% if non-*R882*, p=0.004)
Kim et al.[45]	PB	Pre-HCT	48 (17-71)	33	8540x (mean)	>0.5% 1.86%	18% (recipients) 6.7% (donors)	NR	NR
Heumuller et al.[46]	PB	Post-HCT (≥ 5 y)	78 (69-82)	NR	≥ 200x	≥0.05% NR	4.5% (recipients)	NR	NR
Frick et al.[47]	PB or BM	Pre-HCT	~64 (55-79)	66	2033x (mean)	≥2% 5.9%	16% (donors)	Chronic GVHD CIR/P OS	*DNMT3A*: AdjHR 1.99 (p=0.002) *DNMT3A*: Lower risk (p=0.029) *DNMT3A*: No difference (p=0.57)
Boettcher et al.[48]	PB	Post-HCT (median 16 y)	59 (29-95)	102	582x (mean)	≥1% 3%	31% (recipients) 23.8% (donors)	NR	NR
Grimm et al.[50]	PB (n=113) and	Pre-HCT (BM was	64 (32-76)	10 (PB samples);	≥ 500x	≥3% 11.1%	41.6% (recipients)	Relapse	*DNMT3A, TET2,* or *ASXL1:* No effect

	BM (n=75, results not discussed here)	pre-any treatment)		54 (BM samples)				OS	*DNMT3A*: No effect (p=0.71) *TET2*: 88.1% vs 57% if no *TET2* (p=0.02) *ASXL1:* 4-y OS 100% vs 58.6% if no *ASXL1* (p=0.02)
Newell et al.[51]	BM	Pre- and post-HCT	56 (37-68) for cases	76	2286x (mean)	≥0.5% 5.1%	5.2% (defined as mutation post- but not in pre-HCT sample, confirmed in donor samples)	Clonal Expansion	*DNMT3A*: 2-fold on average (11.4 m follow-up); most rapid increases died within 1 y *ASXL1*: 2-fold on average (3.5 m follow-up) Others, including *TET2*: stable VAF
Oran et al.[52]	PB	Pre-HCT	~62 (55-78)	300	289x (median)	≥2% 6.1%	18% (donors)	Acute GVHD	DTA: No difference in risk between mutations in these genes
Gillis et al.[53]	PB	Pre-HCT	63 (55-80)	75	3873 (median)	≥2% 3.1%	13.7% (donors)	Chronic GVHD	*DNMT3A*: Lower incidence if donor + (34% vs 57%, p=0.04)
Imus et al.[54]	PB or BM	Pre-HCT in recipients	67 (60-78)	48	NR	≥1% NR	62% (recipients)	NRM, OS	Worse with increased VAF and number of mutations
Tanaka et al.[55]	BM	Pre-HCT (post-CR)	53 (17-85)	295	NR	>2.5% 14%	NR	Neutropenia Relapse	*TET2* prolonged neutropenia *ASXL1* (p=0.07) or *TP53* (p=0.05) mutations increase risk: >1 CH mutation increases risk (p=0.04)
Lueck et al.[66]	NR	Pre-HCT	~62 (51-67)	3: DTA	> 100x	≥5%	53.8% (recipients)	AFiH	*DNMT3A*: Incidence in mutated (53%) higher than non-mutated (27%)

[a]Clonal expansion is defined here as an increase in the VAF of pre-existing CH mutations; clonal evolution is acquisition of new CH mutations.

AdjHR, adjusted Hazard Ratio; **AFiH**, atrial fibrillation in-hospital; **BM**, bone marrow; CH**,** clonal hematopoiesis; **CIR/P**, cumulative incidence of relapse/progression; **CR**, complete remission; **d**, days; **DLBCL**, diffuse large B-cell lymphoma; **DRP**, DNA repair pathway genes; **DTA**, *DNMT3A*, *TET2*, or *ASXL1* mutations; **FDR**, false discovery rate; **GVHD**, graft-versus-host disease; **HCT**, hematopoietic cell transplantation; HR, hazards ratio; **HSC**, hematopoietic stem cell; **HUMARA**, human androgen receptor assay; **ICU**, intensive care unit; **IMiD**, immunomodulatory imide drugs; **IQR**, interquartile range; **m**, months; **MNC**, mononuclear cell; **MRD**, measurable residual disease; **NA**, not applicable; **NR**, not reported; **ns**, not statistically significant; **OS**, overall survival; **PB**, peripheral blood; **PBSC**, peripheral blood stem cell; **PFS**, progression-free survival; **PTCy**, post-transplant cyclophosphamide; **RR**, risk ratio; **tMN**, therapy-related myeloid neoplasm; **VAF**, variant allele frequency; **y**, years

Figure S1. Funnel plots of autologous (auto) hematopoietic cell transplantation studies assessing clonal hematopoiesis-associated risk for therapy-related myeloid neoplasms (tMN) and overall survival (OS) with sufficient data to be included in the meta-analysis.



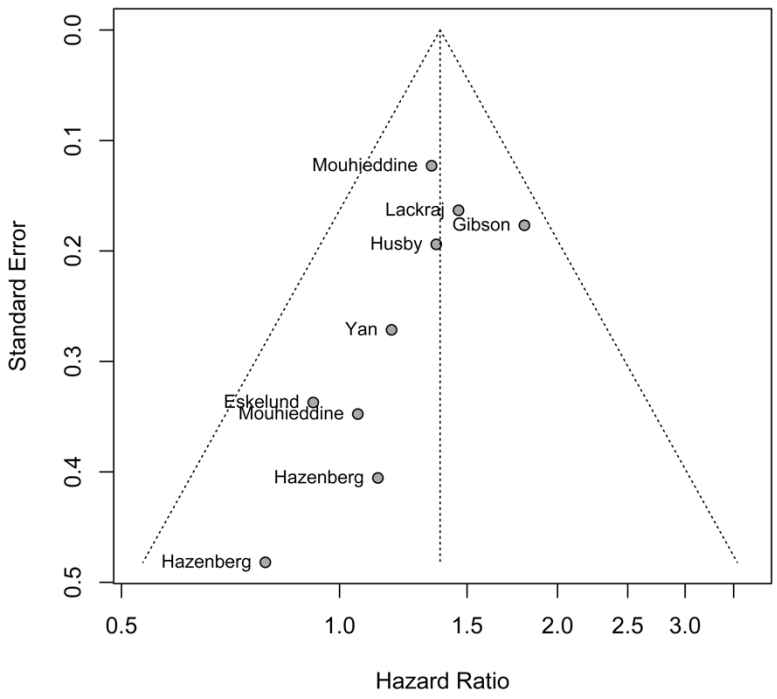


Figure S2. Stratified meta-analysis of the association between clonal hematopoiesis and risk for therapy-related myeloid malignancies (tMN) in patients with lymphoma (top) and multiple myeloma (bottom) receiving autologous (auto) hematopoietic cell transplantation.

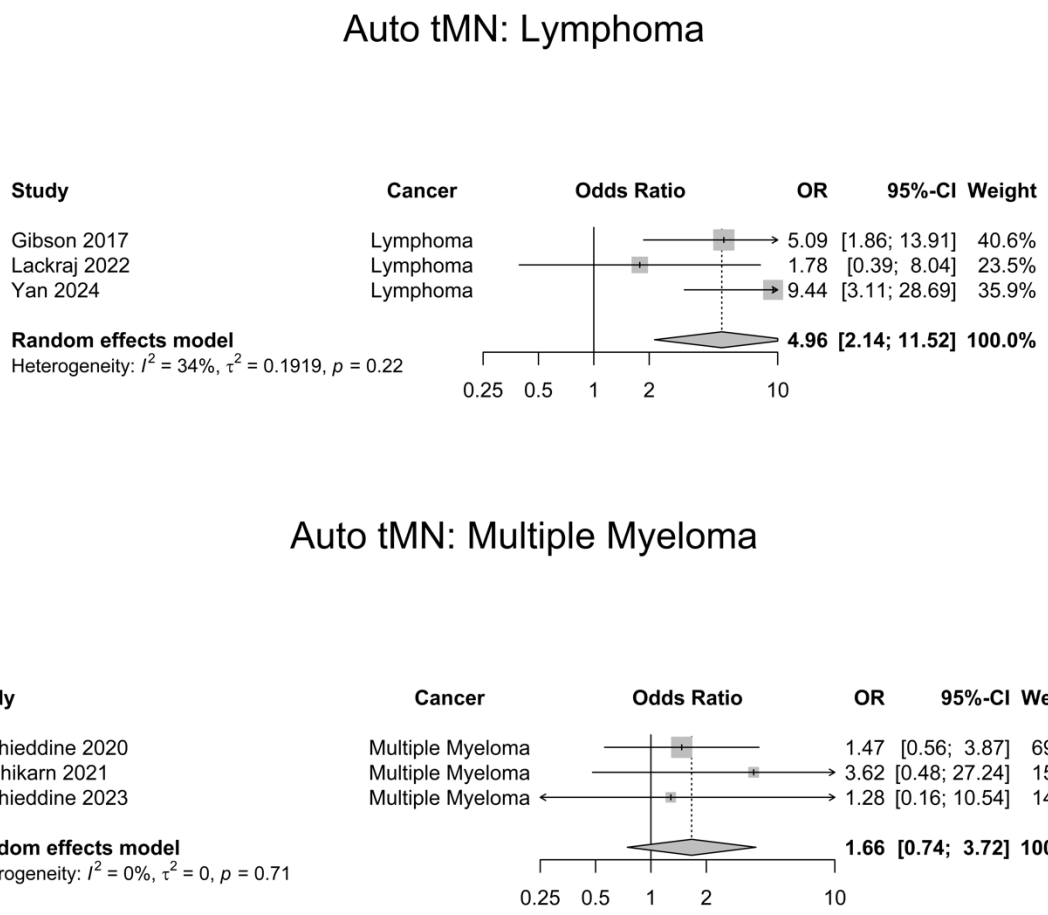


Figure S3. Stratified meta-analysis of the association between clonal hematopoiesis and overall survival in patients with lymphoma (top) and multiple myeloma (bottom) receiving autologous (auto) hematopoietic cell transplantation.

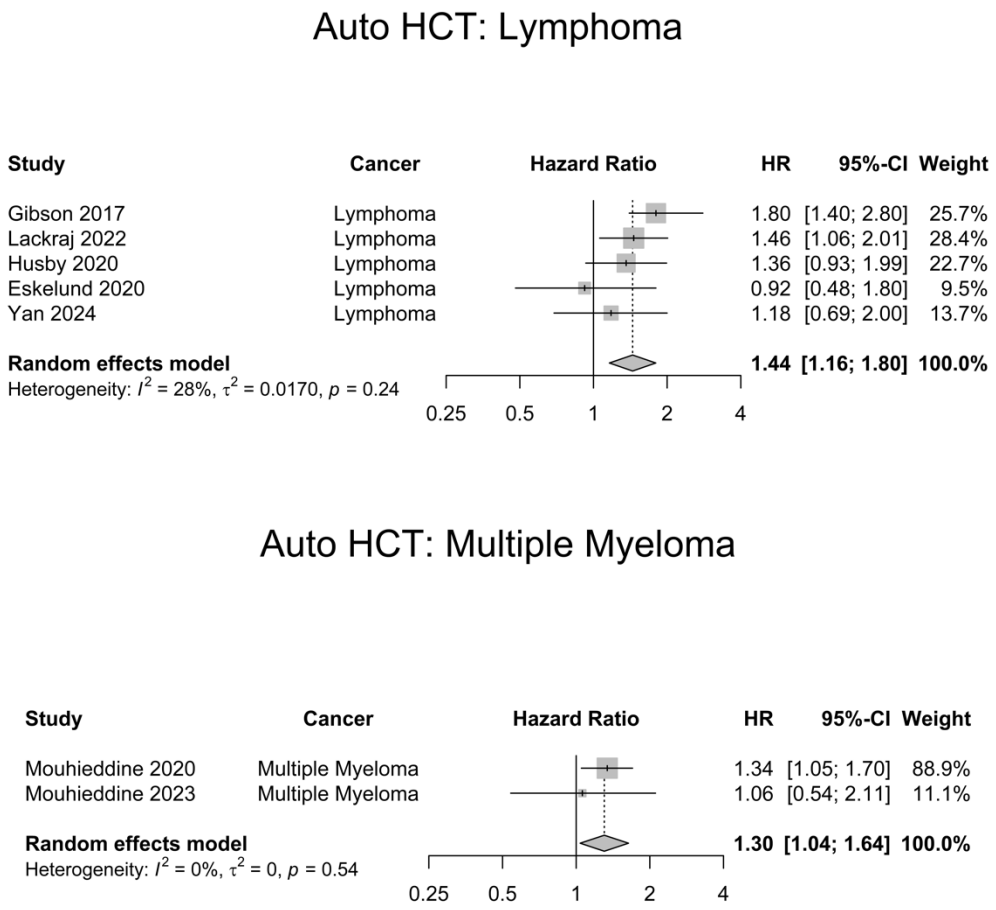


Figure S4. Funnel plots of allogeneic (allo) hematopoietic cell transplantation studies assessing clonal hematopoiesis-associated risk for relapse, overall survival (OS), chronic graft-versus-host disease (cGVHD), and acute graft-versus-host disease (aGVHD) with sufficient data to be included in the meta-analysis.

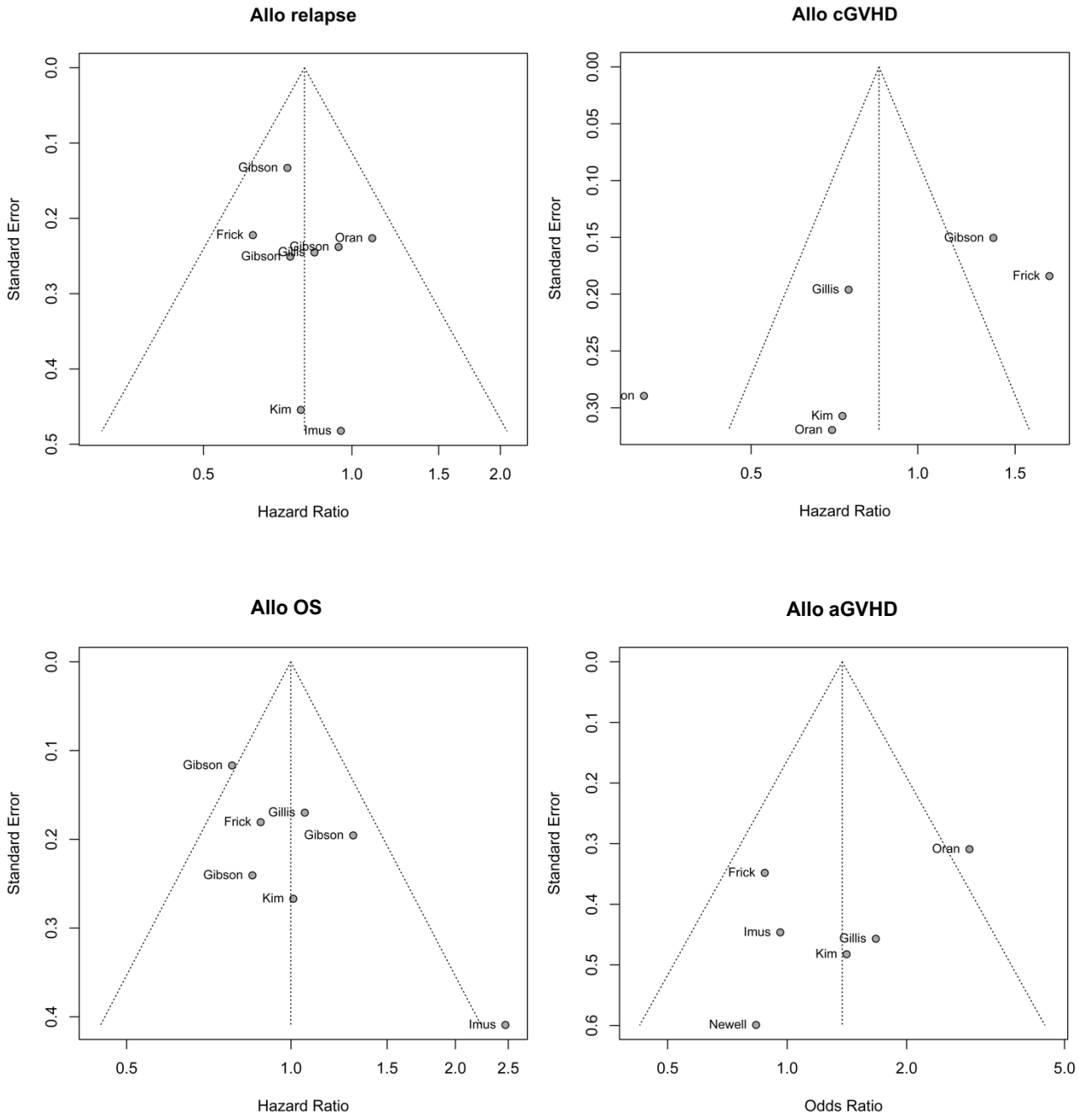
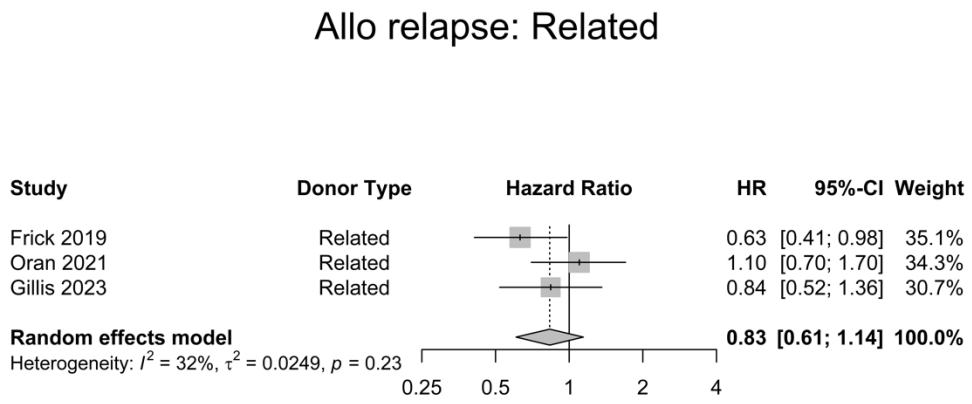
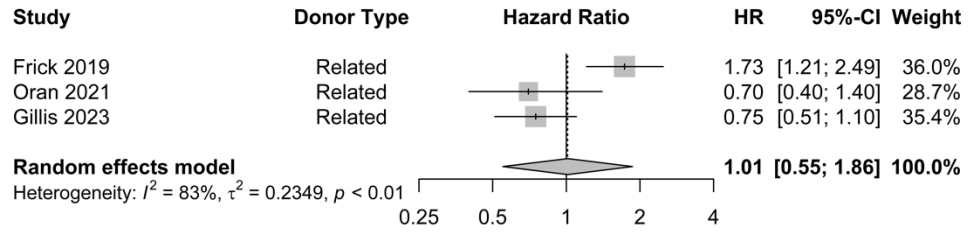
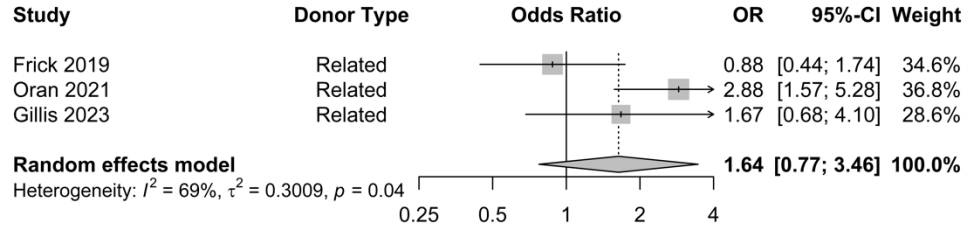


Figure S5. Stratified meta-analysis of the association between clonal hematopoiesis and outcomes (relapse, chronic graft-versus-host disease or cGVHD, and acute GVHD or aGVHD) in studies that included only related allogeneic (allo) hematopoietic cell transplantation donors.







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