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

Nancy Gillis,[1,2*] Amr Ebied,[3*] Zachary J. Thompson[4] and Joseph A. Pidala[5]

[1]Department of Cancer Epidemiology, Moffitt Cancer Center and Research Institute; [2]Department of Malignant Hematology, Moffitt Cancer Center and Research Institute; [3]Department of Epidemiology & Biostatistics, College of Public Health, University of South Florida; [4]Department of Biostatistics and Bioinformatics, Moffitt Cancer Center and Research Institute and [5]Department of Blood and Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center and Research Institute, Tampa, FL, USA

**NG and AE contributed euqally as first authors.*

Correspondence: N. Gillis
Nancy.Gillis@moffitt.org

Received: March 4, 2024.
Accepted: June 13, 2024.
Early view: June 20, 2024.

https://doi.org/10.3324/haematol.2024.285392

Abstract

Hematopoietic cell transplantation (HCT) is the only potentially curative treatment option for many patients with hematologic malignancies. While HCT outcomes have improved drastically over the years, patients and clinicians continue to face numerous survivorship challenges, such as relapse, graft-*versus*-host disease, and secondary malignancies. Recent literature suggests that clonal hematopoiesis (CH), the presence of a recurrent somatic mutation in hematopoietic cells, in HCT patients or donors may be associated with outcomes in autologous and allogeneic HCT. Herein, we perform a review of the literature and summarize reported associations between CH and clinical outcomes in HCT. For commonly reported outcomes, we used meta-analysis methods to provide estimates of effect sizes when combining results. A total of 32 articles with relevant and independent contributions were included, covering both autologous (N=19) and allogeneic (N=13) HCT. The articles report variable risk for developing outcomes according to CH characteristics, patient disease status, and method of HCT. Using meta-analysis of available results, HCT outcomes with statistically significant effects by CH status include therapy-related myeloid neoplasms (odds ratio =3.65; 95% confidence interval [CI]: 2.18-6.10) and overall survival (hazard ratio [HR]=1.38; 95% CI: 1.20-1.58) in autologous HCT and relapse (HR=0.80; 95% CI: 0.68-0.94) in allogeneic HCT. However, heterogeneity, biases, and limitations in the literature provide challenges for informing the translation of CH to clinical decision-making. We conclude with a call to action and discussion of next steps to build upon the current literature and provide granularity to the true clinical impact of CH in the setting of HCT.

Introduction

For many patients with hematologic malignancies, hematopoietic cell transplantation (HCT) is the only potentially curative treatment option.[1-3] Despite improvements in survival rates of patients receiving HCT, disease progression, treatment toxicities (e.g., graft-*versus*-host disease), subsequent cancers, cardiovascular complications, and infections remain major challenges.[1,4] Data suggest that clonal hematopoiesis (CH) may be an important biomarker for identifying patients at increased risk for poor outcomes from HCT.

CH is a premalignant hematological state characterized by somatic mutations in hematopoietic stem and progenitor cells without overt hematologic abnormalities.[5] The genes mutated in CH are largely the same as those pathogenic for myeloid malignancies.[6,7] CH is strongly associated with aging, with a prevalence of 1% in healthy individuals younger than 40, 20% in those over 65, and almost ubiquitous (>90%) in individuals over 80 years of age;[6-8] however, the prevalence of CH varies greatly depending on the limit of detection of somatic mutations.[9,10] Individuals with CH are at increased risk for incident hematologic malignancies, cardiovascular disease, chronic liver disease, severe COVID-19, and mortality.[7,11-13]

Because CH is present in healthy individuals and patients with cancer,[14] HCT donors and patients may be carriers of these mutations. This article used a systematic approach and meta-analyses to synthesize the existing literature on the clinical impact of CH on HCT recipient outcomes stratified by disease and HCT types (i.e., autologous, or auto-, and allogeneic, or allo-HCT). We conclude with a discussion of knowledge gaps, next steps, and a call to action needed to make evidence-based recommendations regarding the management of CH in patients undergoing HCT.

Methods

Search strategy and article selection

We systemically searched for articles indexed in PubMed, Scopus, Embase (Elsevier), and Web of Science (Clarivate). All database searches were last conducted on April 29, 2024. EndNote 20 (Clarivate Analytics, USA) was used to remove any duplicates and select eligible studies. After removal of duplicate articles, titles and abstracts were screened for inclusion. Articles eligible for inclusion were original articles or relevant letters or commentaries that reported measures of the effect of CH, identified in donors and/or recipients, on outcomes in patients undergoing allo- or auto-HCT. Exclusion criteria included reviews, case reports and series, abstracts, non-human studies, studies not written in English, and studies not reporting a measure of risk between groups by CH status. A comprehensive evaluation of the identified studies and abstracts was completed by one author and subsequently evaluated by another author for final inclusion. Inconsistencies that arose were handled through consensus. Additional details on the search strategy are provided in the *Online Supplementary Appendix*.

Meta-analysis

In order to estimate the effect sizes of CH in HCT, we used meta-analyses for all outcomes reported in more than ten auto- and more than five allo-HCT studies. Hazard ratios (HR) and 95% confidence intervals (CI) for outcomes relative to CH status were abstracted from published articles. When HR were not available, odds ratios (OR) and CI were abstracted or calculated. Articles without HR, OR, or data sufficient for calculating OR were excluded from meta-analyses. The measures of effect were combined using the general inverse variance weighting method, employing random effects models due to heterogeneity in the studies. The index of inconsistency (I^2) and τ^2 were used to assess the degree of heterogeneity among studies for each outcome. Sensitivity analysis was performed to explore differences in outcome across subgroups (e.g., cancer type or donor type). The assessment of publication bias was conducted by the visual examination of funnel plots. Meta-analyses were performed using the meta package in R version 4.3.0.

Results

A comprehensive search strategy was employed and, as reassurance, all relevant articles known to us, in addition to others, were retrieved using this strategy. Thirty-two unique publications met inclusion criteria and investigated the effect of CH on outcomes in patients undergoing auto- or allo-HCT (Figure 1). One study that defined CH using X-inactivation-based clonality by the human androgen receptor locus (HUMARA) assay was excluded due to heterogeneity of CH classification.[15] The included studies were published in between 2017-2024 and investigated the association between CH and HCT outcomes across disease cohorts (including acute myeloid leukemia [AML], myelodysplastic syndromes [MDS], lymphoma, multiple myeloma [MM], and heterogenous cohorts) (*Online Supplementary Table S1*). Nineteen articles investigated outcomes in auto-HCT and thirteen articles involved allo-HCT. Study sample sizes ranged from 12 to 1,727 participants.

The effects of CH on the outcomes of HCT patients are summarized in Tables 1 and 2, and *Online Supplementary Table S1* and discussed in detail below. Additional outcomes reported in single studies or with null results are discussed in the *Online Supplementary Appendix*.

Auto-hematopoietic cell transplantation in lymphoid malignancies

Clonal hematopoiesis metrics and prevalence

In auto-HCT, most studies analyzed <100 genes for CH (Figure 2A; *Online Supplementary Table S2*). The most common variant allele frequency (VAF) threshold reported was >2% (47.1%, 8/17) followed by >1% (Figure 2B). In auto-HCT, the recipient is also the donor; therefore, measurement of CH occurs exclusively in the patient, but can be measured either before or after HCT. Most studies with prevalence data assessed CH before auto-HCT (94.1%, 16/17), with a small number reporting CH before and after HCT (17.6%, 3/17), and one study (5.9%) only assessing CH after auto-HCT (*Online Supplementary Table S2*). The median prevalence of CH in auto-HCT was 26.7% (range, 7.6-75.0%). Prevalence was higher in patients with lymphoma than MM (29.9% *vs*. 21.6%); prevalence in AML (28.2%) was reported in one study (Figure 2C).[16]

Peripheral blood stem cell mobilization

One of the first steps for successful auto-HCT is mobilization and collection of $CD34^+$ peripheral blood stem cell (PBSC) that can subsequently be transplanted. Poor PBSC mobilization can lead to HCT delay, longer time to engraftment, worse overall survival (OS), and increased risk for therapy-related myeloid neoplasms (tMN).[17] Thus, upfront identification of patients at risk for poor mobilization may be important to optimize patient outcomes and inform management decisions.

Of seven studies that explored PBSC mobilization efficiency in auto-HCT, most (5 or 71%) found a significant association between CH and mobilization despite differences in classification of the endpoint (Table 1; *Online Supplementary Table S1*). Measurements of PBSC mobilization efficiency in auto-HCT that have been statistically associated with CH status include poor mobilization,[18] days to collect an adequate number of PBSC,[19] risk of failed mobilization and requirement for bone marrow harvest,[19] and mobilization efficiency (i.e., rate).[20] Some data suggest that low $CD34^+$ yield is associated with mutations in specific CH genes, including *PPM1D*,[21,22] *TP53*,[21] and *DNMT3A*,[22] while other studies

found no difference in CD34⁺ yield by CH status.[23,24] Taken together, these data suggest that CH may contribute to inefficient CD34⁺ mobilization. Thus, CH prior to auto-HCT may be important to consider in risk stratification (along with other known risk factors) and for informing selection of patients who are more likely to benefit from plerixafor use.

Neutrophil and platelet engraftment

In cases of delayed engraftment or total engraftment failure after HCT, patients are at increased risk for severe infections, hemorrhage, relapse, and death.[25-27] Delayed engraftment also necessitates prolonged hospital stays, leading to increased costs and resource utilization. It has been hypothesized that bone marrow engraftment may be delayed in patients with CH prior to HCT (i.e., in apheresis products).

Pre-HCT CH has consistently shown a negative effect on platelet engraftment, but the impact on neutrophil engraftment has mixed results In MM, the median time to platelet engraftment was 23 days later for patients with CH than those without (P<0.0001); there was no effect of CH on neutrophil engraftment.[28] The association of CH with platelet engraftment in MM was replicated in a gene-specific study (i.e., *DNMT3A*- and *PPM1D*-CH)[22] and in patients with lymphoma, who also had prolonged neutrophil recovery.[24] Post-HCT CH was also associated with prolonged neutrophil engraftment.[23] Taken together, these data suggest that CH may impact auto-HCT morbidity due to delayed hematopoietic engraftment, especially platelet engraftment.

Therapy-related myeloid neoplasms

One of the most clinically challenging adverse events from cancer treatment, including HCT, is tMN. Defined as myeloid malignancies that occur after radiation or chemotherapy,

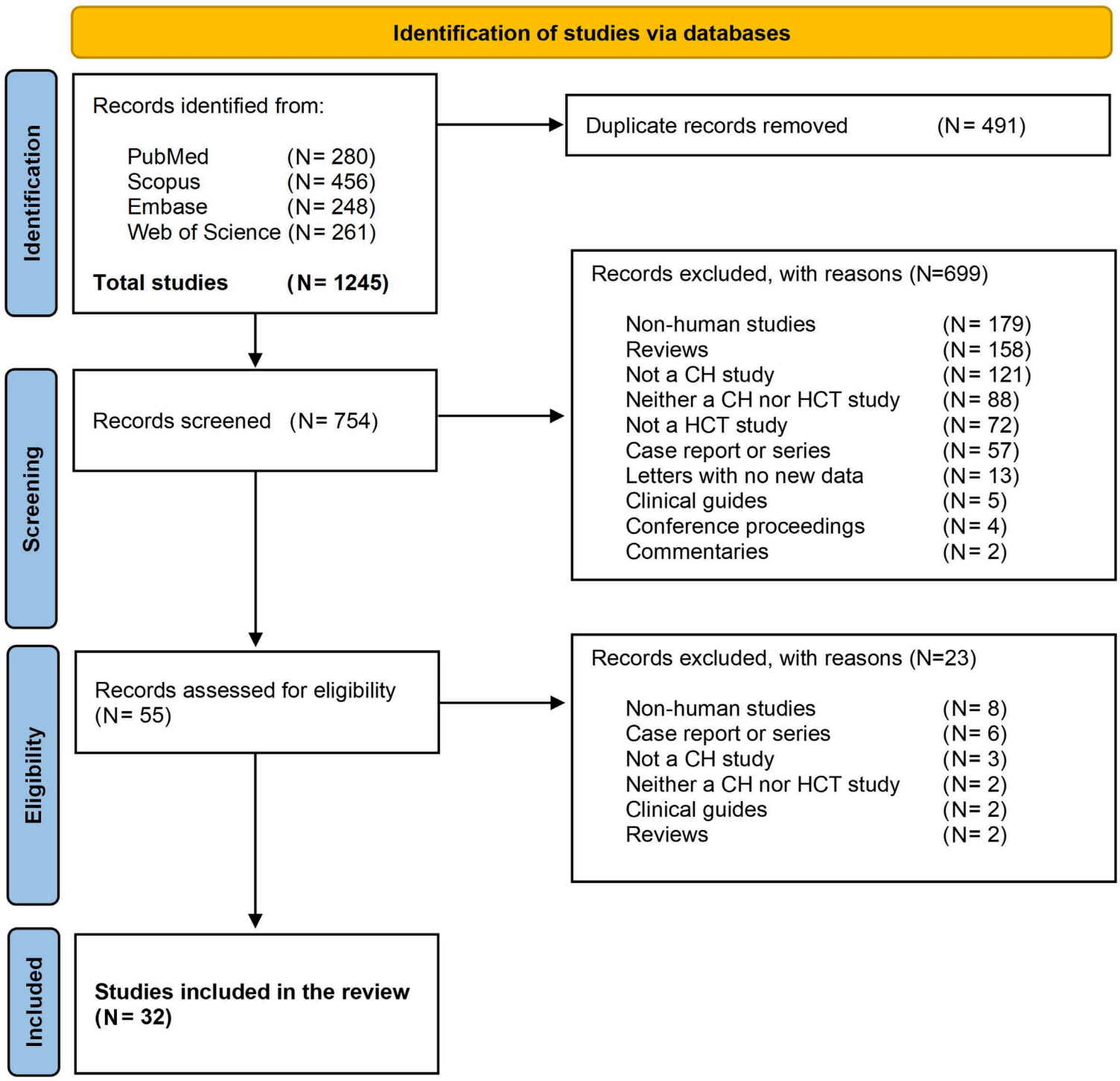


Figure 1. PRISMA flow diagram for the included studies that investigated hematopoietic cell transplantation outcomes based on clonal hematopoiesis status. HCT: hematopoietic cell transplantation; CH: clonal hematopoiesis.

Table 1. Summary of the literature investigating the effects of clonal hematopoiesis on clinical outcomes in autologous hematopoietic cell transplantation.

	PBSC mobilization	Platelet engraftment	Neutrophil engraftment	Cardiovascular events	Incidence of tMN	Relapse	PFS	NRM	OS
Lymphoma									
Gibson *et al.*[19]	↓	-	-	-	↑	-	-	↑	↑[a]
Lackraj *et al.*[24]	NS	Delayed[a]	Delayed	-	NS	NS	NS	-	↑[a]
Husby *et al.*[34]	-	-	-	NS	↑[a]	-	-	-	NS[a]
Yan *et al.*[35]	-	-	-	-	↑[a]	-	-	NS[a]	NS
Eskelund *et al.*[42]	-	-	-	-	-	-	-	-	NS
Multiple myeloma									
Mouhieddine *et al.*[20]	↓	-	-	NS	NS	-	↓[b]	-	↓[b]
Stelmach *et al.*[22]	NS[a]	NS[a]	-	-	-	-	-	-	NS[ab]
Li *et al.*[28]	-	Delayed	NS	-	NS	-	-	NS	NS
Wudhikarn *et al.*[36]	-	-	-	NS[b]	NS	NS	NS	NS	NS
Mouhieddine *et al.*[37]	-	-	-	↑	NS	-	NS	-	NS
Rhee *et al.*[65]	-	-	-	↑	-	-	-	-	-
Mixed lymphoid									
Gifford *et al.*[18]	↓	-	-	-	-	-	-	-	NS
Hazenberg *et al.*[21]	NS[a]	-	-	-	↑	-	-	-	-
Ortmann *et al.*[23]	NS	-	Delayed[a]	-	-	-	-	-	-
Gramegna *et al.*[38]	-	-	-	-	↑	-	-	-	-
Soerensen *et al.*[39]	-	-	-	-	↑	-	-	-	-
Soerensen *et al.*[40]	-	-	-	-	↑[a]	-	-	-	-
Slavin *et al.*[41]	-	-	-	-	-	-	-	↑	-

[a]Mutation-specific effects; [b]treatment-specific effects. Data are stratified by disease type. Down arrows (↓) mean outcome is decreased in presence of clonal hematopoiesis (CH); up arrows (↑) mean outcome is increased in presence of CH; hyphen (-) means outcome is not reported. Data for specific effects are reported in the *Online Supplementary Appendix*. NRM: non-relapse mortality; NS: no significant effect; OS: overall survival; PBSC: peripheral blood stem cell; PFS: progression-free survival; tMN: therapy-related myeloid neoplasm.

Table 2. Summary of the literature investigating the effects of clonal hematopoiesis on clinical outcomes in allogeneic hematopoietic cell transplantation.

	PBSC mobilization	Neutrophil/ platelet engraftment	Leukocyte engraftment	Incidence of DCL	aGVHD	cGVHD	Relapse	PFS	NRM	OS
Matched unrelated donors										
Wong *et al.*[43]	-	-	-	-	-	NS	-	-	-	-
Matched related donors										
Frick *et al.*[47]	NS	-	↑	↑	NS	↑[a]	↓[a]	↑[a]	NS	NS
Boettcher *et al.*[48]	-	-	-	↑	-	-	-	-	-	-
Matched sibling donors										
Oran *et al.*[52]	-	NS	-	-	↑	NS	NS	NS	-	-
Gillis *et al.*[53]	-	-	-	-	NS	NS[a]	NS	-	NS	NS
Mixed donor types										
Gibson *et al.*[44]	-	-	-	-	NS	NS[ab]	NS[ab]	↑[a]	NS	NS[ab]
Kim *et al.*[45]	-	NS	-	-	NS	NS	NS	-	NS	NS
Heumuller *et al.*[46]	-	-	-	-	-	-	-	-	-	-
Grimm *et al.*[50]	-	-	-	-	-	-	NS	-	-	NS[a]
Newell *et al.*[51]	-	NS	-	-	NS	↑	NS	-	-	NS
Imus *et al.*[54]	-	-	-	-	NS	-	NS	↓	↑	↓
Tanaka *et al.*[55]	-	NS[a]	-	-	-	-	NS[a]	-	-	-
Lueck *et al.*[66]	-	-	-	-	-	-	-	-	-	-

[a]Mutation-specific effects; [b]treatment-specific effects. Data are stratified by donor type. Down arrows (↓) mean outcome is decreased in presence of clonal hematopoiesis (CH); up arrows (↑) mean outcome is increased in presence of CH; hyphen (-) means outcome is not reported. Data for specific effects are reported in *Online Supplementary Appendix*. aGVHD: acute graft-*versus*-host disease; cGVHD: chronic graft-*versus*-host disease; DCL: donor cell leukemia; NRM: non-relapse mortality; NS: no significant effect; OS: overall survival; PBSC: peripheral blood stem cell; PFS: progression-free survival.

tMN are aggressive, treatment-refractory malignancies with dismal survival rates.[29,30] Although tMN were historically believed to occur as a result of DNA damage from cytotoxic treatment, recent evidence shows that mutations that drive tMN pathogenesis, such as CH, are present prior to treatment, persist, and may expand.[31-33] In HCT, evidence largely suggests that CH mutations increase in number and VAF after HCT, but longer-term may become more stable (*Online Supplementary Table S1; Online Supplementary Appendix*). This post-HCT expansion of CH is hypothesized to increase risk for progression to tMN.

Risk for tMN is the most consistently studied outcome in the context of CH and auto-HCT. Of the 12 studies reporting effects of CH on tMN, eight included sufficient data for meta-analysis. One of the excluded articles had no tMN cases in patients without CH, so an OR could not be calculated (there were three tMN cases in patients with CH).[21] The combined OR for the development of tMN for auto-HCT patients with CH compared to those without was 3.65 (95% CI: 2.18-6.10) (Figure 3A). As assessed by funnel plots, publication bias (*Online Supplementary Figure S1*) and heterogeneity (I^2=23%) for the tMN outcome were low; however, differences in the impact of CH on tMN are apparent when considering cancer type. In lymphoma, risk for tMN was increased 4- to 7-fold in patients with CH at auto-HCT.[19,34,35] Using meta-analysis, the odds estimate for tMN in lymphoma patients with CH compared to those without CH is 4.96 (95% CI: 2.14-11.52) (*Online Supplementary Figure S2*). In line with biology of DNA damage driving tMN, the effect of CH on tMN risk persisted when considering only DNA repair pathway mutations (DRP; i.e., *PPM1D, TP53, RAD21, BRCC3*);[34] in fact, the most frequent mutations in tMN cases were *PPM1D* and *TP53*, and having more than one CH mutation increased 10-year cumulative incidence

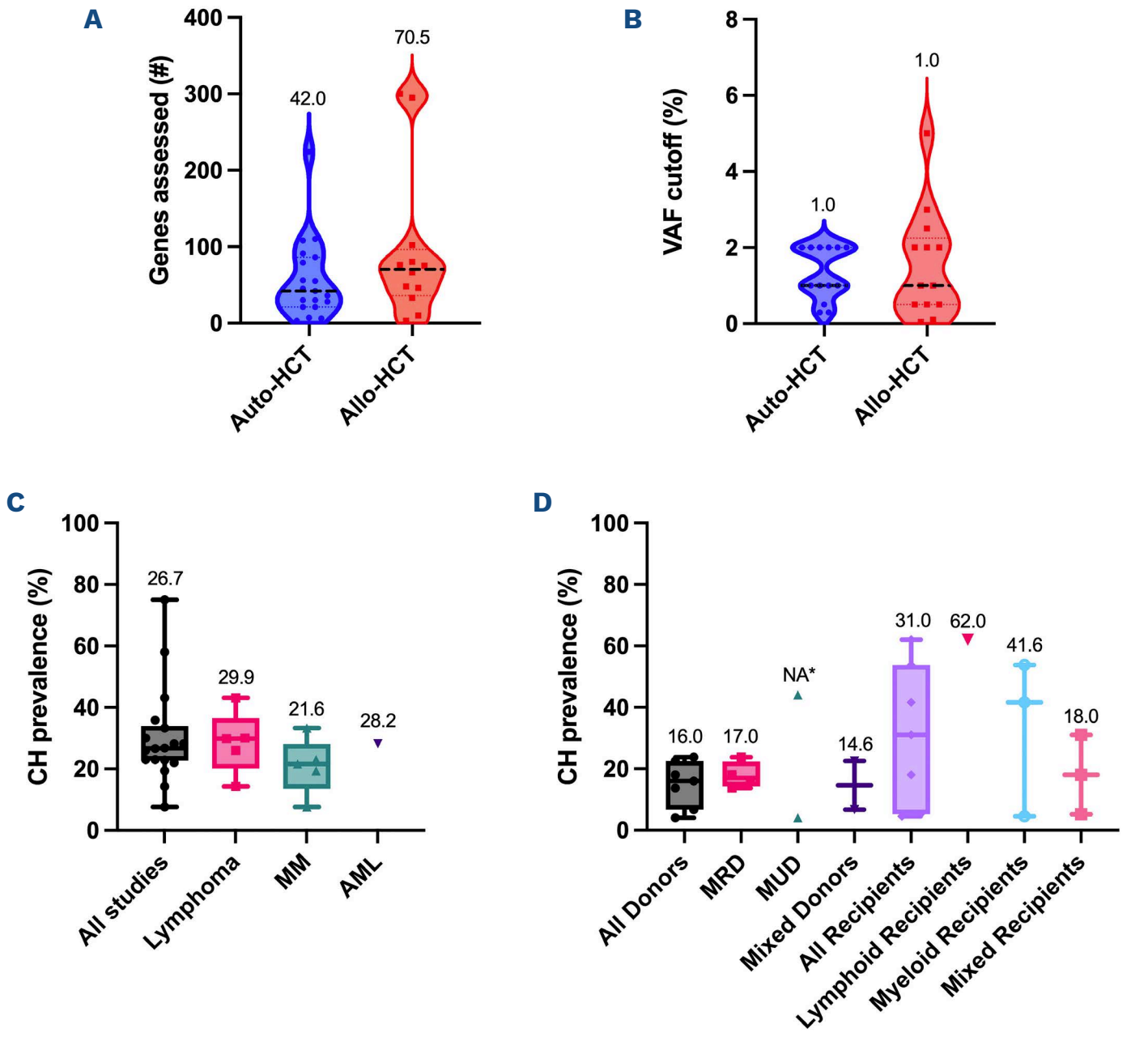


Figure 2. Clonal hematopoiesis metrics and results in published studies. (A) Number of genes assessed for clonal hematopoiesis (CH) mutations in autologous (auto-) and allogeneic (allo-) hematopoietic cell transplantation (HCT). (B) Variant allele frequency (VAF) cutoff used to define CH by HCT type. (C) Prevalence of CH reported in autologous (auto)-HCT studies. Data is presented for all auto-HCT studies and studies that included lymphoma, multiple myeloma (MM), or acute myeloid leukemia (AML) patients only. (D) Prevalence of CH reported in allogeneic (allo)-HCT studies. Data is presented for donors and recipients. Numbers presented are medians; bars are the minimum and maximum values. MRD: matched-related donors; MUD: matched-unrelated donors. *Results for MUD come from a single study that defined CH at a VAF of ≥2% and ≥0.1%.

of tMN (*Online Supplementary Table S2*).[19,35] The study that reported no difference in tMN incidence in patients with lymphoma by CH status only included seven cases of tMN, potentially limiting power to detect a statistical difference.[24] Contrary to findings in lymphoma, studies in MM did not find a significant association between CH before auto-HCT and risk for tMN (pooled OR=1.66; 95% CI: 0.74-3.72) (*Online Supplementary Figure S2*).[20,36,37] Risk for tMN was increased in MM HCT patients who received immunomodulatory (IMiD) drugs, but this risk was not potentiated by CH.[20]

Four studies included cohorts of mixed lymphoid diagnoses and found associations between CH and risk for tMN after HCT despite various study designs.[21,38-40] Most of the CH mutations had low VAF (<2%) at auto-HCT and non-*DNMT3A* mutation VAF significantly increased from auto-HCT to tMN (1% to 37%, *P*=0.002);[39] acquisition of additional CH mutations commonly occurred before tMN diagnosis.[38] Another study that found a 6-fold increased risk of tMN (*P*=0.003) for patients with non-*DNMT3A*- and non-*TET2*-CH at auto-HCT provides further evidence supporting the DNA damage hypothesis for tMN, since the association with tMN risk was only observed after exclusion of non-DRP CH mutations.[40] Thus, presence of CH, especially in DRP genes, may be associated with increased risk for tMN after auto-HCT but the absolute risk for tMN, which are extremely rare events, remains low. Factors driving selective clonal expansion and evolution to promote progression to tMN have not been fully elucidated.

Survival

Disparate results on the impact of CH on survival after auto-HCT exist (Table 1; *Online Supplementary Table S1*). Using meta-analysis of available data, auto-HCT patients with CH are at increased risk of death compared to those without CH (HR=1.38; 95% CI: 1.20-1.58) (Figure 3B); however, due to skewing of the funnel plot, publication bias cannot be ruled out (*Online Supplementary Figure S1*). Two studies report associations between CH and non-relapse mortality (NRM),[19,41] especially driven by tMN and cardiovascular disease. While studies found that CH overall was an independent predictor of OS,[19,24] some found that survival effects were specifically driven by DRP-CH,[24,34] which may further speak to the impact of tMN or DNA damage repair effects on poor outcomes (*Online Supplementary Table S2*). The effect of CH on survival after auto-HCT was persistent when stratified by lymphoid cancer type (*Online Supplementary Figure S3*), but the effect seems to be mediated by treatment

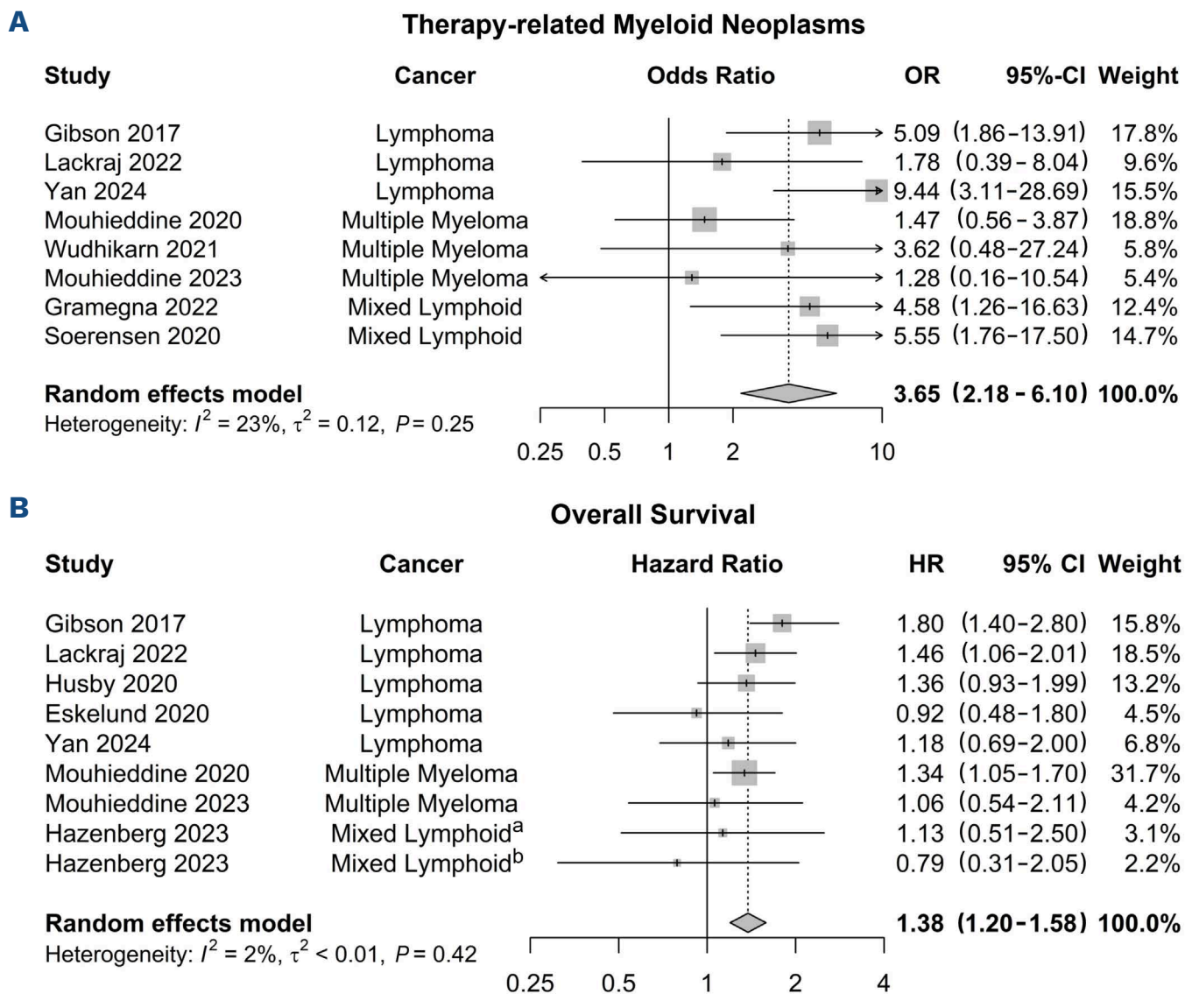


Figure 3. Meta-analyses of studies assessing clonal hematopoiesis as a risk factor for clinical outcomes in patients treated with autologous hematopoietic cell transplantation. (A) Forest plot for the outcome of therapy-related myeloid neoplasms. (B) Forest plot for the outcome of overall survival. [a]Poor peripheral blood stem cell mobilizers; [b]normal peripheral blood stem cell mobilizers. OR: odds ratio; CI: confidence interval; HR: hazard ratio.

in MM. Specifically, significant associations between CH and OS or progression-free survival (PFS) have been observed in MM patients treated with auto-HCT, but the negative impact dissipates when considering patients who received IMiD maintenance therapy.[20,22,36,37] Furthermore, the effect of CH on NRM has not been observed in patients with MM.[28,36] There was also no association with OS detected in patients with mantle cell lymphoma.[42]

Taken together, these data suggest that CH may be particularly important for auto-HCT patients with lymphoma, especially if the mutations occur in the DRP pathway; referral to cardiology and monitoring for tMN development may be especially critical. The negative effects of CH on survival in patients with MM may be abrogated by treatment with IMiD maintenance.

Allogeneic hematopoietic stem cell transplantation

Clonal hematopoesis metrics and prevalence

In allo-HCT, most studies analyzed <100 genes for CH; the most common VAF thresholds were >0.5% and >2% (23%, 3/13 studies each; Figure 2A, B). Most studies with prevalence data assessed CH before allo-HCT (69%, 9/13), with two studies reporting CH status before and after (15%), and two studies (15%) only assessing CH after allo-HCT. In allo-HCT, CH can be measured in the donors and/or recipients. Most allo-HCT studies measured CH in recipients (9/13, 69%), of which three also included measurement of CH in all the paired donors; four studies (31%) focused primarily on CH measurement in donors (*Online Supplementary Table S1*). The median CH prevalence reported for allo-HCT donors was 16.0% (range, 4.0-23.8%) and was similar in studies of matched-related donors (MRD, 17.0%), most of whom were over 50 years (Figure 2D). A study with young matched unrelated donors (MUD) identified CH at a VAF >2% in one donor, but in 44% at a VAF ≥0.1%.[43] The studies with mixed donor pools both assessed low-VAF CH (≥0.5%), but donors were younger in the study with the lower prevalence.[44,45] Studies measuring CH in recipients were heterogenous, with differences in factors such as recipient diagnosis, treatment, and timing of sample relative to HCT, resulting in diverse measures of CH prevalence (Figure 2D). The median prevalence of CH in recipients (31%; range, 4.5-62%) was higher than donors. The study with a low prevalence in myeloid malignancy patients assessed CH post-HCT from young donors.[46] All studies (4/4) that measured CH in recipients prior to allo-HCT had a CH prevalence >15% (range 18-62%) (*Online Supplementary Table S2*).

Donor cell leukemia

Donor cell leukemia (DCL) is a rare but serious complication that may arise after allo-HCT, wherein the recipient is diagnosed with a *de novo* leukemia that develops from engrafted cells of donor origin. Data consistently show that donor CH successfully engrafts in recipients via HCT regardless of donor type (*Online Supplementary Appendix*); thus, it has been hypothesized that donor CH may increase risk for DCL. All three of the included articles that investigated DCL suggest an association with donor CH. Specifically, donor CH was associated with higher incidence of DCL[47] and progression to MDS[48] in MRD HCT (*Online Supplementary Table S1*). A study with MRD and MUD found that recipient DCL mutations were detected in 83% (5/6) of donors.[44] Thus, similar to tMN after auto-HCT, DCL may be increased after allo-HCT from a CH-positive donor, but this event remains rare so identification of additional factors or second hits that drive progression is warranted.

Relapse

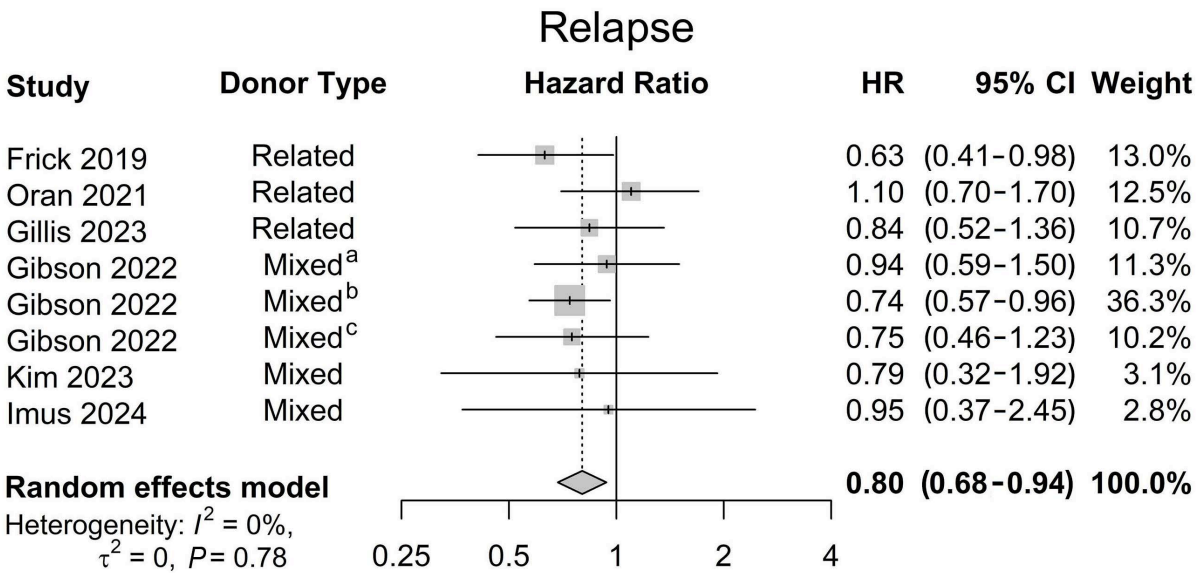
Relapse of the original malignancy is the most frequent cause of treatment failure and mortality after allo-HCT, occurring in up to 45% of patients.[49] Identifying factors that contribute to recipients' immune system evading after initial response to HCT is a critical first step to decreasing risk for relapse.

Although most published data do not show statistically significant associations between donor CH status and relapse (*Online Supplementary Table S2*),[45,50-53] pooled analysis suggests there may be an effect. Meta-analysis of the effect of CH on relapse across allo-HCT studies suggests decreased risk for relapse (HR=0.80; 95% CI: 0.68-0.94) associated with CH (Figure 4A), with little evidence of publication bias (*Online Supplementary Figure S4*). This result persists when removing one study that quantified CH in recipients rather than donors[54] (HR=0.76; 95% CI: 0.60-0.96) and a trend persists when assessing studies that included only related donors (HR=0.83; 95% CI: 0.61-1.14) (*Online Supplementary Figure S5*). The beneficial effect of CH in MRD was largely driven by *DNMT3A*-CH,[47] which was also seen in patients with various donor types who were treated with calcineurin-based graft-*versus*-host disease (GVHD) prophylaxis.[44] Pooled analysis estimated a 33% decreased risk of relapse (HR=0.67; 95% CI: 0.48-0.94) for patients receiving allo-HCT from *DNMT3A*-CH donors. Conversely, donor *ASXL1*- and *TP53*-CH showed a trend for increased relapse in AML patients treated with allo-HCT.[55] Taken together, the literature suggests that donor CH may influence relapse in allo-HCT; however, the impact likely varies based on multiple factors, such as CH mutation, donor type, and treatments received.

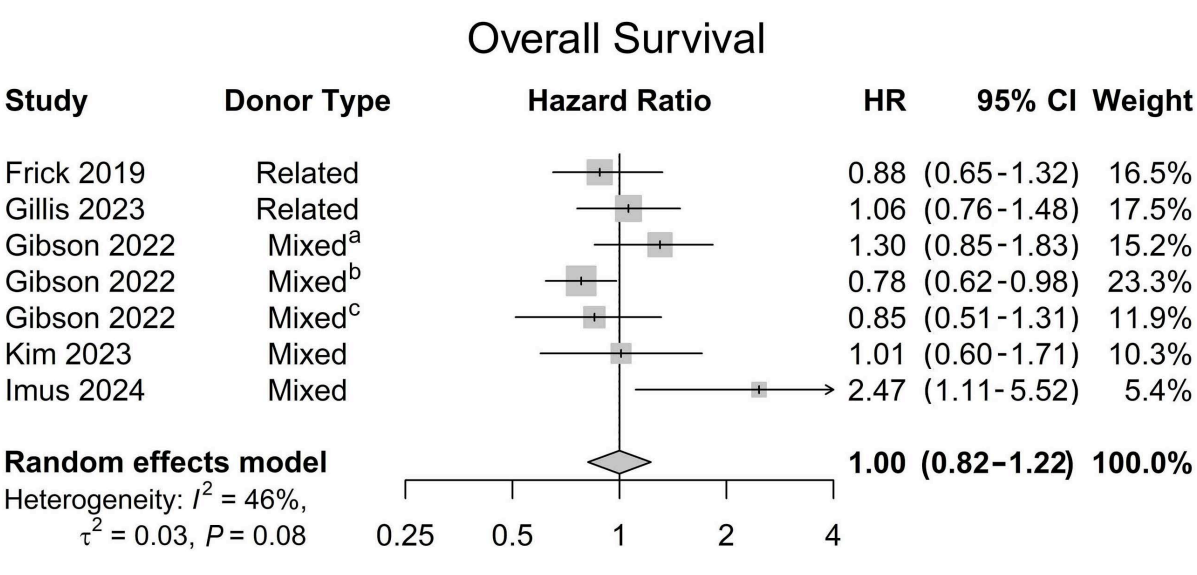
Survival

Most data do not suggest an impact of CH on survival after allo-HCT, with only one study (1/7) reporting an association between CH overall with OS (Table 2; *Online Supplementary Table S1*). The study showing an effect between CH and OS in allo-HCT differed from the others because CH was measured in recipients, rather than donors, prior to HCT.[54] Meta-analysis also suggests that CH does not impact OS in allo-HCT (HR=1.00; 95% CI: 0.82-1.22), with moderate heterogeneity (I^2=46%) (Figure 4B; *Online Supplementary Figure S4*); this result is unchanged when removing the study that measured CH in recipients[54] (HR=0.93; 95% CI: 0.80-

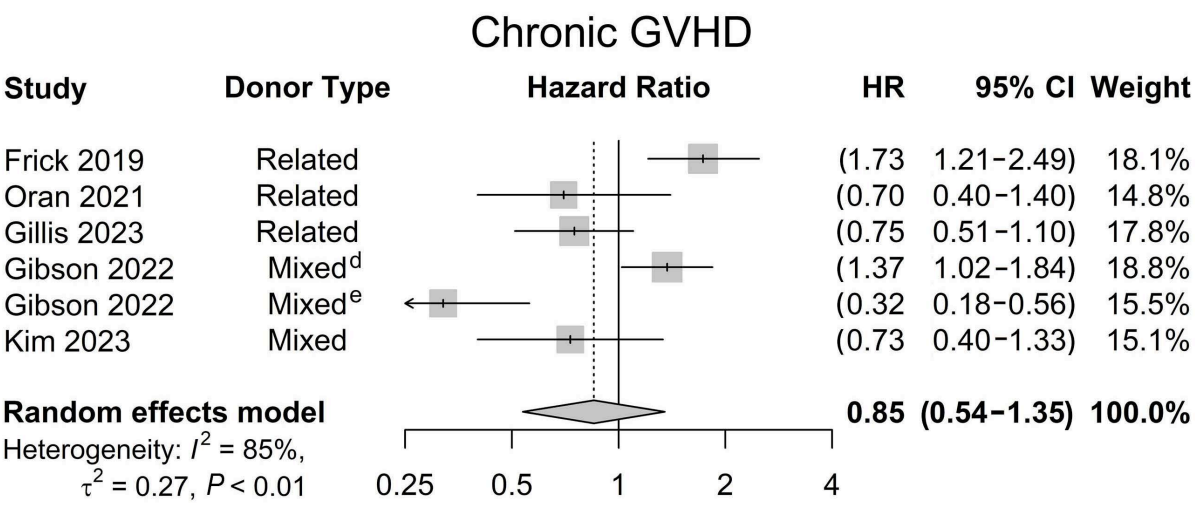
A



B



C



D

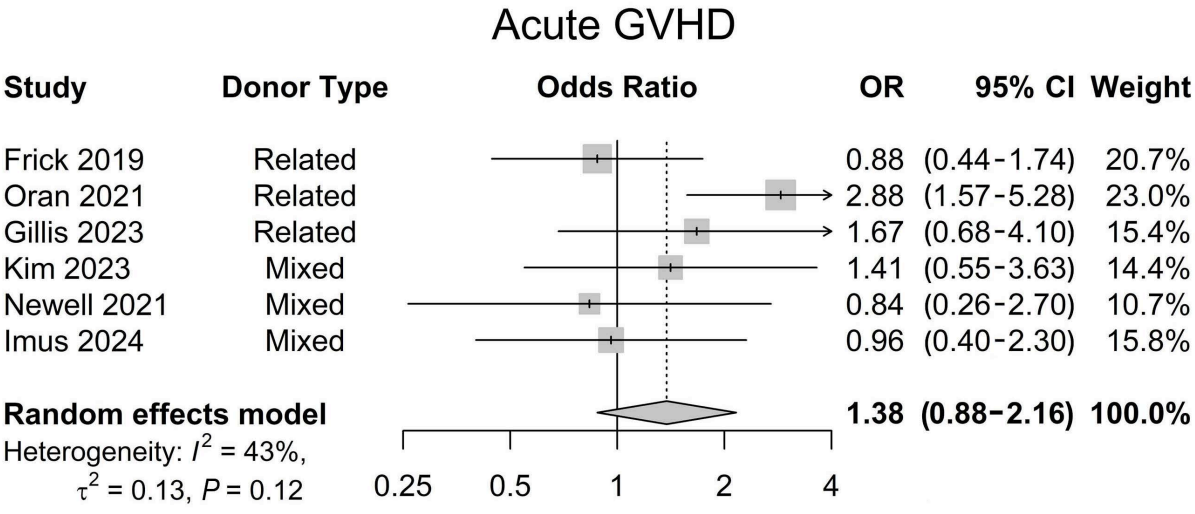


Figure 4. Meta-analyses of studies assessing clonal hematopoiesis as a risk factor for clinical outcomes in patients treated with allogeneic hematopoietic cell transplantation. (A) Forest plot for the outcome of relapse. (B) Forest plot for the outcome of overall survival. (C) Forest plot for the outcome of chronic graft-*versus*-host disease (GVHD). (D) Forest plot for the outcome of acute GVHD. [a]Other clonal hematopoiesis (CH) (non-*DNMT3A*, non-*TET2*); [b]*DNMT3A*-CH only; [c]*TET2*-CH only; [d]*DNMT3A*-CH, no post-transplant cyclophosphamide; [e]*DNMT3A*-CH, received post-transplant cyclophosphamide. OR: odds ratio; CI: confidence interval; HR: hazard ratio.

1.08). As with other outcomes, gene- and subgroup-specific effects between CH and survival have been found (*Online Supplementary Table S2*). For example, donor *DNMT3A*-CH was associated with improved OS (pooled HR=0.80; 95% CI: 0.66-0.98)[44,47] and PFS after allo-HCT, largely driven by patients who did not receive post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis.[44] An OS benefit was also noted in MDS and AML patients who received HCT in non-CR from donors with CH.[47] Suggestive trends for improved disease-free survival, NRM, and chronic GVHD (cGVHD) relapse-free survival have also been reported, specifically in early-stage patients whose MSD had CH, but these findings were limited by small sample sizes.[53] Finally, a study that showed beneficial effects of *TET2*- and *ASXL1*-CH on OS, but recipient pre-HCT samples were used to classify CH status so impact of donor CH on survival was unclear.[50]

Adverse events: graft-versus-host disease

GVHD is a major cause of morbidity, NRM, and inferior quality of life in patients after allo-HCT.[56,57] Presenting with multi-organ tissue inflammation or fibrosis, GVHD occurs as one of three syndromes: acute GVHD (aGVHD), cGVHD, or GVHD overlap syndrome. GVHD occurs when transplanted donor cells recognize the host (i.e., recipient's) cells as foreign and initiate an immune reaction against the host tissues. Thus, it is hypothesized that CH-mediated immune activation[58] in donor cells may contribute to increased risk for GVHD.

The literature on the impact of CH on risk for GVHD shows conflicting results (Table 2; *Online Supplementary Table S1*). Meta-analysis does not indicate that donor CH increases risk for cGVHD (HR=0.85; 95% CI: 0.54-1.35), but high heterogeneity in the data exists (I^2=85%) (Figure 4C; *Online Supplementary Figure S4*). Sensitivity analyses without the stratified study[44] (HR=0.94; 95% CI: 0.58-1.54) and confined to studies with related donors (HR=1.01; 95% CI: 0.55-1.86) also do not detect an association between donor CH overall and risk for cGVHD, but high heterogeneity persists (I^2=77% and 83%, respectively) (*Online Supplementary Figure S5*). However, donor CH was a predictor of risk for cGVHD in two studies, including one confined to MRD in which the effect was largely driven by donor *DNMT3A*-CH (*Online Supplementary Table S2*).[47,51] The gene-specific effect of donor *DNMT3A*-CH on risk for cGVHD was also found in a mixed cohort of patients who did not receive PTCy.[44] Studies in MSD, young MUD, and mixed donor types did not show an association between donor CH and cGVHD risk.[43,45,52,53] When including all studies with sufficient data to quantify aGVHD risk, there is a trend toward increased risk for aGVHD with CH (OR=1.38; 95% CI: 0.88-2.16); however, moderate heterogeneity is noted (I^2=43%) (Figure 4D; *Online Supplementary Figure S4*). These results are consistent when including only studies that quantified CH using donor samples[45,47,52,53] (OR=1.59; 95% CI: 0.90-2.82), and studies with only related donors (HR=1.64; 95% CI: 0.77-3.46), but there is high heterogeneity (*Online Supplementary Figure S5*). Thus, the impact of donor CH on GVHD risk remains unclear, but data indicate that differences likely exist depending on factors such as donor type, prophylaxis received, and CH mutation.

Discussion

In this review, we summarize the literature that investigates the impact of CH on outcomes of patients treated with HCT. Across studies, the median prevalence of CH in donors was 23% (range, 4-75%), corresponding to almost one quarter of HCT donors harboring CH mutations at the time of HCT. CH was more prevalent in auto-HCT than allo-HCT donors and was detected in both younger MUD and older MRD. Notably, in auto-HCT, CH is measured in patients who have been exposed to chemotherapy or radiation and, therefore, are more likely to have CH,[14] and characteristics of the mutations may be different compared to allo-HCT where CH is measured in healthy donors. Data across auto- and allo-HCT show that CH mutations generally expand in recipients after HCT and may lead to the acquisition of new, more aggressive cancer-promoting mutations (*Online Supplementary Appendix*). Based on existing evidence, we posit that these CH dynamics likely explain the observed increased risk for secondary hematologic malignancies, including tMN in lymphoma patients treated with auto-HCT and DCL in allo-HCT recipients. Aside from these consistencies, the current data is largely mixed regarding the impact of donor CH on other clinical outcomes with many nuances.

In auto-HCT, clinical outcomes associated with CH status include decreases in PBSC mobilization (5/7 studies report at least gene-specific effects), OS in patients with lymphoma (3/5 studies report at least gene-specific effects), OS in patients with MM if not treated with IMiD, and increases in time to platelet engraftment (3/3 studies). While lymphoma patients with CH have an almost 5-fold increased risk for tMN after auto-HCT, the impact of CH on risk for tMN in patients with MM receiving auto-HCT is less certain. This may be explained, at least partly, by the fact that MM patients rarely receive cytotoxic chemotherapy or alkylating agents (except for melphalan as part of auto-HCT), which are strongly associated with tMN risk, whereas these treatments are standard for patients with lymphoma. In fact, experimental data suggests that CH tMN risk in MM may be treatment- and mutation-specific (e.g., higher in *TP53*-CH that survives myeloablative conditioning).[59] There is also no direct evidence to support an association between CH and risk of relapse for patients treated with auto-HCT; however, some studies report higher NRM in patients with CH, suggesting that mortality in patients with CH may not be due to relapse, but perhaps driven by tMN or cardiovascular events, which are both increased with CH.[13,32]

Although CH mutations engraft, expand, and persist, there

are limited clinical outcomes consistently associated with donor CH status in allo-HCT. Time to leukocyte engraftment and DCL risk were associated with donor CH status in MRD,[47] but not quantified in other allo-HCT studies. Although not statistically significant within most individual studies, pooled analysis suggests that donor CH may associate with an estimated 20% decreased risk of relapse after allo-HCT. Data suggests that donor *DNMT3A*-CH largely drives the observed associations with relapse, with the effect specifically seen in patients treated with calcineurin-based GVHD prophylaxis.[44,47] These findings are particularly important with the increased use of PTCy,[60] given that the association between donor CH and increased cGVHD and improved relapse, PFS, and OS were only observed in patients not treated with PTCy.[44] These nuanced results emphasize the importance of considering differences in patient characteristics, treatments, and CH mutations when translating findings to inform patient care.

The impact of donor CH with risk for aGVHD and cGVHD after allo-HCT also has mixed results across the literature, with moderate to high heterogeneity detected in meta-analyses. These differences may, in part, be due to differences in the study populations, which impact patient risk and, therefore, statistical power to detect associations. For example, the one study that reported a statistical difference in aGVHD risk by donor CH status included late-aGVHD and a relatively homogenous population.[52] Discordance in cGVHD findings across studies is challenging to explain, although the studies that do report an increased risk from donor CH found that the effect was driven by specific subgroups, including patients with *DNMT3A*-CH donors[47] who did not receive PTCy[44] or only when considering requirement for immunosuppression therapy.[51] Three studies that did not show a statistically significant association between donor CH and cGVHD had results in the opposite direction, where recipients with CH-negative donors trended toward higher incidence of cGVHD.[43,52,53] Other clinical outcomes explored in allo-HCT were reported in single studies and not associated with donor CH.

Overall, few clinical outcomes have been consistently associated with donor CH across HCT studies, with more disparate findings in allo-HCT than auto-HCT. Numerous factors could contribute to these differences. For example, study population affects baseline risk for outcomes, impacting the number of events and statistical power. Study characteristics important to consider include patient and donor demographics, diagnoses and treatment history, type of donors, conditioning regimens and intensity, graft source, GVHD prophylaxis (e.g., use of PTCy), duration of follow-up, etc. These criteria tend to be more diverse in allo-HCT studies and, thus, may help explain lack of associations and replication across studies. Another important difference between studies is the binary classification criteria of CH status. The genes, mutation types, and VAF thresholds used to define CH vary drastically across studies; however, most condense these criteria to classify individuals simply as CH-positive or -negative. The gene-specific effects detected in some studies provide evidence that this approach is not optimal for identifying clinically important CH risk. Statistical power also plays a role in this context. Across the CH literature, including the studies here, *DNMT3A* is by far the most mutated gene. As such, power to detect gene-specific differences is higher when looking at *DNMT3A* than other CH mutations. For example, the largest allo-HCT studies detected *DNMT3A*-CH in 8% (40/500) and 9% (157/1,727) of donors; the next most commonly mutated gene was *TET2*, which was mutated in 2% of donors in both studies.[44,47] Therefore, statistical power is limited to detect gene-specific differences in even the largest studies, let alone most other studies that are smaller. This poses challenges since evidence across the CH literature points to stronger effects for less commonly mutated CH genes (e.g., *TP53, U2AF1*, and spliceosome mutations). Finally, substantial evidence suggests that low-VAF (i.e., <2%) CH in young and older donors engrafts via HCT and commonly expands; however, the various limits of CH detection across studies pose challenges for defining the clinically meaningful VAF cutoff for CH in HCT.

Conclusion and call to action

The literature summarized suggests that CH may impact HCT outcomes; however, studies lack consistent conclusions and suffer from limited power. As well, CH mutation-specific findings (e.g., *DNMT3A*) may arise from higher prevalence of such mutations, rather than true absence of effect for less common mutations. To address these limitations, we suggest that next studies incorporate rigorous case-control designs and leverage larger combined data sets, which would require extensive collaboration and data sharing. The optimal gene panel and VAF threshold for next generation sequencing testing in HCT-CH research has yet to be defined, but standardized approaches across studies would improve reproducibility and make future clinical translation of findings more straightforward. Currently, we support use of any myeloid gene panel, as these contain the most clinically important CH genes and regions; a panel that also captures *PPM1D* (especially the fifth and sixth exons), which are common in CH but not necessarily myeloid malignancies, is preferred. Evidence suggests that low-VAF CH (e.g., ≥0.5%) engrafts and persists in recipients, but the clinical impact of these mutations is unclear; this lower CH threshold (i.e., <1% or 2% VAF) may be particularly important for studies in allo-HCT (i.e., healthy donors) and MUD (i.e., young donors). Weighing sensitivity, specificity, and cost-effectiveness, we recommend sequencing using molecular barcodes and coverage sufficient to detect VAF ≥1%. Uniform methods to filter and classify CH mutations are equally as important; when in doubt, focusing on previously annotated variant lists[61,62] is a reasonably conservative approach. Xenogenic mouse models may also provide a useful tool for studying the link between CH and adverse

HCT outcomes (e.g., GVHD), especially for less common CH mutations.[58,63,64] There may also be important effects of CH on other clinical outcomes, which deserve further study. For example, cGVHD could be explored with respect to severity and phenotype of the syndrome or with attention to patient-reported outcomes. The impact of CH on HCT late effects including secondary malignancies and adverse cardiovascular outcomes, among others, also warrants additional study. Finally, we acknowledge that, while much attention has been paid to the impact of CH in older MRD in allo-HCT, clinical application of these findings is much more complex: assuming CH were clinically available as part of routine donor evaluation, avoiding older MRD with CH would reflect only one major aspect of clinical decision-making. Other major considerations would include patient-level disease risk, urgency in time to HCT, baseline probability to identify well matched MUD, availability, and prioritization of alternative donors (e.g., related haploidentical and mismatched unrelated donors), and the possibility of CH being detected in any of these donors. While CH is not yet a validated and actionable biomarker in this regard, a future state following greater evidence development could include CH, akin to other donor selection strategies above the traditional uses of donor age and HLA matching (e.g., selection of killer cell immunoglobulin-type receptor-advantageous donors or *CCR5*Δ32 homozygous donors for HIV-infected recipients). In summary, evidence suggests that CH may be impactful for patients treated with auto-HCT but, in allo-HCT especially, the heterogeneity of current literature poses insurmountable challenges to make concrete recommendations for or against donor CH testing in HCT.

Disclosures

No conflicts of interest to disclose.

Contributions

NG conceptualized and designed the manuscript, helped screen articles for inclusion, led writing the manuscript, tables, and figures, and oversaw meta-analyses. AE designed the review search strategy, conducted the search, screened potentially eligible articles, and contributed to writing the manuscript, tables, and figures. ZJT conducted the meta-analysis and contributed to figure generation and design. JAP contributed to writing the manuscript and provided a clinical perspective throughout. All authors reviewed and approved the final version of the manuscript.

Funding

This work has been supported in part by the Biostatistics and Bioinformatics Shared Resource at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292).

Data-sharing statement

Data used for this study consists of summary statistics from peer-reviewed publications. Citations for the data are included throughout the article. Questions can be directed to the corresponding author.

References

1. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol. 2013;31(21):2662-2670.
2. Sekeres MA, Guyatt G, Abel G, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020;4(15):3528-3549.
3. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. Blood. 2017;129(13):1753-1762.
4. Hashmi SK, Lee SJ, Savani BN, et al. ASBMT Practice Guidelines Committee survey on long-term follow-up clinics for hematopoietic cell transplant survivors. Biol Blood Marrow Transplant. 2018;24(6):1119-1124.
5. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9-16.
6. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488-2498.
7. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477-2487.
8. Fabre MA, de Almeida JG, Fiorillo E, et al. The longitudinal dynamics and natural history of clonal haematopoiesis. Nature. 2022;606(7913):335-342.
9. Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016;7:12484.
10. Steensma DP, Ebert BL. Clonal hematopoiesis as a model for premalignant changes during aging. Exp Hematol. 2020;83:48-56.
11. Wong WJ, Emdin C, Bick AG, et al. Clonal haematopoiesis and risk of chronic liver disease. Nature. 2023;616(7958):747-754.
12. Bolton KL, Koh Y, Foote MB, et al. Clonal hematopoiesis is associated with risk of severe Covid-19. Nat Commun. 2021;12(1):5975.
13. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. N Engl J Med. 2017;377(2):111-121.
14. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. Cell Stem Cell. 2017;21(3):374-382.
15. Mach-Pascual S, Legare RD, Lu D, et al. Predictive value of clonality assays in patients with non-Hodgkin's lymphoma

undergoing autologous bone marrow transplant: a single institution study. Blood. 1998;91(12):4496-4503.
16. Heini AD, Porret N, Zenhaeusern R, Winkler A, Bacher U, Pabst T. Clonal hematopoiesis after autologous stem cell transplantation does not confer adverse prognosis in patients with AML. Cancers (Basel). 2021;13(13):3190.
17. Barlogie B, Tricot G, Haessler J, et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3,000 patients treated since 1989. Blood. 2008;111(1):94-100.
18. Gifford G, Hesson L, Wong JWH, et al. Poor mobilization of autologous CD34(+) peripheral blood stem cells in haematology patients undergoing autologous stem cell transplantation is associated with the presence of variants in genes implicated in clonal haematopoiesis of indeterminant potential. Br J Haematol. 2021;193(4):841-844.
19. Gibson CJ, Lindsley RC, Tchekmedyian V, et al. Clonal hematopoiesis associated with adverse outcomes after autologous stem-cell transplantation for lymphoma. J Clin Oncol. 2017;35(14):1598-1605.
20. Mouhieddine TH, Sperling AS, Redd R, et al. Clonal hematopoiesis is associated with adverse outcomes in multiple myeloma patients undergoing transplant. Nat Commun. 2020;11(1):2996.
21. Hazenberg CLE, de Graaf AO, Mulder R, et al. Clonal hematopoiesis in patients with stem cell mobilization failure: a nested case-control study. Blood Adv. 2023;7(7):1269-1278.
22. Stelmach P, Richter S, Sauer S, et al. Clonal hematopoiesis with DNMT3A and PPM1D mutations impairs regeneration in autologous stem cell transplant recipients. Haematologica. 2023;108(12):3308-3320.
23. Ortmann CA, Dorsheimer L, Abou-El-Ardat K, et al. Functional dominance of CHIP-mutated hematopoietic stem cells in patients undergoing autologous transplantation. Cell Rep. 2019;27(7):2022-2028.
24. Lackraj T, Ben Barouch S, Medeiros JJF, et al. Clinical significance of clonal hematopoiesis in the setting of autologous stem cell transplantation for lymphoma. Am J Hematol. 2022;97(12):1538-1547.
25. Bernstein SH, Nademanee AP, Vose JM, et al. A multicenter study of platelet recovery and utilization in patients after myeloablative therapy and hematopoietic stem cell transplantation. Blood. 1998;91(9):3509-3517.
26. Wallington-Beddoe CT, Gottlieb DJ, Garvin F, Antonenas V, Sartor MM. Failure to achieve a threshold dose of CD34+CD110+ progenitor cells in the graft predicts delayed platelet engraftment after autologous stem cell transplantation for multiple myeloma. Biol Blood Marrow Transplant. 2009;15(11):1386-1393.
27. Okada Y, Kimura F, Kurita N, et al. Adverse impact of delay of platelet recovery after autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma and multiple myeloma. Cytotherapy. 2023;25(11):1212-1219.
28. Li N, Liang L, Xiang P, Wang Y, Liu L, Fang B. Clonal haematopoiesis of indeterminate potential predicts delayed platelet engraftment after autologous stem cell transplantation for multiple myeloma. Br J Haematol. 2023;201(3):577-580.
29. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
30. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer. 2017;17(9):513-527.
31. Wong TN, Ramsingh G, Young AL, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature. 2015;518(7540):552-555.
32. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study. Lancet Oncol. 2017;18(1):112-121.
33. Takahashi K, Wang F, Kantarjian H, et al. Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study. Lancet Oncol. 2017;18(1):100-111.
34. Husby S, Favero F, Nielsen C, et al. Clinical impact of clonal hematopoiesis in patients with lymphoma undergoing ASCT: a national population-based cohort study. Leukemia. 2020;34(12):3256-3268.
35. Yan C, Richard MA, Gibson CJ, et al. Clonal hematopoiesis and therapy-related myeloid neoplasms after autologous transplant for Hodgkin lymphoma. J Clin Oncol. 2024;42(20):2415-2424.
36. Wudhikarn K, Padrnos L, Lasho T, et al. Clinical correlates and prognostic impact of clonal hematopoiesis in multiple myeloma patients receiving post-autologous stem cell transplantation lenalidomide maintenance therapy. Am J Hematol. 2021;96(5):E157-E162.
37. Mouhieddine TH, Nzerem C, Redd R, et al. Clinical outcomes and evolution of clonal hematopoiesis in patients with newly diagnosed multiple myeloma. Cancer Res Commun. 2023;3(12):2560-2571.
38. Gramegna D, Bertoli D, Cattaneo C, et al. The role of clonal hematopoiesis as driver of therapy-related myeloid neoplasms after autologous stem cell transplantation. Ann Hematol. 2022;101(6):1227-1237.
39. Soerensen JF, Aggerholm A, Rosenberg CA, et al. Clonal evolution in patients developing therapy-related myeloid neoplasms following autologous stem cell transplantation. Bone Marrow Transplant. 2022;57(3):460-465.
40. Soerensen JF, Aggerholm A, Kerndrup GB, et al. Clonal hematopoiesis predicts development of therapy-related myeloid neoplasms post-autologous stem cell transplantation. Blood Adv. 2020;4(5):885-892.
41. Slavin TP, Teh JB, Weitzel JN, et al. Association between clonal hematopoiesis and late nonrelapse mortality after autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2019;25(12):2517-2521.
42. Eskelund CW, Husby S, Favero F, et al. Clonal hematopoiesis evolves from pretreatment clones and stabilizes after end of chemotherapy in patients with MCL. Blood. 2020;135(22):2000-2004.
43. Wong WH, Bhatt S, Trinkaus K, et al. Engraftment of rare, pathogenic donor hematopoietic mutations in unrelated hematopoietic stem cell transplantation. Sci Transl Med. 2020;12(526):eaax6249.
44. Gibson CJ, Kim HT, Zhao L, et al. Donor clonal hematopoiesis and recipient outcomes after transplantation. J Clin Oncol. 2022;40(2):189-201.
45. Kim KH, Kim T, Novitzky-Basso I, et al. Clonal hematopoiesis in the donor does not adversely affect long-term outcomes following allogeneic hematopoietic stem cell transplantation: result from a 13-year follow-up. Haematologica. 2023;108(7):1817-1826.
46. Heumuller A, Wehrle J, Stosch J, et al. Clonal hematopoiesis of indeterminate potential in older patients having received an allogeneic stem cell transplantation from young donors. Bone

Marrow Transplant. 2020;55(3):665-668.
47. Frick M, Chan W, Arends CM, et al. Role of donor clonal hematopoiesis in allogeneic hematopoietic stem-cell transplantation. J Clin Oncol. 2019;37(5):375-385.
48. Boettcher S, Wilk CM, Singer J, et al. Clonal hematopoiesis in donors and long-term survivors of related allogeneic hematopoietic stem cell transplantation. Blood. 2020;135(18):1548-1559.
49. Barrett AJ, Battiwalla M. Relapse after allogeneic stem cell transplantation. Expert Rev Hematol. 2010;3(4):429-441.
50. Grimm J, Bill M, Jentzsch M, et al. Clinical impact of clonal hematopoiesis in acute myeloid leukemia patients receiving allogeneic transplantation. Bone Marrow Transplant. 2019;54(8):1189-1197.
51. Newell LF, Williams T, Liu J, et al. Engrafted donor-derived clonal hematopoiesis after allogenic hematopoietic cell transplantation is associated with chronic graft-versus-host disease requiring immunosuppressive therapy, but no adverse impact on overall survival or relapse. Transplant Cell Ther. 2021;27(8):662 e661-662.
52. Oran B, Champlin RE, Wang F, et al. Donor clonal hematopoiesis increases risk of acute graft versus host disease after matched sibling transplantation. Leukemia. 2022;36(1):257-262.
53. Gillis N, Padron E, Wang T, et al. Pilot study of donor-engrafted clonal hematopoiesis evolution and clinical outcomes in allogeneic hematopoietic cell transplantation recipients using a national registry. Transplant Cell Ther. 2023;29(10):640 e641-640.
54. Imus PH, Pasca S, Tsai HL, et al. Recipient clonal hematopoiesis in allogeneic bone marrow transplantation for lymphoid malignancies. Blood Adv. 2024;8(14):3849-3858.
55. Tanaka T, Morita K, Loghavi S, et al. Clonal dynamics and clinical implications of postremission clonal hematopoiesis in acute myeloid leukemia. Blood. 2021;138(18):1733-1739.
56. Pidala J, Kim J, Anasetti C, et al. The global severity of chronic graft-versus-host disease, determined by National Institutes of Health consensus criteria, is associated with overall survival and non-relapse mortality. Haematologica. 2011;96(11):1678-1684.
57. Malard F, Holler E, Sandmaier BM, Huang H, Mohty M. Acute graft-versus-host disease. Nat Rev Dis Primers. 2023;9(1):27.
58. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842-847.
59. Diamond B, Zicchedda B, Maclachlan K, et al. Tracking the evolution of therapy-related myeloid neoplasms using chemotherapy signatures. Blood. 2023;141(19):2359-2371.
60. Bolanos-Meade J, Hamadani M, Wu J, et al. Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis. N Engl J Med. 2023;388(25):2338-2348.
61. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
62. Bick AG, Weinstock JS, Nandakumar SK, et al. Inherited causes of clonal haematopoiesis in 97,691 whole genomes. Nature. 2020;586(7831):763-768.
63. Patel DA, Schroeder MA, Choi J, DiPersio JF. Mouse models of graft-versus-host disease. Methods Cell Biol. 2022;168:41-66.
64. Park E, Evans MA, Doviak H, et al. Bone marrow transplantation procedures in mice to study clonal hematopoiesis. J Vis Exp. 2021;26(171):e61875.
65. Rhee JW, Pillai R, He T, et al. Clonal hematopoiesis and cardiovascular disease in patients with multiple myeloma undergoing hematopoietic cell transplant. JAMA Cardiol. 2024;9(1):16-24.
66. Lueck C, Panagiota V, Dammann E, et al. Increased late noncardiac nonrelapse mortality in patients with atrial fibrillation diagnosed during their hospital stay for allogeneic stem cell transplantation. Transplant Cell Ther. 2022;28(9):609.