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**Title:** The impact of patient ethnicity on haematopoietic cell transplant outcome: A retrospective cohort study on the UK experience

**Authors:** Neema P Mayor, PhD<sup>1,2</sup>, Richard M Szydlo, PhD<sup>1,3</sup>, Yasmin Sheikh MSc<sup>1</sup>, Julia Lee, MSc<sup>4</sup>, Rachel M Pearce MSc<sup>4</sup>, Caitlin Farrow MA<sup>1</sup>, Michaela Agapiou, PhD<sup>1,2</sup>, Kanchan Rao, MD<sup>5</sup>, Kim Orchard, MD<sup>6</sup>, Prof Eduardo Olavarria, MD<sup>7</sup>, Prof Steven GE Marsh, PhD<sup>1,2</sup>, Prof John A Snowden, MD<sup>4,8</sup>

1. Anthony Nolan Research Institute, Royal Free Hospital, London UK
2. UCL Cancer Institute, Royal Free Campus, UK
3. Imperial College, London, UK
4. British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT), Guy's Hospital, London, UK
5. Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
6. University Hospital Southampton NHS Foundation Trust, Southampton, UK
7. Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
8. Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.

Corresponding Author: Dr Neema Mayor  
Anthony Nolan Research Institute  
Royal Free Hospital  
Hampstead  
London  
NW3 2QG  
UK

Email address: [Neema.Mayor@anthonymolan.org](mailto:Neema.Mayor@anthonymolan.org)

Telephone no.: +44-20-7284-8328

## Abstract

### *Background*

Patient ethnicity has been correlated with different outcomes following Haematopoietic Cell Transplantation (HCT), with patients from minority ethnic backgrounds reported to have worse outcomes compared to White patients. To date, studies have been predominantly performed in the US, where healthcare models are different to many European countries, including the UK. Here we evaluate the impact of patient-reported ethnicity on autologous (auto-) and allogeneic (allo-) HCT outcomes in the UK.

### *Methods*

Patients undergoing allo- or auto-HCT between 01/01/2009-31/12/2019 and registered in the BSBMTCT patient registry were analysed as full cohorts and as separate adult and paediatric cohorts. Patient ethnicity was self-defined and grouped into four broad categories: Asian, Black, 'Other' and White. The primary outcome was five-year Overall Survival (OS).

### *Findings*

20,119 first auto-HCT and 13,978 first allo-HCT were analysed. Median times to follow-up were 60 months (35-89 months) for auto-HCT and 32 months (10-68 months) for allo-HCT patients. After adjustment for prognostic factors, Asian patients undergoing allo-HCT (N=1,081) had significantly worse five-year OS (HR 1.16, P=0.012) than White patients (N=11,705). Differences in OS were most pronounced in paediatric patients (N=2,490, HR 1.67, P=0.00018). In the auto-HCT cohort, there were no associations between ethnicity and five-year OS or other outcomes.

### *Interpretation*

This large UK-based analysis suggests significant variation in survival outcomes following allo-HCT between patients of different ethnicities. The causes are unclear and further research to elucidate and correct these health inequalities is warranted.

### *Funding*

Anthony Nolan Charity and BSBMTCT.

## Research in Context

### *Evidence before this study*

Although this study utilised primary data to conduct a novel analysis, a systematic literature review was also carried out to identify relevant published evidence on the impact of ethnicity on outcomes from haematopoietic cell transplant (HCT) to provide context and insight into the methodology used.

Studies published between 01/01/2000 and 30/09/2024 and including any reference to autologous and allogeneic HCT or bone marrow transplant and ethnicity or race were identified using Boolean search terms via the PubMed database in September 2024. Search terms used were: "stem cell transplant" OR "bone marrow transplant" AND ("ethnicity" OR "race"). Studies were excluded if they were not published in English, if ethnicity was not investigated as an independent variable, or if they were opinion/correspondence pieces.

The pre-existing literature paints a mixed picture of disparities in outcomes after stem cell transplant. A number of US studies have indicated poorer outcomes for patients from a minority ethnic background following HCT, including one recent (2024) US-wide retrospective cohort study showing lower overall survival for adult Hispanic patients receiving unrelated cord blood transplants and higher rates of high-grade acute GvHD in Black paediatric patients (1).

There are however studies which suggest that there are no significant differences in rates of overall survival and other outcomes between patients of different ethnicities, including a large 2023 retrospective cohort study of allo HCT recipients in the US which found no significant impact of ethnicity on survival, relapse or non-relapse mortality (2). Limitations of existing studies including small patient diagnosis groups, the interplay of other factors such as socio-economic status and age, and the US-centric nature of existing research should be noted.

### *Added value of this study*

This is the first known study to investigate the effect of ethnicity on HCT outcomes in the UK using population-wide retrospective cohort data. Prior evidence has been from outside of the UK, and therefore limited in its applicability to the unique demographic and health system context of the UK.

### *Implications of all the available evidence*

Our data suggests that outcomes following allogeneic HCT may be poorer for patients of non-White ethnicities, in particular patients from Asian and 'Other' ethnicities. Further research on the causes of this disparity and methods to achieve greater equity is needed. Ethnicity cannot

be viewed in isolation of other factors such as income, educational attainment, language proficiency, geographic location or other socioeconomic factors. Data on these factors in the UK is poor, limiting the opportunity to further investigate potential health inequalities. In addition, this analysis only includes patients who received HCT – it remains unknown whether ethnicity or other factors affect access to HCT in the UK. This should be an area for further research.

## Introduction

Autologous (auto-) and Allogeneic (allo-) Haematopoietic Cell Transplantations (HCTs) are potentially curative treatments for patients with various malignant and non-malignant disorders. Despite emerging cellular therapies, HCT numbers are rising globally(3, 4. While many factors are known to influence the success of both transplant modalities(5, 6), post-transplant complications remain a significant challenge.

Despite HCT being available to patients for decades, little is known about inequities within the treatment pathway that affect outcomes(7, 8). The impact of ethnicity has been investigated in various non-UK populations, but studies have had differing conclusions.

In the auto-HCT setting, data associating ethnicity with outcome have been inconsistent. Whilst some early studies suggested no association between patient ethnicity and outcomes post-HCT in myeloma(9, 10), or across broader disease categories (11), one study supported inferior outcomes of auto-HCT for patients of Asian/Pacific Islander ethnicities(12).

In the allo-HCT setting, studies have mainly focussed on HLA-matched Related Donor (RD-) and/or Unrelated Donor (UD-) HCT. Early studies suggested Hispanic patients undergoing RD-HCT for an acute or chronic leukaemia had worse Overall Survival (OS) probabilities than White patients(13, 14). In more disease-diverse cohorts, Black and African American patients undergoing RD- or UD-HCT were found to have worse OS than White patients(11, 13); this did not persist for UD-HCT in some settings after further statistical adjustment to include HLA matching(11). Reduced OS probabilities for Black patients were also observed in a study of single-unit umbilical cord blood HCT(15).

Recently, the impact of race/ethnicity on OS was investigated in a cohort of 26,945 patients undergoing UD-HCT between 1988 and 2016 at centres in North American or Japan(16). In comparison to White patients, OS probabilities were significantly improved for Japanese patients but significantly reduced for Black and Hispanic patients. The OS advantage for Japanese patients remained even after adjustment for HLA matching, while the poorer OS for Black patients also persisted. The study concluded that survival post UD-HCT is “*strongly influenced by both race and HLA*”.

Studies exploring HCT outcomes and ethnicity, while not always consistent, indicate a potential impact of patient ethnicity on OS. However, to date most analyses have been based upon data from the United States of America (US). Patient access to HCT has been reported to differ according to patient age, socioeconomic status, geography and insurance

coverage(17), and these barriers to access are likely to intersect with ethnicity. The healthcare system in the US is markedly different than in the UK, where the NHS provides healthcare services to all residents, free at the point of use. The UK population also consists of a different mix of ethnic backgrounds. As such, the direct applicability of previous studies on the relationship between ethnicity and transplant outcomes in the UK population is unknown.

The aim of this study was to investigate whether patient-reported ethnicity is correlated with clinical outcomes after auto- and allo-HCT in a UK patient cohort. Although there is a recognised relationship between ethnicity and other demographic factors in the UK, most notably socio-economic status, this study was limited to only look at ethnicity largely due to the lack of retrospective demographic data.

## **Methods**

### *Study design and participants*

All adult and paediatric patients undergoing a first auto-HCT or allo-HCT at a UK transplant centre between 2009 and 2019, were eligible for inclusion in the study (N=37,492, Figure 1). Patients without sufficient data (N=225) or who didn't consent for their data to be submitted to the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) patient outcome registry (N=638), were excluded from the study. Of the 36,629 remaining patients, 708 were not UK residents and were also excluded. Of all registered UK patients, 1,824 did not have ethnicity data recorded (refused to provide, or missing), or the data were uninterpretable and were also removed. The final eligible cohort consisted of 34,097 patients (auto-HCT, N=20,119; allo-HCT, N=13,978). The cohort was analysed as a whole group (Appendix p2-7) and by adult and paediatric (0-18 years) populations (Table 1). Analysis of the OS of patients excluded from the study found no evidence to suggest that excluded patients had significantly different survival prognoses to those included (Appendix p1).

Clinical outcome data were provided by the BSBMTCT registry which routinely collects minimal essential data and long-term follow-up (minimum 10 years) on all patients undergoing HCT in UK member centres. All data are consented by the patient at the time of transplant to be held in the registry and used for research and service evaluation purposes. The study protocol was approved by the BSBMTCT Executive Committee and the BSBMTCT Clinical Trials Committee.

### *Procedures*

UK patient ethnicity data are captured in the BSBMTCT registry using pre-defined categories identified in the US and included only seven categories. Based on this system, ethnicity data

was coded into four broad categories: White (N=29,566), Black (N=1,168), Asian (N=2,000) and 'Other' (N=1,363), which included any other declared ethnicity (including patients of Hispanic, Native American and Native Hawaiian backgrounds – the additional recorded categories within the database) and individuals reporting more than one ethnicity. All ethnicity was self-defined by the patient. Donor ethnicity is not captured within the BSBMTCT patient registry and was therefore not analysed as part of this study.

Patient and donor HLA typing was recorded within the BSBMTCT registry in several formats including, but not limited to, serological typing, National Marrow Donor Program (NMDP) Multiple Allele Codes (MAC) codes and/or four-field typing resolution. Data was not always complete for each HLA loci, nor at a single locus. HLA matching was scored out of 10 for HLA-A, -B, -C, -DRB1 and -DQB1. HLA-DPB1 typing data was poorly recorded and could not be included into matching models. Pairs were matched at the highest resolution possible up to the Protein antigen recognition domain group (P-group) level, depending on the data provided. Sibling pairs that had partial typing data for only 6-9 alleles but were fully matched for these and were listed as being a matched RD, were upgraded to 10/10 matched. The recorded number of mismatches for patient-donor pairs was used if this was provided and there was no typing data. Patients with some degree of typing recorded, but not enough to report a match score out of 10, were marked as indeterminable, while missing data indicated no HLA typing was recorded for the patient, the donor or both, thus a matching score was not possible. Patients classified as receiving a mismatched RD, but whose HLA matching status was found to be 10/10 matched, were reclassified as a RD. No other donor reclassification was performed.

### *Outcomes*

Overall Survival (OS) was the primary study endpoint, defined as the time from transplant to death from any cause. Surviving patients were censored at the point of last follow-up. Secondary outcomes included acute and chronic Graft-versus-Host Disease (GvHD), disease relapse, Transplant-Related Mortality (TRM), Progression-Free Survival (PFS) and neutrophil engraftment. Acute GvHD (aGvHD) was defined as occurring by day 100 post-transplant and was graded using the Glucksberg scale(18). TRM was death without recurrent disease, while PFS was defined as time to treatment failure (death or relapse). Competing risks included death for relapse analyses, while relapse was the competing event for TRM.

### *Statistical analysis*

All patients that remained after reviewing the inclusion and exclusion criteria listed previously, were assessable. The primary outcome of OS was estimated using the Kaplan-Meier method



and the log-rank test. Secondary outcome analyses including competing events were analysed using the cumulative incidence function and Gray's test(19). Proportions of patients with aGvHD were compared using the chi-squared test. Patient ethnicity variables were adjusted in multivariate analyses for confounding factors where univariate analyses gave  $P \geq 0.2$  using Cox regression, Fine and Gray, or logistic regression. Details of the confounding factors used for each multivariate statistical test are listed in the appropriate results table for each separate analysis (Appendix p9-14). Interaction analyses were performed on each cohort separately, and included all known combinations of interactive terms that may have affected patient outcome. All statistical tests were 2-sided and  $P \leq 0.05$  determined significance. Data were analysed using SPSSv29 (SPSS, Chicago, IL), R V3.4.2, or Stata V17.

#### *Role of the funding source*

The acknowledged funding sources supported the individuals that took part in this study. There was no direct input of the funding sources into the study design, data collection, analysis or interpretation, nor in writing the paper.

#### **Results**

After applying the inclusion and exclusion criteria (Figure 1), 3,395 patients were removed from the final cohort. The final eligible cohort consisted of 34,097 patients (auto-HCT,  $N=20,119$ ; allo-HCT,  $N=13,978$ ) transplanted between 1<sup>st</sup> January 2009 and 31<sup>st</sup> December 2019. The median time of follow-up was 60 months for the auto-HCT (Interquartile Range (IQR) 35-89) and 32 months for the allo-HCT cohorts (IQR 10-68; Appendix p2-7). Patients were predominantly transplanted for malignant diseases in both transplant groups and most had Karnofsky performance scores  $\geq 90\%$  and HCT-CI scores  $\leq 2$ . The median patient ages were 58 and 48 years for auto-HCT and allo-HCT respectively, while the median donor age was 31 for the allo-HCT group. Patient ethnicity was predominantly reported as White for both cohorts (89% and 84%). Most allo-HCT patients received either a 10/10 HLA matched RD or UD, regardless of ethnicity (Appendix p3-8).

Five-year OS for the full auto-HCT cohort was 67% (95% CI 66-68%). There were no significant associations between patient ethnicity and any tested outcome in the cohort overall, when split into adult and paediatric patients, nor in malignant or non-malignant subgroups (Appendix p9-11).

Five-year OS for the full allo-HCT cohort was 55% (95% CI 51-58). After adjusting for confounding clinical factors listed in Appendix p12-14, there were reduced five-year OS

probabilities for Asian patients compared to White patients (HR 1·16, 95% CI 1·03-1·30,  $P=0·012$ ; Figure 2A, Appendix p12-14). No significant differences in OS were observed for the other ethnicity groups. Asian patients also had significantly lower probability of PFS at five-years compared to White patients (HR 1·14, 95% CI 1·02-1·27,  $P=0·019$ ). Ethnicity was associated with significant differences in TRM at 100 days, one-year and five-years (Appendix p15-16) with all ethnicity groups having a higher risk of TRM than White patients. Although significantly worse TRM was observed at early timepoints for patients in the 'Other' ethnicity group compared to White patients, there was no significant difference at five-years (HR 1·15, 95% CI 0·97-1·36,  $P=0·11$ ; Figure 2B; Appendix p15-16). There was no evidence of significant associations between patient ethnicity and the probability of relapse or aGvHD.

Given the potential for differences in demographics, indications for, and method of treatment of adult and paediatric populations, the two subgroups were also analysed separately.

The median time of follow-up was 48 months (IQR 17-76 months) for the paediatric allo-HCT cohort ( $N=2,490$ ). Five-year OS was 76% (95% CI 74-77). After adjusting for confounding clinical factors, significantly lower five-year OS was observed for patients of Asian ethnicity compared to White patients (HR 1·67, 95% CI 1·28-2·19,  $P=0·00018$ ; Appendix p12-14). There were no significant differences in survival for Black patients or those of 'Other' ethnicities, compared to White patients. Similarly, Asian patients had significantly lower five-year PFS (HR 1·44, 95% CI 1·15-1·81,  $P=0·0014$ ) and significantly higher probability of TRM at 100 days (HR 2·18, 95% CI 1·36-3·48,  $P=0·0012$ ), one-year (HR 2·05, 95% CI 1·44-2·94,  $P<0·0001$ ), and five-years (HR 1·94, 95% CI 1·40-2·69,  $P<0·0001$ ; Figure 3A). No significant differences were observed for the other ethnicity groups analysed. No significant differences were found between the different ethnicity groups on the incidence or grade of aGvHD or relapse.

The paediatric allo-HCT cohort were separated into malignant ( $N=1,157$ ) and non-malignant ( $N=1,333$ ) disease groups due to known differences in outcome and prognoses. Five-year OS for the malignant cohort of paediatric patients was 63% (95% CI 60-66) and the median time of follow-up was 38 months (IQR 12-71 months). Inferior outcomes for Asian paediatric allo-HCT patients remained for those with malignant disease, who had reduced five-year OS (HR 1·68, 95% CI 1·18-2·40,  $P=0·0044$ ), PFS (HR 1·47, 95% CI 1·08-2·01,  $P=0·015$ ) and increased TRM at one-year (HR 2·62, 95% CI 1·57-4·38,  $P=0·00025$ ) and five-years (HR 2·26, 95% CI 1·41-3·64,  $P=0·00076$ ) in comparison to White patients. There was no evidence to suggest significant differences for the other ethnicity groups analysed compared to White patients, nor for any other clinical outcome (Appendix p17-18).

The correlation between ethnicity and clinical outcome also remained for those patients with a non-malignant condition. Five-year OS was 87% (95% CI 85-89) and the median time of follow-up was 58 months (IQR 25-79 months). Patients from Asian and 'Other' ethnicities had significantly worse five-year OS than White patients (HR 1.78, 95% CI 1.11-2.84,  $P=0.016$  and HR 1.91, 95% CI 1.06-3.47,  $P=0.032$  respectively). Similarly, evidence for worse PFS was found for Asian (HR 1.51, 95% CI 1.05-2.15,  $P=0.025$ ) and 'Other' patients (HR 1.62, 95% CI 1.01-2.59,  $P=0.044$ ). An association between increased risk of TRM at 100 days (HR 2.30 95% CI 1.18-4.47,  $P=0.014$ ) and at five-years (HR 1.62 95% CI 1.00-2.62,  $P=0.048$ ) was observed for Asian patients compared to White patients. There was no evidence to suggest that patient ethnicity was associated with any other clinical endpoint (Appendix p17-18).

The median time of follow-up was 27 months (IQR 9-64 months) for the adult allo-HCT cohort (N=11,488). Five-year OS for the adult allo-HCT cohort was 51% (95% CI 50-52). After adjusting for confounding clinical factors, there was no significant association between patient ethnicity and the primary outcome of five-year OS (Appendix p12-14). However, significant associations between patient ethnicity and 100d, one-year and five-year TRM risk were observed. Asian, Black and 'Other' patients were found to have a higher probability of TRM compared to White patients at the earlier timepoints (100d and one-year). By five-years, only significant differences in TRM for Asian (HR 1.40, 95% CI 1.19-1.66,  $P<0.0001$ ) and Black (HR 1.33, 95% CI 1.03-1.73,  $P=0.032$ ) patients compared to White patients was observed (Appendix p15-16, Figure 3B). No causes for increased TRM risk were identified.

Five-year OS for the adult allo-HCT cohort with malignant disease (N=11,001) was 49% (95% CI 48-50) and the median time of follow-up was 26 months (IQR 9-62 months). As for the adult allo-HCT cohort overall, there were no significant differences across ethnicity groups in five-year OS. Increased TRM risk was observed in the Asian, Black and 'Other' ethnicity categories compared to White patients at the 100d and one-year timepoints, with these differences maintained at five-years for Asian and Black patients (HR 1.36, 95% CI 1.14-1.62,  $P=0.00064$  and HR 1.38, 95% CI 1.05-1.80,  $P=0.019$  respectively; Appendix p17-18). Unexpectedly, a significantly lower risk of grade 2-4 aGvHD was observed, in Asian and Black patients compared to White patients (HR 0.77,  $P=0.041$  and HR 0.68,  $P=0.047$  respectively; Appendix p17-18).

Five-year OS for the adult allo-HCT cohort with non-malignant disease (N=487) was 78% (95% CI 74.2-82.1) and the median time of follow-up was 49 months (IQR 24-84 months).

Increased TRM risk at five-years was observed for Asian patients compared to White patients, but the subgroup numbers were low, and the 95% CI range was large, suggesting this should be carefully interpreted. There were no significant associations between patient ethnicity and any of the other clinical endpoints tested here, but the same caution in interpretation due to small cohort sizes should be applied here.

No specific causes of death driving either reduced OS or TRM were evident from the data reported for any of the subgroups analysed in this study.

## **Discussion**

Healthcare inequalities, and the impact of patient ethnicity on outcomes, access and experience in healthcare, is a crucial area of research. Some studies indicate that patients from minority ethnic backgrounds face poorer outcomes, and more complications compared to White patients after transplantation(12, 13, 16). However, findings are inconsistent, and many studies focus on the US context. The UK has a unique mix of ethnicities and, in contrast to the US, a system of universal healthcare coverage delivered through the government-funded NHS which means studies based in the US may not be relevant in the UK setting. In this setting, our data suggest that patient ethnicity is not associated with outcomes after auto-HCT, confirming some previous studies(9-11). However, in allo-HCT, after adjustment for several clinical and laboratory factors including HLA matching, our data suggests patients of Asian ethnicity may have worse prognoses overall, an effect that was particularly evident within the paediatric age group. Highly significant differences in TRM were observed in adult malignant disease cohort, with patients in all ethnicity categories having a higher risk of early TRM compared to White patients, and most of the divergence of OS, PFS and TRM occurring at early timepoints i.e. within the first year post-HCT. Whilst this persisted most significantly for Asian patients, for patients of 'Other' ethnicity the difference was less pronounced at later timepoints (Figure 2). As the reduced PFS seen in various analyses is not related to relapse of disease, it can be inferred that it is explained by TRM.

A recent US study highlighted the association of patient ethnicity on clinical outcome, which differed according to whether patients incurred aGvHD and/or cGVHD(20). In this cohort of adult patients with malignant disease, increased rates of TRM were observed for non-Hispanic Black patients compared to non-Hispanic White patients for those who had aGvHD but not cGVHD. While we were unable to analyse cGVHD data in our study due to insufficient data, our observation of increased TRM in non-White patients with malignant disease, even after adjusting for important factors such as HLA matching, is consistent with this US study and that these effects are more pronounced at early timepoints post-HCT.

In contrast to our findings, most previous studies have reported outcomes for patients of Asian ethnicity predominantly being similar to, or exceeding, the White patient comparison groups(11, 16). This may be attributable to differences in the definition of Asian ethnicities, with 'US Asian' typically referring to people of East Asian heritage, while 'UK Asian' predominantly includes individuals of South Asian backgrounds. Therefore, direct comparison of our data analysis to other studies is not appropriate.

Possible explanations for the significantly increased mortality risks for Asian, Black and 'Other' patients in our analysis may include disparities at the HLA loci. Although we adjusted for HLA match scores, we were only able to assess data to a P-group level and could not consider HLA-DPB1 matching. The HLA genes are hyperpolymorphic, with over 38,900 alleles described to date (<https://www.ebi.ac.uk/ipd/imgt/hla/>; July 2024)(21). Recent data have suggested a greater degree of matching across the HLA region of the human Major Histocompatibility Complex (MHC), encompassing more extensive coding and non-coding regions of the HLA genes, correlates with better outcomes post UD-HCT(22-24). While this variation may not be functional, it could be a marker for additional genetic diversity that has evolved differently in MHC haplotypes from different ethnic populations and could contribute to different outcome risks following HCT.

Another potential mechanism for the different outcomes, including TRM, are the genetic associations that influence metabolism of drugs used for myeloablation and immunosuppression in the allo-HCT pathway(25). In addition, certain post-transplant complications such as transplant-associated thrombotic microangiopathy may be increased in non-White populations due to genetic susceptibility, as previously shown(26).

In addition to genetic variation, there are other social, clinical, or demographic factors that could provide additional risks to both auto- and allo-HCT outcomes, but that were out of scope for this study because the retrospective dataset used in this study did not include further demographic data. For example, patient socioeconomic factors have been suggested to impact on HCT outcomes and differ between different ethnic groups(13). Time to transplant is also a known risk factor, with studies highlighting differences in donor attrition rates that correlate with donor ethnicity(27). In such circumstances, it is possible the outcome of HCT may have been impacted by infections and other complications, and prolonged or additional attempts to treat with immunosuppressive therapy whilst donor searches were ongoing. Future studies should attempt to capture a wider range of data to help address these additional factors that impact the HCT pathway.

It is unclear why the differences in outcomes across ethnicities observed in the malignant group are more pronounced in the paediatric population compared with adults. There may be several unidentified biological aspects related to the malignant diseases in this age group, donor-related factors, genetic susceptibility combined with the impact of conditioning agents in developing organs or socio-economic factors in children from recently migrated families that influence these age associations and warrant further research.

We recognise several limitations in this study. Firstly, it is a retrospective study of data reported to the BSBMTCT registry from many UK centres, which, despite standardised minimal essential data reporting requirements, inevitably may be incomplete. Secondly, at the point of analysis, the ethnicity field within the patient registry database consisted of seven non-mutually exclusive categories based on ethnicity codes used in the US that do not broadly represent the UK population. In addition to the three categories analysed here (Asian, Black, White), Hispanic, Native American, and Native Hawaiian are also listed alongside an 'Other' category. A free-text box to capture further details was not consistently used and often included data that was not interpretable (e.g. Other ethnicity-British). Additionally, no further granularity of these variables was available. Finally, ethnicity was self-defined by the patient, which may not always correlate with genetic geographic ancestry(28).

A final consideration is the sole inclusion of those patients who underwent transplantation. The BSBMTCT registry is only responsible for recording data on individuals who undergo HCT. Although no such barriers to auto-HCT exist, the challenge of finding unrelated donors for patients from a minority ethnic background undergoing allo-HCT, is well reported(29, 30). The scope of this study was to determine how ethnicity affected HCT outcome, thus it does not include patients who did not reach the transplantation stage due to a lack of a suitably well HLA-matched donor. Such reduced availability may have impacted on time from diagnosis to allo-HCT and also non-transplant treatment decision making, including whether allo-HCT was performed at all.

In conclusion, this study of UK transplant data found no evidence of a difference in patient outcome prognoses in auto-HCT, but did identify significantly worse outcomes for Asian adult and paediatric patients with both malignant and non-malignant disease, and for Black adult patients with malignant disease, in the allo-HCT setting. The cause of the increased risk could not be identified, and future studies, potentially with greater numbers and/or a disease-specific focus, could evaluate how biological, socioeconomic, or logistical factors (such as efficiency of donor identification), contribute to inequities in patient outcome post-HCT. Further studies,

ideally with larger numbers of prospectively collected patient data relating to ethnicity and other biological and socio-economic factors that are well defined, are warranted to investigate inequities in access to treatment and survival outcomes.

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#### Data Sharing:

All data analysed within this study are available within the BSBMTCT Patient Registry from the date of study publication (<https://bsbmtct.org/>). The study protocol can be made available subject to reasonable request. The study was supported by a data sharing agreement between the BSBMTCT and the Anthony Nolan Research Institute. Access to anonymised data for any future studies is subject to study protocol approval by the BSBMTCT Clinical Trials Sub-Committee and completion of their data sharing agreements.

#### Declaration of interests

We declare no competing interests.

#### Contributions

NPM, RMS, YS, JL, RPM, CF, KO and JAS designed the study. JL, RPM, KO, EO and JAS collected the data. NPM, RMS, JL and RPM curated the data. NPM, RMS and RPM performed statistical analysis. NPM, MA and SGEM performed HLA matching analyses. All authors contributed to the interpretation of the study data. NPM, YS, JL, RMP, CF, MA, KR, KO, EO, SGEM and JAS critically reviewed and edited the manuscript and approved submission of the final version. NPM, RMS, JL and RPM have accessed and verified the data in the study. All authors had access to the statistical analysis data produced during the study.

## References

1. Ballen K, Wang T, He N, Knight JM, Hong S, Frangoul H, et al. Impact of Race and Ethnicity on Outcomes After Umbilical Cord Blood Transplantation. *Transplant Cell Ther.* 2024;30(10):1027 e1- e14.
2. Blue BJ, Brazauskas R, Chen K, Patel J, Zeidan AM, Steinberg A, et al. Racial and Socioeconomic Disparities in Long-Term Outcomes in  $\geq 1$  Year Allogeneic Hematopoietic Cell Transplantation Survivors: A CIBMTR Analysis. *Transplant Cell Ther.* 2023;29(11):709 e1- e11.
3. Bolon YT, Atshan R, Allbee-Johnson M, Estrada-Merly N, Lee SJ. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2022. 2022 [Available from: <https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports>.] Accessed 19<sup>th</sup> July 2023
4. Passweg JR, Baldomero H, Ciceri F, Corbacioglu S, de la Camara R, Dolstra H, et al. Hematopoietic cell transplantation and cellular therapies in Europe 2021. The second year of the SARS-CoV-2 pandemic. A Report from the EBMT Activity Survey. *Bone Marrow Transplant.* 2023;58(6):647-58.
5. Little AM, Akbarzad-Yousefi A, Anand A, Diaz Burlinson N, Dunn PPJ, Evseeva I, et al. BSHI guideline: HLA matching and donor selection for haematopoietic progenitor cell transplantation. *Int J Immunogenet.* 2021;48(2):75-109.
6. Snowden JA, Sanchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. *Bone Marrow Transplant.* 2022;57(8):1217-39.
7. Barker JN, Boughan K, Dahi PB, Devlin SM, Maloy MA, Naputo K, et al. Racial disparities in access to HLA-matched unrelated donor transplants: a prospective 1312-patient analysis. *Blood advances.* 2019;3(7):939-44.
8. Garcia L, Feinglass J, Marfatia H, Adekola K, Moreira J. Evaluating Socioeconomic, Racial, and Ethnic Disparities in Survival Among Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplants. *J Racial Ethn Health Disparities.* 2023.
9. Hari PN, Majhail NS, Zhang MJ, Hassebroek A, Siddiqui F, Ballen K, et al. Race and outcomes of autologous hematopoietic cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant.* 2010;16(3):395-402.
10. Bhatnagar V, Wu Y, Goloubeva OG, Ruehle KT, Milliron TE, Harris CG, et al. Disparities in black and white patients with multiple myeloma referred for autologous hematopoietic transplantation: a single center study. *Cancer.* 2015;121(7):1064-70.
11. Mielcarek M, Gooley T, Martin PJ, Chauncey TR, Young BA, Storb R, et al. Effects of race on survival after stem cell transplantation. *Biol Blood Marrow Transplant.* 2005;11(3):231-9.
12. Patel MI, Schupp C, Gomez SL, Lowsky R, Kohrt HE. Are There Disparities in Transplant-Related Morbidity and Mortality after Hematopoietic Stem Cell Transplant: An Institution-Based Analysis of Autologous and Allogeneic Transplant Recipients. *Blood.* 2014;124(21):1283.
13. Baker KS, Davies SM, Majhail NS, Hassebroek A, Klein JP, Ballen KK, et al. Race and socioeconomic status influence outcomes of unrelated donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2009;15(12):1543-54.
14. Serna DS, Lee SJ, Zhang MJ, Baker K S, Eapen M, Horowitz MM, et al. Trends in survival rates after allogeneic hematopoietic stem-cell transplantation for acute and chronic leukemia by ethnicity in the United States and Canada. *J Clin Oncol.* 2003;21(20):3754-60.
15. Ballen KK, Klein JP, Pedersen TL, Bhatla D, Duerst R, Kurtzberg J, et al. Relationship of race/ethnicity and survival after single umbilical cord blood transplantation for adults and children with leukemia and myelodysplastic syndromes. *Biol Blood Marrow Transplant.* 2012;18(6):903-12.



16. Morishima Y, Morishima S, Stevenson P, Kadera Y, Horowitz M, McKallor C, et al. Race and Survival in Unrelated Hematopoietic Cell Transplantation. *Transplant Cell Ther*. 2022;28(7):357 e1- e6.
17. Hong S, Majhail NS. Increasing access to allotransplants in the United States: the impact of race, geography, and socioeconomics. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):275-80.
18. Glucksberg H, Storb R, Fefer A, Buckner C, Neiman P, Clift R, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18(4):295-304.
19. Fine J, Gray R. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-509.
20. Farhadfar N, Rashid N, Chen K, DeVos J, Wang T, Ballen K, et al. Racial, Ethnic and Socioeconomic Diversity and Outcomes of Patients with Graftversus-Host Disease: A CIBMTR Analysis. *Blood Advances*. 2024.
21. Barker DJ, Maccari G, Georgiou X, Cooper MA, Flicek P, Robinson J, et al. The IPD-IMGT/HLA Database. *Nucleic Acids Res*. 2023;51(D1):D1053-D60.
22. Mayor NP, Hayhurst JD, Turner TR, Szydlo RM, Shaw BE, Bultitude WP, et al. Recipients Receiving Better HLA-Matched Hematopoietic Cell Transplantation Grafts, Uncovered by a Novel HLA Typing Method, Have Superior Survival: A Retrospective Study. *Biol Blood Marrow Transplant*. 2019;25(3):443-50.
23. Mayor NP, Wang T, Lee SJ, Kuxhausen M, Vierra-Green C, Barker DJ, et al. Impact of Previously Unrecognized HLA Mismatches Using Ultrahigh Resolution Typing in Unrelated Donor Hematopoietic Cell Transplantation. *J Clin Oncol*. 2021;39(21):JCO2003643.
24. Petersdorf EW, Malkki M, Gooley TA, Martin PJ, Guo Z. MHC haplotype matching for unrelated hematopoietic cell transplantation. *PLoS Med*. 2007;4(1):e8.
25. Franca R, Stocco G, Favretto D, Giurici N, Decorti G, Rabusin M. Role of Pharmacogenetics in Hematopoietic Stem Cell Transplantation Outcome in Children. *International Journal of Molecular Sciences*. 2015;16(8):18601-27.
26. Jodele S, Zhang K, Zou F, Laskin B, Dandoy CE, Myers KC, et al. The genetic fingerprint of susceptibility for transplant-associated thrombotic microangiopathy. *Blood*. 2016;127(8):989-96.
27. Anthias C, Shaw BE, Bruce JG, Confer DL, Abress LK, Dew MA, et al. Role of Race/Ethnicity in Donor Decisions about Unrelated Hematopoietic Progenitor Cell Donation: Exploring Reasons for Higher Attrition among Racial/Ethnic Minorities. *Biol Blood Marrow Transplant*. 2020;26(3):593-9.
28. Hollenbach JA, Saperstein A, Albrecht M, Vierra-Green C, Parham P, Norman PJ, et al. Race, Ethnicity and Ancestry in Unrelated Transplant Matching for the National Marrow Donor Program: A Comparison of Multiple Forms of Self-Identification with Genetics. *PLoS ONE*. 2015;10(8):e0135960.
29. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med*. 2014;371(4):339-48.
30. Leen G, Stein JE, Robinson J, Maldonado Torres H, Marsh SGE. The HLA diversity of the Anthony Nolan register. *HLA*. 2021;97(1):15-29.

## Figure Legends

**Figure 1: A strobe diagram showing cohort development for this analysis.**

**Figure 2: Adjusted survival curves showing association of patient ethnicity with the probability of A) overall survival and B) TRM at 5-years in the full allogeneic haematopoietic cell transplant dataset (N=13,978).** Numbers at the bottom of the graphs represent the number of at risk and censored (in parenthesis) patients.

**Figure 3: Adjusted survival curves showing association of patient ethnicity with the probability of TRM at 5 years for A) Paediatric (N=2,490) and B) Adult (N=11,488) allogeneic haematopoietic cell transplant subgroups.** Numbers at the bottom of the graphs represent the number of at risk and censored (in parenthesis) patients.