Haematopoietic cell transplantation (HCT) recipients experience an increased risk of cardiovascular disease compared to the general population [1, 2]. Although transplant-related mortality has decreased over the last decades, this has not been through a reduction in death due to cardiovascular disease [3, 4]. Improving cardiovascular outcomes post-transplant is a focus of the International Cardio-Oncology Society [5], and the European Society of Cardiology has recently produced guidelines for risk assessment and surveillance [6].

Given this background, we aimed to investigate the current United Kingdom (UK) and Republic of Ireland (ROI) pre-transplant cardiovascular screening practice. We wanted to understand if screening was performed, which investigations were used and if a left ventricular ejection fraction (LVEF) cut-off was an exclusion criterion for HCT. We also wanted to investigate what cardiology support was available to transplant centres, and if there were dedicated cardio-oncology services. This study surveyed adult and paediatric units.

A 23-item survey was created with three introductory questions and 13 adult and seven paediatric-specific questions (Supplementary Material). Centres could answer both sections, and they had the option to skip questions. The survey was distributed as an internet-based questionnaire ( surveymonkey.com ) through the British Society of Blood and Marrow Transplantation and Cellular Therapy to transplant directors at the 52 UK and ROI transplant centres. The study was open from March 2022 to June 2022, and three reminders were sent out to non-respondents before the survey closed.

A total of 26 centres responded (50% response rate) without duplicates. One adult centre erroneously answered the paediatric section giving 25 complete responses. Response rates were equal across England, Wales and Scotland; however there were no responses from either Northern Ireland or the ROI. Fifty-five percent (18/33) of the centres that perform both autologous and allogeneic transplants and 42% (8/19) of the centres that perform autologous only transplants responded. From the responding centres, 21 only performed adult transplants, three exclusively performed paediatric transplants, and two performed combined adult and paediatric transplants.

Over three quarters of the adult centres (76%) recorded a comorbidity score prior to transplant; the majority used the hematopoietic cell transplantation co-morbidity index [7]. This score has 17 sections, with three corresponding to cardiac disease. Despite not all centres using a co-morbidity score, they all performed some form of cardiovascular screening. One centre only performed routine screening for patients prior to allogeneic transplants, not autografts (Table 1a).

A variety of investigations were used for adults with most centres using trans-thoracic echocardiography (TTE; 90%) and a 12-lead electrocardiogram ( ECG ; 86%). There was infrequent use of serum biomarkers (19%), more advanced cardiac imaging techniques (33%), and cardio-pulmonary exercise testing ( CPEX ; 19%). One centre that had used CPEX stopped at the start of the COVID-19 pandemic.

Most adult centres (81%) used an LVEF measurement to exclude patients from transplantation. There was heterogeneity in the value used for exclusion, ranging from ≤50% to ≤30% with no justification for the difference. Only one centre that used ≤40% as an exclusion criterion specified that they use reduced intensity conditioning (RIC) if the LVEF is ≤50% ( Figure 1 ).

Post-transplantation, 32% of adult centres referred select patients for cardio-oncology review, and a quarter of centres had specific referral criteria. In general, patients were referred on a case-by-case basis if there were clinical concerns or a low LVEF. There was substantial agreement on the cut-off for transplant exclusion, as shown in Figure 1 .

![LVEF transplant cut-off values](image-url)

**FIGURE 1** The spread of LVEF values used as a boundary for transplant exclusion. The figure shows the different LVEF values used as a cut-off and the number of centres using each value. Only one centre specified that, although they used ≤40% as a boundary, if the LVEF was ≤50% a reduced intensity conditioning regimen was used.
TABLE 1 Cardiovascular screening practice in UK transplant centres

| a. Adult responses |
|--------------------|
| **Do you record a co-morbidity score? (n = 21)** |
| Yes | 76% (16) |
| No | 24% (5) |
| **Which score? (n = 16)*** |
| Haematopoietic cell transplantation co-morbidity index (HCT-CI) | 94% (15) |
| Age adjusted HCT-CI | 6% (2) |
| Charlson co-morbidity index | 0% (0) |
| Pre-transplant assessment of mortality (PAM) score | 0% (0) |
| Other | 0% (0) |
| *One centre selected two scores |
| **Do you perform cardiovascular screening on all patients?** |
| Combined allogeneic and autologous centres (n = 14) |
| Yes | 93% (13) |
| No | 7% (1)* |
| *This centre did, however, do cardiovascular screening on all patient having an allogeneic transplant |
| Autologous only transplant centres (n = 7) |
| Yes | 100% (7) |
| No | 0% (0) |
| **Which investigations do you use? (n = 21)** |
| Trans-thoracic echocardiography | 90% (19) |
| 12-lead ECG | 86% (18) |
| Cardiac CT, MRI or nuclear medicine scanning | 33% (7) |
| Serum biomarkers (BNP and/or troponin) | 19% (4) |
| Cardio-pulmonary exercise testing | 19% (4) |
| Other | 0% (0) |
| **Do you have an LVEF cut-off value for transplant candidate selection? (n = 19; two adult centres did not answer)** |
| Yes | 81% (13) |
| No | 19% (6) |
| **Do you refer select patients to cardio-oncology services after stem cell transplant? (n = 19)** |
| Yes - all patients | 0% (0) |
| Yes - select patients | 32% (6) |
| No | 68% (13) |
| **Do you have criteria for cardio-oncology referral? (n = 19)** |
| Yes | 26% (5) |
| No | 74% (14) |

| b. Paediatric responses |
|-------------------------|
| **Do you perform cardiovascular screening on all patients? (n = 5)** |
| Yes | 100% (5) |
| No | 0% (0) |
| **What does your cardiovascular screening involve? (n = 5)** |
| Co-morbidity score | 20% (1) |
| 12 lead ECG | 20% (1) |
| Trans-thoracic echocardiography | 80% (4) |
| Other | 0% (0) |
| **Do you have criteria for cardio-oncology referral? (n = 5)** |
| Yes | 60% (3) |
| No | 40% (2) |
| **Are all patients referred for cardio-oncology follow up? (n = 5)** |
| Yes | 0% (0) |
| No | 100% (5) |
| **Are patients referred for late-effects clinic follow up? (n = 5)** |
| Yes | 100% (5) |
| No | 0% (0) |

Abbreviations: ECG, electrocardiogram; HCT, haematopoietic cell transplantation.

The heterogeneity in the LVEF boundary for adults was surprising (Figure 1). The majority of assessment was performed using TTE, which is associated with significant intra- and inter-observer variability [8]. Previous studies do not support a LVEF boundary cut-off and suggest patients with a moderately impaired LVEF can safely undergo variation in cardiology support; some centres found it difficult to get cardiologists interested, whereas other units had dedicated cardio-oncology clinics. In the most well-defined service, all patients with a history of ischaemic heart disease, heart failure or anthracycline-related cardiomyopathy were referred for cardiology-oncology consultation with a stress echocardiogram or cardiac MRI, and where possible all patients over 60 years were referred for clinical review. If patients had an impaired LVEF the most common pre-transplant pharmacotherapy used was a beta blocker and angiotensin converting enzyme inhibitor combination.

For paediatric centres (Table 1b), all children who had HCT received some form of cardiovascular screening. The majority (80%) had LVEF assessed by TTE, and a small proportion had a 12-lead ECG or co-morbidity score. Sixty percent of the paediatric centres had criteria for cardio-oncology referral. Although children were not routinely referred for cardio-oncology follow up, all were referred to the late effects clinic.
The dataset gathered in this study is available from the corresponding authors.

Other significant knowledge gaps include the utility of blood and imaging biomarkers on long-term risk stratification. Although recommendations on cardiovascular risk assessment and ongoing surveillance exist, the majority are formed from expert consensus. A cardiovascular risk score for the prediction of heart failure and coronary artery disease 10 years post-transplant has been generated using variables available one year after transplant (history of anthracycline exposure, chest radiation, hypertension, age, diabetes, and smoking) [15]. Despite this, the optimal approach to monitoring and treating patients at different levels of risk is unknown, and there are little data to help us predict short term complications arising 100 days to 6 months after HCT in both adult and paediatric patients.

The results of our analysis provide an overview of pre-transplant cardiovascular screening practice in the UK, and the response rate provides an acceptable sample of transplant centre activity. The marked inter-site variability in adult practice reflects the historical absence of guidelines to help centres select patients for pre-transplant screening; however given the publication of recent recommendations, there may be a more uniform approach in the future.

AUTHOR CONTRIBUTIONS

David G. Gent wrote the survey, analysed the responses and drafted the manuscript, table and figure. Muhammad Saif, Julia Lee, Arpad G. Toth, Eleni Tolouli, Rebecca Dobson and David J. Wright reviewed and edited the survey and the manuscript. Julia Lee disseminated the survey and prompted to the transplant centres. David G. Gent, Rebecca Dobson and David J. Wright came up with the concept.

ACKNOWLEDGEMENTS

The authors would like to thank the transplant directors who replied to our survey and gave us a representative sample of pre-transplant cardiovascular screening in the United Kingdom.

CONFLICT OF INTEREST

Professor Wright has received consultancy and speaker fees from Boston Scientific and Medtronic outside the submitted work. All other authors have no relationships relevant to the content of this paper to disclose.

DATA AVAILABILITY STATEMENT

The dataset gathered in this study is available from the corresponding author on request.

REFERENCES

1. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol. 2011;29:2230.
2. Armenian SH, Chow EJ. Cardiovascular disease in survivors of hematopoietic cell transplantation. Cancer. 2014;120:469–79.
3. Bhatia S, Dai C, Landier W, Hageman L, Wu J, Schlichting E, et al. Trends in late mortality and life expectancy after autologous blood or marrow transplantation over three decades: a BMTSS report. J Clin Oncol. 2022;40:1991–2003.
4. Bhatia S, Dai C, Landier W, Hageman L, Wu J, Schlichting E, et al. Trends in late mortality and life expectancy after allogeneic blood or marrow transplantation over 4 decades: a blood or marrow transplant survivor study report. JAMA Oncol. 2021;7:1626–34.
5. Lenihan DJ, Fradley MG, Dent S, Brezden-Masley C, Carver J, Filho RK, et al. Proceedings from the global cardio-oncology summit: the top 10 priorities to actualize for cardio-oncology. JACC CardioOncol. 2019;1:256–72.
6. Lyon AR, López-Fernández T, Couch LS, Asteggiaro R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). Eur Heart J. 2022;23:e333–e465.
7. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106:2912–9.
8. Thavendiranathan P, Grant AD, Negishi T, Carlos Plana J, Popovic ZB, Marwick TH, et al. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes application to patients undergoing cancer chemotherapy. JACC. 2013;61:77–84.
9. Tang WHW, Thomas S, Kalaycio M, Sobecks R, Andresen S, Jarvis S, et al. Clinical outcomes of patients with impaired left ventricular ejection fraction undergoing autologous bone marrow transplantation: can we safely transplant patients with impaired ejection fraction? Bone Marrow Transplant. 2004;34:603–7.

10. Qazilbash MH, Amjad AI, Qureshi S, Qureshi SR, Saliba RM, Khan ZU, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients with low left ventricular ejection fraction. Biol Blood Marrow Transplant. 2009;15:1265–70.

11. Kelsey CR, Scott JM, Lane A, Schwitzer E, West MJ, Thomas S, et al. Cardiopulmonary exercise testing prior to myeloablative allo-SCT: a feasibility study. Bone Marrow Transplant. 2014;49:1330–6.

12. Wood WA, Deal AM, Reeve BB, Abernethy AP, Basch E, Mitchell SA, et al. Cardiopulmonary fitness in patients undergoing hematopoietic SCT: a pilot study. Bone Marrow Transplant. 2013;48:1342–9.

13. Oliveira GH, Al-Kindi SG, Guha A, Dey AK, Rhea IB, deLima MJ. Cardiovascular risk assessment and management of patients undergoing hematopoietic cell transplantation. Bone Marrow Transplant. 2021;56:544–51.

14. Armenian SH, Hudson MM, Mulder RL, Chen MH, Constine LS, Dwyer M, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2015;16:123–36.

15. Armenian SH, Yang D, Teh JB, Atencio LC, Gonzales A, Wong FL, et al. Prediction of cardiovascular disease among hematopoietic cell transplantation survivors. Blood Adv. 2018;2:1756–64.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gent DG, Saif M, Lee J, Tóth AG, Tholouli E, Dobson R, et al. Cardiovascular screening prior to stem cell transplantation in the United Kingdom. eJHaem. 2022;3:1455–1458. https://doi.org/10.1002/jha2.599