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RESEARCH

Telomere length and telomerase reverse transcriptase gene polymorphism as potential markers of complete chimerism and GvHD development after allogeneic haematopoietic stem cell transplantation

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Abstract

Introduction Telomerase reverse transcriptase (TERT) is a catalytic subunit of telomerase that maintains genome stability by maintaining telomere length (TL). The massive proliferation of donor cells in the recipient's body for engraftment results in accelerated telomere shortening. Genetic variability within the *TERT* gene affects telomerase activity, and was shown to influence of haematopoietic stem cell transplantation (HSCT) outcome. In the present study, we aimed to analyse the effect of recipient and donor TL and *TERT* single nucleotide polymorphism (SNP) on the occurrence of post-HSCT complications.

Methods Our study included 120 recipient-donor pairs. *TERT* promoter (*TERT*p) SNP (rs2853669) SNP variant was detected with the use of the LightSNiP typing assay employing real-time polymerase chain reaction (PCR) amplifications. Telomere length measurements were performed using qPCR test kits (ScienCell's Absolute Human Telomere Length Quantification qPCR Assay Kit [AHTLQ], Carlsbad, CA, USA).

Results The presence of *TERT*p rs2853669 *T* allele in the recipient was associated with a higher risk for acute graft-versus-host-disease (aGvHD) manifestation ($p=0.046$) and a significantly shorter aGvHD-free survival ($p=0.041$). The latter association was further confirmed in a Cox proportional hazards model ($p=0.043$). However, no statistically significant association between telomere length and post-transplant complications was observed. Furthermore, we found that shorter TL characterized donors of patients with late complete chimerism at 180 day after HSCT ($p=0.011$).

Conclusion Our results suggest that recipient allele *TERT*p rs2853669 *T* is a marker of unfavourable outcome in the context of aGvHD. Shorter TL in donors could be associated with later achievement of complete chimerism.

Keywords Telomere length · *TERT* gene · Allogeneic haematopoietic stem cell transplantation · Acute graft-versus-host-disease · Complete chimerism

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Introduction

Telomeres are repeats of a nucleotide sequence (TTAGGG) n located at the ends of chromosomes that shorten with each cell division. They are essential for maintaining the structure and stability of chromosomes and are markers of the replicative capacity of cells. A DNA polymerase called telomerase is responsible for the elongation of telomeres at the 3' ends of chromosomes (Blackburn 1991). Telomerase activity has not been identified in most mature somatic cells. However, the activity of this polymerase is a feature of most cancer cells, which allows them to achieve a state of unlimited proliferation (Akincilar et al. 2016). Telomerase is a complex reverse transcriptase whose integral components are an RNA matrix (telomerase RNA component - TERC), the telomerase reverse transcriptase catalytic subunit (TERT) and a complex of six protective proteins called shelterins that protect the ends of chromosomes from excessive degradation (Ramlee et al. 2016). Haematopoietic cells maintain a constant, high level of telomerase activity, which is necessary to sustain their replicative cycle (Weng 2001).

Haematopoietic stem cell transplantation (HSCT) is an important treatment option for many haematologic malignancies, as well as other hereditary and acquired diseases of bone marrow and immune system (Copelan 2006). During transplantation, a small percentage of haematopoietic stem cells are transferred from the donor to the recipient. The transplanted donor haematopoietic cells in the recipient's body undergo significant expansion until homeostatic conditions are restored. In most cases, peripheral blood cell counts and bone marrow cellularity normalize within 2 to 6 months after HSCT (Thornley et al. 2002). However, the function of donor haematopoietic stem cells in the recipient remains insufficient for several years after HSCT (Podestà et al. 1997). Donor stem cells undergo massive proliferation, resulting in accelerated telomere shortening due to excessive turnover of replicating stem cells. This may be a likely indicator of premature ageing of haematopoietic stem cells, ultimately leading to an increased incidence of graft failure and/or clonal abnormalities (Gadalla and Savage 2011; Wynn et al. 1998; Awaya et al. 2002). In addition, pretransplant conditioning creates a highly inflammatory environment that promotes increased haematopoietic stem cell division, may play a role in regulating telomere length after transplantation (Niederwieser et al. 2016; Akiyama et al. 2000). Importantly, haematopoietic stem cells are particularly susceptible to defects in telomere maintenance genes. This is particularly observed in patients with dyskeratosis congenita and aplastic anaemia. In these cases, telomere shortening is caused by loss-of-function mutations in the telomerase complex in *TERT* and *TERC* genes [Du et al. 2009; Terada et al. 2020; Virijevic et al. 2024). Furthermore, the extent to which telomere shortening affects stem cell function appears to be variable and may depend on the degree of telomere dysfunction of individual chromosomes (Hemann et al. 2001; Fiorini et al. 2018).

After HSCT, telomeres in the recipient are typically shorter than in their matched donors (Brümmendorf and Balabanov 2006). Studies with repeated measurements of telomere length in the same person have shown the fastest telomere shortening in the first 12 months after HSCT. This was followed by a rate of telomere shortening that was similar to the expected age-related decline observed in the control group (Brümmendorf et al. 2001; Robertson et al. 2001). Moreover, shorter telomeres have been observed in transplanted haematopoietic cells from older donors and female donors. It is well established that in the general population, women have longer telomeres than men (Mayer et al. 2006; Gardner et al. 2014). In *vitro* and in vivo studies have shown that oestrogen protects telomeres from shortening (Imanishi et al. 2005; Lee et al. 2005). This advantage in telomere length in women disappears after HSCT regardless of the gender of the recipient. After transplantation, the male recipient no longer has a protective hormonal background, and the female recipient may also lack it due to oestrogen deficiency following transplantation (Baerlocher et al. 2009). Furthermore, shorter telomeres have also been observed in patients with chronic graft-versus-host disease (cGvHD) (Akiyama et al. 2000; Baerlocher et al. 2009). This is also consistent with the fact that chronic inflammation and oxidative stress are known to be associated with telomere shortening (Starr et al. 2008). Moreover, Gadalla et al. (2018) demonstrated that a donor with long telomeres increased the chances of survival and reduced the incidence of malignancies in recipients, and longer telomeres prevented infection-related death (Gadalla et al. 2018).

Approximately 90% of all human cancers show transcriptional activation of *TERT* (Holt et al. 1997). The promoter region of this gene is the most important element regulating its expression and, consequently, telomerase activity (Daniel et al. 2012). Several *TERT* single nucleotide polymorphisms (SNPs) have been found to be associated with the development of human solid tumours as well as haematological malignancies (Mocellin et al. 2012; Wysoczanska et al. 2019). One of them, rs2853669 (*C*/*T*), located in the *TERT* promoter region (*TERT*p), is associated with the occurrence of a two hot-spot mutation (sites at positions − 124 and − 146 bp from transcription start site (TSS), affecting the overall expression of the gene (Dratwa et al. 2020a, b; Bell et al. 2016). The presence of these variants determines the formation of an alternative binding motif (11 bp long) for E-twenty-six/ternary complex (ETS/TCF), which leads to reactivation of telomerase and is associated

with a two-fold increase in *TERT* transcription (Horn et al. 2013; Heidenreich et al. 2014).

Critically short telomeres may impact long-term survival, leading to additional risk of degenerative diseases and secondary malignancies (Baerlocher et al. 2009). It appears that identifying recipients at risk of cellular senescence may become an element of monitoring long-term survival after HSCT. The aim of this study was to analyse the relationship of recipient and donor telomere length and the *TERT*p rs2853669 polymorphism with the occurrence of complications after transplantation.

Table 1 Patients' and donors characteristics

Number of donor-recipient pairs	$n=120$
Recipient median age (range), yrs	49 (18–73)
Donor median age (range), yrs	41 (14–73)
Recipient gender, n (%)	
Female	49 (40.8%)
Male	71 (59.2%)
Donor gender, n (%)	
Female	54 (45.0%)
Male	66 (55.0%)
Diagnosis, n (%)	
Chronic myeloid leukemia (CML)	8 (6.67%)
Chronic lymphocytic leukemia (CLL)	1 (0.83%)
Acute myeloid leukemia (AML) + Mixed-phenotype acute leukemia (MPAL) + Myelodysplastic Syndrome (MDS)	57 (47.5%)
Acute lymphocytic leukemia (ALL)	18 (15.0%)
Blastic plasmacytoid dendritic cell neoplasm (BPDCN)	2 (1.67%)
Multiple myeloma (MM) + Plasma cell myeloma (PCM)	9 (7.5%)
Hodgkin lymphoma (HL) + non-Hodgkin lymphoma (NHL) + Diffuse large B-cell lymphoma (DLBC)	18 (15.0%)
Bone marrow failure syndromes	7 (5.83%)
Type of donor, n (%)	
matched unrelated donor (MUD)	1 (1%)
mismatched unrelated donor (MMUD)	1 (1%)
matched sibling donor (MSD)	77 (64%)
haploidentical	41 (34%)
Donor/Recipient sex, n (%)	
Male/Male	44 (37.0%)
Male/Female	27 (22.5%)
Female/Male	22 (18.0%)
Female/Female	27 (22.5%)
Donor/recipient CMV serostatus, n (%)	
negative/negative	13 (11%)
negative/positive	10 (8%)
positive/negative	18 (15%)
positive/positive	79 (66%)
Conditioning, n (%)	
reduced intensity conditioning (RIC)	79 (66%)
myeloablative conditioning (MAC)	38 (32%)
nonmyeloablative (NMA)	2 (2%)

Materials and methods

The study group included 120 recipients (aged 18 to 73) and their 120 donors (aged 14 to 73) treated in five Polish transplant centres. All patients received Peripheral Blood Stem Cell (PBSC) grafts. The majority of patients - seventy-seven recipients (64%) - were grafted from a matched sibling donor (MSD), forty-one (34%) from haploidentical donors, one patient received an allograft from a matched unrelated donor (MUD) and another one from a mismatched unrelated donor (MMUD). The most common haematological disease was acute myeloid leukaemia (AML), diagnosed in 38.3%, followed by acute lymphoblastic leukaemia (ALL), diagnosed in 15% of recipients. Forty-eight (40%) patients developed aGvHD, eight (6%) severe aGvHD, grade III-IV. The patients characteristics and transplant details are presented in Table 1. This study complies with the Declaration of Helsinki and was approved by the Wroclaw Medical University Ethics Committee (identification code KB-561/2019).

DNA extraction

Genomic DNA was isolated from peripheral blood taken on EDTA collected before HSCT using the NucleoSpin Blood kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany) following the recommendation of the manufacturers. DNA concentration and purity were quantified on a DeNovix DS-11 spectrophotometer (DeNovix Inc., Wilmington, DE, USA). The isolated DNA was then stored at −20 °C until *TERT*p genotyping and evaluation of the telomere length in HSCT recipients and their donors.

Genotyping of *TERT*p gene polymorphism

The *TERT*p rs2853669 polymorphism was determined by LightSNiP typing assay (TIB MOLBIOL, Berlin, Germany) using quantitative polymerase chain reaction (qPCR). Amplifications were performed on a LightCycler480 II Real-Time PCR system (Roche Diagnostics International AG, Rotkreuz, Switzerland) according to the recommendations of the manufacturer. The PCR conditions were as follows: 95 °C for 10 min followed by 45 cycles of 95 °C for 10 s, 60 °C for 10 s and 72 °C for 15 s. PCR was followed by one cycle of 95 °C for 30 s, 40 °C for 2 min and gradual melting from 75 to 40 °C.

Quantification of telomere length

Mean telomere length was measured in the genomic DNA samples of 120 HSCT recipients and their donors. DNA was isolated from peripheral blood collected before

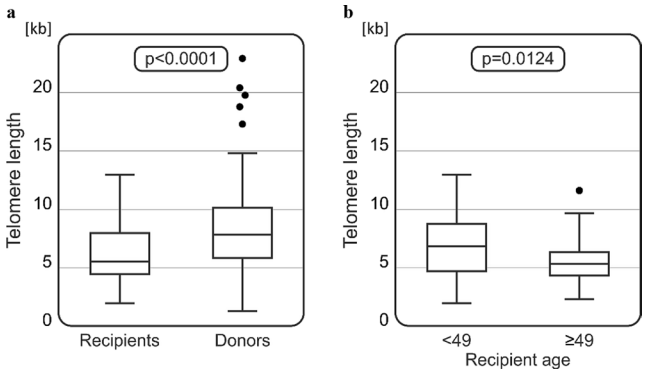

Fig. 1 Telomere length in haematopoietic stem cell transplantation donors and recipients. Telomeres of donors are longer than those of pre-transplant patients (**a**). Furthermore, younger patients (below the median age of 49 yrs) have longer telomeres than older patients (**b**)

transplantation. Subsequently, the samples were diluted with nuclease-free water to a concentration of 5 ng/mL. Telomere length measurements were performed on a LightCycler480 II Real-Time PCR system (Roche Diagnostics International, Rotkreuz, Switzerland) using qPCR test kits (ScienCell's Absolute Human Telomere Length Quantification qPCR Assay Kit [AHTLQ], Carlsbad, CA, USA), as previously described by Dratwa et al. (2020b). The PCR conditions were as follows: 95 °C for 10 min followed by 32 cycles of 95 °C for 20 s, 52 °C for 20 s and 72 °C for 45 s. Data analysis was conducted according to the manufacturer's instructions. All reactions were performed in duplicate.

Statistical analysis

The null hypothesis that there is no difference between the frequency of alleles and genotypes between recipients and donors was verified with the Fisher's exact test, calculated using the online tool (http://vassarstats.net/tab2x2.htm; accessed on: January 2025). Mann-Whitney U test and logistic regression model were used to compare telomere length between HSCT recipients and their donors, and to check for associations between various clinical parameters, transplant outcomes and presence of various genetic variants. Survival of patients was analysed using the Gehan-Breslow-Wilcoxon test and Kaplan–Meier curves, as well as the Cox proportional hazards model. All of these analyses were conducting using the Real Statistics Resource Pack for Microsoft Excel 2013 version 15.0.5023.1000 (Microsoft, Redmond, WA, USA), RStudio (RStudio, PBC., Boston, MA, USA), and GraphPad Prism (version 8.0.1, GraphPad Software, San Diego, CA, USA). P-values <0.05 were considered statistically significant, while those between 0.05 and 0.10 were indicative of a trend.

Table 2 Transplant outcomes

Acute GvHD, *n* (%)	
Yes	48 (40%)
No	72 (60%)
Acute GvHD grade, n (%)	
I	24 (20%)
II	16 (14%)
III	4 (3%)
IV	4 (3%)
Chronic GvHD, n (%)	
Yes	25 (21%)
No	95 (79%)
The overall severity of cGvHD, n (%)	
Mild	6 (25%)
Moderate	13 (54%)
Severe	5 (21%)
Relapse, n (%)	
Yes	15 (13%)
No	104 (87%)
CMV reactivation, n (%)	
Yes	39 (33%)
No	79 (67%)
Current patient status, n (%)	
Alive	97 (81%)
Died	20 (17%)
not known	3 (2%)

Results

Telomere length and age of HSCT recipients and their donors

We observed that telomere length was significantly shorter in HSCT recipients as compared to their donors (median length 5.47 vs. 7.80 kb, $p<0.001$, Fig. 1a), in both paired and unpaired analyses. When the patients were subdivided with respect to the median age at HSCT (49 years), we noticed that the younger patients had longer telomeres than older ones (median length 6.78 vs. 5.27 kb, $p=0.0124$, Fig. 1b).

Telomere length and post-transplant complications

Table 2 characterises transplant recipients after HSCT, taking into account possible complications, disease relapse and current patient status. We analysed telomere length in patients with aGvHD and their donors, and found that shorter telomeres in transplant recipients were associated with longer aGvHD-free survival, although this association was not statistically significant ($p=0.0665$; Fig. 2a). No association between donor telomere length and aGvHD-free survival was observed ($p=0.2445$, Fig. 2b). No association with telomere length (either in recipient or donor) and overall survival, relapse, or chronic GvHD occurrence was detected.

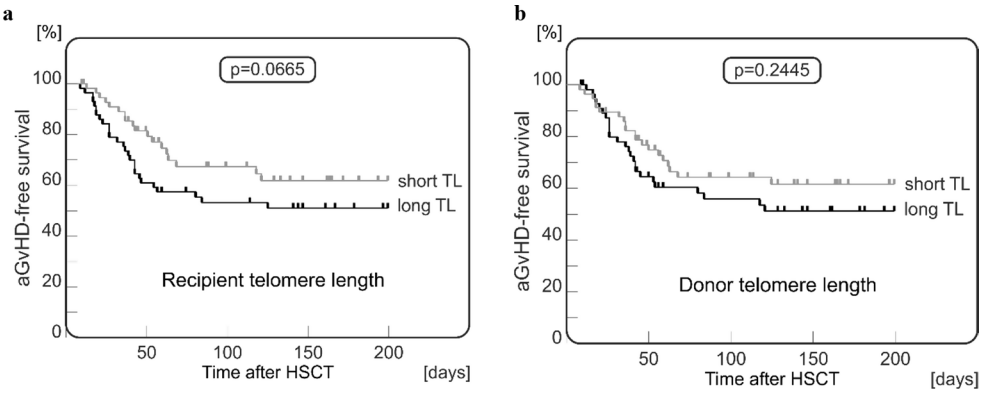

Fig. 2 Acute GvHD-free survival in patients post-HSCT patients with different telomere length (TL) in the recipient (**a**), and the donor (**b**). Longer telomeres are associated with slightly shorter aGvHD-free survival, which is more pronounced in the case of recipient TL. However, neither of these associations is statistically significant

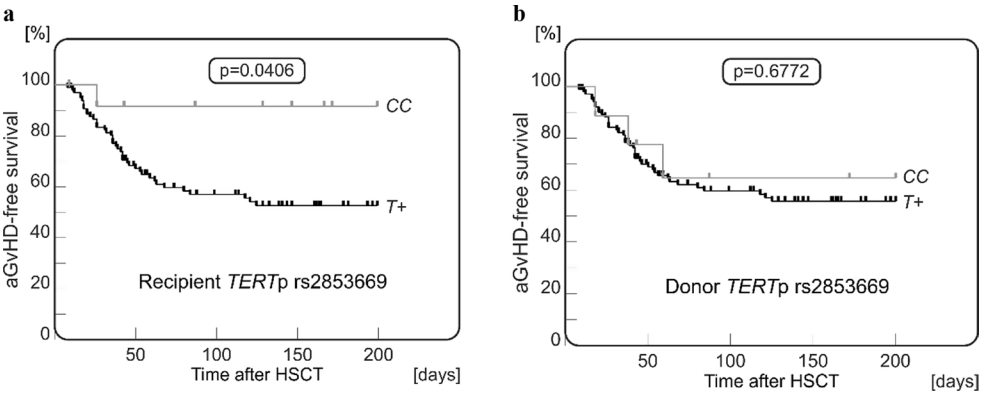

Fig. 3 Acute GvHD-free survival in patients post-HSCT patients with or without allele *TERT*p rs2853669 *T* in the recipient (**a**), and the donor (**b**). The presence of allele *T* in the recipient, but not the donor, is associated with shorter aGvHD-free survival

Regarding aGvHD, we also observed that the incidence of grades II-IV was three times higher in the younger group of recipients (below the median age of 49 years) than in the older group (17/42 vs. 7/53, OR = 3.065, $p = 0.023$). Moreover, a trend was observed whereby the risk of severe aGvHD (grade II to IV) increased sevenfold if the transplant was sex-matched and the donor and recipient were female (7/20 vs. 1/21, OR = 7.35, $p = 0.059$).

We observed an association between the CMV serological status of recipient-donor pairs and telomere length. Telomeres were found to be longer in pairs of patients and donors lacking anti-CMV IgG antibodies before transplantation, compared to pairs with a CMV-seropositive recipient and a CMV-seronegative donor (9.52 kb vs. 7.18 kb; $p = 0.026$). Additionally, we observed a trend for shorter telomere length of CMV-seropositive pairs compared to CMV-seronegative pairs (7.52 kb vs. 9.52 kb; $p = 0.075$). Furthermore, we found that patients who developed viral infections post-HSCT had shorter donor telomeres compared to patients who did not develop any viral infections (6.61 kb vs. 8.37 kb; $p = 0.060$).

Shorter telomeres were also detected in those with late complete chimerism at day 180 after HSCT compared to those who achieved the complete chimerism status earlier, before day 90 (8.94 kb vs. 4.63 kb; $p = 0.011$).

TERT promoter polymorphism and occurrence, severity of aGvHD and aGvHD-free survival

The *TERT*p rs2853669 genotype frequencies in the recipient and donor groups were in Hardy-Weinberg equilibrium ($p < 0.0500$). We did not observe any statistically significant differences in *TERT*p rs2853669 allele and genotype distribution between transplant recipients and donors. Moreover, there were no statistically significant associations between telomere length and frequency of *TERT*p rs2853669 alleles and genotypes.

However, we observed that patients with allele *TERT*p rs2853669 *T* had a significantly shorter aGvHD-free survival ($p = 0.0406$; Fig. 3a). No such association was observed for donor *TERT*p rs2853669 genotypes ($p = 0.6772$; Fig. 3b). Furthermore, we found that the presence of *TERT*p rs2853669 *T* allele in the recipient was associated with a higher risk for aGvHD grades II-IV manifestation ($p = 0.0456$).

We constructed a Cox proportional hazards model of aGvHD-free survival, which includes recipient and donor telomere length (above or below median), recipient and donor *TERT*p rs2853669 (presence or absence of allele *T*), as well as several potential confounding factors (conditioning regimen, HLA incompatibility, recipient and donor sex, recipient and donor age). It confirmed that recipient allele *TERT*p rs2853669 *T*, but not telomere length, is an independent marker of aGvHD-free survival ($p = 0.0428$; Table 3).

Table 3 Multivariate analysis of factors potentially affecting aGvHD-free survival in HSCT recipients

	HR[a] (95%CI[b])	*p*-value
conditioning regimen	0.9767 (0.4656, 2.0490)	0.9504
HLA incompatibility	1.2691 (0.6361, 2.5320)	0.4988
recipient sex	1.2554 (0.6650, 2.3702)	0.4829
donor sex	0.8293 (0.4403, 1.5623)	0.5625
recipient age	0.9814 (0.9581, 1.0051)	0.1233
donor age	1.0167 (0.9900, 1.0441)	0.2218
recipient telomere length	1.2303 (0.6240, 2.4257)	0.5495
donor telomere length	1.4011 (0.7392, 2.6557)	0.3012
recipient*TERT*p rs2853669	**9.0111 (1.0743, 75.5810)**	**0.0428**
donor *TERT*p rs2853669	0.5653 (0.1528, 2.0909)	0.3927

Abbreviations: [a] hazard ratio (HR); [b] confidence interval (CI)

Discussion

A key aspect of allogeneic haematopoietic cell transplantation is the restoration of full haematopoiesis in the recipient from donor stem cells. Thus, timely reconstitution and restoration of donor-derived immune function is crucial for patient's recovery and long-term survival (Ogonek et al. 2016). Multiple factors, including graft cellularity, graft-versus-host disease, infection, and the use of cytokines and other drugs, may interact to modulate posttransplant haematopoietic replication stress and associated leukocyte telomere shortening (Thornley and Freedman 2002).

It is well known that the telomere length of HSCT recipients is shorter than that of donor cells (Wynn et al. 1998; Shay 1998). This observation has also been confirmed in our present study. Two possible hypotheses are currently being considered regarding the shorter telomere length observed in recipients. One posits that telomere shortening following HSCT may be the consequence of extensive cell proliferation necessary to achieve immune reconstruction. Meanwhile, another hypothesis says that damage to normal cells caused by therapy could lead to chronic inflammation in the body, leading to telomere shortening and premature ageing (Cupit-Link et al. 2017). Furthermore, Boettcher et al. (2020) suggested that the difference in telomere length between donor and recipient after transplant translates into approximately 20 years of premature ageing of the recipient's haematopoietic system compared to the donor (Boettcher et al. 2020).

Several studies have investigated the possible effect of donor haematopoietic cell telomere length on recipient outcomes after HSCT. Improved survival was observed in patients with severe aplastic anaemia (SAA), who received cells with longer telomeres from unrelated donors (Gadalla et al. 2015). In another study, 5-year survival improved significantly from 65 to 95% in SAA patients receiving a transplant from a matched sibling whose haematopoietic cell telomere length was in the longest quartile (Barade et al. 2022). However, there was no reduction in the risk of death at 5 years in patients with acute leukaemia who received transplants from donors with long telomeres (Gadalla et al. 2018). Baerlocher et al. (2009) showed that shorter telomeres in patients after HSCT were associated with the presence of cGvHD and receiving cells from a female donor (Baerlocher et al. 2009). While, Barade et al. (2022) demonstrated that short median donor telomere length was associated with a higher incidence of aGvHD in patients with SAA (Barade et al. 2022). Another study showed that severe gastrointestinal aGvHD causes rapid telomere shortening in enterocytes, reaching values 200-fold greater than in the steady state (Hummel et al. 2015). Therefore, we hypothesized that patients with shorter donor telomeres who develop severe aGvHD after transplantation have a poorer prognosis than those with longer telomeres. However, we did not observe any statistically significant association between donor telomere length and the occurrence and prognosis of aGvHD. It should be noted that most studies are based on measuring the relative telomere length of blood cells (mainly leukocyte telomere length) as a surrogate for telomere length in other tissues affected by aGvHD and may not directly reflect telomere length in affected organs.

Most literature indicates that there is no proof of an association between recipient telomere length with transplant outcome. In our present study, there was no association between telomere length (in either recipient or donor) and overall survival, disease relapse, or the occurrence of cGvHD. However, a study by Myllymäki et al. (2020) conducted among patients with myelodysplastic syndrome (MDS) showed that intermediate and short telomere length in blood cells of pre-transplant patients was independently associated with worse overall survival compared to recipients with the longest telomere quartile (Myllymäki et al. 2020). Peffault de Latour et al. (2012) found that shorter leukocyte telomeres before transplantation correlated with higher treatment-related mortality (TRM) after HSCT (Peffault de Latour et al. 2012). TRM is mainly associated with aGvHD and cGvHD, infections, interstitial pneumonia, and toxicity of the HSCT procedure. Interestingly, we observed a trend for longer aGvHD-free survival in patients with shorter pre-transplant telomeres, although this was not confirmed in a multivariate analysis. This observation does not seem be confirmed by earlier studies on HSCT either. However, it was noted that lung transplant patients with short telomeres were less likely to develop acute cellular rejection in the first year after surgery (Courtwright et al. 2016). In the present study, we also found that recipients who had reactivation of viral infections (CMV and/or EBV) after transplantation received haematopoietic cells from donors with shorter telomeres. Park et al. showed that the higher risk of infections in individuals with shorter telomere length could

possibly be caused by impaired adaptive immune function as a consequence of short telomeres (Park et al. 2024).

Our study also included an analysis of *TERT* polymorphism (rs2853669, T>C), located at −245 bp (Ets2 binding site) in the promoter region (*TERT*p). The presence of the *C* allele disrupts the pre-existing ETS2 binding site in *TERT*p, resulting in reduced *TERT* expression (Hsu et al. 2006; Dratwa et al. 2021), thereby counteracting the transactivation activity of the *TERT* promoter hotspot mutation (Park et al. 2014). In our previous study of AML patients, individuals carrying homozygous *CC* rs2853669 genotype were characterized with shorter overall survival than patients with *T* allele while the *CT* heterozygosity seemed to play more favourable role (Park et al. 2024). However, a meta-analysis conducted by Shen et al. showed that among cancer patients with *TERT*p mutations, homozygous *TT TERTp* rs2853669 genotype is associated with a worse prognosis (Shen et al. 2017). In the present study, we observed that patients with allele *TERT*p rs2853669 *T* had a significantly shorter aGvHD-free survival, and a higher risk of severe aGvHD. No such association was observed for donor *TERT*p rs2853669 genotypes. The association with aGvHD-free survival was confirmed in a multivariate analysis that included potential confounding factors.

A potential limitation of our study is the relatively small cohort of HSCT patients. Furthermore, our study group is heterogeneous in terms of donor type and primary disease type, as it includes patients with haematological malignancies and non-malignant diseases. However, this may also be seen as better reflecting the diverse population of HSCT patients developing post-transplant complications. Further studies on larger cohorts of patients would be needed to verify these results.

In conclusion, our main findings suggest that the *TERT*p recipient allele rs2853669 *T* is a marker of adverse outcome in the context of aGvHD development. Shorter telomeres in donors may be associated with higher rates of viral infection and later achievement of full chimerism in HSCT recipients.

Author contributions MDK: conceptualization, methodology, formal analysis, investigation, writing - original draft preparation, writing - review and editing; PL: conceptualization, formal analysis, writing - original draft preparation, writing - review and editing; BW: conceptualization, methodology; DK: investigation, methodology; JS: investigation, data curation; MSK, WF, IS, BNA, PS, MB, AT, GB, SG: data curation, resources; KBK: conceptualization, data curation, resources, writing - review and editing, supervision, project administration, provided funding. All authors have read and agreed to the published version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The studies involving humans were approved by Wroclaw Medical University Ethics Committee (identification code KB-561/2019). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Competing interests The authors declare no competing interests.

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