

Article

Eosinophilia as Monitoring Parameter for Chronic Graft-versus-Host Disease and Vitamin D Metabolism as Monitoring Parameter for Increased Infection Rates in Very Long-Term Survivors of Allogeneic Stem Cell Transplantation—A Prospective Clinical Study

Thomas Neumann ¹, Nadette Peters ¹, Laila Schneidewind ^{1,2}  and William Krüger ^{1,*} 

¹ Department of Hematology and Oncology, University Medical Center Greifswald, D-17475 Greifswald, Germany; thomas.neumann@med.uni-greifswald.de (T.N.); nadette.peters@gmx.de (N.P.); laila.schneidewind@uni-greifswald.de (L.S.)

² Department of Urology, Inselspital, University of Bern, CH-3010 Bern, Switzerland

* Correspondence: william.krueger@med.uni-greifswald.de

Abstract: Background: Our aim is to investigate cardiovascular risk factors, chronic graft-versus-host disease (CGvHD), and vitamin D metabolism in very long-term survivors of adult allogeneic stem cell transplantation (alloSCT). Methods: This study is a prospective unicentric, non-interventional trial. The detailed study protocol is available via the WHO Clinical Trial Registry. Results: We were able to include 33 patients with a mean age of 60.5 years (SD 11.1). Acute myeloid leukemia (AML) was the most frequent underlying disease ($n = 12$; 36.4%). The median survival time was 9.0 years (IQR 8.5–13.0). Relevant cardiovascular risk factors in the study population are the body mass index, cholesterol, LDL cholesterol, and lipoprotein(a). Cardiovascular risk factors have no significant impact on HRQoL. CGvHD of the skin as a limited disease was present in six patients (18.2%), and it has no impact on HRQoL. CGvHD was significantly associated with eosinophilia in peripheral blood ($p = 0.003$). Three patients (9.1%) had a shortage of calcitriol, and one patient (3.0%) took calcium substitution. The shortage is significantly associated with increased infection rates ($p = 0.038$). Conclusions: Cardiovascular risk factors and CGvHD need to be closely monitored. Eosinophilia might be a good and convenient monitoring parameter for CGvHD.

Keywords: allogeneic stem cell transplantation; long-term survivors; cardiovascular risk; graft-versus-host disease; vitamin D metabolism; quality of life



Citation: Neumann, T.; Peters, N.; Schneidewind, L.; Krüger, W. Eosinophilia as Monitoring Parameter for Chronic Graft-versus-Host Disease and Vitamin D Metabolism as Monitoring Parameter for Increased Infection Rates in Very Long-Term Survivors of Allogeneic Stem Cell Transplantation—A Prospective Clinical Study. *BioMed* **2024**, *4*, 293–301. <https://doi.org/10.3390/biomed4030023>

Academic Editor: Wolfgang Graier

Received: 13 July 2024

Revised: 24 August 2024

Accepted: 25 August 2024

Published: 27 August 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Allogeneic stem cell transplantation (alloSCT) is a common treatment for malignant and non-malignant hematological diseases. Advances in the clinical standard operating procedures and supportive care have led to improved outcomes and an increasing number of long-term survivors. Most deaths occur within the first two years, mostly due to relapse, acute or chronic graft-versus-host disease (GvHD), infections, or other acute or chronic adverse events [1–3]. Certainly, patients who survive beyond two years after transplantation also have an increased risk of long-term complications, which may impact their survival, overall outcomes, and health-related quality of life (HRQoL) [2–4]. Reported long-term complications in this special patient population include chronic kidney disease and viral infections, e.g., BK polyomavirus (BKPyV)-associated nephropathy (BKVAN) [2,3,5–11].

Reports in recent years have focused on cardiovascular risk assessment and the significance of chronic GvHD [12–21]. Thereof, chronic GvHD is common and has a deep impact on HRQoL, e.g., Yu et al. reported in their survey that the symptom burden of chronic GvHD is high, and the patients felt that their symptoms' severity interfered with physical

functioning and the activities of daily life [15]. Furthermore, Hansen et al. concluded that patients with more severe chronic GvHD, especially involving the skin and the gastrointestinal tract, are at risk for inferior psychological and physical outcomes, so they may benefit from proactive interventions to optimize functioning [19].

Additionally, data on vitamin D metabolism are sparse, especially regarding long-term survivors (more than five years after alloSCT) in adult alloSCT [20]. This is despite the fact that vitamin D is essential in calcium, phosphate, and bone homeostasis, and acts as an immunomodulator, which influences the innate and adaptive immune systems (to fight against pathogens). Furthermore, it is described that low levels of serum calcitriol are associated with an increased risk of developing immune-related diseases, e.g., psoriasis, type 1 diabetes, multiple sclerosis and, most importantly for the alloSCT patient population, autoimmune diseases like chronic GvHD [21–23].

Therefore, a prospective clinical study to assess the health status and quality of life in long-term survivors of adult aSCT (>5 years following transplantation) at our institution has been conducted. This is a sub-analysis of cardiovascular risk profile and chronic GvHD, as the most relevant factors in this patient population, and their impact on HRQoL. Furthermore, we describe the vitamin D metabolism.

Regarding the primary endpoint, this descriptive analysis focuses on cardiovascular risk and parameters of chronic GvHD and HRQoL, including socioeconomic status, as well as a descriptive analysis on vitamin D metabolism, summarizing calcium, phosphate, and PTH. Secondary endpoints include association of chronic GvHD with immunological factors, the impact of cardiovascular risk and chronic GvHD on HRQoL, and vitamin D and its associations with immunological factors, such as composition of the immune system, abundance of immunoglobulins, incidence of chronic GvHD, and infections that may be related to the shortage of calcitriol.

2. Materials and Methods

2.1. Development of the Study and Study Population

This study was conducted according to the guidelines in the synthesis of qualitative research (ENTREQ) [24]. Firstly, we obtained the approval of the local ethics review board at the University Medicine in Greifswald (BB 146/15 from 20 October 2015). Secondly, this study was registered at WHO Clinical Trial Registry (Universal Trial Number UTN U1111-1176-5256).

Formally, this study is a prospective unicentric, non-interventional trial. The inclusion criteria were as follows: adult patients over 18 years receiving their first allogeneic stem cell transplantation at our institution for underlying hematological disease, at least five years of survival following stem cell transplantation, and no clinical signs of relapse or progress of underlying hematological disease. There were no further exclusion criteria. All relevant patient data were collected according to the study protocol, which can be assessed with the Universal Trial number (UTN).

The patients were assessed at the annual transplantation follow-up, when the study was started and the inclusion criteria were met. From April 2019 until August 2020, we were able to include 33 patients in our study. Three patients from our center, who met the inclusion criteria, declined to participate in this study. Additionally, we have described the methods of this prospective clinical trial before [2,3].

2.2. Definitions, Questionnaire, and Statistical Analysis

The definitions and all assessed parameters are accessible via UTN number.

The EORTC-QLQ-C30, in its current version 3.0, is a well-established and validated questionnaire for HRQoL of oncological patients. It has five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), where a higher value means higher functionality, and nine symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), where the higher score means a higher symptom burden.

Furthermore, a Global Health Score (GHS) can be calculated, meaning a higher score is a better health status. The questionnaire was analyzed according to its manual [25,26].

For each numeric variable, the numeric distribution was assessed by the Kolmogorov–Smirnov test. Descriptive statistics were performed with mean and standard deviation for normal distribution, or with median and IQR for non-parametric data. For parametric continuous variables the Student *t*-test was used, and for parametric categorical variables the chi-square test was used. All reported *p*-values were based on a two-sided hypothesis; *p* < 0.05 was considered to be significant. All statistical calculations were performed using Statistical Package for the Social Sciences 28.0 software (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic Characterization of the Study Population

The analysis included 33 patients with a mean age of 60.5 years (SD 11.1), of whom 20 (60.6%) were male and 13 (39.4%) were female. Acute myeloid leukemia (AML) was the most frequent underlying disease (*n* = 12; 36.4%). The median survival time was 9.0 years (IQR 8.5–13.0). Table 1 shows an overview of the demographic characterization of the study population.

Table 1. Demographic characterization of the study population (*n* = 33).

Parameter	N (%)	Mean (SD)	Median (IQR)
Age	-	60.5 (11.1)	-
Sex	-	-	-
Male	20 (60.6)	-	-
Female	13 (39.4)	-	-
Underlying disease	-	-	-
AML	12 (36.4)	-	-
NHL	11 (33.3)	-	-
MPS	4 (12.1)	-	-
ALL	2 (6.1)	-	-
MDS	2 (6.1)	-	-
MM	2 (6.1)	-	-
Overall survival in years	-	-	9.0 (8.5–13.0)
Donor	-	-	-
Related	9 (27.3)	-	-
Matched-unrelated	15 (45.5)	-	-
Mismatched-unr C: elated	9 (27.03)	-	-
Number of mismatches	-	-	0 (0–0.5)
Donor chimerism >95%	33 (100.0)	-	-
BMI	-	28.4 (4.9)	-
ECOG	-	-	-
0	21 (63.6)	-	-
1	10 (30.3)	-	-
2	2 (6.1)	-	-
CCI	-	-	0 (0–2.5)

SD = standard deviation; IQR = interquartile range; AML = acute myeloid leukemia; NHL = non-Hodgkin lymphoma; MPS = myeloid proliferative syndrome; ALL = acute lymphatic; leukemia; MDS = myeloid dysplastic syndrome; MM = multiple myeloma; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; CCI = Charlson Comorbidity Index.

3.2. Cardiovascular Risk Profile

Relevant cardiovascular risk factors in the study population are the body mass index (BMI; above 25.0), cholesterol (above 6.0 mmol), LDL cholesterol (above 3.4 mmol/L), and lipoprotein(a) (above 300 mg/L). All investigated cardiovascular risk factors with their references are shown in Table 2.

Table 2. Cardiovascular risk factors of the study population ($n = 33$).

Parameter	Median (IQR)	Reference
NTproBNP in pg/mL	106.0 (63.5–175.5)	0–125
HbA1c in %	5.8 (5.5–6.0)	<6.5
Cholesterol in mmol/L	6.1 (5.3–6.9)	<6.0
HDL cholesterol in mmol/L	1.4 (1.1–1.7)	>1.03
LDL cholesterol in mmol/L	3.7 (3.1–4.5)	0–3.34
Triglycerides in mmol/L	1.7 (1.0–2.4)	0–1.9
Lipoprotein(a) in mg/L	311.0 (24.8–442.5)	0–300
EF in %	55.0 (54.0–60.0)	50–60

IQR = Interquartile range.

Additionally, the GHS under 80 is not significantly associated with the cardiovascular risk factor BMI $p = 0.808$, cholesterol $p = 0.848$, LDL cholesterol $p = 0.701$, and lipoprotein(a) $p = 0.265$, respectively. Furthermore, GHS under 50 is also not associated significantly with these factors ($p = 0.290$; $p = 0.269$; $p = 0.450$; and $p = 0.560$). Interestingly, the above factors are also not significantly associated with a physical functioning score under 50 ($p = 0.157$; $p = 0.663$; $p = 1.0$; and $p = 0.515$).

3.3. Graft-versus-Host Disease

Fourteen patients (42.4%) had acute GvHD in their patient history. All these cases of acute GvHD showed skin involvement, and three (9.1%) patients also had an additional involvement of the gastrointestinal tract. Six (18.2%) patients had chronic GvHD in their patient history, and also showed signs of chronic GvHD at the time of study presentation. Interestingly, all six of these patients had limited chronic GvHD of the skin and were receiving local prednisolone therapy. No patient required systemic steroid treatment. Table 3 illustrates the association of chronic GvHD with cellular immunological factors of the innate and adaptive immune system as well as with immunoglobulins. In summary, a significant association of chronic GvHD was only observed with eosinophilia in the peripheral blood ($p = 0.003$).

Table 3. Associations with immunological factors and chronic graft-versus-host disease ($n = 33$).

Immunological Parameter	Median (IQR)	Reference	Association with cGvHD p Value
Lymphocytes in GpT/L	1.9 (1.4–2.7)	1.0–5.0	0.263
Neutrophiles in GpT/L	3.0 (2.4–3.7)	1.5–7.5	0.072
Basophiles in %	0.5 (0.4–0.9)	0–4.0	0.076
Eosinophiles in %	1.5 (1.2–2.8)	0.0–7.0	0.003
T4/T8 ratio	0.9 (0.7–1.3)	0.6–2.8	0.817
NK cells in μ L	300.0 (172.5–431.0)	90–590	0.386
B cells in μ L	275.0 (173.0–378.5)	90–660	0.862
Immunglobuline G in g/L	9.8 (7.7–12.9)	7.0–16.0	0.691
Immunglobuline A in g/L	2.2 (1.8–2.8)	0.7–4.0	0.963
Immunglobulin M in g/L	0.8 (0.6–1.2)	0.4–2.3	0.414
Immunglobulin E in IU/mL	17.0 (6.3–52.0)	0–100	0.400

IQR = interquartile range; cGvHD = chronic graft-versus-host-disease.

3.4. Social Economic Status and Quality of Life

Thirteen (39.4%) patients had a professional activity at the time of study presentation, and twelve (36.4%) of them were full-time workers. However, 17 (51.5%) were already pensioners. Interestingly, 19 (57.6%) patients reported that their financial situation (compared to prior to transplantation) was the same, while 9 (27.3%) reported that it was worse and 5 (15.2%) reported that it is even better, respectively. Table 4 shows the association of all scales of the EORTC-QLQ-C30 with chronic GvHD. Luckily, no significant association was

reported. Furthermore, chronic GvHD is not significantly associated with GHS under 80 ($p = 0.643$) and GHS under 50 ($p = 1.0$).

Table 4. Association between scales of the EORTC-QLQ-C30 and chronic graft-versus-host disease ($n = 33$).

Scores/Scales	Item	Mean (SD)	Association with cGVHD p Value
Global Health Score	GHS	69.5 (20.2)	0.488
Functional Scales	Physical Functioning	81.2 (19.5)	0.488
	Role Functioning	83.3 (22.4)	0.342
	Emotional Functioning	77.6 (19.4)	0.249
	Cognitive Functioning	81.3 (19.9)	0.062
	Social Functioning	87.9 (19.6)	0.230
Symptom Scales	Fatigue	28.0 (25.7)	0.118
	Nausea and Vomiting	3.0 (12.8)	0.789
	Pain	29.3 (30.6)	0.281
	Dyspnea	9.1 (19.1)	0.336
	Insomnia	39.3 (33.9)	0.106
	Appetite loss	3.0 (12.8)	0.090
	Constipation	8.0 (16.7)	0.098
	Diarrhea	9.0 (17.2)	0.098
	Financial Difficulties	11.1 (23.0)	0.694

SD = standard deviation; cGVHD = chronic graft-versus-host-disease.

3.5. Vitamin D Metabolism and Influence on Immunological Factors

Regarding vitamin D metabolism, the mean calcium in mmol/L was 2.3 (SD 0.08; laboratory reference: 2.12–2.52), the mean phosphate in mmol/L was 0.9 (SD 0.15; laboratory reference: 0.60–1.60), calcifediol in $\mu\text{g/L}$ was 25.8 (SD 13.9; laboratory reference: >30.0), calcitriol in ng/L was 46.8 (SD 18.1; laboratory reference: 20.0–62.5), and PTH in pg/mL was 73.9 (SD 82.8; laboratory reference: 15.0–65.0), respectively. One patient (3.0%) took calcium substitution and three patients (9.1%) had a shortage of calcitriol (defined according to the Clinical Subcommittee of the Endocrine Society as a deficiency of calcitriol, as an active metabolite of vitamin D, less than 20 ng/mL).

Table 5 gives an overview on associations of the cellular immune system and immunoglobulins with the shortage of calcitriol. Overall, there is no significant association. Additionally, the shortage is also not significantly linked to chronic GvHD at time of study presentation ($p = 0.464$). Interestingly, the shortage is significantly associated with increased infection rates in patient history ($p = 0.038$). Concerning HRQoL, the shortage of calcitriol is not significantly associated with GHS under 80 ($p = 0.170$) and under 50 ($p = 0.500$). Furthermore, it is not associated with a significant symptom score in pain above 50 ($p = 0.578$).

Table 5. Association of shortage of calcitriol with immunological factors ($n = 33$).

Immunological Parameter	Median (IQR)	Reference	p Value Association with Shortage of Calcitriol
Lymphocytes in GpT/L	1.9 (1.4–2.7)	1.0–5.0	0.950
Neutrophils in GpT/L	3.0 (2.4–3.7)	1.5–7.5	0.287
Basophiles in %	0.5 (0.4–0.9)	0–4.0	0.193
Eosinophiles in %	1.5 (1.2–2.8)	0.0–7.0	0.706
T4/T8 ratio	0.9 (0.7–1.3)	0.6–2.8	0.474
NK cells in μL	300.0 (172.5–431.0)	90–590	0.943
B cells in μL	275.0 (173.0–378.5)	90–660	0.886
Immunglobuline G in g/L	9.8 (7.7–12.9)	7.0–16.0	0.552
Immunglobuline A in g/L	2.2 (1.8–2.8)	0.7–4.0	0.117
Immunglobulin M in g/L	0.8 (0.6–1.2)	0.4–2.3	0.707
Immunglobulin E in IU/mL	17.0 (6.3–52.0)	0–100	0.103

IQR = Interquartile range.

4. Discussion

We conducted a prospective clinical study of the health status and HRQoL in very long-term survivors of alloSCT with a median overall survival time of 9.0 years. Overall, the patients are in a good health condition. Relevant cardiovascular risk factors in the study population are the body mass index (BMI; above 25.0), cholesterol (above 6.0 mmol/L), LDL cholesterol (above 3.4 mmol/L), and lipoprotein(a) (above 300 mg/L), but luckily, they do not seem to have an impact on HRQoL. However, recent reports emphasize the importance of cardiovascular risk assessment and impairment of cardiac function in long-term survivors of alloSCT [14,16]. Despite the fact that our patient population is mostly in good shape, cardiovascular risk factors are still present, so we must agree with the other publications that cardiovascular risk assessment and monitoring is necessary in this special patient group [14,16]. Furthermore, Dillon et al. concluded in their study that their results highlight the potential therapeutic awareness and utility of exercise-based cardiovascular assessment in discovering cardiovascular dysfunction in alloSCT survivors [14]. Consequently, we must state that careful monitoring of cardiovascular risk in this special patient group gives the opportunity for early intervention or even prehabilitation, so there is potential for further improvement of outcome parameters.

Regarding chronic GvHD, we only observed six cases (18.2%) of chronic GvHD, limited disease, all involving the skin. This is in contrast to the literature, where the prevalence is described as high (over 30%) [18,23]. One reason for our observation might be that this is a patient group of very long-term survivors (at least over 5 years), and most other reports arise from populations which survived only for at least 2 years. Additionally, in our study population, chronic GvHD does not have an impact on HRQoL. Diep et al. stated the same. There was a high prevalence of chronic GvHD, but there was no real impact on HRQoL [18]. This finding stays in contrast to most recent reports, where chronic GvHD seems to be the most important clinical factor, which has a strong impact on physical functioning and activities of daily life [12,15]. Furthermore, Hansen et al. reported that patients with chronic GvHD manifesting in the skin and gastrointestinal tract have the most severe symptoms interfering with HRQoL, like mood disturbance, fatigue, and pain. The authors concluded that their results suggest that patients with more severe chronic GvHD, and those with chronic GvHD manifesting in the skin, gastrointestinal tract, or lungs, are at risk for poorer psychological and physical outcomes and may benefit from proactive interventions to optimize functioning [19]. On the whole, we must agree that chronic GvHD, and the impact of physical functioning or psychological problems, needs close monitoring in long-term survivors of alloSCT. This monitoring might further improve outcomes, especially functional ones.

Some authors suggest close immune monitoring in this special patient group, especially when they suffer from GvHD [13,17]. Therefore, we evaluated the association of chronic GvHD with factors of the cellular immune system and immunoglobulins. We only found a significant association between eosinophilia and chronic GvHD. This must be discussed in detail since results from the literature about the association of GvHD and eosinophilia are inconclusive. Most knowledge about this topic arises from retrospective data. Imahashi et al. concluded in their retrospective adult patient cohort of survivors of adult alloSCT that eosinophilia was associated with milder acute GvHD and better prognosis among patients with acute GvHD, but the prognostic value of eosinophilia for GVHD might be limited. Additionally, the pathophysiology behind eosinophilia remains to be investigated [27]. Regarding chronic GvHD, Brandt Mortensen et al. observed in their retrospective study no significant association between chronic GvHD with concomitant eosinophilia and long-term clinical outcomes, and subgroup analyses revealed a considerable confounding effect of ongoing steroid treatment. The authors concluded that prognostic conclusions regarding chronic GvHD with concomitant eosinophilia after alloSCT should be interpreted with caution, and they suggest a prospective evaluation of chronic GvHD with eosinophilia following strict definitions and additional cytokine profiling [28]. However, the study of Beier et al. proposes that the course of eosinophil counts may provide a useful

parameter in the assessment of chronic GvHD development and activity, allowing the potential identification of patient subgroups with ongoing outcomes and reduced chronic GvHD mortality. In this setting, the authors suggest IL-4 and IL-5 as mediators in immune response due to GvHD causing eosinophilia, as well as steroid therapy being a possible confounder [29]. At least to our knowledge, Basara et al. performed the only prospective investigation in this subject area. It was concluded that bone marrow eosinophilia after alloSCT, probably mediated by endogenous IL-2, predicts severe acute GvHD, but its functional significance is not known and should be determined [30]. So, what is special about our patient population in comparison to the other studies? Firstly, we provide prospective data with a point prevalence of chronic GvHD and eosinophilia. Secondly, these are very long-term survivors with a median overall survival time of 9.0 years, and finally, our patients did not take any systemic steroids. In summary of this data situation, we propose that eosinophilia might not be a good prognostic marker, but a good marker for monitoring the activity of GvHD. Furthermore, it is a very convenient as well as cost-effective marker and should be considered because of the economic pressure in the healthcare system. Therefore, further prospective investigations are necessary, including clear definitions and predefined time points of blood collection as well as evaluation of the pathophysiology behind this correlation of eosinophilia and GvHD. In this case, we first suggest to include a panel of proinflammatory interleukins, e.g., IL-2, IL-4, and IL-5, into these prospective studies.

Our study population is also in a good condition regarding HRQoL. The most important symptoms are fatigue and pain. Consequently, clinical monitoring of these symptoms and subsequent treatment are necessary during follow-up.

Interestingly, vitamin D deficiency in long-term survivors of adult alloSCT is significantly linked to increased infection rates. Several studies have linked low vitamin D levels to increased risk of infections [21]. It is also described in clinical evaluations that this deficiency can lead to more severe infections and a worse outcome, e.g., Seok et al. reported in their prospective cohort study of 129 subjects that severe vitamin D deficiency can independently effect poor prognosis related to sepsis [31]. This is also according to experimental investigations. Yeh et al. described in their murine sepsis model that their findings suggest that calcitriol treatment after sepsis induction upregulated the renin–angiotensin-system-associated anti-inflammatory pathway and decreased immune cell infiltration, which may have alleviated the severity of acute lung injury in obese mice [32]. Unfortunately, little is known about the benefits and harms of vitamin D substitution in long-term survivors of adult alloSCT. Still, vitamin D supplementation may have the potential to decrease infection rates in these patients, but further interventional investigations are necessary [31]. Furthermore, vitamin D deficiency might also have an impact on HRQoL, e.g., in terms of bone pain or bone discomfort. Detailed and future investigations should also address this issue. In this context, it deserves mentioning that recent studies mainly focused on COVID-19 infections. However, in long-term survivors of alloSCT, other infections are important to investigate as well, e.g., cytomegalovirus (CMV) infections/reactivations and other types of respiratory virus infections.

Despite some strengths, like the prospective nature of our study and the long overall survival time, we have some limitations as well, e.g., the small sample size, which might lead to selection bias. Consequently, we suggest further prospective multicenter investigations, as discussed before, regarding eosinophilia and GvHD. These studies might reveal more robust results. Additionally, another confounder to mention is the differential influence of immune parameters due to different underlying hematological diseases.

In summary, clinical monitoring of cardiovascular risk factors and GvHD is very important during follow-up in long-term survivors of alloSCT, because early intervention or even prehabilitation can further improve outcomes. Further prospective investigations are necessary. Eosinophilia might be a good and cheap monitoring parameter for GvHD in survivors of alloSCT. Here, prospective investigations are of special relevance; they should include the question about the pathophysiology behind eosinophilia in GvHD. Concerning this pathophysiology, evaluation of proinflammatory cytokines could be an interesting starting point.

5. Conclusions

In summary, clinical monitoring of cardiovascular risk factors and GvHD are very important during follow-up in long-term survivors of alloSCT, because early intervention or even prehabilitation can further improve outcomes. Further prospective investigations are necessary. Eosinophilia might be a good and cheap monitoring parameter for GvHD in survivors of alloSCT. Here, prospective investigations are of special relevance; they should include the question about the pathophysiology behind eosinophilia in GvHD. Concerning this pathophysiology, evaluation of proinflammatory cytokines could be an interesting starting point. Additionally, vitamin D metabolism, and its link to increased infection rates and vitamin D substitution, needs further investigation.

Author Contributions: Conceptualization, T.N. and L.S.; methodology, L.S.; software, L.S.; validation, all authors; formal analysis, T.N. and L.S.; investigation, N.P.; resources, W.K.; data curation, all authors; writing—original draft preparation, all authors; writing—review and editing, all authors; visualization, L.S.; supervision, W.K.; project administration, T.N. and L.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Before starting this study, we obtained the approval of the local ethics review board at the University Medicine in Greifswald (BB 146/15 from 20 October 2015). Furthermore, this study was registered at WHO Clinical Trial Registry (Universal Trial Number UTN U1111-1176-5256).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: All data regarding this study are available upon request from the corresponding author.

Acknowledgments: Firstly, we would like to thank all study participants. Secondly, we would like to thank all the study nurses and nurses of our department who made this study a great success—thank you for your advice.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Wingard, W.R.; Majhail, N.S.; Brazaukas, R.; Wang, Z.; Sobocinski, K.A.; Jacobson, D.; Sorrow, M.L.; Horowitz, M.M.; Bolwell, B.; Rizzo, J.D.; et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J. Clin. Oncol.* **2011**, *29*, 2230–2239. [[CrossRef](#)] [[PubMed](#)]
2. Neumann, T.; Peters, N.; Kranz, J.; Dräger, D.L.; Heidel, F.H.; Krüger, W.; Schneidewind, L. Significance of BK Polyomavirus in Long-Term Survivors after Adult Allogeneic Stem Cell Transplantation. *Biology* **2021**, *10*, 553. [[CrossRef](#)] [[PubMed](#)]
3. Schneidewind, L.; Neumann, T.; Peters, N.; Kranz, J.; Probst, K.A.; Heidel, F.H.; Hakenberg, O.W.; Krüger, W. Significance of men's health in long-term survivors of allogeneic stem cell transplantation. *Bone Marrow Transplant.* **2022**, *57*, 998–1000. [[CrossRef](#)] [[PubMed](#)]
4. Torrent, A.; Ferrá, C.; Batlle, M.; Hidalgo, F.; Jiménez-Lorenzo, M.-J.; Ribera, J.-M. Prospective follow-up of adult long-term survivors of allogeneic haematopoietic stem cell transplantation. *Med. Clin.* **2020**, *157*, 281–284. [[CrossRef](#)]
5. Jo, T.; Arai, Y.; Kondo, T.; Kitano, T.; Hishizawa, M.; Yamashita, K.; Takaori-Kondo, A. Chronic kidney disease in long-term survivors after allogeneic hematopoietic stem cell transplantation: Retrospective analysis at a single institution. *Biol. Blood Marrow Transplant.* **2017**, *23*, 2159–2165. [[CrossRef](#)]
6. Pinana, J.L.; Valcarcel, D.; Martino, R.; Barba, P.; Moreno, E.; Sureda, A.; Vega, M.; Delgado, J.; Briones, J.; Brunet, S.; et al. Study of kidney function impairment after reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. A single center experience. *Biol. Blood Marrow Transplant.* **2009**, *45*, 21–29. [[CrossRef](#)]
7. Liu, H.; Li, Y.-F.; Liu, B.-C.; Ding, J.-H.; Chen, B.-A.; Xu, W.-L.; Qian, J. A multicenter, retrospective study of acute kidney injury in adult patients with nonmyeloablative hematopoietic SCT. *Bone Marrow Transplant.* **2009**, *45*, 153–158. [[CrossRef](#)]
8. Kagoya, Y.; Kataoka, K.; Nannya, Y.; Kurokawa, M. Pretransplant predictors and posttransplant sequels of acute kidney injury after allogeneic stem cell transplantation. *Biol. Blood Marrow Transplant.* **2011**, *17*, 394–400. [[CrossRef](#)]
9. Shimoi, T.; Ando, M.; Munakata, W.; Kobayashi, T.; Kakihana, K.; Ohashi, K.; Akiyama, H.; Sakamaki, H. The significant impact of acute kidney injury on CKD in patients who survived over 10 years after myeloablative allogeneic SCT. *Bone Marrow Transplant.* **2012**, *48*, 80–84. [[CrossRef](#)]
10. Hingorani, S. Renal complications of hematopoietic-cell transplantation. *N. Engl. J. Med.* **2016**, *374*, 2256–2267. [[CrossRef](#)]

11. Haavisto, A.; Mathiesen, S.; Suominen, A.; Lähteenmäki, P.; Sørensen, K.; Ifversen, M.; Juul, A.; Nielsen, M.M.; Müller, K.; Jahnukainen, K. Male sexual function after hematopoietic stem cell transplantation in childhood: A multicenter study. *Cancers* **2020**, *12*, 1786. [[CrossRef](#)] [[PubMed](#)]
12. McErlean, G.; Tapp, C.; Brice, L.; Pradhan, A.; Gilroy, N.; Kabir, M.; Greenwood, M.; Larsen, S.R.; Moore, J.; Gottlieb, D.; et al. Decisional Regret in Long-Term Australian Allogeneic Hematopoietic Stem Cell Transplantation Survivors: A Cross-Sectional Survey. *Clin. Nurs. Res.* **2023**, *32*, 1134–1144. [[CrossRef](#)] [[PubMed](#)]
13. Teshima, T.; Boelens, J.J.; Matsuoka, K. Novel insights into GVHD and immune reconstitution after allogeneic hematopoietic cell transplantation. *Blood Cell Ther.* **2023**, *6*, 42–48. [[PubMed](#)]
14. Dillon, H.T.; Foulkes, S.; Horne-Okano, Y.A.; Kliman, D.; Dunstan, D.W.; Daly, R.M.; Fraser, S.F.; Avery, S.; Kingwell, B.A.; La Gerche, A.; et al. Reduced cardiovascular reserve capacity in long-term allogeneic stem cell transplant survivors. *Sci. Rep.* **2023**, *13*, 2122. [[CrossRef](#)]
15. Yu, J.; Hamilton, B.K.; Turnbull, J.; Stewart, S.K.; Vernaya, A.; Bhatt, V.; Meyers, O.; Galvin, J. Patient-reported symptom burden and impact on daily activities in chronic graft-versus-host disease. *Cancer Med.* **2023**, *12*, 3623–3633. [[CrossRef](#)]
16. Zhao, Y.; He, R.; Oerther, S.; Zhou, W.; Vosough, M.; Hassan, M. Cardiovascular Complications in Hematopoietic Stem Cell Transplanted Patients. *J. Pers. Med.* **2022**, *12*, 1797. [[CrossRef](#)]
17. Novitzky-Basso, I.; Schain, F.; Batyrbekova, N.; Webb, T.; Remberger, M.; Keating, A.; Mattsson, J. Population-based real-world registry study to evaluate clinical outcomes of chronic graft-versus-host disease. *PLoS ONE* **2023**, *18*, 0282753. [[CrossRef](#)]
18. Diep, P.P.; Rueegg, C.S.; Burman, M.M.; Brinch, L.; Bø, K.; Fosså, K.; Landrø, L.; Loge, J.H.; Lund, M.B.; Massey, R.J.; et al. Graft-versus-Host-Disease and Health-Related Quality of Life in Young Long-term Survivors of Cancer and Allogeneic Hematopoietic Stem Cell Transplantation. *J. Adolesc. Young Adult Oncol.* **2023**, *12*, 66–75. [[CrossRef](#)]
19. Hansen, J.L.; Juckett, M.B.; Foster, M.A.; Rumble, M.E.; Morris, K.E.; Hematti, P.; Costanzo, E.S. Psychological and physical function in allogeneic hematopoietic cell transplant survivors with chronic graft-versus-host disease. *Cancer Surviv.* **2023**, *17*, 646–656. [[CrossRef](#)]
20. Gunasekaran, U.; Agarwal, N.; Jagasia, M.H.; Jagasia, S.M. Endocrine complications in long-Term survivors after allogeneic stem cell transplant. *Semin. Hematol.* **2012**, *49*, 66–72. [[CrossRef](#)]
21. Sirbe, C.; Rednic, S.; Grama, A.; Pop, T.L. An Update on the Effects of Vitamin D on the Immune System and Autoimmune Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 9784. [[CrossRef](#)]
22. Lee, C.J.; Wang, T.; Chen, K.; Arora, M.; Brazauskas, R.; Spellman, S.R.; Kitko, C.; MacMillan, M.L.; Pidala, J.A.; Badawy, S.M.; et al. Severity of Chronic Graft-versus-Host Disease and Late Effects Following Allogeneic Hematopoietic Cell Transplantation for Adults with Hematologic Malignancy. *Biol. Blood Marrow Transplant.* **2024**, *30*, 97. [[CrossRef](#)]
23. Yu, J.; Khera, N.; Turnbull, J.; Stewart, S.K.; Williams, P.; Bhatt, V.; Meyers, O.; Galvin, J.; Lee, S.J. Impact of Chronic graft-versus-host Disease on Patient Employment, Income, and Informal Caregiver Burden: Findings from the Living with Chronic GVHD Patient Survey. *Biol. Blood Marrow Transplant.* **2023**, *29*, 470. [[CrossRef](#)] [[PubMed](#)]
24. Tong, A.; Flemming, K.; McInnes, E.; Oliver, S.; Craig, J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Med. Res. Methodol.* **2012**, *12*, 181. [[CrossRef](#)]
25. Aaronson, N.K.; Ahmedzai, S.; Bergman, B.; Bullinger, M.; Cull, A.; Duez, N.J.; Filiberti, A.; Flechtner, H.; Fleishman, S.B.; de Haes, J.C.J.M.; et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J. Natl. Cancer Inst.* **1993**, *85*, 365–376. [[CrossRef](#)] [[PubMed](#)]
26. Fayers, P.M.; Aaronson, N.K.; Bjordal, K.; Groenvold, M.; Curran, D.; Bottomley, A.; on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual*, 3rd ed.; European Organisation for Research and Treatment of Cancer: Brussels, Belgium, 2001.
27. Imahashi, N.; Miyamura, K.; Seto, A.; Watanabe, K.; Yanagisawa, M.; Nishiwaki, S.; Shinba, M.; Yasuda, T.; Kuwatsuka, Y.; Terakura, S.; et al. Eosinophilia predicts better overall survival after acute graft-versus-host-disease. *Bone Marrow Transplant.* **2009**, *45*, 371–377. [[CrossRef](#)] [[PubMed](#)]
28. Brandt Mortensen, K.; Gerds, T.A.; Weis Bjerrum, O.; Lindmark, A.; Sengelov, H.; Lykkegaard Andersen, C. The prevalence and prognostic value of concomitant eosinophilia in chronic graft-versus-host disease after allogeneic stem cell transplantation. *Leuk. Res.* **2014**, *38*, 334–339. [[CrossRef](#)] [[PubMed](#)]
29. Beier, F.; Arbter, K.; Kittan, N.A.; Andreesen, R.; Krause, S.W.; Holler, E.; Hildebrandt, G.C. Regression of eosinophil counts after diagnosis of chronic graft-versus-host disease as a potential marker for improved clinical outcome. *Mol. Clin. Oncol.* **2013**, *2*, 81–86. [[CrossRef](#)]
30. Basara, N.; Kiehl, M.G.; Fauser, A.A. Eosinophilia indicates the evolution to acute graft-versus-host disease. *Blood* **2002**, *100*, 3055. [[CrossRef](#)]
31. Seok, H.; Kim, J.; Choi, W.S.; Park, D.W. Effects of Vitamin D Deficiency on Sepsis. *Nutrients* **2023**, *15*, 4309. [[CrossRef](#)]
32. Yeh, C.-L.; Wu, J.-M.; Su, L.-H.; Yang, P.-J.; Lee, P.-C.; Chen, K.-Y.; Yeh, S.-L.; Lin, M.-T. Intravenous calcitriol administration regulates the renin-angiotensin system and attenuates acute lung injury in obese mice complicated with polymicrobial sepsis. *Biomed. Pharmacother.* **2021**, *141*, 111856. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.