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High GVHD Prevalence in Travel-Based SCT despite Young Patients and HLA Matching

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ABSTRACT

Background: Patients from regions without stem cell transplantation (SCT) facilities often seek treatment abroad and return home for post-transplant care. Although extensive data exist on graft-versus-host disease (GVHD) and its risk factors, information on international SCT patients returning to countries that lack transplant facilities and expertise is scarce and not well documented.

Materials and Methods: We screened 149 transplant recipients and analyzed the data of 91 patients who received transplants abroad and were followed up at our center from January 2019 to December 2022. This observational study used data from electronic medical records and employed descriptive statistics, inferential tests, and relative risk calculations with forest plots to analyze the prevalence of GVDH and its key risk factors.

Results: Of the recipients, 31.8% were residents of nine countries residing in the UAE, and 67.2% were UAE citizens. Adults comprised 48.3% of the recipients, whereas 51.7% were pediatric patients. Hematological malignancy was the most common indication (49%), primarily in adults. Siblings comprised the majority of donors (52.6%), followed by related (23.09%) and unrelated donors (8.9%). Most patients (69.2%) received HLA-identical transplants, followed by 21.9% who received haplo-identical transplants. Among adults, 62.2% developed GVHD compared to 26% of pediatric patients. Recipients from related HLA-identical donors had a 50% prevalence of GVDH, whereas those from unrelated identical donors had a 71% prevalence. The overall prevalence of GVDH was 50% in 87.9% of patients who received allogeneic SCTs.

Conclusion: Despite favorable factors, such as young age and matched related donors, we found a high prevalence of GVDH. Ocular GVHD was less prevalent than expected, and lung GVHD was weakly correlated with established risk factors. Larger multicenter studies are needed to assess and confirm the effect of contributing factors.

Keywords: Graft-versus-host disease; Stem cell transplantation; United Arab Emirates; Risk factors for GVHD; Organ-specific correlations; Travel tourism

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INTRODUCTION

Stem cell transplantation (SCT) is a standard, potentially curative treatment for a diverse range of malignancies and bone marrow (BM) failure syndromes[1]. With a steady increase, the number of transplants surpassed 1.29 million in 2016 worldwide[2]. For years, UAE residents requiring transplants have opted for overseas options and sought care in countries such as the United States, India, Turkey, Egypt, Korea, and Europe. This "transplant tourism," while offering access to potentially life-saving SCT procedure, often translate to fragmented post-transplant care riddled with challenges. Long-distance travel exposes patients to increased infection risk, treatment interruptions, and inconsistent pre- and post-transplant protocols[3]. Published literature on SCT and its associated complications in UAE is scarce. The Department of Health provides a glimpse into the magnitude of this phenomenon, reporting on 325 patients (161 adults and 164 pediatric patients) who underwent SCT outside the UAE between 2016 and 2018[4]. However, in July 2020, the first successful BM transplant in UAE was performed[5]. Unfortunately, the progress of the SCT program was halted by the global covid-19 pandemic, further highlighting the reliance of patients from UAE on transplant tourism.

Graft-versus-Host Disease (GVHD) is the most common and severe post-transplant complication that affects morbidity, mortality, and quality of life[6,7]. With its diverse manifestations, often targeting the skin, gastrointestinal tract, and liver[8], GVHD causes uncertainty over the transplant journey, even under optimal settings[9,10]. Estimates of GVHD incidence can range from 30% to 80% and are influenced by factors such as related or unrelated donors[11,12], Human leukocyte antigen (HLA)-matching between donor and recipient[13], recipient age[14], and even sex disparities[15]. This complexity extends beyond these classical elements and encompasses minor histocompatibility antigens[16] and GVHD prophylaxis protocols [17,18].

The quality of pre- and post-transplant care depends on access to detailed pre-transplant information, the experience of the transplant center, expertise, and accessibility of evolving medications. Unfortunately, these elements often fall short in transplant tourism scenarios where fragmented care and geographical barriers impede optimal post-transplant support. Although extensive data have been published on GVHD and its risk factors, information on international patients who undergo SCT and return to their home countries that lack transplant facilities and expertise is scarce and not well-documented. Furthermore, data regarding how care disruptions and varying immunosuppressive regimens affect GVHD outcomes is limited.

Our retrospective study aimed to fill these gaps by examining GVHD incidence, risk factors, and the need for standardized post-transplant care in this context. We also investigated well-known GVHD risk factors and their potential variations, with a particular focus on organ-specific GVHD. We hope to pave the way for multicenter, well-directed studies on the impact of travel factors on international SCT outcomes.

MATERIALS AND METHODS

This retrospective analysis was conducted at our healthcare institution in Abu Dhabi, UAE. A total of 91 SCT recipients (both adults and children) of 149 transplant recipients who received follow-up care at our institution between January 2019 and December 2022 were included. Patients with incomplete medical records or fewer than two post-transplant clinic visits were excluded to ensure data reliability and completeness. Data were collected from transplant center reports and clinical documents, including recipient and donor demographics, transplant indications, pre-SCT chemotherapy lines, transplant timing, recipient blood group, donor-recipient relationships, conditioning regimens, and GVHD severity/type/organ involvement.

Descriptive statistics and inferential tests (two-sample, variance equality, and chi-squared tests) were applied. The relative risk was calculated for key risk factors and are presented as forest plots. Statistical significance was set at $p<0.05$. Owing to missing data, bivariate analysis was preferred over multivariate analysis to maintain statistical power. Variables with significant missing data (e.g., donor age and HLA alleles) were excluded from the analysis. Subgroup analyses were infeasible because

of data gaps, which limited the detailed stratification of the data.

RESULT

Age, sex, and pre-transplant timing

Among the 91 SCT recipients in our study, 87.9% (n=80) received allogeneic transplantation. Among them, 50% (n=40) developed GVHD. Among all SCT recipients, adults (70%, 28) comprised a larger proportion of GVHD cases than pediatric recipients (30%, 12). Within each group, the prevalence of GVHD was higher in adults (62.2%, 28/45) than that in children (26%, 12/46), as shown in the left panel of Figure 1. While the distribution of pediatric recipients slightly exceeded that of adults (51.65% vs. 48.35%), the overall mean age was 24.47 years. Recipient age was significantly correlated with GVHD occurrence (p=0.004). Compared to adults, pediatric recipients exhibited a reduced risk of GVHD (relative risk (RR)=0.43, 95% confidence interval (CI) 0.27–0.7), whereas adults aged >50 years faced an elevated risk of GVDH (RR=2.17, 95% CI 1.47–3.2) as shown in Figure 2.

Among them, 51 were male and 40 were female. While males exhibited a slightly higher prevalence of GVHD (55% vs. 45%), as shown in the right panel of Figure 1, recipient sex did not show a statistically significant correlation with GVHD (p>0.05). Similarly, no significant association was observed between the donor sex and GVHD (p=0.8).

Acute and chronic GVHD occurred in 52.5% and 47.5% of GVHD cases, respectively. The severity distribution was as follows: severe, 41.6%; moderate, 22.2%; and mild, 36.1%.

The mean time from diagnosis to hematopoietic SCT in our study was 47.8 months, with the average age of recipients being 19.2 years at the time of SCT. This time frame was not significantly correlated with the occurrence of GVHD (p=0.98).

Diverse backgrounds and blood groups

Among the recipients, 31.8% hailed from diverse backgrounds, with Pakistan (5%), Egypt (5%), and Sudan (4%) constituting the next highest population after native UAE patients. The prevalence of GVHD was higher among SCT recipients from Pakistan, Egypt, and Syria, as shown in Figure 3.

Regarding blood group, O+ was the most frequent (39.5%), followed by A+ (28.5%), B+ (17.5%), and O- (4.4%). No statistically significant association was observed between recipient blood group and GVHD occurrence (p=0.1).

Donor relationship

Most donors were siblings (52.6%), followed by related donors (23.09%), and smaller proportions of self- and unrelated donors (12.09%). Prevalence of GVHD in unrelated donors was the highest (63.4%), followed by siblings (58.3%) and related donors (23.8%). A significant association was noted between the overall donor-recipient relationship and GVHD occurrence (p=0.04). Owing to the limited sample size, further analysis of the association strength within the donor relationship subcategories was not feasible**.**

Transplant indication

Common transplant indications included beta thalassemia (20.8%), acute myeloid leukemia and acute lymphoblastic leukemia (14.2% each), severe combined immunodeficiency (12%), and sickle cell disease (7.6%). The frequency of distribution of GVHD and no GVHD based on hematological conditions is shown in Figure 4. Benign hematological conditions were more frequent in pediatric recipients, whereas malignant hematological conditions were predominant in adults, as shown in Figure 5. Indications for SCT influenced the occurrence of GVHD (p=0.007). Recipients with benign hematological disorders exhibited a markedly reduced risk of GVHD than those with malignant conditions (RR=0.47, 95% CI 0.28–0.79 vs. RR=2.12, CI 1.26–3.57) as indicated in Figure 2.

Stem cell sources, pre-transplant chemotherapy, and conditioning regimens

Among stem cell sources, BM was dominant (36%), followed by peripheral (26.3%) and cord blood (4%). The prevalence of GVHD varied as follows: 58% for peripheral blood, 49% for BM, and 4% for cord blood. Furthermore, 42% of the patients who underwent

SCTs did not receive any pre-transplant chemotherapy, 15% received one or three lines each, and 25% received two lines.

The prevalence of GVHD was higher in recipients who received total body irradiation (TBI) as part of the conditioning regimen (69.2%) than in those who did not (31.9%). Moreover, a lower relative risk of GVHD was observed among antithymocyte globulin (ATG) recipients (RR=0.79; 95% CI, 0.37–1.6).

HLA match, GVHD prophylaxis, and mortality

Among SCT recipients, 69.2% received HLA-identical transplants, 21.9% received haploidentical transplants, and 8.9% received non-identical transplants. The prevalence of GVHD varied as follows: 60% in non-identical transplants, 44% in identical transplants, and 42% in haploidentical transplants. Within the identical donor group, 50% of the related donors exhibited GVHD compared to 71% of the unrelated donors. However, HLA matching did not demonstrate a statistically significant association with overall occurrence of GVHD (p=0.66), as shown in Figure 2.

Regarding GVHD prophylaxis, cyclosporine was the primary agent used in 34.6% of the cases, followed by calcineurin inhibitors in 25%. The use of these agents was significantly correlated with the occurrence of GVHD (p=0.03). Unfortunately, 10% of the recipients died during data collection, predominantly adults (77%). Mortality rate was associated with the occurrence of GVHD (p=0.009).

Organ-specific GVHD

The skin was the primary organ involved in GVDH, affecting 35.5% of recipients. The subsequent organs, in descending order of involvement, were the gastrointestinal tract (including the oral tract) (25.5%), ocular (16.6%), liver (14.4%), and lungs (11.1%). Notably, except for lung involvement, the risk factors for organ-specific GVHD largely mirrored those for overall GVHD. Significant correlations were observed among all affected organs (p<0.05), except for the lungs and eyes GVHD (p=0.45) (Table 1).

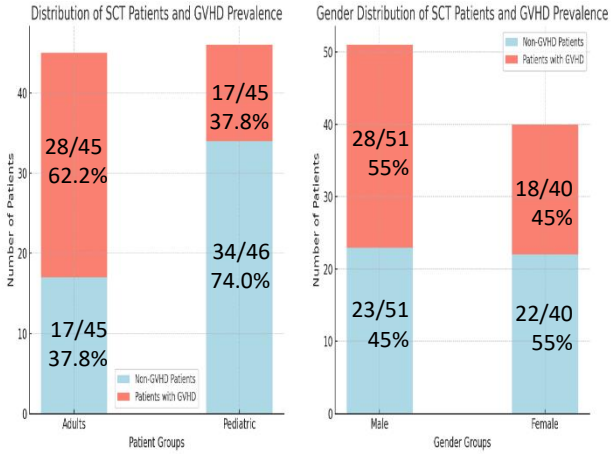

Figure 1. Distribution of stem cell transplantation (SCT) patients and prevalence of graft-versus-host disease (GVHD)

This Figure presents the distribution of SCT patients and the prevalence of GVHD) across different patient and sex groups. The left panel shows the breakdown between adult and pediatric patients, indicating that 45 adults and 46 pediatric patients received SCTs. Among these, 28 adults (62.2%) and 12 pediatric patients (26.1%) developed GVHD. The right panel displays the sex distribution, with 51 male and 40 female patients. Among them, 28 males (55%) and 18 females (45%) developed GVHD. Light blue bars represent non-GVHD patients, while salmon bars represent patients who developed GVHD.

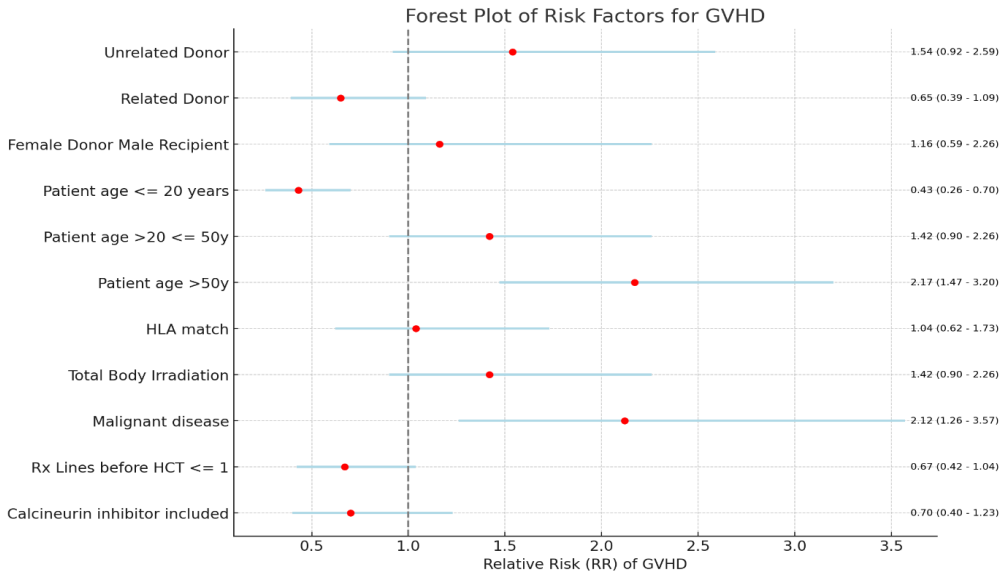

Figure 2. Forest Plot of Risk Factors for GVHD

This forest plot illustrates the relative risk (RR) of GVHD associated with various risk factors. The red dots represent the point estimates of the RR, and the light blue lines indicate the 95% confidence intervals (CIs) for each estimate. A vertical dashed line at RR = 1.0 represents the null hypothesis (no increased risk). Recipients aged >50 years and those with malignant diseases demonstrated a significantly high risk of GVHD.

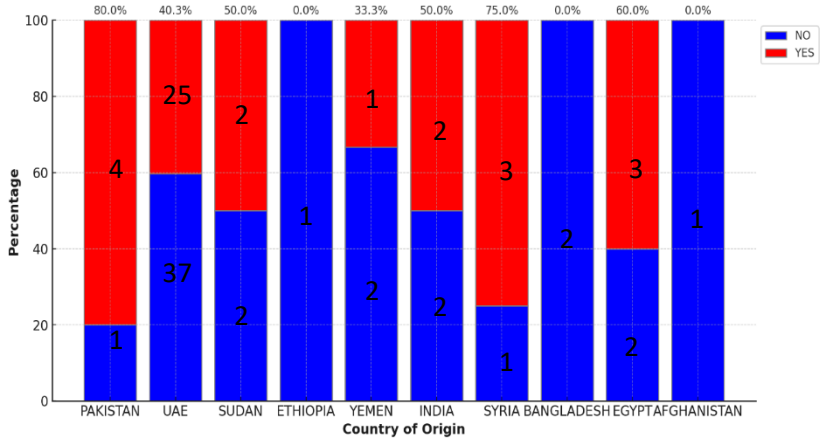

Figure 3. Percentage Distribution of GVHD by Country of Origin of SCT Patients

This bar graph displays the percentage distribution of GVHD among stem cell transplant patients who are residents of the UAE, categorized by their country of origin. The blue bars represent the percentage of patients without GVHD, whereas the red bars indicate the percentage of patients with GVHD. Numbers inside the bars represent number of patients.

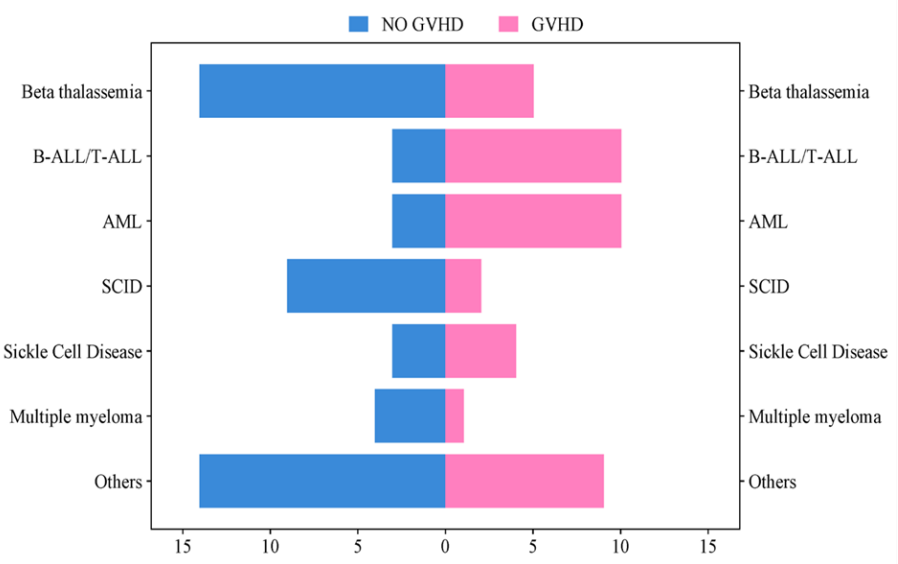

Figure 4. Distribution of Patients with and without GVDH Based on Hematological Conditions

This horizontal bar graph illustrates the distribution of patients with and without GVDH categorized by different hematological diseases. The blue bars represent the number of patients without GVHD, whereas the pink bars indicate the number of patients with GVHD. The diseases included are Beta Thalassemia, B-ALL/T-ALL, AML, SCID, Sickle Cell Disease, Multiple Myeloma, and others. This visualization provides insight into the prevalence of GVHD among patients with various hematological conditions

Table 1: Organ-specific GVHD and associated risk factors (P)

	GVHD			RISK FACTORS (P)				
	Acute	Chronic	n (%)	Recipient Age	SCT Indication	No. Lines of Rx	HLA Match	Donor Relation
SKIN	18	14	32 (35.56%)	0.00	0.06	0.25	0.88	0.02
GIT	12	11	23 (25.56%)	0.00	0.06	0.04	0.1	0.03
LIVER	8	5	13 (14.44%)	0.00	0.32	0.00	0.05	0.15
OCULAR	7	8	15 (16.67%)	0.00	0.41	0.02	0.97	0.03
LUNG	5	5	10 (11.11%)	0.50	0.54	0.12	0.08	0.55

Abbreviations: GIT,Gastrointestinal tract; GVHD,Graft-versus-host-disease; HLA,Human leukocyte antigen; SCT,Stem cell transplantation

DISCUSSION

Our study provides a comprehensive overview of GVHD among SCT recipients returning to the UAE. Most (87.9%, n=80) patients underwent allogeneic transplantation, with half (50%, n=40) developing GVHD. Furthermore, SCT recipients had a higher prevalence of GVHD (62.2%) despite a high proportion (50%) of HLA-identical related donors. This suggests that unique factors associated with travel-based transplants, including care disruptions, inconsistent medical protocols, and physiological stress, contribute to increased susceptibility to GVHD. The absence of robust post-transplant support in the UAE and psychological stress further compound these issues. These findings highlight the need for standardized post-transplant care strategies to reduce GVHD in this vulnerable population.

High GVHD risk was observed

While the overall GVHD rate of 50% aligns with the higher range reported in the literature, the prevalence of GVHD in adult recipients was 62.2 %. This observed rate surpassed the 28% GVHD rate reported in a large-scale study of allogeneic transplants over two decades (1990-2015)[19]. The GVHD prevalence of 71% observed in this study surpasses the 44–50% prevalence of GVHD reported by the National Marrow Donor Program for unrelated donors. The prevalence of GVHD (50%) was significantly higher than the 28% observed in HLA-matched sibling transplants[20]. Higher prevalence of GVHD was observed in this cohort, even when the majority were pediatric recipients (52%), had HLA-identical donors (69.2%), and more than half of the donors were siblings (52.6%)[20]. These characteristics, associated with lower GVHD occurrence, might mask the full effect of potential factors, such as travel complexities and disruptions in post-transplant care.

Younger age lowers GVHD risk

Recipient age emerged as the most influential risk factor for GVHD in our cohort, consistent with established literature [20,13]. As expected, a strong correlation was observed between adult recipients and higher GVHD rates (p=0.004; Figure 2. Compared to adults, pediatric patients exhibited a substantially lower relative risk of GVHD (RR=0.43; 95% CI 0.27–0.7), highlighting the significant impact of age on GVHD development. While existing studies suggest an increased risk for donors aged >30 years[21], our analysis could not explore this relationship because of missing data.

Transplant indication and impact of conditioning regimens

Underlying diseases requiring SCT significantly affect GVHD development. Benign hematological conditions, predominantly affecting pediatric recipients as shown in Figure 5, exhibited a markedly lower GVHD risk than malignant hematological diseases, which are more prevalent in adults[19]. This observation aligns with the broader literature, where primary transplant indications often include hemoglobinopathies, followed by malignancies such as leukemia[2]. Furthermore, SCT indication was identified as an important risk factor, with a significantly higher relative risk of GVHD associated with malignant conditions (RR=2.12; 95% CI, 1.26–3.57) as illustrated in Figure 2. This disparity in risk likely stems from the complex interplay of factors, including variations in conditioning regimens[22], potential use of TBI, and differences in pre-transplant treatment strategies[23].

Sibling/Related donors reduce GVHD risk

Our findings align with the established preference for matched siblings or related donors over matched unrelated donors to mitigate GVHD risk[18,24]. This trend was observed in our data, as unrelated donors exhibited a higher relative risk of GVHD (RR=1.4; 95% CI, 0.9–2.6) than related or sibling donors (p=0.04). Furthermore, consistent with existing literature, our analysis revealed a potential association between donor sex and GVDH occurrence, particularly for male recipients[25]. While the RR in such cases was modest (RR=1.1; 95% CI, 0.59–2.26), it adds to the ongoing investigation of sex-specific factors in GVHD development. However, consistent with broader research, our study did not identify donor sex as a significant overall risk factor for GVHD (p=0.8)[26]. These findings highlight the complex interplay

between donor characteristics and their effect on GVHD risk. While certain relationships and donor sex may exhibit subtle or context-dependent associations, further research is needed to elucidate their precise roles in influencing GVHD development, and to inform optimal donor selection strategies.

Pre-SCT Chemotherapy

The number of pre-SCT chemotherapy regimens was significantly associated with the occurrence of GVHD (p=0.03). Recipients who received one or fewer lines of chemotherapy exhibited a lower relative risk of GVHD than those receiving multiple lines (RR=0.67; 95% CI, 0.42–1.04), as illustrated in Figure 2. This finding suggests that minimizing pre-transplant chemotherapy intensity might offer a potential strategy for mitigating GVHD risk.

Lower susceptibility to GVHD despite HLA mismatch

Contrary to our expectations and the established literature highlighting the importance of HLA matching, we did not find a significant association between HLA matching and GVHD in our cohort (p=0.66), as shown in Figure 2. This finding aligns with existing research, suggesting a lower susceptibility to GVHD among pediatric recipients, even in the context of HLA mismatch or non-identical transplants[19,27]. Given the high proportion of pediatric patients in our study (52%), this factor could potentially explain the observed lack of a strong correlation between HLA matching and GVHD[28].

Peripheral blood stem cells (PBSCs) pose higher GVHD risk

Our findings align with established literature by demonstrating a higher relative risk of GVHD associated with PBSCs than BM as the stem cell source [29,30]. Within our cohort, 58% of the PBSC recipients developed GVHD compared to 49% of the BM recipients. However, our data lacked information on the specific proportion of PBSCs mobilized using colony-stimulating factors (CSFs). As CSF mobilization has also been associated with the risk of GVHD, further analysis of this information could provide deeper insights into the interplay between stem cell sources and mobilization techniques.

Conditioning regimens with or without TBI and GVHD prophylaxis

In our cohort, 69% of the recipients who underwent TBI conditioning developed GVHD, which is consistent with earlier studies reporting a higher prevalence of chronic GVHD with TBI[21,22,31]**.** Conversely, the inclusion of ATG during conditioning has been associated with reduced GVHD risk[22]. Consistent with this trend, our analysis revealed a lower relative risk of GVHD among ATG recipients (RR=0.79; 95% CI, 0.37–1.6)**.** These findings highlight the potential tradeoffs involved in selecting conditioning regimens, emphasizing the need for careful consideration of both GVHD risk and disease control efficacy.

The type of GVHD prophylaxis was also a significant factor (p=0.03)**.** Specifically, regimens containing calcineurin inhibitors appear to be associated with a higher risk of GVHD, thereby warranting further investigation into their role and potential influence on future prophylaxis selection [19].

Unique patterns of organ GVHD

Consistent with the literature, the skin was the most common site of GVHD [32,33]. Recipient age was a key factor influencing organ involvement, which mirrors the findings of Inamoto et al. [34]. Ocular GVHD, however, was less prevalent in our cohort (16%) compared to the reported ranges of 60–90%[35]. Although organ GVHD significantly correlated with the involvement of other organs, lung GVHD did not (Table 1). At 11%, the prevalence of lung GVHD in our study was slightly higher than the previously reported range of 3–10% [36]. Unlike overall GVHD, our analysis of lung GVHD risk factors revealed no significant correlations, which is consistent with the study by Rabanus et al. [37]. Our data also showed significant correlations between manifestations in various organs ($p<0.05$), except for the absence of a link between lung and eye GVHD (p=0.45; Table 1)[33].

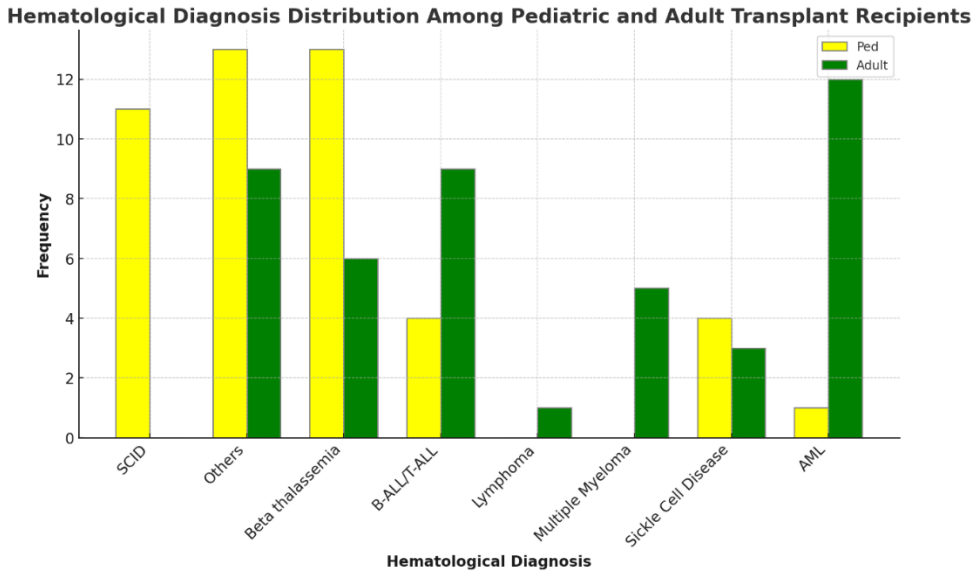

Figure 5. Hematological Diagnosis Distribution among Pediatric and Adult Transplant Recipients

This bar graph presents the frequency distribution of various hematological diagnoses among pediatric (yellow bars) and adult (green bars) transplant recipients. The diagnoses include SCID, Others, Beta Thalassemia, B-ALL/T-ALL, Lymphoma, Multiple Myeloma, Sickle Cell Disease, and AML. This visualization highlights the differing prevalence of these diagnoses between pediatric and adult patient groups.

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Limitations

Our cohort of 91 recipients restricted the subgroup analyses, potentially masking nuanced associations within specific demographic or clinical subgroups. The diverse origins of transplant centers and recipients introduce heterogeneity in treatment approaches and data collection practices. We initially assumed consistent methodologies across centers; however, limitations in accessing specific protocols hindered our ability to account for potential variations. Additionally, gaps in data, including missing donor information and ambiguous clinical records, further challenged precise GVHD categorization (acute vs. chronic) and treatment analysis. The demographic composition of the UAE, with its large expatriate population (88%), presents additional complications. Many patients seek post-diagnostic treatment abroad, leading to fragmented medical records and incomplete follow-up data. This hindered our ability to comprehensively track disease trajectories and treatment outcomes in this specific population.

CONCLUSION

Despite advantageous conditions such as matched related donors, particularly siblings, the prevalence of GVHD remains high. While the general and organ-specific risk factors for GVHD align with the existing literature, lung GVHD showed no clear association with these established risk factors, and ocular GVHD had a lower than expected prevalence. The higher prevalence of GVHD suggests potential contributions from care disruptions, inconsistent medical protocols, the absence of robust post-transplant support in the UAE, and psychological stress associated with travel. Our study, serving as a pilot project, is the first of its kind report on SCT and GVHD in the UAE. These findings highlight the need for standardized post-transplant care strategies to reduce GVHD in this vulnerable population and call for further research to assess the impact of individual contributing factors.

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CONFLICT OF INTEREST

The authors declare no competing interests relevant to the contents of this article.

Ethical Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Sheikh Shakbout Medical City (No. SSMCREC-444, Date: 11/30/2022).

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Data Availability

The de-identified data underlying the results presented in this study are openly available in Mendeley Data at DOI: 10.17632/svwnp5kkrz.1.

Consent

Patient consent was waived due to the retrospective observational nature of the study, which included data extraction from medical records.

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