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CORRESPONDENCE

Trends in GVHD Epidemiology, Prophylaxis and Management: The Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule Staminali Emopoietiche e Terapia Cellulare (GITMO) GVHD24 Study

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To the Editor,

Despite significant advances in transplant techniques, graft-versus-host disease (GVHD) remains one of the most frequent and challenging complications following allogeneic hematopoietic stem cell transplantation (allo-HSCT) in both adult and pediatric recipients [1].

The increased use of mismatched donors, and reduced intensity conditioning regimens (RIC) have expanded the pool of transplant candidates but have also increased the complexity of GVHD prevention and treatment. Posttransplant cyclophosphamide (PTCy) has become an alternative to in vivo T-cell depletion with anti-thymocyte globulin (ATG) and is now widely used. At the same time, new immunomodulatory agents, such as ruxolitinib, ibrutinib, belumosudil, and axatilimab, have reshaped the therapeutic landscape of steroid-refractory/dependent (SR/D) GVHD, although only ruxolitinib currently has both FDA and EMA approval [2–4]. These advances prompted the European Society for Blood and Marrow Transplantation (EBMT) to issue updated recommendations in 2024 [5]. Yet, how these changes have impacted real-world epidemiology and clinical practice remains incompletely understood.

In this context, the Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule Staminali Emopoietiche e Terapia Cellulare (GITMO) launched a retrospective study supplemented by a survey-based analysis of current practices across Italy. This project

combined limited data from the EBMT registry with a web-based survey distributed to all Italian transplant centers. The analysis focused on 2023 activity, providing sufficient follow-up to assess cGVHD while also reflecting the current transplant era. Details of the extracted registry data and the full survey questionnaire are provided in the Supporting Information. The primary aim of this initiative was to define the contemporary epidemiology, prophylaxis, diagnosis, and management of both acute (aGVHD) and chronic (cGVHD) GVHD within Italian transplant centers, while evaluating the adherence to the most recent EBMT recommendations. The project also aimed to identify potential discrepancies in clinical practice and to support the development of targeted educational initiatives and future observational or interventional studies.

A total of 62 GITMO-affiliated centers performed allo-HSCT in 2023 and were invited to participate; 56 centers (90.3%) provided complete data, covering 93.0% of national transplant activity. Among 1862 patients included, 1604 were adults and 258 were pediatric. Acute leukemias accounted for 60.8% of indications. Myeloablative conditioning regimens (MAC) were slightly predominant (57.6%). Haploidentical donors represented 30.3% of procedures, second only to matched unrelated donors (MUD) (35.9%), and peripheral blood was the most frequently used stem cell source (85.3%). Compared with previous Italian transplant periods, we observed an increase in transplants for acute leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms, along with a shift toward less MAC, greater use of peripheral blood as the stem cell source, and a higher proportion of unrelated donors, in line with trends reported internationally (Table S1) [6].

Pediatric patients differed markedly, with a higher prevalence of nonmalignant indications, more frequent use of bone marrow as a stem cell source, and broader reliance on MAC (Table 1), highlighting the need for population-specific strategies in both the prophylaxis and treatment of GVHD [7].

In 2023, 626/1862 patients (33.6%) developed aGVHD, of whom 428/1862 (23.0%) had grade II–IV disease and 163/1862 (8.8%) had severe grade III–IV forms. After a median follow-up of 1.67 years from transplant, cGVHD was diagnosed in 384/1862 patients (20.6%), including 72 with overlap syndrome. According to NIH scoring, 12.6% of all transplanted patients (234) had moderate-to-severe cGVHD (Figure S1).

Compared to historical reports, both aGVHD and cGVHD appeared to have decreased, particularly in pediatric patients [8, 9]. The pediatric cohort showed a lower prevalence of both aGVHD (29.1% vs. 34.3% in adults, $p = 0.096$) and cGVHD (14.7%

TABLE 1 | Italian 2023 transplant population according to type of center.

Features	Adult *N* (%)	Pediatric *N* (%)	*p*
Number of transplant	1604 (86.1)	258 (13.9)	—
Diseases			$p < 0.001$
Acute leukemias	1002 (62.5)	129 (50.0)	
Myelodysplastic syndromes	191 (11.9)	24 (9.3)	
Myeloproliferative neoplasms	147 (9.2)	5 (1.9)	
Lymphoproliferative disorders	178 (11.1)	11 (4.3)	
Multiple myeloma and PCD	20 (1.2)	0 (0)	
Nonmalignant disorders	42 (2.6)	79 (30.6)	
Other indications	24 (1.5)	10 (3.9)	
Conditioning intensity			$p < 0.001$
Myeloablative	885 (55.2)	188 (72.9)	
Reduced intensity	719 (44.8)	70 (27.1)	
Stem cell source			$p < 0.001$
Peripheral blood	1471 (91.7)	118 (45.7)	
Bone marrow	124 (7.7)	137 (53.1)	
Cord blood	9 (0.6%)	3 (1.2)	
Donor type			$p = 0.003$
MRD	293 (18.3)	55 (21.3)	
MUD	599 (37.3)	69 (26.7)	
MMUD	244 (15.2)	37 (14.3)	
Haploidentical	468 (29.2)	97 (37.7)	

Abbreviations: MMUD, mismatched unrelated donor (≤ 7/8 matched); MRD, matched related donor; MUD, matched unrelated donor (at least 8/8 matched); PCD, plasma cell dyscrasia.

vs. 21.6%, $p = 0.012$). These data reflect the changes in patients, and transplant features. In this regard, the extension of T-cell depletion, the availability of effective second-line approaches in SR/D GVHD and improved anti-infectious prophylaxis and treatments may have played a significant role [10].

Nevertheless, 24.3% (152/626) of aGVHD and 31.0% (119/384) of cGVHD cases proved to be SR/D. A higher proportion of SR/D aGVHD cases was observed in the pediatric population (38.7% vs. 22.3%, $p = 0.002$), while no significant differences emerged for SR/D cGVHD (36.8% vs. 30.4%, $p = 0.411$). These findings are consistent with recent international reports, which indicate that 25%–30% of patients still require second-line therapy, highlighting the persistent need for more effective first-line treatments, particularly in younger patients [11].

The survey component of the study provided insights into real-world clinical practices. Nearly all centers adopted the MAGIC criteria for aGVHD (51 centers, 91.1%) and the NIH 2014 consensus for cGVHD (49 centers, 87.5%) diagnosis and grading, indicating widespread adherence to updated definitions [5]. In cases presenting with overlap cGVHD, 26 centers (46.4%) reported using a combination of both aGVHD and cGVHD classification systems. Histology was considered useful but not mandatory for both aGVHD (39/56, 69.6%) and cGVHD (37/56, 66.1%) diagnosis.

For prophylaxis, Italian centers reported near-universal use of T-cell depletion in addition to calcineurin inhibitors (Figure 1), in accordance with European guidelines [5]. ATG was reported in most centers for both matched related (MRD) and unrelated donor transplants, regardless of conditioning intensity (78.6% in MAC vs. 76.8% in RIC, $p = 0.821$; and 75.0% in MAC vs. 75.0% in RIC, $p = 1.000$, respectively). In contrast, PTCy was the preferred approach in mismatched unrelated donors (MMUD) (particularly in adults) and haploidentical transplants. Similarly to MRD and MUD settings, no significant differences in GVHD prophylaxis were observed for MMUD and haploidentical transplants according to conditioning intensity (85.7% in MAC vs. 83.9% in RIC, $p = 0.792$; and 92.8% in MAC vs. 94.6% in RIC, $p = 0.696$, respectively). Only six centers (four of them pediatric) reported ex vivo T-cell depletion, particularly in the haploidentical context (five centers). The distribution of T-cell depletion strategies can be attributed to the efficacy of PTCy prophylaxis demonstrated in recent randomized trials [12]. Nonetheless, in Italy, as in much of Europe [13], the widespread experience with ATG and the lack of direct comparisons with PTCy have likely contributed to a more conservative approach in MRD and MUD transplants, where favorable outcomes have been achieved with ATG-based regimens [14, 15], without the potential cardiac and long-term toxicities associated with PTCy [16].

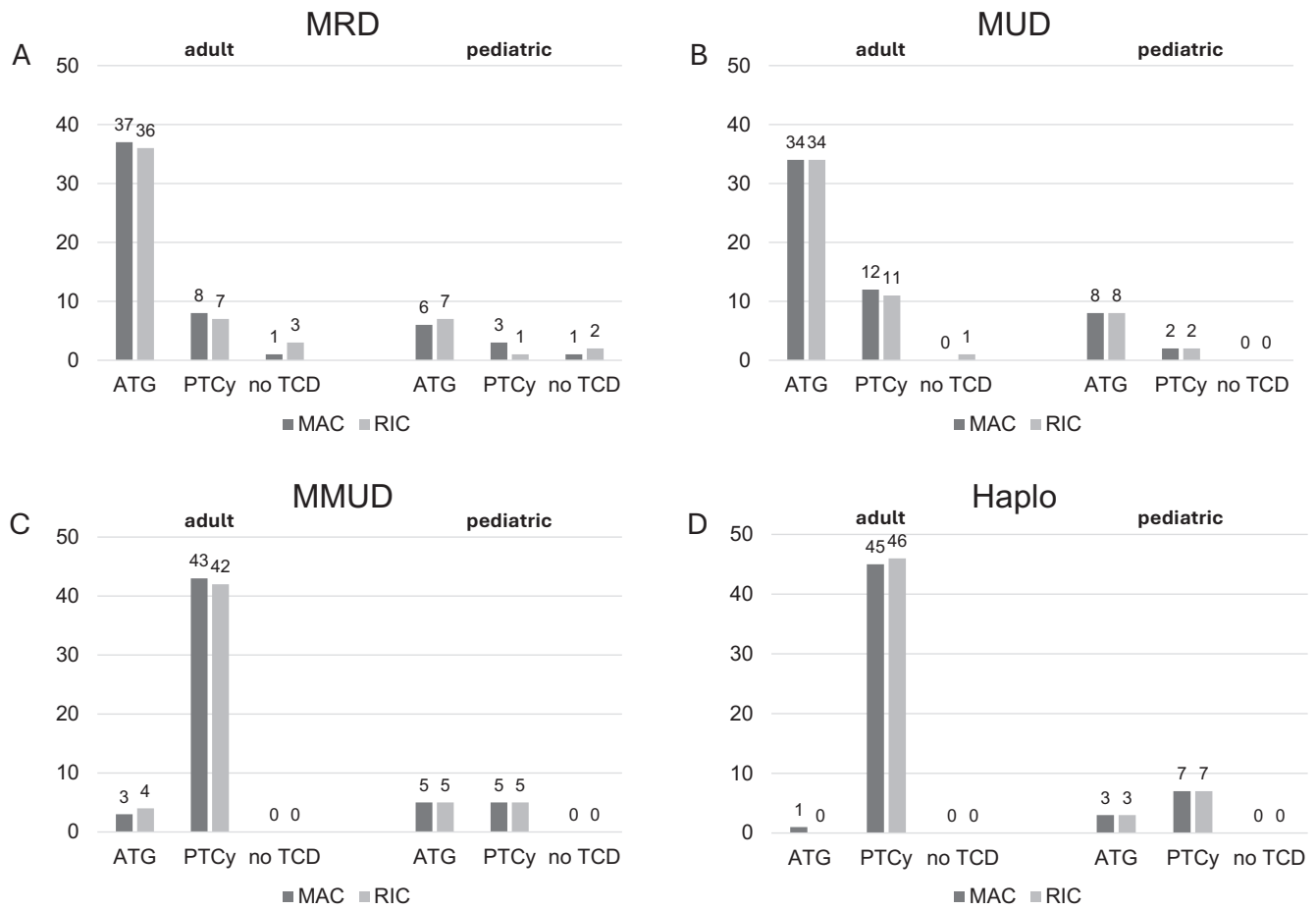

FIGURE 1 | GVHD prophylaxis strategies by donor type and transplant center. The left side of each panel represents adult centers, while the right side corresponds to pediatric centers. Numbers of centers are shown. (A) MRD: matched related donor; (B) MUD: matched unrelated donor; (C) MMUD: mismatched unrelated donor; (D) ATG: anti-thymocyte globulin; Haplo: haploidentical donor; MAC: myeloablative conditioning; PTCy: posttransplant cyclophosphamide; RIC: reduced-intensity conditioning; TCD: T-cell depletion.

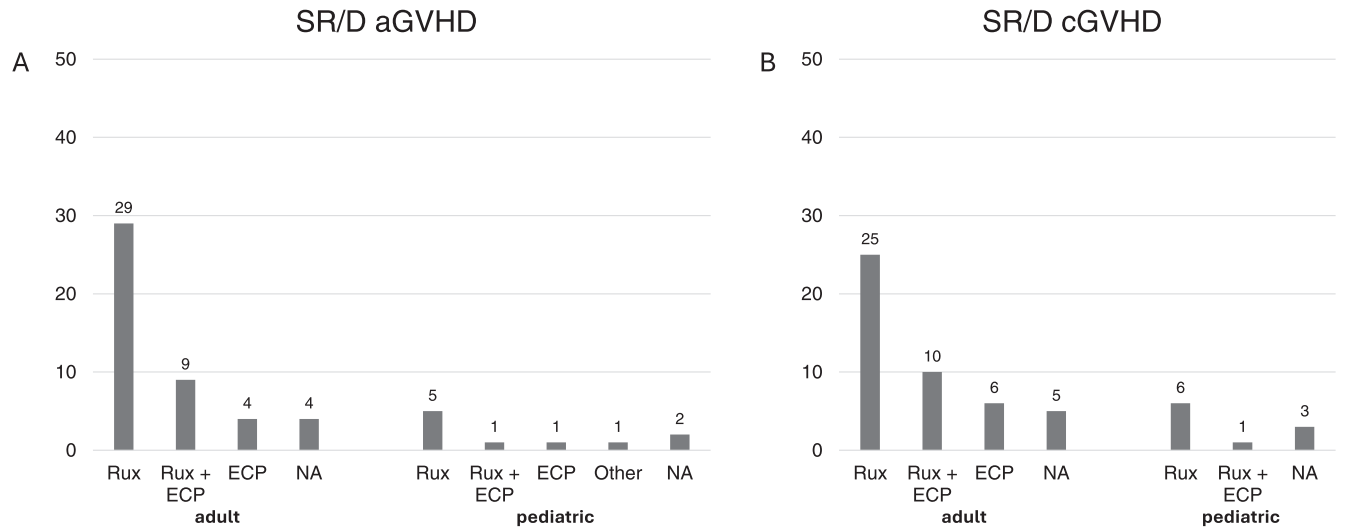

FIGURE 2 | Distribution of treatment strategies for steroid-refractory or steroid-dependent (SR/D) acute GVHD (A) and chronic GVHD (B). The left side of each panel represents adult centers, while the right side corresponds to pediatric centers. Numbers of centers are shown. ECP: extracorporeal photoapheresis; NA: not available as a preferred second-line option; Rux: ruxolitinib.

Considerable heterogeneity was noted in ATG products and dosing. Twenty-five centers used Thymoglobulin (Thymoglobulin, Sanofi, France; ATG-T) and 20 Grafalon (Grafalon, Neovii, Germany; ATG-G), with median total doses of 5 mg/kg (range, 2.5–7.5) and 20 mg/kg (range, 10–45), respectively. Dosing adjustments were frequently reported according to stem cell source, with bone marrow transplants often leading to dose reductions or omission of ATG in 30 centers. Conversely, 26 centers reported increased ATG dosing in nonmalignant disorders. This variability highlights persistent uncertainty and a lack of standardization across centers. Notably, compared to earlier EBMT recommendations [17], current median doses appear lower, possibly reflecting efforts to optimize the risk–benefit ratio by preserving GVHD prevention while maintaining a sufficient graft-versus-leukemia effect [18].

First-line treatment strategies were generally consistent across centers (Figure S2). Additional details on first-line therapy dosing, organ-specific management, response assessment, and tapering approaches are provided in the Supporting Information. Of note, around 10% of centers reported using low-dose corticosteroids or steroid-sparing regimens in first line, with this proportion rising to nearly 40% in severe cGVHD cases. These approaches were predominantly reserved for elderly or comorbid patients, highlighting a personalized and risk-adapted therapeutic paradigm increasingly endorsed in contemporary literature. In addition, accelerated tapering of corticosteroids was frequently implemented in nonresponding patients, supporting the trend toward earlier initiation of second-line therapies to mitigate long-term steroid-related toxicity [5].

All centers confirmed applying NCCN criteria in aGVHD and cGVHD response assessment process [19]. Second-line strategies converged strongly on ruxolitinib, either alone or combined with extracorporeal photopheresis (ECP). For aGVHD, 62.5% of centers used ruxolitinib monotherapy, while 17.8% combined it with ECP; for cGVHD, 55.3% used ruxolitinib alone and 19.6% used it with ECP. ECP monotherapy remained an option (10.7% of cases), particularly in pediatric centers and for cGVHD (Figure 2). These patterns highlight both the wide use of ruxolitinib and the continued role of ECP in Italian practice [20]. Other agents, including ibrutinib or belumosudil, were not reported in routine use, likely due to the lack of EMA approval and limited availability in Italy.

Despite the intrinsic limitations of a retrospective and survey-based design, including incomplete transplant-related variables, the absence of granular patient data such as type of conditioning regimen, CMV serostatus, organ-specific GVHD involvement and outcomes, and a relatively short follow-up, this study provides a comprehensive and contemporary overview of allo-HSCT practices and GVHD epidemiology and management in Italy. Strengths include near-complete national coverage, standardized EBMT registry data, and high survey response rates, offering a valuable benchmark for future research. The findings highlight both adherence to international standards and the progressive adoption of personalized, risk-adapted approaches. Nonetheless, considerable heterogeneity persists, particularly in GVHD prophylaxis strategies (e.g., type and dose of T-cell depletion), underscoring the need for prospective studies to harmonize transplant practices and refine national and international guidelines.

Author Contributions

N.P., M.Mar., and L.Ca. conceptualized the work and designed the study. N.P., C.Z., and M.G.B. performed the statistical analysis and wrote the manuscript. E.D. developed the web-based survey and coordinated communications with the participating centers. All other authors (M.A., A.A., E.A., A.C.B., M.Ba., S.Ba., G.Ba., E.Be., A.Bi., F.Bo., C.Bo., S.Br., L.Br., P.Br., A.Bu., R.Ca., P.Ca., F.Ca., A.M.C., I.M.C., R.Ce., A.Ch., P.Ch., M.Ci., P.Co., A.Cr., A.Cu., N.D.R., F.Fa., R.Fa., M.Fa., V.F., A.G., L.G., A.Gi., G.G., A.Im., C.In., A.P.I., G.L.N., S.L., M.T.L.S., G.M., J.M., A.Me., M.Me., F.Me., N.Mo., M.Mu., C.N., F.Pa., M.Pa., R.Pa., D.Pa., F.P., E.Pi., A.Pic., S.P., A.Pie., F.Po., G.P., A.Pr., L.Pr., A.P., A.R., A.Ra., R.Ri., M.Ro., C.R., D.Ru., D.S., S.Sa., G.Sa., F.Sa., C.Se., B.S., C.Sk., S.Si., A.Sp., F.P.T., C.T., E.T., M.Tu., D.V., F.Z., M.Z., A.Ta., A.Bi., I.D., G.L., E.D., M.Mal., L.Cas., and M.Mar.) contributed clinical data and approved the final version of the manuscript.

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Ethics Statement

This combined registry-based analysis and nationwide survey was approved by the Gruppo Italiano per il Trapianto di Midollo Osseo, Cellule Staminali Emopoietiche e Terapia Cellulare (GITMO).

Consent

Informed consent for inclusion in the EBMT registry was obtained in all patients.

Conflicts of Interest

N.P. served on advisory boards for Novartis and has received travel grants from Neovii and Sanofi. A.C.B. served on advisory boards for Novartis and Sanofi; M.T.L.S. served on advisory boards for Novartis, Sanofi, Mallinckrodt, MEDAC and has received consulting fees/honoraria from Incyte, Sanofi, and Therakos. The other authors declare no conflicts of interest.

Data Availability Statement

Qualified investigators may request de-identified data from this study by contacting GITMO trial office.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** ajh70145-sup-0001-Supinfo.docx.