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The role of obesity on autologous bone marrow transplant and post-transplant outcomes

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Ethics Committee Approval
The study was approved by the Medipol University Institutional Ethics Committee (E-10840098-772.02-6746, dated: December 29, 2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Autologous hematopoietic cell transplantation (AutoHCT), administered at high doses, has improved survival rates among patients with refractory or recurrent lymphoma and multiple myeloma (MM). However, inconsistencies in defining obesity, varying body weight ranges, and heterogeneous patient populations have been examined. Some researchers have hypothesized that significantly overweight patients face a higher risk of transplant-related complications. This study investigates the association between body mass index (BMI), obesity, and autologous peripheral stem cell mobilization.
Methods: A retrospective evaluation of data from 180 patients who underwent peripheral stem cell mobilization at our clinic between 2014 and 2020 was conducted. Excluding patients under 18 years of age, the primary objective was to assess how BMI influences autologous transplant outcomes and mortality. This retrospective cohort study aimed to determine whether obesity constitutes an independent risk factor for autologous bone marrow transplantation.
Results: Among the patients, the most prevalent diagnosis (47.2%) was MM, with notable differences in incidence rates across BMI categories (P=0.039). Obesity and overweight were associated with a higher incidence of MM (47.2%), whereas normal and underweight individuals had predominantly been diagnosed with DLBCL (44.2%). Significant differences in CD34 cell counts were observed among BMI groups (P=0.033). Overweight and obese individuals exhibited lower CD34 cell counts than underweight/normal groups (P=0.033). The treatment group showed significantly higher CD34 cell counts than the G-CSF alone group (P=0.046). Female gender (P=0.022), PLT engraftment (P=0.024), post-chemo-mobilization hospital-stay duration (P=0.019), and G-CSF count were identified as mortality risk factors (P=0.017).
Conclusions: This investigation found no adverse correlation between mortality and weight among patients with various hematological malignancies undergoing AutoHCT. Obesity alone should not be a contraindication for proceeding with AutoHCT in clinically warranted hematological malignancy treatment, as no significant survival differences were observed among overweight, obese, and normal-weight individuals.

Keywords: autologous bone marrow transplant, mobilization, obesity

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Introduction

The increasing global prevalence of overweight and obesity represents a significant public health concern impacting developed and developing nations [1,2].

The pharmacokinetics of high-dose chemotherapy in overweight patients remain poorly understood, with several studies expressing concerns about potential higher toxicity when dosage adjustments aren't made or the potential for increased relapse risk with modifications based on ideal body weight (IBW) [3]. In refractory or recurrent lymphoma, high-dose autologous hematopoietic cell transplantation (AutoHCT) has demonstrated superior long-term disease-free survival compared to standard-dose chemotherapy [4,5]. While new antimyeloma drugs have improved patient outcomes, the most substantial advancement was AutoHCT, a treatment that has significantly enhanced survival rates and remains the most prominent approach in antimyeloma therapy [6]. Risk factors, such as severe disease, advanced age, prior treatments, and biological characteristics, contribute to long-term outcomes following bone marrow transplantation for hematological malignancies. While some of these factors are widely acknowledged, others remain debated.

Obesity has emerged as a risk factor for diseases and premature mortality, as indicated by a wealth of research. Although obesity is recognized for elevating the risk of common medical conditions like cardiovascular disease [7,8], diabetes [9], cancer [10,11], and premature death [12], its role as a definitive risk factor in the context of transplantation initiation has yet to be established. Several studies have examined the effects of obesity, being underweight or overweight status in individuals undergoing hematopoietic stem cell transplantation [13,14]. However, the outcomes of these investigations on the influence of BMI on peripheral stem cell mobilization have shown significant variability and ambiguity. Consequently, our institution explored the relationship between body mass index (BMI) and autologous peripheral stem cell mobilization in obesity. The primary aim was to assess how obesity impacts transplant outcomes within our cohort of autologous transplant recipients, with potential implications for mobilization and cell dosage considerations.

Materials and methods

Patients who underwent peripheral stem cell mobilization at our clinic between 2014 and 2020 were subjected to a retrospective study. The study encompassed parameters such as patients' age, gender, diagnosis, the count of administered chemotherapies, the extent of radiation exposure, and the mobilization strategies employed (including isolated GCF and chemoembolization), all meticulously documented. The registration data comprehensively incorporates disease type, patient age, gender, pretransplantation performance status, disease stage, responsiveness to chemotherapy, date of initial diagnosis, specifics regarding the donor and graft type (derived from either bone marrow or blood stem cells), details about the high-dose conditioning regimen, post-transplantation engraftment, instances of disease recurrence and survival rates, instances of new malignancy development, and the causes of death.

Inclusion criteria encompassed patients falling within the age bracket of greater than 18 years and less than 65 years. The study's evaluated endpoints included relapse rates, overall survival, disease-free survival (LFS), and transplantation-related mortality (TRM). Specifically, TRM was characterized as any mortality occurring within the initial 28 days post-transplantation or at any point during a continuous state of complete remission. Relapse was delineated as the duration prior to a clinical recurrence, progression of the illness, or persistence of the illness. For patients afflicted with chronic disease, events at day 28 were considered relevant for the relapse assessment.

Obesity was characterized by BMI at the time of transplantation, calculated as weight (kg)/height $(m^2)^2$. BMI classifications were based on World Health Organization (WHO) definitions: A BMI of 18 or less indicated underweight, >18–25 was considered normal, >25–30 was categorized as overweight, and a BMI exceeding 30 was classified as obese. In the present study, participants mobilized solely with G-CSF received a daily dose of 5 µg/kg G-CSF administered twice daily for 5 days. In contrast, patients who received G-CSF following chemotherapy were administered cyclophosphamide at 2 g/m^2 for multiple myeloma (MM) patients and 4 g/m^2 for lymphoma patients, followed by G-CSF initiation on day 5. Mobilization failure was defined as the inability to achieve a CD34+ cell count of 2×10^6 cells/kg after G-CSF administration or after a chemotherapy regimen followed by G-CSF.

The study population was divided into three groups based on BMI: underweight and normal, overweight and obese. Various factors, including the number of days of growth factor (G-CSF) administration, CD34+ cell count on the collection day, duration until platelet and neutrophil engraftment, and post-chemoembolization hospital stay length, were assessed for comparison among these groups. The primary focus of the study was to elucidate the impact of BMI on autologous transplant outcomes and adult patient mortality. The objective was to understand how obesity influences post-transplant results, to guide treatment choices and to lay the groundwork for future investigations. Ethical approval for the study was obtained from the Medipol University Institutional Ethics Committee (E-10840098-772.02-6746, dated: December 29, 2021).

Statistical analysis

Patients were stratified into three distinct BMI groups: underweight (BMI <18) and normal (18–24.9), overweight (25.0–29.9), and obese (≥30.0), based on their body mass index. In this investigation, the effect size was calculated through an assessment of the CD34 cell count parameter (in millions/kg) using 20 observations from each BMI group (underweight/normal, overweight, and obese) conducted by the researcher prior to conducting the power analysis. The effect size, denoted as f=0.235 (medium), was computed for this purpose. With a targeted statistical power of 80%, a significance level of 0.05, and employing a two-tailed hypothesis, the subsequent analysis indicated that a total of 180 observations were required, distributed across the three independent groups, with a minimum of 60 observations per group. The analytical procedures were conducted utilizing the G*Power 3.1 software.

Categorical characteristics across the BMI groups were compared using either the Exact or Pearson chi-square test, while continuous variables were assessed through the Mann-Whitney U or Kruskal-Wallis test. Regarding mortality, the initial analysis involved univariate logistic regression (LR) to evaluate its association. Subsequently, a stepwise LR analysis was conducted for variables that displayed significance in the initial univariate analysis. The Spearman correlation coefficient was employed to explore the relationship between two quantitative variables. Quantitative variables were presented as median and interquartile range (IQR), representing the difference between the 75th and 25th percentiles (P75-P25), while qualitative variables were presented in terms of counts and percentages. Statistical significance was considered at a *P*-value of <0.05. For analysis of the clinical data, IBM SPSS version 23.0 was employed.

Results

Table 1 presents the distribution of general patient characteristics among BMI groups. The median age of the 180 cases was 53 years (IQR: 22), and there was a significant difference in the age distribution among BMI categories. Underweight/normal-weight patients were younger than those in the other groups. With a median BMI of 28 and an IQR of 6.7, 37.8% of the patient population was classified as obese. The most prevalent diagnosis among the cases was MM (47.2%), followed by DLBCL (40.6%). The incidence rate in the BMI groups showed a significant difference (*P*=0.039). In obese and overweight cases, MM (47.2% and 44.9%, respectively) was the most frequently observed diagnosis, while in normal and underweight individuals, DLBCL (44.2%) was the predominant one.

Regarding the CD34 cell count on the first collection day, there were noteworthy variations across BMI groups (*P*=0.033). All patients received their initial transplant. The cell count was significantly lower in the overweight and obese categories compared to the underweight/normal groups, as indicated by the post hoc analysis.

Table 2 evaluates demographic variables concerning CD34+ cell count. The median CD34 cell count was 7.4, with an interquartile range of 4.25. The cell count was markedly lower in the obese and overweight categories than in the underweight/normal groups (*P*=0.033). Cases in the treatment group exhibited significantly higher CD34 cell counts than those in the G-CSF alone group (*P*=0.046). No meaningful association was observed between other features and CD34+ cell count.

To identify significant predictors of death, univariate and stepwise multivariate LR models were employed (Table 3). Female gender (*P*=0.022), PLT engraftment (*P*=0.024), hospital stay after chemo-mobilization (*P*=0.019), and G-CSF count were identified as risk factors for mortality (*P*=0.017). The Univariate LR analysis revealed female gender as a statistically significant risk factor (Odds Ratio = 2.80; 95% CI 1.16-6.75, [*P*=0.022]). Individuals with DLBCL faced a significantly higher mortality risk than those with MM (Odds Ratio = 4.84; 95% CI 1.89-12.39, [*P*=0.017]). The individual risk factors for mortality included hospitalization following chemo-mobilization for PLT

Table 1: Baseline characteristics of cancer patient.

	Underweight/normal (n=43)	**Overweight (n=69)**	**Obese (n=68)**	***P*-value**
	n (%)	**n (%)**	**n (%)**	
Gender				
Female	13 (30.2)	24 (34.8)	32 (47.1)	0.153
Male	30 (69.8)	45 (65.2)	36 (52.9)	
Age Median (IQR)	43 (31)	51 (14)	54 (13.5)	0.016
Chemotherapy serial				
1-2	38 (90.5)	54 (85.7)	56 (93.3)	0.374
3-4	4 (9.5)	9 (14.3)	4 (6.7)	
Diagnosis				
HL	8 (18.6)	7 (10.1)	3 (4.5)	0.039
DLBCL	19 (44.2)	30 (43.5)	24 (35.8)	
M. Myeloma	14 (32.6)	31 (44.9)	40 (59.7)	
Other	2 (4.7)	1 (1.4)	0 (0)	
Pre-collection RT				
Yes	8 (19.5)	6 (9.5)	9 (14.3)	0.348
No	33 (80.5)	57 (90.5)	54 (85.7)	
Chemo-mobilization				
G-CSF alone	3 (7.1)	9 (13.8)	7 (10.6)	0.552
Chemotherapy	39 (92.9)	56 (86.2)	59 (89.4)	
CD 34 cell count (million/kg)	8.35 (3.80)	7.40 (5.70)	7.10 (3.80)	0.033
PLT engraftment >20,000 (days)	13 (3)	12 (3)	14 (4)	0.649
PLT engraftment >50,000 (days)	17 (5.5)	13 (5)	16 (3)	0.323
Neutrophil engraftment >500(days)	11 (2)	10 (2)	11 (2)	0.215
Neutrophil engraftment >1000(days)	12 (2)	11 (1)	12 (3)	0.387
G-CSF, days	7 (3)	5 (3)	5 (2)	0.064
Stay in hospital after chemo-mobilization (days)	17 (5)	16 (6)	16 (5)	0.406
Febrile neutropenia in mobilization				
Yes	22 (51.2)	40 (59.7)	37 (55.2)	0.671
No	21 (48.8)	27 (40.3)	30 (44.8)	
Mortality				
Alive	25 (65.8)	44 (81.5)	45 (83.3)	0.101
Dead	13 (34.2)	10 (18.5)	9 (16.7)	
Outcome				
Failure	3 (8.6)	6 (11.5)	2 (4.1)	0.386
Successful	32 (91.4)	46 (88.5)	47 (95.9)	
Poor mobilization with Chemo+G-CSF				
Yes	4 (9.3)	11 (16.4)	7 (10.4)	0.448
No	39 (90.7)	56 (83.6)	60 (89.6)	
3rd-month assessment				
CR	10 (58.8)	15 (60)	19 (65.5)	0.421
PR	3 (17.6)	8 (32)	8 (27.6)	
Progression	4 (23.5)	2 (8)	2 (6.9)	

Descriptive statistics for quantitative variables were given using the median (IQR: percentile 75-percentile 25).

engraftment and mobilization, along with increased G-CSF days. In cases where variables were found together (P>0.05), no statistically significant risk factor was established, according to the stepwise multivariate LR analysis results.

Table 2: Comparison between patient characteristics and CD34+ cell count.

		CD 34 (UL)	
	n	Median (IQR)	*P*-value
Gender			
Female	69	7.1 (4.3)	0.244
Male	111	8 (4)	
Age			
<45	56	7.9 (3.8)	0.336
45-54	51	7.75 (5.6)	
55-59	26	7.5 (4.9)	
60 +	47	7.1 (3.5)	
Chemotherapy serial			
1-2	148	7.7 (4)	0.514
3-4	17	7.15 (2.9)	
Pre-collection RT			
Yes	23	8 (5)	0.848
No	144	7.2 (4.5)	
Diagnosis			
HL	18	7.3 (3.8)	0.089
DLBCL	73	7 (4.2)	
M. Myeloma	85	10 (3.3)	
Other	3	8.15 (5.5)	
BMI			
Underweight/Normal	43	8.38 (3.8)	0.033
Overweight	69	7.4 (5.7)	
Obese	69	7.1 (3.8)	
Chemo-mobilization			
G-CSF alone	19	7 (3.5)	0.046
Chemotherapy	154	7.8 (4.5)	
Disease status			
CR	44	7.4 (5)	0.882
PR	19	7.1 (4.3)	
Progression	8	9.25 (3.35)	

Descriptive statistics for quantitative variables were given using the median (IQR: percentile 75-percentile 25).

Discussion

The present study examined various aspects of obesity and its impact on autologous stem cell transplantation. Obesity stimulates the production of pro-inflammatory cytokines, which subsequently encourage tumor growth [15,16]. Within the adipose compartment, hematopoietic stem cells, lymphocytes, and other hematopoietic cells reside, potentially playing a crucial role in transplant biology and kinetics [15-17]. Several investigations have demonstrated a connection between obesity and unfavorable cancer outcomes [18,19]. Prior studies have identified factors such as age (>60 years), history of radiation exposure, multiple chemotherapy regimens, and previous lenalidomide administration as contributors to poor mobilization [20,21]. While CD34 cell counts declined in groups with risk factors like age and multiple therapies outlined in this study, statistical significance was not established. Moreover, overweight and obese patients displayed reduced CD34+ cell counts. Notably, the association of radiation exposure with outcome aggregation was limited, possibly due to the small proportion of irradiated patients and the diversity of the patient sample. As Moreb et al. [22] indicated, insufficient mobilization risk is notably higher in male MM patients who have undergone multiple chemotherapies and possess a higher optimal body weight. Although gender was identified as a factor influencing mortality, no statistically significant disparity between genders was detected.

The overweight and obese categories had significantly lower cell counts than the underweight/normal groups. Patients with DLBCL faced substantially higher mortality risks than those with MM. Noteworthy mortality risk factors encompassed PLT engraftment values exceeding 50,000 and extended G-CSF administration. A prior single-center study unveiled distinct disadvantages for overweight and obese patients. In the research conducted by Tarella et al. [23], among 121 NHL patients, 28 exhibited a BMI exceeding 28 kg/m^2, with merely five undergoing autologous transplantation. Among the remaining 23 patients, six encountered unspecified dose reductions, shown to impact OS and PFS durations. However, no statistically significant differences in BMI's impact on mortality or disease-free survival were observed. Risk factors for mortality were gender, diagnosis, PLT engraftment values surpassing 50,000, post-chemo-mobilization hospital stays, and G-CSF counts.

Contrastingly, Flegal et al. [24] scrutinized mortality rates related to overweight and obesity in the US population, concluding no escalated mortality rates. Our investigation echoed this pattern, at least in part. Similarly, Wuchter et al. [25] examined a patient cohort mobilized solely through chemotherapy and G-CSF, finding no correlation between body weight and mobilization efficacy. The diversity within patient populations complicates the attainment of definitive conclusions. In contrast, the present study predominantly encompassed

Table 3: Univariate and stepwise multivariate LR analysis of factors for mortality.

	Univariate LR		Stepwise Multivariate LR	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Male vs. Female	2.80 (1.16 6.75)	0.022	1.53 (0.50 4.73)	0.458
Per 10-year increase age	1.01 (0.98 1.03)	0.892		
KT Series 3-4 vs. 1-2	3.39 (0.42 27.41)	0.252		
BMI				
Underweight/Normal	1			
Overweight	0.44 (0.17 1.14)	0.091		
Obese	0.39 (0.14 1.03)	0.056		
Diagnosis				
M. Myeloma	1			
HL	1.22 (0.23 6.54)	0.813	1.15 (0.05 7.61)	0.695
DLBCL	4.84 (1.89 12.39)	0.001	2.20 (0.23 20.66)	0.491
Other	1.38 (0.10 15.18)	0.985	1.43 (0.16 12.87)	0.752
Pre-collection RT	2.54 (0.89 7.26)	0.081		
G-CSF alone and Chemotherapy	0.89 (0.23 3.47)	0.886		
CD 34 (UL) Cell Count	0.93 (0.84 1.04)	0.214		
Stay in hospital after chemo-mobilization (days)	1.08 (1.01 1.15)	0.019	1.00 (0.89 1.12)	0.999
PLT engraftment >20,000 (days)	1.06 (0.98 1.15)	0.153		
PLT engraftment >50,000 (days)	1.07 (1.01 1.14)	0.024	1.06 (0.99 1.13)	0.092
Neutrophil engraftment >500(days)	1.09 (0.90 1.31)	0.370		
Neutrophil engraftment >1000(days)	0.99 (0.95 1.04)	0.795		
G-CSF, days	1.19 (1.03 1.36)	0.017	1.06 (0.85 1.32)	0.614
Febrile neutropenia in mobilization	1.54 (0.67 3.56)	0.309		
Poor mobilization with chemo+G-CSF	0.94 (0.29 3.07)	0.922		
Outcome (Success vs. Failure)	0.46 (0.11 1.93)	0.289		

LR logistic regression, Bold text indicates a statistically significant difference with a *P*-value less than 0.05.

patients mobilized via chemotherapy and G-CSF, wherein CD34 cell counts in the chemotherapy group notably exceeded those in the G-CSF-only group. Additionally, cell counts significantly dwindled within the overweight and obese categories compared to the underweight/normal groups. Evidently, the influence of body weight on mobilization exhibited only partial effectiveness.

Two significant studies conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) yielded congruent findings when investigating autologous outcomes within extensive cohorts of lymphoma and myeloma patients [26,27]. In examining a substantial myeloma cohort, Vogl et al. [26] revealed no discernible distinctions in transplant outcomes between obese and non-obese individuals. Similarly, Navarro et al. [27] ascertained that higher BMI does not impact transplant-related mortality in a comprehensive analysis of autologous lymphoma patients. Additionally, the study reported an elevated overall survival rate among obese patients. Comparing the age distribution, underweight/normal-weight patients displayed lower ages compared to the other groups within the present study. Notably, MM emerged as the predominant diagnosis, followed by DLBCL. Interestingly, MM constituted the prevailing diagnosis among obese and overweight patients, whereas DLBCL held prevalence among individuals with normal and underweight statuses.

Despite the statistically significant disparity in CD34 cell counts between the overweight/obese and underweight/normal groups, it's worth noting that the studies mentioned above collectively indicate that this discrepancy doesn't influence transplant-related mortality. The present study identified several risk factors for mortality, including a PLT engraftment value exceeding 50,000, prolonged hospital stays following chemo-mobilization, and an extended duration of G-CSF administration. Intriguingly, univariate and stepwise multivariate LR models failed to reveal any mortality and survival rate divergence between obese and non-obese patients.

Limitation

The present study has certain limitations, primarily stemming from its retrospective cohort design and the inclusion of diverse disease categories, predominantly lymphoma and myeloma, and the utilization of various mobilization strategies involving G-CSF alone or in conjunction with chemotherapy. Nonetheless, in order to validate and contextualize these findings within contemporary circumstances, additional research efforts are warranted.

Conclusion

The present study uncovered no adverse correlation between obesity and mortality or engraftment among patients with diverse hematological malignancies undergoing AutoHCT. Furthermore, BMI exhibited no impact on neutrophil and platelet engraftment speed. It's worth noting that prior research highlighting negative biases held by physicians toward overweight individuals suggests the potential existence of biases in treatment decisions and processes. The current study dispels the misconception that overweight or obese patients might receive less efficient or safe treatment than their normal-weight counterparts, provided they possess the necessary fitness and qualifications. The study achieves this by demonstrating that diminished CD34+ cell counts do not negatively affect mortality or engraftment. A meticulously designed prospective trial is essential to lend robustness to these findings, ideally through collaborative efforts across multiple centers. Therefore, in clinical scenarios where therapeutic necessity is evident, obesity alone should not deter pursuing AutoHCT for hematological malignancies. This conclusion stems from our inability to discern survival disparities among individuals of varying weight categories: overweight, obese, and normal.

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