Research Article

Clinically Significant Gastrointestinal Toxicity As A Determinant of Prolonged Hospitalization After Autologous Stem Cell Transplantation - A Single-Centre Retrospective Cohort Study

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Abstract

Background: Gastrointestinal (GI) toxicity following autologous stem cell transplantation (ASCT) is common but its contribution to prolonged hospitalization remains poorly defined. We examined the association between clinically significant GI toxicity and early transplant outcomes including prolonged hospital stay in a real-world cohort of hematologic malignancy patients.

Methods: Single-centre retrospective cohort study of 50 consecutive ASCT recipients conducted between April 2022 and December 2025. Clinically significant GI toxicity was defined as grade ≥2 oral mucositis and/or grade ≥2 diarrhea according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The primary endpoint was prolonged hospitalization (>22 days). Univariate odds ratios were calculated for prolonged hospital stay; an exploratory multivariable logistic regression model included GI toxicity, BEAM conditioning, febrile neutropenia, and culture positivity.

Results: Clinically significant GI toxicity occurred in 26 patients (52.0%): grade ≥2 diarrhea in 24 patients (48.0%) and grade ≥2 mucositis in 12 patients (24.0%). Patients with significant GI toxicity had a median hospital stay of 22 days versus 18 days in those without (p=0.065). The strongest univariate predictors of prolonged hospitalization (>22 days) were febrile neutropenia (OR 32.00, 95% CI 5.59–183.03, p<0.001), BEAM conditioning (OR 15.44, 95% CI 2.81–84.72, p<0.001), and culture positivity (OR 6.57, 95% CI 1.51–28.54, p=0.013). In exploratory multivariable analysis, febrile neutropenia and culture positivity retained strong effect sizes but were borderline significant (p=0.060 and p=0.063, respectively).

Conclusions: Clinically significant GI toxicity is highly prevalent after ASCT but prolonged hospitalization is driven primarily by infectious complications and conditioning intensity. BEAM-conditioned patients represent a high-risk subgroup requiring intensified supportive care and proactive discharge planning. These exploratory findings should be validated in larger prospective cohorts.

Keywords: Autologous stem cell transplantation; Gastrointestinal toxicity; Mucositis; Diarrhea; Febrile neutropenia; Engraftment; hospital stay; BEAM; Melphalan; Hematologic malignancies; Conditioning regimens

Introduction

Autologous stem cell transplantation (ASCT) has become the standard consolidation therapy for patients with newly diagnosed multiple myeloma and is widely used as salvage therapy in relapsed/refractory lymphomas, including Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL).[1,2] Over the past two decades, transplant-related mortality (TRM) and overall transplant-related morbidity have decreased substantially due to advances in conditioning regimens, stem cell mobilization and collection techniques, infection prevention strategies, and modern supportive care.[3,4] However, early post-transplant complications remain frequent and clinically significant, and treatment-related toxicities continue to impact patient quality of life and healthcare resource utilization.[5]

Gastrointestinal (GI) toxicity, encompassing oral mucositis and diarrhea, represents one of the most common non-

hematologic complications of myeloablative conditioning regimens used in ASCT.[6,7] These toxicities result from direct cytotoxic effects of high-dose chemotherapy on rapidly dividing epithelial cells of the gastrointestinal tract, as well as subsequent dysbiosis, bacterial translocation, and systemic inflammatory responses.[8,9] The clinical consequences of severe GI toxicity are substantial: patients experience poor oral intake, nutritional deterioration, severe pain and discomfort, delayed post-transplant recovery, and require prolonged hospitalization for supportive care, antimicrobial therapy, and management of infectious complications.[10,11] Additionally, severe mucositis is associated with compromised mucosal integrity and increased bacterial translocation risk, which may substantially increase the risk of bloodstream infections and sepsis during the period of profound neutropenia following high-dose chemotherapy.[12,13]

High-dose melphalan is well-established as a dose-limiting agent with respect to gastrointestinal toxicity in ASCT for multiple myeloma, while BEAM (carmustine, etoposide, cytarabine, melphalan) remains a commonly used myeloablative conditioning regimen for lymphoid malignancies.[14,15] Despite the widespread use of these regimens, comprehensive comparison of the gastrointestinal toxicity burden between BEAM and melphalan-based conditioning in real-world clinical practice remains limited.[16] The Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) clinical practice guidelines emphasize that mucositis is a major complication of cancer therapy requiring standardized assessment, consistent grading using validated instruments such as the Common Terminology Criteria for Adverse Events (CTCAE), and proactive supportive care interventions.[17,18]

Understanding the relationship between clinically significant GI toxicity and early post-transplant morbidity, particularly prolonged hospitalization, has important implications for resource utilization, quality of care metrics, discharge planning, and the development of targeted supportive care protocols.[19,20] The primary aim of this single-centre retrospective cohort study was to examine whether clinically significant gastrointestinal toxicity is independently associated with prolonged hospitalization and other clinically important early post-transplant outcomes in a consecutive series of ASCT recipients with hematologic malignancies managed at a tertiary care centre.

METHODS

Study Design and Population

This was a single-centre retrospective observational cohort study conducted in the bone marrow transplant unit of a tertiary care hospital. The study cohort comprised 50 consecutive patients who underwent autologous stem cell transplantation between April 2022 and December 2025. All patients provided informed consent for treatment and data collection in accordance with institutional policies. This analysis was approved under institutional review board protocols for quality improvement and outcomes research in accordance with Declaration of Helsinki principles.[21]

Inclusion criteria were: (1) autologous stem cell transplantation for confirmed hematologic malignancy; (2) availability of post-transplant gastrointestinal toxicity grading data based on clinical examination; (3) availability of engraftment kinetics and complete hospitalization data; and (4) confirmed diagnosis of multiple myeloma or lymphoma (including Hodgkin lymphoma, diffuse large B-cell lymphoma, or other lymphomas). Exclusion criteria were: (1) allogeneic stem cell transplantation or syngeneic transplantation; (2) tandem transplant episodes (counted separately); (3) missing key outcome data for mucositis severity, diarrhea severity, or total duration of hospitalization; or (4) early death before complete assessment of hematopoietic engraftment or toxicity grading.

Exposure Definition and Outcomes

The primary exposure of interest was clinically significant gastrointestinal toxicity, defined as either grade ≥2 oral mucositis or grade ≥2 diarrhea (or both) according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[22] Grade 2 represents moderate toxicity requiring minimal or non-invasive intervention

and/or limiting instrumental activities of daily living. This definition was selected based on clinical relevance in predicting resource use and complications, as grade 1 toxicities are generally manageable with standard supportive care and do not typically impact hospitalization duration.[23,24]

The primary endpoint was prolonged hospitalization, defined as hospital stay greater than 22 days (the median duration in this cohort). This threshold was selected a priori based on the median length of stay in our cohort and prior literature examining predictors of extended hospitalization in ASCT recipients.[25,26] Secondary endpoints included: febrile neutropenia (defined as fever ≥38.5°C with absolute neutrophil count <0.5 $\times 10^9$/L requiring hospitalization), culture-documented infection from any source, delayed neutrophil engraftment (recovery occurring after day 10), delayed platelet engraftment (recovery occurring after day 11), prolonged duration of granulocyte-colony-stimulating factor (G-CSF) use (>10 days), and occurrence of serious post-transplant complications including veno-occlusive disease (VOD) and engraftment syndrome.[27,28]

Hematopoietic Engraftment Definition

Hematopoietic engraftment was assessed using standard criteria consistent with international guidelines.[29] Neutrophil engraftment was defined as the first of three consecutive days on which the absolute neutrophil count (ANC) was ≥0.5 × 10^9/L. Platelet engraftment was defined as achievement of a platelet count ≥20 × 10^9/L without transfusion support for seven consecutive days. The day of neutrophil and platelet engraftment was recorded for each patient, and these values were subsequently used to determine delayed engraftment according to the predefined study thresholds.

Statistical Analysis

Baseline demographic, disease-related, and transplant-related variables were summarized using standard descriptive statistics. Continuous variables were summarized as median with interquartile range (IQR) and compared using the Mann–Whitney U test for non-parametric comparisons. Categorical variables were summarized as frequency and percentage and compared using Fisher's exact test, which was selected for use because many cells contained counts less than five. Normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms. Univariate logistic regression analysis was performed to calculate odds ratios (OR) with 95% confidence intervals (CI) for binary outcomes including prolonged hospitalization; zero cells in two-by-two contingency tables were corrected using the Haldane–Anscombe correction prior to calculation of odds ratios where applicable.[30]

An exploratory multivariable logistic regression model was constructed to identify independent predictors of prolonged hospitalization. Given the small sample size and limited number of outcomes (n=15 episodes of prolonged hospitalization), the model was deliberately limited to four clinically relevant predictor variables selected a priori: clinically significant GI toxicity, BEAM conditioning regimen (versus melphalan), febrile neutropenia, and culture-documented infection positivity. This parsimonious modeling approach was adopted to reduce overfitting risk in the context of small numbers of events.[31,32] Model performance was evaluated using the apparent area under the receiver operating characteristic curve (AUC). All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. Data analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY).

RESULTS

Baseline and Transplant Characteristics

Table 1 presents the baseline characteristics of the 50 ASCT recipients included in this analysis. The median age was 39 years (IQR 26.5–50.75), with a predominance of male recipients (58.0%). The cohort was relatively balanced between diagnoses, with multiple myeloma accounting for 48.0% (24/50) and lymphoid malignancies (including Hodgkin lymphoma, DLBCL, and other lymphomas) accounting for 52.0% (26/50) of cases. BEAM

conditioning was administered to 52.0% (26/50) of patients, while melphalan-based conditioning was used in 48.0% (24/50). The median CD34+ stem cell dose infused was 8.25 $\times 10^6$/kg, which is within the range recommended by international transplant guidelines. Median neutrophil engraftment occurred on day 10 (IQR 10–11) and platelet engraftment on day 11 (IQR 9.25–12.75). Complete hospitalization data were available for 42 of 50 patients (84.0%), with a median hospital stay of 22 days (IQR 18–24).

Table 1. Baseline and transplant characteristics of the cohort (n=50)

Variable	Result
Patients analysed	50
Age, years (median, IQR)	39 (26.5–50.75)
Male sex	29/50 (58.0%)
Female sex	21/50 (42.0%)
Multiple myeloma	24/50 (48.0%)
Lymphoid malignancies	26/50 (52.0%)
- Hodgkin lymphoma	8/26 (30.8%)
- Diffuse large B-cell lymphoma	12/26 (46.2%)
- Other lymphomas	6/26 (23.1%)
BEAM conditioning	26/50 (52.0%)
Melphalan-based conditioning	24/50 (48.0%)
Previous lines of therapy (median, IQR)	1.5 (1–2)
CD34+ cell dose, $\times 10^6$/kg (median, IQR)	8.25 (6.8–11.52)
Neutrophil engraftment, days (median, IQR)	10 (10–11)
Platelet engraftment, days (median, IQR)	11 (9.25–12.75)
G-CSF duration, days (median, IQR)	10 (8–11)
Hospital stay, days (median, IQR)	22 (18–24)
Hospital stay data available	42/50 (84.0%)
Disease status at transplant: CMR	25/50 (50.0%)
Disease status at transplant: VGPR	22/50 (44.0%)
Disease status at transplant: CR/PR/SD	3/50 (6.0%)

Gastrointestinal Toxicity and Early Transplant Morbidity

The incidence and severity of gastrointestinal toxicity in this cohort are presented in Table 2. Clinically significant GI toxicity (grade ≥2 oral mucositis and/or grade ≥2 diarrhea) occurred in 26 of 50 patients (52.0%). Grade ≥2 diarrhea was notably more prevalent than grade ≥2 oral mucositis (48.0% versus 24.0%), which is consistent with findings from other prospective and retrospective series examining conditioning-related toxicities.[33,34] Any documented GI toxicity of any grade was recorded in 39 patients (78.0%), demonstrating that gastrointestinal effects are nearly universal following high-dose myeloablative conditioning. The severity distribution was relatively favorable compared to some published series: only 2 patients (4.0%) experienced grade 3 oral mucositis and 5 patients (10.0%) experienced grade 3 diarrhea, with no patients experiencing grade 4 toxicity. Serious early transplant complications such as veno-occlusive disease (VOD) or engraftment syndrome were not observed in this cohort, possibly reflecting the relatively young median age, modern supportive care practices, and pharmacokinetic monitoring of conditioning agents where applicable.

Table 2. Gastrointestinal toxicity profile and early transplant morbidity (n=50)

Toxicity / Outcome	n (%)
Grade ≥2 oral mucositis	12/50 (24.0%)

Grade ≥2 diarrhea	24/50 (48.0%)
Clinically significant GI toxicity (grade ≥2 mucositis and/or diarrhea)	26/50 (52.0%)
Febrile neutropenia	15/50 (30.0%)
Culture positivity	13/50 (26.0%)
Hospital stay >22 days	15/42 (35.7%)
Any toxicity recorded (any grade GI toxicity)	39/50 (78.0%)
Veno-occlusive disease (VOD)	0/50 (0.0%)
Engraftment syndrome	0/50 (0.0%)
No oral mucositis	22/50 (44.0%)
Oral mucositis grade 1	16/50 (32.0%)
Oral mucositis grade 2	10/50 (20.0%)
Oral mucositis grade 3	2/50 (4.0%)
Oral mucositis grade 4	0/50 (0.0%)
No diarrhea	20/50 (40.0%)
Diarrhea grade 1	6/50 (12.0%)
Diarrhea grade 2	19/50 (38.0%)
Diarrhea grade 3	5/50 (10.0%)
Diarrhea grade 4	0/50 (0.0%)

Outcomes According to Clinically Significant GI Toxicity Status

Table 3 presents a comparative analysis of early transplant outcomes stratified by the presence or absence of clinically significant GI toxicity. While patients with significant GI toxicity demonstrated numerically higher rates of febrile neutropenia (38.5% versus 20.8%, p=0.224) and prolonged hospitalization (43.5% versus 26.3%, p=0.337), these differences did not reach statistical significance in univariate analysis. The median hospital stay was 4 days longer in patients with GI toxicity (22 days versus 18 days, p=0.065), approaching but not reaching the conventional threshold of statistical significance. This marginal p-value (p=0.065) may reflect limited statistical power in this cohort and warrants investigation in larger prospective studies. Importantly, no significant differences were observed between groups in neutrophil engraftment kinetics, platelet engraftment kinetics, or duration of G-CSF administration, suggesting that GI toxicity is not independently associated with delays in hematopoietic recovery.

Table 3. Early transplant outcomes stratified by clinically significant GI toxicity status

Outcome	No Significant GI Toxicity (n=24)	Significant GI Toxicity (n=26)	p value
Febrile neutropenia	5/24 (20.8%)	10/26 (38.5%)	0.224
Culture positivity	6/24 (25.0%)	7/26 (26.9%)	1.000
Hospital stay >22 days	5/19 (26.3%)	10/23 (43.5%)	0.337
Neutrophil engraftment >10 days	11/24 (45.8%)	10/26 (38.5%)	0.775
Platelet engraftment >11 days	11/24 (45.8%)	9/26 (34.6%)	0.565
G-CSF use >10 days	7/24 (29.2%)	7/26 (26.9%)	1.000
Neutrophil engraftment, median days (IQR)	10 (10–11)	10 (10–11)	0.545
Platelet engraftment, median days (IQR)	11 (11–12)	11 (10–12)	0.732

G-CSF duration, median days (IQR)	10 (8–11)	10 (8–11)	0.811
Hospital stay, median days (IQR)	18 (16–22)	22 (19–24)	0.065

Conditioning Regimen and Transplant Outcomes

Table 4 stratifies early transplant outcomes by conditioning regimen type. BEAM-conditioned patients demonstrated a strikingly higher rate of prolonged hospitalization (61.9%) compared to melphalan-conditioned patients (9.5%; p<0.001). This sixfold difference reflects the inherently greater toxicity and myelosuppressive intensity of the BEAM regimen, which combines four chemotherapeutic agents (carmustine, etoposide, cytarabine, and melphalan) compared to the single-agent melphalan conditioning.[14,35] Febrile neutropenia was markedly more frequent in the BEAM group, occurring in 57.7% of patients versus 0.0% in the melphalan group (p<0.001), which is a striking and clinically important finding. BEAM conditioning was also associated with significantly delayed platelet engraftment (57.7% with >11 day delay versus 20.8%, p=0.010), prolonged G-CSF use (46.2% requiring >10 days versus 8.3%, p=0.004), and slower neutrophil recovery (median 10.5 days versus 10 days, p=0.024). Notably, clinically significant GI toxicity was numerically more common in the BEAM group (57.7% versus 45.8%), but this difference was not statistically significant (p=0.572), suggesting that while both regimens cause GI toxicity, BEAM's impact on hospitalization is primarily mediated through infectious complications rather than through GI effects per se.

Table 4. Early transplant outcomes stratified by conditioning regimen

Outcome	BEAM (n=26)	Melphalan (n=24)	p value
Clinically significant GI toxicity	15/26 (57.7%)	11/24 (45.8%)	0.572
Grade ≥2 oral mucositis	8/26 (30.8%)	4/24 (16.7%)	0.327
Grade ≥2 diarrhea	14/26 (53.8%)	10/24 (41.7%)	0.413
Febrile neutropenia	15/26 (57.7%)	0/24 (0.0%)	<0.001
Culture-documented infection	9/26 (34.6%)	4/24 (16.7%)	0.202
Platelet engraftment >11 days	15/26 (57.7%)	5/24 (20.8%)	0.010
G-CSF use >10 days	12/26 (46.2%)	2/24 (8.3%)	0.004
Hospital stay >22 days	13/21 (61.9%)	2/21 (9.5%)	<0.001
Neutrophil engraftment, median days	10.5	10	0.024
Platelet engraftment, median days	12	10	<0.001
G-CSF duration, median days	10	8	<0.001
Hospital stay, median days	23	18	<0.001

Predictors of Prolonged Hospitalization

Table 5 presents univariate and exploratory multivariable odds ratios for the outcome of prolonged hospitalization (>22 days). In univariate analysis, febrile neutropenia emerged as the strongest predictor of prolonged hospitalization, with an exceptionally large odds ratio of 32.00 (95% CI 5.59–183.03, p<0.001), reflecting the profound clinical impact of infectious complications on hospitalization duration. BEAM conditioning was the

second strongest predictor (OR 15.44, 95% CI 2.81–84.72, p<0.001), and culture positivity from blood or other documented sources was the third (OR 6.57, 95% CI 1.51–28.54, p=0.013). In contrast, clinically significant GI toxicity demonstrated an odds ratio of 2.15 (95% CI 0.58–8.00) but did not reach statistical significance (p=0.337), suggesting that while GI toxicity is prevalent, it is not an independent determinant of prolonged hospitalization in this cohort.

In the exploratory multivariable logistic regression model constructed with the four pre-specified predictors (clinically significant GI toxicity, BEAM conditioning, febrile neutropenia, and culture positivity), both febrile neutropenia and culture positivity retained substantial effect sizes (adjusted OR 12.87, 95% CI 0.90–184.75, p=0.060, and adjusted OR 7.39, 95% CI 0.89–61.08, p=0.063, respectively), although both were borderline statistically significant. This pattern is consistent with limited sample size and number of events, not diminishment of clinical effect. BEAM conditioning, when adjusted for other variables in the model, demonstrated substantial attenuation (adjusted OR 2.83, 95% CI 0.17–47.60, p=0.470), suggesting that the strong univariate association between BEAM conditioning and prolonged hospitalization is substantially confounded or mediated by febrile neutropenia and documented infection. The exploratory multivariable model demonstrated an apparent area under the receiver operating characteristic curve (AUC) of 0.90, indicating reasonable discrimination between patients with and without prolonged hospitalization, although this estimate should be interpreted cautiously given the small sample size and risk of overfitting.

Table 5. Univariate and exploratory multivariable predictors of prolonged hospitalization (>22 days)

Predictor	OR / Adjusted OR	95% CI	p value
UNIVARIATE ANALYSIS			
Significant GI toxicity	2.15	0.58–8.00	0.337
Grade ≥2 oral mucositis	2.20	0.52–9.36	0.451
Grade ≥2 diarrhea	1.23	0.35–4.36	1.000
Febrile neutropenia	32.00	5.59–183.03	<0.001
Culture positivity	6.57	1.51–28.54	0.013
Delayed platelet engraftment (>11 days)	1.66	0.47–5.93	0.525
G-CSF use >10 days	1.90	0.50–7.31	0.488
BEAM conditioning	15.44	2.81–84.72	<0.001
EXPLORATORY MULTIVARIABLE MODEL			
Significant GI toxicity	2.50	0.34–18.45	0.369
BEAM conditioning	2.83	0.17–47.60	0.470
Febrile neutropenia	12.87	0.90–184.75	0.060
Culture positivity	7.39	0.89–61.08	0.063

Abbreviations: OR, odds ratio; CI, confidence interval. Model apparent AUC = 0.90. Multivariable model is exploratory due to small sample size and limited number of events and should be interpreted cautiously. Analysis based on 42 patients with complete hospitalization data (15 with prolonged hospitalization).

DISCUSSION

This single-centre retrospective cohort study examined the relationship between clinically significant gastrointestinal toxicity and prolonged hospitalization after autologous stem cell transplantation for hematologic malignancies. The key finding was that although clinically significant GI toxicity is highly prevalent in ASCT

recipients (52.0%), it was not independently predictive of prolonged hospitalization when other clinical and transplant-related factors were considered. Rather, infectious complications (febrile neutropenia and culture-documented infection) and conditioning regimen intensity (BEAM versus melphalan) emerged as the dominant drivers of prolonged hospitalization duration. These findings have important implications for understanding early post-transplant morbidity and for informing supportive care and discharge planning strategies in ASCT programs.

Prevalence and Spectrum of GI Toxicity

The high prevalence of clinically significant GI toxicity (52.0%) and any documented GI toxicity of any grade (78.0%) in this cohort is consistent with published data from prospective and retrospective series examining conditioning-related toxicities in ASCT.[6,33,34] In a multicenter retrospective study by Gordillo and colleagues that included 100 consecutive ASCT recipients treated with high-dose melphalan, most patients experienced gastrointestinal symptoms; 97% of patients reported diarrhea of any grade, and 74% had at least grade 2 diarrhea.[33] Similarly, Wong and colleagues, in a retrospective examination of 142 ASCT recipients, reported oral mucositis in 68.3% of patients and gastrointestinal mucositis/diarrhea in 95.8%.[36] Our finding that diarrhea was notably more frequent than severe oral mucositis (48.0% vs 24.0%) aligns with the observation that diarrhea generally represents a more prevalent and dose-limiting toxicity than stomatitis in ASCT recipients.[34,37] The severity spectrum observed in our cohort was relatively favorable compared to some published reports, with only 4.0% and 10.0% of patients experiencing grade 3 oral mucositis and grade 3 diarrhea, respectively, and no grade 4 toxicities. This relatively favorable toxicity profile may reflect several factors: the relatively young median age of our cohort (39 years), modern supportive care practices including nutritional interventions and antimicrobial prophylaxis, and careful clinical monitoring with early intervention for symptomatic complications.[10,38]

GI Toxicity and Prolonged Hospitalization

Although patients with significant GI toxicity in our cohort demonstrated a numerically longer median hospital stay (22 days versus 18 days), this 4-day difference approached but did not reach statistical significance (p=0.065). This finding appears to diverge from some published studies, which have reported that severe mucositis and gastrointestinal toxicity are associated with substantially longer hospitalization.[10,39,40] However, several plausible explanations account for this apparent discrepancy. First, prolonged hospitalization in ASCT recipients is inherently multifactorial, driven by numerous interconnected factors including infection management, hematopoietic recovery, and overall treatment toxicity, rather than GI toxicity acting as a sole or primary determinant.[25,26] Second, in modern ASCT practice at tertiary care centres, intensive nutritional support, meticulous hydration management, sophisticated antimicrobial prophylaxis regimens, advanced symptom management including opioid analgesics, and early intervention for complications are implemented routinely, which may substantially mitigate the impact of GI toxicity on hospitalization duration.[11,41] Third, the relatively small sample size in this single-centre cohort (n=42 with complete hospitalization data, n=23 with GI toxicity and complete data) provides limited statistical power to detect an association if one truly exists.[42] A formal power analysis would be required to determine the sample size necessary to detect a clinically meaningful difference in hospitalization duration attributable to GI toxicity.

Febrile Neutropenia and Infection as Primary Drivers

The most striking and clinically important finding in this study was the dominant role of febrile neutropenia in predicting prolonged hospitalization, with an exceptional odds ratio of 32.00 in univariate analysis. This extremely large effect size reflects the well-established and profound clinical reality that patients who develop febrile episodes during the profound neutropenia following myeloablative conditioning require extended hospitalization for multiple reasons: initiation of empiric broad-spectrum intravenous antibiotics, extensive diagnostic evaluation including blood cultures, urinalysis, chest imaging, and potentially central nervous system evaluation, supportive care including intravenous hydration and analgesics, and monitoring for complications such as sepsis or septic

shock.[43,44] Similarly, culture-documented infection positivity showed a strong association with prolonged hospitalization (OR 6.57, p=0.013), underscoring the clinical and resource-utilization impact of documented bacteremia or other culture-positive infections. In the exploratory multivariable model, febrile neutropenia retained a strong effect size (adjusted OR 12.87) with borderline statistical significance (p=0.060), suggesting that infectious complications represent an important independent predictor of prolonged hospitalization even after accounting for conditioning regimen intensity and gastrointestinal toxicity. These findings strongly support current clinical practice paradigms emphasizing early recognition and aggressive treatment of febrile episodes in ASCT recipients, robust infection prevention protocols including antimicrobial and antifungal prophylaxis, high-efficiency particulate air (HEPA) filtration in patient rooms, and skilled nursing care to minimize infection risk during the period of profound immunosuppression.[43,45,46]

Conditioning Regimen Differences and Risk Stratification

BEAM conditioning was associated with a strikingly higher rate of prolonged hospitalization compared to melphalan-based regimens (61.9% versus 9.5%, representing approximately a sixfold difference). This substantial difference likely reflects the inherent toxicity profile of BEAM, which combines four cytotoxic agents (carmustine, etoposide, cytarabine, and melphalan) administered as a potent myeloablative combination.[14] BEAM-conditioned patients in our cohort demonstrated markedly higher rates of febrile neutropenia (57.7% versus 0.0%), significantly delayed platelet engraftment (57.7% with >11 day recovery versus 20.8%), prolonged G-CSF use (46.2% requiring >10 days versus 8.3%), and delayed neutrophil recovery (median 10.5 days versus 10 days). Notably, Kothari and colleagues examined outcomes in 50 patients with relapsed/refractory DLBCL treated with either BEAM or alternative conditioning regimens and found that significant mucosal toxicity was seen with both regimens, with 51% of patients experiencing grade 3 diarrhea and approximately 30% experiencing grade 3 stomatitis.[47] In our multivariable model, the adjusted odds ratio for BEAM conditioning was substantially attenuated (adjusted OR 2.83, p=0.470) compared to the univariate estimate (OR 15.44, p<0.001), strongly suggesting that the relationship between BEAM conditioning and prolonged hospitalization is substantially confounded or mediated by febrile neutropenia and documented infection rather than representing a direct independent effect of BEAM on hospitalization duration. These findings support the designation of BEAM-conditioned patients as a high-risk subgroup within ASCT programs, warranting enhanced surveillance for infectious complications, earlier intervention for fever or other signs of infection, and potentially earlier involvement of infectious disease specialists.

Clinical Implications and Supportive Care Considerations

These findings have several important practical implications for ASCT programs and transplant teams. First, while clinically significant GI toxicity should not be dismissed—it impacts quality of life significantly and may increase infection risk through compromised mucosal integrity—it should be appropriately contextualized as one component of early post-transplant morbidity rather than the sole or primary determinant of prolonged hospitalization. Continued attention to prevention and management of GI toxicity through nutritional interventions, antimicrobial prophylaxis including selective digestive decontamination where applicable, symptom management, and patient education remains warranted.[17,18] Second, the data presented here provide strong support for continued and intensified attention to infection prevention and management protocols, including MASCC/ISOO-recommended mucositis prophylaxis, aggressive early intervention for febrile episodes with empiric broad-spectrum antibiotics, and ongoing surveillance for breakthrough infections.[45,46] Third, patients receiving BEAM conditioning should be recognized as a clearly defined higher-risk subgroup requiring intensified supportive care strategies, including frequent vital sign monitoring, careful assessment for signs of infection, expedited initiation of empiric antibiotics for fever, close monitoring of blood cultures and other culture sources, involvement of infectious disease consultation when appropriate, and proactive discharge planning to minimize unnecessary

prolongation of hospitalization while ensuring safety.[48,49]

Study Limitations

This study has several important limitations that warrant explicit acknowledgment. The retrospective design introduces potential for missing or incompletely recorded data, particularly regarding the detailed characterization of specific infection types, causative organisms, antimicrobial regimens used, and other clinical details relevant to the analysis. The small sample size (n=50, n=42 with complete hospitalization data, n=23 with both GI toxicity and complete hospitalization data) substantially limits statistical power to detect associations and substantially limits generalizability of findings to other ASCT programs with different patient populations, conditioning regimens, supportive care practices, or institutional protocols. The single-centre experience may not reflect patterns, practices, or outcomes in other institutions, particularly tertiary care centres in different geographic regions or health systems with different supportive care standards, antimicrobial prophylaxis protocols, or nursing care models. Potential missing or incompletely recorded data on toxicity grading based on clinical examination (rather than validated instruments completed prospectively), hospitalization duration, comorbidities, and other relevant variables could introduce bias and reduce the validity of estimates. The absence of long-term survival data, patient-reported outcomes, quality-of-life assessment, rehospitalization rates, or late complications limits understanding of the full clinical impact of GI toxicity and conditioning-related complications. The multivariable model developed in this study is explicitly exploratory in nature and may be subject to overfitting given the small number of events (n=15 prolonged hospitalizations) relative to the number of predictor variables considered in model building. Given these significant limitations, as is an observational study, causality cannot be inferred from associations observed, and residual confounding by unmeasured or incompletely recorded factors is possible.[42,50]

CONCLUSIONS

Clinically significant gastrointestinal toxicity is highly prevalent (52.0%) in ASCT recipients and represents an important component of early post-transplant morbidity with substantial impact on quality of life and clinical management requirements. However, this analysis suggests that gastrointestinal toxicity is not independently predictive of prolonged hospitalization when other relevant clinical factors are considered. Instead, prolonged hospitalization after ASCT appears to be driven primarily by infectious complications (febrile neutropenia and culture-documented infection) and conditioning regimen intensity. BEAM-conditioned patients represent a clearly identifiable and high-risk subgroup with markedly increased rates of febrile neutropenia (57.7%), delayed platelet engraftment, prolonged G-CSF use, and markedly increased hospitalization rates (61.9% experiencing >22 day stays), warranting tailored and intensified supportive care strategies, enhanced infection surveillance, and proactive discharge planning.

These exploratory findings suggest that future quality improvement and clinical research efforts should prioritize the development and refinement of infection prevention and management strategies specifically targeting ASCT recipients, with particular emphasis on BEAM-conditioned patients who bear disproportionate risk of infectious complications. While mucositis prevention and aggressive gastrointestinal supportive care remain important quality indicators and should continue to be prioritized as components of comprehensive ASCT supportive care, the evidence presented in this study suggests they should not be overemphasized as the primary determinant of hospitalization duration. Rather, a more balanced approach recognizing gastrointestinal supportive care as one component of comprehensive post-transplant management appears more appropriate. Larger prospective multicenter studies incorporating standardized protocols for prospective toxicity grading, detailed microbiological and infection documentation, quality-of-life assessment instruments, comprehensive resource utilization tracking, and long-term outcome assessment would provide further validation of these exploratory findings and would

inform the development of optimized supportive care models and clinical practice guidelines for ASCT recipients. Such studies should specifically examine the potential benefit of intensified antimicrobial prophylaxis, alternative antimicrobial regimens, selective digestive decontamination, and novel supportive care strategies in high-risk populations such as BEAM-conditioned patients.

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