Early outcomes of gastrostomy feeding in paediatric allogenic bone marrow transplantation: a retrospective cohort study

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Abstract

Background: Nutrition support is an essential component of care for a child undergoing bone marrow transplantation (BMT). Enteral nutrition (EN) is becoming increasingly recognised as having advantages over parenteral nutrition (PN) and recommended as first-line nutrition support. EN has traditionally been provided via nasogastric tube (NGT). Gastrostomies avoid certain complications associated with NGTs and could provide a preferential alternative.

Aims: To compare nutritional and post-transplantation outcomes during admission, the primary outcome being PN use, between children who had a gastrostomy placed prophylactically prior to BMT versus those who had not.

Methods: Electronic medical records of children transplanted between January 2014 and May 2018 within a single-centre were retrospectively reviewed. Outcomes between the gastrostomy group (n = 54) and non-gastrostomy group (n = 91) were compared.

Results: Multivariate regression analyses showed children in the gastrostomy group were less likely to require PN (odds ratio (OR) 0.4; 95% confidence interval (CI) 0.2-0.9; *P* = 0.049), initiated PN later if required (hazard ratio 0.6; 95% CI 0.4-0.8; *P* = 0.005), more often received EN as first-line nutrition support (*P* <0.001) and more frequently required EN post-discharge (OR 2.4; 95% CI 1.1-5.4; *P* = 0.029). No differences were found between groups on length of admission, day 100 overall survival, incidence of graft-versus-host-disease, positive blood cultures and changes in weight or albumin during admission.

Conclusions: Providing EN via gastrostomy is feasible in this population and may be more acceptable to older children than NGTs. Weighing up the potential benefits against the potential risks of prophylactic gastrostomy placement in these high-risk children is a challenging decision. Further research investigating safety, longer-term outcomes and family perceptions of gastrostomy feeding is required.

Keywords: Paediatric; bone marrow transplantation; gastrostomy; parenteral nutrition; enteral nutrition; nutritional status.

1. Introduction

Bone marrow transplantation (BMT) has become a well-recognised treatment for malignant and non-malignant diseases in children [1]. The intensive conditioning regimens used may cause side-effects including nausea, vomiting, diarrhoea, anorexia and mucositis [2]. The receipt of donor cells brings further complications of graft-versus-host-disease (GvHD) which adds to catabolic demands. On commencement of treatment patients experience deterioration in nutritional intake [3] and nutritional status [4], putting them at risk of malnutrition. Negative associations have been found between malnutrition and overall survival (OS), transplant-related mortality and relapse risk [5]. Consequently, nutrition support becomes essential during BMT [6], but there is no consensus on the optimal method for its delivery.

Traditionally parenteral nutrition (PN) has been considered the method of choice in this population [7]. However, the evidence seems to be shifting towards a preference for enteral nutrition (EN) as first-line nutrition support, as recommended by American and European guidelines [8,9]. With the already high risks this population face, it seems prudent PN should only be used when necessary given its association with catheter related complications [10], gut mucosal atrophy and increased line infections [11]. Studies offering first-line EN vs. PN to paediatric BMT patients have reported positive outcomes including better overall survival, less acute GvHD (aGvHD), better platelet engraftment and shorter admissions [12,13]. Furthermore, EN can help maintain gastro-intestinal integrity and reduce potential bacterial translocation [14].

With studies having focused on comparing EN vs. PN, few have directly compared EN interventions. Most paediatric BMT studies have administered EN via nasogastric tubes (NGTs) [12,13,15-17]. NGTs can be placed relatively simply during admission without the need for general anaesthetic and removed as soon as a patient's intake returns to sufficient levels. However, they are susceptible to complications including dislodgement with vomiting, discomfort with mucositis, epistaxis in thrombocytopaenia [14] and placement refusal, all of which meaning PN may need to be used prematurely, or by default.

Gastrostomy feeding offers an alternative route of providing EN, but has not commonly been used in this population due to concerns of infectious complications with neutropenia or thrombocytopenia [18]. Whilst one small retrospective study found more infectious complications in

children with gastrostomies placed for BMT compared to those placed for other purposes [19], others have demonstrated nutritional optimisation without significant complications in similarly high-risk oncology populations [20,21]. The prophylactic placement of gastrostomies before the development of mucositis, gastrointestinal toxicities and thrombocytopaenia, provides the potential for nutrition support to be commenced at the earliest indication and maintained for longer periods without the risk of tube dislodgment by vomiting or removal in severe mucositis. This could reduce the need or duration of PN and its associated complications, allow longer-term nutrition support beyond discharge and reduce admission length if time is not required re-establishing EN following PN. However, balancing these potential advantages against the potential complications of surgery for gastrostomy placement and site infections in this high-risk population [19], is a difficult clinical decision.

Few studies have investigated gastrostomy feeding as an alternative method to NGTs of providing nutrition support in paediatric BMT. The primary objective of this study was to compare PN use between gastrostomy vs. non-gastrostomy fed children during admission for BMT. We hypothesised that gastrostomy fed children used less PN during admission. Secondary objectives were to compare further nutritional and post-transplantation outcomes including weight and albumin changes, incidence of aGvHD, positive blood cultures and day 100 OS, between these two groups.

2. Materials and methods

2.1. Patients

This retrospective cohort study was conducted in the United Kingdom's largest paediatric BMT centre, Great Ormond Street Children's Hospital (GOSH). All consecutive NHS and private patients (<18 years) who received an allogenic BMT following reduced-intensity (RIC) or myeloablative (MAC) conditioning, admitted from January 2014 and discharged by May 2018, were included. A sample-size calculation was not undertaken, but a post-hoc power analysis was planned. The retrospective nature of this study was chosen to obtain a larger sample size than would have been achieved prospectively.

The centre's guidelines offer first-line EN to all children. During a pre-transplantation interview families are provided comprehensive information regarding nutrition support. During this interview families make an informed choice between an NGT to be placed during admission, or prophylactic gastrostomy placed prior to admission to pre-empt the anticipated insult to nutritional status. This study compared two groups; children with a gastrostomy in situ on admission formed the gastrostomy group, those without formed the non-gastrostomy group. Exceptions to these guidelines were those receiving cord blood transplants or with pre-existing gastro-intestinal diseases (such as inflammatory bowel disease), who received first-line PN, and children already established on EN pre-admission who continued their current modality. These children, alongside non-recipients of conditioning or nutrition support, those who had a previous BMT or recruited to another trial applying transplant procedures not used in routine practice, were excluded (Fig. 1).

Patients, GOSHs BMT multi-disciplinary team and a national BMT dietitians group were consulted and contributed to the development of this study. Ethical and organisational approvals were obtained from City, University of London and GOSH, reference number 17BA42.

2.2. Nutrition Support

From admission, all children were encouraged to maintain their oral intake, as able, throughout the transplant process, including a low microbial diet from the BMT ward and bottle or breastfeeding for infants. The target of any individual, or combination of, oral intake and nutrition support interventions

were to meet the child's requirements according to their age, sex and weight, for energy based on the Scientific Advisory Committee on Nutrition (2011) recommendations [22], and remaining macro and micronutrients based on Department of Health (1991) dietary reference values [23]. Intakes were recorded daily by nurses on fluid balance charts. These were assessed by a dietitian a minimum of three times weekly, who then advised families on provision of nutrition support, in conjunction with the BMT multi-disciplinary team.

EN and PN were initiated and provided according to the same guidelines in both groups. EN was initiated when oral intake of food or fluids became insufficient to meet nutritional requirements or weight began to reduce from admission. Children in the non-gastrostomy group had a 5-8 Fr polyurethane NGT placed, unless refused, when the initiation criteria were met. They were not placed systematically on a specific day during transplant. NGTs were promptly replaced if dislodged up to three times, if allowed by the patient. Children in the gastrostomy group received EN via percutaneous endoscopic gastrostomy (PEG), placed prophylactically in the weeks prior to admission.

EN was provided using an age appropriate polymeric formula (1kcal/ml), overnight via a pump with the volume gradually increased to establish tolerance, aiming to provide 50-70% requirements within five days. Once oral intake ceased, pump feeds or boluses were introduced during the day, with hypercaloric formula (1.5kcal/ml) used, if necessary, to provide 100% requirements. In cases of digestive intolerance including diarrhoea, formulae were changed to hydrolysed protein (1-1.5kcal/ml) to aid absorption. Children initiated PN, and ceased EN, in cases of severe mucositis, gut GvHD, NGT refusal or EN intolerance such as intractable vomiting and/or diarrhoea, despite manipulation to the feeding regimen, formula and optimisation of anti-emetic and anti-diarrhoea therapies. PN solutions included standard and tailor made bags with vamin given continuously over 24 hours and lipid over 20 hours. Following engraftment, EN was gradually re-introduced over five days and PN simultaneously titrated and eventually stopped. EN was discontinued when a child's oral intake met $\geq$70% requirements.

2.3. Transplantation procedure and supportive care

All children received allogenic BMT for various malignant and non-malignant diseases, according to the modalities and standard protocols of GOSH. Children received RIC or MAC conditioning, GvHD prophylaxis of ciclosporin with or without short-course methotrexate, corticosteroid or mycophenolate

mofetil and veno-occlusive disease (VOD) prophylaxis of intravenous vitamin K and ursodeoxycholic acid. Donors were preferentially matched sibling, followed by matched family or unrelated, then either mismatch unrelated or haploidentical. Stem cell sources were bone marrow or peripheral blood. Recipient and donor cytomegalovirus (CMV) status, sex mismatch (male recipient, female donor) and CD34+ cell doses were noted, factors known to influence outcomes after allogenic transplant [24,25]. Infection prevention included protective isolation in individual high efficiency particulate air filtered rooms, a low microbial diet, pasteurised bottle feeds and adherence to the unit's antimicrobial prophylaxis policy.

2.4. Data collection

Every child who underwent BMT at GOSH during the study's time-period was initially included from a database of BMT protocols and vetted according to the exclusion criteria (Fig. 1). Data was collected between January and May 2018 by retrospectively free-text searching electronic copies of patients' BMT protocols, medical, nursing and dietetic discharge summaries and the hospital's pathology system for blood results. These sources provided all the necessary demographic, transplant modalities and outcome data necessary to allow comprehensive group comparisons and identify any differences that could confound results. The protocols and discharge summaries for every child, regardless of group allocation, were written according to a set pro forma and consequently provided similar information. Outcomes were selected following a data collection pilot using these information sources in the early stages of the study. Potential outcomes with excessively missing data were excluded, including nutritional intakes from oral and EN, and issues relating to EN tolerance such as incidence of vomiting and diarrhoea. The following outcomes were therefore known to have complete and usable data which was extracted onto an Excel spreadsheet.

205 *2.5. Outcome definitions*

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207 From admission to discharge, the following measures were recorded and compared between
208 groups.

209 Use of nutritional interventions; (a) percent requiring PN for any time-period; (b) number of days
210 PN was provided; (c) days from admission PN was initiated and stopped; (d) percent receiving EN as
211 first-line nutrition support; (e) percent maintained exclusively on EN with no PN requirement; (f) percent
212 requiring EN post-discharge.

213 Changes in nutritional status were also investigated. Weight was measured on admission and daily
214 until discharge. Anthropometric measures were converted from raw to Z-scores, adjusted for age and
215 gender, using the LMS method [26]. Outcomes included; (g) change in weight Z-score; (h) percent
216 losing ≥10% weight, as 10% weight loss in three months after allogeneic BMT has been associated
217 with increased risk of subsequent non-relapse mortality (NRM) [4]; (i) change in albumin (g/L) from
218 admission to the lowest level during admission and discharge; (j) percent having at least one episode
219 of hypoalbuminaemia ≤30g/L.

220 Post-transplantation outcomes; (k) incidence of aGvHD, diagnosed on the presence of clinical
221 symptoms and/or histology markers of skin, liver and gut, graded I-IV using the modified Glucksberg
222 criteria [27]; (l) incidence of VOD, diagnosed using the modified Seattle criteria [28]; (m) length of
223 admission, measured in days from day of transplant/graft (day 0) to discharge; (n) neutrophil
224 engraftment, defined as the first of three consecutive days with a count $\geq 0.5 \times 10^9$/L [29]; (o) percent
225 having at least one bacterial infection confirmed by blood culture; (p) percent admitted to intensive care;
226 (q) OS and NRM at day 100, as strong markers of early BMT toxicity [30]. Biochemical analyses
227 including full blood count, urea, creatinine, electrolytes, liver function tests and blood cultures were
228 performed frequently throughout admission allowing theses post-transplantation outcomes to be
229 reported.

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231 *2.6. Statistics*

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233 All statistical analyses were performed using SPSS Version 24 between June-July 2018. All tests
234 were two-tailed and $p<0.05$ was considered statistically significant. There were no missing data as the

outcomes were selected following a data collection pilot. Outcome assessors were not blinded to participants' group allocation.

Descriptive statistics for categorical variables were expressed as frequencies and percentages and continuous variables by mean and standard deviation if normally distributed, median and interquartile range if skewed. Distribution normality was checked using skewness scores (skewed >±1), Shapiro-Wilk test and histograms.

Baseline characteristics between groups were compared using chi-squared or Fisher's exact test, when appropriate, for categorical variables, and independent samples t-test or Mann Whitney U-test, depending on the data's distribution, for continuous variables.

Outcomes between groups were compared using a hierarchical approach to various regression models to control for confounding factors. Confounders were identified through univariate analysis and only those significantly associated with the outcome ($p<0.05$) were included in the final model. The significant confounders were added to the final model in blocks starting with demographic variables in block one, clinical variables in block two and the variable of interest (group allocation) in block three. Binary outcomes (e.g. presence of VOD), were analysed using logistic regression, continuous outcomes (e.g. PN duration) using linear regression and time-to-event outcomes (e.g. time to PN initiation) using the Kaplan-Meier method and Cox regression, with cases censored if they did not experience the event of interest. Model fits were checked for multicollinearity and normality, linearity, outliers, influential cases and homoscedasticity via residual analysis. Changes in weight Z-score and albumin during admission were analysed using two-way (mixed) ANOVA.

The same statistical methods were used to perform two pre-planned subgroup analyses. Firstly, comparing gastrostomy and non-gastrostomy groups for those that only received MAC. Secondly, patients maintained exclusively on EN vs. those that received EN and further PN (regardless of gastrostomy/non-gastrostomy group). These are similar groups investigated in other studies [12,13]

3. Results

3.1. Study population

A total of 264 children were transplanted over the study's inclusion period. Seventy-four were potentially eligible to form the gastrostomy group, 190 the non-gastrostomy group. After vetting according to the exclusion criteria, data from 145 patients were extracted and analysed: 54 (37%) formed the gastrostomy group, 91 (63%) the non-gastrostomy group (Fig. 1). A post-hoc sample size calculation using G*Power 3.1 based on the primary outcome PN requirement (binary outcome), showed the achieved power was 0.42, small-medium effect size [31].

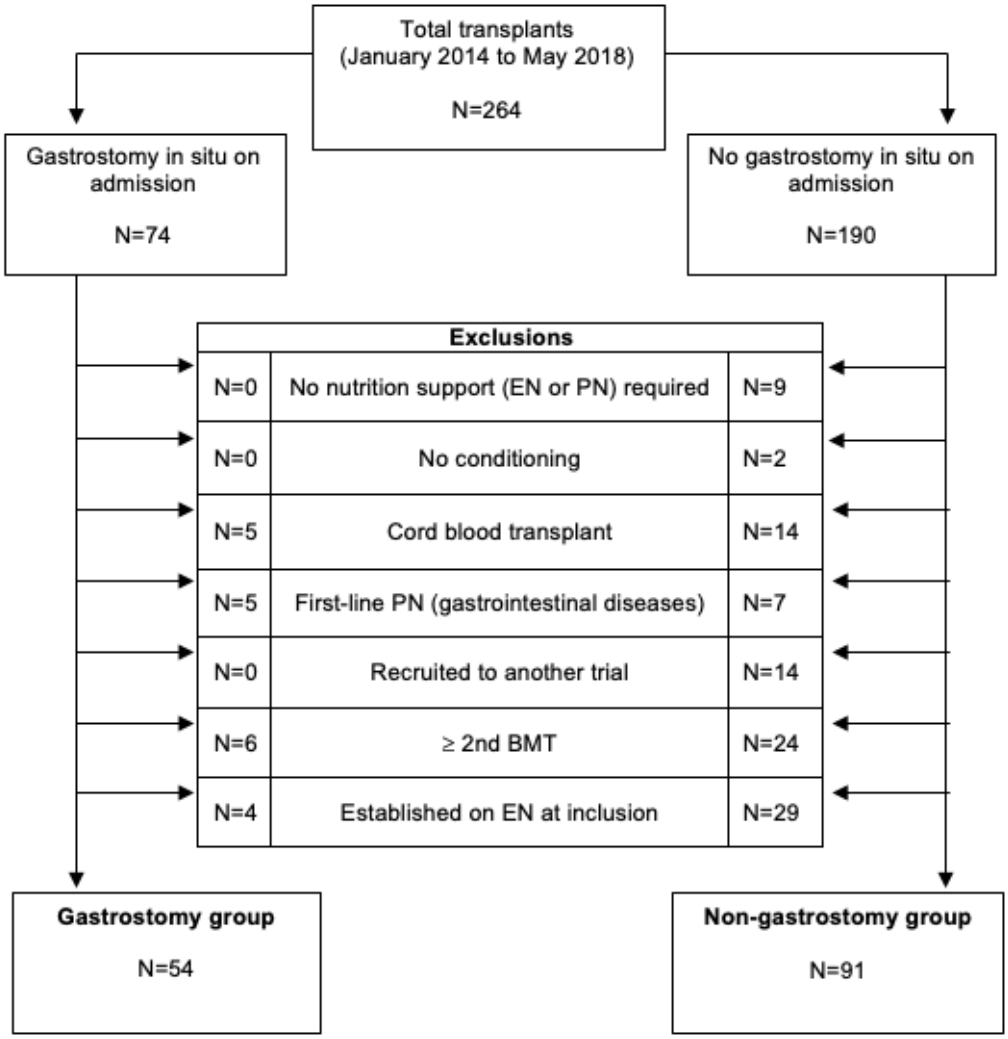

Fig. 1. Flow diagram showing the vetting of potentially eligible patients according to the exclusion criteria to form the gastrostomy and non-gastrostomy groups.

Initial characteristics of patients and their transplantation modalities are summarised in Table 1. Both groups were well matched on most characteristics with the only significant difference between groups being the proportions for recipient CMV serology (p=0.046). The flow of nutrition support modalities used between admission and discharge is shown in Fig. 2. Nutritional and post-transplantation outcomes are summarised in Table 2.

Table 1

Patient's characteristics and transplantation modalities.

	All patients (n= 145)	**Gastrostomy group (n= 54)**	**Non-gastrostomy group (n= 91)**	***P* value**
Age (years), mean ± SD	5.7 ± 4.1	6.3 ± 3.7	5.4 ± 4.3	0.226[a]
Private patient, n (%)	20 (13.8)	4 (7.4)	16 (17.6)	0.133[b]
Gender, Male/Female, n	91/54	34/20	57/34	1.0[b]
Diagnosis, n (%)				0.217[b]
Non-malignant diseases	89 (61.4)	37 (68.5)	52 (57.1)	
Malignant diseases	56 (38.6)	17(31.5)	39 (42.9)	
Disease status at transplant, n (%)				0.292[c]
Stable	88 (60.7)	36 (66.7)	52 (57.1)	
Partial remission	2 (1.4)	0 (0)	2 (2.2)	
CR	6 (4.1)	1 (1.9)	5 (5.5)	
CR 1	10 (6.9)	2 (3.7)	8 (8.8)	
CR ≥ 2	32 (22.1)	14 (25.9)	18 (19.8)	
Progressive disease	7 (4.8)	1 (1.9)	6 (6.6)	
Stem cell source, n (%)				0.715[b]
Bone marrow	99 (68.3)	38 (70.4)	61 (67.0)	
Peripheral blood	46 (31.7)	16 (29.6)	30 (33.0)	
Donor, n (%)				0.550[c]
MSD	38 (26.2)	10 (18.5)	28 (30.8)	
MFD	9 (6.2)	4 (7.4)	5 (5.5)	
MUD	76 (52.4)	32 (59.3)	44 (48.4)	
Haploidentical	7 (4.8)	3 (5.6)	4 (4.4)	
MMUD	15 (10.3)	5 (9.3)	10 (11.0)	
Sex mismatch (male recipient, female donor), n (%)	33 (22.8)	11 (20.4)	22 (24.2)	0.684[b]
Recipient CMV serology, n (%)				**0.046**[b]
Positive	47 (32.4)	12 (22.2)	35 (38.5)	
Negative	98 (67.6)	42 (77.8)	56 (61.5)	
Conditioning regimen, n (%)				0.864[b]
Myeloablative	82 (56.6)	30 (55.6)	52 (57.1)	
Reduced-intensity	63 (43.4)	24 (44.4)	39 (42.9)	
Number of CD 34+ cells infused, mean ± SD	11.0 ± 8.7	10.4 ± 8.4	11.3 ± 8.8	0.586[a]
Anthropometric Z-scores, age and gender adjusted, mean ± SD				
Weight	-0.5 ± 1.6	-0.4 ± 1.7	-0.6 ± 1.6	0.535[a]
Height	-1.2 ± 1.9	-1.1 ± 1.7	-1.2 ± 2.0	0.630[a]
BMI	0.3 ± 1.7	0.3 ± 1.8	0.3 ± 1.6	0.827[a]

Abbreviations: CMV, cytomegalovirus; CR, complete remission; IQR, interquartile range [25%-75%]; MFD, matched family donor; MMUD, mismatched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor; SD, standard deviation.

[a] Comparison using independent samples t-test.

[b] Comparison using Fisher's exact test.

[c] Comparison using Chi-square test.

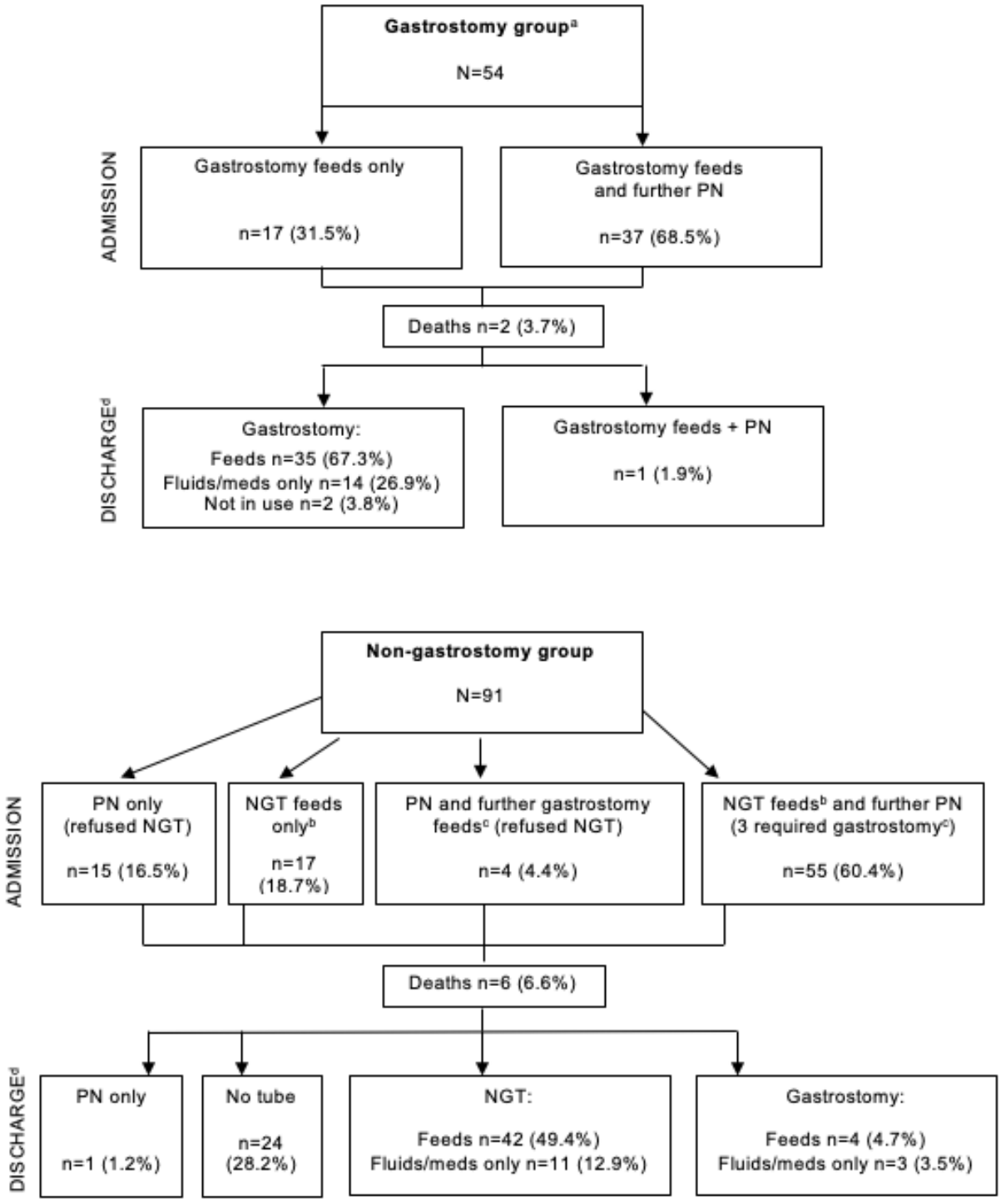

Fig.2. Flow of nutrition support modalities provided between admission and discharge.

[a] Gastrostomies placed prophylactically a median [IQR], 22 [15.8-37.3] days pre-graft.

[b] NGTs placed a median [IQR], day -3 pre-graft, [day -7.5 pre-graft to day 1.5 post-graft].

[c] Gastrostomies placed a median [IQR], 56 [44-92] days post-graft.

[d] Percentages calculated excluding deaths.

Table 2

Nutritional and post-transplantation outcomes.

	All patients (n= 145)	Gastrostomy group (n= 54)	Non-Gastrostomy group (n= 91)	*P* value
PN				
PN requirement, n (%)	111 (76.6)	37 (68.5)	74 (81.3)	**0.049**[a]
Days PN provided[g], median [IQR]	31 [20.0-57.0]	31 [22.0-53.0]	31 [18.0-61.3]	0.140[b]
Day PN initiated from admission, median [IQR]	16 [11.0-38.0]	21 [13.0-94.0]	13 [10.0-25.0]	**0.005**[c]
Day PN stopped from admission, median [IQR]	52 [39.0-80.0]	52 [39.0-82.0]	51 [37.0-79.0]	0.312[c]
EN				
EN provided as first-line nutrition support, n (%)	126 (86.9)	54 (100)	72 (79.1)	**<0.001**[d]
Maintained on EN only, n (%)	34 (23.4)	17 (31.5)	17 (18.7)	**0.049**[a]
Received EN and further PN, n (%)	96 (66.2)	37 (68.5)	59 (64.8)	0.718[d]
Discharged requiring enteral feeds[h], n (%)	82 (59.9%)	36 (69.2)	46 (54.1)	**0.029**[a]
Weight				
Admission weight Z-score, mean ± SD	-0.5 ± 1.6	-0.4 ± 1.7	-0.6 ± 1.6	See section 3.3.[e]
Discharge weight Z-score, mean ± SD	-0.5 ± 1.5	-0.4 ± 1.6	-0.7 ± 1.5	
≥ 10% weight loss during admission, n (%)	8 (5.5)	1 (1.9)	7 (7.7)	0.258[d]
Albumin				
Admission, g/L, mean ± SD	38.7 ± 4.60	38.1 ± 4.1	39.0 ± 4.9	See section 3.3.[e]
Lowest albumin during admission, g/L, mean ± SD	26.6 ± 3.4	26.8 ± 2.8	26.4 ± 3.8	
Discharge, g/L mean ± SD	35.02 ± 4.6	34.8 ± 3.9	35.1 ± 5.0	
Hypoalbuminaemia ≤ 30g/L during admission, n (%)	125 (86.2)	48 (88.9)	77 (84.6)	0.620[d]
aGvHD				
Grade I-II, n (%)	62 (42.8)	25 (46.3)	37 (40.7)	0.448[a]
Grade III-IV, n (%)	8 (5.5)	2 (3.7)	6 (6.6)	0.664[a]
Gut aGvHD, n (%)	11 (7.6)	2 (3.7)	9 (9.9)	0.191[a]
Veno-occlusive disease, n (%)	10 (6.9)	4 (7.4)	6 (6.6)	0.658[a]
Length of admission (day 0 to discharge), median [IQR]	46 [36-76]	45 [36-66]	46 [36-80]	0.625[c]
Days to neutrophil engraftment, mean ± SD	20.4 ± 6.0	20.8 ± 6.1	20.2 ± 6.0	0.877[c]
≥ one positive blood culture for bacteria, n (%)	24 (16.6)	8 (14.8)	16 (17.6)	0.665[d]
Admission to intensive care, n (%)	15 (10.3)	4 (7.4)	11 (12.1)	0.416[d]
Mortality at day 100[i]				
All causes, n (%)	5 (3.5)	0	5 (5.5)	0.081[f]
NRM, n (%)	4 (2.8)	0	4 (4.4)	0.120[f]

Abbreviations: aGvHD, acute graft versus host disease; EN, enteral nutrition; day 0, day of transplantation; IQR, interquartile range [25%-75%]; NRM, non-relapse mortality; PN, parenteral nutrition; SD, standard deviation.

[a] Comparison using logistic regression.

[b] Comparison using linear regression, weighted least squares.

[c] Comparison using Cox regression.

[d] Comparison using Fisher's exact test.

[e] Comparison using two-way (mixed) ANOVA.

[f] Comparison using Kaplan-Meier method, log rank statistic.

[g] Excluding non-recipients of PN (n=34).

[h] Excluding deaths during admission (n=8).

[i] Four died during admission but post day 100. One died between discharge and day 100.

3.2. Nutrition support interventions

Children in the gastrostomy vs. non-gastrostomy group more often received first-line EN (p<0.001), due to NGT refusal in 20.9% of the non-gastrostomy group (Fig. 2, Table 2).

The original odds of receiving PN in the gastrostomy group were 2.18 and in the non-gastrostomy group 4.35 (OR 0.50). After controlling for age, diagnosis and conditioning, those in the gastrostomy group become significantly less likely to require PN (OR 0.42, p=0.049, 95% CI 0.18-0.99) (Table 3A). Rationale for PN included gut aGvHD (n=11), refusal of NGTs in the non-gastrostomy group (n=19), and various transplant related complications, mucositis and intolerance symptoms including vomiting and diarrhoea, which could not be accurately quantified retrospectively, for the remaining 81 children. Time from admission to PN initiation was significantly delayed in the gastrostomy group (HR 0.56, p=0.005, 95% CI 0.37-0.84), after controlling for age, private patients and diagnosis (Table 4A, Fig. 5A). PN duration was no different between groups (p=0.140, 95% CI -12.46-1.78), after controlling for gender and donor (Table 5). Time to PN cessation was no different between groups (gastrostomy group HR 0.88, p=0.558, 95% CI 0.58-1.34), after controlling for donor (Table 4B, Fig. 5B).

The original odds of requiring EN post-discharge in the gastrostomy group were 2.25 and in the non-gastrostomy group 1.18 (OR 1.9). After controlling for age, those in the gastrostomy group were more likely to be discharged requiring EN (OR 2.41, p=0.029, 95% CI 1.09-5.38) (Table 3B). Seven in the non-gastrostomy group required gastrostomy placement for feeds (n=4) or fluids/meds (n=3) prior to discharge, having previously refused NGT (n=4), or failing with NGT feeds (n=3) (Fig. 2).

Gastrostomy vs. non-gastrostomy MAC subgroup analysis was consistent with the above results showing no differences in use of nutrition support interventions, except PN requirement which was not different between groups (gastrostomy group OR 0.51, p=0.258, 95% CI 0.16-1.63).

3.3. Nutritional status

No difference was found between groups of ≥10% weight loss (p=0.258). Mean (SD) weight Z-score remained approximately stable during hospitalisation in both groups, with non-significant main effects for time (p=0.972), interaction (p=0.244), and group (p=0.379) (Fig. 4A). The same pattern was found in the subgroups comparing those maintained exclusively on EN vs. EN+PN and those that

received MAC between the gastrostomy and non-gastrostomy groups. However, in the latter subgroup, despite there being a non-significant main effect for time (p=0.862), and interaction (p=0.584), there was a significant effect between groups (p=0.028) (Fig. 4B).

Between groups, no difference was found in hypoalbuminaemia (p=0.620), or the lowest albumin during admission (p=0.447, 95% CI -0.67-1.51). Throughout hospitalisation there were non-significant main effects between groups (p=0.666), and interaction (p=0.257), but a significant effect for time (p<0.001) (Fig. 4C). The same pattern was found for both subgroups.

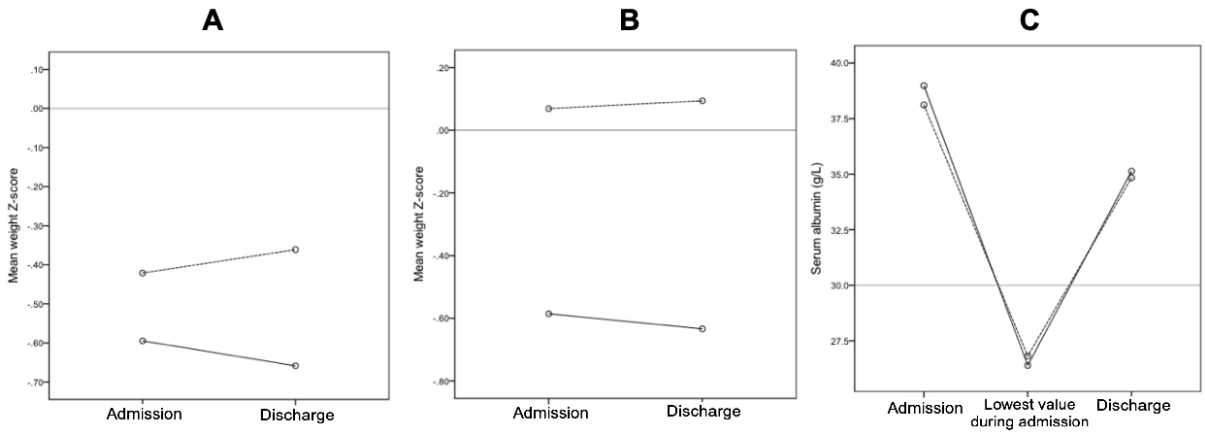

Fig. 4. Changes during hospitalisation between gastrostomy (dotted line) and non-gastrostomy (plain line) groups in mean weight Z-score (A), mean weight Z-score for the MAC subgroup (B) and serum albumin (C).

3.4. Post-transplantation outcomes

Comparing groups, no differences were found in any of the post-transplantation outcomes defined in section 2.5. (Table 2).

The original odds of developing grade I-II aGvHD were 0.86 in the gastrostomy and 0.69 in the non-gastrostomy group (OR 1.25). After controlling for diagnosis, conditioning and stem cell source, group allocation was not significantly associated with grade I-II aGvHD (OR 1.32, p=0.448, 95% CI 0.65-2.67) (Table 3C). The original odds of developing grade III-IV aGvHD were 0.04 in the gastrostomy and 0.07 in the non-gastrostomy group (OR 0.57). After controlling for diagnosis, group allocation was not significantly associated with grade III-IV aGvHD (OR 0.69, p=0.664, 95% CI 0.13-3.71) (Table 3D). The original odds of developing gut aGvHD were 0.04 in the gastrostomy and 0.11 in the non-gastrostomy group (OR 0.36). No predictors were univariately significantly associated with gut aGvHD,

so only group was included in the model which was non-significant (OR 0.35, p=0.191, 95% CI 0.07-1.69) (Table 3E).

The original odds of developing VOD were 0.08 in the gastrostomy and 0.07 in the non-gastrostomy group (OR 1.14). After controlling for diagnosis, group allocation was not significantly associated with VOD (OR 1.36, p=0.658, 95% CI 0.35-5.21) (Table 3F).

Regarding length of admission, after controlling for donor, no difference between groups was found (gastrostomy group HR 1.09, p=0.625, 95% CI 0.77-1.55) (Table 4C, Fig. 5C).

Time to neutrophil engraftment, after controlling for private patients, infused CD34+ cells, stem cell source and conditioning, was no different between groups (gastrostomy group HR 0.97, p=0.877, 95% CI 0.68-1.38) (Table 4D, Fig. 5E).

Day 100 OS was also no different between gastrostomy vs. non-gastrostomy groups (100% vs. 94.5%, p=0.081) (Fig.5F).

The only significant differences found in subgroup analyses were, compared to the EN+PN group, the EN only group had fewer admissions to intensive care (0% vs. 15%, p=0.020), and a shorter admission (EN group HR 3.57, p<0.001, 95% CI 2.29-5.57). (Table 4E, Fig. 5D).

Additional subgroup analysis comparing the 19 children who refused NGTs and received first-line PN to the 126 who received first-line EN, showed those who refused NGTs were older, mean (SD), 9.3 (4.0) vs. 5.2 (3.9), (p<0.001, 95% CI -6.02 to -2.23), but had no significant differences in any post-transplantation outcomes. Interestingly, those that refused NGTs had a longer admission (median [IQR], 63 [39-89] vs. 45 [36-73] days), but this was not significant (Kaplan-Meier log rank statistic p=0.284).

Table 3

Coefficients of the final logistic regression models comparing gastrostomy vs. non-gastrostomy groups.

	b	Standard error	*P* value	OR	95% CI	
					Lower	Upper
A Model (block three) predicting PN use.						
Constant	0.81	0.50	0.105	2.26		
Age	0.16	0.06	**0.011**	1.18	1.04	1.34
Malignant diseases[a]	0.68	0.63	0.286	1.96	0.57	6.79
RIC[b]	-0.59	0.53	0.267	0.55	0.19	1.57
Gastrostomy group[c]	-0.87	0.44	**0.049**	0.42	0.18	0.99
B Model (block two) predicting EN requirements post-discharge.						
Constant	1.30	0.36	<0.001	3.66		
Age	-0.21	0.05	**<0.001**	0.81	0.73	0.90
Gastrostomy group[c]	0.89	0.41	**0.029**	2.41	1.09	5.38
C Model (block two) predicting grade I-II aGvHD.						
Constant	-0.48	0.56	0.394	0.62		
Malignant diseases[a]	0.26	0.0.45	0.565	1.30	0.53	3.16
RIC[b]	-0.62	0.49	0.205	0.54	0.20	1.41
Bone marrow[d]	0.34	0.44	0.436	1.41	0.60	3.33
Gastrostomy group[c]	0.27	0.36	0.448	1.32	0.65	2.67
D Model (block two) predicting grade III-IV aGvHD.						
Constant	-4.34	1.05	<0.001	0.01		
Malignant diseases[a]	2.50	1.09	**0.022**	12.12	1.44	101.96
Gastrostomy group[c]	-0.37	0.86	0.664	0.69	0.13	3.71
E Model (block one) predicting gut aGvHD.						
Constant	-2.21	0.35	<0.001	0.11		
Gastrostomy group[c]	-1.05	0.80	0.191	0.35	0.07	1.69
F Model (block two) predicting VOD.						
Constant	-3.49	0.68	<0.001	0.03		
Malignant diseases[a]	1.45	0.72	**0.044**	4.25	1.04	17.40
Gastrostomy group[c]	0.30	0.69	0.658	1.36	0.35	5.21

Baseline: [a]non-malignant diseases, [b]MAC, [c]non-gastrostomy group, [d]peripheral blood.

Table 4

Coefficients of the final Cox regression models between gastrostomy vs. non-gastrostomy groups (and E comparing EN only vs. EN+PN subgroup).

	b	Standard error	*P* value	HR	95% CI	
					Lower	Upper
A Model (block three) predicting time to PN initiation.						
Age	0.07	0.03	**0.007**	1.07	1.02	1.12
NHS patient[a]	-0.50	0.27	0.063	0.61	0.36	1.03
Malignant diseases[b]	0.70	0.20	**0.001**	2.01	1.36	2.99
Gastrostomy group[c]	-0.59	0.21	**0.005**	0.56	0.37	0.84
B Model (block two) predicting time to PN cessation.						
Related donor (any type)[d]	0.51	0.21	**0.013**	1.67	1.11	2.50
Gastrostomy group[c]	-0.12	0.21	0.558	0.88	0.58	1.34
C Model (block two) predicting time to discharge.						
Related donor (any type)[d]	0.39	0.18	**0.033**	1.47	1.03	2.09
Gastrostomy group[c]	0.09	0.18	0.625	1.09	0.77	1.55
D Model (block three) predicting time to neutrophil engraftment.						
NHS patient[a]	-0.69	0.26	**0.007**	0.50	0.30	0.83
Infused CD34+ cells	0.02	0.01	0.183	1.02	0.99	1.04
Bone marrow[f]	-1.03	0.27	**<0.001**	0.36	0.21	0.60
RIC[g]	-0.01	0.21	0.949	0.99	0.65	1.49
Gastrostomy group[c]	-0.03	0.18	0.877	0.97	0.68	1.38
E Model (block one) predicting time to discharge.						
EN only subgroup[e]	1.27	0.23	**<0.001**	3.57	2.29	5.57

Baseline: [a]private patient, [b]non-malignant diseases, [c]non-gastrostomy group, [d]unrelated donor (any type), [e]EN+PN subgroup, [f]peripheral blood, [g]MAC.

Table 5

Coefficients of the final multiple linear regression model (block three) using weighted least squares, predicting PN duration between gastrostomy and non-gastrostomy groups.

	b	Standard error	*P* value	95% CI	
				Lower	Upper
Constant	22.10	3.50	<0.001	15.17	29.03
Females[a]	8.64	5.00	0.085	-1.21	18.49
Related donor (any type)[b]	-4.60	3.63	0.208	-11.79	2.59
Gastrostomy group*	-5.34	3.59	0.140	-12.46	1.78

Baseline: [a]males, [b]unrelated donor (any type).

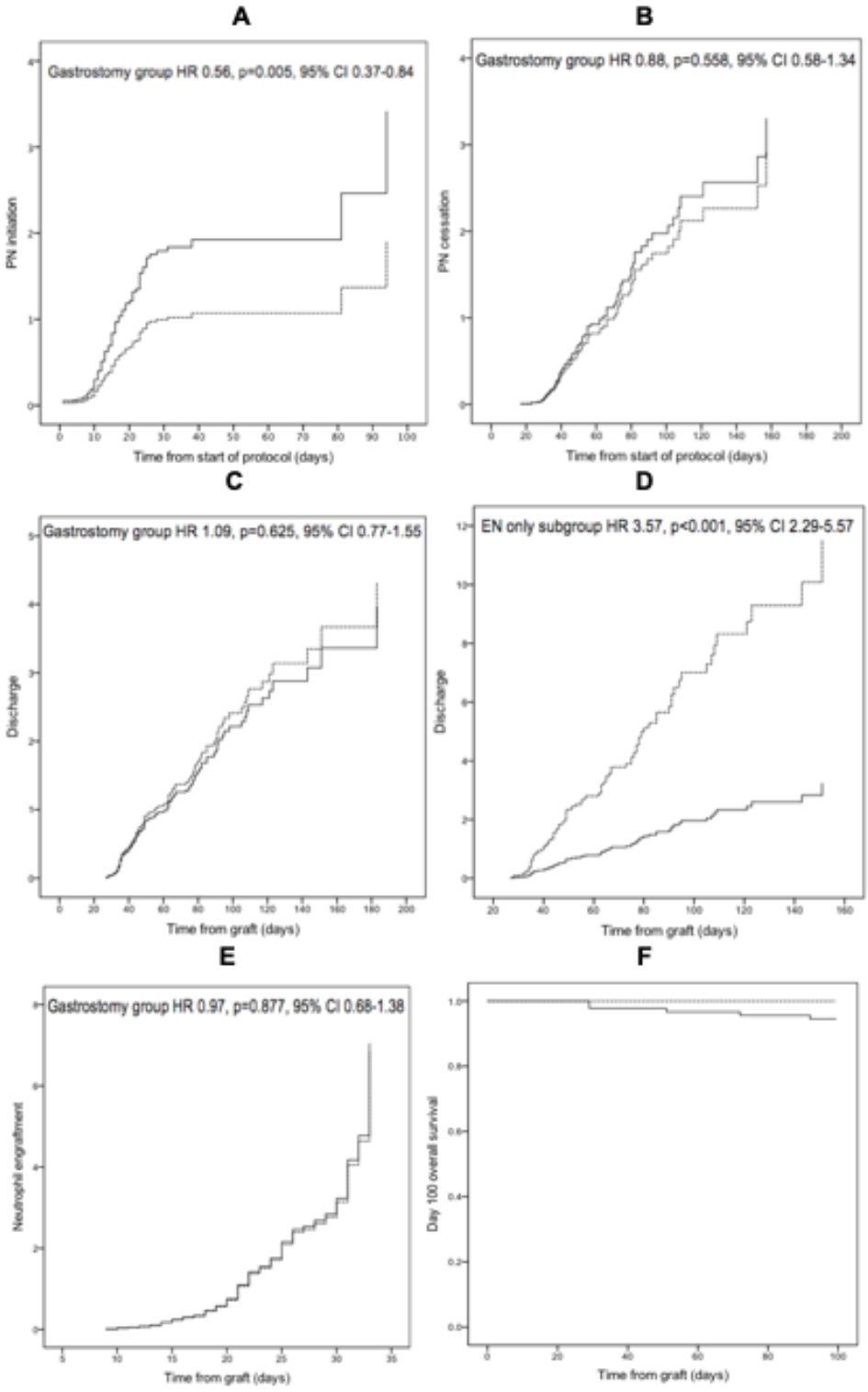

Fig. 5. Cumulative incidence between gastrostomy (dotted line) and non-gastrostomy (plain line) groups of PN initiation (censored: 34 who did not receive PN) (A), PN cessation (censored: 34 who did not receive PN, two discharged on PN, eight deaths whilst receiving PN) (B), discharge (censored: eight deaths during admission) (C), discharge between subgroup receiving EN only (dotted line) and EN+PN (plain line) (censored: eight deaths during admission) (D), neutrophil engraftment (no censored cases) (E), estimated probability of day 100 overall survival (censored: 141 who did not die) (F).

4. Discussion

To our knowledge, this is the second largest cohort investigating nutrition support, and the first regarding prophylactic gastrostomy feeding, in paediatric BMT. Children with a prophylactic gastrostomy were more likely to receive first-line EN, be maintained exclusively on EN without requiring additional PN, initiate PN later if required, and be discharged requiring EN, whilst experiencing similar post-transplantation outcomes and weight and albumin changes during admission.

European adult guidelines recommend first-line EN in BMT [9]. Whilst no equivalent guidelines exist in paediatrics, a recent Cochrane review concluded there is limited evidence to suggest PN is more effective than EN [32]. Paediatric studies are also increasingly recommending first-line EN during BMT [12,13]. Despite every child in this study having the opportunity to receive first-line EN, this approach occurred more frequently in the gastrostomy group. Whilst families who opted for gastrostomy possibly have a more proactive approach to EN, NGT refusal was the reason PN was provided first-line in 21% of the non-gastrostomy group. This issue has been reported elsewhere to lesser extents 3-4% [12,13,17]. These children did not develop more post-transplant complications so received first-line PN inappropriately when they were well enough to receive first-line EN, with additional PN only when appropriate. They were also older, similar findings to other studies [17,33]. Aesthetics or trauma of NGT placement could explain refusal amongst this group, issues likely absent in younger children. Indeed, displeasure of NGT placement and preference for PN with pre-existing IV access has been reported in paediatric oncology [34]. The positioning of a gastrostomy tube could provide a more acceptable method of providing EN to older children and avoid inappropriate PN use.

Overall, 77% required PN, higher than 10-30% reported in similar studies [15-17,35], and some only studied those receiving MAC [12,13]. This high PN use could be explained by the current absence, and need for implementation, of a nutrition support protocol in our unit. Such pathways help guide the decision making of clinicians ensuring appropriate use of nutrition support, and have been shown to reduce PN use [36]. Children in the gastrostomy group were significantly less likely to require PN, and initiated it later if required. Although PN initiation was measured from admission, if accounting for seven days of conditioning, the non-gastrostomy group initiated PN day six post-graft, earlier in comparison to 11-14.5 days [12,13,16], which are more comparable to the gastrostomy group who initiated PN 14 days' post-graft. Despite the gastrostomy group initiating PN later, duration was similar, 31 days,

between groups. Duration ranges widely in the literature from eight [15], to 54 days [33]. Gastrostomies avoid risks associated with NGTs including dislodgement through vomiting, placement contraindication in thrombocytopaenia and pain with mucositis [14]. Coupling these issues with NGT refusal, means they could lead to premature and inappropriate use of PN when it would otherwise be clinically preferable to initiate and maintain EN throughout transplant. Other researchers have advocated the systematic placement of NGTs day one post-graft to overcome these issues [12]. In this study NGTs were placed sooner, on average three days' pre-graft. Although we could not capture the issues that arose with NGTs, perhaps coupling these with NGT refusals, led to greater and earlier need for PN. Alternatively, the high percentage of NGT refusals and earlier PN initiation in the non-gastrostomy group could highlight a lack of perseverance with NGTs and need for a more stringent approach towards their placement and initiation and maintenance of EN via this route.

Significantly more children in the gastrostomy (69%) than non-gastrostomy group (54%) required EN post-discharge, proportions higher than 45% [15] and 47% [16]. Eating difficulties and poor compliance with dietary advice post-discharge have been reported [37], and significant correlations have been found between duration of EN and improvement in weight [35]. These results could reflect our proactive EN approach to support intakes and weight gain post-discharge. We note one study amended their protocol to continue EN post-discharge following BMI reductions during admission with limited regain three months' post-graft in their EN group [13]. The between group differences could be explained by the NGT refusals in the non-gastrostomy group and NGT policy in the community which forbids overnight feeding due to risks of tube dislodgement and feed aspiration, whereas overnight gastrostomy feeding is routinely used. For NGTs the child is therefore limited to having day time feeds which may be stopped prematurely in preference for progression of oral intake. Interestingly, seven children who had not opted for prophylactic gastrostomy required one to provide feeds, fluids and/or medicines for discharge, and perhaps would have benefitted from placement pre-admission.

Regarding nutritional status, weight was approximately maintained for all children between admission and discharge. Overall, 5.5% lost ≥10% weight, comparable to 8% [12]. Other studies have also shown anthropometric maintenance throughout admission, but using mid-upper-arm circumference (MUAC) and triceps skinfold thickness [33,35]. In keeping with other studies, we have shown hypoalbuminaemia to be common following BMT, although the 86% experiencing levels <30g/L is higher than 12% [15] and 41% [12] for the total samples in other studies. We acknowledge, firstly,

638 that discharge weight was not measured on a set day post-graft. However, time to discharge was similar
639 in both groups and hence time of discharge weights should be comparable. Secondly, heights were
640 missing on discharge so BMI could not be reported. Thirdly, weight and albumin are crude markers of
641 nutritional status. Weight can be artificially elevated by PN promoting water retention [38], and
642 hypoalbuminaemia can be attributed to catabolism, fluid redistribution, protein losing enteropathy [39],
643 and an acute phase response to infections [40].

644 No differences were found between gastrostomy and non-gastrostomy, or subgroups, on any post-
645 transplantation outcomes, except the EN only subgroup had a significantly shorter admission than the
646 EN+PN subgroup. Similar subgroup analyses have also found shorter admissions [12], but also less
647 grade III-IV aGvHD, gut aGvHD and faster platelet engraftment [13] in children maintained on EN only.

648 The exclusion of children having a second BMT and those given first-line PN for cord bloods and
649 gastrointestinal disorders, compromises generalisability to children transplanted with these modalities.
650 Furthermore, children with immunodeficiency disorders formed the largest proportion in this study who
651 are only transplanted at one other UK centre, further limiting generalisability to many children
652 transplanted in other UK centres. However, many children in this study had diagnoses including
653 relapsed leukaemias, and both RIC and MAC were included, thus providing evidence directly relevant
654 to the diagnoses and conditioning regimens seen in most UK and international centres.

655 This study has limitations, firstly the absence of randomisation and a control group who received
656 no nutrition support. Whilst RCTs investigating prophylactic gastrostomy placement in adults have been
657 conducted [41], there is an absence of such studies in paediatrics. Similarly, both adult and paediatric
658 studies investigating nutrition support have lacked control groups. Both these issues are likely due to
659 ethical considerations. Secondly, the retrospective design limited the reporting of outcomes including
660 nutritional intakes, duration and tolerance of EN as data on these measures collected under routine
661 clinical care, not for research purposes, was either absent or unusable. This meant we could not make
662 correlations between these measures and outcomes reported herein. Thirdly, this study reported early
663 outcomes, largely during admission, and cannot comment on the long-term impact of gastrostomy
664 feeding post-discharge. Fourthly, although both groups were comparable on demographic and
665 transplantation modalities suggesting minimal selection bias, families who chose a prophylactic
666 gastrostomy are likely to adopt a more proactive approach to EN which may have biased findings in
667 favour of EN with less PN use. Fifth, more gastrostomies were placed between 2014-15 (n=39) than

2016-18 (n=15), which was not analytically considered, as undertaken by Seguy et al. [42]. However, nutritional and medical management remained consistent throughout this study.

Whilst not limitations of this study per se, we acknowledge not reporting other issues relevant to gastrostomy feeding in BMT which were not part of the aims of this study, but could form the basis of future research. Whilst we can report no child needed their gastrostomy removed for any infectious or other complications, we have not reported the complications that arose with gastrostomies, a concern noted by others [18,19]. We intend to report the minor issues that did occur separately. Despite potential benefits of a prophylactic gastrostomy, only 10-15% annually opt for this within our centre. This study did not qualitatively explore families' perceptions of gastrostomy feeding during BMT, an important consideration given comfort, ease of nutrition administration and image are important factors to families regarding nutrition support in this population [34]. Future qualitative studies could help identify factors, including the development of educational materials, which could be used during discussions in pre-admission consultations. This will allow families to make more informed decisions regarding nutrition support prior to their child's admission. Future studies should also prospectively investigate outcomes that could not be measured for this study, including nutritional intakes provided to the child via all nutrition support modalities, and MUAC or bioelectrical impedance as more sensitive markers of nutritional status in these children [43]. Such outcomes should be measured during admission and post-discharge to allow the long-term investigation of correlations between the provision of nutrition support, the impact this has on the child's nutritional status and, consequently, on their medical outcomes.

In conclusion, this study contributes to the growing body of paediatric evidence that first-line EN is feasible in BMT and offers an innovative insight into gastrostomy feeding as an alternative method for its provision, one which may be more acceptable to older children, than traditional NGTs. Weighing the benefits against the potential risks of prophylactic gastrostomy placement in these high-risk children, whilst also accounting for patient acceptability, is a challenging decision. With few studies reporting the use of PEGs in paediatric BMT, we hope this study sparks debate around this controversial issue.

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6. Authorship

All authors were involved in the study's design. JE conceptualised the study, collected and analysed the data and drafted the article. JN and SH advised on data analysis, interpretation and critically revised the drafted article. All approved the final submitted article.

7. Conflicts of interest

The authors declare no conflicts of interest.

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