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

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25

26 **Abstract**

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

33

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

37

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

41

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

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

53

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

## 56 1. Introduction

57

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

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

76 With studies having focused on comparing EN vs. PN, few have directly compared EN  
77 interventions. Most paediatric BMT studies have administered EN via nasogastric tubes (NGTs)  
78 [12,13,15-17]. NGTs can be placed relatively simply during admission without the need for general  
79 anaesthetic and removed as soon as a patient's intake returns to sufficient levels. However, they are  
80 susceptible to complications including dislodgement with vomiting, discomfort with mucositis, epistaxis  
81 in thrombocytopenia [14] and placement refusal, all of which meaning PN may need to be used  
82 prematurely, or by default.

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

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

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

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## 115 **2. Materials and methods**

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### 117 *2.1. Patients*

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119 This retrospective cohort study was conducted in the United Kingdom's largest paediatric BMT  
120 centre, Great Ormond Street Children's Hospital (GOSH). All consecutive NHS and private patients  
121 (<18 years) who received an allogenic BMT following reduced-intensity (RIC) or myeloablative (MAC)  
122 conditioning, admitted from January 2014 and discharged by May 2018, were included. A sample-size  
123 calculation was not undertaken, but a post-hoc power analysis was planned. The retrospective nature  
124 of this study was chosen to obtain a larger sample size than would have been achieved prospectively.

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

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

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### 140 *2.2. Nutrition Support*

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

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

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

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

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### 170 *2.3. Transplantation procedure and supportive care*

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

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

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#### 184 *2.4. Data collection*

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

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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  $\geq 10\%$  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  $\leq 30\text{g/L}$ .

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  $\geq 0.5 \times 10^9/\text{L}$  [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 these post-transplantation outcomes to be  
229 reported.

230

231 2.6. *Statistics*

232

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

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

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

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

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

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

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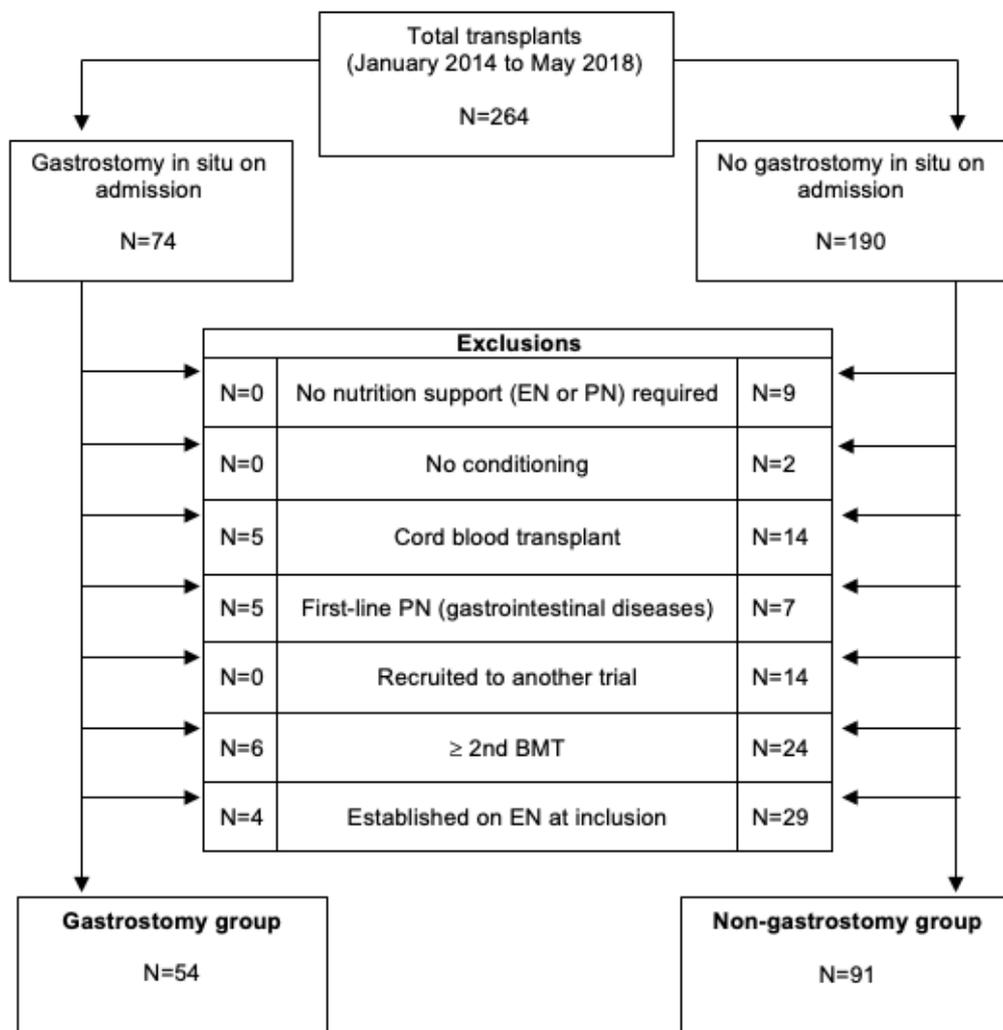
265 **3. Results**

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267 *3.1. Study population*

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



275

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

278

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

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<b>Table 1</b>				
Patient's characteristics and transplantation modalities.				
	<b>All patients (n= 145)</b>	<b>Gastrostomy group (n= 54)</b>	<b>Non-gastrostomy group (n= 91)</b>	<b>P value</b>
<b>Age</b> (years), mean $\pm$ SD	5.7 $\pm$ 4.1	6.3 $\pm$ 3.7	5.4 $\pm$ 4.3	0.226 <sup>a</sup>
<b>Private patient</b> , n (%)	20 (13.8)	4 (7.4)	16 (17.6)	0.133 <sup>b</sup>
<b>Gender</b> , Male/Female, n	91/54	34/20	57/34	1.0 <sup>b</sup>
<b>Diagnosis</b> , n (%)				0.217 <sup>b</sup>
Non-malignant diseases	89 (61.4)	37 (68.5)	52 (57.1)	
Malignant diseases	56 (38.6)	17(31.5)	39 (42.9)	
<b>Disease status at transplant</b> , n (%)				0.292 <sup>c</sup>
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 $\geq$ 2	32 (22.1)	14 (25.9)	18 (19.8)	
Progressive disease	7 (4.8)	1 (1.9)	6 (6.6)	
<b>Stem cell source</b> , n (%)				0.715 <sup>b</sup>
Bone marrow	99 (68.3)	38 (70.4)	61 (67.0)	
Peripheral blood	46 (31.7)	16 (29.6)	30 (33.0)	
<b>Donor</b> , n (%)				0.550 <sup>c</sup>
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)	
<b>Sex mismatch</b> (male recipient, female donor), n (%)	33 (22.8)	11 (20.4)	22 (24.2)	0.684 <sup>b</sup>
<b>Recipient CMV serology</b> , n (%)				<b>0.046<sup>b</sup></b>
Positive	47 (32.4)	12 (22.2)	35 (38.5)	
Negative	98 (67.6)	42 (77.8)	56 (61.5)	
<b>Conditioning regimen</b> , n (%)				0.864 <sup>b</sup>
Myeloablative	82 (56.6)	30 (55.6)	52 (57.1)	
Reduced-intensity	63 (43.4)	24 (44.4)	39 (42.9)	
<b>Number of CD 34+ cells infused</b> , mean $\pm$ SD	11.0 $\pm$ 8.7	10.4 $\pm$ 8.4	11.3 $\pm$ 8.8	0.586 <sup>a</sup>
<b>Anthropometric Z-scores</b> , age and gender adjusted, mean $\pm$ SD				
Weight	-0.5 $\pm$ 1.6	-0.4 $\pm$ 1.7	-0.6 $\pm$ 1.6	0.535 <sup>a</sup>
Height	-1.2 $\pm$ 1.9	-1.1 $\pm$ 1.7	-1.2 $\pm$ 2.0	0.630 <sup>a</sup>
BMI	0.3 $\pm$ 1.7	0.3 $\pm$ 1.8	0.3 $\pm$ 1.6	0.827 <sup>a</sup>

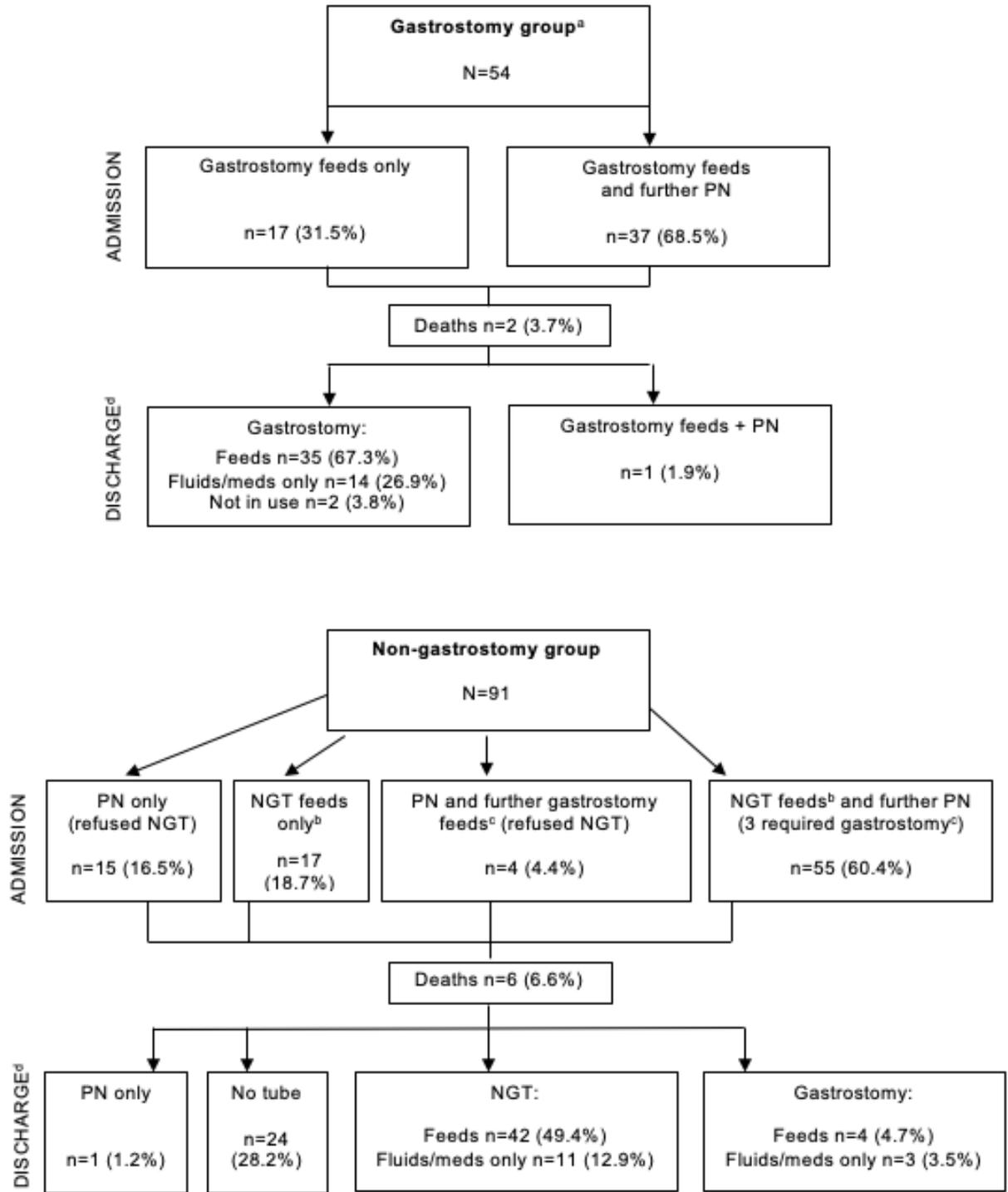
Abbreviations: CMV, cytomegalovirus; CR, complete remission; IQR, interquartile range [25%-75%]; MFD, matched family donor; MMUD, mismatched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor; SD, standard deviation.

<sup>a</sup> Comparison using independent samples t-test.

<sup>b</sup> Comparison using Fisher's exact test.

<sup>c</sup> Comparison using Chi-square test.

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

347 <sup>a</sup> Gastrostomies placed prophylactically a median [IQR], 22 [15.8-37.3] days pre-graft.

348 <sup>b</sup> NGTs placed a median [IQR], day -3 pre-graft, [day -7.5 pre-graft to day 1.5 post-graft].

349 <sup>c</sup> Gastrostomies placed a median [IQR], 56 [44-92] days post-graft.

350 <sup>d</sup> Percentages calculated excluding deaths.

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

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.

<sup>a</sup> Comparison using logistic regression.  
<sup>b</sup> Comparison using linear regression, weighted least squares.  
<sup>c</sup> Comparison using Cox regression.  
<sup>d</sup> Comparison using Fisher's exact test.  
<sup>e</sup> Comparison using two-way (mixed) ANOVA.  
<sup>f</sup> Comparison using Kaplan-Meier method, log rank statistic.  
<sup>g</sup> Excluding non-recipients of PN (n=34).  
<sup>h</sup> Excluding deaths during admission (n=8).  
<sup>i</sup> Four died during admission but post day 100. One died between discharge and day 100.

### 405 3.2. Nutrition support interventions

406

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

409 The original odds of receiving PN in the gastrostomy group were 2.18 and in the non-gastrostomy  
410 group 4.35 (OR 0.50). After controlling for age, diagnosis and conditioning, those in the gastrostomy  
411 group become significantly less likely to require PN (OR 0.42,  $p = 0.049$ , 95% CI 0.18-0.99) (Table 3A).

412 Rationale for PN included gut aGvHD ( $n = 11$ ), refusal of NGTs in the non-gastrostomy group ( $n = 19$ ),  
413 and various transplant related complications, mucositis and intolerance symptoms including vomiting  
414 and diarrhoea, which could not be accurately quantified retrospectively, for the remaining 81 children.

415 Time from admission to PN initiation was significantly delayed in the gastrostomy group (HR 0.56,  
416  $p = 0.005$ , 95% CI 0.37-0.84), after controlling for age, private patients and diagnosis (Table 4A, Fig. 5A).

417 PN duration was no different between groups ( $p = 0.140$ , 95% CI -12.46-1.78), after controlling for gender  
418 and donor (Table 5). Time to PN cessation was no different between groups (gastrostomy group HR  
419 0.88,  $p = 0.558$ , 95% CI 0.58-1.34), after controlling for donor (Table 4B, Fig. 5B).

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

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

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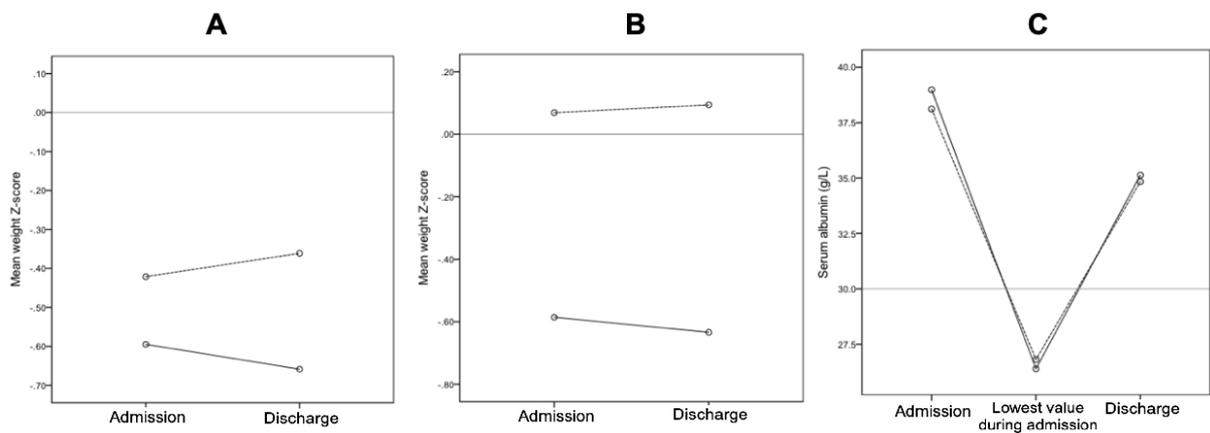
### 429 3.3. Nutritional status

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

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

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



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443

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

446

### 447 3.4. Post-transplantation outcomes

448

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

451

452 The original odds of developing grade I-II aGvHD were 0.86 in the gastrostomy and 0.69 in the  
453 non-gastrostomy group (OR 1.25). After controlling for diagnosis, conditioning and stem cell source,  
454 group allocation was not significantly associated with grade I-II aGvHD (OR 1.32,  $p=0.448$ , 95% CI  
455 0.65-2.67) (Table 3C). The original odds of developing grade III-IV aGvHD were 0.04 in the gastrostomy  
456 and 0.07 in the non-gastrostomy group (OR 0.57). After controlling for diagnosis, group allocation was  
457 not significantly associated with grade III-IV aGvHD (OR 0.69,  $p=0.664$ , 95% CI 0.13-3.71) (Table 3D).  
458 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,

459 so only group was included in the model which was non-significant (OR 0.35,  $p=0.191$ , 95% CI 0.07-  
460 1.69) (Table 3E).

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

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

466 Time to neutrophil engraftment, after controlling for private patients, infused CD34+ cells, stem  
467 cell source and conditioning, was no different between groups (gastrostomy group HR 0.97,  $p=0.877$ ,  
468 95% CI 0.68-1.38) (Table 4D, Fig. 5E).

469 Day 100 OS was also no different between gastrostomy vs. non-gastrostomy groups (100% vs.  
470 94.5%,  $p=0.081$ ) (Fig.5F).

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

474 Additional subgroup analysis comparing the 19 children who refused NGTs and received first-line  
475 PN to the 126 who received first-line EN, showed those who refused NGTs were older, mean (SD), 9.3  
476 (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-  
477 transplantation outcomes. Interestingly, those that refused NGTs had a longer admission (median [IQR],  
478 63 [39-89] vs. 45 [36-73] days), but this was not significant (Kaplan-Meier log rank statistic  $p=0.284$ ).

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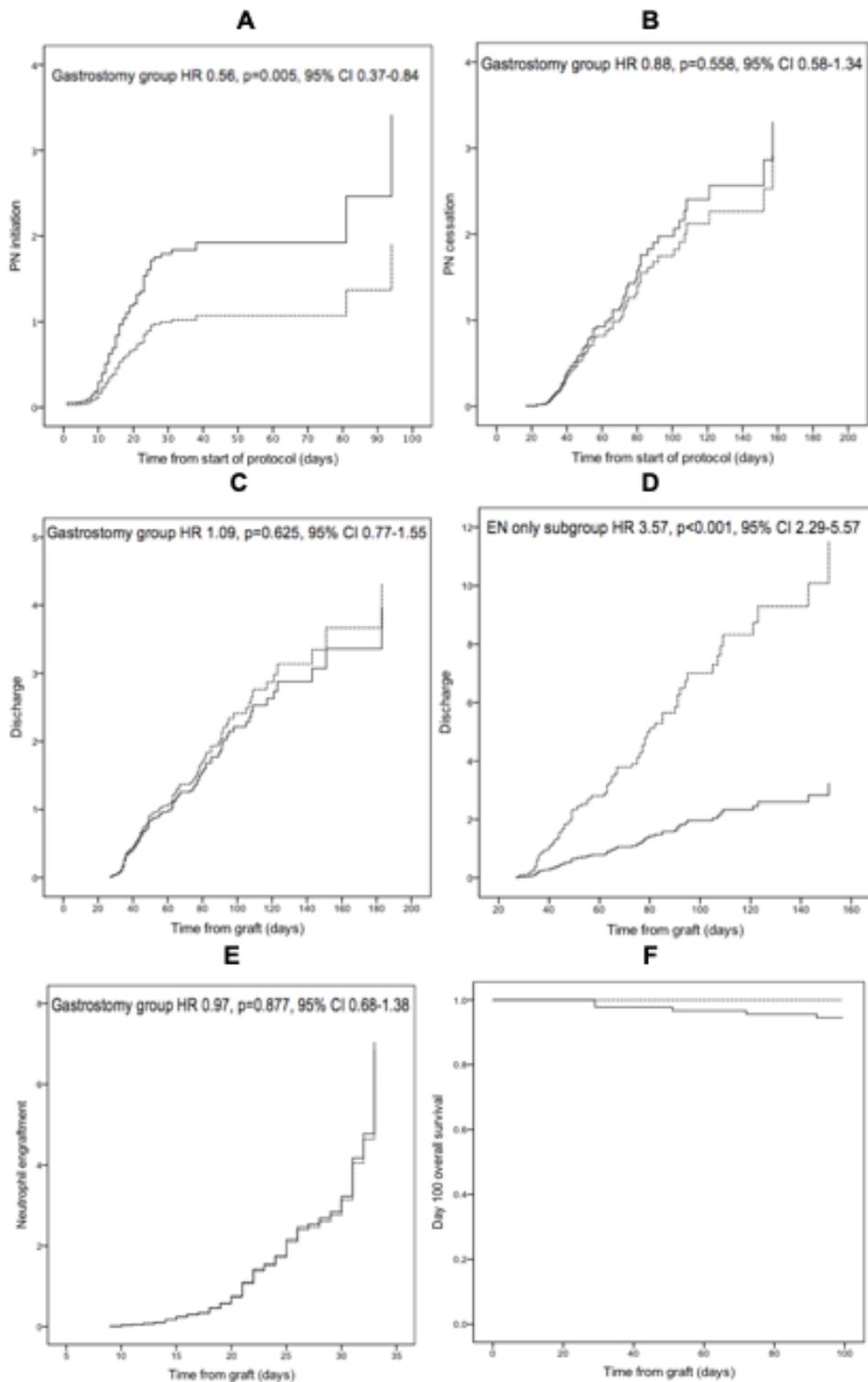
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<b>Table 3</b>						
Coefficients of the final logistic regression models comparing gastrostomy vs. non-gastrostomy groups.						
	<i>b</i>	Standard error	<i>P</i> value	OR	95% CI	
					Lower	Upper
<b>A Model (block three) predicting PN use.</b>						
Constant	0.81	0.50	0.105	2.26		
Age	0.16	0.06	<b>0.011</b>	1.18	1.04	1.34
Malignant diseases <sup>a</sup>	0.68	0.63	0.286	1.96	0.57	6.79
RIC <sup>b</sup>	-0.59	0.53	0.267	0.55	0.19	1.57
Gastrostomy group <sup>c</sup>	-0.87	0.44	<b>0.049</b>	0.42	0.18	0.99
<b>B Model (block two) predicting EN requirements post-discharge.</b>						
Constant	1.30	0.36	<0.001	3.66		
Age	-0.21	0.05	<b>&lt;0.001</b>	0.81	0.73	0.90
Gastrostomy group <sup>c</sup>	0.89	0.41	<b>0.029</b>	2.41	1.09	5.38
<b>C Model (block two) predicting grade I-II aGvHD.</b>						
Constant	-0.48	0.56	0.394	0.62		
Malignant diseases <sup>a</sup>	0.26	0.045	0.565	1.30	0.53	3.16
RIC <sup>b</sup>	-0.62	0.49	0.205	0.54	0.20	1.41
Bone marrow <sup>d</sup>	0.34	0.44	0.436	1.41	0.60	3.33
Gastrostomy group <sup>c</sup>	0.27	0.36	0.448	1.32	0.65	2.67
<b>D Model (block two) predicting grade III-IV aGvHD.</b>						
Constant	-4.34	1.05	<0.001	0.01		
Malignant diseases <sup>a</sup>	2.50	1.09	<b>0.022</b>	12.12	1.44	101.96
Gastrostomy group <sup>c</sup>	-0.37	0.86	0.664	0.69	0.13	3.71
<b>E Model (block one) predicting gut aGvHD.</b>						
Constant	-2.21	0.35	<0.001	0.11		
Gastrostomy group <sup>c</sup>	-1.05	0.80	0.191	0.35	0.07	1.69
<b>F Model (block two) predicting VOD.</b>						
Constant	-3.49	0.68	<0.001	0.03		
Malignant diseases <sup>a</sup>	1.45	0.72	<b>0.044</b>	4.25	1.04	17.40
Gastrostomy group <sup>c</sup>	0.30	0.69	0.658	1.36	0.35	5.21
Baseline: <sup>a</sup> non-malignant diseases, <sup>b</sup> MAC, <sup>c</sup> non-gastrostomy group, <sup>d</sup> peripheral blood.						

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<b>Table 4</b>						
Coefficients of the final Cox regression models between gastrostomy vs. non-gastrostomy groups (and E comparing EN only vs. EN+PN subgroup).						
	<i>b</i>	Standard error	<i>P</i> value	HR	95% CI	
					Lower	Upper
<b>A Model (block three) predicting time to PN initiation.</b>						
Age	0.07	0.03	<b>0.007</b>	1.07	1.02	1.12
NHS patient <sup>a</sup>	-0.50	0.27	0.063	0.61	0.36	1.03
Malignant diseases <sup>b</sup>	0.70	0.20	<b>0.001</b>	2.01	1.36	2.99
Gastrostomy group <sup>c</sup>	-0.59	0.21	<b>0.005</b>	0.56	0.37	0.84
<b>B Model (block two) predicting time to PN cessation.</b>						
Related donor (any type) <sup>d</sup>	0.51	0.21	<b>0.013</b>	1.67	1.11	2.50
Gastrostomy group <sup>c</sup>	-0.12	0.21	0.558	0.88	0.58	1.34
<b>C Model (block two) predicting time to discharge.</b>						
Related donor (any type) <sup>d</sup>	0.39	0.18	<b>0.033</b>	1.47	1.03	2.09
Gastrostomy group <sup>c</sup>	0.09	0.18	0.625	1.09	0.77	1.55
<b>D Model (block three) predicting time to neutrophil engraftment.</b>						
NHS patient <sup>a</sup>	-0.69	0.26	<b>0.007</b>	0.50	0.30	0.83
Infused CD34+ cells	0.02	0.01	0.183	1.02	0.99	1.04
Bone marrow <sup>f</sup>	-1.03	0.27	<b>&lt;0.001</b>	0.36	0.21	0.60
RIC <sup>g</sup>	-0.01	0.21	0.949	0.99	0.65	1.49
Gastrostomy group <sup>c</sup>	-0.03	0.18	0.877	0.97	0.68	1.38
<b>E Model (block one) predicting time to discharge.</b>						
EN only subgroup <sup>e</sup>	1.27	0.23	<b>&lt;0.001</b>	3.57	2.29	5.57
Baseline: <sup>a</sup> private patient, <sup>b</sup> non-malignant diseases, <sup>c</sup> non-gastrostomy group, <sup>d</sup> unrelated donor (any type), <sup>e</sup> EN+PN subgroup, <sup>f</sup> peripheral blood, <sup>g</sup> MAC.						

<b>Table 5</b>					
Coefficients of the final multiple linear regression model (block three) using weighted least squares, predicting PN duration between gastrostomy and non-gastrostomy groups.					
	<i>b</i>	Standard error	<i>P</i> value	95% CI	
				Lower	Upper
Constant	22.10	3.50	<0.001	15.17	29.03
Females <sup>a</sup>	8.64	5.00	0.085	-1.21	18.49
Related donor (any type) <sup>b</sup>	-4.60	3.63	0.208	-11.79	2.59
Gastrostomy group*	-5.34	3.59	0.140	-12.46	1.78
Baseline: <sup>a</sup> males, <sup>b</sup> unrelated donor (any type).					



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**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).

## 578 4. Discussion

579

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

585 European adult guidelines recommend first-line EN in BMT [9]. Whilst no equivalent guidelines  
586 exist in paediatrics, a recent Cochrane review concluded there is limited evidence to suggest PN is  
587 more effective than EN [32]. Paediatric studies are also increasingly recommending first-line EN during  
588 BMT [12,13]. Despite every child in this study having the opportunity to receive first-line EN, this  
589 approach occurred more frequently in the gastrostomy group. Whilst families who opted for gastrostomy  
590 possibly have a more proactive approach to EN, NGT refusal was the reason PN was provided first-  
591 line in 21% of the non-gastrostomy group. This issue has been reported elsewhere to lesser extents 3-  
592 4% [12,13,17]. These children did not develop more post-transplant complications so received first-line  
593 PN inappropriately when they were well enough to receive first-line EN, with additional PN only when  
594 appropriate. They were also older, similar findings to other studies [17,33]. Aesthetics or trauma of NGT  
595 placement could explain refusal amongst this group, issues likely absent in younger children. Indeed,  
596 displeasure of NGT placement and preference for PN with pre-existing IV access has been reported in  
597 paediatric oncology [34]. The positioning of a gastrostomy tube could provide a more acceptable  
598 method of providing EN to older children and avoid inappropriate PN use.

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

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

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

632       Regarding nutritional status, weight was approximately maintained for all children between  
633 admission and discharge. Overall, 5.5% lost  $\geq 10\%$  weight, comparable to 8% [12]. Other studies have  
634 also shown anthropometric maintenance throughout admission, but using mid-upper-arm  
635 circumference (MUAC) and triceps skinfold thickness [33,35]. In keeping with other studies, we have  
636 shown hypoalbuminaemia to be common following BMT, although the 86% experiencing levels  $< 30\text{g/L}$   
637 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

668 2016-18 (n=15), which was not analytically considered, as undertaken by Seguy et al. [42]. However,  
669 nutritional and medical management remained consistent throughout this study.

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

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

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## 702 **6. Authorship**

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

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## 708 **7. Conflicts of interest**

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710 The authors declare no conflicts of interest.

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713

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## 718 **9. References**

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