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Original article

Malnutrition and cachexia are associated with poor CAR T-cell therapy outcomes including survival

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SUMMARY

Background & aims: Chimeric Antigen Receptor (CAR) T-cell therapy has emerged as a revolutionary treatment for patients with refractory or relapsed B-cell malignancies. However, a significant proportion of patients experience negative outcomes, including severe inflammatory toxicities and relapse. Cachexia and malnutrition are known secondary syndromes in many cancer patients, attributed to the effects of active malignancy, systemic inflammation, and cumulative treatment burden; however, further research is required to accurately characterise these issues in CAR T-cell patients. The aims of this service evaluation were to explore the changes in nutritional status (malnutrition and cachexia) in CAR T-cell therapy patients and the potential impact on patient outcomes including survival. Additionally, we describe the utilisation of dietetic resources in this specific patient population in a London tertiary referral centre.

Methods: Adult haematology patients receiving licensed CD19-targeting CAR T-cell therapy at University College London Hospital between 01/04/19 and 01/09/21 were included. Data were collected from the time of treatment consent, and throughout admission to day of discharge: body weight (BW), C-reactive protein, albumin, lactate dehydrogenase, nutrition-risk screening scores (hospital-specific) and dietetic input. Clinical outcomes such as 12-month all-cause mortality, intensive care unit (ICU) admission, high-grade toxicities, and length of hospital stay (LoS) were also recorded. Cachexia and malnutrition were defined using the modified Glasgow Prognostic Score (mGPS) and Global Leadership Initiative on Malnutrition (GLIM) consensus, respectively.

Results: 114 patients (55.6 ± 15.1 years; 57% males) with B-cell non-Hodgkin's lymphoma ($n = 109$) and B-cell acute lymphoblastic leukaemia ($n = 5$), receiving axicabtagene ciloleucel ($n = 89$) and tisa-genlecleucel ($n = 25$) were included. Median LoS for treatment was 34 (27–38) days. Prior to treatment, 31.5% of patients developed malnutrition, with pre-cachexia/refractory cachexia (mGPS) identified in 43.6% of patients. This altered nutritional status pre-treatment was significantly associated with adverse patient outcomes post-infusion; mGPS was independently associated with inferior overall survival (HR = 3.158, CI = 1.36–7.323, $p = 0.007$), with malnutrition and mGPS associated with increased LoS ($p = 0.037$), sepsis ($p = 0.022$) and ICU admission ($p = 0.039$). During admission, patients experienced significant BW loss (-5.6% (-8.8 to -2.4); $p < 0.001$), with 68.4% developing malnutrition. Malnutrition screening during admission identified 57% patients at-risk, with 66.6% of patients referred to dietetics; however, there was a lack of malnutrition screening and dietetic referrals prior to treatment.

Conclusion: Pre-treatment malnutrition and cachexia was significantly associated with adverse CAR T patient outcomes, including mGPS cachexia status independently associated with inferior overall survival. Further research in this novel space is essential to confirm the extent and impact of nutritional issues, to assist with implementing dietetic pathways, and to identify potential interventions with a view to optimising outcomes.

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1. Introduction

The rapidly expanding field of CAR T-cell therapy is revolutionising treatment outcomes for patients with relapsed or refractory B-cell malignancies [1]. Utilising a patient's own T-cells to treat their disease, these immune cells are genetically engineered with a synthetic receptor *ex vivo*, to enable the identification and targeting of antigens on specific cancer cells *in vivo* [2]. Although the feasibility of CAR T-cell therapy is being investigated in various cancers, CD19-targeting CAR T-cell therapy for B-cell malignancies has been the most successful to date [2–4]. Consequently, several CD19-targeting CAR T-cell products have been approved for use in the United Kingdom (UK) National Health Service (NHS) in patients with refractory or relapsed B-cell malignancies since 2018 [5]. For those who do not respond to (or relapse after) CAR T-cell therapy, few curative treatment options are available [6]; therefore, identifying and managing potential determinants of patient outcomes is key to improving the efficacy of this treatment modality and facilitating its expansion beyond haematological malignancies.

Altered nutritional status syndromes such as malnutrition and cachexia are commonly under-diagnosed and undertreated problems facing cancer patients [7]. Malnutrition and cachexia in oncology and haematology have been shown to negatively impact treatment efficacy, severity of side effects, infection rates, quality of life, financial healthcare costs and prognosis [7]. The importance of screening and providing tailored nutrition advice from trained allied health professionals to prevent these nutritional concerns in standard cancer therapies is a well-established, essential component of multidisciplinary cancer care [7]. However, for the novel field of CAR T-cell therapy, there is currently limited research available regarding the incidence or impact of altered nutritional status syndromes, their potential determinants, or the need for allied health services.

Patients receiving CAR T-cell therapy experience a unique and potentially detrimental combination of factors that present heightened biological plausibility for malnutrition and cachexia risk. Many of these elements relate to inflammation, driven by the refractory/relapsed disease status of eligible patients, and by the common side effects of CAR T-cell therapy, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS, a potentially life-threatening side effect caused by the rapid release of inflammatory cytokines post CAR T-cell infusion occurs in 54–93% of patients [8]. ICANS, the pathophysiology of which is less well understood, can affect up to 64% of patients and encompasses symptoms such as altered speech, cognition, and consciousness [9].

Additionally, 15–47% of patients require intensive care unit (ICU) treatment [10], with sepsis one of the leading causes for ICU admission [11]. Patients requiring ICU often experience significant muscle wasting [12], which can be exacerbated by the profound inflammatory response associated with sepsis [13]. The potential for secondary nutritional effects in this patient group is further compounded by corticosteroids used to treat CAR T-cell associated toxicities, and the prolonged inpatient stay for treatment, both known to exacerbate muscle wasting [14,15]. Given this distinctive treatment modality and its unique side effect profile, provision of standard nutritional oncology care may not be appropriate, warranting further research.

The primary aim of this retrospective service evaluation was to characterise the changes in nutritional status (malnutrition and cachexia) experienced by haematology patients prior to, and during their admission for CD19-targeting CAR T-cell therapy at University College London Hospital (UCLH). Our secondary aim was to determine if changes to nutritional status (prior to, and during admission) were associated with inferior patient outcomes, including 12-month all-cause mortality, ICU admission, length of stay and treatment toxicities (ICANS, CRS and sepsis). Furthermore, we

propose a potential pathway to optimise the nutritional status of CAR T-cell patients throughout treatment.

2. Material & methods

A retrospective service evaluation was undertaken using convenience sampling at UCLH between April 2019 to September 2021. All adults (≥ 18 years) with haematological malignancies receiving NHS-licensed CD19-targeting CAR T-cell therapies (axicabtagene ciloleucel [axi-cel] and tisagenlecleucel [tisa-cel]) were included. Patients receiving any other form of CAR T-cell therapy were excluded. This service evaluation was conducted in accordance with the UK Framework for Health and Social Care Research (Health Research Authority (HRA)).

Data were extracted from electronic health records (EHR) at various timepoints along the patients' treatment pathway (Fig. 1), including:

- *Pre-treatment period*: from the patient's initial review at UCLH CAR T-cell clinic, up to 15 days prior to CAR T-cell infusion (*Day minus 15*). During this pre-treatment period, routine patient care includes T-cell apheresis (withdrawal of patient's T-cells), and additional anti-cancer therapies (bridging therapies – BT) if appropriate whilst awaiting CAR T-cell manufacturing.
- *Admission for CAR T-cell therapy*: from lymphodepletion (chemotherapy administered in the week prior to infusion to reduce lymphocyte count [16]), to the day of hospital discharge.
- *12-months post CAR T-cell infusion*: review of adverse outcomes (all-cause mortality).

2.1. Pre-CAR T-cell treatment data collected

2.1.1. Patient characteristics and treatment history

Patient demographics, diagnosis, treatment history, serum lactate dehydrogenase (LDH) and ferritin levels, and BT were collected (Fig. 1).

- BTs were categorised according to intensity and type, as per Roddie et al. (2023) [17]. This includes: none (no BT), corticosteroids, radiotherapy (RT), immunotherapy, combined-modality therapy (CMT, i.e. chemotherapy and RT) or chemotherapy, subdivided into Rituximab-Bendamustine-Polatumumab (RBP), low-dose therapy (LDT), or high-dose therapy (HDT): Gemcitabine-based (HDT-Gem), Ifosfamide-based (HDT-Ifos), or Others (HDT-Other) (Supplementary Table 1).

2.1.2. Nutritional status pre-treatment

Where available, serum levels of C-reactive protein (CRP) and albumin at treatment consent were collected. Repeated body weight measurements taken over the duration of the pre-treatment period, from consent to Day minus 15, were also recorded.

2.1.3. Dietetic services

Any information regarding dietetic services provided to patients was reviewed, including nutrition screenings, dietetic referrals, and interventions.

2.2. During CAR T-cell treatment admission data collected

2.2.1. CAR T-cell therapy treatment and adverse outcomes

Information collected included: CD19-targeting CAR T-cell therapy products, length of hospital stay (LoS), rate of ICU

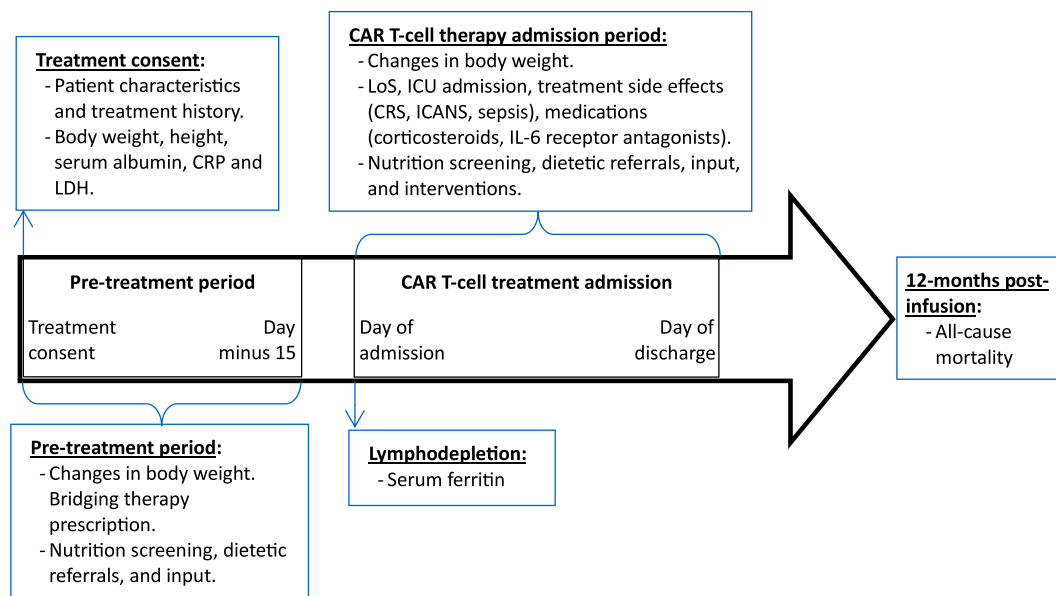


Fig. 1. Study flowchart for data collection. Abbreviations: C-Reactive Protein, CRP; Lactate Dehydrogenase, LDH; length of hospital stay, LoS; intensive care unit, ICU; cytokine release syndrome, CRS; Immune Effector Cell-Associated Neurotoxicity Syndrome, ICANS; interleukin-6, IL-6.

admission, incidence and grading of toxicity (including CRS, ICANS and sepsis) and toxicity management strategies such as interleukin-6 (IL-6) receptor antagonists and corticosteroids (dexamethasone, prednisolone and methylprednisolone). Sepsis incidence was diagnosed by treating physicians; the presence and severity of CRS and ICANS were evaluated daily also by treating physicians, according to the American Society for Transplantation and Cellular Therapy consensus (graded 1–5) [9].

2.2.2. Nutritional status during admission

Repeated body weight measurements taken throughout the admission were collected, from the first day of admission to day of discharge.

2.2.3. Dietetic services

Information regarding dietetic services provided were reviewed, including nutrition screenings, dietetic referrals, and interventions. UCLH guidelines recommend the use of the internally developed Nutrition Screening Tool (NST) by nursing staff for all inpatients, on admission, and weekly thereafter (Supplementary Table 2). Patients with an NST score ≥ 7 are considered at-risk of malnutrition and require referral to dietetics for full assessment and management.

2.3. Definitions: Malnutrition and cachexia

Baseline cachexia prevalence at treatment consent was identified using the modified Glasgow Prognostic Score (mGPS): no cachexia (mGPS 0 – Albumin ≥ 3.5 g/dL and CRP < 10 mg/L), undernourished (mGPS 0 – Albumin < 3.5 g/dL and CRP < 10 mg/L), pre-cachexia (mGPS 1 – Albumin ≥ 3.5 g/dL and CRP ≥ 10 mg/L) and refractory cachexia (mGPS 2 – Albumin < 3.5 g/dL and CRP ≥ 10 mg/L) [18] (Supplementary Table 3).

Malnutrition incidence was identified both *pre-treatment* (treatment consent to Day minus 15), and *during* CAR T-cell admission (first to last day of admission), using the Global Leadership Initiative on Malnutrition (GLIM) consensus definition, including the phenotypical criteria of weight loss or low BMI [19]. Additional phenotypical criteria of reduced muscle mass and

strength/function were not evaluated, as this data was not available in this retrospective cohort. The aetiological GLIM criteria were met by all patients, attributed to the chronic or recurrent mild to moderate inflammation associated with malignant disease (Supplementary Table 3).

2.4. Statistical analysis

Statistical analysis was undertaken using SPSS V.29 (IBM). Data are presented as mean (standard deviation – SD) or median (interquartile range – IQR) and/or [range]. Elevated serum LDH levels were defined using UCLH's upper limit of normal: (male: ≥ 250 IU/L, females: ≥ 214 IU/L); elevated serum ferritin defined using quartile analysis (high: upper quartile, low: lower three quartiles). Continuous variables were analysed using Spearman correlation coefficient, simple group comparisons completed by Mann–Whitney U tests, and categorical data analysed using Chi-squared test. Wilcoxon signed-rank tests were used to analyse changes over time for non-parametric data. Group differences on continuous variables were evaluated using analyses of variance (one-way ANOVA). Univariate and multivariate Cox regression was used to evaluate the prognostic impact of mGPS scores on survival outcomes (12-month overall survival – OS). Statistical significance was set as $p < 0.05$.

3. Results

A total of 114 patients, receiving axi-cel (78.1%, $n = 89$) or tisa-cel (21.9%, $n = 25$) were included. 43.0% ($n = 49$) of patients were women, with a median age of 60 (47–67) years. The median number of previous systemic therapies received was 2 (2–3), and the median days from consenting for treatment to CAR T-cell therapy infusion was 56 (47–71) days. Median LoS for CAR T-cell treatment was 34 (27–38) days; 19.3% ($n = 22$) of patients required ICU support during their treatment admission, with a median ICU LoS of 88 (39–265) hours. Baseline elevated serum LDH levels (marker of tumour burden [20]) were present in 84% ($n = 84$) of patients, with elevated ferritin levels post lymphodepletion, a

marker of inflammation, present in 67.4% ($n = 62$) of patients (Table 1).

3.1. Pre-treatment

3.1.1. Malnutrition and cachexia

Using body weight change over the pre-treatment period, or BMI at Day minus 15, 31.5% ($n = 36$) of patients were identified as malnourished pre-treatment (GLIM criteria [19], Table 2). At time of consenting for treatment (baseline), 101 of 114 (88.6%) patients had a single measurement of serum CRP and albumin available to assess cachexia status using mGPS [18], with pre-cachexia (mGPS 1) and refractory cachexia (mGPS 2) identified in 41.6% ($n = 42$) and 2% ($n = 2$), respectively (Table 2).

Univariate Cox regression analysis found that patients with baseline pre-cachexia or refractory cachexia experienced significantly increased risk of mortality at 12-months (HR = 3.158, CI = 1.36–7.323, $p = 0.007$) (Fig. 2) compared to patients without cachexia. Notably, after adjusting for the potential confounding variable of baseline serum LDH levels with multivariable Cox regression, pre-cachexia and refractory cachexia remained an independent negative prognostic marker for OS (HR = 3.012; 95% CI = 1.27–7.12, $p = 0.012$). Additionally, patients with baseline pre-cachexia or refractory cachexia experienced greater percent body weight loss pre-treatment ($p = 0.038$) and longer LoS ($p = 0.037$; Table 3). Malnutrition pre-treatment was significantly associated with increased ICU admissions during CAR T-cell treatment (16.4% vs 30.5%, $p = 0.039$).

3.1.2. Pre-treatment bridging therapies

Additional anti-cancer bridging therapies (BT) are commonly administered during the pre-treatment period between the T-cell apheresis and admission; primarily to stabilise disease during the CAR T-cell manufacturing process. BTs vary in intensity, with their

individual selection based on patient and clinician preferences [17]. Most patients at UCLH received BT (87.7%, $n = 100$), with the majority (64.0%, $n = 73$) undergoing chemotherapy (Supplementary Table 1). Using one-way ANOVA, percent body weight change pre-treatment (available for 88.6% ($n = 101$) of patients) was analysed according to BT prescription, with a significant difference between BT groups identified ($p < 0.001$; Table 4). CMT patients ($-10.1\% \pm 6.7$) lost significantly more body weight than those receiving RBP ($-2.5\% \pm 4.6$, $p = 0.047$), RT ($-2.0\% \pm 3.7$, $p = 0.039$), HDT-Gem ($-1.4\% \pm 3.8$, $p = 0.028$), or no BT patients ($+2.7\% \pm 5.6$, $p < 0.001$). Those who received RBP ($p = 0.021$) or HDT-Ifos ($-4.8\% \pm 4.1$, $p = 0.002$) lost significantly more body weight than patients not receiving BT ($+2.7\% \pm 5.6$). No significant difference in body weight change was seen in patients receiving LDT ($-1.6\% \pm 3.0$) or HDT-Other ($-3.9\% \pm 2.7$) compared to any other BT groups. The twelve patients who did not receive BT were the only group to increase body weight during this pre-treatment period.

3.1.3. Dietetic services

During the pre-treatment period, no patients in our facility were screened for malnutrition risk, or referred to dietetic services.

3.2. During CAR T-cell treatment admission

3.2.1. Malnutrition and body weight change

During the hospital admission, patients experienced significant body weight loss ($p < 0.001$), with median percent body weight change -5.6% (-8.8 to -2.4%) (Table 2). Using the GLIM criteria, 78 (68.4%) patients developed moderate/severe malnutrition over the course of their treatment admission (Table 3). No association was found between either 1) CAR T-cell product or 2) baseline serum LDH levels and percent body weight change during admission. Patients' BMI on admission are shown in Table 2 [21]. Using Cox regression analysis, neither increased BMI (defined as BMI ≥ 25 kg/

Table 1
UCLH CAR T-cell patient demographics.

Patient characteristics	CAR T-cell therapy patients ($n = 114$)
Patient age (years)	60 (47–67) [18–78]
Male (n , %)	65 (57.0)
Female (n , %)	49 (43.0)
Ethnicity (n , %)	
White British	45 (39.5)
Other White Background	29 (25.4)
White Irish	8 (7.0)
Other Asian Background	5 (4.4)
Black African	2 (1.8)
Mixed White and Black Caribbean	1 (0.9)
Other Ethnic Group	5 (4.4)
Not Disclosed	19 (16.6)
Diagnosis (n , %)	
De novo diffuse large B-cell lymphoma	76 (66.7)
Transformed indolent lymphomas	24 (21)
Primary mediastinal large B-cell lymphoma	8 (7.0)
B-cell acute lymphoblastic leukaemia	5 (4.4)
Intravascular lymphoma	1 (0.9)
Number of previous systemic therapies (excluding BTs) received prior to CAR T-cell therapy	2 (2–3) [2–7]
Time from consenting for treatment to CAR T-cell infusion (days)	56 (47–71) [41–266]
CAR T-cell therapy received (n , %)	
Axicabtagene ciloleucel (axi-cel)	89 (78.1)
Tisagenlecleucel (tisa-cel)	25 (21.9)
Length of hospital stay (days)	34 (27–38) [15–102]
Mortality (all-cause) at 12-months (n , %)	29 (25.4)
Baseline serum CRP levels (mg/L) ($n = 102$)	6.6 (2.5–32.3) [1–343]
Baseline serum LDH levels (IU/L) ($n = 100$)	291 (235–403) [155–2463]
Serum ferritin post lymphodepletion (ug/L) ($n = 92$)	719 (306–1301) [18–9608]

Abbreviations: BT; Bridging Therapy; BMI, Body Mass Index; CRP, C-Reactive Protein; LDH, Lactate Dehydrogenase. Data shown as number (percent) or median (IQR) [range].

Table 2
Nutritional status characteristics of CAR T-cell patients.

Nutritional status characteristics	CAR T-cell therapy patients
Pre-CAR T-cell therapy	
>5% body weight loss pre-treatment (n, %) (n = 101)	29 (28.7)
Pre-treatment GLIM malnutrition status (n, %) (n = 114)	
Nil	78 (68.5)
Moderate malnutrition	26 (22.8)
Severe malnutrition	10 (8.7)
Baseline mGPS score (n, %) (n = 101)	
Undernourished (mGPS 0 - Albumin: <3.5 g/dL, CRP: <10 mg/L)	0 (0.0)
No signs (mGPS 0 - Albumin: ≥3.5 g/dL, CRP: <10 mg/L)	57 (56.4)
Pre-cachexia (mGPS 1 - Albumin: ≥3.5 g/dL, CRP: ≥10 mg/L)	42 (41.6)
Refractory cachexia (mGPS 2 - Albumin: <3.5 g/dL, CRP: ≥10 mg/L)	2 (2.0)
During CAR T-cell therapy admission (n = 114)	
BMI category on admission (n, %)	
Underweight (<18.5 kg/m ²)	4 (3.5)
Healthy weight range (18.5–24.9 kg/m ²)	45 (39.5)
Overweight (25–29.9 kg/m ²)	44 (38.6)
Obese Class 1 (30–34.9 kg/m ²)	10 (8.8)
Obese Class 2 (35–39.9 kg/m ²)	6 (5.2)
Obese Class 2 (≥40 kg/m ²)	5 (4.4)
Percent body weight change during treatment admission (%)	–5.6 (–8.8 to –2.4) [–26.4 to +11.8]
>5% body weight loss during treatment admission (n, %)	69 (60.5)
During treatment GLIM malnutrition status (n, %)	
Nil	36 (31.6)
Moderate malnutrition	53 (46.5)
Severe malnutrition	25 (21.9)

Abbreviations: GLIM, Global Leadership Initiative on Malnutrition; mGPS, modified Glasgow Prognostic Score; CRP, C-Reactive Protein; BMI, Body Mass Index. Data shown as number (percent) or median (IQR) [range].

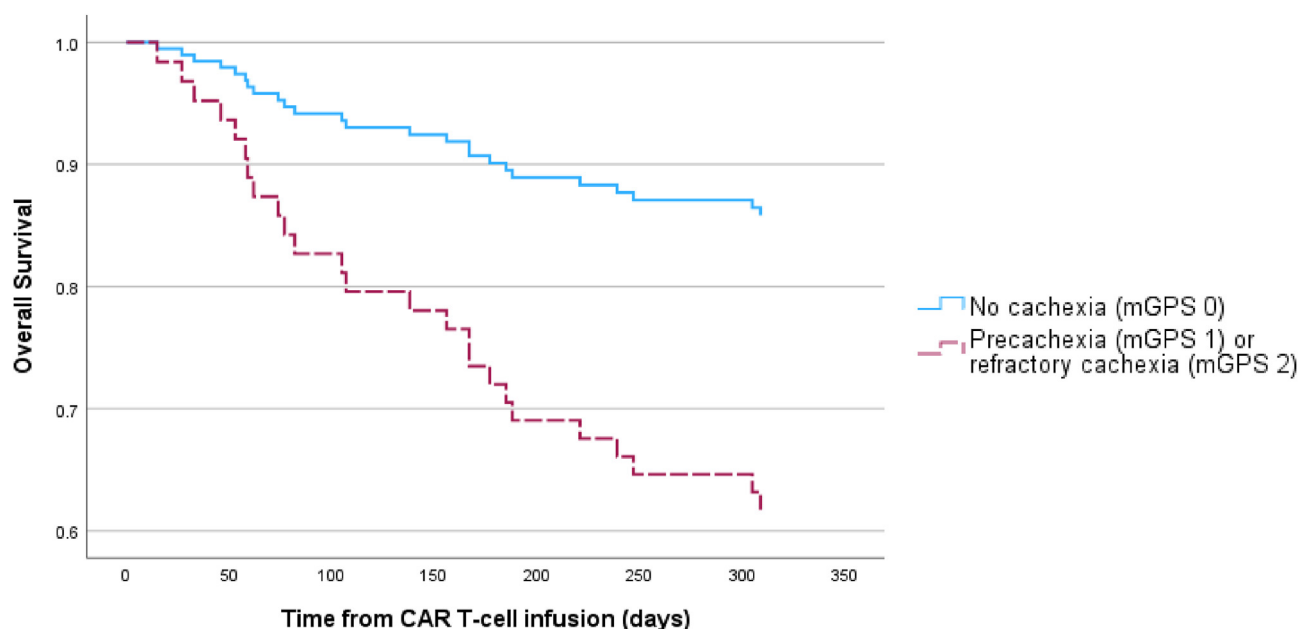


Fig. 2. modified Glasgow Prognostic Score (mGPS) cachexia status pre-treatment was associated with 12-month overall survival (Cox regression) $p = 0.007$.

m²) or low BMI (defined as BMI <20 kg/m²) on admission were significantly associated with 12-month OS.

3.2.2. Treatment side effects and medications

The incidence of side effects during admission, including sepsis, CRS and ICANS can be seen in Table 5. Both 1) baseline mGPS cachexia and 2) pre-treatment malnutrition status were associated with a higher risk of sepsis development ($p = 0.022$ and $p = 0.048$, respectively; Table 3). However, pre-treatment nutritional status (mGPS cachexia and malnutrition) was not associated with grade ≥2 ICANS or CRS. BMI on admission was not associated with any treatment-related toxicities.

The use and duration of medications with potential secondary metabolic effects were reviewed, including corticosteroids with glucocorticoid effects (dexamethasone, prednisolone, and methylprednisolone) and IL-6 receptor antagonists (tocilizumab) (Table 5). No significant associations were found between the use of either of these medications and the development of malnutrition during the admission.

3.2.3. Dietetic services, screening, and nutritional interventions

During admission, 64.9% ($n = 74$) of patients were referred to dietetic services; with increased referral rates seen in patients with baseline pre-cachexia or refractory cachexia ($p = 0.002$; Table 3).

Table 3

Patient characteristics and outcomes by baseline mGPS groups.

Parameter	Baseline mGPS 0 (no cachexia) (n = 57)	Baseline mGPS 1 (pre-cachexia) or 2 (refractory cachexia) (n = 44)	p-value
Patient characteristics and pre-treatment measures			
CAR T-cell product – axicabtagene ciloleucel (n, %)	48 (84.2)	33 (75.0)	0.249
Length of stay (days)	34 [15–66]	35 [19–102]	0.037
Baseline serum LDH levels (IU/L)	252 [159–2463]	357 [155–1336]	<0.001
Percent body weight loss pre-treatment (%)	–1.0 [–13.0 to 7.8]	–4.7 [–18.8 to 5.5]	0.038
Presence of malnutrition pre-treatment (n, %)	12 (21.1)	20 (45.5)	0.009
During treatment admission measures			
Serum ferritin levels at lymphodepletion (ug/L)	474 [37–3230]	993 [18–9608]	0.003
Percent body weight loss during admission (%)	–5.6 [–26.4 to 11.8]	–5.8 [–16.9 to 11.0]	0.574
BMI on admission (kg/m ²)	26.5 [18.7–43.6]	25.2 [17.6–52.5]	0.489
Referral to dietetics during admission (n, %)	31 (54.4)	37 (84.1)	0.002
Sepsis during admission (n, %)	17 (29.8)	23 (52.3)	0.022
CRS grade ≥2 during admission (n, %)	24 (42.1)	24 (54.5)	0.214
ICANS grade ≥2 during admission (n, %)	11 (19.3)	14 (31.8)	0.148

Abbreviations: mGPS, modified Glasgow Prognostic Score; LDH, Lactate Dehydrogenase; BMI, Body Mass Index; NST, Nutrition Screening Tool; CRS, Cytokine Release Syndrome; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome. Data shown as number (percent) or median [range].

Note: For body weight loss pre-treatment values, n = 90 (mGPS 0: n = 51; mGPS 1 or 2: n = 39). For serum LDH levels, n = 94 (mGPS 0: 55, mGPS 1 or 2: n = 39). For serum ferritin levels, n = 81 (mGPS 0: n = 42, mGPS 1 or 2: n = 39).

Table 4

Percent body weight changes in CAR T-cell therapy patients by bridging therapies.

Bridging Therapy	Patients (n = 101)	Change in body weight (%)
Combined modality therapy (CMT)	4 (4.0)	–10.1 (±6.7) ^{a,b,c,d}
High dose chemotherapy, Ifosphamide-based (HDT-Ifos)	12 (11.8)	–4.8 (±4.1) ^e
High dose chemotherapy, Gemcitabine-based (HDT-Gem)	12 (11.8)	–1.4 (±3.8) ^a
High dose chemotherapy, others (HDT-Other)	2 (2.0)	–3.9 (±2.7)
Low dose chemotherapy (LDT)	3 (3.0)	–1.6 (±3.0)
Rituximab-Bendamustine-Polatumuzumab (RBP)	35 (34.7)	–2.5 (±4.6) ^{b,f}
Radiotherapy (RT)	19 (18.9)	–2.0 (±3.7) ^c
Corticosteroids alone	1 (1.0) [*]	–3.2
Immunotherapy	1 (1.0) [*]	–0.1
No bridging therapy	12 (11.8)	+2.7 (±5.6) ^{d,e,f}

^{a,b,c,d,e,f} Values denoted by different superscript letters indicate $p < 0.05$ (one-way ANOVA). Data presented as number (percent) or mean (± standard deviation).

^{*} to meet the minimum requirements for post-hoc testing, groups with n = 1 were removed from analysis.

Table 5

Incidence of treatment side effects (Sepsis, CRS and ICANS), and toxicity management strategies during admission.

Side Effect Incidence and Medication Usage	Patients (n = 114)
Sepsis during admission (n, %)	45 (39.5)
Maximum CRS grade experienced during admission (graded 1–5)	2 (1–2) [1–3]
CRS grade ≥2 during admission (n, %)	54 (47.4)
CRS grade ≥2 (days)	3 (2–4) [1–8]
Maximum ICANS grade experienced during admission (graded 1–5)	2 (1–3) [1–5]
ICANS grade ≥2 during admission (n, %)	28 (24.6)
ICANS grade ≥2 (days)	4 (3–8) [2–25]
Corticosteroid required during admission (n, %)	46 (40.4)
Corticosteroid usage duration (days)	12 (±7.9)
Corticosteroid use ≥7 days (n, %)	32 (28.1)
Tocilizumab required during admission (n, %)	73 (64.0)

Abbreviations: CRS, Cytokine Release Syndrome; ICANS, Immune Effector Cell-Associated Neurotoxicity Syndrome. Data shown as number (percent), mean (± standard deviation) or median (IQR) [range]. Corticosteroids used include dexamethasone, prednisolone, and methylprednisolone.

Note: For maximum CRS and ICANS grade values, only patients who developed any grade of CRS (n = 104) or ICANS (n = 48) during treatment were included.

Referral reasons included nutritional risk (75.6%, n = 56) and nutrition impact symptoms (24.4%, n = 18). The median number of dietetic reviews completed for referred patients was 4 (2–6). Of those referred, dietetic interventions included: oral dietary modifications and/or oral nutritional supplements in 72.9% (n = 54) of patients, enteral nutrition in 18.9% (n = 14), and parenteral nutrition in 8.2% (n = 6). Referred patients lost significantly more body weight during the admission (–6.1% [–26 to +11.8]) compared to patients not referred to dietetics (–3.9% [–11.8 to +4.8], $p < 0.001$).

Using UCLH's internally developed malnutrition screening tool (NST), 57% (n = 65) of patients scored ≥7, indicating at-risk of malnutrition.

4. Discussion

In this service evaluation, we sought to characterise the changes in nutritional status experienced by CD19-targeting CAR T-cell therapy patients at UCLH, and its potential impact on clinical

outcomes. Furthermore, we explore the dietetic resource utilisation in this group, to identify current practices and areas for development.

In our cohort, baseline cachexia status (mGPS 1 and 2) was independently associated with inferior OS. This is consistent with recently published data showing the negative impact of adverse nutrition parameters pre-CAR T-cell treatment (including weight loss and immuno-nutritional scores) on progression-free survival and OS [20,22]. However, to our knowledge, our study is the first to identify mGPS cachexia scores as a predictor of OS independent of serum LDH, a marker of disease burden [20]. This highlights the significance of using mGPS as a potential determinant for adverse outcomes in this patient group, and the need for early screening and intervention.

Malnutrition, pre-cachexia and refractory cachexia prior to CAR T-cell therapy were associated with increased LoS, ICU admission, and sepsis. The increased rate of adverse outcomes associated with poor nutritional status in our cohort mirrors those observed in standard cancer therapies [7,23], stem cell transplants [24,25], and more recently in CAR T-cell therapy [20,22]. This underscores the necessity for research to further explore its impact in this space, encompassing broader outcome measures not yet investigated such as quality of life, fatigue, and healthcare costs, given their well-documented association with nutritional status in standard cancer settings [7]. In contrast to data from Akhtar et al. (2023) where mGPS 2 equivalent (using standard Glasgow Prognostic Score) was associated with higher rates of grade ≥ 3 CRS and any grade ICANS [26], we did not find associations between these toxicities and nutritional status. Differing cohorts, assessment timepoints, and mGPS/toxicity gradings for analysis may explain these contrasting results, warranting additional investigation.

Factors associated with greater pre-treatment weight loss included baseline cachexia and receiving intensive BT. Given the increasing use of intensive BT in CAR T-cell therapy [17], identifying these higher-risk patients may facilitate early nutrition screening and intervention prior to initiation of BT, with the goal of minimising weight loss and muscle wasting, potentially reducing pre-treatment malnutrition incidence and improving treatment outcomes.

A substantial proportion of patients developed malnutrition (68.4%) during their admission, far exceeding the rate observed in standard haematology treatment settings (26%) [27]. With minimal comparative data available, the drivers for this elevated malnutrition rate in our CAR T-cell population requires further research. Weight loss during admission was not associated with CAR T product, LDH levels, or use of CAR T-cell toxicity management medications including corticosteroids and IL-6 receptor antagonists. This is despite the known exacerbation of muscle atrophy associated with corticosteroid use [14], and the potential role of IL-6 receptor antagonists in attenuating inflammatory-driven weight loss [31]. Malnutrition prevalence is known to increase in patients with advanced cancers [7], which is significant for this CAR T-cell population given their refractory/relapsed disease status. Due to the common occurrence of fluid retention secondary to corticosteroid use [32] and CRS [33], evaluating the intrinsic and extrinsic factors driving this elevated malnutrition rate using body weight alone may be challenging. Future research should consider the use of sensitive body composition assessments (e.g. dual-energy x-ray absorptiometry (DEXA), computerised tomography (CT), bioelectrical impedance [19]) and measures of muscle strength/function (e.g. hand-grip strength) to assist with identifying the contributors to poor nutritional status post-CAR T-cell infusion, including the potential role of inflammatory processes such as CRS.

In our service evaluation, BMI on admission was not associated with treatment toxicities or OS, which is consistent with data from

Wudhikarn et al. (2021) [28]. To further characterise the impact of pre-CAR T-cell body composition beyond simple anthropometric measures such as BMI, several groups have utilised CT imaging in this setting. Santos et al. (2022) observed that increased visceral adipose tissue (AT) at lymphodepletion was negatively associated with CRS severity and early onset [29]. In a similar study, Rejeski et al. (2023) showed that increased total abdominal AT (but not BMI) was associated with improved response to CAR T-cell therapy [20]. The authors concluded that the obesity paradox as described in other cancer settings [23], may extend to CAR T-cell therapy. These results further highlight the importance of sensitive body composition assessments in CAR T-cell therapy research and clinical care. This may in the future enable identification of patients with protective or adverse features such as increased abdominal AT, or sarcopenic obesity (low muscle mass and function alongside BMI >30 kg/m² [30]), which is often overlooked in clinical oncology practice despite its association with poor outcomes [23].

Using the UCLH Nutrition Screening Tool (NST), 57% of patients during admission were identified as at-risk of malnutrition, with 64.9% referred to dietetic services. Conversely, in the pre-treatment setting, patients did not undergo formal malnutrition screening, or receive dietetic referrals or input, despite 43.6% presenting with pre-cachexia/refractory cachexia. As CAR T-cell services continue to expand internationally and awareness of the impact of altered nutritional status becomes increasingly apparent, further research, collation of multidisciplinary evidence and development of guidelines to support this aspect of CAR T patient care will be essential. Given the current emerging evidence, we propose the following preliminary dietetic pathway to enable prompt screening and intervention in this setting (Fig. 3). This includes consistent monitoring of nutrition parameters associated with patient outcomes [20,22], sensitive body composition assessments [19], measures of muscle strength/function, and early malnutrition screening using tools validated in haemato-oncology [7,34]. As evidence regarding recommended dietetic interventions specific to CAR T patients is limited, adherence to current haemato-oncology dietetic guidelines is advisable, pending further research [35].

With continued research, expansion of this pathway to incorporate services such as prehabilitation, initiated upon treatment consent, could be considered to optimise pre-treatment nutritional status. The benefits of CAR T-cell prehabilitation, including exercise and nutrition interventions, have been suggested [20,36] and trialled in selected countries [37], given their association with superior treatment outcomes in oncology and surgical settings [38]. Formal health economic analyses are recommended to determine the cost-effectiveness of introducing different multidisciplinary CAR T-cell pathways, such as the proposed dietetic pathway, compared to multimodal prehabilitation interventions.

4.1. Limitations

This investigation has the following limitations: the retrospective design with convenience sampling, and small sample size ($n = 114$) due to the novel nature of the treatment. In recognising the inherent constraints of service evaluations, caution should be exercised when interpreting these results as they cannot be assumed generalisable; however, it is noteworthy that this cohort's demographic profile extends beyond UCLH's catchment, as patients from across the UK are referred to this specialist centre (Supplementary Table 4). Despite limiting inclusion to licensed CD19 targeting CAR T-cell products, there remains heterogeneity within our selected population, primarily stemming from variations in patients' diagnoses (Table 1). The quality and completeness of the data retrospectively collected (using EHR) may be limited;

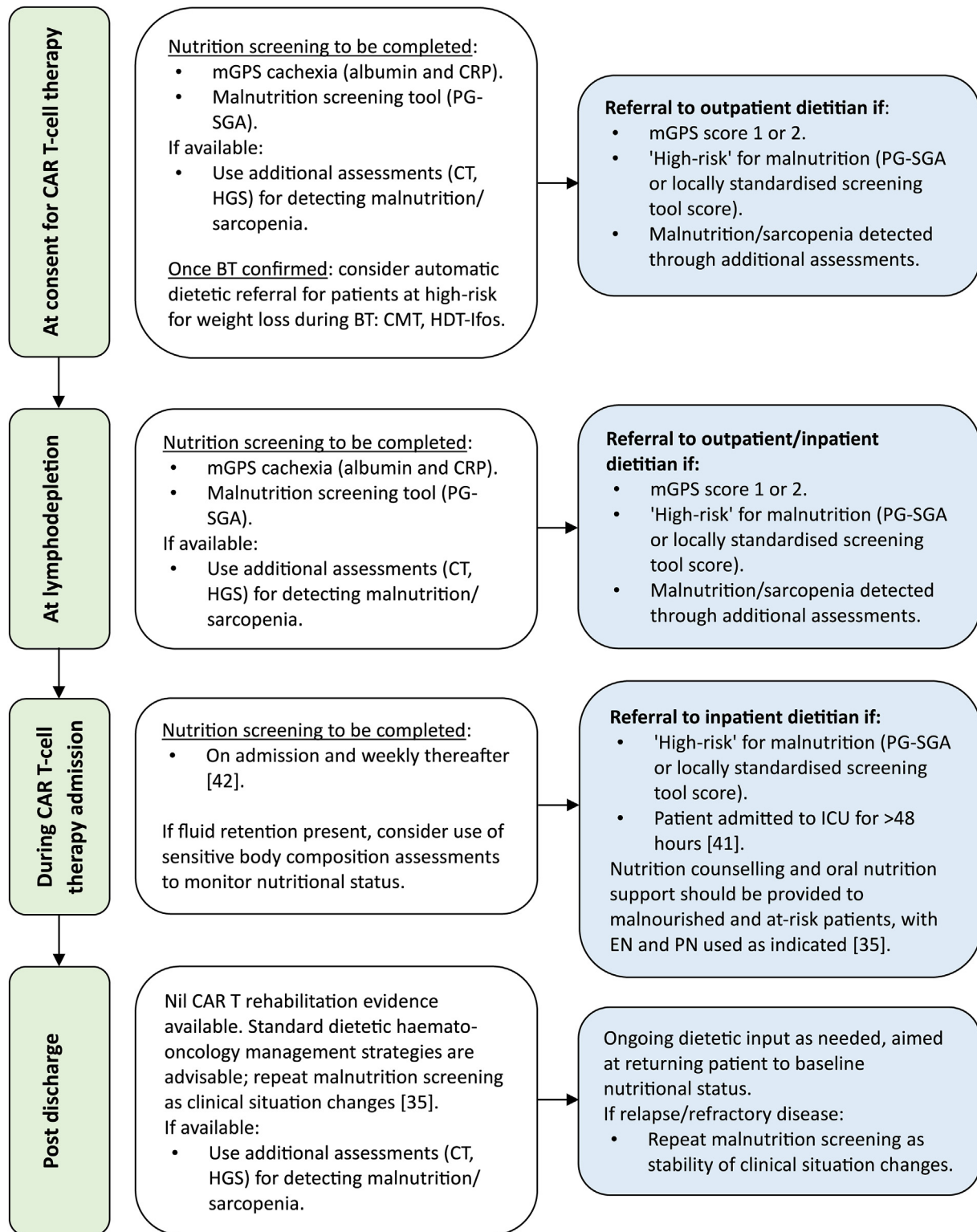


Fig. 3. Proposed preliminary dietetic management pathway for CAR T-cell patients at UCLH, utilising emerging evidence and key references [35,41,42].

Abbreviations. modified Glasgow Prognostic Score, mGPS; C-Reactive Protein, CRP; Patient-Generated Subjective Global Assessment, PG-SGA; computerised tomography, CT; hand-grip strength, HGS; bridging therapy, BT; combined modality therapy, CMT; High-dose chemotherapy Ifosphamide-based, HDT-Ifos.

pre-treatment weight history and baseline serum CRP/albumin available in $n = 101$.

Assessment of muscle mass and strength/function, anorexia and fatigue, used in various cachexia and malnutrition diagnostic tools

[19,39,40], are not routinely conducted in clinical care at present. Consequently, we were unable to comprehensively characterise cachexia status in our cohort, using solely baseline serum CRP and albumin levels, with CRP known to be a non-specific inflammatory

marker. Similarly, weight loss and low BMI alone were used to determine GLIM malnutrition status phenotypically, as data regarding reduced muscle mass and strength/function was not available retrospectively. Nevertheless, these findings serve as proof-of-concept, prompting the need for ongoing research in this emerging field.

5. Conclusion

This service evaluation highlights both the high rates of malnutrition experienced by patients during CAR T-cell treatment, and the independent association between pre-treatment nutritional status and patient outcomes, including inferior overall survival. As CAR T-cell therapy extends beyond the realms of haematological malignancies, application of sensitive nutrition assessments, and evaluation of early intervention strategies should be a focus of future work, aimed at optimising nutritional status and subsequently, clinical outcomes. Parallel expansion and implementation of dietetic resources should be considered a key component of individualised care for CAR T-cell therapy patients, shaping the future of comprehensive treatment strategies.

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Author contributions

B.C., N.A.D., C.E.W. and A.S. were involved in conceptualisation and methodology. N.A.D., C.E.W. and A.S. provided supervision. B.C. and N.A.D. were involved in statistical analysis. B.C. was involved in investigation, project administration, and writing (original draft). All authors were involved in writing (review and editing).

Declaration of competing interest

C.R. has served on advisory boards and received honoraria from Kite/Gilead, Novartis, Autolus and Bristol Myers Squibb. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnesp.2024.05.020>.

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