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Role of Frailty in Assessing Eligibility for CAR T-Cell Therapy in Haematology

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ABSTRACT

Background and Objectives: Frailty is a key consideration in determining whether a patient is robust enough for CAR T-cell therapy; however, it should not represent a barrier to treatment. Our study aimed to describe the extent of research concerning frailty in haematology adult and paediatric patients being considered for CAR T-cell therapy and its potential impact on their eligibility.

Methods: Following the Joanna Briggs Institute guidelines, we adopted a scoping review methodology. Our search was conducted across the databases CINAHL, Cochrane, Embase, Medline, PubMed, Google Scholar, clinicaltrials.gov, clinical trials register.eu, and euclinicaltrials.eu for studies published from 2017 to March 2nd 2024. Studies were screened by independent teams of reviewers using the web application Rayyan.

Results: Our review included 12 studies, with varied study designs. No study in a pediatric CAR T-cell setting was found. A wide variation in assessing frailty before CAR T-cell therapy was evident, with ECOG being the most frequently used assessment tool.

Conclusions: An appropriate frailty assessment before CAR T-cell therapy promotes the productive use of resources and proper patient selection. Using a geriatric assessment and incorporating an assessment tool such as the CAR HEMATOTOX has the potential for assessing frail CAR T-cell therapy patients.

1 | Introduction

In 2017, the US Food and Drug Administration (FDA) first approved chimeric antigen receptor T-cell therapy (CAR T-cell therapy) [1]. This innovative treatment has positively changed the trajectory of prognosis in many hematological malignancies [2, 3]. Access for all age groups to this potentially curative therapy is vital in improving outcomes for this patient population. While frailty is a key consideration in deciding whether a patient is robust enough for treatment, it should not represent a barrier to treatment [4, 5].

CAR T-Cell therapy consists of a cellular product collected by apheresis from the patient, which is then manufactured to become a pharmaceutical product of genetically engineered T-cells, which are reinfused into the patient post-lymphodepleting chemotherapy [6]. The many toxicities associated with this treatment are widely documented and include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), hemophagocytic lymphohistiocytosis (HLH), hypo-gammaglobulinaemia, B cell aplasia, febrile neutropenia, infections, and cytopenias [3, 6]. A large proportion of patients experience adverse events [2, 3], and patients must undergo a rigorous preassessment before undergoing therapy to mitigate these adverse events [2, 5, 7–9].

In a CAR T-Cell therapy study of older vulnerable patients with relapsed/refractory large B cell lymphomas, no excess toxicities in this group were reported compared to groups of younger patients

[5]. This finding is of special interest as this cohort of patients would be associated with significant toxicity and mortality in the setting of chemo immunotherapy [5], which may influence clinicians' preconceptions of these patients' abilities to tolerate CAR T-cell therapy.

Similarly, in clinical trials of CAR T-cell therapy, the patients included may not reflect the reality of patients in current practice, as there is usually a strict inclusion criterion for trials [2, 4, 7]. This creates difficulty in treatment decisions based on trial data concerning older patients. It highlights the potential for undertreating an older patient and the need for an individualized assessment in considering their eligibility for CAR T-cell therapy.

Frailty is a complex entity, yet it has a profound effect on treatment decisions and estimating goals of care. Its consideration has multifactorial components such as age, function, mobility or falls, cognition, mood, co-morbidities, polypharmacy, geriatric syndromes, nutrition, and social support [7, 10]. Frailty can be defined as a state of vulnerability [7, 8, 10], with an inability to care for oneself and an overall physical and mental decline [11]. Frailty is considered reversible [11], and deliberation should be made regarding frailty as a pre-existing condition or because of a diagnosis of a haematology malignancy [4]. There are many factors related to frailty, thus rendering frailty assessment a key element in screening patients for CAR T-cell therapy, which is associated with many toxicities.

The concept of frailty in paediatric patients is perhaps odd given their young age and frailty's association with gerontology. However, frailty and sarcopenia in paediatric settings are thought to be highly relevant, but they are under-researched [12]. Frailty scores have been used in paediatrics in a study of children with chronic liver disease [13]. The relevance to CAR T-cell therapy is that paediatric patients have already had intensive treatment, which could have been both challenging and complex, making them a vulnerable patient population [14]. Paediatric patients in this situation may carry many of the hallmarks of frailty, except for the association with gerontology.

Given the complexity of frailty and the heterogeneous nature of haematological malignancies that receive CAR T-cell therapy, this scoping review aimed to examine frailty in haematology patients and its impact on their eligibility for CAR T-cell therapy. In particular, the review aimed to determine the prevalence of frailty assessment before CAR T-cell therapy, the role frailty assessments have in pre-assessing patients for CAR T-cell therapy, and any implication of frailty on patients' eligibility for CAR T-cell therapy.

2 | Methods

This scoping review follows the Joanna Briggs guidelines for scoping reviews, which incorporate the PRISMA extension for scoping reviews checklist [15]. The study protocol was registered with the Open Science Framework on the 15th of April 2024 with DOI number of 10.17605/OSF.IO/8NDBJ.

A health services information specialist assisted in developing and validating a systematic search strategy. The following databases were searched: CINAHL, Cochrane, Embase, Medline, PubMed, Google Scholar, clinicaltrials.gov, clinicaltrialsregister.eu, and euclinicaltrials.eu. The search was concluded on March 2, 2024 (Supporting Information).

After removing duplicates, the search results were uploaded to Rayyan, a web application for managing systematic reviews [16]. Two teams of four reviewers (JC, AB, JMcG, DC) independently screened titles and abstracts. The same two teams also reviewed articles selected for full-text screening. A fifth reviewer (MD) addressed conflicts at the title and abstract and full-text screening stages following discussion.

Inclusion criteria were any study or protocol of any research design, including conference abstracts, that involved patients with a haematology malignancy approved for CAR T-cell therapy by the FDA and reported on the assessment of frailty or related concepts, such as geriatric assessments, performance status, and sarcopenia. A time limit of studies published from 2017 was set, as this was the year CAR T-cell therapy was first approved. Paediatric patients were also included, given that CAR T-cell therapy is approved for patients who have failed previous lines of treatment, and there is potential for this paediatric population to be particularly vulnerable. Data extraction was undertaken by the first author (JC) and checked by the last author (MD), using charting forms per the JBI framework [15].

3 | Results

In total, 331 records were identified following removal of duplicates. Following title and abstract screening, 63 studies were put forward for full text review. Twelve studies were then included in our review (Figure 1).

The included studies had varied designs, mostly retrospective, with one state-of-the-art review [17], and one quasi-experimental [7]. No study in a paediatric CAR T-cell setting was found. One study had fewer than 50 patients [18], three had samples between 50 and 100 [19–21], and six reported samples between 100 and 500 [8, 22–26]. (Table 1).

3.1 | The Prevalence of Reporting on Frailty Assessment Prior to CAR T-Cell Therapy

Eight of the included studies explicitly discussed using frailty assessment tools before CAR T-cell therapy [7, 17, 18, 20, 22, 24–26]. However, there was significant heterogeneity between the assessments used. Many different frailty assessments were noted, and patients were mainly assessed using various tools [17, 22, 25]. The most common frailty assessments used were the Eastern Cooperative Oncology Group (ECOG), with four studies including it [17, 18, 20, 22]. The Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) was also included in four studies [17, 22, 23, 25], and the Geriatric Assessments in one [7]. (Table 2).

3.2 | Role of Frailty Assessments in the Preassessment of Patients for CAR T-Cell Therapy

The early assessment of frailty as a means of identifying patients at risk of adverse events during CAR T-cell therapy and

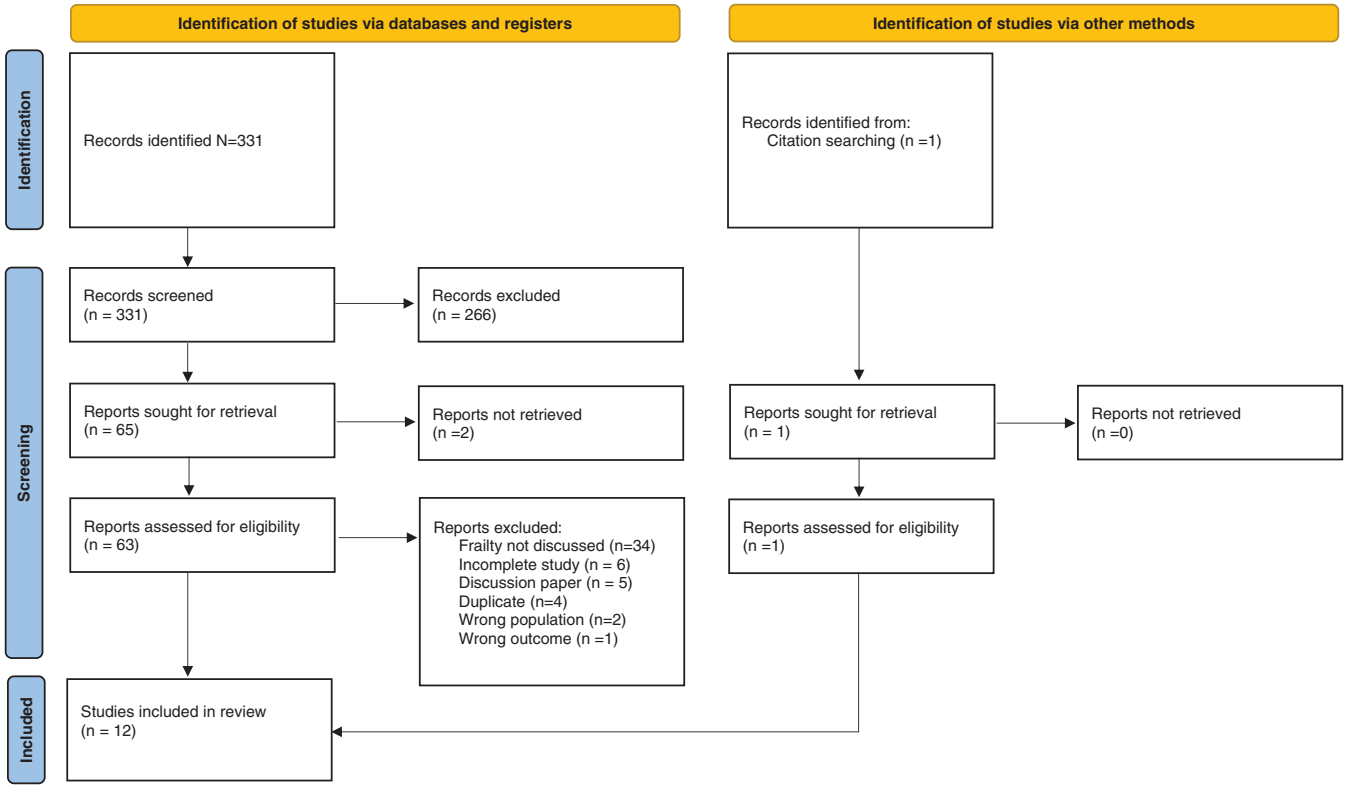

FIGURE 1 | PRISMA scoping review flow diagram.

mitigating these circumstances for an improved outcome is a concept that was identified in two studies [8, 21]. Frail patients are at increased risk of death during CAR T-cell therapy, so specific monitoring for them is key in optimising their care [8], and profound frailty may be a reason not to do CAR T-cell therapy [26].

3.3 | Implications of Frailty on Patients' Eligibility for CAR T-Cell Therapy

Further concepts identified from our study regard eligibility for CAR T-cell therapy. CAR T-cell therapy is a treatment that should not be limited without a proper assessment [18, 23]. The concern of toxicities being more extreme in frail patients receiving CAR T-cell therapy potentially can be balanced by assessing frailty, and these concerns should not limit patients from receiving this treatment [17, 19, 20, 22].

4 | Discussion

Our review found significant heterogeneity within the possible frailty assessment options available before CAR T-cell therapy, and no standardisation has been established. Various assessment tools were identified, individually or in a combination format. What is difficult to verify is which is most suitable for patients undergoing CAR T-cell therapy and which will be the most efficient in terms of time to assess and human resources.

In the 2021 best practice guidelines for CAR T-cell therapy for adults and children, performance status was recommended to be assessed by ECOG, Karnofsky scale, or the Lanksy scale in children [27]. Performance scores such as ECOG or the Karnofsky scale do not always capture frailty, for example regarding polypharmacy [28, 29]. However, ECOG was one of our review's most frequently used assessment tools. Moreover, the Lanksy scale is either patient-or parent-reported [30], which can lead to bias. Therefore, an assessment tool suitable for paediatric CAR T-cell therapy candidates is needed. Determining the most appropriate assessment tool is challenging, as finding one that addresses all aspects of frailty and CAR T-cell therapy could prove problematic [28]. However, an effective combination may be the answer.

The HCT-CI, an assessment tool for allogenic stem cell transplant (SCT) patients, was reported in four studies in our review. It is used to assess comorbidities before allogenic transplant that may affect a patient's outcome post the procedure that is not related to relapse [31]. However, this tool can potentially miss patients who may not be robust enough for an allogenic SCT but could potentially avail of CAR T-cell therapy. Frailty is not something that is linear or that can easily be divided into neat sections. There can be patients who are identified as fit or unfit; however, some patients could have reversible factors or be improved with interventions [28]. The role of an appropriate frailty assessment specifically designed for CAR T-cell therapy would be to identify these patients who are at risk of being overlooked. Given that CAR T-cell therapy has the potential for curative intent, this risk represents a significant disservice to patients who are in a supposed grey area of frailty.

A geriatric assessment was described in one study [7]. Geriatric assessments include a medical, functional, socioeconomic, psychological, and nutritional examination [32]. A geriatric assessment

TABLE 1 | Study characteristics.

Citation details and number	Location	Study aim	Study design	Population and sample size	Funding
Azoulay et al. [8]	France, Spain, USA, UK, Russia, Canada, Germany & Austria	To describe the management and outcomes of CAR T-cell recipients presenting with severe toxicity or sepsis	Retrospective and prospective observational cohort study design	241 haematology patients who were admitted to ICU post CAR T-cell therapy	Respiratory Research Groups in Onco-Haematological resuscitation
Barata et al. [25]	USA	This study examined changes in cognition in the first year after CD19-directed CAR T-cell therapy for lymphoma, as well as CAR T-cell therapy-specific risk-factors (e.g., ICANS, CRS) and non-specific risk factors (e.g., baseline quality of life, frailty) for worsening cognition	Prospective study design	118 patients with NHL who had CAR T ell Therapy	National Institutes of Health and a 2017 Moffitt Team Science Award
Kuhnl et al. [23]	UK	To assess outcomes of large B-cell lymphoma patients approved for CAR T-cell therapy in the UK who are deemed unfit for autologous stem cell transplant	Retrospective analysis design	404 patients with large B-cell lymphoma approved for CAR T-cell therapy	NIHR UCLH Biomedical Research Centre
Davies et al. [22]	USA	To evaluate the clinical characteristics and outcomes of frail patients with RRMM who received BCMA-targeted CAR T cell therapy	Retrospective analysis design	136 myeloma patients	Not described
Dima et al. [19]	USA	The primary aim of this study was to evaluate real-world outcomes of patients treated with standard of care ide-cel who did not meet the KarMMa-1 trial inclusion criteria	Retrospective analysis design	69 relapsed, refractory multiple myeloma patients	No funding received
Lin et al. [7]	USA	To assess geriatric vulnerabilities before CAR T-cell therapy. Patients were to have a comprehensive geriatric assessment before undergoing CAR T-cell therapy.	Quasi-experimental study design	$N = 75$: $n = 48$ (geriatric consultation group & $n = 27$ usual care group)	National Institute of Health & National Cancer Institute
Modi et al. [24]	USA	To evaluate the prevalence and impact of frailty defined by a simplified frailty score in patient with Multiple Myeloma who are receiving CAR T-cell therapy	Cross-sectional study design	139 patients with Multiple Myeloma	Not described
Montoro-Lorite et al. [18]	Spain	To describe the profile of older people with cancer who are treated with CAR T-cell therapy at Hospital Clínic Barcelona and to analyse the relationship between age, comorbidities, geriatric syndromes and days of admission	Observational retrospective study design	16 patients ≥ 50 years	None described

(Continues)

TABLE 1 | (Continued)

Citation details and number	Location	Study aim	Study design	Population and sample size	Funding
Neuendorff et al. [17]	N/A	To discuss key questions on cellular therapies in older adults illustrated by patient case review	State-of-the-art review	N/A	None described
Paillassa et al. [26]	France	To describe the characteristics of the non-eligible patients and the causes of non-eligibility for CD19 CAR T-cells at the treating centre	Retrospective analysis	Assessment of 221 patients deemed potentially eligible for CD 19 CAR T Cell Therapy	None described
Prica et al. [21]	Canada	To determine if frailty assessments pre-CAR T can predict those at higher risk for acute toxicities, PFS, and OS, as well as evaluate changes in frailty over time	Cohort/ Observational study	52 patients	None described
Trando et al. [20]	USA	The study aimed to identify the potential predictive factors of therapy response and described the outcomes of non-responders.	Retrospective analysis	66 patients with R/R DLBCL who received either tisa-cel or axi-cel in a single centre study	No funding received

has been noted as a comprehensive way to assess for frailty. It may be best utilised with the input of a geriatrician and as a method of choice when evaluating patients with haematology malignancies for frailty [4, 28]. A geriatric assessment in haematology has been developed but has not been fully validated. Nonetheless, using an objective assessment that will guide treatment decisions could benefit clinicians [33]. Ongoing trials examining geriatric assessments in the context of CAR T-cell therapy may play a key role in informing frailty assessment before CAR T-cell therapy.

Although CAR T-cell therapy is safe and effective in older adults and should be considered early in treatment [34], this population is often underrepresented in clinical trials. It can, therefore, be difficult for clinicians to decide the correct course of treatment as a result [4, 17, 35]. When considering frail patients for treatment, clinicians may have many considerations for patients to have an individualised approach, such as prognosis, cause of frailty, benefits of treatment versus supportive care, consideration of a less intensive treatment, and questioning if interventions reverse frailty to enable a patient to receive treatment [28]. In the context of CAR T-cell therapy, clinicians will also need to consider ways to limit toxicities, such as multidisciplinary meeting discussion, limiting the amount of disease burden before treatment, timely admission to ICU, CAR T product selection, and early use of tocilizumab [2]. CAR T-cell therapy use will continue to grow and become more accessible to real-world patients, and consideration of its use in frail patients is multifaceted. There is a critical need for clinicians to be able to assess a patient's risk and optimise the patient's condition before they undergo treatment [2].

Aspects that could influence a patient's eligibility, as identified by our study, would be the early identification of frailty [8, 21], not limiting CAR T-cell therapy without a proper assessment [18, 23], and having a balanced opinion on the risk of toxicities in frail patients [17, 19, 20, 22]. Moreover, the International Myeloma Working Group Frailty Score illustrates the impact of appropriate frailty assessments. A study of patients with relapsed/refractory myeloma found that this frailty score could be crucial in identifying vulnerable patients, enabling clinicians to make the correct treatment decisions [36]. The CAR HEMATOTOX (CAR-HT) model was developed to identify patients most at risk of the haematotoxic effects of CAR T-cell therapy, using pre-treatment markers associated with haemotoxicity (platelet count, haemoglobin, and ANC) and baseline inflammation (e.g., C-reactive protein and ferritin) [37].

The CAR-HT has been validated in haematological malignancies such as Large B Cell Lymphoma, Mantle Cell Lymphoma, and Multiple Myeloma and does appear to help in guiding patient selection and in allocating resources [38, 39]. Notably, patients found to have a high CAR-HT score had an increased risk of infection and may have worse patient outcomes with a prolonged hospital stay [37, 38], and while it is not specific to frailty, many of its objectives could apply to frail patients with the potential for CAR T-cell therapy.

Specifically, infections can be the most significant contributing factor to non-relapse mortality, and this is particularly true for various haematological malignancies undergoing CAR T-cell therapy [38, 39]. Given the heavily pre-treated

TABLE 2 | Summary of findings.

Study	Implications for future research	Pre-assessment of frailty before CAR T-cell therapy	Implications of frailty on eligibility for CAR T-cell therapy
Azoulay et al. [8]	Studies examining the standardisation of management of CAR T-cell recipients in ICU are warranted	Results suggest that a frailty evaluation should take place prior to CAR T-cell therapy to identify patients at increased risk of death should they develop CRS, ICANS or sepsis. No frailty assessment tool was specifically identified	Frail patients receiving CAR T-cell therapy are at increased risk of death so they need to have early identification to ensure specific monitoring
Barata et al. [25]	Similar study where patients are homogenously treated for ICANs and CRS Future prospective studies should include a more heterogeneous patient population with examination of baseline risk factors for toxicity such as ferritin and LDH level on perceived cognition Future prospective studies that examine perceived cognition and objective neurocognitive performance in the first year after CAR T-cell therapy and beyond	• Karnofsky Performance Status • Hematopoietic Cell Transplantation Comorbidity Index • Grip Strength Data • Everyday Cognition Questionnaire • Patient-Reported Outcomes • Measurement Information System-29 Profile v2.1	Not discussed
Kuhnl et al. [23]	Not described	• Hematopoietic Cell Transplantation Comorbidity Index	Fitness for CAR T-cell therapy in elderly and comorbid patients should be assessed early on in treatment so that all treatment options are considered
Davies et al. [22]	Not described	Patients were divided into two groups: frail and non-frail. Frailty was defined by using the simplified frailty index, which consisted of: • Age • ECOG • Performance Status • Haematopoietic Cell Transplantation-Specific Comorbidity Index	This study showed that physical fitness and comorbidities did not impact toxicities such as CRS and ICANS after CAR T-cell therapy, and that their presence should not be used to preclude patients from receiving this therapy.
Dima et al. [19]	Not described	Not described	The presence of one or more of the exclusion criteria for the KARMMa-1 trial should not represent a barrier to CAR T-cell therapy
Lin et al. [7]	Studies investigating the practicalities of incorporating geriatric assessments prior to CAR T cell treatment.	Formal geriatric consultation with geriatric assessment.	No frailty tools described. No criteria for ineligibly for CAR T-cell therapy described in paper.
Modi et al. [24]	Studies looking at role of pre-habitation and other modalities to reduce inflammatory burden prior to CAR T-cell therapy are warranted	• Glasgow-prognostic score	Glasgow Prognostic Score is highly predictive of survival even after adjusting for the presence of high risk disease

(Continues)

TABLE 2 | (Continued)

Study	Implications for future research	Pre-assessment of frailty before CAR T-cell therapy	Implications of frailty on eligibility for CAR T-cell therapy
Montoro-Lorite et al. [18]	Not described	• ECOG • Barthel scales	Age or underlying co morbidities did not mean a longer admission for CAR T-cell therapy. There was a greater correlation between CAR T-cell therapy admission days and altered geriatric syndromes than with age or comorbidities
Neuendorff et al. [17]	Further studies into the impact of comorbidities and frailty on eligibility for CAR T-cell therapy	• Hematopoietic Cell Transplantation-Comorbidity Index • Objective Timed Up and Go, Grip Strength • Patient reported Instrumental Activities of Daily Living assessment • Karnofsky performance index • Eastern Cooperative Oncology Group • Montreal Cognitive Assessment • Mental Health Index • Nutritional status.	Existing evidence suggests that CAR T-cell therapy can be safely delivered to older patients and holds potential for unprecedented efficacy in relapsed/refractory DLBCL.
Paillassa et al. [26]	Not described	• A screening form was completed by the referring hospital • Patient was evaluated by a predetermined eligibility criteria • In cases of severe comorbidities or age > 70 Frailty Index was used by ICU physician to assess patient • Eligibility was then finally determined by a local board with a case by case analysis	Major frailty is a cause to exclude patients from receiving CAR T-cell therapy
Prica et al. [21]	Enrolment is ongoing and data on larger number of patients with longer term follow-up are needed	• Baseline assessment of frailty then again at month 1, 3, 6, and 12 • Clinical Frailty Score	• Clinical Frailty Score is the only measurement of frailty found to have clinically significant changes between time points suggesting an element of reversible functional impairment related to patients' lymphoma. • Conducting serial frailty assessments in patients undergoing CAR T-cell therapy is feasible.
Trando et al. [20]	Not described	• ECOG on assessment	• The rates of CRS and ICANS were similar between subjects > 70 years old and ≤ 70 years old. • The study suggests that old and frail patients do not have an increased incidence of CRS or ICANS and, thus, it is safe for them to receive CAR T-cell therapy. • The study reported that age stratification (≤ 70 vs. > 70) did not result in a statistically significant difference in PFS or OS • The study found stratification by baseline ECOG status (0–1 vs. 2–4) to be associated with a statistically significant difference in PFS and OS.

nature of this patient population, the expanding role of CAR T-cell therapy in differing haematological malignancies and their propensity for frailty, using a dual pre-assessment such as the CAR-HT score with a geriatric assessment could be an important method in predicting poor outcomes and minimising treatment effects such as infection in frail patients [7, 37, 38, 40].

However, consideration should be given to the use of CAR-HT in patients who have received multiple blood transfusions, as

this may affect their baseline ferritin level, which was one reason why it was adjusted in the B Cell ALL population [39]. The adaptability of this assessment tool shows flexibility in how the CAR-HT tool can be adjusted to be used in other haematological malignancies and in younger age groups. While the CAR-HT score has been used in adults only, an adjusted version called ALL-Hematotox (ALL-HT) has been developed for children, adolescents, and young adults with B cell ALL, with ferritin replaced by bone marrow disease status as part of the assessment [39].

The CAR-HT tool is available online and is easy to use [37], reducing time and resources, and with institutional recognition and coordination, implementing a geriatric assessment is possible [7]. Future research could focus on patient outcomes combining the use of a comprehensive geriatric assessment and the CAR-HT score, and offer the possibility of identifying toxicity risks, guiding post-CAR T-cell therapy management, and ameliorating the circumstances of frailty.

Perhaps unsurprisingly, no paediatric studies were identified in our scoping review. For many paediatric patients, their previous treatment has been complex, and post CAR T-cell therapy, their recovery can involve severe complications [14]. CAR T-cell therapy in paediatrics has not progressed as rapidly as in adults. There are significant challenges that need to be overcome to gain access to this treatment, such as complicated production logistics, limited access to clinical sites, financial issues, and a restrictive criterion regarding patient suitability [41]. CAR T-cell therapy in this patient population is mainly used in the setting of relapsed/refractory B Cell ALL. Nonetheless, there is increasing research in patients with other high-risk malignancies [41, 42]. Moreover, there is a paucity of research in the areas of frailty and sarcopenia in paediatrics [12, 43], however, sarcopenia can be a common problem in paediatric patients with a haematological malignancy and can result in prolonged hospital stays, decreased physical activity, and declined physical outcomes [43]. Sarcopenia is also a prognostic indicator for invasive fungal infection [43], which is particularly relevant in the CAR T-cell therapy setting given its association with the risk of infection [38]. Guidelines on managing paediatric patients receiving CAR T-cell therapy recommend that patients have an acceptable performance status according to the relevant treatment protocol and the institution's guidelines, with evaluation from ICU clinicians and neurologists to help guide patient selection [42].

There is a need for prospective studies and clinical trials in paediatrics and young adults concerning toxicity moderation and strategies to optimise patients' condition prior to CAR T-cell therapy [14]. Patients of all ages will benefit from CAR T-cell therapy [35], and decisions to treat should be based on a comprehensive assessment, something which future research needs to focus on within the haematology malignancy paediatric population. CAR T-cell therapy is a revolutionary new treatment, and its benefits need to be distributed equitably among all patient populations regardless of age, race, and ethnicity [35].

It is encouraging to note that there are clinical trials underway that would be relevant to assessing frailty in CAR T-cell therapy. Nonetheless, further research will be needed. Recommendations for future research include the identification of suitable patients for CAR T-cell therapy, how they are assessed, and what assessment to use [7, 23].

Other future research recommendations include studies that examine the evidence of benefit and value of geriatric assessments in CAR T-cell therapy [7], and the evaluation of quality of life and patient-centred outcomes to understand the impact of CAR T-cell therapy in older patients [44]. Further recommended research would be a prospective study into the impact of frailty and comorbidities on eligibility for CAR T-cell therapy using larger patient populations and longer-term term follow up [17, 21, 45]. The effects of CRS and ICANS on the cognition of frail patients and their neurotoxic effects are also an area that warrants future research [25].

Patients with the potential to receive CAR T-cell therapy face many uncertainties which may impact their mental health [46]. As frailty and depression can occur in a significant number of older adults [47], coupled with facing the impact of a worthwhile but potentially hazardous treatment such as CAR T-cell therapy, the incorporation of proper mental health assessment is worthy of future research. Identifying potential mental health difficulties prior to treatment may guide clinicians in preemptively having supports in place for vulnerable patients [46].

Finally, the need for patient and public involvement in CAR T-cell research demands more attention [44]. By incorporating patients and their care givers into CAR T-cell research planning, the relevance of findings could be improved [48]. Moreover, patients feel the ultimate impact of the success or failure of cancer treatments, particularly with CAR T-cell therapy where further treatment choices would not be curative. Essentially, appropriate assessment allows clinicians to prevent over-treating frail patients or under-treating patients who may have some of the hallmarks of frailty but are robust enough to receive the treatment [49].

This scoping review has some limitations. The various frailty assessment tools used in the studies made comparisons between studies difficult. In addition, the study designs were primarily retrospective, thus providing limited evidence.

5 | Conclusion

Our review has found a wide variation in assessing frailty before CAR T-cell therapy, thus requiring a standardised approach. An appropriate frailty assessment before CAR T-cell therapy facilitates the effective use of resources and enables proper patient selection. Without a standardised approach, clinicians could use a comprehensive geriatric assessment tailored to incorporate the CAR-HT. Combining the use of a comprehensive geriatric assessment and the CAR-HT score offers the possibility of identifying toxicity risks, guiding post-CAR T-cell therapy management, and ameliorating the circumstances of frailty.

Author Contributions

J.C.: conceptualisation, methodology, investigation, analysis, writing original draft, review, and editing. J.Mc.G., D.C., and A.B.:

conceptualisation, methodology, investigation, review. M.D.: conceptualisation, methodology, investigation, review and editing, supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data supporting this study is available publicly in CINAHL, Cochrane, Embase, Medline, PubMed, Google Scholar, clinicaltrials.gov, clinicaltrialsregister.eu and euclinicaltrials.eu as described in the Supporting Information.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Study Protocol for Role of Frailty in Assessing Eligibility for CAR T-Cell Therapy in Haematology. **Data S2:** Plain language summary.