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REVIEW ARTICLE

VIA MEDICA

Identifying frailty in older people living with diffuse large B-cell lymphoma: a systematic review

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is a common neoplasm in older people; in this group, personalized therapies are important because while some patients are frailer, others are fitter. However, knowledge is lacking as to which frailty identification tools are most commonly used in older patients living with DLBCL. The aim of this systematic review was to address this knowledge gap.

Material and methods: We searched the PubMed, EMBASE, and Cochrane databases and Google Scholar for studies published before December 2022. We included studies conducted with DLBCL patients aged 60 years or older, where a frailty classification (i.e. fit, unfit, or frail) had been reported in the context of prognostication and/or personalization of treatment.

Results: Sixteen studies were included in our review, with a total of 8,705 DLBCL patients (mean age 76 years, 54% men). Overall, 42% were classified as 'frail', and 40% as 'fit'. The most frequent frailty identification method was the Comprehensive Geriatric Assessment (CGA) (simplified: 75%, full: 13%), followed by the physical phenotype (6%) and the cumulative deficits index (6%) tools. The most common CGA domains utilized in the classification of frailty were the evaluation of basic activities of daily living (86%), instrumental activities of daily living (63%), comorbidities (81%), and geriatric syndromes (19%).

Conclusion: Two in five DLBCL patients aged 60 years or older were classified as frail, and an almost equal proportion as fit, most commonly post-application of simplified CGA. More studies are required to validate specific frailty identification instruments in this population.

Key words: frailty, geriatric oncology, comprehensive geriatric assessment, diffuse large B-cell lymphoma

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Introduction

The geriatric evaluation of older cancer patients is very important in order to guide oncological treatment decisions and provide opportunities for non-oncological management [1]. A systematic study that included hematological malignancies found that after a geriatric assessment, the oncological treatment plan was altered in a median 31% of patients [2].

The gold standard geriatric assessment is the Comprehensive Geriatric Assessment (CGA), which is

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a multi-dimensional diagnostic process focused on determining an older person's medical, functional and psychosocial capabilities in order to develop a coordinated and integrated plan for treatment and follow-up [3]. While the identification of frailty is an indication for CGA, CGA can also help in placing patients along the fitness-frailty continuum [4], informing patient optimization strategies, helping to personalize treatments, and improving prognostication in older oncological patients [5–8].

Although CGA offers a more complete perspective of an older patient [9], over the past two decades multiple frailty identification tools have emerged in clinical practice and research [10], the most commonly used being the phenotype and the cumulative deficits (frailty index) models. The phenotype identifies physical frailty when three or more of the following are present: exhaustion, shrinkage (unintentional weight loss), weakness (low handgrip strength), slowness (low gait speed), and low physical activity [11, 12]. The cumulative deficits model measures the proportion of health deficits present in an older individual from a list of 30–70 possible deficits, wherein a higher proportion indicates greater frailty [13, 14].

Diffuse large B-cell lymphoma (DLBCL) accounts for more than 30% of non-Hodgkin lymphomas (NHL), and its frequency is higher in those over 60 years of age [15]. Importantly, even in older people, it is a potentially curable disease if chemotherapy is administered at the appropriate doses and if the adverse reactions to treatment are minimized [16]. The efficacy and safety of DLBCL treatment is difficult to predict in older people for various reasons, including changes in the pharmacokinetics and pharmacodynamics of drugs associated with the aging process, the presence of comorbidities, polypharmacy, and social factors. The International Society of Geriatric Oncology (SIOG) recommends CGA with the aim of detecting previously unidentified impairments, predicting adverse reactions related to chemotherapy and overall mortality, and improving cancer treatment selection [17]. The SIOG in an expert opinion considered CGA as an important instrument in evaluating older/frail patients and choosing appropriate therapies in patients with DLBCL [18].

In 2019, the SIOG recommended that CGA be used in patients with prostate cancer, with the aim of being classified into three groups: 'healthy' or 'fit' patients, who should have the same treatment options as younger patients; 'vulnerable' patients who are candidates for geriatric optimization interventions, which if successful could receive standard treatment; and 'frail' patients with major impairments who should receive adapted or palliative treatment [19]. Currently, knowledge is lacking as to which frailty identification/classification tools are most commonly used in older patients living with DLBCL [20]. The objective of this systematic review was to address this knowledge gap.

Material and methods

We searched PubMed, Google Scholar and the Cochrane Database of Systematic Reviews for studies related to patients aged 60 or more years living with DLBCL, published before December 2022. Case reports, editorials, comments, and reviews were excluded. Our study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [21] (Supplementary Table 1: *see* this article on the journal's website).

Search strategy

The search terms were "Comprehensive geriatric assessment", "elderly", "diffuse large B-cell lymphoma", and "frailty".

Inclusion criteria

We included studies conducted with DLBCL patients aged 60 years or older, where a frailty classification (fit, unfit/vulnerable, frail) had been reported using CGA or any frailty identification tool in the context of prognostication and/or personalization of treatment.

Quality assessment

The quality of observational studies and randomized controlled trials was appraised with STROBE [22] and the Consolidated Standards of Reporting Trials (CONSORT) [23], respectively. Two investigators independently evaluated the quality of the studies.

Data extraction

By using a common data extraction template, all relevant information was independently abstracted from the selected studies by both reviewers. Information was collated on study characteristics including authors' names, country, year of publication, design, sample size, and the frailty identification method used.

Statistical analysis

For each study, the proportions of frail/vulnerable/fit patients were ascertained and averaged across studies.

Results

Sixteen studies were included, with a total of 8,705 DLBCL patients (mean age 75.9 years, 53.8% men). Figure 1 shows a flowchart of these studies. Nine studies were observational (cohort) and the other seven were non-randomized clinical trials (*see* Table I). The 16 studies were conducted in Italy [24–31], China [32–34], Australia [35], Taiwan [36], Norway [37], Mexico [38], and Canada [39].

In 11 studies, patients were classified into three categories (fit, unfit, or frail), while in the other five studies, they were classified into two groups (fit or frail). One study

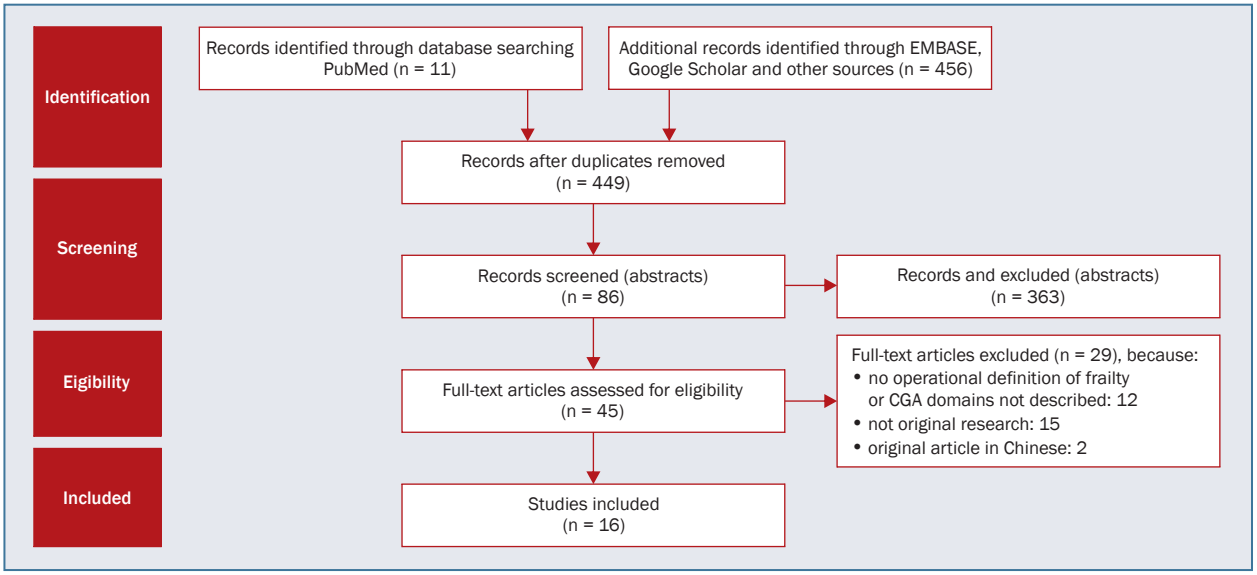

Figure 1. Study screening flowchart; CGA — Comprehensive Geriatric Assessment

Table I. Characteristics of included studies

Study	Country	Type of study	Age (mean)	Sex (male %)	Number of patients	Frailty classification			Quality assessment: STROBE [%]
						Frail [%]	Unfit	Fit [%]	
Zhang et al. (2022)	China	Non-randomized clinical trial	73	52	31	4 (12.9)	10	17 (54.8)	83.3
Vijenthira et al. (2022)	Canada	Cohort	75	57.1	5,527	2,699 (48.8)		2,828 (51.2)	93.3
Xu et al. (2022)	China	Non-randomized clinical trial	80	77	30	24 (80.0)	6	(0)	96.7
Bocci et al. (2022)	Italy	Non-randomized clinical trial	84	64	22	22 (100.0)		(0)	93.3
Merli et al. (2021)	Italy	Cohort	76	50	1,207	221 (18.3)	334	652 (54.0)	90
Isaksen et al. (2021)	Norway	Cohort	79	52	747	228 (30.5)	265	254 (34.0)	90
Bai et al. (2020)	China	Non-randomized clinical trial	69	57.7	78	28 (35.9)	5	45 (57.7)	76.6
Chou et al. (2020)	Taiwan	Cohort	73	57.9	76	27 (35.5)		49 (64.5)	80
Ong et al. (2019)	Australia	Cohort	73	55.8	138	52 (37.7)	29	57 (41.3)	96.7
Storti et al. (2018)	Italy	Non-randomized clinical trial	81	58	45	45 (100.0)		(0)	90
Lastra-German et al. (2018)	Mexico	Cohort	70	42.9	49	20 (40.8)	23	6 (12.2)	83.3
Tucci et al. (2015)	Italy	Cohort	77	52.6	173	66 (38.2)	28	79 (45.7)	90
Merli et al. (2013)	Italy	Non-randomized clinical trial	78	43	318	94 (29.6)		224 (70.4)	90

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Table I (cont.). Characteristics of included studies

Study	Country	Type of study	Age (mean)	Sex (male %)	Number of patients	Frailty classification			Quality assessment: STROBE [%]
						Frail [%]	Unfit	Fit [%]	
Marchesi et al. (2013)	Italy	Cohort	78	49.32	73	21 (28.8)	28	24 (32.9)	90
Spina et al. (2012)	Italy	Non-randomized clinical trial	75	41	100	13 (13.0)	32	55 (55.0)	90
Olivieri et al. (2012)	Italy	Cohort	74	50.5	91	15 (16.5)	22	54 (59.3)	83.3

STROBE — Strengthening the Reporting of Observational studies in Epidemiology

used the term "superfrail" referring to patients with ADL ≤4; IADL ≤5; age ≥80 years; 1 CIRS grade 3 or >8 CIRS grade 2 [28]. Overall, 41.7% were classified as 'frail', and 39.6% as 'fit', with significant variability across studies (Table I).

The most frequent frailty identification method used was the CGA (simplified: 75%, full: 13%), followed by the physical phenotype (6%) and the cumulative deficits (6%) models. The most common CGA domains used in the classification of frailty were the evaluation of basic activities of daily living (BADLs) (86%), instrumental activities of daily living (IADLs) (63%), comorbidities (81%), and geriatric syndromes (19%). The most commonly used disability tools were the Katz Activities of Daily Living scale (ADL) (81%) [40], and the Lawton Instrumental Activities of Daily Living scale (IADL) (63%) [41]. The most common comorbidity scale was the Cumulative Illness Rating Scale-Geriatric (CIRS-G) (69%) [42] (Supplementary Table 2: *see* this article on the journal's website).

In three studies, the aim was to validate the use of a simplified CGA (sCGA) at diagnosis and to integrate it into a prognostic score for older patients with DLBCL [25, 29, 37]. The study by Merli et al. [25] validated an sCGA model that identified those who were frail, and found that poor results were achieved in this group only if they were treated with rituximab-containing combination chemotherapy. Isaksen et al. [37] validated an sCGA model that managed to identify frail patients, who, when treated with R-CHOP, achieved better survival, without a significant increase in treatment-related mortality. Although full-dose R-CHOP was associated with superior survival in fit patients, it was not better than R-miniCHOP in the unfit and the frail [37]. Tucci et al. validated a CGA model that was able to identify older DLBCL non-fit patients in whom curative treatment was not better than palliation [29]. Lastra-German et al. [38] used modified frailty phenotype criteria, and Vijenthira et al. [39] used a frailty index [43].

Discussion

Our systematic review found that two in five DLBCL patients aged 60 years or older were classified as frail, and an almost equal proportion were classified as fit, most commonly post-application of simplified CGA, which in turn most frequently consisted of disability and multimorbidity scales (ADL, IADL and CIRS-G). The data suggests that the population of older people living with DLBCL has remarkable biological heterogeneity, and that when it comes to treatment, one size most certainly does not fit all.

This means that a geriatric assessment is highly likely to add value in terms of patient optimization, treatment personalization, and prognostication.

Currently, five CGA-based frailty classification schemes have been described in older cancer patients. Three of them classify patients into fit, vulnerable, or frail [5, 44–46]. The Lymphoma Italian Foundation (FIL) has also proposed an sGCA that has three categories (fit, unfit and frail) [47]. This has been used in patients with lymphoma, takes less than 10 minutes to perform, and has been used in the context of treatment options and outcomes in patients with DLBCL [24, 25]. It therefore seems the most optimal method of geriatric assessment devised so far. Ferrat et al. [48] have described a classification system which they call 'latent class typology', which classifies patients into four groups (relatively healthy or 'LC1', malnourished or 'LC2', cognitively and/or mood impaired or 'LC3', and globally impaired or 'LC4'). The performance of four frailty classifications has recently been compared, and the authors concluded that all had good prognostic performance in both older inpatients and older outpatients living with various cancers [5].

Our study found that most studies used sCGA to categorize frailty in older people living with DLBCL, which mostly uses ADL, IADL and CIRS-G; this mirrors the FIL model [25, 29, 49, 50], which consists of evaluating ADL, IADL, chronological age (>80 years vs <80 years), and comorbidities assessed by CIRS-G (adjusted for hematological comorbidities).

The operational criteria for classifying patients as frail are those aged ≥80 years with dependence in multiple ADL (score <6), IADL (score <8), and/or with significant comorbidities (≥1 comorbidity with a score of 3–4, ≥5 comorbidities with a score of 2 [47]. The sCGA FIL model adds the IPI (International Prognostic Index), the Elderly Prognostic

Index (EPI), and hemoglobin levels [47]. Currently, other instruments are validated for use in non-Hodgkin lymphoma patients, among which are the ACA index and IADL--ACA [age, albumin <3.7 g/dL, Charlson Comorbidity Index (CCI), IADL], Geriatric-8 (G8), fTRST (Flemish version of the triage-screening tool), Vulnerable Elders Survey (VES-13), CRASH (Chemotherapy Risk Assessment Scale for High--Age Patients), and CARG-TT (Cancer Aging and Research Group toxicity tool) [47].

In 2021, Tavares et al. [51] published a systematic review on treatment of very elderly (>80 years) patients with DLBCL. They found that of 38 studies (13 retrospective and 25 phase II/III clinical trials), only 16% used CGA as an inclusion criterion or as a guide to therapeutic regimen choice [51].

Our study found that the average prevalence of frailty in older patients living with DLBCL was 42%. Handforth et al. published in 2015 a systematic study of a total of 20 studies evaluating 2,916 older patients with cancer, also finding a prevalence of frailty of 42%. Another finding was that 80% of the studies used CGA as the reference standard for frailty identification, 16% used the phenotype model, and 4% used both CGA and the phenotype model. It should be noted that in Handforth et al.'s study [52], only 10% of patients were living with lymphoma.

Our study has some limitations. The included studies did not elaborate on important aspects of the implementation of CGA, such as the average time required for the evaluation nor which health professionals performed it. Since most of the studies we included implemented sCGA as opposed to full CGA, the time required may be an important practical consideration. Furthermore, our study could not compare different versions of sCGA in their ability to predict clinical outcomes (e.g. adverse events, overall survival, progression-free survival, and adverse drug reactions), and there is scope for future studies to help validate, homogenize and standardize frailty stratification models in geriatric oncology, in such a way that the categorization of patients would be accurate and of high patient and professional value.

In the meantime, the identification of frailty in older DLBCL patients by means of CGA is an opportunity for patient optimization and treatment personalization. More studies are required to validate specific frailty identification instruments in this population.

Article information and declarations

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TJO — concept and design; TJO, RRO — acquisition, analysis, interpretation of data, drafting of manuscript, critical revision of manuscript for important intellectual content. RRO — supervision.

Conflict of interests
The authors declare no conflict of interest.

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Ethic statement
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

Supplementary material
Supplementary Tables 1 and 2.

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