VIA MEDICA

REVIEW ARTICLE

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Comprehensive geriatric assessment and clinical outcomes of frail older adults with diffuse large B-cell lymphoma: a meta-analysis

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ABSTRACT

Introduction. Comprehensive geriatric assessment (CGA) is used to personalize cancer treatments in frail older adults. However, its utility to guide treatments in frail older patients with diffuse large B-cell lymphoma (DLBCL) is not well known. We performed a meta-analysis of evidence published in this area.

Material and methods. We searched PubMed and Google Scholar for studies published between January 2000 and January 2023 that included patients aged ≥ 65 years with a diagnosis of DLBCL who underwent CGA before treatment (CGA-modulated studies) and who did not (non-CGA-modulated studies). We evaluated clinical outcomes in frail/unfit patients in terms of complete response (CR), incidence of grade ≥ 3 toxicity, and 2-year overall survival (OS) in both types of studies.

Results. Fifteen studies [8 CGA-modulated (n = 733, median age 76, 54% male, 52% frail/unfit) and 7 non-CGA-modulated (n = 2447, median age 76, 52% male, 32% frail/unfit)] were included. In the CGA-modulated studies, the CR proportion of frail/unfit patients was 34% (95% CI 23–46%) *vs*. 28% (95% CI 19–38%) in the non-CGA-modulated studies (p = 0.436). Grade 3–4 hematological toxicity in frail/unfit patients was 26% (95% CI 5–55%) *vs*. 36% (95% CI 13–63%) (p = 0.583), respectively. Two-year OS of frail/unfit patients was 52% (95% CI 38–66%) *vs*. 27% (95% CI 19–36%) (p = 0.003), respectively.

Conclusions. Although the proportion of frail/unfit patients was lower in non-CGA-modulated studies, CGA-modulated studies reported higher OS. CGA could be useful to guide the treatment plan in older patients with DLBCL. Randomized clinical trials with standardized CGA instruments are necessary to confirm these findings.

Keywords: comprehensive geriatric assessment, diffuse large B-cell lymphoma, frailty, meta-analysis, older adults, outcomes

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type of malignant lymphoma and constitutes about 40% of non-Hodgkin lymphoma (NHL) cases. The mean age at onset is 65 years, and its incidence increases with age [1]. The standard therapeutic regimen is 6 courses of combined therapy with rituximab and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone). The 5-year overall survival (OS) rate is 50–60%, and complete response (CR) and 5-year OS decrease with age [2].

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Prognostic scores such as the International Prognostic Index (IPI) have been adopted in DLBCL patients. Among other criteria such as disease stage, the IPI considers older chronological age (> 60 years) and worse performance status [Eastern Cooperative Oncology Group (ECOG) Performance Status > 2] as markers of higher risk [3–5]. Rituximab-CHOP (R-CHOP) is standard first-line therapy. However, about 40% of older patients do not tolerate the standard dose of R-CHOP due to such causes as comorbidities, malnutrition, and the presence of other geriatric syndromes [6]. Frailty is defined as physiological vulnerability to stressors, is more related to biological than chronological age [7], and encapsulates many of the systemic dysregulations that are associated with poorer outcomes in geriatric oncology [8].

In frail older adults, the application of comprehensive geriatric assessment (CGA) has been shown to improve outcomes in the acute general hospital setting [9]. This is because CGA is a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional capabilities of older adults to develop a coordinated plan to maximize overall health with aging [2]. Therefore, by performing a CGA, the frailty status of an older adult can be improved, conferring more resilience before he/she experiences a planned stressor. This has been exemplified in prehabilitation of frail older adults undergoing elective surgery [10]. Some abbreviated CGA tools have been made available for implementation in research studies [11].

Comprehensive geriatric assessment is used to personalize cancer treatments in frail older adults. However, its utility to guide treatments in frail older DLBCL patients is not well known [12]. We performed a meta-analysis of evidence published in this area, with a specific aim to compare the outcomes of non-CGA-modulated studies versus CGA-modulated studies, in terms of CR, incidence of grade ≥ 3 toxicity, and 2-year OS.

Material and methods

We searched PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews for studies including DLBCL patients aged above 64 years. The research period ranged from January 2000 to January 2023. 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) [13] (Tab. S1 in supplementary file).

Search strategy

The search terms were "Comprehensive geriatric assessment", "diffuse large B-cell lymphoma", "chemotherapy", "immunochemotherapy", "Humanized anti-CD19 CART", and "frailty".

Inclusion criteria

Studies that met the following criteria were included a) patients equal to or older than 65 years and diagnosed with DLBCL; b) CGA was used to categorize patients into fit or unfit/frail, prospectively or retrospectively. "CGA-modulated studies" were those in which CGA was used to select patients (frail/unfit or fit) for a specific chemotherapy scheme. Those in whom this criterion was not used to qualify them for specific chemotherapy or was done retrospectively were called "non-CGA-modulated studies"; c) Studies reported clinical outcome data such as overall survival (OS), complete response (CR), and the incidence of at least grade 3 hematological toxicity [14].

Quality assessment

The quality of the studies was appraised according to the Reporting of Observational Studies in Epidemiology (STROBE) [15].

Statistical analyses

Outcomes of CGA-modulated studies were compared to those of non-CGA-modulated studies in frail/unfit patients. The statistical comparison of proportions was carried out with the Chi-square statistic.

When possible, overall estimates in the pooled analysis were obtained using Stata 13 software (Stata Corp LP, College Station, TX) and the Meta XL (www.epigear.com) add-in for Microsoft Excel [12]. A pooled prevalence was calculated with 95% confidence interval (CI) by combining estimates from selected studies based on a random-effects model [13]; this is a variant of the inverse of the variance method, and it incorporates intra- and inter-variability of studies. Heterogeneity between estimates was assessed using the I^2 statistic, which describes the percentage of variation across studies not caused by sampling error [16]. To perform the meta-analysis of two-year OS of frail/unfit patients in the studies, only those studies that reported such outcomes were selected.

Results

After screening 814 citations, 15 studies (8 cohort and 7 non-randomized clinical trials) were included (Fig. 1). The total number of patients was 3180, mean age 76.4 ± 4.1 years, and 53.2% were male. Eight studies were carried out in Italy [17–24], 3 in China [25–27], 1 in Australia [28], 1 in Japan [29], 1 in Mexico [30], and 1 in Norway [31] (Tab. 1).

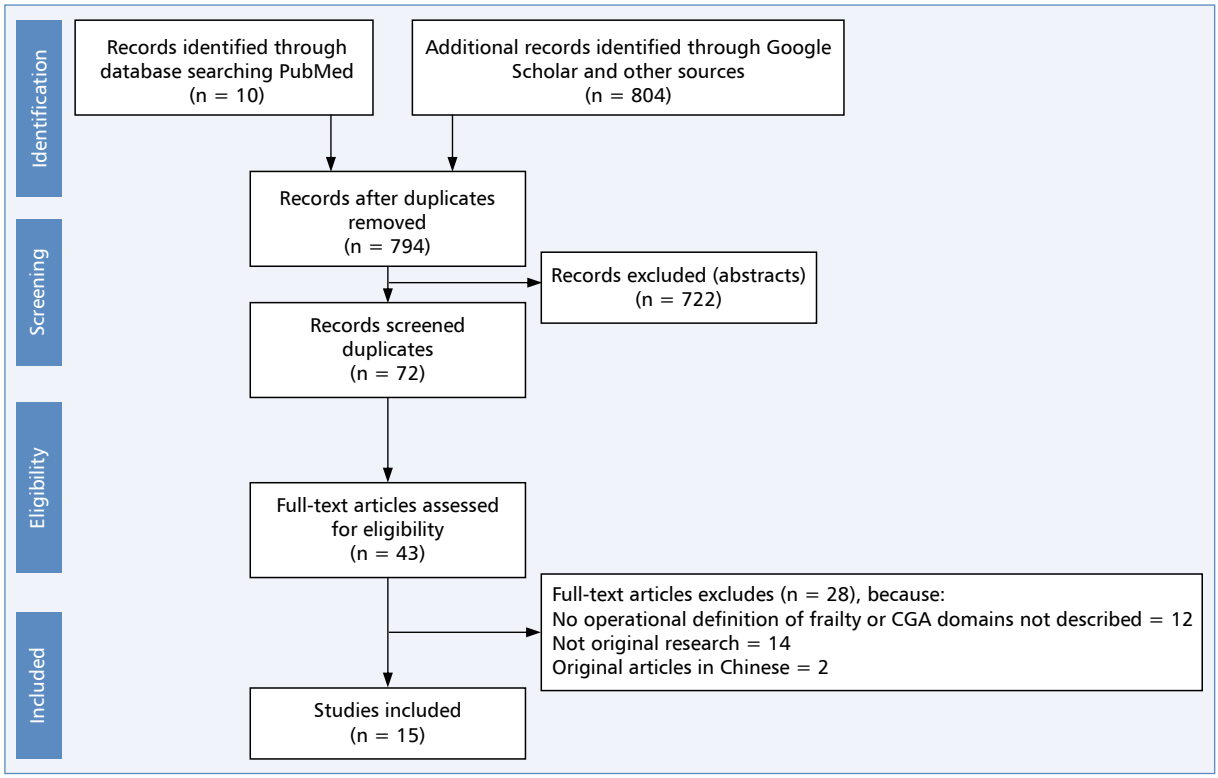

Figure 1. Study flowchart; CGA — comprehensive geriatric assessment

For the categorization of patients according to CGA, simplified CGA (sCGA) was used in 80% of the studies [17–28], full CGA [29, 31] in 13.3%, and the frailty phenotype model [30] in 6.7%. The instruments used for CGA and operational criteria for the identification of frail/unfit and fit patients are in Table S1 in the supplementary file. One study only included frail patients [20] (Tab. 1).

The prevalence of frail, unfit, and fit patients was 32% (95% CI 25–40), 27% (95% CI 21–32), and 47% (95% CI 38–58), respectively.

Eight studies were CGA-modulated (n = 733, median age 76, 54% male, 52% frail/unfit) and 7 non-CGA-modulated (n = 2447, median age 76, 52% male, 32% frail/unfit) (Tab. 2).

In five-eighths of CGA-modulated treatment studies *vs*. three-eighths of non-CGA-modulated treatment studies, two-year OS of frail/unfit patients was 52% (95% CI 38–66) and 27% (95% CI 19–36) (p = 0.003), respectively (Fig. 2). A meta-analysis of three-year or five-year OS was not performed because there were not enough studies reporting it (minimum 2 studies).

In six-ninths of CGA-modulated treatment studies *vs.* three-ninths of non-modulated treatment studies, the CR of frail/unfit patients was 34% (95% CI 23–46) and 28% (95% CI 19–38) (p = 0.436), respectively (Fig. 3).

In four-sixths of CGA-modulated treatment studies with *vs*. two-sixths of non-modulated treatment studies, grade 3–4 hematological toxicity in frail/unfit patients was 26% (95% CI 5–55%) and 36% (95% CI 13–63%) (p = 0.583), respectively (Fig. 4). While in two-fourths of CGA-modulated treatment studies *vs.* two-fourths of non-modulated treatment studies, grade 3–4 non-hematological toxicity in frail/unfit patients was 22% (95% CI 11–36%) and 31% (95% CI 25–37%) (p = 0.106), respectively (Fig. 5).

Discussion

We performed a metanalysis to compare the outcomes of non-CGA-modulated versus CGA-modulated studies in the treatment of frail/unfit older adults with DLBCL, in terms of CR, incidence of grade ≥ 3 toxicity, and 2-year OS. Although the proportion of frail patients was lower in non-CGA-modulated studies and the studies had no significant differences in CR or grade 3–4 hematological/non-hematological toxicity, CGA-modulated studies reported higher two-year OS.

Two systematic studies with similar findings have previously been published, with studies covering the period up to 2016 [32] and 2020 [33]. Regarding the usefulness of CGA as a guide for selecting a thera-

Table 1. Characteristics of included studies

Study	Country	Type of study	Age [median]	Sex [male %]	Number of patients	Prevalence of frailty [%]	Frailty criteria	Categories	Quality assessment: STROBE [%]
CGA-modulated studies									
Xu et al. (2022)	China	Non-randomized clinical trial	80	77	30	80	sCGA	Fit, unfit, frail	96.7
Bocci et al. (2022)	Italy	Non-randomized clinical trial	84	64	22	99	sCGA	Unfit, frail, "superfrail"	93.3
Bai et al. (2020)	China	Non-randomized clinical trial	69	57.7	78	36	sCGA	Fit, unfit, frail	76.6
Storti et al. (2018)	Italy	Non-randomized clinical trial	81	58	45	99	sCGA	Frail	90
Lastra-German et al. (2018)	Mexico	Cohort	70	42.9	49	41	Phenotype	Fit, unfit, frail	83.3
Merli et al. (2013)	Italy	Non-randomized clinical trial	78	43	318	29.6	sCGA	Fit, Frail	90
Spina et al. (2012)	Italy	Non-randomized clinical trial	75	41	100	13	sCGA	Fit, unfit, frail	90
Olivieri et al. (2012)	Italy	Cohort	74	50.5	91	16	sCGA	Fit, patients with comorbidities, frail	83.3
non-CGA-modulated studies									
Tanaka et al. (2022)	Japan	Cohort	79	52.6	78	53	Full CGA	Independent, dependent	80
Zhang et al. (2022)	China	Non-randomized clinical trial	73	52	31	13	sCGA	Fit, unfit, frail	83.3
Merli et al. (2021)	Italy	Cohort	76	50	1207	18	sCGA	Fit, unfit, frail	90
Isaksen et al. (2021)	Norway	Cohort	79	52	747	34	full CGA	Fit, unfit, frail	90
Ong et al. (2019)	Australia	Cohort	73	55.8	138	38	sCGA	Fit, unfit, frail	96.7
Tucci et al. (2015)	Italy	Cohort	77	52.6	173	38	sCGA	Fit, unfit, frail	90
Marchesi et al. (2013)	Italy	Cohort	78	49.32	73	28.77	sCGA	Fit, intermediate, frail	90

CGA — comprehensive geriatric assessment

Table 2. Treatment, comprehensive geriatric assessment, and outcomes for frail older adults with diffuse large B-cell lymphoma

Studies	Treatment	Complete response (CR)	Overall survival (OS)	Event-free survival (EFS)/progression--free survival (PFS)	Treatment-related mortality (TRM)	Adverse drug reaction (ADR)
CGA-modulated studies						
Xu et al. (2022)	Unfit or frail: ibrutinib, rituximab, lenalidomide	Complete response rate: Unfit/frail: 56.7% (95% CI 37.4–74.5), overall response: 66.7% (95% CI 47.2–82.7)	2 years: Unfit/Frail (66.7%; 95% CI 46.9–80.5)	PFS: 2 years: 53.3% (95% CI 34.3-69.1)	Missing	Hematological grade 3–4 toxicity: neutropenia (23%) thrombocytopenia (10%), and anemia (7%)
Bocci et al. (2022)	Metronomic all-oral DEVEC [prednisolone/deltacortene, vinorelbine (VNR), etoposide (ETO), cyclophosphamide] combined with i.v. rituximab (R)	Overall response (ORR) and complete remission rate (CRR): 64%	2 years: frail: 54% (95% CI 32–72)	EFS: 54% (95% CI = 32––72)	Missing	Treatment-related serious adverse events (27%)
Bai et al. (2020)	Fit: R-CHOP, unfit + frail: R-CHOP with reduced dose of anthracycline, R-CVP, or R-miniCHOP	Fit (84.4%), unfit + frail (51.5%) (p = 0.002)	2 years: fit (98%), unfit + frail (69%) (p = 0.0013). 3 years: fit (91%), unfit + frail (69%) (p = 0.021)	2 years PFS: fit (72%), unfit + frail (69%) (p = 0.77). 3 years PFS: fit (72%), unfit + frail (35%) (p = 0.0013)	0%	Hematological grade 3–4 toxicity: fit (51.1%), unfit + frail (54.5%) (p > 0.05).
Storti et al. (2018)	Frail: bendamustine and rituximab	Frail: 53%	2 years: Frail (51%)	The median progression-free survival: 10 months	Missing	Total grade 3–4 toxicity (51.1%). Hematological grade 3–4 toxicity 46.7%). Non-hematologicalal grade 3–4 toxicity (15.6%)
Lastra-German et al. (2018)	Fit: R-CHOP, unfit: R-CHOP, frail: R-COP	Fit (66.6%), unfit (78.3%), frail (40.0%) (p = 0.121)	2 years: fit (87%, unfit (82%), frail (59%) (p = 0.159)	Mean 2-year disease-free survival (DFS): frail (87%), fit (100%) (p = 0.287).	Missing	Grade 3–4 hematological toxicity: fit (83.3%), unfit (65.2%), frail (45%) (p = 0.192). Nonhematological toxicity: fit (33%), unfit (65%), frail = 70%. (p = 0.445)
Merli et al. (2013)	Treatment of frail patients: polychemotherapy with anthracyclines (includes CHOP, mini-CEOP, CNOP, P-VEBEC); polychemotherapy without anthracyclines (includes CVP); mono-chemotherapy, radiotherapy, palliation	NR	Worse OS, hazard ratio: frail *vs.* fit: 3.09 (95% CI 2.2––4.33; p < 0.001)	NR	NR	Treatment-related complications/toxicity (22% of deaths, 18% of treated patients)

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Table 2 cont. Treatment, comprehensive geriatric assessment, and outcomes for frail older adults with diffuse large B-cell lymphoma

Studies	Treatment	Complete response (CR)	Overall survival (OS)	Event-free survival (EFS)/progression--free survival (PFS)	Treatment-related mortality (TRM)	Adverse drug reaction (ADR)
Spina et al. (2012)	A. No comorbidities: rituximab ± CHOP; Mild cardiopathy (NYHA class II or CIRS-G grade 2): R ± CEOP; Severe cardiopathy (NYHA class III/IV or CIRS-G grade ≥ 3): R ± CVP B. 100%, if ADL 6 or IADL 7–8; 75%, if ADL 5 or IADL 6; % (p = 0.11) 50%, if ADL < 5 or IADL < 5	Fit (85%), unfit (72%), frail (85%) (p = 0.34); > 80 y (83%); all (70.6%)	5 years: fit (76%), unfit (53%;), frail (29%) (p = 0.001)	5y EFS: 80% (> 80 y: 67%, p = 0.96); 5 y EFS: 52% (> 80 y: 46%, p = 0.06)	4%	Total grade 3–4 toxicity: fit (31%), unfit (48%), frail (58%) (p = 0.11). Toxic deaths (5%, 9%, and 11%, respectively) (p > 0.05)
Olivieri et al. (2012)	Fit: R-CHOP, intermediate: R-CDOP, frail: Mini-CHOP	Fit (81.5%), patients with comorbidities (64%), Frail (60%). Fit *vs.* frail + patients with comorbidities (p = 0.0408)	37 months. Fit (34%), patients with comorbidities (9.5%), frail (7.1%). Fit *vs.* frail + patients with comorbidities (p = 0.0044)	5 y EFS: fit (18.9%) patients with comorbidities (9.5%), frail (7.1%)	Early toxic deaths: fit (1.9%), patients with comorbidities (9.2%), frail (6.7%). Fit *vs.* frail + patients with comorbidities (p < 0.05	Hematological grade 3–4 toxicity: fit (7%), patients with comorbidities (0%), frail (7%). Fit *vs.* patients with comorbidities + frail (p > 0.05)
Non-CGA-modulated studies						
Tanaka et al. (2022)	CHOP-like (R-CHOP, R-CHOP + RTx; R-THPCOP; R-EPOCH; R-ECOP; R-CHOEP, CHOP) = 72 (92.3); low toxicity regimen (R-mini-CHP, = 6 (7.7); R-oral sobuzoxane and etoposide)	Dependent (70.7%); independent (78.4%)	4-year survival rate: independent (72.7%); dependent (56.9%).	Missing	Missing	Non-hematological toxicity: dependent (53.7%), independent (16.2%);
Zhang et al. (2022)	Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy	ORR, CR, and PR rates in the fit group were 88.2%, 58.8%, and 29.4%, respectively, while the ORR, CR, and PR rates in the unfit/frail group were 64.3%, 42.9%, and 21.4%, respectively	Median OS in the fit group (not reached) was better	The fit group had a higher median PFS rate than the unfit/frail group (11.4 months *vs.* 7.0 months; p = 0.037)	Missing	Hematological grade 3–4 toxicity: fit (23.5%), unfit/frail (50%)
Merli et al. (2021)	Full dose: R-CHOP, R-COMP, R-VNCOPB, R-DAEPOCH, R-CNOP, R-CEOP Reduced dose: R-mini-CHOP and similar Palliative therapy: R-Bendamustine, R-CVP, R-other (without anthracycline), rituximab only RT, cyclophosphamide, surgery, etoposide, prednisone, metronomic chemotherapy	NR	3 years: fit (87%), unfit (69%), frail (42%) (p < 0.001)	NR	NR	NR

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Table 2 cont. Treatment, comprehensive geriatric assessment, and outcomes for frail older adults with diffuse large B-cell lymphoma

Studies	Treatment	Complete response (CR)	Overall survival (OS)	Event-free survival (EFS)/progression--free survival (PFS)	Treatment-related mortality (TRM)	Adverse drug reaction (ADR)
Isaksen et al. (2021)	Treatment intensity was divided into 4 categories: full-dose R-CHOP, attenuated R-CHOP, anthracycline-free regimen, and no chemotherapy	Missing	2 years: fit (82%); unfit (47%); frail (14%); $p < 0.001$).	Missing	Missing	NR
Ong et al. (2019)	Fit: R-CHOP (55/57), R-CHEP (1/57), R-PACEBOM (1/57), unfit: R-CHOP (16/29), R-miniCHOP (8/20), R-CEOP (3/29), R-CHEP (1/57), frail: R-CHOP (34/52), R-miniCHOP (11/52), R-CEOP (6/52), R-CNOP (1/52)	Missing	2 years: fit (90%), unfit (71%), frail (56%). 3-year: fit (82%), unfit (60%), frail (53%)	PFS: 2-year fit (79%); unfit (64%), frail (65%). 3-year fit (66%), unfit (58%), frail (46%)	Fit (4%), unfit (10%), frail (10%)	Any grade ≥ 3 toxicity: fit = 72%, unfit = 62%, frail = 79%
Tucci et al. (2015)	Unfit and frail: full-dose therapy (CHOP or CHOP-like regimens with rituximab). Remaining patients received palliation [low-dose chemotherapy without anthracyclines, and prednisone (COP), low-dose COP], rituximab as a single agent, corticosteroids alone, oral mono chemotherapy or anthracycline-based cycles at a relative dose intensity less than 70%)	ORR, overall response rate (complete remission + partial remission): curative unfit = 14 (82%), frail 13 (72%), palliative: unfit = 7 (64%), frail = 25 (52%)	2 years: fit (84%), non-fit (frail + unfit) (47%) $p < 0.0001$	Missing	Missing	Nonhematological toxicity of grade 3–4: curative or palliative intent (45% *vs.* 38%; $p = 0.3$)
Marchesi et al. (2013)	Curative anthracycline-based treatment, Full-intensity R-CHOP, attenuated R-CHOP, conservative without anthracyclines (R-CVP)	Irrespective of the type of treatment, the overall response (OR), the complete response (CR), and the failure rates were 80.5%, 55.2%, and 19.5%, respectively	Irrespective of the type of treatment, "fit" and "intermediate" patients had similar outcomes, whereas "frail" patients showed a significantly worse 2-year OS rate than the other two patient categories ($p < 0.001$)	2-year OS and PFS rates were 39.7%	Missing	Curative *vs.* conservative treatments and the CGA stratification did not significantly affect the occurrence of grades 3–4 toxicities and toxic death incidence

ADLs — activities of daily living; CEOP — cyclophosphamide, epirubicin, vinblastine, prednisone; CHOEP — addition of etoposide to CHOP mini-CHP subtraction of vincristine from 50% dose CHOP; CIRS-G — Cumulative Illness Rating Scale-Geriatric; CNOP — cyclophosphamide, mitoxantrone, vincristine, prednisone; COP — cyclophosphamide, vincristine, prednisolone; CVP — cyclophosphamide, vincristine, prednisone; DA-R-EPOCH (o R-DAELPOCH) — rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DEVEC — prednisolone–etoposide–vinorelbine–cyclophosphamide; ECOP — addition of etoposide to COP; EPOCH — consists of continuously infused etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, IADLs — instrumental activities of daily living; NYHA — New York Heart Association; PACEBOM — prednisolone, doxorubicin, cyclophosphamide, etoposide, bleomycin, vincristine, and methotrexate; P-VEBEC — prednisone, vinblastine, epirubicin, bleomycin, etoposide, cyclophosphamide; R — rituximab; R-CHOP — rituximab + CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone); R-COMP — rituximab, cyclophosphamide, vincristine, myocet, prednisone; R-COP — rituximab + cyclophosphamide, vincristine, and prednisolone; RTx — radiotherapy; R-VNCOP-B — rituximab, etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisolone, bleomycin; THPCOP — addition of pirarubicin to COP

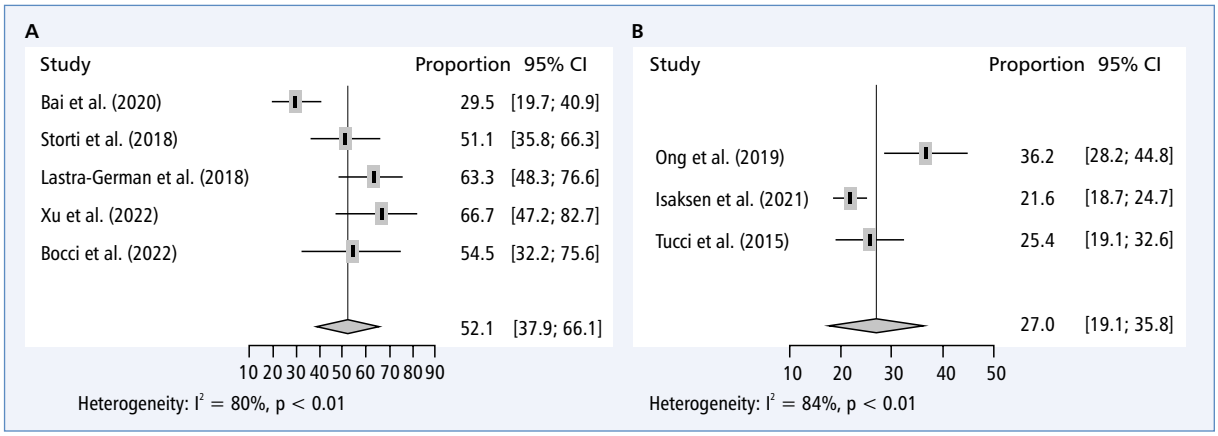

Figure 2. Forest plot of frequencies of two-year overall survival (OS) of frail/unfit patients; **A.** OS2: comprehensive geriatric assessment (CGA)-modulated studies; **B.** OS2: Non CGA-modulated studies; CI — confidence interval

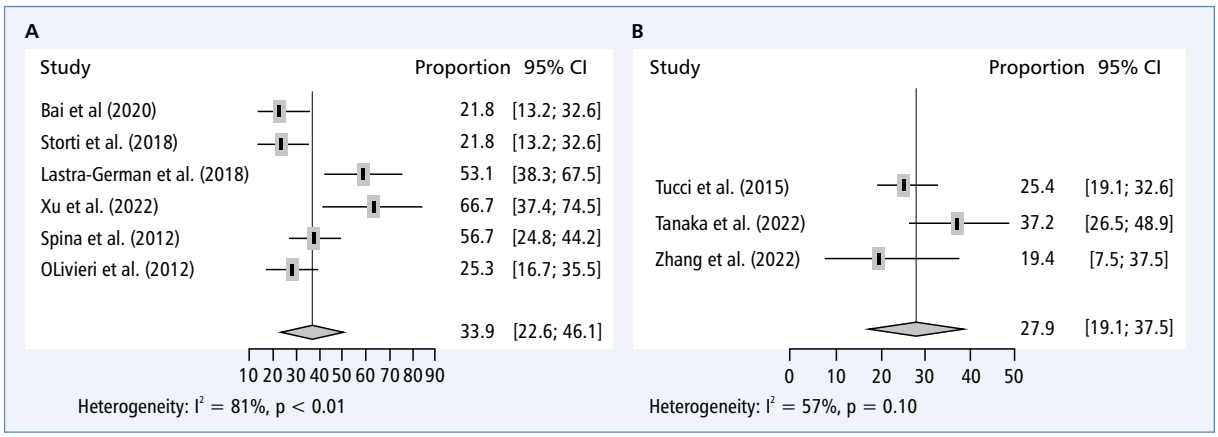

Figure 3. Forest plot of frequencies of complete response (CR) of frail/unfit patients; **A.** CR: comprehensive geriatric assessment (CGA)-modulated studies; **B.** CR: Non CGA-modulated studies; CI — confidence interval

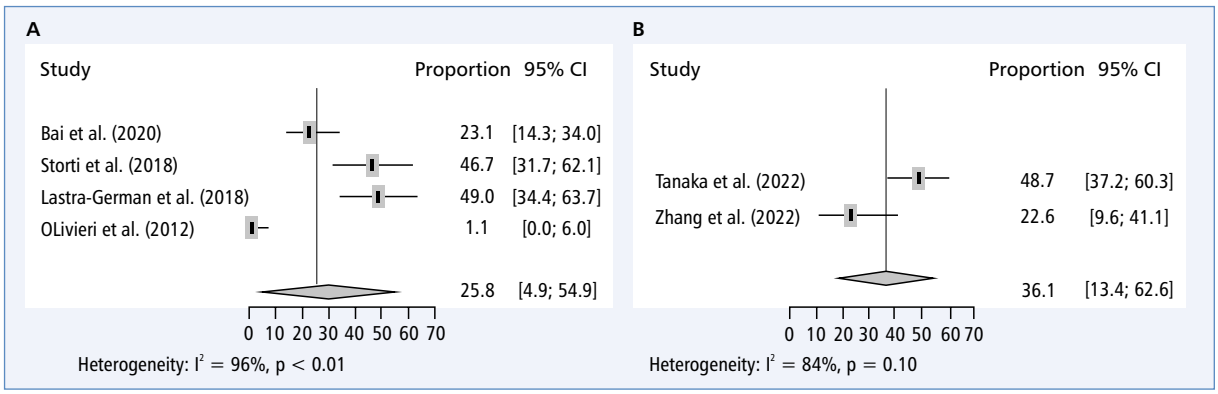

Figure 4. Forest plot of frequencies of grade 3–4 hematological toxicity in frail/unfit patients; **A.** Grade 3–4 hematologic toxicity in frail/unfit patients [comprehensive geriatric assessment (CGA)-modulated studies]; **B.** Grade 3–4 hematologic toxicity in frail/unfit patients (Non CGA-modulated studies); CI — confidence interval

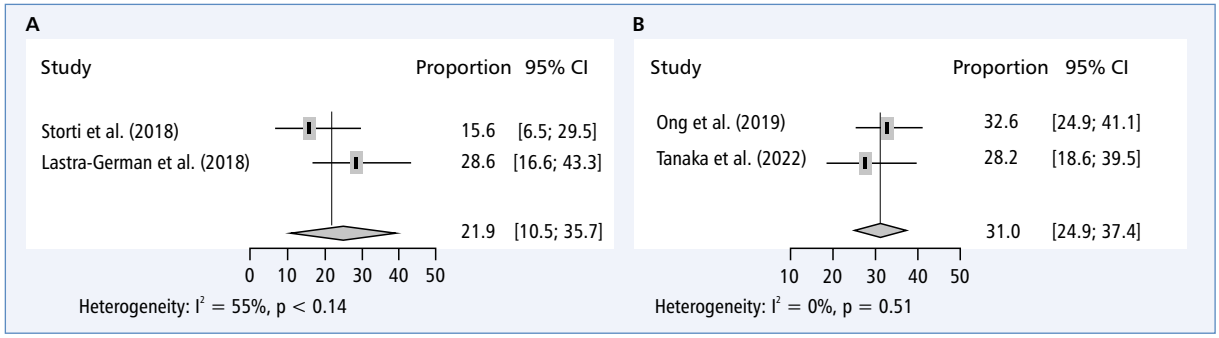

Figure 5. Forest plot of frequencies of grade 3–4 non-hematological toxicity in frail/unfit patients; **A.** Grade 3–4 hematologic toxicity in frail/unfit patients [comprehensive geriatric assessment (CGA)-modulated studies]; **B.** Grade 3–4 hematologic toxicity in frail/unfit patients (non CGA-modulated studies); CI — confidence interval

peutic scheme in older DLBCL patients, there are currently two approaches. The first supports the performance of CGA as a guide in the selection of a therapeutic scheme based on risk stratification [34]. The other approach, based on a 2019 consensus, does not recommend using CGA in determining the chemotherapy regimen for older DLBCL patients. However, it concedes that CGA is useful in identifying issues that may have been overlooked and clarifies that using CGA is not ruled out in cancer patients [35].

There may be mechanisms by which categorization of patients with CGA could improve outcomes, especially in frail DLBCL patients. This strategy could reduce overtreatment in frail and undertreatment in fit patients. Frail patients have been reported to have high treatment-related mortality, especially if treated with full-dose regimens [19, 29, 36]. Frail patients have high rates of treatment discontinuation due to adverse reactions, which leads to disease progression that affects their survival, and the low tolerance to chemotherapy can be partly explained by other comorbidities [29]. The severity of these comorbidities is detected during a CGA, in which instruments such as the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) can identify frailty when grade 3–4 comorbidities are present [37]. Modifying the dose of chemotherapy (R-CHOP) has been shown to decrease adverse reactions to chemotherapy in frail patients, without impairing the efficacy of treatment [18, 30]. In this regard, it has been postulated that the explanation for the reduced doses of anthracycline in frail patients having the same therapeutic results is that the half-life of this medication is prolonged due to the aging process and patients' comorbidities [12, 38, 39].

Comprehensive geriatric assessment is potentially one of the strategies to predict chemotherapy tolerability, that is, it could have prognostic capacity with regard to the severity of adverse reactions associated with chemotherapy. In our study, no significant differences were found in grade ≥ 3 hematological and non-hematological toxicity. The latter may be due to only 2 studies on each side of the comparison. Regarding instruments to predict adverse reactions in DLBCL patients, two strategies have been described, among which are the Elderly Prognostic Index (EPI) [22] and the Norwegian score [31]. However, it should be noted that the last two proposals contain data from CGA (e.g. activities of daily living and CIRS-G).

This study has some limitations. For example, the frail/unfit were compared as if they were a single group because most of the studies reported their data in this way. The analysis was not performed only with frail patients due to a small number of studies with such data. For the same reason, the meta-analysis was performed only with two-year OS because few studies reported data for three or five-year OS. Similarly, only a few studies reported the frequency of CR and grade 3–4 hematological and non-hematological toxicity. Carrying out a joint analysis of CGA as if it were a standard or homogeneous instrument might also be debatable, given that the different studies used different models for the CGA (sCGA, full CGA, and the phenotype model), which use different criteria (Tab. S2 in supplementary file). Another limitation of this study is that it only evaluated the usefulness of CGA in the reduction of the incidence of grade ≥ 3 toxicity and not in relation to specific types of adverse drug reactions (ADR). It is known that toxicities for chemo or non-chemo protocols may be different; for example, the ADR called "immune effector cell-associated neurotoxicity syndrome (ICANS)" occurs only with chimeric antigen receptor (CAR) T-cell therapy [40].

Conclusions

In conclusion, our metanalysis suggests that CGA could serve as a guide for the treatment plan in older DLBCL patients and lead to better patient survival. Randomized clinical trials are necessary to confirm these findings as well as the standardization and homogenization of the instruments used in CGA.

Article Information and Declarations

Author contributions

T.J.O.: concept and design, acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript; X.V.: analysis, and interpretation of the data, critical revision of the manuscript; B.E.B.: acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript; R.R.-O.: acquisition, analysis, and interpretation of the data, drafting of the manuscript, critical revision of the manuscript, supervision.

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Conflict of interest

None.

Supplementary material

Tables S1 and S2.

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Supplementary material

Table S1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (from [13])

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	6

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Table S1 cont. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist (from [13])

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see item 16)]	
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	8
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	1

Table S2. Frailty classification in older patients with diffuse large B-cell lymphoma

Study	Operational definition		
	Frail	Unfit	Fit
CGA-modulated studies			
Xu et al (2022)	Frail: ADL < 5; IADL < 6; CIRS-G: ≥ 1 grade 3–4 comorbidities or > 8 comorbidities grade 2 score; age ≥ 80 o morbidities), age ≥ 80 unfit	Unfit: ADL6-5; IADL ≤ 6–7; CIRS-G: no comorbidities score 3–4 and 5–8 comorbidities score 2, age ≥ 80 fit	Fit: ADL6-6; IADL = 8; CIRS-G: no comorbidities score 3–4 and < 5 comorbidities score 2
Bocci et al. (2022)	Frail: age ≥ 80 years and CIRS-G: ≥ 1 score = 3–4; ≥ 5 score 5 = 2; ADL < 6; and IADL < 8 scores	Unfit: < 80: CIRS-G: ≥ 1 score = 3–4; > 8 score = 2; ADL < 5; and IADL < 6; unfit: ≥ 80: CIRS-G: ≥ 0 score = 3–4; < score = 2; ADL = 6; and IADL = 8	
Bai et al. (2020)	Frail: ADL < 5 or IADL < 6; or MCIRS-G: ≥ 1 comorbidity score 3–4 (or > 8 comorbidity score 2) or age ≥ 80 yr unfit	Unfit: ADL = 5 or IADL = 6–7 or MCIRS-G = no comorbidity score 3–4 (and 5–8 comorbidity score 2) or; age ≥ 80 yr fit	Fit: ADL = 6 and IADL = 8 and MCIRS no comorbidity score 3–4 (and < 5 comorbidity score 2); and; age = And < 80 yr
Storti et al. (2018)	Frail: inpatients aged between 70 and 80 years, ADL < 4 or IADL < 5 or 1 grade 3 comorbidity or > 8 grade 2 comorbidities (CIRS-G) were required; in patients older than 80 years, ADL > 5 or IADL > 6 or 5–8 grade 2 comorbidities were required		

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Table S2 cont. Frailty classification in older patients with diffuse large B-cell lymphoma

Study	Operational definition		
	Frail	**Unfit**	**Fit**
Lastra-German et al. (2018)	≥ 3 points: frail 1. Unintentional loss of ≥ 5 kg during the past year 2. Physical exhaustion: The previous week… a) "Did you feel that everything required a lot of effort?"; b) „Did you feel that you could not go on?"; "Moderate amount" or "most of the time" in any circumstance scores as positive; 3. Low physical activity: Lowest quintile adjusted for gender; 4. Slowness: 4-meter gait speed below the lowest quintile adjusted for height*; 5. Weakness: grip strength below the lowest quintile adjusted for BMI	1–2 points: unfit	0 points: fit
Merli et al. (2013)	Frail: ≥ 80 years; or frail: < 80 years who were not fit according to one or more of the previous features were also considered as frail	Missing	Fit: < 80 years and had an ADL = 6, < 3 grade 3 CIRS-G comorbidities and no grade 4 comorbidities (hematological comorbidities were not investigated), and none of the criteria defining the presence of geriatric syndrome
Spina et al. (2012)	Frail: ADL < 5, or IADL < 5. CIRS-G: ≥ 1 grade 3 comorbidities (or > 5 grade 2 comorbidities)	Unfit: an ADL = 5, and/or an IADL = 5 or 6; CIRS-G: no grade 3 comorbidities (or 3–5 grade 2 comorbidities)	Fit: ADL = 6, and/or an IADL = 7 or 8; CIRS-G: no grade 3 comorbidities (or < 3 grade 2 comorbidities)
Olivieri et al. (2012)	Frail: age ≥ 85 years and dependence ≥ 1 ADLs and geriatric syndromes: ≥ 1. Frail: CIRS-G score ≥ 3	Patients with comorbidities: CIRS-G score 0–2	Fit (no frail, no patientes with comorbidities)
non-CGA-modulated studies			
Study	**Frail**	**Prefrail**	**Fit**
Tanaka et al. (2022)	Dependent: ≥ 1 problems in 6 CGA domains; a) ADL Barthel Index < 100; b) IADL (Lawton and Brody) < 5; c) Psychological status GDS-15 > 10; d) Cognitive function Hasegawa's dementia scale (HDS-R) ≤ 20; e) Nutritional status MNA < 17; g) Comorbidities Charlson comorbidity index ≥ 5 MNA < 17; comorbidities Charlson comorbidity index ≥ 5	Missing	Independent = remaining cases were definedas „independent"
Zhang et al. (2022)	Frail: > 80 y or ≤ 80 y with CIRS-G: any grade 3 or 4 comorbidities or > 8 grade 2 comorbidities or with higher scores on the ADLs/IADLs scales	Unfit ≥ 80y with an ADL = 5, an IADL = 6–7, CIRS-G: no grade 3 or 4 comorbidities, and 5–8 grade 2 comorbidities	Fit ≤ 80 y with normal ADLs and IADLs scores, CIRS-G: no grade 3 or 4 comorbidities, and < 5 grade 2 comorbidities

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Table S2 cont. Frailty classification in older patients with diffuse large B-cell lymphoma

Study	Operational definition		
	Frail	**Unfit**	**Fit**
Merli et al. (2021)	Frail: age ≥ 80 years and CIRS-G: ≥ 1 score = 3–4; ≥ 5 score 5 = 2; ADL < 6; and IADL < 8 scores	Unfit: < 80: CIRS-G: ≥ 1 score = 3–4; > 8 score = 2;ADL < 5; and IADL < 6 unfit: ≥ 80: CIRS-G: ≥ 0 score = 3–4; < score = 2; AD = 6; and IADL = 8	Fit: ≤ 80: CIRS-G: ≥ 0 score = 3–4; ≤ 8 score = 0; ADL ≥ 5; and IADL ≥ 6
Isaksen et al. (2021)	Frail: Katz Activities of Daily Living (ADL): independent = 1, dependent = 2; Charlson Comorbidity Index (CCI): score 0–1 = 1; score 2 = 1.5; score ≥ 3 = 2; Geriatric Nutritional Risk Index (GNRI): absent/low = 1; moderate = 2; severe = 2.5; age: < 85 = 1; ≥ 85 = 2; total score: multiply obtained scores (rank: 1–20) (example: ADL = 2, CCI = 2; GNRI = 2; age: 2. Total Score = 2 × 2 × 2 × 2 = 16). Frail: total score > 3	Unfit: score: 1.5–3	Fit score = 1
Ong et al. (2019)	Frail: those not meeting CGA-fit or unfit criteria were classified CGA-frail	Unfit: aged ≥ 80 years, with ADL = 5, IADL = 7, no CIRS-G grade 3–4 comorbidities and up to 5–8 grade 2 comorbidities	Fit: aged < 80 years, with no limitations in ADL (score 6/6) and IADL (score 8/8), CIRS-G no severe comorbidities grade 3–4/4 (excluding haematological comorbidities) and < 5 grade 2–4 comorbidities
Tucci et al. (2015)	Frail: ADL ≤ 4, IADL ≤ 5, CIRS-G ≥ 1 comorbidity score 3–4 or > 8 comorbidity score 2, age ≥ 80	Unfit: ADL ≤ 5, IADL ≤ 7–6, CIRS-G no comorbidity score 3–4 and 5–8 score 2, age ≥ 80	Fit: ADL ≤ 6, IAL ≤ 8, CIRS-G no comorbidity score 3–4 and < 5 score 2
Marchesi et al. (2013)	Frail (CGA 3): ≥ 1 of the following parameters: age > 85 years, presence of a geriatric syndrome, ADL score < 6) and ≥ 3 moderate morbidities or one or more severe morbidities	Intermediate (CGA 2) < 85 years old, ADL = 6; and at least one moderate morbidity but no geriatric syndromes	Fit: < 85 years, ADL = 6 and no moderate morbidities and geriatric syndromes

ADL — Activities of Daily Living; CIRS-G — Cumulative Illness Rating Scale-Geriatric; IADL — Instrumental Activities of Daily Living Scale