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FUNCTIONAL STATUS IN A GERIATRIC ONCOLOGY SETTING: A REVIEW

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Keywords: functional status; older adults; cancer; overall survival; treatment decision; chemotoxicity; treatment feasibility; postoperative complications.

ABSTRACT:

Background: Comprehensive Geriatric Assessment (CGA), is used in older patients with cancer to identify frailties, which can interfere with specialized treatment, and to help with therapeutic care. Functional Status (FS) is a domain of CGA in which Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) are evaluation tools.

Objective: Our study reviewed the data available on the most frequently used tools to assess ADL and IADL in a geriatric oncology setting and their predictive values on overall survival (OS), toxicity, treatment feasibility or decision and postoperative complications.

Design: This review was based on a systematic search of the MEDLINE® database for articles published in English and French between January 1, 2010, and December 31, 2017. In the final analysis, 40 out of 4061 studies were included.

Results: The most common ADL and IADL scales used are the Katz ADL (KL-ADL) in 25 studies and the Lawton IADL (IADL₈) in 22 studies. FS is predictive of OS in 11 out of 24 studies, chemotoxicity in 2 out of 7 studies, treatment feasibility in 2 out of 5 studies, treatment decisions in 2 out of 3 studies, and postoperative complications in 4 out of 6 studies.

Conclusion: FS is of prognostic value in a geriatric oncology setting despite heterogeneous methodology and inclusion criteria, in the studies included. Additional research is needed to explore more precisely the prognostic value of FS in overall survival, toxicity, treatment feasibility or decision and postoperative complications, in older cancer patients.

INTRODUCTION

A Comprehensive Geriatric Assessment (CGA) is defined “as a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are cataloged, need for services assessed and a coordinated care plan developed” [1]. This multidimensional diagnostic process builds an inventory of the health issues of older patients in various domains: mobility, psychosocial, nutritional, cognitive and functional status [2–4].

Functional status (FS) is a CGA domain for which many tools have been developed in the geriatric population. Since 20 years, oncologists and geriatricians have been working to integrate CGA into oncological practices for older patients with cancer for twenty years. The International Society of Geriatric Oncology (SIOG) recently explored the different FS assessment methods [5] and concluded that the most common tools were Activities of Daily Living (ADL) and/or Instrumental Activities of Daily

Living (IADL). In the American Society of Clinical Oncology (ASCO) guidelines, the Expert Panel recommends only IADL for assessing function [6]. The Katz index for Activities of Daily Living (KL-ADL) [7] covers six basic functions: bathing, dressing, toileting, moving, bowel and bladder control, and eating. The Barthel index (B-ADL) [8] is especially used in rehabilitation settings and measures the ability to perform 10 different functions: personal hygiene, bathing, feeding, toileting, climbing stairs, dressing, bowel and bladder control, mobility, and chair/bed transfers. The MOS physical health (MOS_{PH}) [9,10] measures the ability to perform a selection of 10 physical functions from bathing/dressing to vigorous activities.

Alongside ADL, Instrumental Activities of Daily Living (IADL) is also used to assess FS. The most frequently used tool is the Lawton Instrumental Activities of Daily Living scale (IADL₈) [11], which measures eight community activities: handling finances, shopping, food preparation, housekeeping, using the telephone, doing the laundry, using transportation, and taking medication. A short IADL tool (IADL₄) based on 4 questions was developed during the PAQUID study [12] and only measures handling finances, using the telephone, using transportation, and taking medication. This short IADL, already common in daily medical practice, is being increasingly used as a tool in research [13]. The KL-ADL and IADL₈ scales are self-assessment questionnaires that can be completed with the help of a caregiver or a practitioner, if necessary. The Older Americans Resources and Services (OARS) Multidimensional Functional Assessment Questionnaire [14] measures the ability to carry out activities required to preserve independence in the community and comprises seven items including shopping, meal preparation, making telephone calls, and money management. The P-ADL (modified Katz physical activities of daily living) [15] and the NE-ADL (Nottingham extended activities of daily living) [16] scales measure activities such as housekeeping, leisure activities, food preparation, and mobility. The Pepper Assessment Tool for Disability comprises nineteen items and is used to assess instrumental activities, activities of daily living, and mobility [17]. Other tools [18] including the Rosow-Breslau Health Scale [19], the Nagi Scale [20], the Geronte scale [21], and the Duke Activity Status Index [22] have been developed but are used much less.

Rather than these FS evaluation tools, oncologists prefer to assess FS using performance status tools that evaluate the general impact of cancer on patients. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) [23] classifies patients based on activity level, self-care ability, and ability to work (0-4). The Karnofsky Performance Status (KPS) is a global indicator of patient function reported by the physician ranging from “normal” to “dead” (0-100%) [24,25].

Our objective was to review the data available on the tools most frequently used to assess ADL and IADL in a geriatric oncology setting and their predictive values on overall survival (OS), toxicity and/or treatment feasibility, postoperative complications, and treatment decisions.

94 **MATERIALS AND METHODS**

95 **Data sources**

96 This review was based on a systematic search of the MEDLINE database for articles published in
97 English or French between January 1, 2010, and December 31, 2017. The MeSH terms “activities of
98 daily living”, “instrumental activities of daily living” (OR “self-care rehabilitation” OR “health status
99 assessment”), etc., “functional status”, “functional decline”, “frailty”, “frailty markers”, “geriatric
100 assessment” (OR “geriatric assessment” OR “comprehensive geriatric assessment”) etc., “elderly”, (OR
101 “aged” OR “older person”) etc., were combined with “neoplasms” (OR “cancer” OR “malignancy”), etc.
102 All the terms used are detailed in Appendix A.

103 **Study eligibility criteria**

104 We selected studies that focused on the prognostic value of ADL and/or IADL tools for OS,
105 chemotoxicity, treatment feasibility, postoperative complications or treatment decisions in older
106 inpatients or outpatients (mean age over 70 years old) with cancer (including hematologic
107 malignancies). The studies selected were retrospective or prospective and observational or
108 interventional with a sample size of at least 30 patients. We excluded editorials, case studies, studies
109 published as abstracts, and score creation studies.

110 Data recorded included the publication date, country, study design, aim of the study, sampling method
111 and sample size, characteristics of the participants included in the study (age, cancer type, cancer
112 stage, treatment...), ADL or IADL assessment methods used, the outcomes associated with the
113 baseline ADL or IADL impairment, and details of the statistical analyses.

114 **Study selection process**

115 Articles were initially selected according to the PRISMA guidelines (Fig. 1), by two senior geriatric
116 oncology consultants (ALC, RB) and an experienced clinical research coordinator (EN) based on the
117 titles, abstracts, and eligibility criteria described above. When one or more of the investigators were
118 uncertain about whether the article fulfilled the eligibility criteria, the abstract was included and the same
119 three reviewers analyzed the full text. Disagreements were resolved by consensus. After the selection
120 process, 40 studies were used to assess FS tools in current geriatric oncology practices.

In each study, we analyzed which FS tools were used, the impact of these tools, and the selected cut-off for OS, treatment decisions, treatment feasibility, chemotherapy toxicity, and postoperative complications. Finally, we analyzed the statistical analyses from which the conclusions were drawn. The records were managed in excel tables and the calculations were performed using SPSS 17.0 for Windows and Stata.

Quality methodology

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines [26], the Reporting of Observational Studies in Epidemiology (STROBE) [27], and the Methodological Index for Non-Randomized Studies (MINORS) in non-comparative studies [28] were used by two reviewers (ALC and EN) to assess the quality of the studies included.

RESULTS

The systematic search provided 4061 potentially eligible studies for this review, which were screened according to the title and the abstract. The full texts of the 87 remaining articles were then reviewed (Fig.1). Ultimately, 40 papers were included in the final analysis.

Quality assessment (Appendices B and C)

We assessed the quality of the 40 studies using the MINORS guidelines to analyze the 34 non-randomized observational and interventional studies, and the STROBE and PRISMA guidelines to analyze the six randomized interventional studies.

Under the MINORS assessment criteria, the ideal score is 16 for non-randomized studies.

The STROBE and PRISMA guidelines were used to assess the quality of six interventional randomized studies. All the randomized studies included [29–34] described the study design, the setting in which the study was conducted, the follow-up method, the amount of missing data, and how the authors dealt with the missing data. Furthermore, the authors described the statistical methods [29–34].

Characteristics of the studies included (Appendix D)

Sixteen studies were conducted between 2016 and 2017 [30–32,35–46,67], thirteen between 2013 and 2015 [29,33,47–57], and eleven between 2010 and 2012 [13,34,58–66]. Twenty-seven studies were conducted in Europe [13,29–40,44,45,47–49,52,55,57–61,65,66], nine in America [43,44,46,50,51,54,56,62,63], and four in Asia [42,53,64,67].

Twenty-six studies were prospective observational studies [13,35–40,44–52,55–61,63–65], seven retrospective observational studies [41–43,53,54,62,67], 6 randomized clinical trials [29–34], and one non-randomized interventional study [66].

Thirty-seven studies included cancer pathologies regardless of the stage [6,13,29–31,34–42,44–55,57–67] and three metastatic cancer only [29–31].

Eighteen studies included patients with any type of cancer [38,39,41,43,44,49,50,52–56,58,59,61,63–65], six only included colorectal cancers [29,30,36,37,57,67], six investigated hematological malignancies [13,42,47,48,62,66], six concerned lung cancer [31,32,34,35,40,60], one breast cancer [33], 2 ovarian cancer [45,46], and one head and neck tumors [51].

Regarding the oncological treatment, twenty studies included systemic treatment (chemotherapy, immunotherapy, and targeted therapy) [13,29–34,39,40,42,45–48,50,53,56,62,64,66], twelve included all types of oncological treatment [35,36,38,41,49,55,58–61,63,65], and eight exclusively surgical treatment [37,43,44,51,52,54,57,67].

Overview of functional status tools to assess ADL and IADL (Appendix D)

The most common Activities of Daily Living scales used were KL-ADL in 25 studies [31–41,45,49,51,52,54,55,58–63,65,66], B-ADL in seven studies [42,44,48,53,57,64,67], and MOS_{PH} in two studies [46,50].

The KL-ADL scale was the most frequently used regardless of the time period but more often in Europe and America, whereas the B-ADL scale was used in Asia. One study used Duke's activity index that incorporates ADL and mobility [43].

The most popular Instrumental Activities of Daily Living tool was the IADL₈ (22 studies) [29,30,32,33,35–37,39,41,42,44,45,47,51–54,59,60,64–66]. The IADL₄ (4 items) was used in three studies [13,31,40], the OARS in five studies [38,46,50,56,63], and the NE-ADL and P-ADL scales were each used in one study [57,61].

The IADL₈ tool was the most frequently used regardless of the time period and the location or stage of the tumor. The P-ADL and NE-ADL scales were not used in 2016 and 2017. The IADL₄ was only carried out in France whereas OARS was more used in America.

With regard to the use of performance status scales, the ECOG-PS was preferred (24 studies) [13,31–38,40,42,45,46,49,52,53,55,58,60,62–65] over the KPS (six studies) [29,30,48,50,51,56].

ADL, IADL, and performance status scales were analyzed together in nineteen studies [31–33,35–40,42,45,46,50,52,53,60,63–65].

Functional status cut-off (Tables 1 and 2)

For the ECOG-PS, the cut-off was < 2 vs. ≥ 2 in nineteen studies [13,31,32,34–39,42,45,49,53,55,58,62–65]. In three studies the reported cut-off was < 1 vs. ≥ 1 [33,40,52].

Aparicio *et al.* used the KPS scale to divide the population into three sub-groups (60-70%, 80-90%, and 100%) [29,30]. Deschler *et al.* used a $< 80\%$ vs. $\geq 80\%$ cut-off [48], Gerude *et al.* used a $\leq 80\%$ vs. $> 90\%$ cut-off [51], and Garja *et al.* used the KPS as a continuous variable [50].

The loss of ability to perform at least one activity on the KL-ADL scale was used to differentiate dependent versus independent patients in 24 studies [31–41,45,49,52,54,55,58–63,65,66]. Seven authors used the B-ADL tool: a patient was deemed dependent when they lost the ability to perform at least one activity (< 100) [42,44,48,53,57,64,67]. The Duke's index incorporates mobility impairment and the cut-off was < 4 metabolic equivalents (METs) vs. ≥ 4 METs, which correspond to dependent and independent, respectively [43].

The cut-off was the same in twenty of the twenty-two studies assessing FS using the IADL₈ scale: patients were deemed dependent when they lost the ability to perform at least one activity [29,30,33,35–37,39,41,42,44,45,52–54,59,60,64–67]. Similarly, for the IADL₄ scale, patients were also characterized as dependent with the loss of at least one activity [13,31,40]. The number of activities assessed was, however, heterogeneous, as most men only performed five out of the eight items on the IADL₈ scale; this was avoided when the IADL₄ was used. The OARS scale was employed in four studies with the same cut-off. Patients were considered dependent once they were no longer able to perform at least one activity [38,46,50,63]. According to the NE-ADL scale, patients presenting a score under 44 / 66 were deemed dependent [57] and according to the P-ADL scale, dependency was defined as the loss of ability to perform at least one activity [61].

FS as a predictor of OS (table 3)

Out of the 40 studies, 24 analyzed the impact of FS on OS [13,30,33,35,39,41,42,44–49,57,60–63,65,66].

Out of the twenty-two studies using regression analysis, eleven showed a significant association between the FS scores and OS [30,34,35,39,41,47–49,57,62,63]. The impact of IADL on OS was analyzed in nineteen studies [13,31–33,35,39,40,42,44–47,57,60,61,65,66] and was confirmed by regression analysis in only five studies [30,41,47,57,62]. Seventeen studies analyzed the impact of ADL on OS [31,33–35,39–42,44,48,49,60–63,65,66]; regression analysis confirmed the positive impact of ADL in six studies [34,39,48,49,62,63] and PS was a significant prognostic factor of OS in six studies [34,35,40,48,49,63].

Analyses were adjusted according to age in four studies [13,33,39,49], to gender in one study [41] and according to age, sex and number of comorbidities in one study [63]. In these adjusted analyses, the

impact of IADL on OS was confirmed in one study [41] and the impact of ADL on OS in three studies [39,49,63].

FS and treatment decisions (table 4)

Three of the studies included described the predictive value of FS on treatment decisions [38,58,59]. The KL-ADL tool was a FS predictive of treatment decision value in two studies [38,58]. The results of these studies showed a significant correlation between the ADL scores and changes in treatment decisions.

Collinearity between CGA domains was assessed and taken into account for regression analysis in one study [58] but no specific adjustments were made in other studies.

FS as a predictor of chemotoxicity and treatment feasibility (table 4)

Regression analysis was conducted in seven studies to evaluate the predictive value of FS on chemotherapy toxicity [29,33,36,46,56,63,64]. IADL (IADL₈) was significantly associated with toxicity in two studies [29,33] and PS (ECOG-PS) was an independent predictive factor of toxicity in another study [64].

Two studies were adjusted according to age [33,64], one according to gender [29] and one according to gender, age and comorbidities [63]. IADL has an impact on chemotoxicity in two adjusted analyses [29,33].

Concerning treatment feasibility [29,46,50,53,55], ADL (KL-ADL) and PS (ECOG-PS) were predictive of chemotherapy feasibility in one study [55], and the IADL₈ score was also an independent predictive factor for early discontinuation of active treatment in another study [53].

Concerning treatment feasibility, two studies were adjusted according to gender [29,50].

FS as a predictor of postoperative complications (table 4)

Six studies described the predictive value of FS on post-surgery complications [37,43,51,52,54,67]. Four studies [37,43,52,67] classified postoperative complications according to severity using the Clavien-Dindo classification system [68]. ADL dependence (B-ADL [67], KL-ADL [37], and MET [43]) was associated with major postoperative complications and the IADL₈ score was associated with postoperative delirium [54].

In one study, the analysis was adjusted according to gender [52] and according to gender, age and comorbidities in one study [43]. The Duke's index has an impact on postoperative complications in one study with adjustments [43].

DISCUSSION

Functional status is a crucial domain of comprehensive geriatric assessment, so it is widely used to analyze autonomy and help with treatment decisions in oncology settings. To our knowledge, no other systematic review has focused on analyzing both the use of FS tools in older adults diagnosed with cancer and the prognostic value of these tools with regards to OS, chemotoxicity, treatment feasibility, treatment decisions or postoperative complications. In 2002, Garman *et al* [18] reviewed the different FS tools used at the time. However, oncogeriatric research has grown exponentially since then and numerous studies have been published. The strengths of this review include the systematic methodology used to identify all relevant articles using three independent reviewers, its focus on a narrow subject, and the quality assessment of the studies included. This work provides very practical, up-to-date data for the assessment of FS in daily practice and shows that KL-ADL and IADL₈ are the most frequently used FS scores to assess ADL and IADL, respectively. We report that ADL and IADL are prognostic factors of adverse outcomes for older patients with cancer in both systemic and surgically treated populations.

This review also has some limitations. We only used one database and the findings are limited by the quality of the studies included. The methodology and statistical analyses are heterogeneous in the majority of studies, for example, comparison analyses were conducted in seven studies but no regression analysis. Other studies featured heterogeneous sample populations (diverse tumor types, staging and treatments were analyzed as a unique sample without stratification), thus weakening the conclusions of the studies. We decided not to include studies evaluating score creation, studies in which FS scores were used in a composite score of frailty or analysis of FS decline, as the purpose of our study was to analyze FS alone. Studies investigating the Chemotherapy Risk Assessment Scale for High-Age patients (CRASH) [69] or the Cancer and Aging Research Group (CARG) score [70] were not included, even though they have an impact on chemotoxicity in older patients, because they both contain very few FS items [6]. Studies testing the prognostic value of frailty indexes using Fried [71] or Rockwood scores [72] in cancer-specific mortality or chemotoxicity were not included either [73]. We also excluded studies analyzing the prognostic value of FS on endpoints other than OS, toxicity, treatment feasibility, treatment decisions or post-operative complications but kept studies where the prognostic value of FS was not analyzed at all, as our primary goal was to determine the ADL and IADL tools most frequently used in an oncogeriatric setting.

We analyzed the quality of the studies included: six randomized studies used the STROBE and PRISMA guidelines and 34 non-comparative studies used the MINORS guidelines. We did not exclude

any studies based on their methodological quality because no study is statistically perfect and we wanted to present a global view of the methodology as well as the tools used to measure and analyze FS in the literature over the past seven years. The statistical approaches used to analyze the predictive value of FS were widely heterogeneous. For example, survival analyses generally ranged from diagnosis to death or the last follow-up. In the studies included, OS was calculated from surgery, admission, treatment initiation, inclusion, randomization or CGA to death or last follow-up. These variations in methodology along with the lack of homogeneity in the treatment of the population, type or stage of cancer could account for the contradictory results reported in these 40 papers.

In 2012, Puts *et al* reviewed 73 studies to provide an overview of all geriatric assessment instruments used in an oncology setting and reported that 68 out of 73 CGA studies analyzed the ADL domain mostly using the KL-ADL score (56%), and that 65 out of 73 teams explored the IADL domain using the IADL₈ scale (62%) [4]. In comparison with Puts *et al*'s review, this new review shows that KL-ADL (73.5%) and IADL₈ (81.5%) were more frequently used. Our study states the use of two different PS scales, four different ADL scales, and five different IADL scales. However, our review confirms that KL-ADL and IADL₈ are the predominant tools for measuring ADL and IADL in older cancer patients, followed by KL-ADL and B-ADL. The MOS_{PH} was used in only two analyses and NE-ADL, P-ADL, OARS, and IADL₄ are rarely used, although in practice, the IADL₈ scale leads to discrepancies in older population. Indeed, with IADL₈, all eight domains were assessed for women, whereas items in the domains of food preparation, housekeeping, and laundering were omitted for men. This disparity encouraged the current guidelines to recommend the use of the same score for both genders. Recently, a Geriatric COre Data sEt (G-CODE) using tools or items validated in older cancer and non-cancer populations was proposed. IADL₄ was selected for G-CODE according to an explicit consensus approach (modified Delphi method) [74]. The generalization of the IADL₄ score, which overcomes the differences in scoring and reduces examination time, should be considered in the future for trials enrolling older cancer patients.

Previously, the ECOG-PS and the KPS are the most common scores used in oncology to measure FS. However, these PS tools do not measure the ability to perform basic functions in older adults as they were validated in younger patients. ECOG-PS and KPS are often mentioned in clinical observations or inclusion criteria but are generally not analyzed for their prognostic value with regard to the endpoints studied in geriatric oncology studies. Both FS and PS were analyzed in the same regression analysis in seven studies (four on OS, two on toxicity, one on treatment decision and one on postoperative outcomes). Four studies have an impact on OS in regression analysis [34,35,48,63], in three of them both PS and FS are predictive [34,48,63], and in one study only PS has an impact [35]. Two studies

analyze the impact of both tools on toxicity [63,64], but only PS is predictive in one study [64]. The impact of both tools on treatment decisions is analyzed in one study and only ADL is predictive of treatment modifications [58]. When PS and FS were included simultaneously in the regression analysis, only ADL was predictive of post-operative complications in the one study analyzed [37]. The majority of studies used only one FS tool (ADL or IADL) with PS or not. In this regard, the difference in impact between FS and PS can be difficult to determine. However, in OS studies, both PS and ADL showed prognostic value (four out of eleven studies). In fact, ECOG-PS and KPS describe functional ability (same ADL domain) but poorly reflect functional impairment in older cancer patients [23,75], as they do not include many areas of impaired functioning commonly seen in older patients (e.g., continence).

Most studies used the same cut-off to determine dependence in ADL or IADL scores. The loss of ability to perform at least one ADL or IADL activity was generally used to detect impairment, as recommended by the literature and by the SIOG. For the ECOG-PS, the cut-off was < 2 vs. ≥ 2 in most studies [31,34–39,42,45,49,53,55,58,62–65]. In current clinical trials, patients with an ECOG-PS of 0 to 1 are often included, while patients with a PS of 2 or worse are usually excluded, as this cut-off (≥ 2) is predictive of poor outcomes for cancer populations in some studies [76]. Even though most studies compared populations using the usual cut-off, some used different ones thus adding to the heterogeneity of the results of the studies.

Eleven studies showed a significant association between FS scores and OS [30,34,35,39,41,47–49,57,62,63]. Five studies [30,41,47,57,62] used regression analysis to identify IADL and OS, and six studies [34,39,48,49,62,63] to identify ADL. In comparison with OS, the other endpoints studied in this review were less analyzed. Treatment decisions were analyzed in three studies [38,58,59]; KL-ADL was predictive in populations treated for any type of cancer or undergoing any therapy in two of these studies [38,58]. Five studies in our systematic review analyzed oncological treatment feasibility [29,46,50,53,55]. KL-ADL and ECOG-PS [55], as well as IADL₈ [53], were associated with treatment feasibility in two studies; IADL₈ was significantly associated with chemotoxicity in two studies [29,33]. Few studies have analyzed specifically the prognostic value of the CGA domains [2] with regards to oncological treatment toxicity and feasibility in older cancer patients. Six studies analyzed FS and postoperative complications [37,43,51,52,54,67]. IADL₈ was associated with postoperative delirium in one study [54] and ADL with major postoperative complications in three studies [37,43,67]. FS seems to be predictive of OS after surgical treatment but few studies on surgical treatment outcomes were eligible for this work.

More prospective randomized studies are needed to identify the precise prognostic role of FS in adverse outcomes for older patients with cancer. The integration in future studies of more homogenous populations combined with the exploration of the predictive value of geriatric domains with more standardized designs and methodologies would yield more reproducible results. This limitation was already highlighted in Puts et al.'s study (2012) [4] limited by the heterogeneous scientific quality of the studies included. A meta-analysis using the source material of several prospective randomized studies with similar inclusion criteria should provide a reliable answer to the predictive value of ADL or IADL.

CONCLUSION

The most common tools used worldwide to assess FS in geriatric oncology settings are KL-ADL and IADL₈. With both tools, impairment widely defined as the loss of ability to perform at least one activity. The ECOG-PS is the scale most frequently used in oncology to estimate functional status in the adults, though it is not specifically designed for older patients. A line of evidence seems to point towards the predictive value of ADL with regards to OS and outcomes of postoperative complications, whereas IADL seems to be predictive of treatment feasibility and chemotoxicity outcomes in older patients treated for cancer. However, a consensus is needed regarding the methodology and statistical analyses used in geriatric oncology trials to obtain more reliable insights into the predictive value of the geriatric domains with regards to oncological treatment outcomes.

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CONFLICT OF INTEREST:

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS:

Concept and Design: AL. Couderc

Data Acquisition: AL. Couderc, E. Nouguerède, R. Boulahssass

Quality Control of Data and Algorithms: AL. Couderc, E. Nouguerède, R. Boulahssass

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Fig.1: Study flow chart according to PRISMA model (2009)

Appendix A: MeSH Search exact wording

Appendix B: Quality assessment of included studies using MINORS

Appendix C: Statistical Methodology of the analyzed studies

Appendix D: Frequency of the different functional status measurement tools

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Study	Functional status measure tool → cut-off and stratification
Aparicio 2017 ^[30]	K-PS → 60-70 vs. 80-90 vs. 100 IADL₈ → Abnormal < 8 (loss of at least 1 activity) vs. normal ≥ 8

654 **Table 1:** FS tools and cut-off used when survival was the objective of the analyzed study

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<i>Bila</i> 2015 ^[47]	IADL₈ → < 3 vs. ≥ 3
<i>Corre et al</i> 2016 ^[31]	ECOG-PS → ≤1 receive doublet chemotherapy vs. 2 receive mono-chemotherapy KL-ADL → 6 fit or vulnerable patients vs. ≤ 5 frail patients (loss of at least 1 activity) IADL₄ → 0 fit patients vs. 1 vulnerable patients vs. ≥ 2 frail.
<i>Deschler</i> 2013 ^[48]	K-PS → < 80 vs. ≥ 80 B-ADL → < 100 vs. 100 (loss of at least 1 activity)
<i>Decoster</i> 2017 ^[35]	ECOG-PS → ≤1 vs. ≥ 2 / KL-ADL → Abnormal > 6 to 24 vs. normal =6 IADL₈ → Abnormal < 8 for women and < 5 for men vs. normal =8 for women, =5 for men
<i>Ferrat</i> 2015 ^[49]	ECOG-PS → 0-1 vs. 2 vs. ≥ 2 KL-ADL → > 6 vs. < 6 (loss of at least 1 activity)
<i>Girones</i> 2012 ^[60]	ECOG-PS → no cut-off reported KL-ADL₍₅₎ → dependent (≤ 4/5) vs. independent (5/5) (loss of at least 1 activity) IADL_{8 (6)} → dependent (≤ 5/6) vs. independent (6/6) (loss of at least 1 activity)
<i>Hamaker</i> 2011 ^[61]	KL-ADL → impaired (loss of at least 1 activity) vs. normal P-ADL → impaired (loss of at least 1 activity) vs. normal
<i>Jonna</i> 2016 ^[41]	KL-ADL → Dependence < 17/18 vs. independent ≥ 17/18 (loss of at least 1 activity) IADL₈ → Dependence < 20/24 vs. independent ≥ 20/24 (loss of at least 1 activity)
<i>Karampeazis</i> 2017 ^[32]	ECOG-PS → 0 vs. 1 vs. 2 KL-ADL → Abnormal < 6 (loss of at least 1 activity) vs. normal 6 IADL₈ → Abnormal < 7 (loss of at least 2 activities) vs. normal 7
<i>Kenis</i> 2017 ^[39]	ECOG-PS → ≤ 1 vs. ≥ 2 / KL-ADL → Abnormal > 6 to 24 vs. normal =6 IADL₈ → Abnormal < 8 for women and < 5 for men vs. normal =8 for women, =5 for men
<i>Le Caer</i> 2017 ^[40]	ECOG-PS → 0 vs. ≥ 1 / KL-ADL → Abnormal < 6 vs. normal =6 IADL₈ → Abnormal ≤ 2 vs. Normal >2
<i>Nabhan</i> 2012 ^[62]	ECOG-PS → > 2 / ADL → loss of at least 1 activity
<i>Naito</i> 2016 ^[42]	ECOG-PS → < 2 vs. ≥ 2 B-ADL → impaired (loss of at least 1 activity) vs. normal (< 100 vs. 100) IADL₈ → impaired (loss of at least 1 activity) vs. normal
<i>Ommundsen</i> , 2014 ^[57]	B-ADL → Frail < 19/30 vs. Non-frail ≥ 19/30 NE-ADL → Independent > 43/66 vs. dependent < 44/66
<i>Perrone</i> 2015 ^[33]	ECOG-PS → 0 vs. 1 / KL-ADL → < 6 impaired (loss of 1 activity) vs. ≥ 6 normal IADL₈ → impaired < 8 (loss of at least 1 activity) vs. ≥ 8 normal
<i>Peyrade</i> 2011 ^[13]	ECOG-PS → <2 vs. ≥ 2 / IADL₄ → With limitation < 4 (loss of at least 1 activity)
<i>Quoix</i> 2011 ^[34]	ECOG-PS → ≤ 1 vs. 2 KL-ADL → Independent 6 vs. dependent < 6 (loss of at least 1 activity)
<i>Schmidt</i> 2017 ^[44]	B-ADL → Independent 100 vs. dependent <100 (loss of at least 1 activity) IADL₈ → Independent 8 vs. dependent < 8 (loss of at least 1 activity)
<i>Soubeyran</i> 2012 ^[65]	ECOG-PS → ≤ 2 vs. >2 KL-ADL → Abnormal ≤ 5 (loss of at least 1 activity) vs. normal > 5 IADL₈ → Abnormal ≤ 7 (loss of at least 1 activity) vs. normal > 7
<i>Spina</i> 2012 ^[66]	KL-ADL → Abnormal <6 (loss of at least 1 activity) vs. normal 6 IADL₈ → Abnormal <8 (loss of at least 1 activity) vs. normal ≥ 8
<i>Tinquaut</i> 2016 ^[45]	ECOG-PS → < 2 vs. ≥ 2 KL-ADL → Abnormal < 6 vs. normal 6 (loss of at least 1 activity) IADL₈ → Abnormal < 25 vs. normal ≥ 25 (loss of at least 1 activity)

ECOG-PS: Eastern Cooperative Oncology Group Performans Status **K-PS:** Karnofsky Performans Status; **MOS-PS:** Medical Outcome Study Physical Health; **KL-ADL:** Katz Activities of Daily Living; **B-ADL:** Barthel Index; **P-ADL:** Modified Katz Physical Activities of Daily Living; **NE-ADL:** Nottingham Extended Activities of Daily Living scale; **IADL₈:** Lawton Instrumental Activities of Daily Living; **IADL₄:** short Lawton Instrumental Activities of Daily Living; **OARS:** Older Americans Resources and Services.

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Table 2: FS tools and cut-off used when toxicity, treatment feasibility, post-surgical complication and treatment decision were the objective of the analyzed study

Study	Functional status measure tool → cut-off and stratification
Toxicity and treatment feasibility end point	
Aparicio 2013 ^[29]	K-PS → 60-70 vs. 80-90 vs. 100 IADL₈ → 1 abnormal < 8 (loss of at least 1 activity) vs. normal ≥ 8
Decoster 2017 ^[36]	ECOG-PS → < 2 vs. ≥ 2 / KL-ADL → loss of at least 1 point IADL₈ → loss of at least 1 point
Garja 2015 ^[50]	KPS → used as continuous variable / MOS_{PH} → used as a continuous variable OARS → used as a continuous variable
Kim 2014 ^[53]	ECOG-PS → < 2 vs. ≥ 2 B-ADL → dependent (loss of at least 1 activity) < 100 vs. independent 100 IADL₈ → dependent (loss of at least 1 activity) < 5 vs. independent 5
Laurent 2014 ^[55]	ECOG-PS → < 2 vs. ≥ 2 KL-ADL → loss of at least 1 activity
Mohile 2013 ^[56]	KPS → cut-off not reported
Puts 2011 ^[63]	ECOG-PS → < 2 vs. ≥ 2 / KL-ADL → At least 1 disability vs. no disabilities OARS → At least one disability vs. no disabilities
Shin 2012 ^[64]	ECOG-PS → < 2 vs. ≥ 2 / B-ADL → dependent (loss of at least one activity) vs. Independent IADL₈ → dependent (loss of at least one activity) vs. independent
Von Gruenigen 2017 ^[46]	ECOG-PS → no cut-off reported MOS_{PH} → used as a continuous variable : mean = 42 (range = 0-100) OARS → used as a continuous variable : mean = 12 (range = 2-14)
Surgical complications end point	
Fagard 2017 ^[37]	ECOG-PS → ≤ 1 vs. ≥ 2 / KL-ADL → Abnormal > 6 vs. Normal = 6 IADL₈ → Abnormal < 8 for women and < 5 for men vs. Normal = 8 for women, = 5 for men
Gerude 2014 ^[51]	KPS → ≤ 80 vs. > 90 / KL-ADL → < 5 dependent vs. ≥ 5 independent IADL → < 18 dependents vs. ≥ 18/27 independent
Huisman 2015 ^[52]	PS → ≤ 1 vs. > 1 KL-ADL → 0 vs. > 0 (loss of at least 1 activity) IADL₈ → 8 vs. < 8 (loss of at least 1 activity)
Korc-Grodzicki 2015 ^[54]	KL-ADL → Dependence (loss of at least 1 activity) IADL₈ → Dependence (loss of at least 1 activity)
Lee 2016 ^[67]	B-ADL → Dependence (loss of at least 1 activity) IADL → Dependence (loss of at least 1 activity)
Saraiva 2017 ^[43]	Duke's Index → < 4 METs dependent vs. ≥ 4 METs independent
Treatment decision endpoint	
Caillet 2011 ^[58]	ECOG-PS → ≥ 2 KL-ADL → loss of at least 1 point (dependence)
Chaibi 2011 ^[59]	KL-ADL → independent 6 vs. dependent < 6 (loss of at least 1 point) IADL₈ → independent 8 vs. dependent < 8 (loss of at least 1 point)
Farcet 2016 ^[38]	ECOG-PS → < 2 vs. ≥ 2 KL-ADL → 6 vs. < 6 (loss of at least 1 activity) OARS → one impaired activity

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ECOG-PS: Eastern Cooperative Oncology Group Performans Status **K-PS:** Karnofsky Performans Status; **MOS-PS:** Medical Outcome Study Physical Health; **KL-ADL:** Katz Activities of Daily Living; **B-ADL:** Barthel Index; **P-ADL:** Modified Katz Physical Activities of Daily Living; **NE-ADL:** Nottingham Extended Activities of Daily Living scale; **IADL₈:** Lawton Instrumental Activities of Daily Living; **IADL₄:** short Lawton Instrumental Activities of Daily Living; **OARS:** Older Americans Resources and Services.

Study	Study design	Functional status predictive value significance
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667 **Table 3:** Impact of FS on survival, outcomes analysis
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		*significant in univariate analysis **significant in regression analysis	°not significant in univariate analysis °°not significant in regression analysis
Aparicio 2017 [30]	Interventional randomized Phase III trial N=123, 4 years follow-up	Normal IADL score HR=1.99; [1.12-3.55]; p=0.02** was an OS independent prognosis factor in regression analysis. K-PS score wasn't associated with OS (p=0.42°).	
Bila 2015 [47]	Observational prospective N=110, 7 years follow-up	IADL ≥ 3 is reported associated with longer overall survival (log rank 6.62, p<0.001**).	
Corre 2016 [31]	Interventional randomized Phase III trial N=494, 3 years follow-up	FS assessments were significantly associated with TTFS in univariate analysis (PS = 2, HR=2.72 [2.05-3.60] p<0.0001*; ADL dependence HR=1.53 [1.18-1.98] p=0.0012*; IADL frailty HR=2.77 [2.05-3.75] p<0.0001*) but weren't included in the regression analysis.	
Deschler, 2013 [48]	Observational prospective N=195, 3.5 years follow-up	PS HR=2,14 [1,10-4,15] p=0,02** ; HR=2,45 [1,23-4,87] p=0,01** and ADL HR=2,60 [1,37-4,93] p=0,004** ; HR=2,10 [1,13-3,89] p=0,02** were prognosis factors of OS in 2 different models.	
Decoster 2017 [35]	Observational prospective N=245, 6 years follow-up	Neither ADL nor IADL were predictive of OS (p=0.131° and 0.055° respectively); PS was predictive of OS (OR=0.57; [0.42-0.76]; p<0.001**)	
Ferrat, 2015 [49]	Observational prospective N=993, 1 year follow-up	In PS model, (PS=2 HR=1.57 [1.10-2.44]; PS=3-4 HR=3.33 [2.42-4.58] p<0,001**), and ADL model (ADL ≤5 HR=1.73 ; [1,31-3,00] ; p<0,001**) were independent prognosis factors of 1 year survival.	
Girones, 2012 [60]	Observational prospective N=83, 2 years follow-up	In log rank analysis, ADL wasn't associated with survival (p=0.49°), but PS and IADL were significantly associated (p <0.001* for both variables).	
Hamaker 2011 [61]	Observational prospective N=292, 1 year follow-up	ADL was associated with 1-year mortality (HR=1.45 ; [1.08-1.98] ; p=0.02*), but was eliminated in the regression analysis (p>0.05). IADL wasn't associated with one year survival (p=0.69°).	
Jonna 2016 [41]	Observational retrospective N=803, 8 years follow-up	ADL and IADL were significantly associated with shorter survival (both p value <0.0001*) in the univariate analysis. Only IADL was used for the regression analysis (OR=1.34 ; [1.12-1.60] ; p=0.002**) and was an independent survival prognosis factor.	
Karampeazis, 2017 [32]	Interventional randomized trial N=106, 3 years follow-up	Abnormal IADL was significantly correlated with inferior OS median in univariate analysis (p=0.002*).	
Kenis 2017 [39]	Observational prospective N=439, 7 years follow-up	Baseline ADL , IADL were associated with OS in univariate analysis (p=0.009*, 0.003* respectively); IADL baseline wasn't tested in regression cox model, ADL baseline was predictive of OS (HR=0.71 [0.54-0.92] p=0.010**). PS wasn't tested	
Le Caer 2017 [40]	Observational prospective N= 194, 4 years follow-up	Neither ADL nor IADL were predictive of OS (p=0.14° and 0.17° respectively). PS ≥ 1 was predictive of shorter survival in both uni and multivariable analysis (HR=1.5, [1.1-2.0]; p=0.01*; HR=1.4; [1.02-1.9]; p=0.04**)	
Nabhan 2012 [62]	Observational retrospective N= 303, 10 years follow-up	Dependence in ADL was significantly predictive of OS in both aggressive (HR=3.07; IC95=1.78-5.28; p<0.0001**) and indolent non-Hodgkin lymphoma (HR=5.13; [2.06-12.77]; p=0.0004**)	
Naito 2016 [42]	Observational retrospective N=93, 4 years follow-up	Only IADL OR= 2.32 [1.18-4.43] p=0.015* was associated with survival in univariate analysis (ADL OR=2.00 [0.99-3.86] p=0.054°) but neither ADL nor IADL were in the regression analysis.	
Ommundsen 2014 [57]	Observational prospective N=178, 5 years follow-up	IADL was independent 5-year survival predictive factor in regression analysis (HR=2.3; [1.3-4.0] : p=0.006**).	
Perrone, 2015 [33]	Interventional randomized Phase III trial N=299, 6 years follow-up	Neither ADL HR=1.27 [0.70-2.31] p=0.43°, nor IADL HR=0.99 [0.64-1.52] p=0.95° were survival prognosis factors	
Peyrade 2011 [13]	Observational prospective N=150, 3.7 years follow-up	PS and IADL were associated with survival in univariate analysis (HR=2.9 [1.8-4.9] p<0.0001* and HR=1.8 [1.0-3.1] p=0.0394* respectively). Only IADL was used in the regression analysis and wasn't significantly associated with OS (HR=1.9 [1.0-3.9] p=0.064°)	
Puts 2011 [63]	Observational prospective N=112, 10 months follow-up	High PS and ADL disability were predictive of 6 month survival (HR=10.44; IC95=1.82-59.80; p=0.08** and HR=4.91; IC95=1.16-20.86; p=0.031** respectively)	
Quoix, 2011 [34]	Interventional randomized Phase III trial N=451, 3.5 years follow-up	Independence in ADL and PS ≤ 1 were survival independent prognosis factors (HR=0.67; [0.51-0.87] p=0.003** and HR=0.58; [0.46-0.74] ; p<0.0001** respectively)	
Schmidt 2017 [44]	Observational prospective N=131, 1 year follow-up	ADL and IADL weren't associated with 1-year survival in univariate analysis (p=0.20° and 0.56° respectively). Hence, the regression model didn't include these variables.	
Soubeyran, 2012 [65]	Observational prospective N=348, 6 months follow-up	PS was associated with early death in univariate analysis (p<0.001*) but is reported not significant in the regression analysis. ADL (p=0.065°) and IADL weren't significant in the univariate. analysis	
Spina 2012 [66]	Interventional non-randomized N=100, 12 years follow-up	In univariate analysis dependence in ADL and IADL were associated with shorter survival (p=0.0001* and 0.01* respectively), but weren't significant in regression analysis (p=0.44° and 0.32°° respectively).	
Tinquaut 2016 [45]	Observational prospective N=266, 2 or 4 years follow-up	IADL was reported to be associated with shorter survival. Several regression models were tested, IADL was included in model c, d and e and wasn't significant in either model d (p=0.13°°, 0.09°°, 2.33°°).	
Von Gruenigen 2017 [46]	Observational Prospective N=207, 3 years follow-up	IADL was associated with OS in Carboplatin/Paclitaxel treatment arm of univariate analysis (p=0.013*)	

PS: Performans Status **ADL:** Activities of Daily Living; **IADL:** Instrumental Activities of Daily Living; **HR:** Hazard ratio; **OR:** Odd ratio; **FS:** Functional Status; **OS:** Overall Survival; **ORR:** Objective Response Rate; **TTFS:** Treatment- Failure- Free Survival; **QoL:** Quality of Life;

Table 4: Impact of FS on toxicity, treatment feasibility, surgical complication and treatment decision, outcomes analysis

Study	Study design	Functional status predictive value significance	
		*significant in univariate analysis **significant in regression analysis	°not significant in univariate analysis °°not significant in regression analysis
Toxicity and treatment feasibility end point			
Aparicio 2013 ^[29]	Interventional randomized Phase III trial N=123	IADL score was associated with the appearance of grade 3-4 toxicity within 3 months after starting treatment in regression analysis (OR=4.67 [1.42-15.32]; p=0.011**) but wasn't associated with dose reduction (p=0.188°; 0.646°°). PS wasn't associated with either toxicity or dose reduction (p=0.736° and 0.464° respectively).	
Decoster 2017 ^[36]	Observational prospective N=193	Neither ADL, IADL nor PS were significantly associated with hematologic or non-hematologic grade 3-4 toxicity (p=0.810°; 0.936°; 0.237° and p=0.087°°; 0.934°; 0.934° respectively)	
Garja 2015 ^[50]	Observational prospective N=500	Neither ADL, IADL nor PS were significant predictors of primary dose reductions	
Kim 2014 ^[51]	Observational retrospective N=98	PS, ADL and IADL were significantly associated with treatment discontinuation (respectively p=0.001*; 0.001* and <0.001*) in comparison analysis. Only IADL was used in regression analysis and was an independent prognosis factor of treatment discontinuation (OR=3.06 [1.03-9.12] ; p=0.045**)	
Laurent 2014 ^[55]	Observational prospective n=385	Both PS (aOR=4.0 [1.87-8.7]; p<0.0001**) and ADL (aOR=3.01 [1.28-7.09]; p=0.01**) were independent prognosis factors of chemotherapy feasibility in 2 different analysis.	
Mohile 2013 ^[56]	Observational prospective N=207	No association were found between any GA domain and increased toxicity in either chemotherapy alone or chemotherapy associated with bevacizumab groups (data not shown)	
Puts 2011 ^[53]	Observational prospective N=112	neither PS, ADL, nor IADL were significant predictive factors of toxicity at 3 months	
Shin 2012 ^[54]	Observational prospective N=64	PS is predictive of occurrence of significant toxicity (OR=38.52 [1.25-1191.97], p=0.037**), neither ADL nor IADL were significant predictors of toxicity occurrence (p=0.63° and 0.29° respectively)	
Von Gruenigen, 2017 ^[46]	Observational prospective N=207	ADL and higher IADL score were significantly associated with completion of 4 chemotherapy cycles (OR=1.36; p=0.002* and OR=1.21 [1.05-1.04]; p= 0.008* respectively). Only IADL was associated with grade 3+ toxicity (OR=0.83; [0.72-0.96]; p=0.013*).	
Perrone 2015 ^[33]	Interventional randomized Phase III trial N=299	IADL was reported to be associated with severe non hematologic toxicity in regression analysis (p=0.03**)	
Surgical complications end point			
Fagard 2017 ^[37]	Observational prospective N=190	PS was predictive of post-operative complication in univariate but wasn't in multivariable (p(wald)=0.042*), IADL wasn't predictive of post-operative complications, whether ADL was predictive in uni and multivariable analysis (OR=0.31; IC95=0.14-0.69; p=0.004**)	
Gerude 2014 ^[51]	Observational prospective N=67	PS, ADL and IADL were significantly associated with post-operative complication (respectively: RR=1.76, [1.06-2.92], p=0.45*; RR=1.26; [1.26-2.22]; p=0.45* RR=2.19; [1.21-3.94]; p=0.005*)	
Huisman 2015 ^[52]	Observational prospective N=328	ADL wasn't associated to surgical complications (p>0.05°°).	
Korc-Grodzicki, 2015 ^[54]	Observational retrospective N=416	IADL was an independent prognosis factor of post-operative delirium (OR= 2.39 [1.39-4.09] p=0,001**), when ADL wasn't (OR=1.49 [0.86-2.57]; p=0,147°).	
Lee 2016 ^[67]	Observational retrospective N=240	Dependence in ADL was an independent prognosis factor of major postoperative complications in regression analysis (OR=16.369 [1.233-217.12]; p=0.034**)	
Saraiva 2017 ^[43]	Observational retrospective N=138	Independence in ADL associated with reduced odds of postoperative complications in regression analysis (OR=0.11, [0.02–0.85]; p=0.034**)	
Treatment decision endpoint			
Caillet, 2011 ^[58]	Observational prospective N=375	0.5 points decrease in ADL score was independent prognosis factor of changes in the initial treatment decision (OR=0.25; [1.04-1.49]; p=0.016**). PS wasn't significantly associated with changes in the treatment plan (p=0.74°°).	
Chaibi, 2011 ^[59]	Observational prospective N=161	Patient with higher rate of ADL dependence were generally in lower dose-intensity group of treatment (p<0.01*).	
Farcet, 2016 ^[38]	Observational prospective N=217,	ADL was predictive of final recommendation (OR=0,4 [0,2-0,8]; p=0,01**). IADL and PS were significantly associated with final treatment decision in the univariate analysis (OR=0,4 [0,2-0,7]; p=0,002* and OR=0,3 [0,1-0,8]; p=0,01* respectively) but weren't in the regression analysis.	

PS: Performans Status ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; HR: Hazard ratio; OR: Odd ratio; aOR: adjusted Odd ratio FS: Functional Status;