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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.

27 **ABSTRACT:**

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

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

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

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

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

46

47 **INTRODUCTION**

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

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

59 Living (IADL). In the American Society of Clinical Oncology (ASCO) guidelines, the Expert Panel
60 recommends only IADL for assessing function [6]. The Katz index for Activities of Daily Living (KL-ADL)
61 [7] covers six basic functions: bathing, dressing, toileting, moving, bowel and bladder control, and
62 eating. The Barthel index (B-ADL) [8] is especially used in rehabilitation settings and measures the
63 ability to perform 10 different functions: personal hygiene, bathing, feeding, toileting, climbing stairs,
64 dressing, bowel and bladder control, mobility, and chair/bed transfers. The MOS physical health
65 (MOS_{PH}) [9,10] measures the ability to perform a selection of 10 physical functions from
66 bathing/dressing to vigorous activities.

67 Alongside ADL, Instrumental Activities of Daily Living (IADL) is also used to assess FS. The most
68 frequently used tool is the Lawton Instrumental Activities of Daily Living scale (IADL₈) [11], which
69 measures eight community activities: handling finances, shopping, food preparation, housekeeping,
70 using the telephone, doing the laundry, using transportation, and taking medication. A short IADL tool
71 (IADL₄) based on 4 questions was developed during the PAQUID study [12] and only measures
72 handling finances, using the telephone, using transportation, and taking medication. This short IADL,
73 already common in daily medical practice, is being increasingly used as a tool in research [13]. The KL-
74 ADL and IADL₈ scales are self-assessment questionnaires that can be completed with the help of a
75 caregiver or a practitioner, if necessary. The Older Americans Resources and Services (OARS)
76 Multidimensional Functional Assessment Questionnaire [14] measures the ability to carry out activities
77 required to preserve independence in the community and comprises seven items including shopping,
78 meal preparation, making telephone calls, and money management. The P-ADL (modified Katz physical
79 activities of daily living) [15] and the NE-ADL (Nottingham extended activities of daily living) [16] scales
80 measure activities such as housekeeping, leisure activities, food preparation, and mobility. The Pepper
81 Assessment Tool for Disability comprises nineteen items and is used to assess instrumental activities,
82 activities of daily living, and mobility [17]. Other tools [18] including the Rosow-Breslau Health Scale
83 [19], the Nagi Scale [20], the Geronte scale [21], and the Duke Activity Status Index [22] have been
84 developed but are used much less.

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

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

93

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.

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

126 **Quality methodology**

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

131 **RESULTS**

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

135 **Quality assessment (Appendices B and C)**

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

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

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

144 **Characteristics of the studies included (Appendix D)**

145 Sixteen studies were conducted between 2016 and 2017 [30–32,35–46,67], thirteen between 2013 and
146 2015 [29,33,47–57], and eleven between 2010 and 2012 [13,34,58–66]. Twenty-seven studies were
147 conducted in Europe [13,29–40,44,45,47–49,52,55,57–61,65,66], nine in America
148 [43,44,46,50,51,54,56,62,63], and four in Asia [42,53,64,67].

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

152 Thirty-seven studies included cancer pathologies regardless of the stage [6,13,29–31,34–42,44–55,57–
153 67] and three metastatic cancer only [29–31].

154 Eighteen studies included patients with any type of cancer [38,39,41,43,44,49,50,52–56,58,59,61,63–
155 65], six only included colorectal cancers [29,30,36,37,57,67], six investigated hematological
156 malignancies [13,42,47,48,62,66], six concerned lung cancer [31,32,34,35,40,60], one breast cancer
157 [33], 2 ovarian cancer [45,46], and one head and neck tumors [51].

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

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

163 The most common Activities of Daily Living scales used were KL-ADL in 25 studies [31–
164 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
165 studies [46,50].

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

169 The most popular Instrumental Activities of Daily Living tool was the IADL₈ (22 studies) [29,30,32,33,35–
170 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],
171 the OARS in five studies [38,46,50,56,63], and the NE-ADL and P-ADL scales were each used in one
172 study [57,61].

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

176 With regard to the use of performance status scales, the ECOG-PS was preferred (24 studies) [13,31–
177 38,40,42,45,46,49,52,53,55,58,60,62–65] over the KPS (six studies) [29,30,48,50,51,56].

178 ADL, IADL, and performance status scales were analyzed together in nineteen studies [31–33,35–
179 40,42,45,46,50,52,53,60,63–65].

180 **Functional status cut-off (Tables 1 and 2)**

181 For the ECOG-PS, the cut-off was < 2 vs. ≥ 2 in nineteen studies [13,31,32,34–
182 39,42,45,49,53,55,58,62–65]. In three studies the reported cut-off was < 1 vs. ≥ 1 [33,40,52].

183 Aparicio *et al.* used the KPS scale to divide the population into three sub-groups (60-70%, 80-90%, and
184 100%) [29,30]. Deschler *et al.* used a $< 80\%$ vs. $\geq 80\%$ cut-off [48], Gerude *et al.* used a $\leq 80\%$ vs. $>$
185 90% cut-off [51], and Garja *et al.* used the KPS as a continuous variable [50].

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

192 The cut-off was the same in twenty of the twenty-two studies assessing FS using the IADL₈ scale:
193 patients were deemed dependent when they lost the ability to perform at least one activity [29,30,33,35–
194 37,39,41,42,44,45,52–54,59,60,64–67]. Similarly, for the IADL₄ scale, patients were also characterized
195 as dependent with the loss of at least one activity [13,31,40]. The number of activities assessed was,
196 however, heterogeneous, as most men only performed five out of the eight items on the IADL₈ scale;
197 this was avoided when the IADL₄ was used. The OARS scale was employed in four studies with the
198 same cut-off. Patients were considered dependent once they were no longer able to perform at least
199 one activity [38,46,50,63]. According to the NE-ADL scale, patients presenting a score under 44 / 66
200 were deemed dependent [57] and according to the P-ADL scale, dependency was defined as the loss of
201 ability to perform at least one activity [61].

202 **FS as a predictor of OS (table 3)**

203 Out of the 40 studies, 24 analyzed the impact of FS on OS [13,30,33,35,39,41,42,44–49,57,60–
204 63,65,66].

205 Out of the twenty-two studies using regression analysis, eleven showed a significant association
206 between the FS scores and OS [30,34,35,39,41,47–49,57,62,63]. The impact of IADL on OS was
207 analyzed in nineteen studies [13,31–33,35,39,40,42,44–47,57,60,61,65,66] and was confirmed by
208 regression analysis in only five studies [30,41,47,57,62]. Seventeen studies analyzed the impact of ADL
209 on OS [31,33–35,39–42,44,48,49,60–63,65,66]; regression analysis confirmed the positive impact of
210 ADL in six studies [34,39,48,49,62,63] and PS was a significant prognostic factor of OS in six studies
211 [34,35,40,48,49,63].

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

214 impact of IADL on OS was confirmed in one study [41] and the impact of ADL on OS in three studies
215 [39,49,63].

216 **FS and treatment decisions (table 4)**

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

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

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

224 Regression analysis was conducted in seven studies to evaluate the predictive value of FS on
225 chemotherapy toxicity [29,33,36,46,56,63,64]. IADL (IADL₈) was significantly associated with toxicity in
226 two studies [29,33] and PS (ECOG-PS) was an independent predictive factor of toxicity in another study
227 [64].

228 Two studies were adjusted according to age [33,64], one according to gender [29] and one according
229 to gender, age and comorbidities [63]. IADL has an impact on chemotoxicity in two adjusted analyses
230 [29,33].

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

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

235 **FS as a predictor of postoperative complications (table 4)**

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

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

244 **DISCUSSION**

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

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

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

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

284 In 2012, Puts *et al* reviewed 73 studies to provide an overview of all geriatric assessment instruments
285 used in an oncology setting and reported that 68 out of 73 CGA studies analyzed the ADL domain
286 mostly using the KL-ADL score (56%), and that 65 out of 73 teams explored the IADL domain using the
287 IADL₈ scale (62%) [4]. In comparison with Puts *et al.*'s review, this new review shows that KL-ADL
288 (73.5%) and IADL₈ (81.5%) were more frequently used. Our study states the use of two different PS
289 scales, four different ADL scales, and five different IADL scales. However, our review confirms that KL-
290 ADL and IADL₈ are the predominant tools for measuring ADL and IADL in older cancer patients,
291 followed by KL-ADL and B-ADL. The MOS_{PH} was used in only two analyses and NE-ADL, P-ADL,
292 OARS, and IADL₄ are rarely used, although in practice, the IADL₈ scale leads to discrepancies in older
293 population. Indeed, with IADL₈, all eight domains were assessed for women, whereas items in the
294 domains of food preparation, housekeeping, and laundering were omitted for men. This disparity
295 encouraged the current guidelines to recommend the use of the same score for both genders. Recently,
296 a Geriatric COre Data sEt (G-CODE) using tools or items validated in older cancer and non-cancer
297 populations was proposed. IADL₄ was selected for G-CODE according to an explicit consensus
298 approach (modified Delphi method) [74]. The generalization of the IADL₄ score, which overcomes the
299 differences in scoring and reduces examination time, should be considered in the future for trials
300 enrolling older cancer patients.

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

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

318 Most studies used the same cut-off to determine dependence in ADL or IADL scores. The loss of ability
319 to perform at least one ADL or IADL activity was generally used to detect impairment, as recommended
320 by the literature and by the SIOG. For the ECOG-PS, the cut-off was < 2 vs. ≥ 2 in most studies [31,34–
321 39,42,45,49,53,55,58,62–65]. In current clinical trials, patients with an ECOG-PS of 0 to 1 are often
322 included, while patients with a PS of 2 or worse are usually excluded, as this cut-off (≥ 2) is predictive of
323 poor outcomes for cancer populations in some studies [76]. Even though most studies compared
324 populations using the usual cut-off, some used different ones thus adding to the heterogeneity of the
325 results of the studies.

326 Eleven studies showed a significant association between FS scores and OS [30,34,35,39,41,47–
327 49,57,62,63]. Five studies [30,41,47,57,62] used regression analysis to identify IADL and OS, and six
328 studies [34,39,48,49,62,63] to identify ADL. In comparison with OS, the other endpoints studied in this
329 review were less analyzed. Treatment decisions were analyzed in three studies [38,58,59]; KL-ADL was
330 predictive in populations treated for any type of cancer or undergoing any therapy in two of these
331 studies [38,58]. Five studies in our systematic review analyzed oncological treatment feasibility
332 [29,46,50,53,55]. KL-ADL and ECOG-PS [55], as well as IADL₈ [53], were associated with treatment
333 feasibility in two studies; IADL₈ was significantly associated with chemotoxicity in two studies [29,33].
334 Few studies have analyzed specifically the prognostic value of the CGA domains [2] with regards to
335 oncological treatment toxicity and feasibility in older cancer patients. Six studies analyzed FS and
336 postoperative complications [37,43,51,52,54,67]. IADL₈ was associated with postoperative delirium in
337 one study [54] and ADL with major postoperative complications in three studies [37,43,67]. FS seems to
338 be predictive of OS after surgical treatment but few studies on surgical treatment outcomes were eligible
339 for this work.

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

347 **CONCLUSION**

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

357

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361 **CONFLICT OF INTEREST:**

362 The authors declare that they have no competing interests.

363

364 **AUTHOR'S CONTRIBUTIONS:**

365 Concept and Design: AL. Couderc

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

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

373 **Appendix A:** MeSH Search exact wording

374 **Appendix B:** Quality assessment of included studies using MINORS

375 **Appendix C:** Statistical Methodology of the analyzed studies

376 **Appendix D:** Frequency of the different functional status measurement tools

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Study	Functional status measure tool → cut-off and stratification
<i>Aparicio 2017</i> ^[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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Bila 2015 ^[47]	IADL ₈ → < 3 vs. ≥ 3
Corre et al 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) IADL ₄ → 0 fit patients vs. 1 vulnerable patients vs. ≥ 2 frail.
Deschler 2013 ^[48]	K-PS → < 80 vs. ≥ 80 B-ADL → < 100 vs. 100 (loss of at least 1 activity)
Decoster 2017 ^[35]	ECOG-PS → ≤1 vs. ≥ 2 / KL-ADL → Abnormal > 6 to 24 vs. normal =6 IADL ₈ → Abnormal < 8 for women and < 5 for men vs. normal =8 for women, =5 for men
Ferrat 2015 ^[49]	ECOG-PS → 0-1 vs. 2 vs. ≥ 2 KL-ADL → > 6 vs. < 6 (loss of at least 1 activity)
Girones 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)
Hamaker 2011 ^[61]	KL-ADL → impaired (loss of at least 1 activity) vs. normal P-ADL → impaired (loss of at least 1 activity) vs. normal
Jonna 2016 ^[41]	KL-ADL → Dependence < 17/18 vs. independent ≥ 17/18 (loss of at least 1 activity) IADL ₈ → Dependence < 20/24 vs. independent ≥ 20/24 (loss of at least 1 activity)
Karampeazis 2017 ^[32]	ECOG-PS → 0 vs. 1 vs. 2 KL-ADL → Abnormal < 6 (loss of at least 1 activity) vs. normal 6 IADL ₈ → Abnormal < 7 (loss of at least 2 activities) vs. normal 7
Kenis 2017 ^[39]	ECOG-PS → ≤ 1 vs. ≥ 2 / KL-ADL → Abnormal > 6 to 24 vs. normal =6 IADL ₈ → Abnormal < 8 for women and < 5 for men vs. normal =8 for women, =5 for men
Le Caer 2017 ^[40]	ECOG-PS → 0 vs. ≥ 1 / KL-ADL → Abnormal < 6 vs. normal =6 IADL ₈ → Abnormal ≤ 2 vs. Normal >2
Nabhan 2012 ^[62]	ECOG-PS → > 2 / ADL → loss of at least 1 activity
Naito 2016 ^[42]	ECOG-PS → < 2 vs. ≥ 2 B-ADL → impaired (loss of at least 1 activity) vs. normal (< 100 vs. 100) IADL ₈ → impaired (loss of at least 1 activity) vs. normal
Ommundsen, 2014 ^[57]	B-ADL → Frail < 19/30 vs. Non-frail ≥ 19/30 NE-ADL → Independent > 43/66 vs. dependent < 44/66
Perrone 2015 ^[33]	ECOG-PS → 0 vs. 1 / KL-ADL → < 6 impaired (loss of 1 activity) vs. ≥ 6 normal IADL ₈ → impaired < 8 (loss of at least 1 activity) vs. ≥ 8 normal
Peyrade 2011 ^[13]	ECOG-PS → <2 vs. ≥ 2 / IADL ₄ → With limitation < 4 (loss of at least 1 activity)
Quoix 2011 ^[34]	ECOG-PS → ≤ 1 vs. 2 KL-ADL → Independent 6 vs. dependent < 6 (loss of at least 1 activity)
Schmidt 2017 ^[44]	B-ADL → Independent 100 vs. dependent <100 (loss of at least 1 activity) IADL ₈ → Independent 8 vs. dependent < 8 (loss of at least 1 activity)
Soubeyran 2012 ^[65]	ECOG-PS → ≤ 2 vs. >2 KL-ADL → Abnormal ≤ 5 (loss of at least 1 activity) vs. normal > 5 IADL ₈ → Abnormal ≤ 7 (loss of at least 1 activity) vs. normal > 7
Spina 2012 ^[66]	KL-ADL → Abnormal <6 (loss of at least 1 activity) vs. normal 6 IADL ₈ → Abnormal <8 (loss of at least 1 activity) vs. normal ≥ 8
Tinquaut 2016 ^[45]	ECOG-PS → < 2 vs. ≥ 2 KL-ADL → Abnormal < 6 vs. normal 6 (loss of at least 1 activity) IADL ₈ → Abnormal < 25 vs. normal ≥ 25 (loss of at least 1 activity)

656 **ECOG-PS:** Eastern Cooperative Oncology Group Performans Status **K-PS:** Kamofsky Performans Status; **MOS-PS:** Medical Outcome Study
657 Physical Health; **KL-ADL:** Katz Activities of Daily Living; **B-ADL:** Barthel Index; **P-ADL:** Modified Katz Physical Activities of Daily Living; **NE-ADL:**
658 Nottingham Extended Activities of Daily Living scale; **IADL₈:** Lawton Instrumental Activities of Daily Living; **IADL₄:** short Lawton Instrumental
659 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:** Kamofsky 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 ^[64]	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;