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## FUNCTIONAL STATUS IN OLDER PATIENTS WITH CANCER

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## **Abstract:**

*Background:* Functional Status (FS) is an important domain in Comprehensive Geriatric Assessment (CGA) and is most often evaluated using the Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) scales separately.

*Method and objectives:* This secondary analysis of a previous prospective cohort study was conducted between September 2015 and May 2018 at Marseille University Hospital, France, on 613 cancer outpatients aged  $\geq 70$  years.

The first objective of this study was to determine the prevalence of FS impairment in older outpatients with cancer using a combination of the information collected with the ADL and short IADL scales. Our second objective was to describe the potential impact of this combined FS on three-month unplanned hospitalizations and three-month mortality in this population.

*Results:* The median age was 81 years and 61.2% were men. The most common types of tumours were lung and thoracic (22.3%). Concerning FS, 255 patients (41.6%) had unimpaired ADL-IADL, 131 patients (21.4%) had IADL impairment, 38 patients (6.2%) had ADL impairment, and 189 patients (30.8%) had impaired ADL-IADL. In the multivariate Cox analysis, metastatic stage (adjusted Hazard Ratio (aHR) = 1.79; 95% CI [1.14-2.80]) and impaired ADL-IADL (aHR = 3.46; 95% CI [1.89-6.33]) were independently associated with three-month mortality. In the logistic regression model, impaired ADL-IADL (adjusted Odd ratio (aOR) = 3.64; 95% CI [1.84-7.20]) was the only factor independently associated with three-month unplanned hospitalizations.

*Interpretation:* The combined use of the ADL and IADL scales to evaluate functional status in older patients with cancer is of significant prognostic value regarding the risks of three-month unplanned hospitalizations and mortality.

## **Keywords:**

Functional status; Older patients; Cancer management; Mortality; Unplanned hospitalization.

## **Introduction**

In recent years, oncologists and geriatricians have been working together to integrate Comprehensive Geriatric Assessments (CGA) into oncological practice for older patients with cancer. The International Society of Geriatric Oncology (SIOG) and the National Comprehensive Cancer Network currently recommend systematically performing a CGA in older patients treated for cancer [1,2]. Functional status (FS) is an important domain in CGA [3–6], and according to the SIOG [4], Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) are both useful to assess FS. However, the American Society of Clinical Oncology (ASCO) Expert Panel recommends using the IADL for assessing FS [7]. Although many tools have been developed for screening functional decline, the Katz ADL scale and the Lawton IADL scale are the two most widely used scales in the international literature [8,9]. The Katz ADL scale covers basic functions in six questions: self-bathing, dressing, going to the toilet, moving, bowel and bladder control, and eating [8]. The Lawton IADL scale [9] measures eight activities: handling finances, shopping, food preparation, housekeeping, telephone use, laundry, use of transportation, and medication management. However, as the performance of some of these tasks varies across gender and age groups, a short version of the Lawton IADL scale (short IADL) was developed during the PAQUID study [10] and is now commonly used. This short IADL measures only four activities: handling finances, telephone use, use of transportation, and medication management (each activity is rated as one out of four and is considered as impaired if < 4). For both tools, the loss of independence in performing at least one activity is the main cut-off used to determine impaired FS [11]. In older adults, functional decline is associated with an increased risk of poor survival, institutionalization, and hospitalization [12,13]. In older adults with cancer, impaired FS is often associated with treatment decision and feasibility [14], as well as increased chemotoxicity [15] and postoperative complications [16,17]. Most studies have shown an association between FS and poor survival [18–24] but not all [25]. FS is most often evaluated using ADL alone [20] or sometimes using ADL and IADL separately [22]. To our knowledge, only Pamoukdjian *et al.* have used the ADL and short IADL scales together to define “disability” in older outpatients treated for cancer [26].

IADL assesses the more complex acts of daily living, which are usually impaired earlier in older patients than the basic acts of daily living assessed with ADL. However, in older community-dwelling patients with cancer, loss of autonomy in one of the four instrumental daily living activities assessed with the short IADL may be a greater obstacle to outpatient

follow-up than a loss of autonomy in one of the daily living activities assessed with ADL. Indeed, mild cognitive impairment in physically independent patients living at home can lead to difficulties taking medication or using the telephone and be responsible for delays in medical care. To promote outpatient care for older community-dwelling patients with cancer, it is important to identify FS impairment that may increase the risk of hospitalization and early death.

The first objective of this study was to determine the prevalence of impaired FS in a heterogeneous group of older cancer outpatients using a combination of the information collected with the ADL and short IADL scales. Our second objective was to describe the potential impact of this combined assessment of FS on three-month unplanned hospitalizations and three-month mortality in this population.

## **Material and methods**

### *Study design and population*

This prospective, observational cohort study was originally conducted between September 2015 and May 2018 at Marseille University Hospital, France, on 621 older patients with cancer to analyze the association of high serum B12 levels with C-reactive protein in older patients with cancer [27]. Geriatric, oncological, and survival data from this study were secondarily analyzed to evaluate the prognostic value of FS for three-month survival and unplanned hospitalizations; eight patients with incomplete or missing FS assessments were excluded from the analysis. Patients enrolled were all patients with cancer aged 70 years or older living at home or in a nursing home, or hospitalized in rehabilitation units, referred by Oncology and Surgery units to the geriatric oncology unit for a CGA before initiation of any oncological treatment. This CGA was performed in an outpatient setting by a geriatrician at the Geriatric Day Hospital.

All the patients were registered at baseline in accordance with the French database and Privacy law (Commission Nationale de l'Informatique et Liberté CNIL registration number: 2017-33).

### *Data collection and baseline measurements*

Oncological, geriatric, and biological data were collected prospectively. Functional status was determined using the Activities of Daily Living (ADL) scale according to Katz *et al.*

(impaired < 6) [8] and the short Instrumental Activities of Daily Living (short IADL) scale according to Barberger-Gateau *et al.* (impaired < 4) [9,10].

Geriatric frailties were detected using the G8 screening tool (impaired  $\leq 14/17$ ) [28] and the ECOG-PS vulnerability score (impaired  $\geq 2$ ) [29]. The following geriatric domains were also assessed: nutritional status according to the Body Mass Index (BMI), the Mini Nutritional Assessment scale (MNA) [30], and albumin levels. The definition of malnutrition was derived from the recommendations of the French Department of Health (BMI < 21 and/or albumin levels < 35 g/l and/or MNA < 17).

Mobility was assessed using gait speed (impaired < 0.8 m/s) [31], the Timed Up and Go Test (impaired TUG  $\geq 20$  s) [32], the one leg balance test (impaired < 5 s) [33], and fall history in the three months prior to the CGA.

Moreover, patients were asked about their demographic characteristics and lifestyle (age and living place). The main medical information was obtained from the medical records: tumour site and extension (localized or advanced disease).

#### *Follow-up data*

Patient follow-up was limited to three months. Three-month unplanned hospitalizations and three-month mortality were retrospectively collected at the end of the follow-up period and defined as one or more unplanned hospitalizations lasting more than 24 hours during the three months following the CGA and death within three months following the CGA, respectively.

#### *Functional status*

We created a new variable, "Functional Status", combining the ADL and short IADL scales and comprising three items: 0-0 (unimpaired ADL-IADL), 1-0 (ADL impairment or IADL impairment), and 1-1 (impaired ADL-IADL).

#### *Statistical analysis*

All quantitative variables are presented using descriptive statistics: number of subjects and percentages. Qualitative variables are described by absolute frequencies and percentages (proportion). Pearson's Chi-squared test or Fisher's exact test was used when appropriate to compare geriatric and oncological factors associated with FS as an independent variable in relation to socio-demographic, geriatric, oncological, and biological data. Variables with  $p < 0.05$  were considered significant.

Pearson's Chi-squared test was performed to determine the factors associated with unplanned hospitalizations. Multivariate analysis was conducted using a logistic regression test.

Mortality analysis was performed using a Cox regression model. A p-value  $\leq 0.05$  was considered statistically significant. Statistical analyses were performed using R studio version 0.99.902 and SPSS software (version 17.0) for windows.

## **Results**

### *Patient characteristics (Table 1)*

Out of the 621 patients recruited [27], eight patients were excluded due to missing data concerning functional status. The final study sample comprised 613 patients.

The median age was 81 years (interquartile range 70 to 98 years), the mean age was  $81 \pm 0.2$  years (youngest patient was 70 years, oldest was 98 years), and 61.2 % were men. A large majority of patients (89.1%) were community-dwelling patients; only 4.7% were living in nursing homes and 6.2% were in rehabilitation units at the time of the survey. The most frequent types of tumours were lung and thoracic (22.3%), digestive, head and neck tumours (25.6%), prostate cancer (17.3%), and urological and gynaecological cancers (16.2%). Other localizations included breast cancer (n = 48; 7.8%), haematological malignancies (n = 36; 5.9%), dermatological cancers (n = 26; 4.2%), and sarcoma (n = 4; 0.6%). A total of 209 patients with solid tumours (36.6%) had metastatic cancer. Detailed demographic, clinical, and geriatric characteristics are presented in Table 1.

### *Functional Status (Table 1)*

Concerning FS, 255 patients (41.6%) had unimpaired ADL-IADL, 169 patients (27.6%) had either impaired IADL or ADL of which 21.4% impaired IADL and 6.2% impaired ADL (see supplementary data 2 for details), and 189 patients (30.8%) had impaired ADL-IADL. Women, patients > 85 years old, living in nursing homes or rehabilitation units, suffering from malnutrition, with an ECOG-PS  $\geq 2$ , a G8  $\leq 14$ , a TUG  $\geq 20$  s, a one leg balance test < 5 s, a gait speed < 0.8 m/s, or with a history of falls in the past three months were more likely than others to have impaired ADL-IADL.

### *Mortality within three months*

In our study, 31 patients (5.1%) died within three months; no survival data were available for 46 patients (data for these patients was censored at the date they were last known to be alive). The majority of the early deaths (19 out of 31 patients; 61.3%) were attributable to cancer progression. The median follow-up time was ten months (range 1 to 35 months). In the univariate Cox analysis, the risk of three-month mortality was significantly higher in the

oldest patients, those living in rehabilitation units, those who were malnourished, those with metastatic cancer, impaired ADL-IADL, impaired TUG ( $\geq 20$  sec), impaired one leg balance test ( $< 5$  s) or fall history in the last three months, or impaired G8 and PS (detailed table in Supplementary data 3). Table 1 shows that several geriatric domains were associated with FS, and consequently the only geriatric variable included in the multivariate analysis was FS analysed regardless of gender, age, cancer stage, or metastatic status. In the multivariate Cox analysis, metastatic stage (aHR = 1.79; 95% CI [1.14-2.80]) and impaired ADL-IADL (aHR = 3.46; 95% CI [1.89-6.33]) were independently associated with mortality within three months (Figure 1).

#### *Unplanned hospitalization within three months*

Sixty-five patients (10.6 %) had at least one unplanned hospitalization within three months; no data were available for thirty-four patients. In the univariate analysis, the risk of three-month unplanned hospitalizations was significantly higher in patients in rehabilitation units, those with impaired functional status (impaired ADL-IADL), and those who were malnourished (detailed table in Supplementary data 3). In the logistic regression model, impaired ADL-IADL (OR = 3.64; 95% CI [1.84-7.20]) was the only factor independently associated with outcome (Figure 2).

### **Discussion**

ADL and IADL are considered equally important to evaluate FS in older patients treated for cancer because they provide useful complementary information for the management of this population. According to our results, impaired functional status assessed using a combination of the ADL and short IADL scales has an important impact on three-month mortality and the risk of unplanned hospitalizations within three months in a study sample comprising a large majority of older community-dwelling patients with cancer. To our knowledge, only one previous study has used both scores to assess and predict poor outcomes in older patients with all types of cancer [26].

In our study, some factors were associated with ADL-IADL impairment at initiation of oncological treatment. Our results show that age over 85 years is associated with functional impairment, which is consistent with previous analyses [34]. We also observed an association between female gender and functional impairment. Moreover, our study is one of only a few to highlight this finding [35]. Nutritional status determined according to the BMI, albumin levels and MNA, was also associated with impaired ADL-IADL in accordance with other

oncological and geriatric studies [19,36]. As the ADL scale only contains self-reported mobility items, ASCO recommends considering objective measures of assessing physical function and using ADL deficit to characterize frailty [7]. Consequently, in CGA, assessing physical function and conducting mobility tests (gait speed, grip strength, one leg balance test, Timed Up and Go test, fall history) in addition to the ADL and IADL scales would provide a comprehensive assessment of FS in older patients with cancer [37,38]. In our study, ADL-IADL impairment was significantly associated with mobility disorders evaluated according to TUG, gait speed, one leg balance test, and fall history. The latter, an indicator of mobility disorders, is also associated with ADL impairment in the literature [37,38].

ADL-IADL impairment had a negative impact on three-month survival in our ambulatory population treated for cancer. IADL is the first FS scale impacted by mild cognitive impairment, so its use is recommended by the SIOG and ASCO guidelines [7]. The ADL scale comprises basic self-care functions including mobility with walking and grooming items, and is also impaired in the case of mobility disorders or severe cognitive disorders. In the literature, the respective impacts of ADL impairment [18–21] and IADL impairment [21–23] on mortality in older patients with cancer have already been demonstrated, more often among hospitalized older patients. In our outpatient sample, the combination of impaired basic (ADL) and instrumental (IADL) functions had an impact on three-month mortality, irrespective of the cancer localization. The importance of overall functional status on survival is in accordance with one study evaluating changes in ADL and IADL two to three months after initiation of chemotherapy in older patients treated for cancer: ADL impairment was strongly associated with poor overall survival and IADL impairment was also a prognostic factor for poor overall survival but less prominent (HR 2.34 and 1.25, respectively) [19]. These results show the importance of managing ADL and IADL impairment with interventions at home to improve three-month survival in older patients treated with chemotherapy.

In our work, impaired ADL-IADL increased the risk of unplanned hospitalizations within three months. This is the first study to show the impact of a combination of the two scales on the risk of three-month unplanned hospitalizations in older patients irrespective of cancer site and severity. In another study, IADL impairment was independently associated with unplanned hospitalizations of patients with ovarian cancer [39], and an analysis carried out previously in our cohort showed an association between IADL impairment and unplanned hospitalizations within 1 month [27]. IADL impairment also had an impact on chemotoxicity in some studies [15] whereas ADL was predictive of oncological treatment feasibility in one

study [40]. This shows the importance of these two FS tools on the outcome of older patients treated for cancer. Functional impairment at the beginning of oncological treatment must be managed for all functional activities through multidisciplinary interventions, regardless of the loss of function. Measures to help or improve self-bathing or mobility must be implemented at the same time and given the same importance as assistance with managing medication, organizing transport, or any instrumental activities that may be impaired before ambulatory patients initiate cancer treatment.

This study has some limitations. Firstly, it was a monocentric study, and survival and unplanned hospitalizations were calculated after geriatric evaluation and not initiation of oncological treatment; furthermore, vital status at three months was missing for 46 patients (7%) this is a little over the number of death occurrence at three months which may be underestimated. This study also included various tumour types and sites but the detailed oncological treatments were not recorded. Finally, functional impairment was evaluated at oncological treatment initiation and was not followed up, so functional decline was not measured in our study. However, our study had several strengths. An important strength was the inclusion of a large number of older ambulatory patients (613 persons). Additionally, both ADL and IADL were integrated into our work, in particular to determine the impact on mortality and unplanned hospitalizations in older adults with cancer.

### **Conclusion**

Functional impairment in both ADL and IADL is an important short-term prognostic factor for mortality and the risk of unplanned hospitalizations in older outpatients with cancer. Some geriatric and biological factors were associated with functional impairment in both ADL and IADL such as age, living place, mobility disorders, or nutritional status evaluated according to the BMI, albumin levels, and MNA. Evaluation of functional status during CGA in older patients at initiation of cancer treatment should integrate combined information from both the ADL and IADL scales.

**Credits, Author statement:** *Study concepts and design:* AL. Couderc, P. Suchon, B. Saliba-Serre, D. Rey, E. Nouguerede, R. Arcani, L. Farnault, A. Daumas, A. Courcier, L. Greillier, F. Barlesi, F. Duffaud, S. Salas, R. Costello, G. Venton and P. Villani. *Study design:* AL. Couderc, P. Suchon, B. Saliba-Serre, D. Rey, E. Nouguerede, R. Arcani, L. Farnault, A. Daumas, A. Courcier, L. Greillier, F. Barlesi, F. Duffaud, S. Salas, R. Costello, G. Venton and P. Villani. *Data acquisition:* AL. Couderc. *Quality control of data and algorithms:* AL.

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### **Declaration of competing interest**

None of the authors have any conflicts of interest to disclose.

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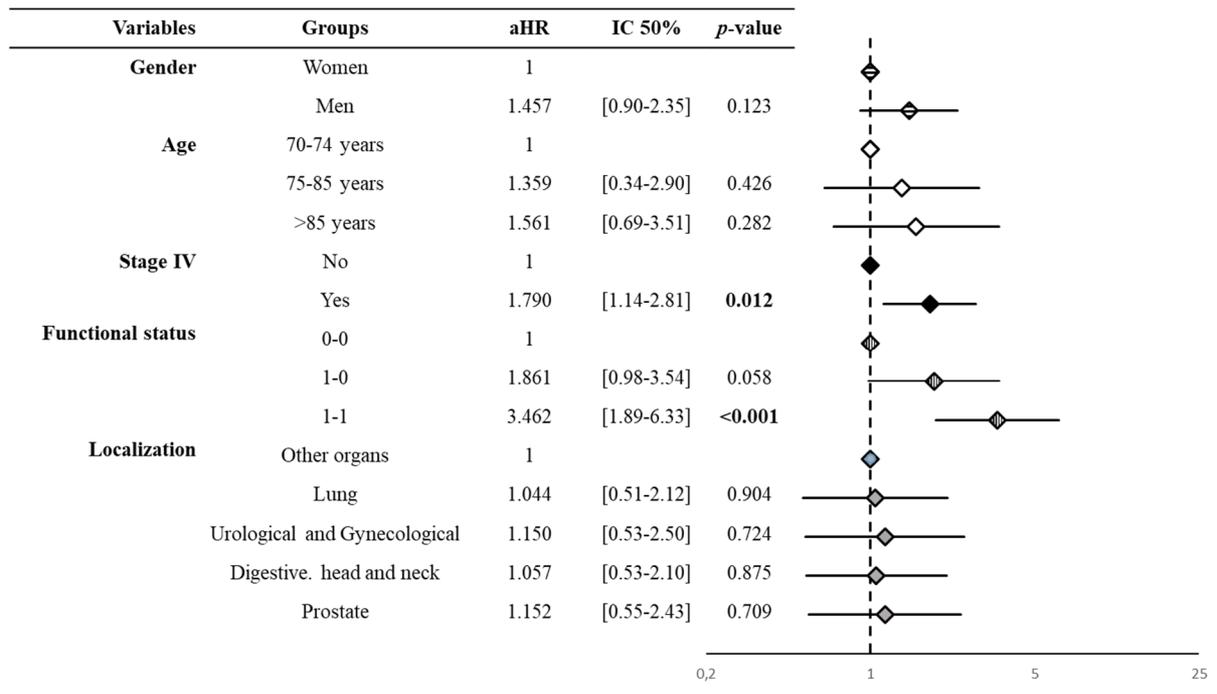
**Table 1:** Demographic, oncological, and geriatric characteristics of older cancer patients according to functional status (n=613)

Variables	Total sample N = 613		unimpaired ADL-IADL N = 255		ADL or IADL impairment N = 169		impaired ADL-IADL N = 189		p-value
	n	%	n	%	n	%	n	%	
<b>Gender</b>									
Women	238	38.8	59	23.1	73	43.2	106	56.0	<b>&lt;0.001</b>
Men	375	61.2	196	76.9	96	56.8	83	44.0	
<b>Age (years)</b>									
70-74	91	14.8	45	17.6	20	11.8	26	13.7	<b>&lt;0.001</b>
75-85	372	60.7	178	69.9	106	62.7	88	46.6	
>85	150	24.5	32	12.5	43	25.5	75	39.7	
<b>Living place</b>									
Home	546	89.1	251	98.4	152	89.9	143	75.7	<b>&lt;0.001</b>
Nursing home	29	4.7	2	0.8	7	4.2	20	10.6	
Follow-up and rehabilitation unit	38	6.2	2	0.8	10	5.9	26	13.7	
<b>Tumour type</b>									
Thoracic and lung	137	22.3	63	24.7	34	20.1	40	21.2	0.342
Digestive, Head and neck	157	25.6	61	23.9	25	14.8	47	24.9	
Prostate	106	17.3	38	14.9	49	29.0	33	17.5	
Urological and Gynaecological	99	16.2	48	18.8	35	20.7	26	13.7	
Other*	114	18.6	45	17.7	26	15.4	43	22.7	
<b>Stage (n=572 solid tumors)</b>									
I-III	363	63.4	157	65.1	100	62.9	106	61.6	0.753
IV	209	36.6	84	34.9	59	37.1	66	38.4	
<b>Malnutrition**</b>									
Yes	136	22.2	24	9.4	130	76.9	73	38.6	<b>&lt;0.001</b>
No	477	77.8	231	90.6	39	23.1	116	61.4	
<b>TUG (n=594)</b>									
< 20 s	392	66.0	225	88.9	52	31.3	53	30.3	<b>&lt;0.001</b>
≥ 20 s	202	34.0	28	11.1	114	68.7	122	69.7	
<b>One Leg Balance test (n=543)</b>									
≥ 5 s	114	21.0	84	34.6	26	17.7	4	2.6	<b>&lt;0.001</b>
< 5 s	429	79.0	159	65.4	121	82.3	149	97.4	
<b>Gait speed (n=542)</b>									
≥ 0.8 m/s	376	69.3	203	82.8	108	67.0	65	47.8	<b>&lt;0.001</b>
< 0.8 m/s	166	30.7	42	17.2	53	33.0	71	52.2	
<b>Fall within 3 months (n=612)</b>									
No	502	82.0	235	92.2	135	79.9	132	70.2	<b>&lt;0.001</b>
Yes	110	18.0	20	7.8	34	20.1	56	29.8	
<b>ECOG-PS (n=555)</b>									
< 2	417	75.1	208	90.0	122	77.7	87	52.1	<b>&lt;0.001</b>
≥ 2	138	24.9	23	10.0	35	22.3	80	47.9	
<b>G8 (/17) (n=513)</b>									
≤ 14	420	81.9	144	65.8	123	89.8	153	97.5	<b>&lt;0.001</b>
> 14	93	18.1	75	34.2	14	10.2	4	2.5	

\*Other refers to the following localizations: haematological (n = 36), breast (n = 48), dermatological (n = 26), sarcoma (n = 4)

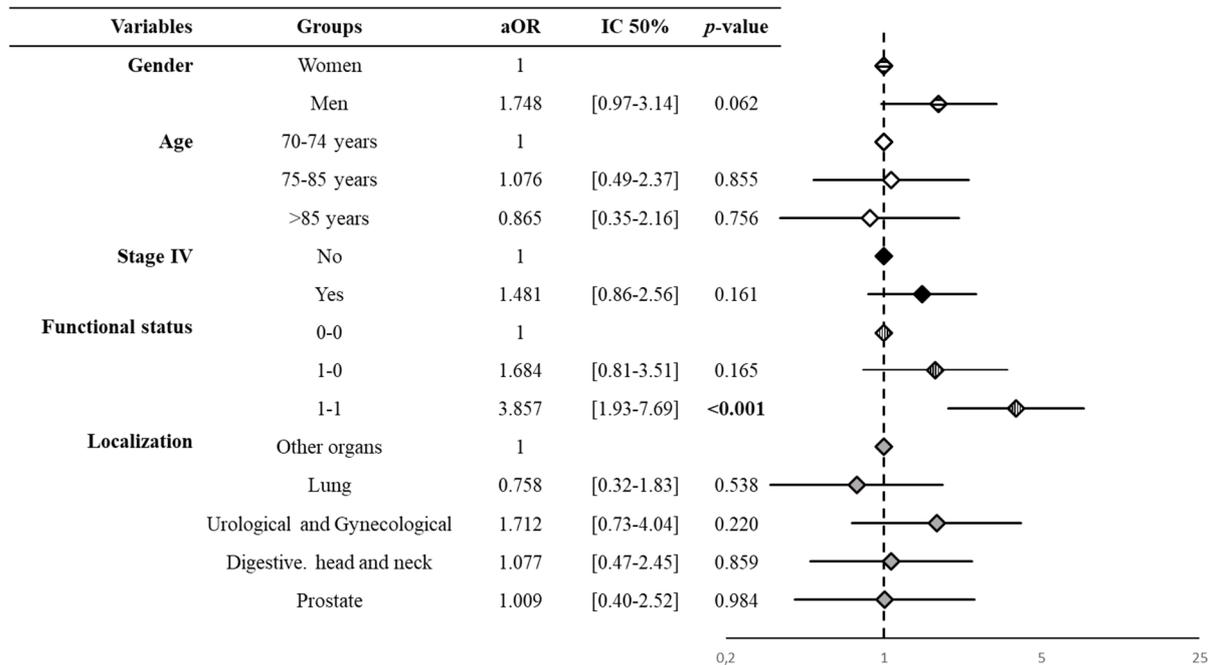
\*\* Malnutrition was defined as follows: BMI < 21 and/or albumin levels < 35 g/l and/or MNA < 17

ECOG-PS = performance status, TUG = Timed Up and Go test



**Figure 1:** Three-month mortality analysis in older cancer patients (Cox regression model) (n =533)

Functional status: 0-0 (unimpaired ADL-IADL), 1-0 (ADL impairment or IADL impairment), and 1-1 (impaired ADL-IADL); aHR: adjusted Hazard Ratio; CI: confidence interval



**Figure 2:** Three-month unplanned hospitalizations in older cancer patients (Logistic regression model) (n = 541)

Functional status: 0-0 (unimpaired ADL-IADL), 1-0 (ADL impairment or IADL impairment), and 1-1 (impaired ADL-IADL); aOR: adjusted Odds Ratio; CI: confidence interval