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1 **Obesity survival paradox in cancer patients: results**
2 **from the Physical Frailty in older adult cancer**
3 **patients (PF-EC) study**

4
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39 **Abstract**

40 **Background & aims:** the obesity survival paradox is an emergent issue in oncology, but its
41 existence remains unclear particularly in older cancer patients. We aimed to assess the obesity
42 survival paradox in older cancer patients.

43 **Methods:** all consecutive cancer outpatients 65 years and older referred for geriatric
44 assessment (GA) before a decision on cancer treatment between November 2013 and
45 September 2016 were enrolled in the PF-EC cohort study. The main outcome was 6-month
46 mortality. A Cox univariate and multivariate proportional hazard regression models were
47 performed with baseline GA, oncological variables (cancer site, extension and treatment
48 modalities) and C-reactive protein (CRP). We assessed the prognostic value of body mass
49 index categories (i.e. malnutrition < 21 , $21 \leq$ normal weight ≤ 24.9 , $25 \leq$ overweight ≤ 29.9
50 and obesity $\geq 30 \text{ kg/m}^2$) in the whole study population and according to the metastatic status.

51 **Results:** 433 patients with a mean age of 81.2 ± 6.0 years were included, 51% were women,
52 44.3% had digestive cancers, 18% breast cancer and 14.5% lung cancer and 45% metastatic
53 cancers. Eighty-eight of these patients (20.3%) were obese at baseline. Mortality rate was
54 17% during the 6-month follow-up period. After adjustment for sex, gait speed, Mini-Mental
55 State Examination, cancer site and exclusive supportive care, obesity (compared to normal
56 weight) was independently and negatively associated with 6-month mortality only in
57 metastatic patients (aHR 0.17, 95% CI [0.03–0.92], $P = 0.04$).

58 **Conclusion:** our study confirms the obesity survival paradox in older cancer patients only in
59 the metastatic group.

60

61 **Keywords:** *cancer, metastasis, obesity survival paradox, geriatric assessment, older people.*

62

63 **Background**

64 The prevalence of obesity (body mass index (BMI) ≥ 30 kg/m²) is increasing worldwide,
65 with about 40% of people between 65-74 years old and 30% over 75 years old being obese
66 [1]. Moreover, 60% to 70% of newly diagnosed cancers concern older patients [2]. Obesity is
67 a major risk factor of morbidity in older people. It is associated with an increased risk of
68 cancers (breast, colon, uterine, leukaemia), cardiovascular morbidity (stroke, myocardial
69 infarction), disability, number of medications, metabolic syndrome and osteoarthritis, and it
70 decreases mobility and quality of life [1]. Obesity is also a well-known risk factor of mortality
71 in middle-aged people, but recent studies have demonstrated that this association is not seen
72 for adults aged 65 and over. This is termed the “obesity survival paradox” [1].

73 Over the past decade, the obesity survival paradox has been specifically observed in
74 cancer patients with local and metastatic disease in several studies [3]: patients treated for
75 colorectal [4,5] and renal cancer [6,7], patients with lymphoma undergoing autologous
76 haematopoietic cell transplantation [8] and metastatic patients requiring radiotherapy [9].

77 To our knowledge, only one study has assessed the obesity survival paradox
78 specifically in older cancer patients. In this recent study, the association between BMI and
79 overall survival (OS) during a 10-year follow-up was assessed in 97 patients 60 years and
80 over with acute myeloid leukaemia before chemotherapy [10]. Median age was 68 years, the
81 median OS was 316 days and 32% of patients were obese. A BMI <25 kg/m² compared to
82 obesity (≥ 30 kg/m²) was an independent predictor of mortality (HR = 2.14, 95% CI, 1.21–
83 3.77).

84 The older cancer population is heterogeneous in comorbidities, physical reserves,
85 functional status and socioeconomic environment [11]. Geriatric assessment (GA) is therefore
86 recommended by the International Society of Geriatric Oncology (SIOG) [12] to detect
87 vulnerabilities likely to lead to poor outcomes and treatment complications [13–15].

88 To date, no studies have assessed the obesity survival paradox in older cancer patients
89 after adjustment for GA domains, and the existence of the obesity survival paradox in such
90 patients remains unclear. We postulated that obesity was positively associated with OS in
91 older cancer patients. We aimed to assess the existence of the obesity survival paradox in
92 older cancer patients of the whole study population and according to the metastatic status.
93

94 **Methods**

95 **Study design and population**

96 The Physical Frailty in Elderly Cancer patients (PF-EC) survey is an open prospective
97 observational two-centre cohort study that started in November 2013. All consecutive patients
98 aged 65 years and over referred for geriatric assessment in two university hospitals in the
99 greater Paris area of France, Avicenne Hospital in Bobigny and Jean Verdier Hospital in
100 Bondy, were included. Patients were referred by oncologists, radiotherapists, surgeons, or
101 other specialists when a new diagnosis of cancer was highly suspected or confirmed
102 histologically and when frailty was suspected, during the two weeks before a cancer treatment
103 decision.

104 For the present analysis, we included all outpatients, regardless of cancer type, stage
105 or treatment, who presented up to September 30, 2016. The inclusion date was the date of the
106 first geriatric oncology visit.

107 Informed consent was obtained from the patients before inclusion. The study was
108 approved by the local ethics committee (CLEA, Avicenne Hospital, Bobigny, France).

109

110 **Data collection:**

111 In this study, we followed the STrengthening the Reporting of OBservational studies in
112 Epidemiology (STROBE) recommendations for the reporting of observational
113 epidemiological studies [16].

114

115 **Cancer and demographic data:** Demographic data (age, sex), tumour characteristics (site,
116 extension: local, locally advanced or metastatic/diffuse) and Eastern Cooperative Oncology
117 Group Performance Status (ECOG-PS) were obtained at the first geriatric oncology visit as

118 part of the GA. Cancer treatment modalities were categorised as exclusive supportive care or
119 not and were collected during the 6-month follow-up.

120 **Body mass index**

121 Weight and height were measured at the first geriatric oncology visit to calculate body mass
122 index (BMI) which was categorised in four classes according to the World Health
123 Organization and the French nutritional guidelines: BMI < 21 (malnutrition), $21.0 \leq \text{BMI} \leq$
124 24.9 (normal weight), $25.0 \leq \text{BMI} \leq 29.9$ (overweight) and BMI ≥ 30 (obesity). Obesity was
125 described as moderate ($30.0 \leq \text{BMI} \leq 34.9$), severe ($35.0 \leq \text{BMI} \leq 39.9$) or morbid (BMI \geq
126 40.0) [17,18].

127

128 **Geriatric assessment**

129 At the first geriatric oncology visit, each patient underwent GA following the recently
130 updated recommendations of the International Society of Geriatric Oncology [19].
131 Comorbidities were assessed by the Cumulative Illness Rating Scale-Geriatric (CIRS-G) [20].
132 A total score dichotomised by a median of 14, or the presence of at least one grade 3 (severe)
133 or grade 4 (very severe) comorbidity excluding the current cancer, was considered to indicate
134 impairment. Polypharmacy was defined as taking five or more drugs a day. Dependency was
135 defined by an Activities of Daily Living (ADL) score of less than or equal to 5/6 or a four-
136 item simplified (use of telephone, transports, medications, and money management)
137 Instrumental ADL (IADL) that was less than 4/4 [21,22]. Mobility was assessed by gait speed
138 (GS) measured over a short distance (4 m) in metres/second (m/s) [23]. A slow GS was
139 defined as < 0.8 m/s because this threshold has shown a strong and independent association
140 with early death in older cancer patients [23,24]. Repeated falls were defined as at least two
141 falls in the previous year. Depressed mood was defined as a Mini-Geriatric Depression Scale

142 (Mini-GDS) score of at least 1/4 [25]. Cognitive impairment was defined by a Mini-Mental
143 State Examination (MMSE) score of less than 24/30 [26].

144

145

146 **Muscle weakness**

147 Maximum hand grip strength (kilograms) measured twice for each hand using a CAMRY
148 hand-held dynamometer (model EH101) was used to assess muscle weakness (MW) at the
149 first geriatric oncology visit. MW was defined by the thresholds adjusted for gender and BMI
150 derived from the frailty phenotype established by Fried *et al.* [27].

151

152 **Covariate**

153 Inflammation was assessed by C-reactive protein (CRP) level measured by
154 immunoturbidimetric assay during the first 3 weeks after the GA. Abnormal CRP was defined
155 as ≥ 10 mg/l [28].

156

157 **Outcomes**

158 The primary outcome was overall 6-month mortality following the GA to assess predictors of
159 early death. Vital status was determined by telephoning patients or their family or from
160 medical records.

161

162 **Statistical analysis**

163 We used numbers for descriptive data, proportions for qualitative variables and means with
164 SDs or medians with interquartile (IQR) range (25th-75th) for quantitative variables.
165 Comparisons between obese and non-obese and then between metastatic and non-metastatic
166 patients were carried out using the chi-square test or Fisher's exact test for qualitative

167 variables and the Student *t* test or Wilcoxon's test for quantitative variables as appropriate.
168 We assessed correlation by using the Spearman rho test as appropriate for categorical
169 variables. Multicollinearity between variables was defined as a rho test ≥ 0.50 .

170 Baseline factors associated with obesity were analysed by univariate and multivariate
171 logistic analyses. Variables yielding *P* values less than 0.2 in the univariate analysis were
172 considered for inclusion in the multivariate analysis.

173 Survival curves were plotted according to the Kaplan-Meier method. Comparisons
174 according to BMI categories in the whole study population and in patient subsets according to
175 the metastatic status were performed by the log-rank test. Cox univariate and multivariate
176 proportional hazard regression models were performed with baseline characteristics
177 associated with 6-month mortality. Model assumptions were verified. Continuous variables
178 were shown per their standard deviations. Variables yielding *P* values less than 0.2 in the
179 univariate analysis were considered for inclusion in the multivariate analyses. We conducted a
180 stratified analysis in patient subsets according to the metastatic status. All analyses were
181 adjusted for sex, gait speed, cancer-site, cancer-extension and supportive care.

182 All tests were two-sided at a significance level of 0.05. Multiple imputation was performed to
183 handle missing data for MMSE (MICE package using predictive mean matching method as
184 appropriate for numeric variables). The data were analysed using R statistical software
185 version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria, [http://www.R-](http://www.R-project.org)
186 [project.org](http://www.R-project.org)).

187

188

189 **Results**

190 **Patients**

191 Of the 457 consecutive older cancer outpatients aged 65 and over who were referred for GA
192 up to September 30, 2016, and were potentially eligible, 433 were finally eligible for this
193 study (Figure 1).

194

195 **Baseline characteristics of patients (Table 1)**

196 Median age was 82 (IQR 77–85) years. The majority were women, had solid tumours (95%),
197 local (20%) and locally advanced (35%) cancer. Colorectal and breast cancer were the two
198 most common types, whereas urological malignancies were uncommon (4.8%). Obesity
199 affected 20.3% (88/433) of patients, of whom 70 (79.5%) were moderately obese, 15 (17%)
200 were severely obese and 3 (3.5%) morbidly obese. Geriatric assessment showed that most
201 patients had significant impairment in several domains: two-thirds of patients had severe
202 comorbidities, polypharmacy and muscle weakness. IADL dependency was more frequent
203 than ADL dependency and concerned two-thirds of patients. More than half of patients had
204 slow gait speed and cognitive impairment. Less than half of patients had depressive mood and
205 CRP \geq 10 mg/l. Repeated falls were uncommon.

206 **Comparison between obese and non-obese patients**

207 In univariate analysis, male sex, locally-advanced cancer (compared to local cancer), total
208 CIRS-G and grade 3 comorbidity, polypharmacy, ADL dependency and slow gait speed were
209 the variables positively and significantly associated with obesity. Metastatic cancer
210 (compared to local cancer) and CRP \geq 10 mg/l were the variables negatively and significantly
211 associated with obesity. In multivariate analysis, breast cancer, total CIRS-G and slow gait
212 speed were positively and independently associated with obesity. CRP \geq 10 mg/l was
213 negatively and independently associated with obesity. Moreover, when multivariate analysis

214 included ADL or IADL as covariate instead of slow gait speed, ADL ($P = 0.10$) and IADL (P
215 $= 0.74$) were not independently associated with obesity.

216 **Comparison between metastatic and non-metastatic patients**

217 Metastatic patients did not differ by mean age ($P = 0.06$), proportion of exclusive supportive
218 care ($P = 0.94$), total comorbidities ($P = 0.46$), polypharmacy ($P = 0.61$), ADL and IADL (P
219 $= 0.09$ and 0.77 respectively), gait speed ($P = 0.45$), muscle strength ($P = 0.68$), mini-GDS (P
220 $= 0.90$) and MMSE ($P = 0.19$). In contrast, metastatic patients had more aggressive cancers
221 (lung, pancreas and bile ducts) ($P < 0.0001$), a lower BMI ($P = 0.01$) with a smaller
222 proportion of obese patients (16%), were more frequently men ($P < 0.0001$) and had
223 significantly higher CRP levels ($P = 0.01$).

224

225 **Predictors of overall 6-month mortality**

226 Mortality rate during the 6-month follow-up after the initial GA was 17% (95% CI, 13.8–
227 21%). Median overall survival was not reached.

228 Kaplan-Meier survival analysis plotted by BMI category alone showed no significant
229 difference between obesity and other categories (i.e. normal weight, overweight and
230 malnutrition) in the whole study population (Figure 2). However, there was a trend towards a
231 protective effect of obesity on 6-month mortality (P log rank test = 0.06).

232 In univariate analysis (Table 2), breast cancer and haematological malignancies
233 (compared to colorectal cancer) were negatively associated with 6-month mortality. In
234 contrast, male gender, lung, liver, pancreas and bile ducts, gynaecological malignancies,
235 oesophageal and gastric and other cancers (compared to colorectal cancer), locally-advanced
236 and metastatic cancer, exclusive supportive care, slow gait speed, muscle weakness, cognition
237 impairment and $CRP \geq 10\text{mg/l}$, were positively associated with 6-month mortality. Age,
238 comorbidities, BMI categories and depressed mood were not significantly associated with 6-

239 month mortality. Because of the multicollinearity between GS, ADL/IADL and ECOG-PS,
240 we used only GS as clinical variable of functional status in multivariate analyses [29].
241 Because of the multicollinearity between total CIRS-G total and grade 3 comorbidity and
242 polypharmacy, we used only the CIRS-G total score as clinical variable to assess the burden
243 of comorbidities in multivariate analyses. Due to the non-linear association between BMI and
244 survival, we compared BMI categories to normal weight to perform our analyses.

245 In multivariate analysis (Figure 3), BMI categories were still not independently
246 associated with 6-month mortality in the whole study population or in non-metastatic patients.
247 In metastatic patients, obesity compared to normal weight was the only BMI category
248 independently and negatively associated with 6-month mortality after adjustment for sex, gait
249 speed, MMSE, cancer site and exclusive supportive care.

250

251 **Discussion**

252 In this cohort of consecutive older outpatients with currently untreated cancer at various sites
253 and stages, obesity defined by BMI ≥ 30 kg/m² compared to normal weight was not
254 independently associated with 6-month mortality in the whole study population or in non-
255 metastatic patients. In the stratified analysis, obesity was independently and negatively
256 associated with 6-month mortality in metastatic patients after adjustment for sex, gait speed,
257 MMSE, cancer site and exclusive supportive care. Breast cancer, comorbidities and slow gait
258 speed were the variables independently and positively associated with obesity. In contrast,
259 inflammation defined by CRP levels ≥ 10 mg/l was independently and negatively associated
260 with obesity.

261 Our findings are consistent with a large retrospective study by Tsang *et al.* [9]. In this
262 study, 4,010 metastatic cancer patients requiring a radiotherapy with a median age of 59.6
263 years (range: 18.4–94) and with an ECOG-PS 0-1 were included. The median follow-up time
264 was 24.4 months (range 0.13–164.1). Obesity (BMI ≥ 30 kg/m²) compared to normal weight
265 was independently associated with overall survival (HR 0.67, CI 95%, 0.56–0.80). In
266 agreement with these authors, one of the main explanations of the obesity paradox in
267 metastatic cancer patients arises from the inverse association between BMI and fatty acid
268 synthase (FASN) expression. FASN is an oncogene that encodes for rate-limiting enzymes
269 involved in fatty acid synthesis, a process essential for tumour growth and which is
270 overexpressed in several malignancies [9]. Hakimi *et al.* showed that FASN is significantly
271 downregulated in obese patients with renal cell carcinoma and has a beneficial effect on
272 cancer-specific survival [7]. However, in our study we observed the observation of obesity
273 survival paradox only in metastatic patients and this deserves discussion. Metastatic status is
274 related to a high malignant potential that requires higher levels of energy [9]. One of the main
275 energy sources for malignant cells arises from elevated adipose tissue lipolysis and increasing

276 fatty acid oxidation [9]. Accordingly, there is probably a greater fat loss in metastatic patients
277 due to aggressive tumour behaviour with higher energy demand. This probably could explain
278 the significantly lower BMI in metastatic patients in our cohort, in which obese patients had
279 an advantage in overall survival due to higher fat reserves.

280 In a recent multicentre prospective observational study that included 1,306
281 consecutive older patients hospitalised in an emergency department (mean age 85 ± 6 years)
282 geriatric assessment was carried out in all patients [30]. Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was found
283 in 19.6% and was negatively and independently (after adjustment for age, mobility disorders,
284 dementia syndrome, dependency and comorbidities) associated with overall 1-year (HR 0.8,
285 95% CI, 0.6–1.0, $P = 0.05$) and 2-year (HR 0.8, 95% CI, 0.6–1.0, $P = 0.03$) survival. Among
286 these obese patients, 12.9% had cancer. In agreement with the authors of this study, we
287 support the existence of two distinct subtypes of obesity, as has been suggested in the
288 literature [31]: metabolically healthy obesity (MHO) and metabolically unhealthy obesity
289 (MUO). About 20-30% of obese patients may have MHO, which is characterised by the
290 absence of metabolic complications of obesity, by low inflammation and low disability [31].
291 This approach could explain in part the obesity survival paradox. Accordingly, there was
292 probably a natural selection of MHO in our cohort since it comprised older people with
293 significant comorbidities and no significant disability which they survived until recently
294 developing a cancer.

295 More recently, a multicentre prospective cohort study conducted in 6,662 community-
296 dwelling older women aged 75 and older confirmed the obesity survival paradox [32]. The
297 risk of death during the 5-years follow-up of frail women (frailty defined by the Fried model)
298 compared with not-frail normal weight women, decreased with increase of BMI after
299 adjustment for age, cardiovascular drugs, hospital admission in the last 12 months and
300 functional status: HR (frail-underweight) = 2.04 [1.23–3.39]; HR (frail-normal weight) = 3.07

301 [2.21–4.26]; HR (frail-overweight) = 1.83 [1.31–2.56]; HR (frail-obese) = 1.76 [1.15–2.70]; *P*
302 < 0.001. However, the obesity survival paradox in cancer patients remains debatable. Obesity
303 survival paradox observation may involve methodological biases such as reverse causality,
304 confounding, detection bias, or collider bias [33]. The non-obese population may include
305 patients who had lost weight as a result of more severe illness, while BMI is not an optimal
306 measure of body fat and obese older patients may be affected by selective survival bias.
307 Nevertheless, several authors have argued that such biases may not solely explain the obesity
308 paradox [33,34].

309 The strengths of our study are the study design and the internal consistency with other
310 large studies (ONCODAGE, ELCAPA) conducted in older cancer patients (age, cancer site,
311 cancer extension at inclusion). Moreover, to our knowledge, this is the first study that
312 confirmed the obesity survival paradox in older cancer patients after adjustment for several
313 geriatric domains.

314 However, our study has several limitations. Firstly, because of the small size of the
315 severe and morbid obesity subgroups we were unable to determine the prognostic value of
316 obesity in these patients. Secondly, the history of weight loss was not considered in our study,
317 and this probably limited the association between obesity and digestive cancers related to
318 obesity (oesophageal, gastric, colorectal or pancreatic cancers). Digestive cancers often lead
319 to a major weight loss before diagnosis. Thirdly, due to the short follow-up time, we were
320 unable to confirmed the obesity survival paradox in non-metastatic patients.

321 Finally, our results suggest that in older cancer patients, BMI probably does not yield
322 sufficient understanding of the heterogeneous nature of obesity. A more comprehensive
323 approach would include on the one hand, an estimation of body composition in obese patients
324 (particularly with assessment of abdominal adiposity) and on the other hand, the history of
325 weight loss [35,36].

326

327 **Conclusion:**

328 We confirmed the obesity survival paradox in older cancer patients only in the metastatic
329 subgroup. This result may be linked with the downregulation of fatty acid synthase expression
330 in obese patients, an oncogene that is overexpressed in metastatic disease.

331

332 **Conflicts of interest**

333 None declared

334

335 **Authors' contributions**

336 Conception and design: FP, TA, FCP, VL, GS, EP

337 Acquisition of data: FP, TA, BD, PW, NG, LZ

338 Analysis and interpretation of data: FP, TA, FCP, BD, LZ, EP

339 Drafting the article: FP, FCP, EP

340 Reviewing the article: FP, TA, FCP, BD, VL, PW, NG, GS, LZ, EP

341 Final approval: FP, TA, FCP, BD, VL, PW, NG, GS, LZ, EP

342

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344

345

346 **REFERENCES**

- 347 1. Kalish VB. Obesity in older adults. *Prim Care* 2016; 43: 137–44, ix.
- 348 2. Lewis JH, Kilgore ML, Goldman DP et al. Participation of patients 65 years of age or
349 older in cancer clinical trials. *J Clin Oncol* 2003; 2: 1383–9. 3.
- 350 3. Lennon H, Sperrin M, Badrick E, Renehan AG. The obesity paradox in cancer: a
351 review. *Curr Oncol Rep* 2016; 18: 56.
- 352 4. Kroenke CH, Neugebauer R, Meyerhardt J *et al.* Analysis of body mass index and
353 mortality in patients with colorectal cancer using causal diagrams. *JAMA Oncol* 2016; 2:
354 1137–45.
- 355 5. Aparicio T, Maillard E, Ducreux M *et al.* Obesity in metastatic colorectal cancer:
356 Pooled
357 analysis of FFCD trials. *J Clin Oncol* 2016; 34(15_suppl): 3532-3532.
- 358 6. Parker AS, Lohse CM, Cheville JC, Thiel DD, Leibovich BC, Blute ML. Greater
359 body mass index is associated with better pathologic features and improved outcome among
360 patients treated surgically for clear cell renal cell carcinoma. *Urology* 2006; 68: 741–6.
- 361 7. Hakimi AA, Furberg H, Zabor EC *et al.* An epidemiologic and genomic investigation
362 into the obesity paradox in renal cell carcinoma. *J Natl Cancer Inst.* 2013; 105: 1862–70.
- 363 8. Navarro WH, Loberiza FR, Bajorunaite R *et al.* Effect of body mass index on
364 mortality of patients with lymphoma undergoing autologous hematopoietic cell
365 transplantation. *Biol Blood Marrow Transplant* 2006; 12:541–51.
- 366 9. Tsang NM, Pai PC, Chuang CC *et al.* Overweight and obesity predict better overall
367 survival rates in cancer patients with distant metastases. *Cancer Med* 2016; 5: 665–75.
- 368 10. Brunner AM, Sadrzadeh H, Feng Y *et al.* Association between baseline body mass
369 index and overall survival among patients over age 60 with acute myeloid leukemia. *Am J*
370 *Hematol* 2013;88: 642–6.

- 371 11. Liuu E, Caillet P, Curé H *et al.* [Comprehensive geriatric assessment (CGA) in
372 elderly with cancer: For whom?]. *Rev Med Interne* 2016; 37: 480–8.
- 373 12. Decoster L, Puyvelde KV, Mohile S *et al.* Screening tools for multidimensional
374 health problems warranting a geriatric assessment in older cancer patients: an update on SIOG
375 recommendations. *Ann Oncol* 2015; 26: 288–300
- 376 13. Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of
377 geriatric assessments in predicting treatment tolerance and all-cause mortality in older
378 patients with cancer. *Oncologist* 2012; 17: 1439–49.
- 379 14. Ferrat E, Paillaud E, Laurent M, Le Thuaut A, Caillet P, Tournigand C *et al.*
380 Predictors of 1-year mortality in a prospective cohort of elderly patients with cancer. *J*
381 *Gerontol A Biol Sci Med Sci* 2015; 70: 1148–55.
- 382 15. Laurent M, Paillaud E, Tournigand C *et al.* Assessment of solid cancer treatment
383 feasibility in older patients: a prospective cohort study. *Oncologist* 2014; 19: 275–82.
- 384 16. Vandembroucke JP, von Elm E, Altman DG *et al.*; STROBE Initiative. Strengthening
385 the Reporting of Observational Studies in Epidemiology (STROBE): explanation and
386 elaboration. *Int J Surg* 2014; 12: 1500–24.
- 387 17. Executive summary of the clinical guidelines on the identification, evaluation, and
388 treatment of overweight and obesity in adults. *Arch Intern Med* 1998; 158: 1855–67.
- 389 18. Raynaud-Simon A, Revel-Delhom C, Hébuterne X, French Nutrition and Health
390 Program, French Health High Authority. Clinical practice guidelines from the French Health
391 High Authority: nutritional support strategy in protein-energy malnutrition in the elderly. *Clin*
392 *Nutr* 2011; 30: 312–9.
- 393 19. Wildiers H, Heeren P, Puts M *et al.* International Society of Geriatric Oncology
394 consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 2014; 32: 2595–
395 603.

- 396 20. Miller MD, Paradis CF, Houck PR *et al.* Rating chronic medical illness burden in
397 geropsychiatric practice and research: application of the Cumulative Illness Rating Scale.
398 Psychiatry Res 1992; 41: 237–48.
- 399 21. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of
400 ADL. Gerontologist 1970; 10: 20–30.
- 401 22. Lawton MP, Brody EM. Assessment of older people: self-maintaining and
402 instrumental activities of daily living. Gerontologist 1969; 9: 179–86.
- 403 23. Pamoukdjian F, Paillaud E, Zelek L *et al.* Measurement of gait speed in older adults
404 to identify complications associated with frailty: A systematic review. J Geriatr Oncol 2015;
405 6: 484–96.
- 406 24. Pamoukdjian F, Lévy V, Sebbane G *et al.* Slow gait speed is an independent predictor
407 of early death in older cancer outpatients: results from a prospective cohort study. J Nutr
408 Health Aging 2017; 21: 202–6.
- 409 25. Clément JP, Nassif RF, Léger JM, Marchan F. [Development and contribution to the
410 validation of a brief French version of the Yesavage Geriatric Depression Scale]. L'Encéphale
411 1997; 23: 91–9.
- 412 26. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: A practical method for
413 grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.
- 414 27. Fried LP, Tangen CM, Walston J *et al.* Frailty in older adults: evidence for a
415 phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146–56.
- 416 28. Shine B, de Beer FC, Pepys MB. Solid phase radioimmunoassays for human C-
417 reactive protein. Clin Chim Acta 1981; 117: 13–23.
- 418 29. Pamoukdjian F, Aparicio T, Zelek L *et al.* Impaired mobility, depressed mood,
419 cognitive impairment and polypharmacy are independently associated with disability in older

420 cancer outpatients: The prospective Physical Frailty in Elderly Cancer patients (PF-EC)
421 cohort study. *J Geriatr Oncol.* 2017 May;8(3):190-195.

422 30. Lang PO, Mahmoudi R, Novella JL *et al.* Is obesity a marker of robustness in
423 vulnerable hospitalized aged populations? Prospective, multicenter cohort study of 1 306
424 acutely ill patients. *J Nutr Health Aging* 2014; 18: 66–74.

425 31. Alam I, Ng TP, Larbi A. Does inflammation determine whether obesity is
426 metabolically healthy or unhealthy? The aging perspective. *Mediators Inflamm* [Internet].
427 2012 Oct 4. Available from: <https://www.hindawi.com/journals/mi/2012/456456/abs/>

428 32. Boutin E, Natella PA, Schott AM *et al.* Interrelations between body mass index,
429 frailty, and clinical adverse events in older community-dwelling women: The EPIDOS cohort
430 study. *Clin Nutr* 2017 Aug 5; pii: S0261-5614(17)30264-9. doi: 10.1016/j.clnu.2017.07.023.

431 33. Caan BJ, Kroenke CH. Next steps in understanding the obesity paradox in cancer.
432 *Cancer Epidemiol Biomarkers Prev* 2017; 26: 12. doi: 10.1158/1055-9965.EPI-16-0764.

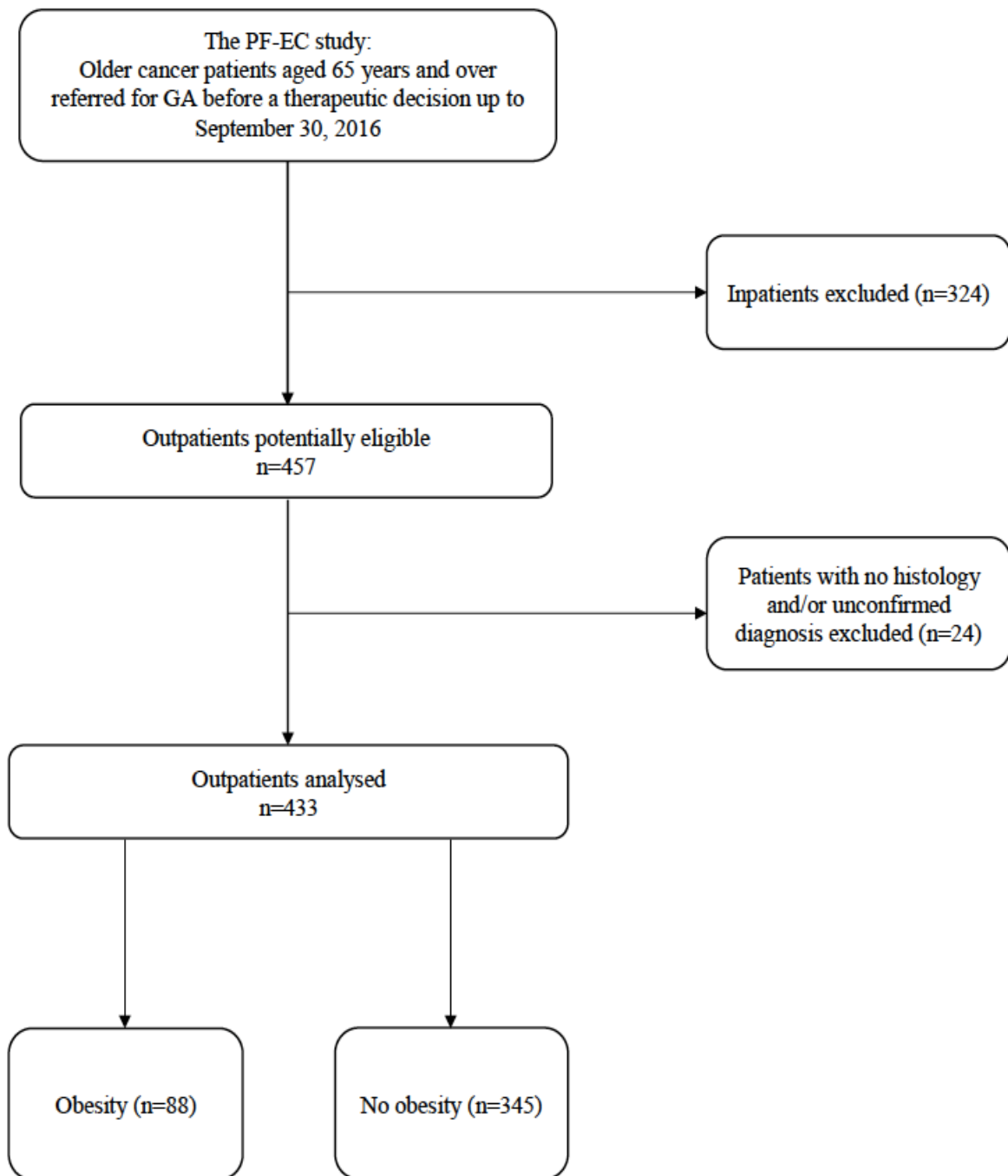
433 34. Sperrin M, Candlish J, Badrick E *et al.* Collider bias is only a partial explanation for
434 the obesity paradox. *Epidemiology* 2016; 27: 525–30.

435 35. Ebadi M, Martin L, Ghosh S *et al.* Subcutaneous adiposity is an independent predictor
436 of mortality in cancer patients. *Br J Cancer* 2017; 117: 148–55.

437 36. Martin L, Birdsell L, MacDonald N *et al.* Cancer cachexia in the age of obesity:
438 skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J*
439 *Clin Oncol* 2013; 31: 1539–47.

440 **Figure 1. Flow the selection of patients**

441



442

443 **Table 1. Baseline characteristics of 433 consecutive older cancer outpatients and factors**
444 **independently associated with obesity**
445

Variables	Univariate analysis			Multivariate analysis			
	All patients n = 433 (%)	BMI \geq 30 kg/m ² n = 88 (20.3%)	BMI <30 kg/m ² n = 345 (79.7%)	P ^a	aOR	95%CI	P
Age (years)							
Mean +/- SD	81.2 +/- 6.0	80.5 +/- 6.3	81.4 +/- 5.9	0.23			
Quartiles				0.69			
65-76	101 (23)	22 (25)	79 (23)				
77-81	115 (26)	24 (27)	91 (26.3)				
82-84	87 (21)	20 (23)	67 (19.4)				
85-103	130 (30)	22 (25)	108 (31.3)				
Sex (male)	212 (49)	33 (37.5)	179 (52)	0.01	0.98	0.51-1.88	0.96
Cancer site				0.08			0.38
Colorectal	81 (19)	13 (15)	68 (19.7)		1 (reference)		
Breast	79 (18)	27 (30.8)	52 (15)		2.62	1.11-6.17	
Lung	63 (14.5)	10 (11)	53 (15.3)		1.22	0.46-3.22	
Liver	61 (14)	14 (16)	47 (14)		1.55	0.63-3.80	
Pancreas and bile ducts	26 (6)	3 (3.4)	23 (6.6)		0.85	0.20-3.51	
Gynaecological malignancies	26 (6)	7 (8)	19 (5.5)		1.67	0.49-5.65	
Oesophageal and gastric	23 (5.3)	2 (2.3)	21 (6)		0.40	0.07-2.08	
Haematological malignancies	23 (5.3)	4 (4.5)	19 (5.5)		1.16	0.30-4.40	
Urological malignancies ^b	21 (4.9)	4 (4.5)	17 (4.9)		1.62	0.41-6.38	
Other ^c	30 (7)	4 (4.5)	26 (7.5)		0.82	0.22-2.96	
Cancer extension				0.04			0.16
Local	85 (20)	16 (18)	69 (20)		1 (reference)		
Locally advanced cancer	153 (35)	41 (47)	112 (32.5)		1.82	0.88-3.74	
Metastatic	195 (45)	31 (35)	164 (47.5)		1.13	0.52-2.40	
ECOG-PS \geq 2 (yes)	195 (45)	47 (53)	148 (43)	0.08			

Exclusive supportive care (yes)	74 (17)	13 (15)	61 (18)	0.49			
Missing data = 8							
Comorbidities (CIRS-G)							
Total ≥ 14	215 (49.6)	59 (67)	156 (45)	0.0002	2.16	1.25-3.76	0.006
Grade 3 (severe) ≥ 1	263 (61)	65 (74)	198 (57)	0.004			
Grade 4 (very severe) > 1 (excluding current cancer)	95 (22)	24 (27)	71 (20.5)	0.17	1.34	0.72-2.49	0.34
Polypharmacy (yes)							
	283 (66)	70 (79.5)	213 (62)	0.0009			
Dependency							
ADL $\leq 5/6$	138 (32)	41 (47)	97 (28)	0.0009			
IADL < 4	274 (63)	63 (72)	211 (61)	0.06			
Mobility							
Slow GS (< 0.8 m/s)	235 (54)	63 (72)	172 (50)	0.0002	2.30	1.25-4.25	0.007
Muscle weakness (missing data = 8)	287 (67.5)	66 (75)	221 (64)	0.09	0.92	0.49-1.72	0.79
Repeated falls (missing data = 5)							
	72 (17)	19 (21.5)	53 (15)	0.16	1.15	0.60-2.20	0.66
Mood							
Mini-GDS $\geq 1/4$	191 (44.5)	39 (44.3)	152 (44)	0.86			
Cognition							
MMSE $< 24/30$	237 (55)	55 (62.5)	182 (53)	0.10	1.18	0.67-2.08	0.55
Inflammation							
CRP (mg/l) ≥ 10	193 (44.5)	29 (33)	164 (47.5)	0.01	0.55	0.31-0.96	0.03

ADL: activities of daily living

BMI: body mass index

CIRS-G: Cumulative Illness Rating Scale-Geriatric

CRP: C-reactive protein

ECOG-PS: Eastern Cooperative Oncology Group Performance Status

GS: gait speed

IADL: instrumental activities of daily living

IQR: interquartile range (25th-75th)

Mini-GDS: Mini-Geriatric Depression Scale

MMSE: Mini-Mental State Examination

a Comparisons between obese and non-obese patients using the chi-square test or Fisher's exact test for qualitative variables and Student *t* test or Wilcoxon's test for quantitative variables.

b prostate = 12, urothelial = 4, kidney = 3, bladder = 2

c unknown primary site = 8, mesothelioma = 5, cutaneous epidermidis carcinoma = 4, anal = 3, sarcoma = 2, melanoma = 2, oral carcinoma = 2, duodenal = 2, thymoma = 1, non-differentiated carcinoma = 1.

447 **Table 2. Overall 6-month mortality in univariate Analysis**

Variables	Univariate analysis	
	HR [95% CI]	<i>P</i> ^a
BMI categories:		0.06
Normal Weight	1 (reference)	
Malnutrition	1.84 [0.94-3.60]	
Overweight	1.07 [0.61-1.88]	
Obesity	0.62 [0.28-1.36]	
Age (per 6.0 years increase)	1.01 [0.97-1.05]	0.41
Sex (male)	1.68 [1.05-2.70]	0.02
Cancer site		0.0001
Colorectal	1 (reference)	
Breast	0.39 [0.12-1.25]	
Lung	2.12 [0.95-4.73]	
Liver	1.21 [0.49-2.99]	
Pancreas and bile ducts	2.55 [0.97-6.69]	
Gynaecological malignancies	1.27 [0.40-4.07]	
Oesophageal and gastric	2.71 [1.03-7.12]	
Haematological malignancies	0.33 [0.04-2.62]	
Urological malignancies ^b	2.56 [0.93-7.06]	
Other ^c	3.14 [1.27-7.72]	
Exclusive supportive care (yes)	2.99 [1.81-4.94]	<0.0001
Cancer extension		<0.0001
Local	1 (reference)	
Locally advanced	4.15 [1.24-13.8]	
Metastatic	7.54 [2.34-24.2]	
Comorbidities (CIRS-G)		
Total ≥ 14	1.25 [0.78-1.99]	0.33
Grade 3 (severe) ≥ 1	1.03 [0.64-1.66]	0.88
Grade 4 (very severe) > 1 (excluding current cancer)	1.03 [0.63-1.88]	0.75

Mobility:		
Slow GS (<0.8 m/s)	2.88 [1.69-4.92]	<0.0001
Muscle weakness (missing data = 8)	2.52 [1.35-4.71]	0.002
Mini-GDS \geq 1/4	1.12 [0.70-1.79]	0.61
MMSE < 24/30	2.23 [1.34-3.71]	0.001
CRP (mg/l) \geq 10	4.01 [2.37-6.78]	<0.0001

BMI: body mass index

CIRS-G: Cumulative Illness Rating Scale-Geriatric

CRP: C-reactive protein

GS: gait speed

IQR: interquartile range

Mini-GDS: Mini-Geriatric Depression Scale

MMSE: Mini-Mental State Examination

HR: hazard ratio.

Continuous variables were shown per their standard deviations.

a log-rank test

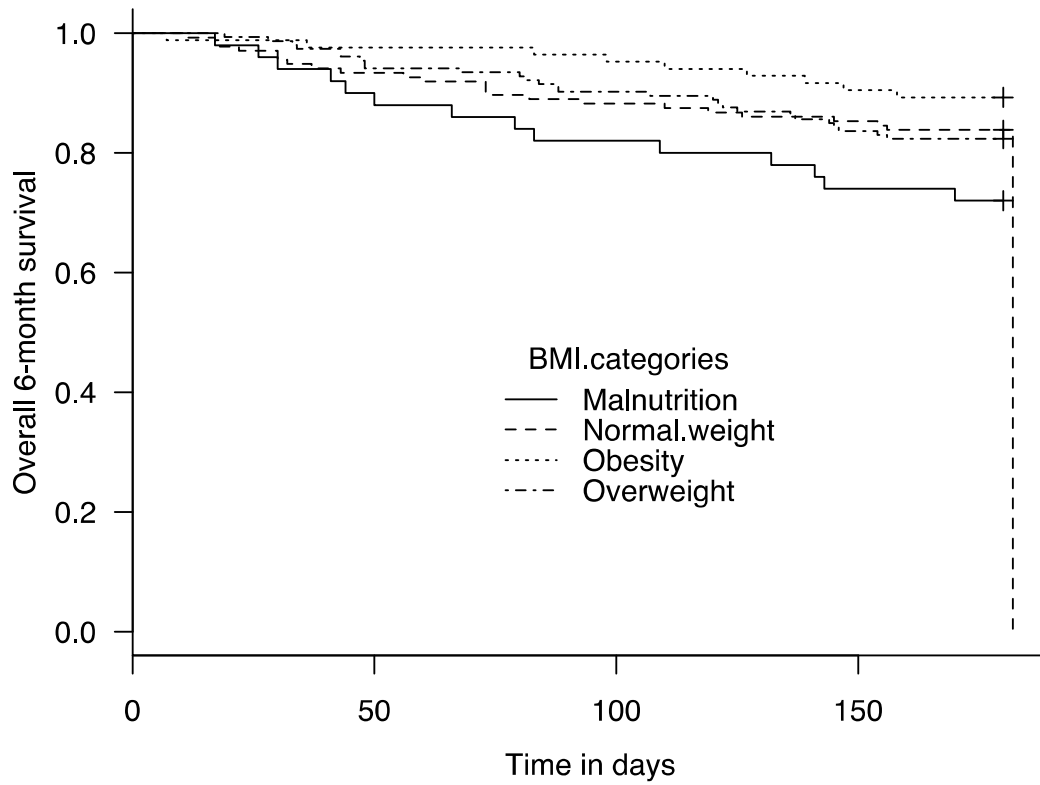
b prostate = 12, urothelial = 4, kidney = 3, bladder = 2

c unknown primary site = 8, mesothelioma = 5, cutaneous epidermidis carcinoma = 4, anal = 3, sarcoma = 2, melanoma = 2, oral carcinoma = 2, duodenal = 2, thymoma = 1, non-differentiated carcinoma = 1.

448

449

450 **Figure 2. Kaplan-Meier survival plotted by BMI category following GA in 433 older**
 451 **cancer outpatients**
 452



	Number at risk			
	0	50	100	150
Malnutrition	50	45	41	37
Normal.weight	136	127	120	116
Obesity	84	82	80	76
Overweight	153	144	138	128

453 *P* value (log-rank) = 0.06

454 BMI: body mass index

455 Malnutrition: BMI < 21 kg/m²

456 Normal weight: 21 < BMI < 25 kg/m²

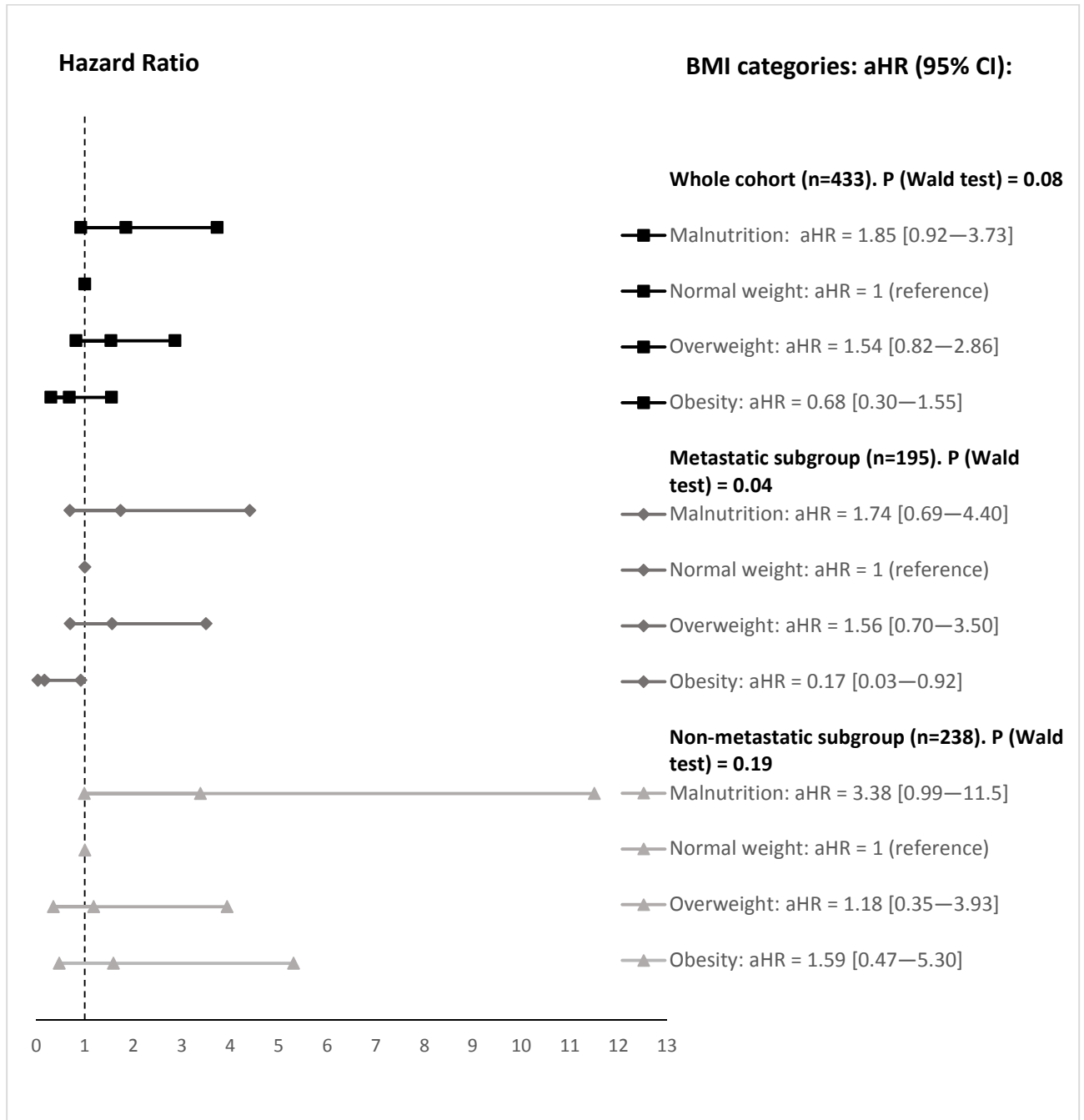
457 Overweight: 25 < BMI < 30 kg/m²

458 Obesity: BMI ≥ 30 kg/m²

459 **Figure 3. Forest plot of adjusted hazard ratio^a for body mass index (BMI) categories for**
 460 **prediction of 6-month mortality in older cancer patients after geriatric assessment**

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462



463
464

^aBMI categories were adjusted for sex, slow gait speed, MMSE, cancer site and exclusive supportive care.