Screening for frailty among older patients with cancer using blood biomarkers of inflammation

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Abstract

Introduction: As frailty is associated with inflammation, biomarkers of inflammation may represent objective measures that could facilitate the identification of frailty. Glasgow prognostic score (GPS), combines C-reactive protein (CRP) and albumin, and is scored from 0-2 points. Higher score indicates a higher degree of inflammation.

Objectives: To investigate whether (1) GPS is associated with frailty, (2) GPS could be used to screen for frailty, (3) IL-6 and TNF-α add to the accuracy of GPS as a screening tool, and (4) GPS adds prognostic information in frail older cancer patients.

Methods: Prospective, observational study of 255 patients ≥ 70 years with solid malignant tumours referred for medical cancer treatment. At baseline, frail patients were identified by a modified Geriatric Assessment (mGA), and blood samples were collected.

Results: Mean age was 76.7 years, 49.8% were frail, and 56.1% had distant metastases. The proportion of frail patients increased with higher GPS (GPS zero: 43.2%, GPS one: 52.7%, GPS two: 94.7%). GPS two was significantly associated with frailty (OR 18.5), independent of cancer type, stage, BMI and the use of anti-inflammatory drugs. The specificity of GPS was high (99%), but the sensitivity was low (14%). Frail patients with GPS two had poorer survival than patients with GPS zero-one. TNF-α and IL-6 did not improve the accuracy of GPS when screening for frailty.

Conclusion: Frailty and GPS two are strongly associated, and GPS two is a significant prognostic factor in frail, older cancer patients. The inflammatory biomarkers investigated are not suitable screening tools for frailty.

Introduction:

As the population grows older, the number of older patients with cancer increases (1). Due to large variations in health status, these patients represent a major challenge in clinical practice as some patients tolerate and benefit from standard cancer treatment whereas others have an increased risk of adverse reactions and questionable benefit of the therapy. Chronological age alone is a poor parameter for appropriate treatment decisions or estimation of life expectancy (1, 2).

Frailty is widely recognized as a state of increased vulnerability to stressors due to reduced functional reserves (2, 3), but there is no consensus on how it should be identified. A Geriatric Assessment (GA), which includes a systematic evaluation of comorbidity, cognitive and physical function, nutritional status, affective components and social situation (4), is considered the best clinical approach to assess vulnerability, and has frequently been used to identify frailty in oncology (5). To achieve a more targeted application of this relatively comprehensive procedure, a simple screening followed by a full assessment when deficits are detected, has been proposed (6). However, existing

frailty screening tools have poor sensitivity and specificity (7), and there is a need to develop more precise or complementary methods to differentiate between fit and frail older patients with cancer. Biomarkers are attractive options as they are objectively measured and easily applicable in routine clinical practice.

Ageing and inflammation are so closely related that the expression "inflammaging" has been coined (8). Many age-related conditions such as dementia, depression, and sarcopenia share an inflammatory pathogenesis (9). Hence, inflammation seems to play an important role in the development of frailty (10). Increased circulating levels of acute phase proteins such as C-reactive protein (CRP) and pro-inflammatory cytokines have been associated with both functional impairment and different measures of frailty (11-14). However, CRP also tends to increase with age, body mass index (BMI) and sedentary lifestyle (15), as well as with infectious diseases and cancer.

The negative impact of systemic inflammation in malignancies is well-known. The Glasgow prognostic score (GPS), for instance, which is based on the blood biomarkers of inflammation, CRP and albumin, is validated in more than 60 studies of cancer patients and predicts survival, weight and muscle loss (16).

The aims of this study were to investigate a) the association between GPS and frailty, b) if GPS could be used to screen for frailty, c) if the inflammatory markers Interleukin-6 (IL-6) and Tumor Necrosis Factor- α (TNF-α) add to the accuracy of GPS as a screening tool, and d) to explore if GPS adds prognostic information among frail older patients with cancer.

Methods

Design and patients:

In this prospective, observational multicenter study, patients were consecutively recruited from eight outpatient cancer clinics at two university hospitals and six local hospitals in South East Norway from January 2013 until April 2015. The inclusion criteria were: age ≥70 years, histologically verified solid malignant tumor, referral to a specialist oncology service for a new cancer diagnosis or the first relapse after previous curative cancer treatment, and written informed consent. The patients were followed for two years or until death.

The study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (2012/104) and registered at clinicaltrials.gov (NCT01742442).

Assessments

Pre-treatment baseline assessments included clinical and demographic data, a modified geriatric assessment, blood sampling, Eastern Cooperative Oncology Group (ECOG) performance status, cancer type, cancer stage, location of metastases, planned treatment, and whether treatment intent was curative or palliative.

Modified Geriatric Assessment (mGA)

Our Geriatric Assessment (GA) was performed by trained oncology nurses instead of a multidisciplinary team, and it did not contain all aspects of a comprehensive Geriatric Assessment (CGA) (1), which is why it is referred to as a modified GA (mGA). Eight different domains were assessed; comorbidity, activities of daily living (ADL), symptoms of depression, falls, polypharmacy, cognitive- and physical function, and nutritional status.

Patients were classified as frail according to a modification of the Balducci criteria(17) that has formerly been applied to identify frailty in older patients with cancer by Kristjansson et al. and Ommunndsen et al. (18, 19). In accordance with Balducci's criteria and those used by Kristjansson and Ommundsen, our patients were categorized as frail if they reported one of the following deficits: Dependencies in ADL, significant comorbidity, or at least one or more geriatric syndromes (impaired cognitive function, depression, malnutrition, or falls). Furthermore, similar to Kristjansson et al, we included polypharmacy, which has also been proposed as a criterion by Winograd et al (20). As a performance measure, which provides additional important information to the GA, the Timed Up and Go (TUG) test was added to our mGA (21). Although closely similar to the model applied by Kristjasson et al, our mGA as not been validated.

The eight different domains were assessed by renowned and validated instruments (19), with defined cut-offs for impairments within each frailty domain (Table 1) (22-28). Table 1 summarizes how the different domains were assessed, which tools were used and which pre-defined cut-off values were chosen.

Blood analyses

Blood samples were collected at the time of inclusion. CRP and albumin were analyzed on a Cobas c501 instrument (Roche Diagnostics, USA). EDTA-plasma samples were stored in a biobank at -80°C, and analyzed for TNF-α and IL-6 by an Immulite 1000 Instrument (Siemens Health Care Diagnostics Inc, Deerfield, IL, USA) using kits from the Immulite Immunoassay System. The analytic sensitivity of the IL-6 kit is 2 pg/ml, and 1.7 pg/ml for the TNF-α kit.

GPS

The GPS is based on CRP and albumin. CRP ≤ 10mg/L and albumin ≥ 35 g/L = 0 points, CRP > 10mg/L or albumin < 35 g/L = 1 point, and CRP > 10mg/L and Albumin < 35g/L = 2 points. The higher the score, the higher the level of inflammation. A modified version of the GPS (mGPS) has been applied and tested in several studies (16, 29). The mGPS is also based on CRP and albumin, but hypoalbuminemia without an elevated CRP gives a score of 0.

Statistics

In our main, pre-specified analyses, GPS was treated as a categorical variable as appropriate, whereas IL-6 and TNF-α were used as continuous variables as generally recommended for the investigation of prognostic factors(30).The association between frailty and GPS was first investigated with a bivariate logistic regression model (Model-1a). To test how well the model discriminated between frail and non-frail patients, the C-index was calculated. Further, a number of multiple logistic regression models were estimated. The models adjusting for either IL-6 (Model-2a) or TNF-α (Model-3a) or both (Model-4a) were estimated first. Then the four models were adjusted for diagnostic groups (breast-, prostate-, colorectal-, other gastrointestinal (GI), lung-and other cancer), stage of disease (localized disease, locally advanced or metastatic), BMI, and the use of anti-inflammatory drugs (NSAIDs and steroids) (Model 1b, 2b, 3b and 4b, respectively). The C-index was calculated for all multiple regression models and compared to the C-index for Model-1a. For explorative purposes, all analyses were repeated using the mGPS instead of the GPS, and with IL-6 and TNF-α categorized into quartiles. The latter was done to enable comparison to studies where this approach has been applied (31-33).

Finally, as another exploratory analysis, overall survival (OS) was compared between subgroups defined according to frailty status and GPS scores by Kaplan-Meier plots and log-rank test. Statistical

significance was defined as $p < 0.05$. The statistical analyses were performed by SPSS v24 and StataSE v14.

Results

A total of 307 patients were included. One withdrew consent and 51 patients were excluded due to missing mGA data or blood samples (Figure 1). Thus, 255 patients were eligible for the present study, 112 (43.9%) were women, and the mean age was 76.9 years. The most common cancers were colorectal (n= 69, 27.1%), lung (n= 55, 21.6%) and prostate cancer (n = 47, 18.4%) (Table 2). A total of 216 patients (84.7%) were rated as ECOG PS 0-1, 143 (56.1%) had metastatic disease, and 127 (49.8%) were frail according to our mGA (Table 2). Among these, 68 (53,5% of all frail patients) had deficits in one domain, 37 (29,1%) in two and 22 (17,3%) in three or more domains.

Inflammatory response

The majority of patients had a low level of systemic inflammation according to the GPS; 162 patients (63.5%) presented with GPS zero, 74 (29.0%) with GPS one, whereas 19 (7.5%) had GPS two. The groups were comparable in terms of gender and age (45.1%, 41.9%, and 42.1% were women and mean age was 77.0, 76.8, and 75.8, for GPS zero, one, and two respectively). The frequency of metastatic disease and poor ECOG status increased with increasing GPS-score (Table 3). We also observed that the proportion of patients who received curative treatment was highest among those with GPS zero (GPS 0: 44.4%, GPS 1: 2.7%, and GPS 2: 10.5%).

Of the 162 patients with GPS zero, 43.2% were frail, corresponding proportions for GPS one and GPS two were 52.7% and 94.7% (Table 3). Consequently, the sensitivity of GPS two as a screening tool for frailty was poor (only 14%), whereas the specificity was 99%.

In the overall study cohort, the mean value of IL-6 was 10.3 pg/ml (SD 19.6) and the mean value of TNF-α was 12.0 pg/ml (SD 6.4). For frail patients, mean IL-6 was 11.2 pg/ml (SD 15.4), and for the non-frail patients 9.3 pg/ml (SD 23.1). Mean (SD) for TNF-α were 12.3 pg/ml (5.6) and 11.7 pg/ml (7.1) for frail and non-frail patients, respectively.

Main regression analyses

Both bivariate (Table 4) and all multivariate (Table 5) regression analyses showed a highly significant association between GPS two and frailty. In the bivariate model (Model-1a), OR for being frail with GPS two was 23.7 (95% CI 3.1;181.5, p=0.002). After adjusting for diagnosis, stage of disease, BMI and the use of anti-inflammatory drugs (Model 1b, table 4), the OR was 18.5 (95% CI 2.3;148.2, p=0.006). The C-indices for the bivariate and multivariate model were 0.60 (95% CI 0.54;0.66), and 0.68 (0.62;075), respectively (Table 4). The difference was statistically significant, indicating that the discrimination of frail versus non-frail patients improved by adding the clinical covariates.

When applied as continuous variables,IL-6 and TNF-α were not statistically significantly associated with frailty, neither in bivariate nor multivariate analyses. When adding IL-6, TNF-α, or both to the model including GPS only (Model 1a), the association between frailty and GPS two remained highly significant (Table 5), whereas the C-indices decreased (Table 5). However, this decrease, suggesting poorer models, was significant only for the model adding TNF-α to GPS.

Finally, the models including GPS and IL-6, TNF-α or both were also adjusted for diagnosis, stage of disease, BMI and the use of anti-inflammatory drugs (Models 2b, 3b and 4 b, Table 5). In all

models, frailty and GPS two remained highly and significantly associated. The C-indices (Table 5) were all significantly higher for these models compared to those without clinical covariates, but not significantly different from the C-index for model 1b (adjusted for clinical covariates, not IL-6 and TNF-α). Hence, the models improved by adding diagnosis, stage of disease, BMI and use of anti-inflammatory drugs, whereas the inflammatory markers, Il-6 and TNF, did not contribute to the discrimination between frail and non-frail patients.

The only statistically significant clinical covariate was the use of anti-inflammatory drugs. Interestingly, the use of such medication increased the odds for being frail (OR 2.3, 95% CI 1.1; 4.8, p=0.017) in Model-1b.

Exploratory regression analyses

Repeating the analyses using mGPS instead of GPS did not significantly change the results (data not shown). When running the analyses dividing IL-6 and TNF-α values into quartiles instead of using them as continuous variables, bivariate analyses showed a statistically significant association between frailty and the upper quartiles of both IL-6 and TNF-α. However, when adjusting for covariates, this association was no longer significant. Adding IL-6 and / or TNF-α values divided into quartiles did not significantly strengthen any of the GPS models.

Survival

We have previously shown that patients who were frail according to our mGA had inferior survival compared to non-frail patients (19). This was also the case in the present subset of patients. Frail patients had a median survival of 458 days, compared to 892 days for non-frail patients. We compared survival between non-frail patients with GPS zero-one, frail patients with GPS zero-one, and frail patients with GPS two, and found significant differences between these groups ($p<0.001$ for log-rank test), with a median survival of 898 days, 520 days and 245 days, respectively. Only one patient with GPS two was non-frail, and was excluded from the analysis.

Discussion

In this cohort of 255 older patients with a variety of cancer diagnoses, we found a strong association between high levels of inflammation (GPS two) and frailty, independent of cancer type, stage of disease, BMI, and the use of anti-inflammatory drugs. The higher the GPS score, the higher the probability of being frail. Most noticeable, 95% of the patients with GPS two were frail. We also found that frail patients with GPS two had poorer survival than frail patients with GPS zero or GPS one. To our knowledge, only one smaller study (n=52) has formerly investigated the relationship between frailty and GPS in older patients with cancer, and the results corroborate our findings. In that study, however, frailty was identified using the Edmonton Frail Scale (34), and mGPS was used instead of GPS. Their results demonstrated a significant correlation between mGPS and frailty. In our study, we found that the use of mGPS instead of GPS did not alter the results. The negative prognostic impact of a systemic inflammatory response, here demonstrated with increasing GPS score among frail patients, are in line with findings from a series of studies of cancer patients (15, 35). To the best of our knowledge, the potential ability of IL-6 or TNF-α to add information to frailty screening by means of GPS, has not

formerly been investigated, but several studies have previously shown an association between frailty and inflammatory cytokines,, especially with respect to Il-6 (13, 36). Former results are, however, not entirely consistent (37), various factors have been taken into account in the analyses and various scaling methods for cytokines have been used. In our analyses, we adjusted for several other factors that might influence the level of inflammatory markers, such as BMI, the use of anti-inflammatory drugs, cancer diagnosis and stage of the disease. All patients were screened for fever at inclusion. Only five had fever, and it is unlikely that there were "false" high values of CRP, IL-6 or TNF-α due to infectious diseases. Furthermore, most former studies have been undertaken in non-cancer populations (14), or in patients with localized cancer (38). In our population, a large proportion had metastatic disease, and even if cancer diagnosis and stage of disease were controlled for, it is possible that the patients' actual tumor volume influences the level of IL-6 (39, 40). A higher tumor burden might therefore be masking the impact IL-6 has on frailty. A higher detection level in our assay compared to other studies (41) may also have contributed to negative results. These considerations should be taken into account in the interpretation of our results. Thus, we conclude, as formerly advocated by Hubbard et al (14), that further studies are needed to clarify how biomarkers of inflammation correspond with frailty in various groups of cancer patients. Our results should also be interpreted in light of our frailty definition. As we defined impairment in only one domain as sufficient to be classified as frail, it is possible that patients who might be seen as pre-frail were included. However, our frailty definition was based on widely accepted indicators (19) assessed by renowned and validated methods, and on criteria closely similar to what has previously been applied (18, 43). Additionally, strict cut-offs were defined for impairments within each frailty domain (Table 1) (22-28), and we have formerly demonstrated that frailty according to our definition was independently predictive of survival (19). Hence, we believe that our definition is fully acceptable, although we cannot argue that it captures the true concept of frailty as no gold standard for identification exist. The heterogeneity of our study cohort is considered a strength. The different age, ECOG PS, cancer diagnoses and treatment intent, reflects the heterogeneity commonly seen in a daily oncology practice.

In summary, we have demonstrated a highly significant association between GPS two and frailty, with GPS two being highly specific for frailty. However, due to low sensitivity (14%), GPS alone cannot be recommended as a screening tool, and adding IL-6 and TNF-α to the statistical model did not improve the sensitivity. Our study does, however, point towards an added prognostic value provided by GPS when added to mGA. By combining the two tools, we were able to identify a subgroup of frail patients with GPS two, with a particularly poor prognosis.

To conclude, we were not able to confirm that the biomarkers investigated can be used as a screening tool for frailty, but frailty and GPS two are strongly associated. Furthermore, our results indicated that GPS two adds significant prognostic information to GA in older cancer patients

Acknowledgement
We want to thank Heidi Kristin Bø and Randi Sivesind for organizing the biobank and for analyzing the blood samples. We also like to thank the cancer nurses at the participating hospitals for their contribution in the assessment and follow-up of the patients, and an additional thanks to the local investigators Morten Brændengen, Oslo University Hospital and Olav Yri at Akershus University Hospital.

Declaration of conflicting interests
The authors declare no conflicts of interest with respect to the research, authorship or publication of this article.

Author contribution

All authors have contributed and participated in the research and preparation of the article. All authors have approved the final article.

Funding:
This study was funded by Innlandet Hospital Trust.

Table 1. The modified Geriatric Assessment (mGA)

Domain	Assessment method	Range	Rated by	Cut-off value for frailty
Nutritional status	PG-SGA[a]		Nurse/ Patient	Considered severely malnourished by nurse or self-reported weight loss ≥10% the last 6 months.
Comorbidity	OARS[b]	0-15 (Higher score indicates more comorbidities)	Patient	>3 points
Medications, polypharmacy	ATC[c]	0-13	Nurse/ MD	>7 regular medications (ointments & common vitamins excluded)
Falls			Nurse	Patient reports ≥2 falls the last 6 months
Activities of daily living	EORTC QLQ-C30 Q5[d]		Patient	If reported yes a little/quite a bit/very much on question 5
Depressive symptoms	GDS-15[e]	0-15 (Higher score indicates more symptoms)	Patient	≥7 points
Physical function	TUG[f]		Nurse	>14 seconds

Cognitive function	MMSE[g]	0-30 (Higher score indicates better function)	Nurse	<24 points

[a]Patient-generated Subjective Global Assessment, [b]The Physical Health Section of the Older Americans' Resources and Services Questionnaire, [d]Anatomical Therapeutic Chemical Classification System, [d]The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire, [e]Geriatric depression scale, [f]Timed up and Go test, [g]Norwegian Revised Mini Mental State Examination.

Table 2. Baseline characteristics

	All n (%)	**Frail n (%)**	**Non-frail n (%)**
Total	255 (100)	127 (49.8)	128 (50.2)
Age, mean	76.7	77.4	75.5
Gender			
Female	112 (43.9)	58 (45.7)	54 (42.2)
Diagnosis			
Breast	28 (11)	9 (7.1)	19 (14.8)
Prostate	47 (18.4)	21 (16.5)	26 (20.3)
Other GI[a]	30 (11.8)	16 (12.6)	14 (10.9)
Lung	55 (21.6)	32 (25.2)	23 (18.0)
Colorectal	69 (27.1)	33 (26)	36 (28.1)
Other	26 (10.2)	16 (12.6)	10 (7.8)
ECOG[b]			
0	110 (43.1)	38 (29.9)	72 (56.3)
1	106 (41.6)	58 (45.7)	48 (37.8)
2	34 (13.3)	26 (20.5)	8 (6.3)
3	3 (1.2)	3 (2.4)	-
4	1 (0.4)	1 (0.8)	-
Missing	1	1	-
Treatment			
Curative intent[c]	76 (29.8)	26 (20.5)	50 (39.1)
Palliative chemotherapy	122 (47.8)	72 (56.7)	50 (39.1)
Other palliative systemic cancer treatment	40 (15.7)	19 (15.0)	21 (16.4)
Non-systemic palliative treatment[d]	17 (6.7)	10 (7.9)	7 (5.5)
Stage			
Localized	64 (25.1)	26 (20.5)	38 (29.7)
Locally advanced	48 (18.8)	21 (16.5)	27 (21.1)
Metastatic	143 (56.1)	80 (63.0)	63 (49.2)
Use of anti- inflammatory drugs	44 (17.3)	28 (22.0)	16 (12.5)

BMI[e]			
Mean	24.8	24.5	25.1

[a]Other Gasto Intestinal, [b]Eastern Cooperative Oncology Group performance status [c]Referred for neoadjuvant treatment, adjuvant treatment after curative surgery or curative radiotherapy [d] Radiotherapy, palliative surgery or palliative care [e] Body Mass Index

Table 3. Patients characteristic according to GPS

	All n (%)	GPS[a]0 n (%)	GPS1 n (%)	GPS2 n (%)
Total	255	162	74	19
Frail	127 (49.8)	70 (43.2)	39 (52.7)	18 (94.7)
Non-frail	128 (50.2)	92 (56.8)	35 (47.3)	1 (5.3)
ECOG[b] status				
0	110 (43.1)	90 (55.6)	18 (24.3)	2 (10.5)
1	106 (41.6)	58 (35.8)	40 (54.3)	8 (42.1)
2	34 (13.3)	11 (6.8)	16 (21.6)	7 (36.8)
3	3 (1.2)	2 (1.3)	-	1 (5.3)
4	1 (0.4)	-	-	1 (5.3)
Missing	1 (0.4)	1 (0.6)	-	-
Treatment				
Curative intent[c]	76 (29.8)	72 (44.4)	2 (2.7)	2 (10.5)
Palliative chemotherapy	122 (47.8)	52 (32.1)	55 (74.3)	15 (78.9)
Other palliative systemic cancer treatment	40 (15.7)	30 (18.5)	9 (12.2)	1 (5.3)
Non-systemic palliative treatment[d]	17 (6.7)	8 (4.9)	8 (10.8)	1 (5.3)
Stage				
Localized	64 (25.1)	60 (37.0)	4 (5.4)	-
Locally advanced	48 (18.8)	30 (18.5)	15 (20.3)	3 (15.8)
Metastatic	143 (56.1)	72 (44.4)	55 (74.3)	16 (84.2)
BMI[e]				
Mean	24.8	25.1	24.4	24.1
Anti-inflammatory drugs	44 (17.3)	28 (17.3)	13 (17.6)	3 (15.8)

[a] Glasgow Prognostic Score, [b] Eastern Cooperative Oncology Group Performance Status, [c] Referred for neoadjuvant treatment, adjuvant treatment after curative surgery or curative radiotherapy, [d]Radiotherapy, palliative surgery or palliative care, [e] Body mass Index

Table 4. Results of bivariate logistic regression analysis (Model-1a) and multiple logistic

Variable	Bivariate Model-1a		Multivariate Model-1b	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
GPS[a]				
0	1	-	1	-
1	1.5 (0.8; 2.5)	0.176	1.1 (0.6; 2.1)	0.839
2	23.7 (3.1; 181.5)	**0.002**	18.5 (2.3; 148.2)	**0.006**
C-index	0.60 (0.54; 0.66)	**-**	0.68 (0.62; 0.75)	**0.[014b]**
Additional inflammatory markers				
IL6	*1.0 (1.0; 1.0)*	*0.450*	-	-
TNF-α	*1.0 (1.0; 1.1)*	*0.470*	-	-
Diagnosis				
Breast	*1*	-	1	-
Prostate	*1.7 (0.6; 4.5)*	*0.286*	1.1 (0.4; 3.3)	0.837
Other GI	*2.4 (0.8; 7.0)*	*0.106*	1.4 (0.4; 4.8)	0.586
Lung	*2.9 (1.1; 7.7)*	***0.027***	1.7 (0.6; 5.3)	0.332
Colorectal	*1.9 (0.8; 4.9)*	*0.161*	1.7 (0.6; 4.3)	0.301
Other	*3.4 (1.1; 10.4)*	***0.033***	2.6 (0.7; 8.8)	0.139
Stage				
Localized	*1*	-	1	-
Locally advanced	*1.1 (0.5; 2.4)*	*0.740*	0.8 (0.3; 2.0)	0.678
Metastatic	*1.9 (1.0; 3.4)*	***0.043***	1.4 (0.7; 2.8)	0.377
BMI[c]	*1.0 (0.9; 1.0)*	*0.253*	1.0 (0.9; 1.0)	0.233
Anti-inflammatory drugs	*2.0 (1.0; 3.9)*	***0.046***	2.3 (1.1; 4.8)	**0.021**

[a] Glasgow Prognostic Score
[b] p-value C-index model 1a vs C-index model 1b
c Body mass Index

Model 1a, bivariate model including GPS.

regression, adjusted for covariates (Model-1b), with frail/non-frail as dependent variable.

Table 5. Results of multiple logistic regression analyses

Variable	Model-2a		Model-3a		Model-4a		Model-2b		Model-3b		Model-4b	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
GPS[a]												
0	1	-	1	-	1	-	1	-	1	-	1	-
1	1.5 (0.9; 2.7)	0.147	1.5 (0.8; 2.6)	0.178	1.6 (0.9; 2.8)	0.151	1.2 (0.6; 2.3)	0.696	1.1 (0.6; 2.2)	0.768	1.2 (0.6; 2.4)	0.641
2	25.8 (3.3; 203.5)	**0.002**	24.0 (3.1; 185.8)	**0.002**	26.0 (3.3; 206.5)	**0.002**	21.5 (2.6; 180.5)	**0.005**	19.3 (2.4; 156.4)	**0.006**	22.2 (2.6; 187.9)	**0.004**
IL6[b]	1.0 (1.0; 1.0)	0.607			1.0 (1.0; 1.0)	0.614	1.0 (1.0; 1.0)	0.454			1.0 (1.0; 1.0)	0.465
TNFα[c]			1.0 (1.0; 1.0)	0.882	1.0 (1.0; 1.0)	0.916			1.0 (0.9; 1.0)	0.637	1.0 (1.0; 1.0)	0.662
Diagnosis												
Breast							1	-	1	-	1	-
Prostate							1.1 (0.4; 3.2)	0.869	1.1 (0.4; 3.3)	0.840	1.1 (0.4; 3.2)	0.870
Other GI[d]							1.4 (0.4; 4.7)	0.635	1.4 (0.4; 4.8)	0.605	1.3 (0.4; 4.6)	0.651
Lung							1.8 (0.6; 5.4)	0.312	1.7 (0.6; 5.3)	0.337	1.8 (0.6; 5.4)	0.317
Colorectal							1.7 (0.6; 4.3)	0.306	1.6 (0.6 4.3)	0.320	1.6 (0.6; 4.2)	0.323
Other							2.5 (0.7; 8.5)	0.157	2.5 (0.7; 8.6)	0.152	2.4 (0.7; 8.4)	0.169
Stage												
Localized							1	-	1	-	1	-
Locally adv.							0.6 (0.4; 2.1)	0.729	0.8 (0.4; 2.1)	0.709	0.9 (0.4; 2.1)	0.757
Metastatic							1.4 (0.7; 2.8)	0.371	1.4 (0.7; 2.9)	0.358	1.4 (0.7; 2.9)	0.354
BMI[e]							1.0 (0.9; 1.0)	0.220	1.0 (0.9; 1.0)	0.214	1.0 (0.9; 1.0)	0.204
Anti-inflammatory drugs							2.4 (1.2; 5.1)	**0.017**	2.4 (1.1; 4.9)	**0.020**	2.5 (1.2; 5.1)	**0.017**
C-index	0.57 (0.50; 0.64)		0.56 (0.49; 0.63)		0.56 (0.49; 0.64)		0.69 (0.62; 0.75)		0.68 (0.61; 0.75)		0.68 (0.62; 0.75)	

p-value model-1a vs Multiple model	0.118	**0.030**	0.054	**0.010**	**0.017**	**0.013**

[a]Glasgow Prognostic Score, [b]Interleukin 6, [c]Tumor necrosis factor alpha, [d]Other Gastro Intestinal, [e]Body Mass Index

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