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Research Paper

Association of Glasgow Prognostic Score with frailty, mortality and adverse health outcomes in older patients with cancer: A prospective cohort study

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ABSTRACT

Introduction: To balance benefits and risks of cancer treatment in older patients, prognostic information is needed. The Glasgow Prognostic Score (GPS), composed of albumin and C-reactive protein (CRP), might provide such information. This study first aims to investigate the association between GPS and frailty, functional decline, and health-related quality of life (HRQoL) decline as indicators of health problems in older patients with cancer. The second aim is to study the predictive value of GPS for mortality, in addition to clinical predictors.

Materials and Methods: This prospective cohort study included patients aged ≥70 years with a solid malignant tumor who underwent a geriatric assessment and blood sampling before treatment initiation. GPS was calculated using serum albumin and CRP measured in batch, categorized into normal (0) and abnormal GPS (1–2). Outcomes were all-cause mortality and a composite outcome of decline in daily functioning and/or HRQoL, or mortality at one year follow-up. Daily functioning was assessed by Activities of Daily Living and Instrumental Activities of Daily Living questionnaires and HRQoL by the EQ-5D-3L and EQ-VAS questionnaires.

Results: In total, 192 patients with a median age of 77 years (interquartile range 72.3–81.0) were included. Patients with abnormal GPS were more often frail compared to those with normal GPS (79 % vs. 63 %, $p = 0.03$). Patients with abnormal GPS had higher mortality rates after one year compared to those with normal GPS (48 % vs. 23 %, $p < 0.01$) in unadjusted analysis. Abnormal GPS was associated with increased mortality risk (hazard ratio 2.8, 95 % CI 1.7–4.8). The area under the receiver operating characteristics curve of age, distant metastasis, tumor site, comorbidity, and malnutrition combined was 0.73 (0.68–0.83) for mortality prediction, and changed to 0.78 (0.73–0.86) with GPS ($p = 0.10$). The composite outcome occurred in 88 % of patients with abnormal GPS versus 83 % with normal GPS ($p = 0.44$).

Discussion: Abnormal GPS was associated with frailty and mortality. The addition of GPS to clinical predictors showed a numerically superior mortality prediction in this cohort of older patients with cancer, although not statistically significant. While GPS may improve the stratification of future older patients with cancer, larger studies including older patients with similar tumor types are necessary to evaluate its clinical usefulness.

Trial Registration: The TENT study is retrospectively registered at the Netherlands Trial Register (NTR), trial number NL8107. Date of registration: 22-10-2019.

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1. Introduction

To balance benefits and risks of cancer treatment in older patients, prognostic information is needed. Although older patients are heterogeneous in terms of comorbidity and frailty [1], data on prognostic factors for cancer treatment for this group is lacking due to insufficient inclusion of older adults in clinical trials [2]. In current clinical practice a geriatric assessment (GA) can be performed to identify geriatric deficits that predict treatment outcomes and thereby identify patients at high risk of adverse outcomes [3], such as mortality, treatment toxicity, decline in physical functioning, and decline in quality of life. Older patients may prioritize quality of life and daily functioning over length of life [4,5]. However, these outcomes are less often studied. Blood biomarkers can provide prognostic information additional to tumor and frailty characteristics, thereby improving the identification of patients at high risk of adverse health outcomes.

The Glasgow Prognostic Score (GPS) is a combination score of blood concentration of albumin and C-reactive protein (CRP) that reflects systemic inflammation and serves as a marker of nutritional status. Albumin and CRP are routinely and easily measured blood biomarkers. Low albumin and high CRP levels are associated with increased cancer mortality [6,7] and GPS has previously been validated for mortality prediction across different tumor types [8]. A number of recent systematic reviews and meta-analyses confirmed the association between GPS and mortality in colorectal [9], ovarian [10] and lung cancer [11]. However, the vast majority of these studies was performed in on average younger patients. Aging can result in chronic low-grade inflammation accompanied by increased levels of inflammatory markers, which contribute to the development and progression of frailty and aging-related diseases like cancer [12,13]. Therefore, these results might be different in older patients. However, only a limited number of studies have investigated the prognostic value of GPS exclusively in older patients with cancer. In our recent systematic review, we demonstrated that the majority of those studies reported a significant association between high GPS and an increased mortality risk in patients with various tumor types [14]. A recent study by Chiang et al. yielded comparable findings in older patients with colorectal cancer [15]. Only one study investigated the value of GPS additional to frailty characteristics and found that GPS added prognostic value for mortality [16]. No studies investigated GPS in association with functional or quality of life outcomes [14].

The present study first aims to investigate the association between GPS and frailty, functional decline, and health-related quality of life (HRQoL) decline, which serves as an indicator of health problems, in older patients with solid tumors. The second aim is to study the predictive value of GPS for mortality, in addition to clinical predictors.

2. Materials and Methods

2.1. Study Design and Setting

The present study is a substudy of the Triage of Elderly Needing Treatment (TENT) study, an ongoing prospective multicenter study that is embedded in a routine clinical care pathway. Patients aged ≥70 years who are candidates for intensive treatment, such as major surgery, (chemo-)radiotherapy or immune therapy, undergo a GA before treatment initiation. In routine care, interventions or pretreatment optimization were recommended according to existing guidelines when geriatric deficits were present [17]. Patients are followed until one year after treatment initiation or death. The collection of blood samples is part of the TENT study, but not mandatory. The TENT study was approved by the Medical Ethics Committee (ID number NL53575.058.15) at the Leiden University Medical Center (LUMC). All patients provided written informed consent. Details on the design and rationale of the care pathway and TENT study were described elsewhere [18].

The manuscript has been written according the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies [19].

2.2. Patients

Patients with a solid malignant tumor who underwent blood sampling and were included between August 2016 and October 2020 at LUMC or Haga Hospital were eligible.

2.3. Data Collection

2.3.1. Patient Characteristics

The following data were collected from digital patient files: age, sex, body mass index (BMI), smoking status and history, World Health Organization (WHO) performance score (PS), primary tumor site, presence of distant metastasis, curative or palliative treatment intent, and treatment. HRQoL was assessed using the EuroQol five dimensions questionnaire (EQ-5D-3L), including the visual analogue scale (EQ-VAS; range 0 to 100, higher score indicates higher health-related quality of life) [20]. The EQ-5D-3L score is recalculated to an index score according to a set of weights applicable to the Netherlands, as described by Lamers et al. [21] (range − 0.33 to 1.0, values less than 0 represent health states regarded as worse than being dead and 1 represents full health). The EQ-VAS was obtained using a verbal description of the question and the verbal answer was registered on a numerical rating scale.

2.3.2. Geriatric Assessment and Frailty Definition

Frailty was defined using the GA. The GA evaluated four geriatric

Table 1
Geriatric assessment.

Geriatric assessment		Test	Range	Cut-off value
Somatic domain	Comorbidity	CCI [40]	0 to 33 points	≥1 points No points assigned to the 'solid tumor' category if no other tumors were present
	Polypharmacy	N/A	N/A	Number of medications ≥5
	Malnutrition	MNA-SF® [41]	0 to 14 points	≤11 points
Psychological domain	History of delirium	N/A	N/A	Yes
	Dementia diagnosis	N/A	N/A	Yes
	Cognitive impairment	6CIT [42]	0 to 28 points	>7 points
Functional domain	Fall incident	N/A	N/A	≥1 in past 6 months
	Institutionalization	N/A	N/A	Yes
	ADL dependency	Katz ADL [43]	0 to 6 points	≥2 points
	IADL dependency	Lawton IADL [44]	Men: 0 to 5 points Women: 0 to 8 points	Men: ≤4 points Women: ≤7 points
Social domain	Living situation	N/A	N/A	Living alone

Abbreviations: 6CIT, Six-item Cognitive Impairment Test; ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index; IADL, Instrumental Activities of Daily Living; MNA-SF®, Mini Nutritional Assessment Short Form; N/A, Not applicable.
Patients who had deficits in at least two domains were classified as frail. A domain had deficits if at least one individual test score was abnormal.

domains, the somatic, psychological, functional, and social domains, using previously validated tests. Table 1 lists the test used for the assessment of the domains and their cut-off values. A patient had deficits in a domain if at least one individual test score was abnormal. Patients who had deficits in at least two domains were classified as frail. We chose this definition of frailty because it closely resembles clinical practice where the comprehensive GA is the gold standard to define frailty [17]. We used this definition of frailty in our previous publications [22,23]. We also calculated the 10-Item Frailty Index Based on a comprehensive GA (FI-CGA-10) [24] to validate our frailty definition, which previously has been validated in older patients with cancer [25]. Details on the FI-CGA-10 definition and calculation are described in the study by Baltussen et al [23] Data on GA were extracted from digital patients files or case report forms.

2.3.3. Follow-up

Patients were followed for one year after treatment initiation or until death. Data on mortality were obtained from digital patient files or municipal registries. Patients were contacted by telephone after one year to collect data on the living situation and to obtain the Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), EQ-5D-3L, and EQ-VAS questionnaires. If patients were not reached by telephone the questionnaires were sent to acquire a written response.

2.3.4. Blood Samples and Laboratory Measurements for GPS

Serum blood samples were collected at the time of inclusion, before treatment initiation, and stored at −80 °C. Serum albumin and CRP were measured in batch and in duplicate. Serum albumin was analyzed using a colorimetric assay (Roche Cobas 8000 Modular [C502]). The lower and upper limits of detection were 10 g/L and 336 g/L. The coefficient of variation was 0.45 %. CRP was analyzed using a turbidimetric assay (Roche Cobas 8000 Modular [E602]). The lower and upper limits of detection were 0.3 mg/L and 700 mg/L. The coefficient of variation was 3.4 %. The GPS was calculated as follows: 0 points if CRP ≤10 mg/L and albumin ≥35 g/L, 1 point if CRP >10 mg/L or albumin <35 g/L, 2 points if CRP >10 mg/L and albumin <35 g/L.

2.4. Outcomes

Multiple outcomes were assessed: one-year all-cause mortality and the adverse health outcomes functional decline and decline in HRQoL after one year in patients that survived. A large proportion of patients died within one year, in whom a decline in daily functioning or HRQoL could no longer occur. Mortality can be viewed as the final stage of loss of functionality and quality of life. Therefore, we designed a composite outcome of functional decline and/or HRQoL decline or mortality at one year follow-up. The composite outcome was a binary outcome and occurred when a patient either experienced a decline in daily functioning and/or a decline in HRQoL or died. Functional decline was defined as either decline in ADL (≥1 point increase in Katz ADL score compared to baseline or new institutionalization) or IADL decline (≥1 point decrease in Lawton IADL score compared to baseline). Decline in HRQoL was defined as either decline in EQ-5D-3L index score or EQ-VAS using the minimal clinically important differences (MCID) compared to baseline (MCID EQ-5D-3L index score ≥ 0.06, MCID EQ-VAS ≥7) [26]. Data on mortality status were complete in all patients. Therefore, all patients that died could be included in the composite outcome analyses. Patients that survived were only included in the composite outcome analyses if data on daily functioning and HRQoL were complete at baseline and one-year follow-up.

2.5. Statistical Methods

Data were presented as numbers with percentages for categorical variables and mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables, as appropriate. Differences between groups were assessed by a chi-square test, Fisher exact test, independent samples *t*-test or Mann-Whitney *U* test. The correlation between frailty and the FI-CGA-10 was evaluated using a Pearson correlation. GPS was categorized as normal (GPS 0) or abnormal (GPS 1 and 2 merged because of low number of patients in GPS 2 category). The association between GPS and frailty at baseline was assessed using a chi-square test. Univariable Cox regression analysis was performed to study the association between GPS and mortality. Hazard ratios (HR) with 95 % confidence interval (CI) were calculated. The Cox proportional hazards assumption was examined using log-minus-log survival plots and by using an interaction term with time in the time-dependent Cox regression model. The Cox proportional hazards assumption was not violated in all analyzed variables. The prediction accuracy of possible single predictors for one-year mortality was tested for age, sex, primary tumor site, presence of distant metastasis, Charlson Comorbidity Index (CCI), malnutrition, frailty, and GPS using a receiver operating characteristic (ROC) curve with the area under the curve (AUC) assessed with Cox regression analyses. A number of these clinical predictors were then combined in a clinical model. These clinical predictors were chosen based on known predictors from clinical experience, statistical significance in univariable Cox regression analyses, and non-dependence with other predictors assessed using a Pearson correlation. Next, clinical predictors were combined with GPS in multivariable Cox regression analyses and their AUCs were calculated to test whether addition of GPS improved the mortality prediction accuracy. Comparison of two AUCs was performed using the DeLong method [27] by MedCalc® Statistical Software version 20.115 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2022). The association between GPS and the composite outcome was assessed using the chi-square test. We performed two sensitivity analyses, in which we (a) defined missing data on functional or HRQoL decline as 'no decline' and (b) defined missing data on functional or HRQoL decline as 'decline'. Lastly, because GPS is composed of albumin and CRP levels and both are associated with increased mortality in (predominantly younger) patients with cancer in previous studies [6,7], we also performed the Cox regression analyses and mortality prediction analyses for continuous levels of albumin and CRP as single biomarkers and as continuous variables combined in the same model. CRP was natural logarithmic transformed to reduce the skewness of the distribution. A *p*-value of <0.05 was considered statically significant. Missing data are addressed in the table legends. Analyses were performed using SPSS software version 25 and figures were created using Graphpad PRISM 9.0.1.

3. Results

A total of 488 patients with a solid malignant tumor were included in the TENT study during the inclusion period. In 192 (39.3 %) out of 488 patients a blood sample was available and they were included in this substudy; 296 (60.7 %) patients did not provide a blood sample. Reasons for not providing a blood sample were no consent or practical or logistical reasons such as insufficient time remaining before treatment initiation or the absence of an opportunity for an additional hospital visit.

3.1. Baseline Characteristics

Table 2 shows the baseline characteristics of the 192 patients included in the present study. The median age was 77 years (IQR 72.3–81.0) and 104 patients (54.2 %) were male. According to the GA, 129 patients (68.3 %) were frail. Our frailty definition was strongly correlated with the FI-CGA-10 frailty index (Pearson correlation = 0.73). The most frequent primary tumor sites were cancers of the upper gastrointestinal tract (n = 52, 27.1 %), gynaecologic cancers (n = 34, 17.7 %), and colorectal cancers (n = 25, 13.0 %). A total of 33 patients (17.2 %) had metastatic disease. Most patients were treated with curative intent (n = 137, 71.4 %). The median time between blood sample

Table 2
Baseline characteristics.

Characteristics	Total population $n = 192$
Age, years, median (IQR)	77.0 (72.3–81.0)
Male sex, n (%)	104 (54.2)
BMI (kg/m^2), mean (SD)	26.5 (4.9)
Smoking, history or current	113 (58.9)
WHO PS, n (%)	
0–1	79 (41.1)
2	20 (10.4)
3–4	6 (3.1)
Unknown	87 (45.3)
Primary tumor site, n (%)	
Head and neck	19 (9.9)
Upper GI	52 (27.1)
Colorectal	25 (13.0)
Hepatobiliary or pancreas	9 (4.7)
Lung	10 (5.2)
Breast	16 (8.3)
Gynaecologic	34 (17.7)
Urologic	18 (9.4)
Other [a]	9 (4.7)
Distant metastasis, n (%)	
No	157 (81.8)
Yes	33 (17.2)
Unknown	2 (1.0)
Treatment intent, n (%)	
Curative	137 (71.4)
Palliative	55 (28.6)
Treatment plan, n (%)	
Surgery with/without (neo)adjuvant therapy	107 (55.7)
(Chemo)radiotherapy	35 (18.2)
No anti-tumor treatment	19 (9.9)
Chemotherapy	8 (4.2)
Other [b]	23 (12.0)
EQ-5D-3L index score, median (IQR)	0.84 (0.78–1.0)
EQ-VAS, mean (SD)	68.6 (15.6)
Albumin (g/L), mean (SD)	40.8 (3.5)
Albumin <35 g/L, n (%)	11 (5.7)
CRP (mg/L), median (IQR)	3.3 (1.5–10.8)
CRP >10 mg/L, n (%)	54 (28.1)
GPS, n (%)	
0	133 (69.3)
1	53 (27.6)
2	6 (3.1)
Geriatric screening and assessment	
Charlson Comorbidity index ≥1, n (%)	138 (71.9)
Polypharmacy, n (%)	113 (58.9)
Malnutrition, n (%)	98 (51.3)
Cognitive impairment according to 6CIT, n (%)	29 (15.5)
Dementia diagnosis, n (%)	3 (1.6)
Previous delirium, n (%)	27 (14.2)
ADL dependency, n (%)	9 (4.8)
IADL dependency, n (%)	65 (34.8)
Fall <6 months, n (%)	46 (24.2)
Living situation, n (%)	
At home, alone	68 (35.4)
At home, with others	119 (62.0)
Institutionalized	4 (2.1)
Sheltered housing	1 (0.5)
Frail, n (%)	129 (68.3)

Abbreviations: 6CIT, Six-item Cognitive Impairment Test; ADL, Activities of Daily Living; BMI, Body mass index; CRP, C-reactive protein; EQ-5D-3L, EuroQol five dimensions questionnaire; EQ-VAS, EuroQol visual analogue scale; GI, Gastrointestinal; GPS, Glasgow Prognostic Score; IADL, Instrumental Activities of Daily Living; IQR, Interquartile range; n, number; SD, standard deviation; WHO PS, WHO performance score.
Missing data: EQ-5D-3L n = 31, EQ-VAS n = 9, malnutrition n = 1, cognitive impairment n = 5, previous delirium n = 2, ADL dependency n = 3, IADL dependency n = 5, fall < 6 months n = 2, frail n = 3.
[a] Other tumor sites: Adrenal n = 1, bone n = 1, skin melanoma n = 2, soft tissue n = 3, thyroid n = 1, unknown primary tumor n = 1.
[b] Other treatment: Chemotherapy and immune therapy n = 2, chemotherapy and radiotherapy n = 4, chemotherapy and targeted therapy n = 2, chemotherapy, hormonal therapy and targeted therapy n = 1, chemotherapy, radiotherapy and immune therapy n = 1, hormonal therapy n = 5, immune therapy n = 2, radiofrequent ablation n = 1, radiotherapy and hormonal therapy n = 2, wait and see n = 3.

collection and treatment initiation was 18 days (IQR 9–27). All patients had albumin and CRP levels within the lower and upper limits of detection. The mean albumin level was 40.8 g/L (SD 3.5) and 11 patients (5.7 %) had an albumin <35 g/L. The median CRP level was 3.3 mg/L (IQR 1.5–10.8) and 54 patients (28.1 %) had a CRP >10 mg/L. A total of 133 patients (69.3 %) was classified as normal GPS and 59 patients (30.7 %) as abnormal GPS (GPS 1 $n = 53$ [27.6 %], GPS 2 $n = 6$ [3.1 %]). Baseline characteristics of patients who did not provide a blood sample are shown in Supplementary Table 1 in Appendix A. They were slightly different in primary tumor site (most frequent: upper gastrointestinal tract cancers $n = 67$ [22.6 %], gynaecologic cancers $n = 62$ [20.9 %], colorectal cancers $n = 54$ [18.2 %]), and patients were less often classified as frail (62.1 %).

3.2. GPS and Frailty at Baseline

Table 3 shows the GA results according to GPS category. Patients

Table 3
Geriatric assessment results stratified by Glasgow Prognostic Score category.

	GPS normal	GPS abnormal	*P* value [a]
	$n = 133$	$n = 59$	
Frailty, n (%)	83 (63.4)	46 (79.3)	0.03
Domains geriatric assessment, n (%)			
Deficit somatic domain	115 (87.1)	58 (98.3)	0.02
Deficit in psychological domain	38 (29.2)	12 (20.3)	0.20
Deficit in functional domain	55 (42.0)	32 (55.2)	0.09
Deficit in social domain	51 (38.3)	17 (28.8)	0.20
Somatic domain, n (%)			
Charlson Comorbidity index ≥1	91 (68.4)	47 (79.7)	0.11
Polypharmacy	78 (58.6)	35 (59.3)	0.93
Malnutrition	60 (45.5)	38 (64.4)	0.02
Psychological domain, n (%)			
Cognitive impairment according to 6CIT	22 (17.1)	7 (12.1)	0.38
Dementia diagnosis	2 (1.5)	1 (1.7)	1.00
Previous delirium	22 (16.8)	5 (8.5)	0.13
Functional domain, n (%)			
ADL dependency	4 (3.1)	5 (8.5)	0.14
IADL dependency	39 (30.2)	26 (44.8)	0.05
Fall <6 months	31 (23.7)	15 (25.4)	0.79
Social domain, n (%)			
Living situation			
At home, alone	51 (38.3)	17 (28.8)	0.20
At home, with others	78 (58.6)	41 (69.5)	0.15
Institutionalized	3 (2.3)	1 (1.7)	1.00
Sheltered housing	1 (0.8)	0 (0)	1.00

Abbreviations: 6CIT, Six-Item Cognitive Impairment Test; ADL, Activities of Daily Living; GPS, Glasgow Prognostic Score; IADL, Instrumental Activities of Daily Living.
Missing data per group: GPS normal: Frailty n = 2, somatic domain n = 1, psychological domain n = 3, functional domain n = 2, malnutrition n = 1, cognitive impairment n = 4, previous delirium n = 2, ADL dependency n = 3, IADL dependency n = 4, fall < 6 months n = 2.
GPS abnormal: Frailty n = 1, functional domain n = 1, cognitive impairment n = 1, IADL dependency n = 1.
[a] P value for difference between patients in GPS normal and GPS abnormal group, calculated with χ^2 test.

with abnormal GPS were significantly more often classified as frail (79.3 %) compared to patients with normal GPS (63.4 %, $p = 0.03$). This is largely explained by more patients with CCI ≥ 1 and more malnutrition among patients with abnormal GPS, resulting in a higher proportion of deficits in the somatic domain among patients with abnormal GPS (98.3 %) compared to normal GPS (87.1 %, $p = 0.02$).

3.3. GPS and One-Year All-Cause Mortality

Within one year, 58 patients (30.2 %) had died. The one-year mortality rate was 47.5 % in patients with abnormal GPS and 22.6 % in normal GPS ($p < 0.01$). Cox regression analysis showed a statistically significant association between abnormal GPS compared to normal GPS and all-cause mortality in the crude analysis (abnormal GPS HR, 2.8; 95 % CI, 1.7–4.8). Table 4 shows the association between predictors and area under the ROC curves for observed versus predicted one-year mortality for clinical predictors and GPS. Among the clinical predictors, primary tumor site had the highest AUC of 0.69 (95 % CI 0.62–0.77). GPS had an AUC 0.63 (95 % CI 0.54–0.72). Combining the clinical predictors age, primary tumor site, presence of distant metastasis, CCI ≥1 and malnutrition resulted in an AUC 0.76 (95 % CI 0.68–0.83). When GPS was added, the performance moderately improved the AUC to 0.79 (95 % CI 0.73–0.86), however, this was not statistically significant ($p = 0.10$).

3.4. GPS and Composite Outcome

Fig. 1 shows the results of the composite outcome functional decline and/or HRQoL decline or mortality stratified by GPS category. After one year of follow-up, data on functional decline, HRQoL decline, and mortality were complete in 173 patients (90.1 %). The vast majority of these patients experienced the composite outcome within one year after treatment initiation ($n = 146$, 84.4 %). When stratified by GPS category, we found a large difference in mortality rate; however, when functional and HRQoL decline were combined in the composite outcome this difference disappeared (abnormal GPS 87.5 % vs. normal GPS 82.9 %, $p = 0.44$). Only 12.5 % of patients with abnormal GPS and 12.1 % with normal GPS survived and experienced no functional or HRQoL decline. Both sensitivity analyses showed comparable results.

3.5. Albumin and CRP

We also performed the mortality analyses for continuous levels of albumin (g/L) and CRP (natural log transformed) as single biomarkers and both combined in the same model (Table 4). We found similar results. Crude Cox regression analyses showed a statistically significant association between low albumin (HR, 0.88; 95 % CI, 0.82–0.94) and high CRP (HR, 1.4; 95 % CI, 1.2–1.7) and all-cause mortality within one year. Albumin alone had an area under the ROC curve of 0.65 (95 % CI 0.56–0.73) for mortality prediction and CRP of 0.62 (95 % 0.52–0.71). Albumin and CRP levels as continuous variables taken together in the same model resulted in an AUC of 0.65 (95 % CI 0.56–0.74). Addition of albumin or CRP to the clinical model (AUC 0.76 [95 % CI 0.68–0.83]) improved the AUC to 0.79 (95 % CI 0.72–0.86), though both changes in AUC were not statistically significant different compared to the clinical model (albumin $p = 0.13$, CRP $p = 0.14$). Addition of both albumin and CRP (continuous) to the clinical model improved the AUC to 0.80 (95 % CI 0.74–0.87), also a not statistically significant change in AUC compared to the clinical model ($p = 0.06$).

Table 4
Association between predictors and area under the receiver operating characteristic curve for prediction of one-year all-cause mortality.

	Univariate Cox regression analysis		ROC curve analysis	
Predictors	HR (95 % CI)	*P* value	AUC (95 % CI)	*P* value [a]
Age, years	1.0 (1.0–1.1)	0.46	0.57 (0.47–0.66)	N/A
Primary tumor site			0.69 (0.62–0.77)	N/A
Colorectal	1			
Head and neck	7.3 (0.9–62.3)	0.07		
Upper GI	13.9 (1.9–103)	0.01		
Hepatobiliary or pancreas	16.9 (2.0–144.7)	0.01		
Lung	8.8 (0.9–85.0)	0.06		
Breast	4.5 (0.5–43.7)	0.19		
Gynaecologic	7.7 (1.0–60.4)	0.05		
Urologic	6.5 (0.7–58.5)	0.09		
Other [b]	13.1 (1.5–117.5)	0.02		
Distant metastasis, yes	1.5 (0.8–2.8)	0.21	0.56 (0.47–0.65)	N/A
CCI ≥1	1.4 (0.8–2.6)	0.29	0.56 (0.47–0.65)	N/A
Malnutrition, yes	1.9 (1.1–3.3)	0.02	0.61 (0.52–0.70)	N/A
Frailty, yes	1.3 (0.7–2.4)	0.36	0.54 (0.45–0.63)	N/A
Abnormal GPS	2.8 (1.7–4.8)	<0.01	0.63 (0.54–0.72)	N/A
Albumin (g/L)	0.9 (0.8–0.9)	<0.01	0.65 (0.56–0.73)	N/A
CRP (lnCRP)	1.4 (1.2–1.7)	<0.01	0.62 (0.52–0.71)	N/A
Albumin (g/L) + CRP (lnCRP)	N/A	N/A	0.65 (0.56–0.74)	N/A
Predictors combined				
Clinical predictors: age, primary tumor site, distant metastasis, CCI, malnutrition	N/A	N/A	0.76 (0.68–0.83)	N/A
Clinical predictors + abnormal GPS	N/A	N/A	0.79 (0.73–0.86)	0.10
Clinical predictors + albumin (g/L)	N/A	N/A	0.79 (0.72–0.86)	0.13
Clinical predictors + CRP (lnCRP)	N/A	N/A	0.79 (0.72–0.86)	0.14
Clinical predictors + albumin (g/L) + CRP (lnCRP)	N/A	N/A	0.80 (0.74–0.87)	0.06

Abbreviations: AUC, Area under the curve; CCI, Charlson comorbidity index; CI, Confidence interval; CRP, C-reactive protein; GI, Gastrointestinal; GPS, Glasgow Prognostic Score; HR, Hazard ratio; lnCRP, natural-log CRP; N/A, not applicable; ROC, Receiver Operating Characteristic curve.

[a] P value for the comparison to the clinical predictors model.

[b] Other tumor sites: Adrenal n = 1, bone n = 1, skin melanoma n = 2, soft tissue n = 3, thyroid n = 1, unknown primary tumor n = 1.

4. Discussion

We demonstrated that an abnormal GPS, composed of albumin and CRP, is associated with frailty in older patients with cancer and with a three-fold increased risk of mortality in the first year. In addition to clinical predictors, we found only a modest non-significant improvement in mortality prediction. Lastly, a large proportion of patients experienced the composite outcome in the first year after treatment initiation, but this was not associated with GPS.

The association between GPS and frailty is also highlighted by previous studies in older patients with cancer that found similar results [28,29]. Our findings regarding the relationship between GPS, albumin, and CRP with mortality in older patients with solid tumors are largely in

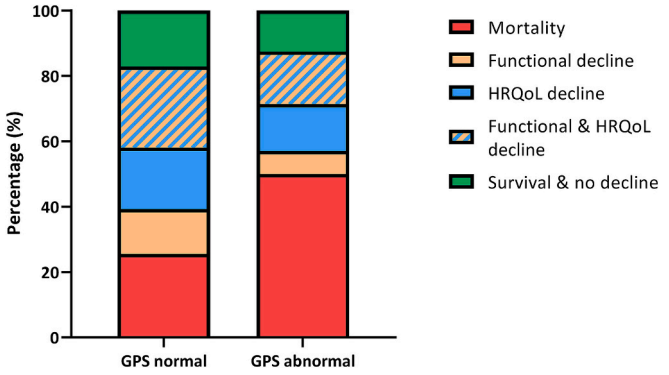

Fig. 1. Composite outcome at one year after treatment initiation, stratified by GPS category.
Percentage of patients that died, experienced functional decline, health-related quality of life decline, both functional and health-related quality of life decline, or survived and experienced no decline, compared to baseline.
Percentages stratified by GPS category. Absolute numbers: Total group with complete data $n = 173$.
GPS normal $n = 117$, $n = 30$ died (25.6 %), $n = 16$ functional declined (13.7 %), $n = 22$ HRQoL declined (18.8 %), $n = 29$ functional and HRQoL declined (24.8 %), $n = 20$ survived and experienced no decline (17.1 %).
GPS abnormal $n = 56$, $n = 28$ died (50.0 %), $n = 4$ functional declined (7.1 %), $n = 8$ HRQoL declined (14.3 %), $n = 9$ functional and HRQoL declined (16.1 %), $n = 7$ survived and experienced no decline (12.5 %).
Abbreviations: GPS, Glasgow Prognostic Score; HRQoL, Health-related quality of life.

line with existing literature in adult patients with different tumor types [6,7,30–32]. A previous study examined the association between modified GPS (mGPS) and mortality in patients with gastric cancer, stratified by age (younger than 75 years and older than 75 years) [33]. In both age groups, high mGPS was associated with a threefold increased mortality risk in the univariate analysis. Few studies investigated the relationship between these biomarkers exclusively in older patients. A study conducted by Oubaya et al. examined 1800 patients aged ≥70 years with various solid tumors in a pooled analysis of three prospective multicenter cohort studies. They found significant associations of GPS, albumin and CRP with one-year mortality in adjusted analyses (all $p <$ 0.001) [34]. In this study, all biomarkers improved a prediction model for mortality that included tumor characteristics, Eastern Cooperative Oncology Group performance score, and G-8 score. The association between GPS and mortality was present in both patients at risk and not at risk of frailty according to the G-8, although associations were stronger for patients not at risk of frailty. Three other studies performed in older patients with cancer reported the association of mortality with GPS [16,29], albumin, [16] and CRP [16,35]. In a prospective multicenter study comprising 255 patients, Harneshaug et al. demonstrated that frail patients with GPS 2 had a higher mortality rate than patients with GPS 0–1 ($p < 0.001$) [29]. In a prospective cohort study of 328 patients aged 65 and over who had undergone surgery for a solid malignant tumor, Brattinga et al. observed that patients with elevated CRP levels (≥10 mg/L) had an increased mortality risk until three years after surgery (HR 1.50 (95 % CI 1.04–2.16) in multivariate Cox regression analysis [35]. Baitar et al. conducted a prospective multicenter study that included 328 patients aged 70 years and over with various types of tumors. They showed that GPS 1 and 2, low levels of albumin, and high levels of CRP were associated with an increased mortality risk in univariate and multivariate Cox regression analyses (all $p < 0.05$). They also demonstrated that addition of albumin and CRP levels improved their prognostic model (age, stage of disease, and tumor type) for mortality, however addition of GA data was superior [16]. Our results show that GPS is associated with an increased mortality risk in a cohort comprising a substantial proportion of frail patients. Additionally, the AUC for mortality prediction of GPS alone was marginally higher than that of frailty alone, suggesting that GPS offers at least comparable prognostic information regarding mortality in our cohort. Taken together, our results add to the literature of this older age group.

To the best of our knowledge, no previous studies have explored the relationship between GPS and functional or HRQoL decline in a longitudinal study design. We found that a strikingly large proportion of patients experienced the composite outcome, which shows that many patients that survived experienced functional decline, had deteriorating HRQoL or both within one year after treatment initiation. Only 16 % of patients survived without experiencing decline. Although we found no association of GPS with these outcomes except for mortality, these findings emphasize the importance of studying other outcomes besides mortality.

The growing number of older patients with cancer emphasises the importance of easily obtained prognostic information to stratify patients by those who will benefit from cancer treatment and those at high risk of adverse outcomes and a poor prognosis. The American Society of Clinical Oncology [36] recommends performing a GA to assess the level of frailty to support treatment decisions and guide targeted interventions in older patients. However, geriatric screening and assessment are still not part of routine care due to barriers such as time and finances [37]. Since GPS is composed of the readily available blood biomarkers albumin and CRP, it could easily be incorporated in clinical practice. If the GPS can provide prognostic information at least similar to clinical predictors, it might improve the identification of patients with a poor prognosis, be used as screening tool supplementary to the G-8, or replace more time consuming assessments performed in clinical practice. Larger clinical studies, including older patients with similar tumor types who undergo a GA, are needed to further investigate clinical usefulness. This would be beneficial in the elimination of uncertainties regarding the precision of the estimate and the statistical significance, as was the case in the present study. In case of significant results, the next step could be to conduct a randomized controlled trial in which the efficacy of treatment decisions and interventions based on clinical predictors and GPS would be investigated. Outcomes of interest would be daily functioning, quality of life, and reduction of treatment complications or toxicity, preferably without compromising mortality rates. In addition, other molecular blood biomarkers in addition to GPS may provide additional prognostic information in future studies [38,39].

The present study has a number of strengths. This is the first study that investigated the relation of GPS to outcomes that are relevant to older patients [4,5], i.e. decline in daily functioning and HRQoL. Albumin and CRP levels were centrally and simultaneously measured in all patients who were included in the present substudy of the TENT study. The studied biomarkers are already routinely and easily measured, and results are therefore easily incorporated in clinical practice. The GA conducted before treatment initiation provided valuable data regarding the presence of geriatric impairments at baseline, in contrast to the baseline characteristics reported by many other studies that include older patients. Finally, the study included an older population seen in daily routine care and is therefore representative for clinical practice. Our study also has several limitations. First, only 39 % of patients included in the TENT study had a blood sample available for albumin and CRP measurements. We provided insight into patient selection and showed that patients without blood sample available had mostly similar baseline characteristics, with the exception of slightly different primary tumor sites, namely a higher prevalence of head and neck and colorectal cancer and a lower prevalence of upper gastrointestinal cancer. Additionally, a lower proportion of cognitive impairment and frailty among this group probably led to the selection of a more frail study population in the present study. Patients with an abnormal GPS were more often classified as frail compared to patients with normal GPS, although both groups comprised a high proportion of frailty. Consequently, the observed association between GPS and mortality, or its predictive ability, may be overestimated. Second, only 6 % of patients had albumin levels <35 g/L. Consequently, the majority of patients with abnormal

GPS had elevated CRP levels, which probably contributed most to the effect of GPS. However, despite the low proportion of decreased albumin levels, albumin was still significantly associated with increased mortality risk and had a similar area under the ROC curve for mortality prediction when combined with clinical predictors compared to GPS. Third, measuring CRP instead of high-sensitivity CRP (hs-CRP) might be a limitation for analyzing the continuous levels of CRP. Hs-CRP can detect CRP levels below 10 mg/L more precisely. This would not influence GPS analyses, but possibly would influence analyses containing CRP as continuous variable due to a different distribution in CRP levels below 10 mg/L. Fourth, our cohort was relatively small and heterogeneous in primary tumor site and treatment. The sample size may have resulted in an inaccuracy of the estimates in the statistical analyses and hampered stratification for primary tumor site. The heterogeneity in primary tumor site and treatment both have a significant impact on prognosis. Fifth, almost 70 % of included patients were frail. This may partly be explained by using the MNA-SF® to measure malnutrition, which includes heterogenous questions and could thereby lead to an increased prevalence of frailty. The high proportion of frailty in this cohort could have diminished the effect of frailty as mortality predictor and hampers interpretation of these analyses. Sixth, the one-year follow-up period mag have been a relatively long period of time to detect changes in daily functioning or HRQoL during treatment. Lastly, 10 % of patients had to be excluded from the composite outcome analysis due to missing data at baseline or follow up. We performed two sensitivity analyses that resulted in comparable results.

5. Conclusion

Abnormal GPS was associated with frailty and mortality. The addition of GPS to clinical predictors showed a numerically superior mortality prediction in this cohort of older patients with cancer, although not statistically significant. While GPS may improve the stratification of future older patients with cancer, larger studies including older patients with similar tumor types are necessary to evaluate its clinical usefulness.

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Author Contributions

All authors have read and approved of the submission of this manuscript. YvH, ST, BCvM, NAdG, SPM, JEAP and FvdB contributed to the study concept and design. YvH, ST, PJEvdB, NAdG, CH, GL, SPM, JEAP and FvdB contributed to acquisition of data. YvH and PJEvdB performed statistical analysis. All authors contributed to the analysis and interpretation of data. YvH, ST, BCvM, PJEvdB, SPM, JEAP and FvdB drafted the manuscript. All authors contributed to critical revisions of the manuscript for important intellectual content and approved the final version of the manuscript.

Declaration of Competing Interest

The authors have no conflicts.

Data Availability

The data that support the findings of this study are available on reasonable request from the corresponding author, YvH. The data are not publicly available due to privacy concerns.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2024.102075.

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