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Hand grip strength in patients with advanced cancer: A prospective study

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Abstract

Background Hand grip strength (HGS) is a widely used functional test for the assessment of strength and functional status in patients with cancer, in particular with cancer cachexia. The aim was to prospectively evaluate the prognostic value of HGS in patients with mostly advanced cancer with and without cachexia and to establish reference values for a European-based population.

Methods In this prospective study, 333 patients with cancer (85% stage III/IV) and 65 healthy controls of similar age and sex were enrolled. None of the study participants had significant cardiovascular disease or active infection at baseline. Repetitive HGS assessment was performed using a hand dynamometer to measure the maximal HGS (kilograms). Presence of cancer cachexia was defined when patients had ≥5% weight loss within 6 months or when body mass index was <20.0 kg/m^2 with ≥2% weight loss (Fearon's criteria). Cox proportional hazard analyses were performed to assess the relationship of maximal HGS to all-cause mortality and to determine cut-offs for HGS with the best predictive power. We also assessed associations with additional relevant clinical and functional outcome measures at baseline, including anthropometric measures, physical function (Karnofsky Performance Status and Eastern Cooperative of Oncology Group), physical activity (4-m gait speed test and 6-min walk test), patient-reported outcomes (EQ-5D-5L and Visual Analogue Scale appetite/pain) and nutrition status (Mini Nutritional Assessment).

Results The mean age was 60 ± 14 years; 163 (51%) were female, and 148 (44%) had cachexia at baseline. Patients with cancer showed 18% lower HGS than healthy controls (31.2 ± 11.9 vs. 37.9 ± 11.6 kg, $P < 0.001$). Patients with cancer cachexia had 16% lower HGS than those without cachexia (28.3 ± 10.1 vs. 33.6 ± 12.3 kg, $P < 0.001$). Patients with cancer were followed for a mean of 17 months (range 6–50), and 182 (55%) patients died during follow-up (2-year mortality rate 53%) (95% confidence interval 48–59%). Reduced maximal HGS was associated with increased mortality (per −5 kg; hazard ratio [HR] 1.19; 1.10–1.28; $P < 0.0001$; independently of age, sex, cancer stage, cancer entity and presence of cachexia). HGS was also a predictor of mortality in patients with cachexia (per −5 kg; HR 1.20; 1.08–1.33; $P = 0.001$) and without cachexia (per −5 kg; HR 1.18; 1.04–1.34; $P = 0.010$). The cut-off for maximal HGS with the best predictive power for poor survival was <25.1 kg for females (sensitivity 54%, specificity 63%) and <40.2 kg for males (sensitivity 69%, specificity 68%).

Conclusions Reduced maximal HGS was associated with higher all-cause mortality, reduced overall functional status and decreased physical performance in patients with mostly advanced cancer. Similar results were found for patients with and without cancer cachexia.

Keywords cachexia; cancer; functional assessment; hand grip strength; methodology; prognostication

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Introduction

Hand grip strength (HGS) is an easy and non-invasive method to assess muscle strength in the clinical setting.[1] In the general population, low HGS is associated with increased all-cause mortality and higher cardiovascular, respiratory and cancer risks.[2] In patients with advanced cancer, HGS is also associated with malnutrition, altered cognitive function and poor prognosis after surgery.[3,4] However, in the largest interventional cancer cachexia trial evaluating orally active anamorelin, a selective agonist for the 'ghrelin/growth hormone secretagogue receptor' with anabolic and appetite-enhancing effects, compared with placebo in patients with advanced non-small cell lung cancer, no difference was observed in HGS.[5] With a 1-kg increase in lean body mass, anamorelin did not result in a change in HGS. Investigators and regulators need standards for the use of HGS in interventional cancer cachexia trials, including recommendations for optimal application and cut-off values. These recommendations need to be investigated further and elaborated in prospective studies.

Recently, in a retrospective study from China, investigators reported that low HGS was associated with poor survival in patients with cancer based on a cohort of 8257 patients.[6] Another study from China published results of HGS in 1434 patients with cancer cachexia and found that low HGS was associated with poorer 1-year survival in patients with cancer cachexia and also calculated sex-specific cut-off points for HGS of the non-dominant hand (males 19.9 kg, females 14.3 kg), but the exact methodology for deriving these values was not mentioned.[7] It remains unclear whether these cut-off values can be applied in Caucasian patients. Therefore, our study aimed to prospectively evaluate the association of HGS with all-cause mortality in patients with advanced-stage cancer without any significant cardiovascular disease or active infection to establish reference values for a European-based population.

Methods

Patient population

We prospectively recruited 333 Caucasian patients with cancer for HGS testing and mostly advanced-stage cancer admitted to the Department of Oncology at the Charité – Universitätsmedizin Berlin, Germany, between October 2017 and July 2021. All patients with cancer were ≥18 years of age with a histologically confirmed active cancer and were able to sign the informed consent form independently. Exclusion criteria for our study were (1) the presence or history of significant cardiac disease (i.e., left ventricular ejection fraction [LVEF] < 50% on echocardiography, history of myocardial infarction and coronary artery disease [diagnosed by invasive coronary angiography or severe cardiac valve dysfunction]); (2) ongoing antibiotic therapy or clinical signs of an acute infection (e.g., COVID); (3) a second cancer diagnosis in the past 5 years prior to enrolment; and (4) presence of severe chronic obstructive pulmonary disease (COPD) GOLD stage III/IV (except in patients with lung cancer where all GOLD stages were allowed).

We also recruited healthy control participants of similar sex and age (ratio 1:5) to patients with cancer. All control participants were healthy and without significant cardiac disease or acute infection. Participants in either group were not excluded for the presence of type II diabetes mellitus and/or controlled arterial hypertension.

Study protocol

In all patients with cancer and healthy controls, a detailed medical history, Charlson Comorbidity Index,[8] and a physical examination were performed. HGS was assessed in all participants using a hand dynamometer (Jamar Hand Dynamometer, IL, USA). Patients and healthy controls were instructed to sit upright with elbows in 90° flexion and take four serial, alternate maximal strength tests with the hand dynamometer on both hands for 3 s per try. Participants were asked to start the HGS assessment with their dominant hand (right-handed or left-handed). Maximal HGS was defined as the highest result from both hands. To compare maximal HGS with other possible HGS assessments, we also assessed the first HGS test and then averaged all HGS tests. All assessments were systemically documented for dominant, non-dominant, right, left and both hands, respectively. To assess HGS change over time, we assessed HGS longitudinally in a subgroup of randomly chosen patients. In 49 patients, the HGS assessment

was repeated 1 day after the initial assessment, and in 22 patients 3–6 months after baseline.

At baseline, the following evidence-based assessments were also performed, including anthropometric assessments (mid-arm and calf circumference),[9] physical function (Karnofsky Performance Status [KPS][10] and Eastern Cooperative of Oncology Group [ECOG] performance status[11]), physical activity (4-m gait speed test[12] and 6-min walk test[13]), patient-reported outcomes (PROs; EQ-5D-5L questionnaire[14] and Visual Analogue Scale [VAS] for appetite[15] and pain[16]), nutrition (Mini Nutritional Assessment [MNA][17]) and biomarkers (modified Glasgow Prognostic Score [mGPS], including a combination of C-reactive protein [CRP] and albumin levels[18,19]).

We also grouped patients with cancer according to the presence of cachexia at baseline and compared them with healthy controls. For this purpose, cancer cachexia was defined according to the international consensus criteria by Fearon et al.[20] when one or more of the following three criteria were present: (1) weight loss $\geq$ 5% in the previous 6 months, (2) presence of a body mass index (BMI) $<$ 20 kg/m^2 and any degree of weight loss $>$ 2% or (3) the presence of sarcopenia assessed by mid-upper-arm muscle area by anthropometry (men $<$32 cm, women $<$18 cm) and any degree of weight loss $>$ 2% at baseline. Advanced-stage cancer was defined as stage III/IV Union for International Cancer Control (UICC),[21] stage III/IV for Ann Arbor classification[22] and stage III for Durie and Salmon classification.[23] Follow-up was performed by the regular interrogation of the electronic medical records. All patients gave written informed consent. The study was approved by the local ethics committee and conforms to the Declaration of Helsinki.

Statistical analyses

We performed the Kolmogorov–Smirnov test for the assessment of normal distributions. The normally distributed parameters are shown as mean ± standard deviation (SD), and not normally distributed parameters as the median and interquartile range (IQR). Student's *t*-test and analysis of variance (ANOVA) with Fisher's post hoc test, the Mann–Whitney *U* test, the Kruskal–Wallis test and the χ^2 test with Fisher's exact test were used as appropriate. Cox proportional hazard analysis was used for survival analyses in patients with cancer. We used the χ^2 goodness-of-fit tests for the hazard regression model to verify the proportional hazard assumption. Hazard ratios (HRs), 95% confidence intervals (CIs) and *P*-values are presented. The minimum follow-up for survival was 180 days. We defined sex-specific cut-points using receiver operating characteristic (ROC) analyses and conducted the Kaplan–Meier cumulative survival plots for illustrative purposes. The Bland–Altman plot was performed to evaluate the reproducibility of repeated HGS measures and to show limits of agreement.[24] The coefficient of variation (shown as absolute and percentages) was calculated as the SD of the differences divided by the mean of the HGS results under consideration. A paired *t*-test was conducted to compare HGS results assessed longitudinally, and individual parallel plots were performed for illustrative purposes. In all analyses, a $P < 0.05$ was considered statistically significant. Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Version 26.0 (IBM Co., Armonk, NY, USA) and SAS/STAT software, Version 9.4 (SAS Institute Inc.).

Results

Study population

The 333 patients with cancer and 65 healthy controls were similar with respect to sex and age (*Table 1*). Baseline characteristics including comorbidities were captured, and the study cohort's distribution of cancer types is displayed in *Table S1*. One hundred seventy (51%) patients with cancer were females and 44% were diagnosed to have cancer cachexia. Almost all patients with cachexia had an advanced stage (134, 91%) and they had more comorbidities than patients without cancer cachexia. One hundred fifteen (35%) patients with cancer had a previous treatment with immune checkpoint inhibitors (ICIs). In *Table 2*, results of HGS and other evidence-based assessments (anthropometric profile, physical function, physical activity, PROs, nutrition and biomarkers) are listed.

Hand grip strength assessment

Patients with cancer showed on average 18% lower maximal HGS values in comparison with healthy controls (31.2 ± 11.9 vs. 37.9 ± 11.6 kg, $P < 0.001$) (*Figure 1*). Patients with cancer cachexia had on average 16% lower maximal HGS than patients without cancer cachexia (28.3 ± 10.1 vs. 33.6 ± 12.3 kg) and 25% lower HGS than healthy participants (both $P < 0.001$) (*Figure 1*). Forty-five (13%) patients were left-handed. Most patients with cancer (83%) reached their maximum HGS on the right hand and 17% on the left hand. Also, 36% of patients reached their maximum HGS with the first try on their right hand (*Figure 2*). Some patients (right-handed patients: 35 of 276, left-handed patients: 3 of 57) reached their maximum HGS only on the fourth try (*Figure 2*). Repeated maximal HGS measures performed on the first and second days of the assessment showed a very high correlation (r = 0.971) and a coefficient of variation of 5.4% (*Figures 3A* and *4*). In a subgroup of 22 patients, repeated maximal HGS measures after 3–6 months showed a coefficient of variation of 11.8% (*Figures 3B* and *4*). To compare these results

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Table 1 Baseline characteristics

Variable	Patients with cancer $n = 333$	Healthy controls $n = 65$	*P*-value	Patients with cancer cachexia $n = 148$	Patients without cancer cachexia $n = 185$	ANOVA[a] *P*-value
Clinical parameters						
Age (years)	60 ± 14	59 ± 8	0.11	63 ± 13	60 ± 15	0.093
Female sex (*n*, %)	170 (51)	39 (60)	0.19	78 (53)	92 (50)	0.36
Charlson Comorbidity Index (points)	6.4 ± 2.7	1.5 ± 0.7	**<0.001**	7.1 ± 2.3	5.8 ± 2.8	**<0.001**
Body mass index (kg/m^2)	24.3 ± 5.0	25.7 ± 3.7	**0.011**	22.8 ± 4.5$^{***, \#\#\#}$	25.6 ± 5.1	**<0.001**
Cancer stage III/IV (*n*, %)	282 (85)	—	—	134 (91)$^{**, \#\#\#}$	148 (80)$^{\#\#\#}$	**<0.001**
Solid tumour cancer (*n*, %)	219 (66)	—	—	119 (80)$^{***, \#\#\#}$	100 (54)$^{\#\#\#}$	**<0.001**
Anti-cancer therapy naïve (*n*, %)	83 (25)	—	—	27 (18)$^{***, \#\#\#}$	56 (30)$^{\#\#\#}$	**<0.001**
Comorbidities						
Hypertension (*n*, %)	135 (41)	25 (39)	0.76	63 (43)	72 (39)	0.76
Diabetes (*n*, %)	40 (12)	1 (2)	**0.007**	17 (12)$^{\#\#}$	23 (12)$^{\#\#}$	**0.038**
Hypercholesterolaemia (*n*, %)	105 (32)	42 (65)	**<0.001**	44 (30)	61 (33)	**<0.001**
Chronic kidney disease (*n*, %)	24 (7)	0	0.020	19 (13)	5 (3)	**<0.001**
Medication at study entry						
ACEi/ARBs (*n*, %)	77 (23)	13 (20)	0.58	39 (26)	38 (21)	0.39
Beta-blockers (*n*, %)	52 (16)	2 (3)	**0.005**	26 (18)$^{\#}$	26 (14)$^{\#\#}$	**0.017**
Antidiabetics (*n*, %)	16 (5)	0	0.086	8 (5)	8 (4)	0.17
Lipid-lowering drugs (*n*, %)	35 (11)	4 (6)	0.37	20 (14)	15 (8)	0.14
Opioids (*n*, %)	76 (23)	0	**<0.001**	42 (28)$^{**, \#\#\#}$	34 (18)$^{\#\#\#}$	**<0.001**
Corticosteroids (*n*, %)	89 (27)	0	**<0.001**	36 (25)$^{\#\#\#}$	53 (29)$^{\#\#\#}$	**<0.001**

Note: Normal distributed variables are presented as means ± SD, non-parametric variables as median (interquartile range) and nominal variables as percentage. *P*-values for normal distributed variables are determined using unpaired *t*-test/ANOVA. *P*-values for non-parametric variables are determined using the Mann–Whitney *U* test/Kruskal–Wallis *H* test. *P*-values for nominal variables are computed according to the χ^2 test. *P*-values < 0.05 are bolded.
Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ANOVA, analysis of variance; ARBs, angiotensin receptor blockers.
[a]ANOVA *P*-value for comparison between healthy controls versus patients with cancer with cachexia versus patients with cancer without cachexia.
$^{**}P < 0.01$ versus non-cachectic patients.
$^{***}P < 0.001$ versus non-cachectic patients.
$^{\#}P < 0.05$ versus healthy controls.
$^{\#\#}P < 0.01$ versus healthy controls.
$^{\#\#\#}P < 0.001$ versus healthy controls.

with other possible HGS assessments, we also systemically calculated coefficients of variation for different HGS assessments (dominant, non-dominant, right, left and both hands). The results are shown in *Table S2*. The coefficient of variation after 1 day was lowest when the strongest tests on both hands were compared with each other.

Other evidence-based assessments

As shown in *Table 2*, patients with cancer cachexia had the lowest values of anthropometric parameters (mid-arm and calf circumference), reduced physical function (ECOG and KPS) and decreased physical activity (4-m gait speed test and 6-min walk test) than patients without cancer cachexia and healthy controls. Using PROs (EQ-5D-5L, VAS appetite and VAS pain), patients with cancer cachexia rated their current condition worse than other subgroups. We also observed meagre nutritional status (MNA) and poor prognosis as assessed by the mGPS score (= 2 points) in the same subgroup. We further analysed the association of these parameters to HGS and displayed the results in *Table 3*. The correlations between maximal HGS and other assessments (except for VAS) were of moderate magnitude (mostly ranging from ~0.3 to 0.6).

Survival analysis

Patients were followed for overall survival for a mean of 17 months (minimum 6 months, maximum 50 months), and 182 (55%) patients died during follow-up (1-year mortality 47% [41–52%] and 2-year mortality 53% [48–59%]). Maximal HGS was an independent prognostic marker in multivariable Cox analyses (*Table 4*) adjusted for sex, age, cancer stage III/IV, cancer type and presence of cachexia. After addition of the following variables to the multivariable Cox analyses: presence of hypertension, diabetes, hyperlipidaemia and previous ICI treatment, the results did not materially change (*Table S3*). Maximal HGS was also an independent predictor of mortality in the subgroups of patients with and without cancer cachexia (*Table 4*). *Table S4* shows the Cox survival analyses with 3-, 6-, 12- and 24-month plots shown for all participants, patients with cancer cachexia and patients with-

Table 2 Hand grip strength and other evidence-based assessments

Variable	Patients with cancer $n = 333$	Healthy controls $n = 65$	*P*-value	Patients with cancer cachexia $n = 148$	Patients without cancer cachexia $n = 185$	ANOVA[a] *P*-value
Hand grip strength (HGS)						
Maximal HGS (kg)	31.2 ± 11.9	37.9 ± 11.6	**<0.001**	28.3 ± 10.1***, ###	33.6 ± 12.3##	**<0.001**
Right hand						
1st measure (kg)	29.0 ± 11.7	35.3 ± 11.6	**<0.001**	25.9 ± 10.3***, ###	31.4 ± 12.2#	**<0.001**
2nd measure (kg)	28.8 ± 11.7	35.5 ± 11.3	**<0.001**	26.2 ± 10.6***, ###	30.9 ± 12.1##	**<0.001**
3rd measure (kg)	28.6 ± 11.9	35.4 ± 11.3	**<0.001**	26.1 ± 10.7***, ###	30.7 ± 12.4##	**<0.001**
4th measure (kg)	28.7 ± 11.6	35.8 ± 11.5	**<0.001**	25.7 ± 10.2***, ###	30.9 ± 12.2##	**<0.001**
Left hand						
1st measure (kg)	27.0 ± 11.1	32.7 ± 11.4	**<0.001**	24.7 ± 10.4***, ###	28.9 ± 11.5###	**<0.001**
2nd measure (kg)	26.8 ± 10.9	32.7 ± 11.3	**<0.001**	24.5 ± 10.1***, ###	28.6 ± 11.1#	**<0.001**
3rd measure (kg)	26.3 ± 10.8	33.0 ± 10.9	**<0.001**	23.9 ± 9.9***, ###	28.2 ± 11.2##	**<0.001**
4th measure (kg)	27.0 ± 10.4	32.2 ± 9.8	**0.003**	24.4 ± 9.7***, ###	29.6 ± 10.5	**<0.001**
Body composition						
Mid-arm circumference (cm) ($n = 284$)	28 ± 4	29 ± 3	**0.003**	26 ± 4***, ###	28 ± 4	**<0.001**
Calf circumference (cm) ($n = 284$)	35 ± 5	38 ± 3	**<0.001**	34 ± 5***, ###	36 ± 5#	**<0.001**
Physical function						
ECOG performance status (points)	1.7 ± 1.3	1.0 ± 1.3	**<0.001**	2.1 ± 1.3***, ###	1.4 ± 1.3###	**<0.001**
Karnofsky Performance Status (%)	73 ± 24	85 ± 19	**<0.001**	65 ± 25***, ###	79 ± 22###	**<0.001**
Physical activity						
4-m gait speed test (m/s) ($n = 255$)	1.8 ± 0.4	1.5 ± 0.3	**<0.001**	1.0 ± 0.4***, ###	1.2 ± 0.4###	**<0.001**
6-min walk test (m) ($n = 142$)	440 ± 102	584 ± 95	**<0.001**	419 ± 118###	450 ± 94###	**<0.001**
Patient-reported outcomes						
EQ-5D-5L (index) ($n = 278$)	0.697 ± 0.282	0.955 ± 0.114	**<0.001**	0.656 ± 0.284*, ###	0.727 ± 0.277###	**<0.001**
VAS appetite (mm) ($n = 316$)	63 (30–85)	79 (48–93)	**0.012**	56 (24–80)***, ###	64 (33–90)###	**0.003**
VAS pain (mm) ($n = 310$)	9 (0–34)	3 (0–25)	0.069	10 (0–39)***, ###	5 (0–26)	**<0.001**
Nutrition						
Mini Nutritional Assessment (points) ($n = 300$)	20 ± 5	27 ± 2	**<0.001**	18 ± 7***, ###	22 ± 5	**<0.001**
Biomarkers						
Modified Glasgow Prognostic Scale = 2 points (*n*, %)	101 (30)	0	**<0.001**	63 (43)***, ###	38 (21)###	**<0.001**

Note: Normal distributed variables are presented as means ± SD, non-parametric variables as median (interquartile range) and nominal variables as percentage. *P*-values for normal distributed variables are determined using unpaired *t*-test/ANOVA. *P*-values for non-parametric variables are determined using the Mann–Whitney *U* test/Kruskal–Wallis *H* test. *P*-values for nominal variables are computed according to the χ^2 test. *P*-values < 0.05 are bolded.

Abbreviations: ANOVA, analysis of variance; ECOG, Eastern Cooperative Oncology Group; HGS, hand grip strength; VAS, Visual Analogue Scale.

[a]ANOVA *P*-value for comparison between healthy controls versus patients with cancer with cachexia versus patients with cancer without cachexia.

*$P < 0.05$ versus non-cachectic patients.

***$P < 0.001$ versus non-cachectic patients.

#$P < 0.05$ versus healthy controls.

##$P < 0.01$ versus healthy controls.

###$P < 0.001$ versus healthy controls.

out cancer cachexia, respectively. We also determined survival analysis for different HGS assessments (dominant, non-dominant, right, left and both hands; *Table S5*), and the calculated prognostic powers were all similar.

The best sex-specific cut-offs for survival prediction were also calculated (*Tables S6A* and *S6B*). The maximal HGS cut-off with the best predictive power of poor survival during the entire follow-up period was <25.1 kg for female patients (area under the curve [AUC] = 0.591, sensitivity 54%, specificity 63%, $P = 0.041$) and <40.2 kg for male patients with cancer (AUC = 0.712, sensitivity 69%, specificity 68%, $P < 0.0001$) (*Figure 5A*). In *Figure 5B,C*, the best sex-specific maximal HGS cut-offs of poor survival are shown separately for patients with and without cancer cachexia. In general, patients with cancer with lower HGS ($n = 174$, 52%) were older and had more often comorbidities (*Table 5*). Physical function, physical activity and PROs were also reduced in these patients in comparison with patients with higher maximal HGS.

Discussion

In this study, we systemically and prospectively assessed HGS in patients with cancer. We assessed HGS longitudinal changes, the prognostic value of maximal HGS at different follow-up times and the best sex-specific cut-off values for HGS as prognosticator. In general, low HGS was predictive

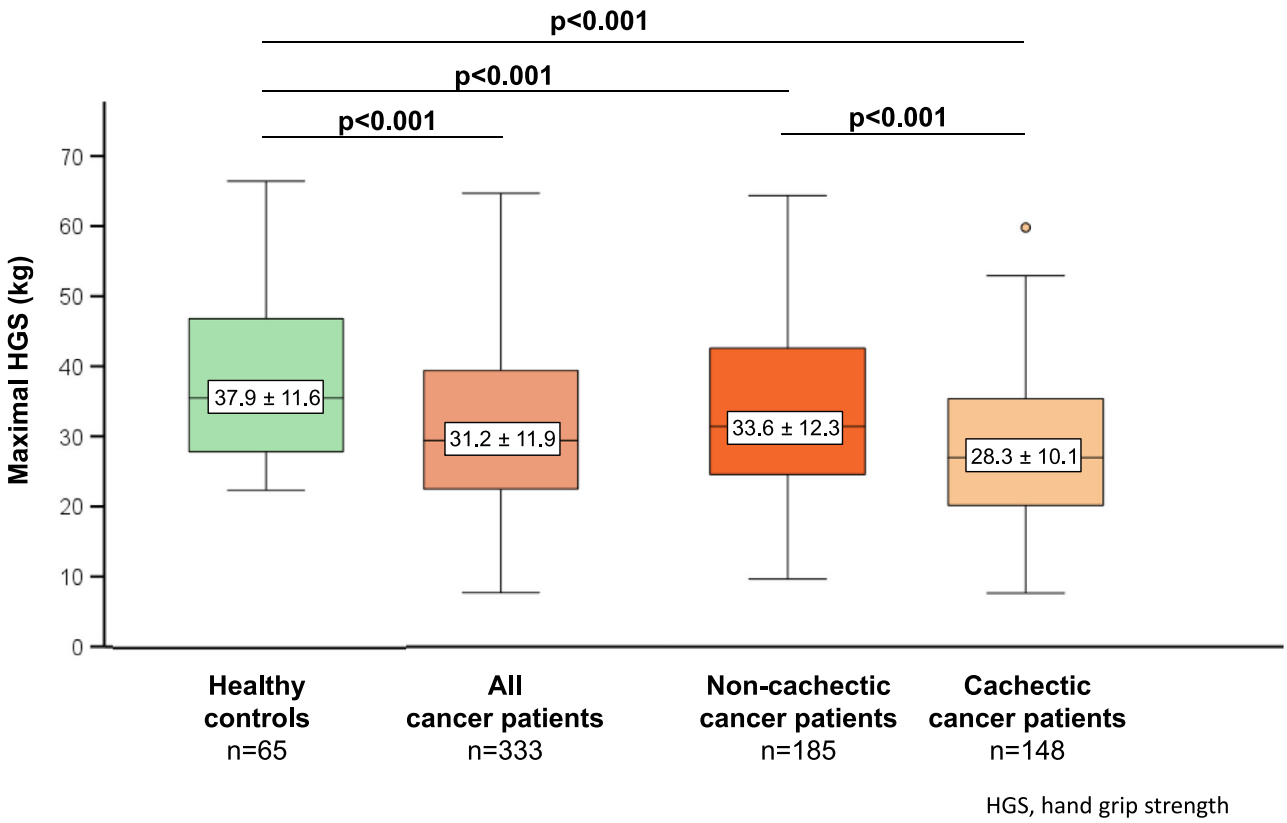

Figure 1 Maximal hand grip strength (HGS) in healthy controls and cancer patients.

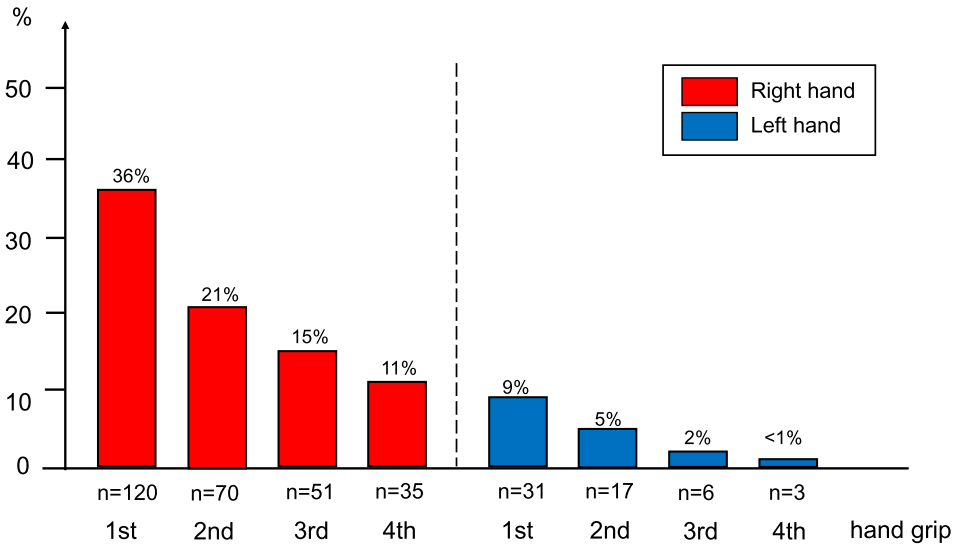

Figure 2 Overview at which try the maximal hand grip strength was achieved in all cancer patients.

for poor survival in patients with cancer, independent of the presence of cachexia, and in male and female patients. The best sex-specific cut-offs for survival prediction in all patients with cancer were <25.1 kg for female patients and <40.2 kg for male patients with cancer. Further, repeated HGS measures showed appropriate CIs and reliable consistency at

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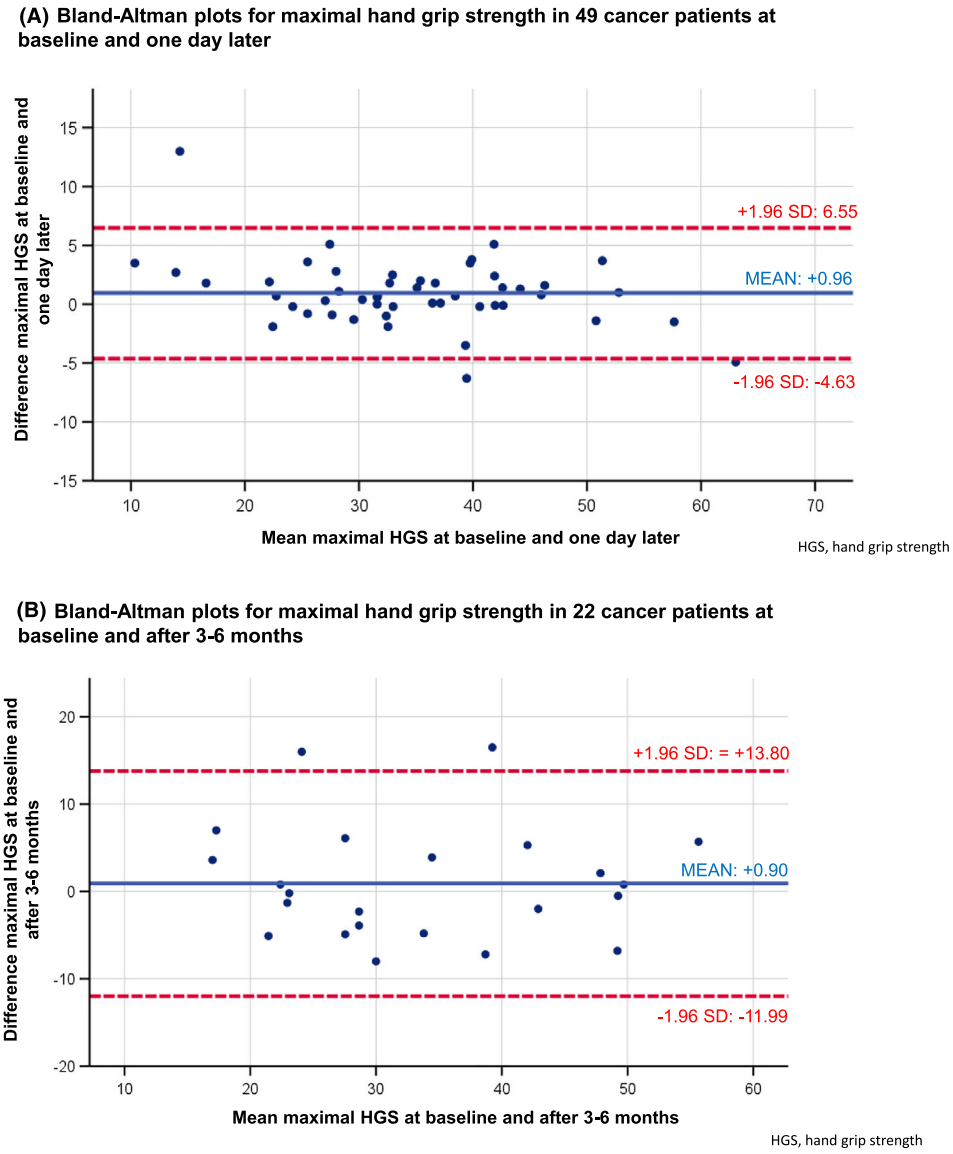
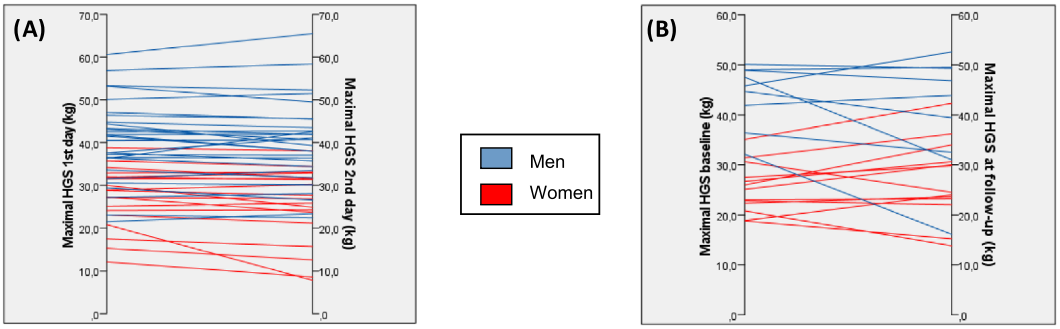


Figure 3 (A) Bland–Altman plots for maximal hand grip strength (HGS) in 49 cancer patients at baseline and 1 day later. (B) Bland–Altman plots for maximal HGS in 22 cancer patients at baseline and after 3–6 months.

follow-up assessments. Lastly, maximal HGS was significantly associated with results of functional assessments and PROs (*Table 3*). The only PRO measure that HGS was not predictive for was an assessment of pain.

Low grip strength is a potent predictor of poor patient outcomes including longer hospital stays, increased functional impairments and higher mortality risk in older people.[25] In our study, we could confirm that HGS was predictive for all-cause mortality in patients with mostly advanced-stage cancer. Interestingly, our results also demonstrated that maximal HGS was predictive after 3, 6, 12 and 24 months. Maximal HGS of men was higher than that of women, which is in line with the results of recently published Chinese studies.[6,26] Average HGS in our (Caucasian) patients was higher than in the Chinese studies. Our patients were somewhat bigger (average BMI 19.6[7] vs. 24.3 kg/m^2 in our study), which likely is relevant here, but methodological differences for the assessment of HGS may exist. We also observed slightly better HGS predictive power in male patients with cancer compared with their female counterparts. Song et al.[7] also described a greater impact of low HGS on overall mortality in men with cancer cachexia compared with women. This finding can be explained by multiple factors known to have an impact on grip strength and may lead to an increased decline of HGS in male patients with cancer, such as previous lifestyle, health status and socio-economic status.[27,28]

In comparison with the aforementioned study, our established HGS cut-off points were higher than the ones calcu-



Variable	n	1. Mean ± SD (kg)	2. Mean ± SD (kg)	Paired t-test	Coefficient of variation		Correlation	
				p-value	kg	(%)	r-value	p-value
HGS baseline on 1st and 2nd day	49	35.1 ± 10.6	34.1 ± 11.6	0.023	2.0	5.4	0.971	<0.001
Men	29	40.3 ± 9.4	40.0 ± 9.7	0.41	2.0	4.1	0.965	<0.001
Women	20	27.5 ± 7.0	25.7 ± 8.6	0.020	2.1	10.7	0.941	<0.001
HGS baseline and follow-up: 3-6 months after baseline	22	34.1 ± 11.9	33.2 ± 12.1	0.52	5.0	11.8	0.849	<0.001
Men	9	45.5 ± 7.4	41.4 ± 11.8	0.11	6.0	11.9	0.797	0.006
Women	13	25.3 ± 5.0	26.9 ± 8.0	0.27	4.3	11.8	0.828	<0.001

Figure 4 Individual parallel plots of (A) maximal hand grip strength (HGS) at the first and second days of assessment and (B) maximal HGS at baseline and follow-up after 3–6 months.

Table 3 Correlation for maximal hand grip strength versus other parameters

Measurement	All patients with cancer $n = 333$	
	r_s (95% confidence interval)	*P*-value
Spearman's correlation		
Male sex	0.59 (0.51 to 0.66)	**<0.001**
Cancer stage I–IV	−0.17 (−0.27 to −0.07)	**0.002**
Cancer entity: Haematologic vs. solid	0.20 (0.09 to 0.30)	**<0.001**
Anti-cancer therapy naïve: Yes vs. no	0.14 (0.03 to 0.25)	**0.010**
Pearson's correlation		
Age (years)	−0.32 (−0.40 to −0.22)	**<0.001**
Body mass index (kg/m^2)	0.35 (0.25 to 0.45)	**<0.001**
Charlson Comorbidity Index (points)	−0.29 (−0.39 to −0.19)	**<0.001**
Mid-arm circumference (cm) ($n = 284$)	0.47 (0.37 to 0.56)	**<0.001**
Calf circumference (cm) ($n = 284$)	0.45 (0.36 to 0.55)	**<0.001**
ECOG performance status (points)	−0.24 (−0.33 to −0.18)	**<0.001**
Karnofsky Performance Status (%)	0.22 (0.11 to 0.32)	**<0.001**
4-m gait speed test (m/s) ($n = 255$)	0.50 (0.39 to 0.59)	**<0.001**
6-min walk test (m) ($n = 142$)	0.47 (0.34 to 0.58)	**<0.001**
EQ-5D-5L (index) ($n = 278$)	0.32 (0.23 to 0.42)	**<0.001**
VAS appetite (mm) ($n = 316$)	0.33 (0.24 to 0.43)	**<0.001**
VAS pain (mm) ($n = 310$)	−0.04 (−0.16 to 0.08)	0.52
Mini Nutritional Assessment (points) ($n = 300$)	0.23 (0.12 to 0.33)	**<0.001**
Modified Glasgow Prognostic Scale (points)	−0.23 (−0.33 to −0.12)	**<0.001**

Note: *P*-values < 0.05 are bolded.
Abbreviations: ECOG, Eastern Cooperative of Oncology Group; VAS, Visual Analogue Scale.

lated for Chinese-based patients with cancer.[27] This difference can also be explained by the distinct anthropometric profile of the two study cohorts. When compared with current normative data from Western studies,[29,30] our established HGS cut-off points of the patients in both sexes appeared below the specified normative values. Therefore, this finding may suggest that patients with cancer develop muscle loss and physical impairment interrelated to the cancer and/or its treatment. Notably, in our study, low HGS was also significantly associated with other evidence-based prognostic indicators, including physical function, physical activity, PROs, nutrition and biomarkers (see *Tables 2* and *3*). These findings further support a good association of HGS with other evidence-based assessments.

Table 4 Univariable and multivariable Cox survival analyses in patients with cancer

		Univariable				Multivariable[a]		
n	Parameter	HR	95% CI	χ^2	*P*-value	HR	95% CI	*P*-value
All 333 patients with cancer (182 deaths, 55%)	Maximal HGS (per −5 kg)	1.16	1.08–1.24	20.3	**<0.0001**	1.19	1.10–1.28	**<0.0001**
148 patients with cachexia (96 deaths, 65%)	Maximal HGS (per −5 kg)	1.15	1.04–1.27	7.6	**0.007**	1.20	1.08–1.33	**0.001**
185 patients without cachexia (86 deaths, 46%)	Maximal HGS (per −5 kg)	1.12	1.03–1.23	6.6	**0.012**	1.18	1.04–1.34	**0.010**

Note: *P*-values < 0.05 are bolded.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Sex as strata and adjusted for age (years), cancer stage III/IV (yes vs. no), cancer entity (solid vs. hematologic) and cachexia (yes vs. no).

In a subgroup of participants, we analysed HGS changes over time. The low CIs and high consistency 1 day after the first assessment indicate that HGS is a reliable and reproducible method. As expected, the reliability decreased somewhat after 3–6 months, and the variation range of SDs increased. Further, we were able to determine HGS changes over time and the expected range of differences (coefficient of variation). To the best of our knowledge, detailed data concerning repeated measures of maximal HGS in patients with cancer are lacking. Consequently, the data presented here are of great interest when designing future clinical trials. In addition, we found that maximal HGS assessment of both hands had the lowest coefficient of variation versus other HGS assessments (e.g., dominant hand, non-dominant hand and right hand) used in other clinical trials.[3,31] Thus, we believe these results address the optimal utility of maximal HGS assessment in clinical trials using HGS as an endpoint in patients with cancer of European ancestry.

In ROMANA I and II, two randomized, double-blinded studies, anamorelin as a novel drug targeting cancer cachexia was compared with a placebo. Endpoints of ROMANA I and II were changes in lean mass and HGS after 6 and 12 weeks, and all patients had cancer cachexia as an inclusion criterion. In ROMANA I and II,[5] HGS assessment was performed one time only and only on the non-dominant hand, whereas our assessments were performed on both sides and four times on each hand. Our HGS results are only partially comparable with those from ROMANA I and II with regard to HGS assessment methodology. However, the baseline characteristics for patients with cancer cachexia were very similar between our studies, and the reported average HGS results (31.8 kg in ROMANA I and 28.2 kg in ROMANA II[5]) were also similar to our results in this study. At the end of the trial, there was no significant change in HGS in response to anamorelin therapy in ROMANA I and II (nominal change after 12 weeks ~0.5 kg). Our follow-up results showed no significant change in HGS after 3–6 months with a nominal reduction of on average 1.1 kg (in 22 patients where this assessment was performed again after 3–6 months). We conclude that it is mostly the lack of efficacy of the drug that 'caused' the no change in HGS in ROMANA I and II, but suboptimal methodology for the HGS assessment may also have contributed to higher variability of observed than necessary.

This study's strengths include the prospective HGS assessment in a population with a variety of cancer types. We also believe that determining the best HGS cut-off points may be highly relevant for defining endpoints for future cancer cachexia clinical trials including solid tumours and/or hematologic malignancies.[32] We note that there is no consensus on how to perform HGS measurement in patients with cancer.[33] It was described that maximal HGS is dependent on the number of attempts and at least three attempts in succession are advised.[34] We assessed HGS four times on both hands. Interestingly, we found that some patients had their highest try only with the fourth try (11%) and, therefore, recommend that performing four HGS assessments on each hand is reasonable, noting the fourth HGS assessment took <1 min to complete.

Limitations

As a limitation, there may be additional confounders that have an impact on HGS such as anti-cancer therapy and other worsening clinical condition or comorbidities. Thus, we included patients with cancer with and without prior anti-cancer therapy in our study cohort. As several studies reported an association between cardiac disease and declined HGS,[35–37] we included only patients with cancer without any significant cardiac disease or acute infection to minimize risks of bias. Because repeat assessment of HGS was not done in all our study participants, future studies should focus more on HGS assessment over time in a larger cohort—to better understand which patients loose HGS over time and which patients do not. Lastly, completion of assessments for the various additional clinical and functional outcome items (e.g., 4-m gait speed test and 6-min walk test) at baseline was not always possible, because of patients' inability to complete the examinations—whereas HGS assessment was possible in these patients. Therefore, we believe that HGS assessment may be an appropriate method in this particularly vulnerable patient population, when planning future trials targeting cancer cachexia. It is essentially always possible to assess HGS in almost all patients

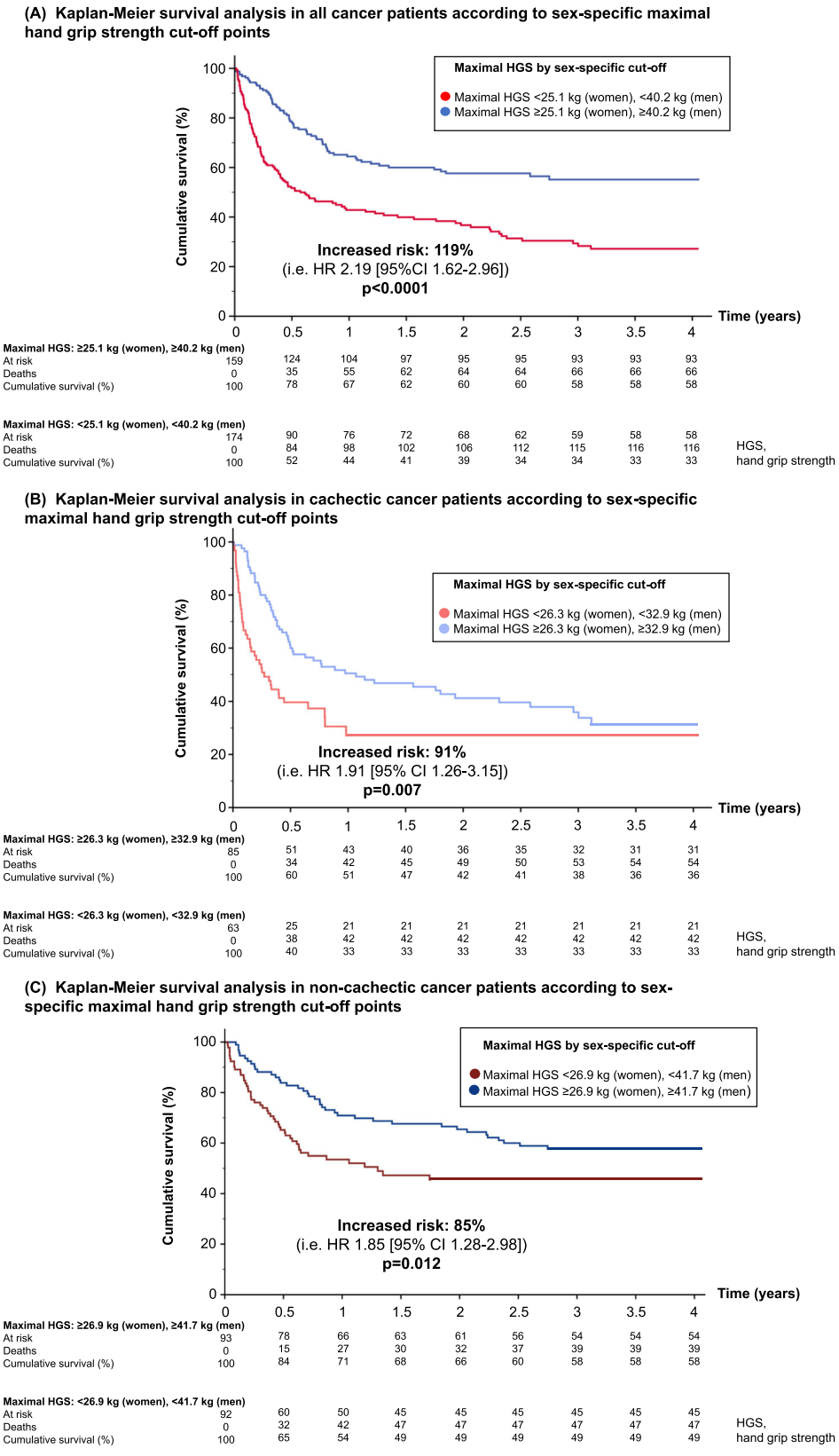


Figure 5 (A) Kaplan–Meier survival analysis in all cancer patients according to sex-specific maximal hand grip strength (HGS) cut-off points. (B) Kaplan–Meier survival analysis in cachectic cancer patients according to sex-specific maximal HGS cut-off points. (C) Kaplan–Meier survival analysis in non-cachectic cancer patients according to sex-specific maximal HGS cut-off points. CI, confidence interval; HR, hazard ratio.

Table 5 Baseline characteristics in all patients with cancer according to their sex-specific hand grip strength cut-offs

Variable	HGS cut-off Women: <25.1 kg Men: <40.2 kg *n* = 174	HGS cut-off Women: ≥25.1 kg Men: ≥40.2 kg *n* = 159	*P*-value
Clinical parameters			
Age (years)	65 ± 13	56 ± 14	<**0.001**
Female sex (*n*, %)	91 (52)	79 (50)	0.63
Charlson Comorbidity Index (points)	7.1 ± 0.2	5.6 ± 0.2	<**0.001**
Body mass index (kg/m^2)	24.0 ± 4.5	25.9 ± 5.2	**0.002**
Cancer stage III/IV (*n*, %)	161 (93)	121 (76)	<**0.001**
Solid tumour cancer (*n*, %)	127 (73)	92 (58)	**0.004**
Anti-cancer therapy naïve (*n*, %)	34 (20)	49 (31)	**0.017**
Presence of cachexia (*n*, %)	97 (56)	51 (32)	<**0.001**
Maximal HGS overall (kg)	25.8 ± 7.4	39.9 ± 10.1	<**0.001**
Comorbidities			
Hypertension (*n*, %)	83 (48)	52 (33)	**0.005**
Diabetes (*n*, %)	29 (17)	11 (7)	**0.006**
Hypercholesterolaemia (*n*, %)	58 (33)	47 (30)	0.48
Chronic kidney disease (*n*, %)	16 (9)	8 (5)	0.14
Medication			
ACEi/ARBs (*n*, %)	46 (26)	31 (20)	0.13
Beta-blockers (*n*, %)	35 (20)	17 (11)	**0.018**
Antidiabetics (*n*, %)	8 (5)	8 (5)	0.85
Lipid-lowering drugs (*n*, %)	24 (14)	11 (7)	**0.041**
Opioids (*n*, %)	53 (31)	23 (15)	<**0.001**
Corticosteroids (*n*, %)	46 (27)	43 (27)	0.93
Body composition			
Mid-arm circumference (cm) (*n* = 133 vs. 151)	27 ± 4	29 ± 4	<**0.001**
Calf circumference (cm) (*n* = 133 vs. 151)	34 ± 4	37 ± 4	<**0.001**
Physical function			
ECOG performance status (points)	2.2 ± 1.1	1.2 ± 0.9	<**0.001**
Karnofsky Performance Status (%)	64 ± 22	82 ± 14	<**0.001**
Physical activity			
4-m gait speed test (m/s) (*n* = 117 vs. 138)	0.9 ± 0.4	1.2 ± 0.3	<**0.001**
6-min walk test (m) (*n* = 46 vs. 96)	377 ± 117	471 ± 80	<**0.001**
Patient-reported outcomes			
EQ-5D-5L index (*n* = 116 vs. 162)	0.660 ± 0.284	0.730 ± 0.277	<**0.001**
VAS appetite (mm) (*n* = 163 vs. 153)	47 (17–75)	73 (45–90)	<**0.001**
VAS pain (mm) (*n* = 161 vs. 149)	10 (0–40)	12 (0–35)	0.49
Nutrition			
Mini Nutritional Assessment (points) (*n* = 133 vs. 171)	17.8 ± 4.7	22.2 ± 4.2	<**0.001**
Biomarkers			
Modified Glasgow Prognostic Scale = 2 points (*n*, %)	76 (44)	25 (16)	<**0.001**

Note: Normal distributed variables are presented as means ± SD, non-parametric variables as median (interquartile range) and nominal variables as percentage. *P*-values for normal distributed variables are determined using unpaired *t*-test. *P*-values for non-parametric variables are determined using the Mann–Whitney *U* test. *P*-values for nominal variables are computed according to the χ^2 test. *P*-values < 0.05 are bolded.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; ECOG, Eastern Cooperative Oncology Group; HGS, hand grip strength; VAS, Visual Analogue Scale.

with cancer with and without cachexia and it has strong clinical and prognostic meaning.

Conclusions

Low maximal HGS was associated with poor overall survival of patients with mostly advanced cancer with and without cachexia. HGS cut-off points for male and female patients with the best predictive power for survival were established for this Caucasian population. Our findings indicate that HGS may be a useful component in the risk assessment of patients with cancer, and it can serve as a valuable surrogate endpoint in clinical trials due to its strong association with functional performance markers, many PROs (except for pain) and survival. The simple and inexpensive method of HGS assessment has clinical value and should be considered in future clinical trials of patients with cancer with and without cachexia.

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ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[38]

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Conflict of interest statement

UW is supported by a Clinical Fellowship Grant from the BIH (Berlin Institute of Health) and has received speaker fees and/or contributions to congresses from Abbott, AstraZeneca, Bayer, Berlin Chemie, Bristol Myers Squibb, GE Healthcare, Pfizer, Philips and Servier, all outside the submitted work. JA reports travel support from Janssen, BMS and Alexion. UK served on advisory boards for Roche, Janssen-Cilag, Celgene, Takeda, BMS, Gilead, Hexal, Pfizer, AstraZeneca and Pentixapharm; received clinical research support from Janssen-Cilag, Novartis, Takeda, BMS, Roche and Pfizer; and received travel support from Roche, BMS, Gilead, Takeda, Janssen-Cilag and Celgene. LB has received honoraria from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Pfizer, Roche, Sanofi and Seattle Genetics and received research support from Bayer and Jazz Pharmaceuticals. AAM reports honoraria and lecture fees from Amgen, Berlin Chemie, Daichi Sankyo, Edwards Lifesciences, Novartis and Sanofi, all not related to this work. MT reports honoraria, lecture fees and grant support from Edwards Lifesciences, AstraZeneca, Bayer, Novartis, Berlin Chemie and Daiichi Sankyo, all not related to this work. TR reports honoraria, lecture fees and grant support from Edwards Lifesciences, AstraZeneca, Bayer, Novartis, Berlin Chemie, Daiichi Sankyo, Boehringer Ingelheim, Novo Nordisk, Cardiac Dimensions and Pfizer, all not related to this work. SvH has been a paid consultant for and/or received honoraria payments from AstraZeneca, Bayer, Boehringer Ingelheim, Brahms, Chugai, Grünenthal, Helsinn, Hexal, Novartis, Pharmacosmos, Respicardia, Roche, Servier, Sorin and Vifor. He also reports research support from Amgen, AstraZeneca, Boehringer Ingelheim, Innovative Medicines Initiative (IMI) and the German Center for Cardiovascular Research (DZHK). AJSC declares having received honoraria and/or lecture fees from AstraZeneca, Boehringer Ingelheim, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia and Viatris. SDA reports grants and personal fees from Vifor and Abbott Vascular; reports personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards, Farraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious and V-Wave; and declares that he is named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 and DE 102007022367), but he does not benefit personally from the related issued patents. EJR has served as a member of the Scientific Advisory Board for Napo Pharmaceuticals, Care4ward, Actimed Therapeutics and Meter Health and has also served as a consultant for Veloxis Therapeutics, BYOMass, Takeda and Enzychem Lifesciences Pharmaceutical Company. UL reports research grant to the institution from Amgen, Bayer and Novartis and speaker or consulting honorary from AstraZeneca, Bayer, Boehringer Ingelheim, Amgen, Sanofi, Novartis and Novo Nordisk. MSA reports personal fees from Servier, outside the submitted work. All other authors declare no conflict of interest.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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