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Patient-reported ability to walk 4 m and to wash: New clinical endpoints and predictors of survival in patients with pre-terminal cancer

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Abstract

Background Maintaining the ability to perform self-care is a critical goal in patients with cancer. We assessed whether the patient-reported ability to walk 4 m and wash oneself predict survival in patients with pre-terminal cancer.

Methods We performed a prospective observational study on 169 consecutive hospitalized patients with cancer (52% female, 64 ± 12 years) and an estimated 1–12 months prognosis at an academic, inpatient palliative care unit. Patients answered functional questions for 'today', 'last week', and 'last month', performed patient-reported outcomes (PROs), and physical function assessments.

Results Ninety-two (54%) patients reported the ability to independently walk 4 m and 100 (59%) to wash 'today'. The median number of days patients reported the ability to walk 4 m and wash were 6 (IQR 0–7) and 7 (0–7) days ('last week'); and 27 (5–30) and 26 (10–30) days ('last month'). In the last week, 32% of patients were unable to walk 4 m on every day and 10% could walk on 1–3 days; 30% were unable to wash on every day and 10% could wash on 1–3 days. In the last months, 14% of patients were unable to walk 4 m on every day and 10% could only walk on 1–10 days; 12% were unable to wash on every day and 11% could wash on 1–10 days. In patients who could walk 'today' average 4 m gait speed was 0.78 ± 0.28 m/s. Patients who reported impaired walking and washing experienced more symptoms (dyspnoea, exertion, and oedema) and decreased physical function (higher Eastern Cooperative Oncology Group Performance Status, and lower Karnofsky Performance Status and hand-grip strength [unable vs. able to walk 'today': 205 ± 87 vs. 252 ± 78 Newton, $P = 0.001$; unable vs. able to wash 'today': 204 ± 86 vs. 250 ± 80 Newton,

$P = 0.001$]). During the 27 months of observation, 152 (90%) patients died (median survival 46 days). In multivariable Cox proportional hazards regression analyses, all tested parameters were independent predictors of survival: walking 4 m 'today' (HR 0.63, $P = 0.015$), 'last week' (per 1 day: HR 0.93, $P = 0.011$), 'last month' (per 1 day: HR 0.98, $P = 0.012$), 4 m gait speed (per 1 m/s: HR 0.45, $P = 0.002$), and washing 'today' (HR 0.67, $P = 0.024$), 'last week (per 1 day HR 0.94, p=0.019), and 'last month' (per 1 day HR 0.99, $P = 0.040$). Patients unable to walk and wash experienced the shortest survival and most reduced functional status.

Conclusions In patients with pre-terminal cancer, the self-reported ability to walk 4 m and wash were independent predictors of survival and associated with decreased functional status.

Keywords Self-care; Palliative care; Walking ability; Washing ability; Cancer; Independence

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Introduction

Maintaining independence as long as possible is one of the most essential and desired goals for patients with cancer. With cancer progression, most patients experience an increased dependency on external supports along with a decreased quality of life and patient satisfaction.[1] The ability for self-care and independent living are strongly desired elements of patients' dignity. Maintenance of basic functional self-care is integral to patient autonomy and self-management, including the ability to walk short distances and wash oneself. These are crucial components that may determine if patients with pre-terminal cancer remain self-sufficient. If patients cannot perform these basic activities, they lose their self-care ability, hastening their loss of independence and feelings of loss of confidence, depression, and isolation.

Clinicians' assessments, such as the Karnofsky Performance Status (KPS)[2] and Eastern Cooperative Oncology Group (ECOG) Performance Status[3] have historically captured physical functioning. In contrast, clinicians capture patients' functional health using assessments such as basic activities of daily living, mobility, and instrumental activities of daily living.[4] However, patient-reported outcomes (PROs) are increasingly utilized in assessing patients' physical functioning and quality of life in clinical trials.[5] Despite the clinical importance and impact of patients' ability for self-care in patients with pre-terminal cancer, few PROs have been assessed and validated in this specific phase of cancer. Clinicians require simple and clinically meaningful PROs to evaluate patients' ability for self-care when patients with cancer are most vulnerable. Therefore, we prospectively tested whether novel functional assessment endpoints in patients with pre-terminal cancer can predict survival, including a patient-reported ability to ambulate 4 m and/or wash. These new and easy-to-use PROs could represent new endpoints for interventional trials in pre-terminal patients with cancer. Furthermore, they may help refine prognostication to inform the distribution of additional clinical resources to support patients at the highest risk of poor clinical outcomes.

Methods

Patients

From August 2019 until November 2021, we enrolled 169 hospitalized, pre-terminally ill patients with cancer in a palliative care unit at Charité-Universitätsmedizin, Berlin. Inclusion criteria were (1) willing and able to participate in a prospective observational study and independently sign the consent form; (2) histologically confirmed cancer diagnosis; (3) advanced/incurable stage cancer; (4) receiving care on a palliative care unit with an expected survival ranging from 1–12 months per the treating oncologist. Information about patients' clinical condition, medical history, co-morbidities, and drug therapy was recorded from medical records and per patient report. We collected venous blood from each patient to analyse blood parameters. The local Ethics Committee approved the study and it complied with the Declaration of Helsinki.

Endpoint-related questions

Participants were asked questions relative to three time points: the day of the examination ('today') as well as 1 week ('last week') and 1 month ('last month') before the day of the examination. The investigator asked each patient six questions: (1) Are you able to walk 4 m today? (2) How many days were you able to walk 4 m in the last week? (3) How many days were you able to walk 4 m in the last month (30 days)? (4) Are you able to wash yourself today? (5) How many days were you able to wash yourself in the last week? (6) How many days were you able to wash yourself in the last month (30 days)?

If patients answered that they could walk 4 m on the day of examination, a 4 m gait speed test[6] was performed twice, and the average gait speed was calculated. Patients needed to walk the 4 m independently but were allowed to use a walking aid. For patients stating they were unable to walk

4 m on the day of examination, we accepted this statement, and a gait speed of 0 m/s was recorded. We defined the ability to wash as being capable of independently washing oneself in the bathroom/shower without help during the washing period; alternatively, to wash oneself in bed alone with a washing bowl and sponge that the caregivers provided. For patients stating they could not independently wash on the examination day, we accepted this statement and recorded it.

Patient-reported outcomes

On the examination day, we assessed the following PROs: resting perceived dyspnoea[7] and resting perceived exertion[8] (per the Borg scale), dyspnoea according to the New York Heart Association (NYHA) classification,[9] self-rated health,[10] KPS[2], ECOG Performance Status,[3] and a visual analogue scale (mm) for appetite[11] and pain.[12] In addition, we measured hand-grip strength[13] using a digital hand-dynamometer (JAMAR® Plus, Patterson Medical, UK).

Statistical analysis

IBM Statistical Package for the Social Sciences (SPSS) 26.0 and SAS/STAT software, Version 9.4 Copyright © 2022 SAS Institute Inc. were used for statistical analysis. The power calculation was based on detecting differences between subgroups within endpoints using a log-rank test. With an allocation ratio of 1 and a possible rate of censoring of 20%, a total sample size of 166 subjects achieves a power of 85% to detect a hazard ratio of 0.60 when the significance level (alpha) is 0.05 using a two-tailed log-rank test (calculated with nQuery[14]). Data are presented as median with interquartile range (IQR) or mean ± standard deviation (SD). If normal distributions could reasonably be assumed, group means were compared using the Student's unpaired two-sample *t*-test; otherwise, we used the Mann–Whitney *U* test (also known as Wilcoxon rank sum test). We used one-way ANOVA analysis for normally distributed variables for more than two comparison groups and the Kruskal-Wallis test as a non-parametric test. Chi-squared test was preferably used for the analysis of contingency tables; only when at least one cell assignment was smaller than five we used Fisher's exact test. Cox proportional hazards regression was used for survival analyses with results displayed as hazard ratios (HR) and 95% confidence intervals (95% CI) and adjusted for age, sex, solid cancer, and ECOG Performance Status ≥3. Kaplan–Meier curves for the first 12 months of follow-up were constructed for illustrative purposes. Best cut-offs for the ability to walk 4 m or wash with the most significant split were chosen based on the standardized log-rank test for 1, 2, 3, 6, 12 months, and the entire follow-up period.[15] In this exploratory study, significance tests have a descriptive character and are therefore not corrected for multiplicity.[16] A *P*-value <0.05 was deemed statistically significant in all analyses.

Results

Study population

One hundred sixty-nine consecutive hospitalized patients with cancer receiving care on the palliative care unit were prospectively assessed from August 2019 until November 2021 (52% female, average age 64 ± 12 years). One hundred fifty-four (91%) patients had solid cancers and 15 (9%) had haematological malignancies (Table S1). Overall, patients had a mean Charlson co-morbidity index[17] of 8 points, and 44% were actively receiving cancer-directed therapy, 85% received prior systemic cancer therapy (58% ≥ 2 previous lines of therapy), and almost half had received previous radiation. Patients' prior cancer treatment is captured in Table 1. Ninety-two (54%) patients could walk 4 m on the examination day, and 100 (59%) were able to wash oneself on the examination day. In the 92 patients who could walk, the average 4 m gait speed was 0.78 ± 0.28 m/s. The median number of days that patients reported they were able to walk 4 m in the 'last week' and 'last month' were 6 (IQR 0–7) and 27 (5–30); and the median number of days patients were able to wash independently was 7 (0–7) and 26 (10–30) days, respectively (Table 1 and Figure 1A–C). Patients who were not able to independently walk 4 m or wash 'today' more frequently had a KPS < 40% and ECOG Performance Status ≥3 (Tables 1, 2 and 4).

Survival analysis

During 27 months of follow-up (from baseline until January 2022), 152 (90%) patients died, and the median survival was 46 days. Specifically, 1, 2, 3, 6, and 12 month survival rates were 62% (95% CI 54–68%), 41% (34–49%), 31% (25–38%), 18% (13–24%), and 14% (9–20%), respectively. In multivariable Cox proportional hazards regression analyses (adjusted for age, sex, solid cancer, and ECOG Performance Status ≥3, Table 3), all newly tested parameters were independent predictors of survival. These parameters included walking 4 m 'today' (HR 0.63, *P* = 0.015), 'last week' (per 1 day: HR 0.93, *P* = 0.011), 'last month' (per 1 day: HR 0.98, *P* = 0.012); 4 m gait speed (per 1 m/s: HR 0.45, *P* = 0.002); ability to wash 'today' (HR 0.67, *P* = 0.024), 'last week' (per 1 day: HR 0.94, *P* = 0.019), 'last month' (per 1 day: HR 0.99, *P* = 0.040). The Kaplan–Maier curves underline the survival benefit of those patients who could walk 4 m or wash on the examination day (Figure 2A,B). When the ability 'to walk 4 m today' and 'to wash today' were combined in one multivariable

Table 1 Baseline characteristics in pre-terminal patients with cancer according to their self-reported ability/inability to independently walk 4 m today and wash on the examination day ('today')

Variable	All patients (n = 169)	Patients not able to walk 4 m today (n = 77)	Patients able to walk 4 m today (n = 92)	P-value	Patients not able to wash today (n = 69)	Patients able to wash today (n = 100)	P-value
Clinical characteristics							
Age (years)	64 ± 12	66 ± 12	63 ± 13	0.21	67 ± 11	62 ± 13	**0.006**
Female sex, n (%)	88 (52)	36 (47)	52 (57)	0.21	34 (49)	54 (54)	0.55
Solid cancer, n (%)	154 (91)	66 (86)	88 (96)	**0.030**	60 (77)	94 (94)	0.11
Body mass index (kg/m^2)	22 ± 6	23 ± 5	22 ± 4	0.19	23 ± 5	22 ± 4	0.07
Charlson co-morbidity index (points)	8 ± 2	8 ± 2	8 ± 2	0.52	8 ± 2	8 ± 2	0.48
ECOG Performance Status ≥3, n (%)	131 (76)	76 (99)	55 (60)	<**0.001**	66 (96)	65 (65)	<**0.001**
Karnofsky Performance Status <40%, n (%)	57 (34)	48 (62)	9 (10)	<**0.001**	42 (61)	15 (15)	<**0.001**
Current anti-cancer therapy, n (%)	74 (44)	32 (42)	42 (46)	0.59	23 (33)	51 (51)	**0.023**
≥2 previous lines of systemic anti-cancer therapy, n (%)	98 (58)	46 (60)	52 (57)	0.67	35 (51)	63 (63)	0.11
Prior systemic anti-cancer therapy, n (%)	143 (85)	64 (83)	79 (86)	0.62	51 (74)	92 (92)	**0.001**
Prior radiotherapy, n (%)	77 (46)	35 (46)	42 (46)	0.98	29 (48)	48 (48)	0.44
Ability to walk 4 m 'today'							
Patients able to walk 4 m on the day of examination, n (%)	92 (54)	-	-	-	10 (15)	82 (82)	<**0.001**
No. of days patients were able to walk (in the last week)	6 (0–7)	0 (0–2)	7 (7–7)	<**0.001**	0 (0–3)	7 (7–7)	<**0.001**
No. of days patients were able to walk (in the last month)	27 (5–30)	10 (0–20)	30 (30–30)	<**0.001**	10 (0–20)	30 (30–30)	<**0.001**
Ability to wash 'today'							
Patients able to wash on the day of examination, n (%)	100 (59)	18 (23)	82 (89)	<**0.001**	-	-	-
No. of days patients were able to wash (the last week)	7 (0–7)	0 (0–4)	7 (7–7)	<**0.001**	0 (0–2)	7 (7–7)	<**0.001**
No. of days patients were able to wash (in the last month)	26 (10–30)	15 (2–24)	30 (30–30)	<**0.001**	10 (0–20)	30 (30–30)	<**0.001**
Laboratory parameters							
Albumin (g/L)	30 (26–36)	28 (25–31)	31 (27–35)	<**0.001**	28 (25–31)	32 (27–35)	<**0.001**
Haemoglobin (g/dL)	9.5 ± 1.5	9.2 ± 1.4	9.7 ± 1.6	**0.019**	9.3 ± 1.5	9.7 ± 1.5	0.10
Leukocytes (/nL)	7.3 (5.1–11.1)	9.0 (5.1–13.2)	6.8 (5.1–9.9)	**0.027**	9.7 (5.8–13.7)	6.8 (4.7–9.8)	**0.005**
Co-morbidities							
Chronic kidney disease, n (%)	36 (21)	17 (22)	19 (21)	0.82	13 (19)	23 (23)	0.52
COPD, n (%)	16 (10)	7 (9)	9 (10)	0.88	7 (10)	9 (9)	0.80
Arterial hypertension, n (%)	78 (46)	40 (52)	38 (41)	0.17	38 (55)	40 (40)	0.053
Coronary artery disease, n (%)	18 (11)	10 (13)	8 (9)	0.37	9 (13)	9 (9)	0.40
Diabetes mellitus type 2, n (%)	25 (15)	15 (19)	10 (11)	0.12	12 (17)	13 (13)	0.43
Medications on examination day							
Opioids, n (%)	93 (55)	45 (54)	48 (52)	0.42	41 (59)	52 (52)	0.34
Antidepressants, n (%)	27 (16)	15 (19)	12 (18)	0.24	11 (16)	16 (16)	0.97
Corticosteroids, n (%)	27 (16)	13 (17)	14 (15)	0.77	13 (19)	14 (14)	0.40
NSAIDs, n (%)	11 (7)	7 (9)	4 (4)	0.23	6 (9)	5 (5)	0.34
Antiemetics, n (%)	33 (20)	12 (16)	21 (23)	0.24	10 (15)	23 (23)	0.17
Antibiotics due to an infection, n (%)	62 (37)	37 (48)	25 (27)	**0.006**	31 (45)	31 (31)	0.072
Anticoagulants, n (%)	10 (6)	3 (4)	7 (8)	0.35	3 (4)	7 (7)	0.53
ACE-I/ARBs, n (%)	29 (17)	12 (16)	17 (19)	0.62	11 (16)	18 (18)	0.73
Beta-blockers, n (%)	31 (18)	17 (22)	14 (15)	0.25	17 (25)	14 (14)	0.079
Diuretics, n (%)	38 (23)	21 (27)	17 (19)	0.17	21 (30)	17 (17)	**0.040**
Spironolactone, n (%)	9 (5)	6 (8)	3 (3)	0.30	6 (9)	3 (3)	0.16

Values are means ± SD for normal distribution, median and interquartile range (IQR) for non-normal distribution variables, or n (%) for nominal variables. P-values for nominal variables refer to the two comparison groups. P-values <0.05 are bold.

ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; chronic kidney disease, estimated glomerular filtration rate <30; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; NSAID, non-steroidal anti-inflammatory drug; NSAIDs, nonsteroidal anti-inflammatory drugs.

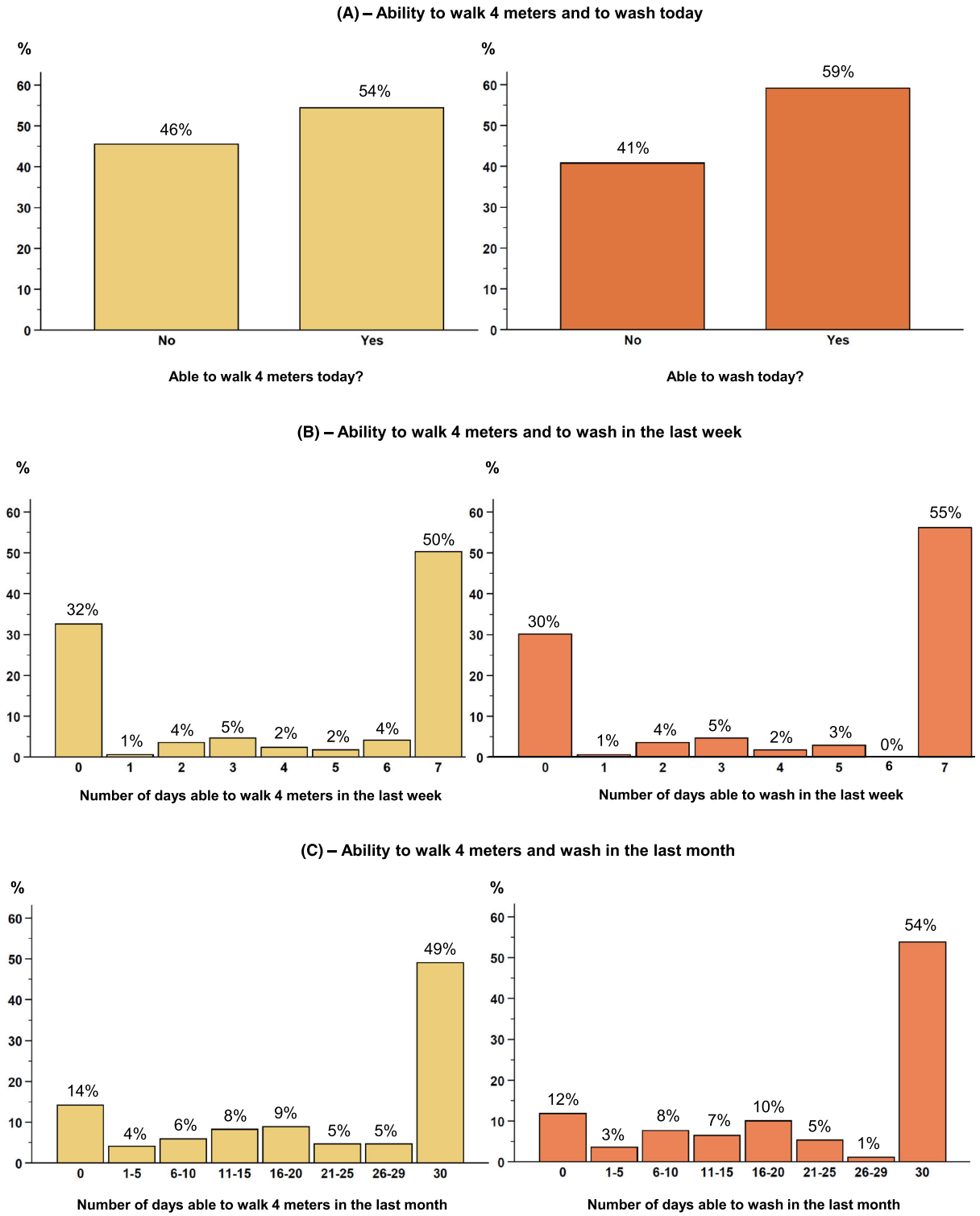

Figure 1 (A) Ability to walk 4 m and to wash today. (B) Ability to walk 4 m and to wash in the last week. (C) Ability to walk 4 m and wash in the last month.

survival model, patients that could neither walk nor wash experienced the shortest survival (Harrell's C-statistic 0.61) (Table 3, Figure 2C). Regarding survival prediction across different timespans, the best cut-offs for the ability to walk 4 m and to wash are shown in Table S2A,B. For the ability to walk 4 m, the best cut-off for the 'last week' and the

Table 2 Baseline characteristics according to the combined self-reported ability to independently walk 4 m 'today' and/or wash 'today'

Variable	Patients not able to walk 4 m AND not able to wash today (n = 59)	Patients not able to walk 4 m or not able to wash today (n = 28)	Patients able to walk 4 m and able to wash today (n = 82)	P-value
Clinical characteristics				
Age (years)	68 ± 11[§ #]	62 ± 13	63 ± 13	**0.037**
Female sex, n (%)	28 (48)	14 (50)	46 (56)	0.58
Solid cancer, n (%)	51 (86)	24 (86)	79 (96)	0.068
Body mass index (kg/m^2)	23 ± 5[§]	21 ± 4	22 ± 4	**0.046**
Charlson co-morbidity index (points)	8 ± 2	8 ± 2	8 ± 2	0.44
ECOG Performance Status ≥3, n (%)	59 (100)[§§, ###]	24 (86)[#]	48 (59)	**<0.001**
Karnofsky Performance Status <40%, n (%)	40 (69)[§§§, ###]	10 (36)[##]	7 (9)	**<0.001**
Current anti-cancer therapy, n (%)	21 (36)	13 (46)	40 (49)	0.28
≥2 previous lines of anti-cancer systemic therapy, n (%)	32 (54)	17 (61)	49 (60)	0.77
Prior systemic anti-cancer therapy, n (%)	46 (78)	23 (82)	74 (90)	0.13
Prior radiotherapy, n (%)	27 (46)	10 (36)	40 (49)	0.49
Ability to walk 4 m 'today'				
Patients able to walk 4 m on the day of examination, n (%)	0 (0)[§§§, ###]	10 (36)[###]	82 (100)	**<0.001**
No. of days patients were able to walk (in the last week)	0 (0–0)[§§, ###]	3 (0–6)[###]	7 (7–7)	**<0.001**
No. of days patients were able to walk (in the last month)	7 (0–17)[§§, ###]	21 (14–29)[###]	30 (30–30)	**<0.001**
Ability to wash 'today'				
Patients able to wash on the day of examination, n (%)	0 (0)[§§§, ###]	18 (64)[###]	82 (100)	**<0.001**
No. of days patients were able to wash (the last week)	0 (0–0)[§§§, ###]	6 (3–7)[###]	7 (7–7)	**<0.001**
No. of days patients were able to wash (in the last month)	10 (0–20)[§§§, ###]	28 (16–30)[###]	30 (30–30)	**<0.001**
Laboratory parameters				
Albumin (g/L)	27 (24–30)[###]	31 (27–36[##]	32 (27–35)	**<0.001**
Haemoglobin (g/dL)	9.2 ± 1.5	9.5 ± 1.3	9.7 ± 1.6	0.092
Leukocytes (/nL)	8.2 (5.1–14.1)[##]	10.4 (6.4–12.7)[##]	6.4 (4.5–9.6)	**0.005**
Co-morbidities				
Chronic kidney disease, n (%)	13 (22)	4 (14)	19 (23)	0.60
COPD, n (%)	6 (10)	2 (7)	8 (10)	0.90
Arterial hypertension, n (%)	32 (54)	14 (50)	32 (39)	0.18
Coronary artery disease, n (%)	9 (15)	1 (4)	8 (10)	0.24
Diabetes mellitus type 2, n (%)	12 (20)	3 (11)	10 (12)	0.33
Medications on examination day				
Opioids, n (%)	36 (61)	14 (50)	43 (52)	0.51
Antidepressants, n (%)	10 (17)	6 (22)	11 (13)	0.54
Corticoteroids, n (%)	11 (19)	4 (14)	12 15)	0.82
NSAIDs, n (%)	6 (10)	1 (4)	4 (5)	0.45
Antiemetics, n (%)	8 (14)	6 (21)	19 (23)	0.35
Antibiotics due to an infection, n (%)	26 (44)[#]	16 (57)[##]	20 (25)	**0.003**
Anticoagulants, n (%)	3 (5)	0 (0)	7 (9)	0.28
ACE-Is/ARBs, n (%)	10 (17)	3 (11)	16 (20)	0.61
Beta-blockers, n (%)	15 (25)	4 (14)	12 (15)	0.25

(*Continues*)

Table 2 (continued)

Variable	Patients not able to walk 4 m AND not able to wash today (n = 59)	Patients not able to walk 4 m or not able to wash today (n = 28)	Patients able to walk 4 m and able to wash today (n = 82)	P-value
Diuretics, n (%)	17 (29)	8 (29)	13 (16)	0.13
Spironolactone, n (%)	5 (9)	2 (7)	2 (2)	0.21

Values are means ± SD for normal distribution, median and interquartile range (IQR) for non-normal distribution variables, or n (%) for nominal variables. P-values for nominal variables refer to all comparison groups. P-values <0.05 are bold.
ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; chronic kidney disease, estimated glomerular filtration rate <30; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; NSAID, non-steroidal anti-inflammatory drug; NSAIDs, nonsteroidal anti-inflammatory drugs.
$^{\S}P < 0.05$.
$^{\S\S}P < 0.01$.
$^{\S\S\S}P < 0.001$ vs. patients not able to walk 4 m or not able to wash today.
$^{\#}P < 0.05$.
$^{\#\#}P < 0.01$.
$^{\#\#\#}P < 0.001$ vs. patients able to walk 4 m and able to wash today

'last month' was ≥2 and ≥14 days, respectively; for gait speed, it was ≥0.50 m/s; and for the ability to wash, the best cut-off ranged between ≥5 and ≥6 days, and ≥21 and ≥28 days, respectively, for all timespans.

Biomarkers

Patients who could not walk 4 m on the examination day compared with those who could walk had lower values of haemoglobin and albumin, and higher values of leukocytes (Table 1). Patients that could not independently wash on the examination day compared with those that could had lower values of albumin and higher values of leukocytes (Table 1).

Patient-reported outcomes and functional testing

For further analysis regarding other PROs and functional status, we used the best cut-offs to predict 2 month survival (a clinically relevant period for patients and caregivers in this setting, Table S2A,B). Patients with reduced walking and washing ability more often showed dyspnoea, exertion, peripheral oedema, poor or very poor self-rated health, lower KPS, higher ECOG Performance Status, and reduced hand-grip strength (Tables 4 and S3A–C).

Discussion

We found that patient-reported ability to independently walk 4 m and wash represent significant and independent predictors of survival in patients with pre-terminal cancer. These novel findings may serve as clinically meaningful endpoints in interventional trials that can be rapidly completed and easily implemented. Notably, we used validated assessments that further supported the validity of these novel endpoints, including patient perceived dyspnoea[7] and exertion[8] at rest, self-rated health,[10] KPS,[2] ECOG Performance Status,[3] and handgrip strength[18] that were significantly better in patients who could walk 4 m, walk faster or wash on the examination day, showing that these new functional assessment endpoints are also clinically relevant.

Patients with advanced cancer should maintain independence and 'normality' as long as possible.[1] Each patient has his or her own definition of what normal is, and as patients approach their end of life, their perspectives and goals might change. An essential component of normality and autonomy is the ability for self-care, which helps even very sick patients to maintain at least some independence, personal privacy, and self-control (i.e., the ability of self-management).[19,20] Data demonstrate that self-care training in patients with cancer can increase quality of life[21]; self-care and the ability to

Table 3 Cox proportional hazards regression analyses in pre-terminal patients with cancer (n = 169)

Variable	Univariable			Multivariable adjusted*		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Patient-reported ability to walk 4 m						
Able to walk 4 m today (yes vs. no)	0.69	0.50–0.95	**0.023**	0.63	0.43–0.91	**0.015**
No. of days patients were able to walk in the last week (per 1 day)	0.94	0.89–0.99	**0.016**	0.93	0.88–0.98	**0.011**
No. of days patients were able to walk in the last month (per 1 day)	0.98	0.97–0.995	**0.009**	0.98	0.97–0.996	**0.012**
4 m gait speed (per 1 m/s)	0.57	0.39–0.82	**0.002**	0.45	0.27–0.75	**0.002**
Patient-reported ability to wash						
Patients able to wash today (yes vs. no)	0.71	0.51–0.98	**0.037**	0.67	0.48–0.95	**0.024**
No. of days patients were able to wash in the last week (per 1 day in the last week)	0.95	0.90–0.996	**0.034**	0.94	0.89–0.990	**0.019**
No. of days patient washed him/herself in the last month (per 1 day)	0.98	0.97–0.998	**0.023**	0.99	0.97–0.999	**0.040**
Combined model**						
Patients able to walk 4 m today and able to wash today (yes vs. no)	0.63	0.44–0.90	**0.010**	0.57	0.38–0.85	**0.006**
Patients either not able to walk 4 m or not able to wash	0.60	0.37–0.97	**0.038**	0.59	0.36–0.98	**0.036**
Patients not able to walk 4 m and not able to wash	Reference					

*Adjusted for age, sex, solid vs. haematologic, ECOG ≥3 (yes vs. no).
***P*-value for the combined model $P < 0.001$, subgroup difference between Patients able to walk 4 m and able to wash *vs* Patients not able to walk 4 m or not able to wash: univariable HR 0.95 (95% CI 0.60–1.51) $P = 0.83$; multivariable HR 1.03 (95% CI 0.64–1.66) $P = 0.91$. *P*-values <0.05 are bold.

mentally cope with the cancer disease are strongly related.[22] To some extent, self-care can be learned and trained with the help of clinicians, friends, partners, relatives, and/or by personal experience. Major components of this learning include the physical ability for self-care, monitoring one's physical condition, interacting with friends and relatives, keeping an open mind with positive thinking, and achieving one's wishes.[23]

A meta-analysis of 21 studies, including 400 patient interviews at the end of life, identified three main themes that described how patients' dignity could be impaired: the loss of control and functionality, autonomy, and identity.[20] During the interviews, investigators identified an overarching theme that patients wished for self-control and self-determination over the process of dying. This study also showed that each patient had their own opinion of what it meant for them to lose their dignity (e.g., losing the ability to use a bathroom by oneself, needing to be dressed by others, having to eat at predefined times, or depending on another person for 24 h/day).[20]

Therefore, we prospectively assessed new and simple patient-reported functional assessment endpoints for clinical associations and survival prediction in pre-terminal patients with cancer. Namely, we asked the patients about their ability to walk 4 m and wash at three intervals ('today', 'last week', and 'last month'). Especially in patients approaching the end of life, it is essential to aid the clinician with succinct and convenient questions that can be utilized in a focused conversation with a patient without using and analysing lengthy questionnaires. For example, standard patient questionnaires for patients with cancer receiving palliative care do exist, such as the Palliative Prognostic Index[24] and the European Organization for Research and Treatment Quality of Life in Palliative Cancer Care Patients (EORTC QLQ-C15-PAL),[25] but both contain 9 to 15 separate questions with multiple answer choices. Additionally, the clinician needs to take the time to calculate a score from the answer choices, limiting the quick and routine use of these tools in every pre-terminal patient with cancer in less than a minute. Other questionnaires, such as the Palliative Prognostic Score,[26] require an additional blood sample, limiting its routine use.[27] Another questionnaire, the Palliative Performance Scale,[28] is shorter but still relies on five separate questions, each including four to five answer choices. We believe our novel PROs and approach mirror the two most widely used (and most simple) existing clinician performance scales—the KPS[2] and ECOG Performance Status[3]—with the added advantages of being patient-reported and specifically developed and validated for patients with cancer approaching the end of life.

To our knowledge, this is the first time that these new patient-reported functional assessment endpoints have been prospectively assessed in pre-terminal patients with cancer with 1–12 months of anticipated survival. The 4 m

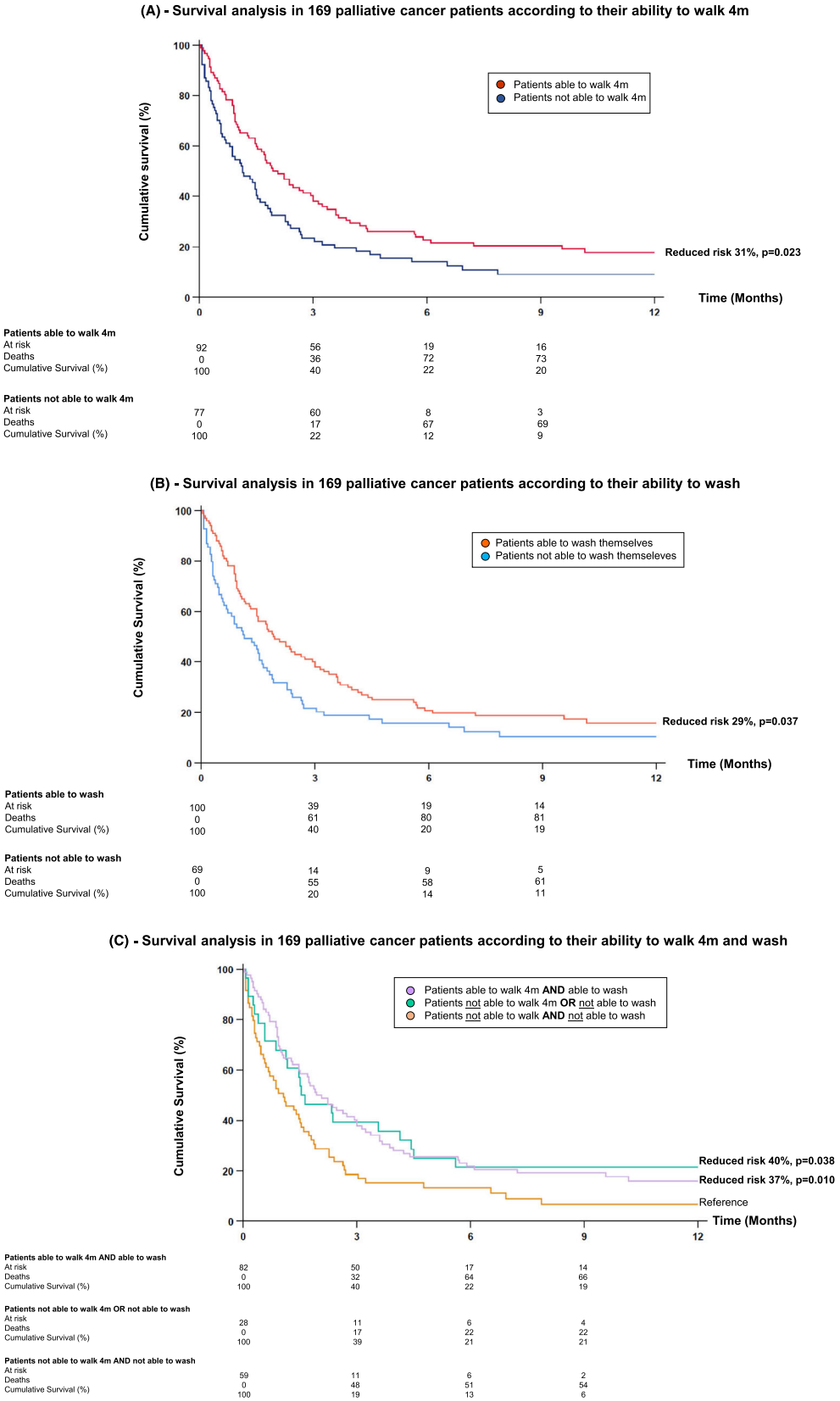

Figure 2 (A) Survival analysis in 169 palliative cancer patients according to their ability to walk 4 m. (B) Survival analysis in 169 palliative cancer patients according to their ability to wash. (C) Survival analysis in 169 palliative cancer patients according to their ability to walk 4 m and wash.

Table 4 Patient-reported outcomes and functional testing in n = 169 pre-terminal patients with cancer

Variable	Patients not able to walk 4 m today (*n* = 77)	Patients able to walk 4 m today (*n* = 92)	*P*-value	Patients not able to wash today (*n* = 69)	Patients able to wash today (*n* = 100)	*P*-value
Dyspnoea NYHA ≥3, *n* (%)	58 (95)	35 (38)	**<0.001**	56 (81)	37 (37)	**<0.001**
Peripheral oedema, *n* (%)	28 (37)	16 (17)	**0.004**	26 (38)	18 (18)	**0.003**
ECOG Performance Status ≥3, *n* (%)	76 (99)	55 (60)	**<0.001**	66 (96)	65 (65)	**<0.001**
Karnofsky Performance Status <40%, *n* (%)	48 (62)	9 (10)	**<0.001**	42 (61)	15 (15)	**<0.001**
Resting perceived dyspnoea (Borg scale, 0–10 points)	4 (2–7)	2 (1–5)	**0.002**	5 (3–7)	2 (1–4)	**<0.001**
Resting perceived exertion (Borg scale, 0–10 points)	7 (4–8)	5 (3–7)	**0.009**	7 (5–8)	5 (3–7)	**<0.001**
Poor or very poor self-rated health, *n* (%)	64 (83)	63 (69)	**0.007**	55 (80)	72 (72)	0.092
Visual analogue scale (appetite) (mm)	24 (9–60)	35 (10–69)	0.22	24 (10–51)	35 (10–78)	0.17
Visual analogue scale (pain) (mm)	20 (5–60)	20 (0–50)	0.41	20 (3–60)	20 (0–50)	0.63
Hand-grip strength (N)	205 ± 87	252 ± 78	**0.001**	204 ± 86	250 ± 80	**0.001**

Values are means ± SD for normal distribution, median and interquartile range (IQR) for non-normal distribution variables, or *n* (%) for nominal variables. *P*-values for nominal variables refer to the two comparison groups. *P*-values <0.05 are bold.
ECOG, Eastern Cooperative Oncology Group; mm, millimetre; N, Newton; NYHA, New York Heart Association.

gait speed has been used for survival prediction in patients with cancer receiving treatment.[29] However, asking patients to self-report their ability to ambulate 4 m has not been previously described. We believe the concept of asking people about their ability to independently walk 4 m or to wash 'today', 'last week', and 'last month' is completely novel as a prognostication tool in this setting. Moreover, these new, succinct, practical, and easy-to-use functional assessment endpoints could be applied in future interventional trials in pre-terminally ill patients with cancer when evaluating novel methods to optimize the ability for self-care.

Additionally, these new PROs could be easily implemented in everyday clinical decision-making. Depending on patients' ability to walk short distances or wash, structured, supportive care interventions, including individualized physiotherapy, nutritional supplementation, optimization of pain medications, and psychological support, could be further targeted to maintain or enhance those abilities. When considering physical performance and overall functional status using our best cut-offs at a 2 month survival prediction, these questions could also help clinicians recognize when timely advance care planning discussions are necessary, further enhancing the relevancy and practicality of these discussions.[30] Lastly, identifying patients with cancer at the highest risk of losing their independence through simple PROs may also help triage limited clinical resources and expertise to minimize healthcare utilization and associated costs, which requires further prospective validation.

Limitations

In this study, we included patients with cancer with 1–12 months of anticipated survival receiving care on an inpatient palliative care unit willing and able to participate in a prospective, observational study. Given the study's prospective nature, including 169 pre-terminally ill patients is an appropriate number for testing these new endpoints, especially given that all seven endpoints predicted survival in multivariable analyses. Future studies are warranted to assess and validate these new functional endpoints in patients with cancer with shorter or longer prognoses. These endpoints should also be assessed in patients with cancer in the ambulatory outpatient setting. For the new functional endpoints, we mainly relied on the patients' reporting of the ability to walk or wash in the past week/month. We could only validate the patients' answers on the examination day by letting them perform a 4 m gait speed test if they reported they could do so safely. In general, we observed that patients knew very well whether they could walk 'today' or not. Still, future studies should repeatedly assess the ability to independently walk or wash at regular time intervals.

Conclusions

In pre-terminally ill patients with cancer, the self-reported ability to independently walk 4 m and wash are independent predictors of survival and associated with functional status. Utilizing these new PRO endpoints in interventional clinical trials of patients with cancer and limited prognoses could optimize prospective interventional clinical trial methods. Furthermore, applying these easy assessments in routine clinical care may enhance the triage of limited clinical resources, expertise, and timely clinical interventions.

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Conflict of Interest

MSA reports personal fees from Servier, outside the submitted work. EJR has served as a member of the Scientific Advisory Board for Napo Pharmaceuticals, Care4ward, Actimed Therapeutics, and Meter Health. EJR has also served as a consultant for Veloxis Therapeutics and BYOMass and Takeda, Enzychem Lifesciences Pharmaceutical Company. 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, Astra Zeneca, Bayer, Berlin Chemie, Bristol-Myer Squibb, GE Healthcare, Pfizer, Philips, and Servier, all outside the submitted 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. MR received honoraria from AstraZeneca and Novo Nordisk. TR has received personal support for invited talks and participation in advisory boards from Novartis, Astra Zeneca, Bayer, Daiichi Sankyo, Berlin Chemie outside the scope of this work. MT has received personal support for invited talks and participation in advisory boards from Novartis, Astra Zeneca, Bayer, Daiichi Sankyo, Asklepios, Berlin Chemie outside the scope of this work. LHL has served on the advisory board for Daiichi Sankyio, Senaca, Astra Zeneca, and Servier, as an external expert for Astra Zeneca and received speakers' honoraria from Novartis and MSD. SvH reports research support from Amgen, Boehringer Ingelheim, IMI, and the German Center for Cardiovascular Research (DZHK). AJSC declares having received honoraria and/or lecture fees from Astra Zeneca, Bayer, Boehringer Ingelheim, Menarini, Novartis, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Impulse Dynamics, Respicardia, Viatris. TF reports personal fees from Bayer, BiosenseWebster, Bristol Myers Squibb, CSL Behring, Enanta, Fresenius Kabi, Galapagos, Immunic, IQVIA, Janssen, KyowaKirin, Lilly, LivaNova, Minoryx, Novartis, Recordati, Roche, Servier, Viatris, and Vifor for statistical consultancies including data monitoring committees, all outside the submitted work. JB reports being a consultant for Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, BoehringerIngelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Impulse Dynamics,Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Roche, and Vifor. SDA reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, Astra Zeneca, 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 & DE 102007022367), but he does not benefit personally from the related issued patents. LB received honoraria from Seattle Genetics, Sanofi, Astellas, Amgen, consultancy fee from Gilead, Hexal, and Menarini, consultancy fee and Honoraria Abbvie, BMS/Celgene, Daiichi Sankyo, Janssen, Jazz Pharmaceuticals, Novartis and Pfizer, and research funding from Bayer and Jazz Pharmaceuticals. UK received consultancy fee from Gilead, Abbvie, Roche, AstraZeneca, Takeda, Lilly, BMS/Celgene, Janssen, Pentixapharm. JA received travel grants from Alexion, Jazz, Celgene, all outside the submitted work. All other authors declare no conflict of interest.

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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