

Predictive factors for toxicity in Geriatric Oncology: Sarcopenia and mobility indices

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The author declares no conflict of interest

Sarcopenia and toxicity

- Sarcopenia was initially defined in 1989 as an age-related loss of muscle mass only (*Rosenberg IF. J Nutr. 1997 suppl 5*)
- Since 2010, the definition has been gradually refined to consensually refer to a **syndrome**:
 - European Working Group On Sarcopenia (EWGOS) 1 et 2 *Cruz-Jentoft AJ et al. Age Ageing, 2010 et 2019*
 - International Working Group on Sarcopenia (IWGS) *Fielding RA et al. JAMDA, 2011*
 - Asian Working Group on Sarcopenia (AWGS) 1 et 2 *Chen LK et al. JAMDA, 2014 et 2020*

Consensus	Year	Screening	Definition				
			Muscle Mass		Muscular Strength		Muscular Performance
EWGOS 1	2010	No	↓ DXA, BIA, CT or MRI	AND	↓ Hand-grip strength (kg) [M < 30, F < 20]	OR	↓ GS < 0.8 m/s or SPPB < 9/12 or TGUG ≥ 20 s
IWGS	2011	No	↓ DXA	AND	No	-	↓ GS < 1 m/s
AWGS 1	2014	No	↓ DXA or BIA	AND	↓ Hand-grip strength (kg) [M < 26, F < 18]	AND	↓ GS < 0.8 m/s
EWGOS 2	2019	Yes (SARCF)	↓ DXA, BIA, CT or MRI	AND	↓ Hand-grip strength (kg) [M < 27, F < 16] Or 5 Rising from a chair > 15 s	AND (severity)	↓ GS < 0.8 m/s or SPPB < 9/12 or TGUG ≥ 20 s
AWGS 2	2019	Yes (SARCF)	↓ DXA or BIA	AND	↓ Hand-grip strength (kg) [M < 28, F < 18] 5 Rising from a chair > 12 s	AND (severity)	↓ GS < 1 m/s or SPPB < 9/12

EWGOS: European Working Group On Sarcopenia; IWGS: International Working Group on Sarcopenia; AWGS: Asian Working Group on Sarcopenia; DXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; CT: computed tomography; MRI: magnetic resonance imagery. M: male; F: female. GS: gait speed; SPPB: short physical performance battery; TGUG: timed get up and go test. SARCF: strength, assistance with walking, rise from a chair, climb stairs, and falls. ↓: reduced muscle mass; Bold = consensus names, and syndromic combination.



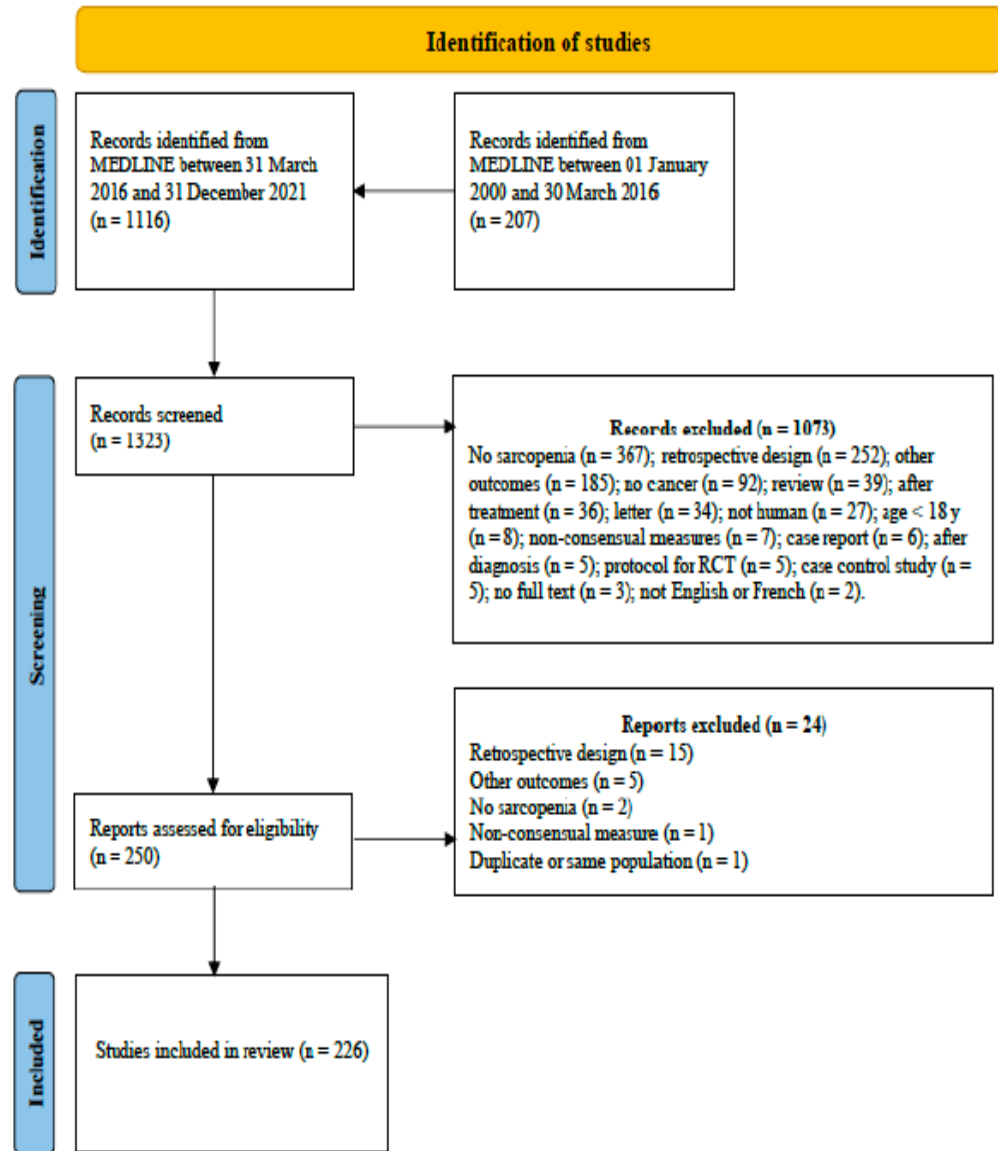
Systematic Review

Pre-Therapeutic Sarcopenia among Cancer Patients: An Up-to-Date Meta-Analysis of Prevalence and Predictive Value during Cancer Treatment

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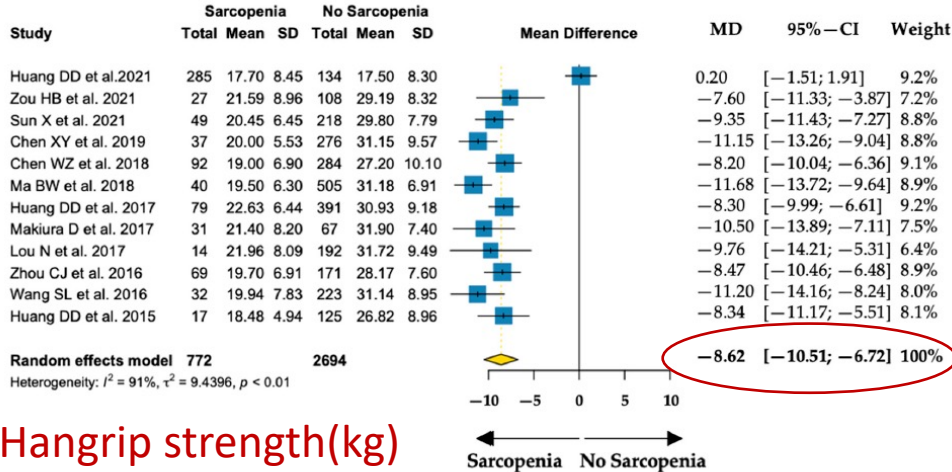
Abstract: This study will address the prevalence of pre-therapeutic sarcopenia (PS) and its clinical impact during cancer treatment among adult cancer patients ≥ 18 years of age. A meta-analysis (MA) with random-effect models was performed via a MEDLINE systematic review, according to the PRISMA statement, focusing on articles published before February 2022 that reported observational studies and clinical trials on the prevalence of PS and the following outcomes: overall survival (OS), progression-free survival (PFS), post-operative complications (POC), toxicities (TOX), and nosocomial infections (NI). A total of 65,936 patients (mean age: 45.7–85 y) with various cancer sites and extensions and various treatment modes were included. Mainly defined by CT scan-based loss of muscle mass only, the pooled prevalence of PS was 38.0%. The pooled relative risks were 1.97, 1.76, 2.70, 1.47, and 1.76 for OS, PFS, POC, TOX, and NI, respectively (moderate-to-high heterogeneity, I^2 : 58–85%). Consensus-based algorithm definitions of sarcopenia, integrating low muscle mass and low levels of muscular strength and/or physical performance, lowered the prevalence (22%) and heterogeneity ($I^2 < 50%$). They also increased the predictive values with RRs ranging from 2.31 (OS) to 3.52 (POC). PS among cancer patients is prevalent and strongly associated with poor outcomes during cancer treatment, especially when considering a consensus-based algorithm approach.

- N = 226 articles
- 2008-2022
- 65936 patients
 - Mean age = 45-85 ans
 - 17295 ≥ 65y
 - 419 ≥ 75y
- Asian (51%), men (66%), BMI < 30 kg/m² (69,5%)
- Various cancer sites (22%), gastric (20,5%) or colorectal (17%)
- Surgery (61%), chemotherapy (6%), immune-therapy or targeted therapy (1%)



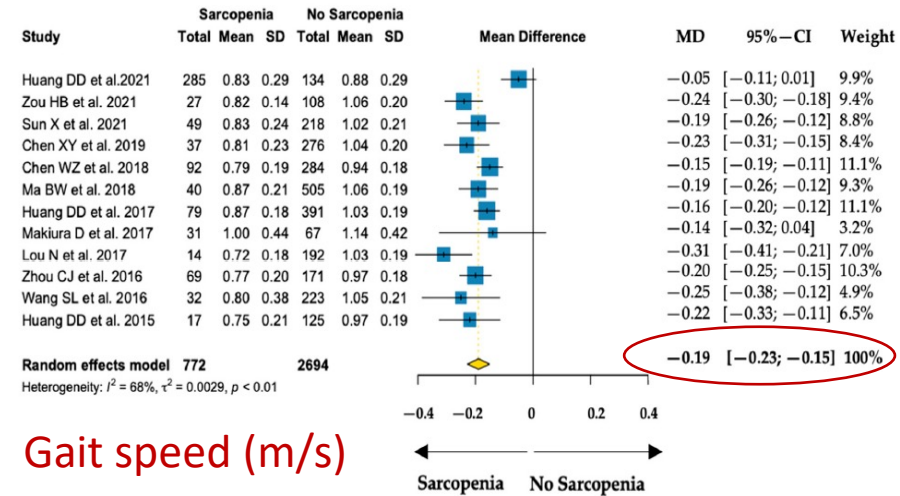
Compared to no sarcopenia, Handgrip strength and gait speed are significantly lower in sarcopenia among cancer patients

A



Handgrip strength(kg)

B



Gait speed (m/s)

Pre-therapeutic sarcopenia is significantly associated with severe treatment-related toxicity (≥ Grade 3) and/or dose-limiting toxicity among cancer patients

19 studies, 2980 patients

- 1172 sarcopenic
- 1808 no sarcopenic

RR = 1.47 [1.17-1.85]

(moderate heterogeneity: $I^2 = 71\%$)

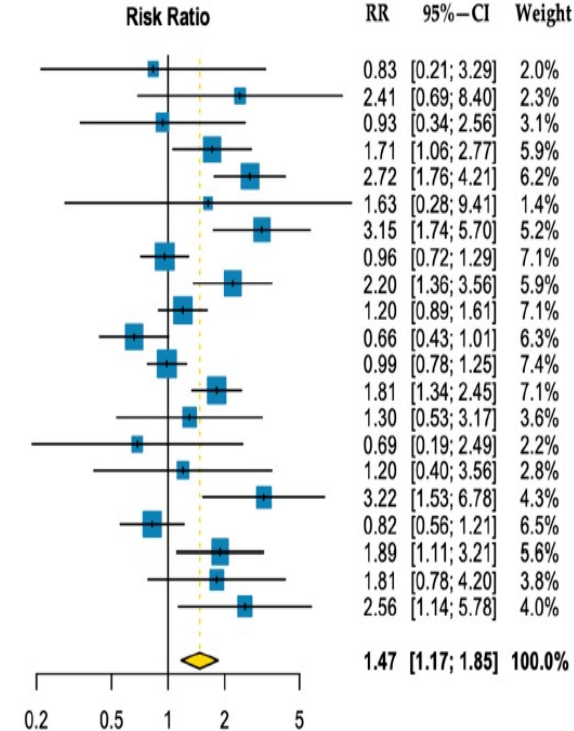
No studies using consensual algorithms

→ Homogeneity regarding chemotherapy

(RR = 1.98 [1.55-2.54]), and targeted therapy

(RR = 1.63 [1.05-2.54]) in breast or head-and-neck cancers ($I^2 < 50\%$)

Study	Sarcopenia		No Sarcopenia	
	Events	Total	Events	Total
Ferini G et al. 2021	2	8	6	20
Lee CH et al. 2021	8	41	3	37
Takeda T et al. 2021	12	61	4	19
Xu YY et al. 2021	34	94	19	90
Huang CH et al. 2020	59	65	14	42
Jin K et al. 2020	3	57	2	62
Ueno A et al. 2020	7	10	16	72
Yu J II et al. 2020	31	75	165	383
van Rijn-Dekker MI et al. 2020	26	189	35	561
Huillard O et al. 2019	48	89	41	91
Panje CM et al. 2019	15	31	22	30
Sasaki S et al. 2019	76	135	48	84
Kurita Y et al. 2018	40	42	21	40
Williams GR et al. 2018	6	12	5	13
Sato S et al. 2018	5	34	3	14
Heidelberger V et al. 2017	6	34	5	34
Wendrich AW et al. 2017	27	61	7	51
Miyata H et al. 2016	21	44	29	50
Tan BH et al. 2014	24	44	13	45
Huillard O et al. 2013	12	32	6	29
Prado CM et al. 2009	7	14	8	41
Random effects model		1172		1808
Heterogeneity: $I^2 = 71\%$, $\tau^2 = 0.1655$, $p < 0.01$				



...and next ?

- Pre-therapeutic sarcopenia defined as a loss of muscle mass only was significantly associated with \geq Grade 3 **endocrine-therapy toxicity in non metastatic breast cancer** (mean age = 61y) (*G.F. Pereira Aleixo et al. Breast Cancer Res Treat; 2022*)

Mobility indices and toxicity

- PubMed database search (May 2023)
- Research algorithm: (gait speed OR short physical performance battery OR timed get up and go test OR handgrip strength OR one leg stance balance) AND older adults AND cancer AND toxicity
- N = 26 articles

Table 1 Baseline Characteristics (N = 30).

Covariate	N (%)
Age	78.1 ± 6.4 ^a
Gender	
Male	13 (43)
Female	17 (57)
Cancer subtype	
Diffuse-large B cell	17 (57)
CLL/SLL	6 (20)
Follicular	2 (7)
Low-grade B-cell	2 (7)
Hodgkin's	2 (7)
T-cell	1 (3)
Stage	
I/II	8 (27)
III/IV	19 (63)
Unknown	3 (10)
Chemotherapy regimen	
R-CHOP	18 (60)
BR	7 (23)
ABVD	1 (3)
CHOP	1 (3)
FCR	1 (3)
CHLO + OBIN	1 (3)
Brentuximab, bendamustine	1 (3)
Charlson comorbidity index	
<3	18 (60)
3-4	9 (30)
≥5	3 (10)

Abbreviations: ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; BR = bendamustine, rituximab; CHLO + OBIN = chlorambucil, obinutuzumab; CLL = Chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SLL = Small lymphocytic leukemia.

^a Data presented as mean ± SD.

Predicting the Risks of Aggressive-Intent Chemotherapy Toxicity in Older Patients With Lymphoma: A Prospective Observational Pilot Study

Canada, 2022

Vinita Dhir,¹ Manjula Maganti,² Dmitry Rozenberg,³ Vishal Kukreti,¹ John Kuruvilla,¹ Michael Crump,¹ Anca Prica, MD, MSc, FRCPC¹

Abstract

In this prospective cohort study, thirty patients 70 years or older with lymphoma were recruited to assess the feasibility of different tests and models to predict chemotherapy-related adverse events. The results suggest the Clinical Frailty Scale shows promising utility, and this relatively easy test can be administered in an outpatient clinic to help older adults and clinicians with chemotherapy decision-making.

Introduction: Lymphoma is a disease of older patients and while treatment is subtype specific, curative or aggressive intent combination chemotherapy is often recommended. However, there has been limited evidence on which to base treatment decisions for older adults. Our objectives were to assess the utility of risk stratification measures and serial functional tests in predicting chemotherapy toxicity and as well the feasibility of conducting these in older adults undergoing chemotherapy for lymphoproliferative disorders. **Materials and Methods:** This prospective cohort study recruited lymphoma patients 70 years or older planned for systemic chemotherapy. The Cancer and Aging Research Group (CARG) risk stratification tool and Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) were calculated at baseline. The Clinical Frailty Scale (CFS), Charlson Comorbidity Index score, grip strength and gait speed test, and toxicity events, were assessed at baseline and serially throughout treatment. Sarcopenia was calculated on CT scans at baseline, midway through treatment, and 1-month after completion of therapy. The primary endpoint was to assess the feasibility of applying these measures in busy ambulatory clinics. These measures were also correlated with clinical outcomes including ≥grade 3 adverse events (AEs), hospitalizations and emergency department visits, dose changes or delays, and overall survival. **Results:** In total, 30 patients were enrolled (mean age 78.1 ± 6.4 years), of whom 20 were treated with curative intent. A total of 16 patients (53%) experienced grade ≥3 AEs, 9 (56%) of which led to a chemotherapy delay. On univariable analyses, CFS score, a high CARG score, a high CRASH score, and the gait speed were associated with grade ≥3 AEs, while only CFS remained significant on multivariable analysis. On univariable analysis, patients with a medium to high risk CRASH score were more likely than low risk patients to have an unplanned emergency department visit or hospitalization. **Conclusions:** The CFS seems to predict toxicity in this cohort study, with gait speed, CARG and CRASH scores being potentially additional predictive methods of evaluation.

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Keywords: Aging, Frailty, Geriatric oncology, Physical performance testing, Lymphoma

Table 3 Univariable GEE Regression Analysis Results for Grade ≥3 Toxicity. Boldface indicates statistically significant p-values.

Covariate	N (%)	Patients With Grade ≥3 AEs (%)	OR (95% CI)	P-value
CARG risk score				
Low (0-5)	5 (17)	1 (20)	Reference	
Intermediate (6-9)	18 (60)	8 (44)	5.99 (0.89, 40.23)	.065
High (10-19)	7 (23)	4 (57)	10.05 (1.33, 75.6)	.025
CRASH risk score				
Low to medium: 0 to 6	13 (43)	1 (8)	Reference	
Medium to High: 7 to >9	17 (57)	12 (71)	3.32 (1.24, 8.94)	.017
CFS scale				
<4	23 (77)	8 (35)	Reference	
≥4	7 (23)	5 (71)	7.45 (1.85-23.9)	.005
Grip strength (lbs)	-	-	1.00 (0.85, 1.18)	.976
4-metre gait speed	-	-	0.90 (0.83, 0.99)	.02
Sarcopenia at baseline				
No	8 (38)	2 (29)	Reference	
Yes	13 (62)	5 (71)	2.17 (0.49, 9.53)	.303
CCI	-	-	1.27 (0.98, 1.65)	.069

Abbreviations: AEs = adverse events; CARG = Cancer and Aging Research Group; CCI = Charlson Comorbidity Index; CFS = Clinical Frailty Scale; CRASH = Chemotherapy Risk Assessment Scale for High-Age Patients; GEE = Generalized estimating equations.

Table 1. Baseline characteristics of the study cohort (N = 105)

Characteristic	No.	%	Median (range)
Age at diagnosis, y			64 (60-75)
60-64	54	51.4	
65-70	37	35.3	
71-75	14	13.3	
Sex			
Male	65	61.9	
Female	40	38.1	
AML disease type			
De novo	73	69.5	
Secondary	32	30.5	

CLINICAL TRIALS AND OBSERVATIONS

CME Article

Geriatric assessment predicts nonfatal toxicities and outcomes for intensively treated older adults with AML

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KEY POINTS

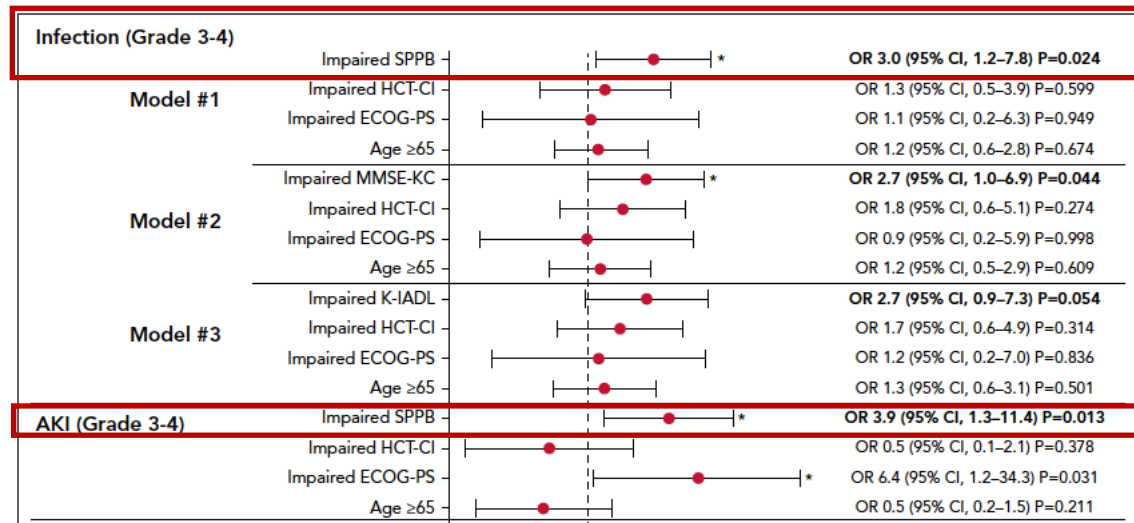
- GA focusing on physical function and depression improves the power of survival prediction models for older patients with AML.
- Cognitive and physical impairments are associated with nonfatal toxicities during induction chemotherapy in older patients with AML.

Given that there are only a few prospective studies with conflicting results, we investigated the prognostic value of multiparameter geriatric assessment (GA) domains on tolerance and outcomes after intensive chemotherapy in older adults with acute myeloid leukemia (AML). In all, 105 newly diagnosed patients with AML who were older than age 60 years and who received intensive chemotherapy consisting of cytarabine and idarubicin were enrolled prospectively. Pretreatment GA included evaluations for social and nutritional support, cognition, depression, distress, and physical function. The median age was 64 years (range, 60-75 years), and 93% had an Eastern Cooperative Oncology Group performance score <2. Between 32.4% and 69.5% of patients met the criteria for impairment for each domain of GA. Physical impairment by the Short Physical Performance Battery (SPPB) and cognitive dysfunction by the Mini-Mental State Examination in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Assessment Packet (MMSE-KC) were significantly associated with nonfatal toxicities, including grade 3 to 4 infections (SPPB, $P = .024$; MMSE-KC, $P = .044$), acute renal failure (SPPB, $P = .013$), and/or prolonged hospitalization (≥ 40 days) during induction chemotherapy (MMSE-KC, $P = .005$). Reduced physical function by SPPB and depressive symptoms by the Korean version of the short form of geriatric depression scales (SGDS-K) were significantly associated with inferior survival (SPPB, $P = .027$; SGDS-K, $P = .048$). Gait speed and sit-and-stand speed were the most powerful measurements for predicting survival outcomes. Notably, the addition of SPPB and SGDS-K, gait speed and SGDS-K, or sit-and-stand speed and SGDS-K significantly improved the power of existing survival prediction models. In conclusion, GA improved risk stratification for treatment decisions and may inform interventions to improve outcomes for older adults with AML. This study was registered at the Clinical Research Information Service as #KCTD0002172.

Korea, 2022

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Acute kidney Injury





Original article

Is skeletal muscle loss associated with chemoradiotherapy toxicity in nasopharyngeal carcinoma patients? A prospective study

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SUMMARY

Background: Our study explored to investigate whether skeletal muscle loss before concurrent chemoradiotherapy (CCRT) can predict treatment-related toxicity in this population.**Methods:** Computed tomography (CT) scan of the third lumbar were used to assess and calculate the SMA (skeletal muscle area), SMI (skeletal muscle index), SMD (skeletal muscle density), SMG (skeletal muscle gauge) and estimate LBM (lean body mass). Handgrip strength (HGS) and daily walk speed were evaluated. Predictive factors linked to toxicity were assessed by logistic regression models and adjusted odds ratios (OR) of treatment toxicity were reported.**Results:** A total of 82 patients were evaluated (67.1% males, 45.7 ± 10.7 years). Skeletal muscle loss was not associated with severe radiotherapy toxicity. In males, sarcopenia increases the risk of dose-limiting toxicity (DLT) (OR: 4.00, 95% CI = 1.20–13.36, *p* = 0.024). DLT is associated with reduced SMA (OR: 0.97, 95% CI = 0.94–1.00, *p* = 0.041), SMI (OR: 0.91, 95% CI = 0.84–0.99, *p* = 0.042) and LBM (OR: 0.90, 95% CI = 0.81–0.99, *p* = 0.041). Reduced HGS was significantly associated with grade 3–4 leukopenia (OR: 0.92, 95% CI = 0.86–0.98, *p* = 0.007), and was associated with any grade 3–4 toxicity (OR: 0.94, 95% CI = 0.89–0.99, *p* = 0.013). There is a strong correlation between LBM and HGS (Pearson's *r* = 0.71, *p* < 0.001).**Conclusions:** Skeletal muscle loss was not associated with severe radiation oral mucositis and dermatitis but associated with any grade 3–4 toxicity and severe gastrointestinal reactions in NPC patients. In males, sarcopenia before treatment is predictive of DLT. Increased HGS is independently associated with a reduced risk of hematological toxicity.

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China, 2021

Table 3

Multivariate analysis of association between severe toxicity with different muscle measurements.

Variables	Entire cohort (n = 82)				Males (n = 55)			
	Any Grade 3/4 toxicity		Nausea		Leukopenia		DLT	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>		
Sarcopenia								
HGS (1 kg increase)	0.94 (0.89–0.99)	0.013			0.92 (0.86–0.98)	0.007	4.00 (1.20–13.36)	0.024
SMD (1HU increase)			0.86 (0.76–0.97)	0.011				
SMA (1 cm ² increase)	0.98 (0.96–1.00)	0.032					0.97 (0.94–1.00)	0.041
SMI (1 cm ² /m ² increase)							0.91 (0.84–0.99)	0.042
LBM (1 kg increase)	0.94 (0.88–1.00)	0.033					0.90 (0.81–0.99)	0.041

NOTE: Adjusted for age and cancer stage.

RESEARCH ARTICLE

Open Access



France, 2018

Dynapenia could predict chemotherapy-induced dose-limiting neurotoxicity in digestive cancer patients

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Abstract

Background: FIGHTDIGO study showed the feasibility and acceptability of handgrip strength (HGS) measure in routine in 201 consecutive patients with digestive cancer treated with ambulatory chemotherapy. The present study focuses on the second aim of FIGHTDIGO study: the relationships between pre-therapeutic dynapenia and chemotherapy-induced Dose-Limiting Toxicities (DLT).

Methods: In this ancillary prospective study, DLT were analyzed in a sub-group of 45 chemotherapy-naïve patients. Two bilateral consecutive measures of HGS were performed with a Jamar dynamometer before the first cycle of chemotherapy. Dynapenia was defined as HGS < 30 kg (men) and < 20 kg (women). DLT and/or Dose-Limiting Neurotoxicity (DLN) were defined as any toxicity leading to dose reduction, treatment delays or permanent treatment discontinuation.

Results: Two-thirds of chemotherapies were potentially neurotoxic ($n = 31$ [68.7%]) and 22 patients (48.9%) received FOLFOX (5FU, leucovorin plus oxaliplatin) regimen chemotherapy. Eleven patients (24.4%) had pre-therapeutic dynapenia. The median number of chemotherapy cycles was 10 with a median follow-up of 167 days. Twenty-two patients experienced DLT (48.9%). There was no significant association between pre-therapeutic dynapenia and DLT ($p = 0.62$). Nineteen patients (42.2%) experienced DLN. In multivariate analysis, dynapenia and tumoral location (stomach, biliary tract or small intestine) were independent risk factors for DLN (HR = 3.5 [1.3; 9.8]; $p = 0.02$ and HR = 3.6 [1.3; 10.0]; $p = 0.01$, respectively).

Conclusions: Digestive cancer patients with pre-therapeutic dynapenia seemed to experience more DLN. HGS routine measurement may be a way to screen patients with frailty marker (dynapenia) who would require chemotherapy dose adjustment and adapted physical activity programs.

Trial registration: NCT02797197 June 13, 2016 retrospectively registered.

Keywords: Dynapenia, Antineoplastic agents, Digestive system neoplasms, Sarcopenia, Dose-limiting toxicity, Muscle strength

Characteristics ^a	Value
Age, mean ± SD	66.2 ± 12.3
Sex	
Male	21 (46.7)
Female	24 (53.3)
Body Mass Index, mean ± SD, kg/m ²	23.2 ± 4.1
BMI categories, No. (%)	
Malnutrition ^b	7 (15.6)
Normal	24 (53.3)
Overweight ^c	14 (31.1)
ECOG PS, No. (%)	
0	12 (26.7)
1	31 (68.9)
2	2 (4.4)
mGPS ^d , No. (%)	
0	17 (43.6)
1	17 (43.6)
2	5 (12.8)
Hospitalizations number, median [range]	10 [0–18]
Follow-up, median [range], days	167 [0–185]
Primary tumor location, No. (%)	
Colon and rectum	22 (48.9)
Esophagus	3 (6.7)
Stomach	5 (11.1)
Biliary tract	1 (2.2)
Pancreas	9 (20.0)
Small intestine	1 (2.2)
Neuroendocrine tumor	2 (4.4)
Unknown	2 (4.4)
Stage, No. (%)	
Local	20 (44.4)
Locally advanced	6 (13.3)
Metastatic	19 (42.2)
Type of treatment, No. (%)	
Chemotherapy	38 (84.4)
Chemotherapy and biotherapy	7 (15.6)
Chemotherapy protocol, No. (%)	
5FU + OXALIPLATIN	22 (48.9)
5FU + IRINOTECAN + OXALIPLATIN	7 (15.6)
5FU alone	6 (13.3)
GEMCITABINE	5 (11.1)
5FU-DACARBAZINE	2 (4.4)
5FU + IRINOTECAN	1 (2.2)
GEMCITABINE + OXALIPLATIN	1 (2.2)
VP16 + CISPLATINE	1 (2.2)

Characteristics ^a	Value
Neurotoxic chemotherapy ^e , No. (%)	31 (68.9)
Biotherapy protocol, No. (%)	
BEVACIZUMAB	6/7 (85.7)
CETUXIMAB	1/7 (14.3)
Dynapenia, No. (%)	11 (24.4)

Table 3 Factors associated with chemotherapy-induced Dose-Limiting Neurotoxicity (DLN)

Characteristics ^a	DLNs (n = 19)	No DLN (n = 26)	Univariate analysis <i>p</i> value	Multivariate analysis ^d	
				HR [95% CI]	<i>p</i> value
Maximum handgrip strength, mean ± SD	29.1 ± 10.3	28.5 ± 9.1	0.64		
Dynapenia			0.13		0.02
No	12 (63.2)	22 (84.6)		1	
Yes	7 (36.8)	4 (15.4)		3.5 [1.3; 9.8]	
Age, mean ± SD	65.9 ± 11.5	66.5 ± 13.1	0.89		
ECOG PS			0.04		0.03
0	8 (42.1)	4 (15.4)		1	
1 or 2	11 (57.9)	22 (84.6)		0.4 [0.2; 0.9]	
mGPS ^b			0.39		
0	8 (50.0)	9 (39.1)			
1	8 (50.0)	9 (39.1)			
2	0 (0.0)	2 (21.7)			
Primary Tumor location			0.02		0.01
Stomach – Biliary tract – Small Intestine	6 (31.6)	1 (4.2)		3.6 [1.3; 10.0]	
Other location	13 (68.4)	23 (95.8)		1	
Stage			0.49		
Local	10 (52.6)	10 (38.5)			
Locally advanced	1 (5.3)	5 (19.2)			
Metastatic	8 (42.1)	11 (42.3)			
BMI, mean ± SD, kg/m ²	23.9 ± 3.4	22.8 ± 4.5	0.048		
Overweight, No. (%) ^c			0.02		
Yes	9 (47.4)	5 (19.2)			
No	10 (52.6)	21 (80.8)			

Conclusions

- Pre-therapeutic sarcopenia and/or impaired mobility indices (slow gait speed, low SPPB or low handgrip strength) are consistently associated with \geq Grade 3 treatment-related toxicity among older adults with cancer.
- These associations are closely linked to the frailty
- There is an urgent need to agree on an operational definition of sarcopenia and on the optimal mobility index to use for:
 - Clinical practice (early screening for early functional rehabilitation)
 - Clinical research (encourage the use of sarcopenia and/or mobility indices as stratification variables in the development of future clinical trials in geriatric oncology)
 - Improve study comparability

Thanks for your attention