Compared with survivors of childhood acute lymphoblastic leukemia (ALL), few studies have explored the neurocognitive sequelae of treatment among survivors of sarcoma [3, 6-8] and none of these were conducted in Chinese populations.

Frailty as a Marker of Physiological Aging and its Association with Neurocognitive Outcomes in Survivors of Childhood Cancer

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Background

- Emerging evidence is supporting the role of "premature aging" in cancer-related neurocognitive impairment
- While most studies on aging and neurocognitive outcomes are conducted in the adult cancer populations, few studies have investigated the physiological markers of aging in childhood cancer survivors

Objectives

- To: evaluate the association of frailty (a physiological aging marker) and neurocognitive outcomes among survivors of childhood cancer

Methods

- This cross-sectional study was conduced at the Long-term Follow-up clinics of an academic hospital in Hong Kong
- **Inclusion criteria:**
  - Adult survivors (aged ≥18 years old) at recruitment
  - Diagnosed with cancer before 18 years old
  - Had survived at least 5 years post-cancer diagnosis
- **Exclusion criteria:**
  - Pre-existing developmental conditions (e.g. autism, Down syndrome), or non-cancer conditions that affect cognitive function (e.g. traumatic brain injury)
- **Neurocognitive outcomes:**
  - Attention (CPT-III)
  - Visual memory (Modified Taylor Complex Figure)
  - Motor-processing speed (Grooved Pegboard)
  - Visuomotor processing speed (TMT-A)
  - Cognitive flexibility (TMT-B)
  - Cognitive complaints (CCSS-Neurocognitive Questionnaire)
- **Frailty:**
  - Survivors underwent a clinical evaluation and bioelectrical impedance analysis
  - They were classified as "prefrail" or "frail" based on the Fried's frailty phenotype criteria **(Figure 1)**
  - Asian or local thresholds for used to define "frailty" for each criterion
- **Covariates:**
  - Chronic health conditions (CHC), cancer diagnoses, age at diagnosis, treatment modalities (extracted from electronic health records)
- **Statistical analysis:**
  - General linear modeling to evaluate the association of neurocognitive *T*-scores with (1) frailty ("frail" *versus* "prefrail"/"non-frail") and (2) T/S ratio (continuous variable)
  - Adjusted for age, sex and clinical/treatment covariates

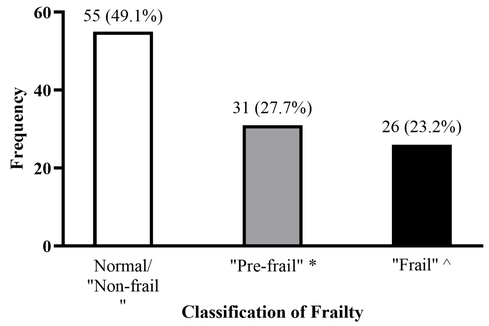
Results

- This study recruited 112 survivors of childhood cancer (Table 1)

Table 1: Clinical Characteristics	
Age (years)	28.4 [SD=6.9]
Sex: Male	57 (50.9%)
Age at follow-up	28.8 [SD=6.9]
Age at diagnosis (years)	9.1 [SD=5.4]
Years from diagnosis (years)	18.9 [SD=7.9]
Cancer diagnoses	
Hematological cancers	67 (59.8%)
Solid tumor	5 (4.5%)
Non-CNS solid tumor	40 (35.7%)
Chronic health conditions (CHC)	
Yes	46 (41.1%)
Endocrine/Metabolic	14 (12.5%)
Cardiovascular	15 (13.4%)
Vision	9 (8.0%)
Pulmonary	7 (6.3%)

- Half of the cohort were classified as "pre-frail" or "frail" **(Figure 1)**
- As compared to "non-frail"/"pre-frail" survivors, "frail" survivors were more likely to have developed a CHC (53.8% versus 25.0%, *P*=0.034) and were younger at cancer diagnosis (6.5 versus 9.5 years; *P*=0.037).

Figure 1: Classification of "Frailty" Based on the Fried Criteria



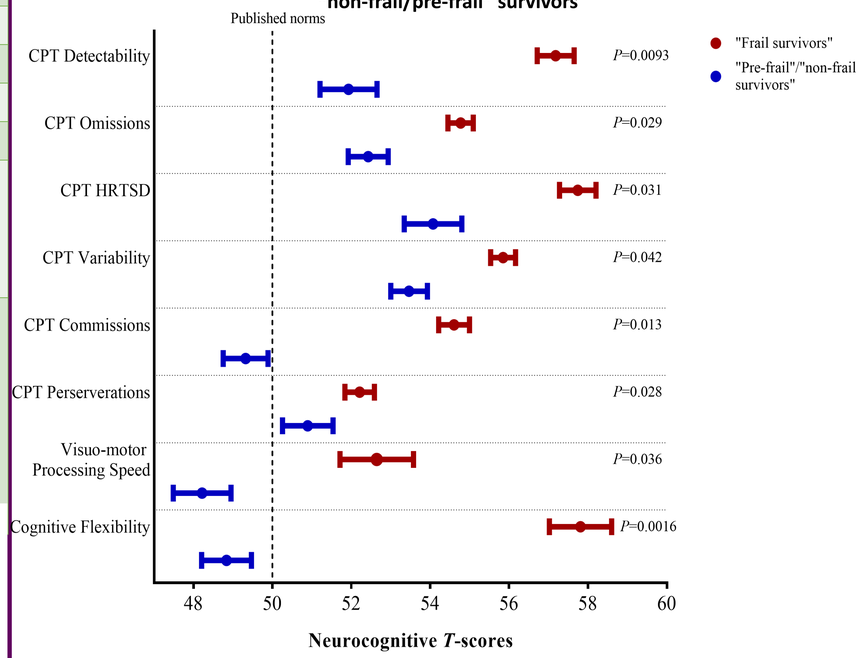
Based on the Fried Criteria, participants were considered
* "Pre-frail" if they had fulfilled 2 of the following criteria:
^ "Frail" if they had fulfilled ≥ 3 of the following criteria:

(1) low lean muscle mass based on bioelectrical impedance analysis (appendicular skeletal muscle index ≤ 7.0kg/m^2 for males, ≤ 5.7 kg/m^2 for females - Asian Working Group for Sarcopenia)
(2) exhaustion (Multidimensional Fatigue Scale *T*-score ≤ 1.3 SDs below population mean)
(3) low energy expenditure (reported ≤ two sessions of 20 minutes of light physical activity [3 METs] per week)
(4) Slowness (≥ 7 seconds to walk 15 feet for women < 159 cm and men < 173 cm tall or ≥ 6 seconds to complete the distance for women ≥ 159 cm tall and for men ≥ 173 cm tall)
(5) weakness (hand-held dynamometer and body mass index–specific cut points for sitting hand-grip strength)

Results

- "Frail" survivors performed worse than "non-frail"/"pre-frail" survivors on multiple cognitive measures **(Figure 2)**

Figure 2: Comparison of cognitive measures between "frail" survivors and "non-frail/pre-frail" survivors



Models are adjusted for age, sex and clinical/treatment covariates.
A higher T-score is indicative of worse neurocognitive outcome.

- "Frail" survivors also reported more cognitive problems than "non-frail"/"pre-frail" survivors **(Table 2)**

Table 2: Association between frailty and self-reported cognitive problems on the CCSS-NCQ.						
	Task efficiency		Organization		Memory	
	Est.	*P*	Est.	*P*	Est.	*P*
"Frail" survivors Ref: Non-frail/pre-frail	2.62	**0.003**	1.89	**0.029**	1.80	**0.003**

Conclusion

- Aging processes might play a mechanistic role in neurocognitive impairment among childhood cancer survivors
- Future work should investigate targeted interventions that mitigate physiological and cognitive aging, such as exercise and lifestyle modification programs

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Funded by the Hong Kong Research Grant Council, General Research Fund (Ref: 14605421)