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A Weighted Composite Intrinsic Capacity Score to Predict Frail-ty in Community-Dwelling Older Persons

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Abstract

Background: Intrinsic Capacity (IC) encompasses various aspects of one's re-serves. We aim to investigate the independent associations of the 5 Intrinsic Capacity (IC) domains with frailty and to develop a Weighted Composite Intrinsic Capacity Score that is associated with frailty status, predicts frailty progression and adverse health outcomes.

Methods: Prospective cohort study set in mobile IPPT-S (Individual Physical Proficiency Test for Seniors) screening plat-forms situated in public housing blocks and community centers in Northeastern Singapore since 2017. Participants include 743 community-dwelling older adults above 50 years old who can ambulate independently with or without walking aids. IC domains and their respective measurements: Vitality (Mini Nutritional Assessment-Short Form questionnaire, appendicular skeletal mass index), locomotion (Short Physical Performance Battery, 6-minute walk test), sensory (self-reported hearing and vision), cognition (subjective self-report, locally validated cognitive assessment), psychological (15-item Geriatric Depression Scale, self-reported anxiety/depression). Frailty was assessed by the modified Fried phenotypic criteria. Adverse health outcomes including falls and hospitalizations were surveyed with standardized questionnaires.

Results: With all other do-mains controlled, vitality and locomotion were significantly associated with frailty status. Weighted Composite IC Score =-3.17 + 1.16xVitality +2.06xLocomotion +0.34xSensory+0.25xCognition+ 0.37x Psychological, with a score of 1 for domains with no deficits and 0 for those with deficits. The Weighted Composite IC Scores were associated with frailty status, and discriminated frail from robust older adults (Area Under Curve 0.87, 95% CI 0.82-0.93).

Conclusion: Personalized monitoring and interventions targeted towards nutrition, body composition, mobility, physical training should be prioritized. More work is required to develop a Weighted Composite IC Score can be used to monitor one's global reserves and predict frailty progression and its health outcomes.

Keywords: Frailty; Intrinsic Capacity; Frailty progression; Locomotion; Mobility

Abbreviations: WHO: World Health Organization; IC: Intrinsic Capacity; SMI: Skeletal Mass Index; MNA-SF: Mini Nutritional-Short Form; SPPB: Short Physical Performance Battery; 6MWT: 6 Minute Walk Test; C-MMSE: Chinese version of the Mini Mental State Examination; GDS: Geriatric Depression Scale; EQ-5D: EuroQol-5 Dimensions; PAVS: Physical Activity Vital Sign; EPV: Events per Predictor Variable; ANOVA: Analysis of Variance; PPV: Positive Predictive Value; AUC: Area Under Curve; ROC: Receiver Operator Characteristic; ADLs: Activities of Daily Living; IDADLs: Instrumental Activities of Daily Livings; CFS: Clinical Frailty Scale; ICOPE: Integrated Care for Older People; TUG: Timed Up and Go; BEST: Balance Evaluation Systems Test

Introduction

A globally ageing population poses great challenges with older adults often affected by multi-morbidities with slow progression [1,2]. Traditionally, a disease-centered approach is emphasized to establish an individual's nosological diagnoses, deficits and limitations based on clinical phenotype, leading to reactive

algorithmic medical responses [3,4]. However, this approach is inadequate as diseases are often presented heterogeneously, functional abilities are not sufficiently evaluated, and interventions are often reactive rather than preventative [4-6].

Thus, World Health Organization (WHO) shifts discourse to a function-centered model focusing on the attributes that allow a person to do what he/she values [7]. In the center of this model is Intrinsic Capacity (IC), which is the physical and mental capacities that an individual has in reserve [1,7,8]. As the geriatric syndrome, frailty, entails underlying di-minished reserves resulting in vulnerability to stressors, this study will transcend disease-only focus to using this novel and holistic function-centered IC framework to identify important specific targets that should be preferentially monitored and managed in frailty [9,10].

WHO's concept of intrinsic capacity is an aggregation of one's mental and physical capacities [7]. It consists of 5 domains: cognition, locomotion, sensory, vitality, psychological [5]. These domains represent reserves that one has, which seems to contrast with the concept of frailty, usually characterized by the deficits and decline in functions, making one more vulnerable to stressors. These seemingly opposite perspectives are actually complementary. The decline in IC may reflect deficits in functional reserves, predisposing frail older adults to increased vulnerability [11]. Thus, understanding the relationships be-tween IC and frailty can facilitate functional maintenance and prevent adverse health out-comes.

Previous studies have explored IC domain's association with frailty in cross sectional [12,13] and longitudinal studies [14]. An area requiring more investigation is that the 5 domains do not appear to be operating at the same level in determining one's total intrinsic capacity [15]. Thus, finding each domain's individual effects whilst controlling for other domains deems necessary. To put this into context, vitality seems to contribute to the other 4 domains in addition to its independent effects on intrinsic capacity. Thus, a possible conceptual framework was hypothesized as cognitive, psychological, locomotor, sensory being overt expressions of underlying biological reserves as represented by vitality [15]. To complicate things even further, the domains affect each other as well. For instance, research has shown cognitive influence on gait (locomotion domain) [16]. Thus, it is possible that the domains are interrelated and exert their effects at different levels.

To date, González-Bautista et al. has performed Cox's proportional hazards models including 6 domains (sensory domain was split into hearing and vision domains) simultaneously to detect the strongest predictors that estimate hazard ratios for frailty [12]. However, since the study was a secondary analysis, their inclusion criteria were more stringent, affecting generalizability. Their measurements of each domain were also less comprehensive as their objective was to evaluate a screening tool [8]. For example, for the vitality domain, only self-reported weight loss or appetite loss were evaluated, however, muscle mass, nutritional assessments were not accounted for. Thus, more work is needed in this area.

To explore this gap, our primary aim is to first investigate the independent association of vitality with baseline frailty status in community dwelling older adults by putting all 5 IC domains in one model. Vitality was chosen as the primary domain since studies have suggested it as the major driver of IC [17]. Subsequently, we aim to investigate the in-dependent associations of the remaining 4 domains- locomotion, cognition, psychological, sensory domains with baseline frailty status in community dwelling older adults. Finally, we aim to develop a Weighted Composite IC score that considers the differential contributions of each domain to frailty and to test its association with frailty status, frailty progression and health-related outcomes of frailty. As current research has been calculating composite (total) IC scores without considering the difference in contributions from each domain [14,18,19], we will offer a way to calculate a Weighted Composite IC score to account for the different weightages of each domain. Overall, we aim to understand functional and biological reserves in managing frailty and to facilitate healthy aging.

Materials and Methods

Participants and Setting

Data is from IPPT-S (Individual Physical Proficiency Test for Seniors), a community-based mobile frailty and fitness screening platform in north-eastern Singapore. The geriatric screening includes multi-domain surveys with physical fitness assessments and follow-ups annually. Inclusion criteria were age >50 years old, community dwelling, able to ambulate independently (with or without walking aid) [20,21]. We excluded residents of nursing or sheltered homes, and those unable to ambulate for at least 4 meters independently [20,21].

All physical tests were assessed and measured on-site by the observers/researchers. Baseline questionnaires were gathered via face-to-face (at baseline) or phone (at 1 year follow-up) interviews. The use of telephone interviews for follow-up was necessary owing to physical restrictions imposed during the Covid-19 pandemic. All participants gave written informed consent, which included provision for publication of anonymized data. Study was approved on 16/04/2018 by Sing Health Institution-al Review Board (2018/2115).

Measures

Intrinsic Capacity

Each domain was measured by evidence-based and widely used IC metrics as stated below, then given a score of 0, 1, or 2 [14,22]. A score of 0 or 1 was defined as deficit in the respective domain [14].

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i. **Vitality:** Vitality was assessed by nutritional status and appendicular skeletal mass index (SMI). The Mini Nutritional-Short Form (MNA-SF) has a range of 0-14; a score of <8 suggests malnutrition, 8-11 as at-risk of malnutrition, and 12-14 as normal nutrition [23,24]. SMI was calculated as sum of fat-free lean mass of 4 limbs divided by height-squared, values attained by multi-frequency segmental Bioelectrical Impedance Analysis (BIA, MC-780, TANITA, Tokyo, Japan). In accordance to Asian Working Group for Sarcopenia 2019, low muscle mass was defined as <7.0kg/m^2 for men and <5.7kg/m^2 for women [25]. A score of 2 was assigned to those with normal nutritional status and muscle mass; 1 for either at-risk of malnutrition/malnourished or low muscle mass; 0 for at-risk of malnutrition/malnourished and low muscle mass.

ii. **Locomotion:** Locomotion was assessed by the Short Physical Performance Battery (SPPB) and 6 Minute Walk Test(6MWT). The SPPB includes 3 physical tests: chair-stand, balance, gait speed (4 meter walk) [26-28]. Each test was assigned a score and the sum reflects the total SPPB score (range 0-12). A score of less than 9 on SPPB was considered impaired performance as defined by Asian Working Group for Sarcopenia (AWGS) 2019 consensus [25]. The 6MWT measures the maximum distance that a person can walk in 6 minutes, mainly assessing one's maximal exercise endurance [29]. A total distance walked <400m was considered impaired performance [30,31]. A score of 2 was assigned if both SPPB and 6 MWT were unimpaired; 1 if there was impairment in either SPPB or 6 MWT; 0 if there was impairment in both SPPB and 6 MWT [14].

iii. **Cognitive:** Cognitive capacity was assessed based on the modified Chinese version of the Mini Mental State Examination (C-MMSE) and subjective report. On C-MMSE, locally-validated age- and education-adjusted cut-offs were used to indicate impaired performance - 21 and 24 for <6 and >6 years in those < 75 years old, and 19 and 23 for <6 and >6 years of education in > 75 years old [32]. Participants were also asked "Do you feel you have more problems with memory than most?" and answered with a "yes" or "no" response. This question was extracted from the short form Geriatric Depression Scale (GDS) to assess subjective memory issues [33]. A score of 2 was assigned to those without reported subjective memory problems and unimpaired C-MMSE; 1 if reported subjective memory problems but without impaired C-MMSE; 0 if reported subjective memory problems and impaired C-MMSE.

iv. **Sensory:** Participants answered 2 questions, whether they had "problems due to hearing" and "problems due to poor vision" [34-36]. A score of 0 was assigned to those with both, 1 for either, and 2 for no visual and hearing problems.

v. **Psychological:** The psychological domain was assessed by the short form Geriatric Depression Scale (GDS) and a question from EuroQol-5 Dimensions (EQ-5D). On the 15-item GDS, a score ≥5 indicates depression [33]. The question from EQ-5D screens for anxiety/depression, ranging from "I am not anxious or depressed" with a score of 0 to "I am extremely anxious or depressed" with a score of 4 [36]. A score of 0 was assigned to those with GDS-15>5; 1 for EQ-5D anxiety/depression>1 but GDS-15<5; 2 for GDS<5 and EQ-5D anxiety/depression=0.

Frailty

Frailty status was assessed via the modified Fried Phenotype, which includes 5 com-ponents: exhaustion, slow gait speed, weak grip strength, low body mass index (BMI<18.5kg/m^2), low physical activity. Those who met at least 3 of these criteria were de-fined as frail; those who met 1-2 criteria were defined as pre-frail, and those who met no criteria were defined as robust [37].

Exhaustion was assessed by the Centre for Epidemiological Studies-Depression Scale that asked how often participants felt the statements "everything I did was an effort" and "I could not get going" were applicable in the past week on a 4-point Likert Scale. An affirmative answer for either or both questions deemed exhaustion [38]. The grip strength was measured by a JAMAR hand dynamometer, with 2 trials for each hand, and the maximum value of 4 trials was recorded. Weak grip strength was defined as <18kg for women and <28 kg for men, in accordance with Asian Working Group for Sarcopenia 2019 [25]. Gait speed was assessed using 10-meter walk at usual pace, with a 2-meter acceleration and deceleration zone. Slow gait speed was defined as <1.0 m/s [25]. Physical activity was reported using the Physical Activity Vital Sign (PAVS) that quantifies time spent on physical exercise and activities [39]. Values below the lowest quartile of time was defined as physical inactivity. Frailty progression was defined as either robust to prefrail or frail, prefrail to frail, or remaining frail on 1-year follow-up [14].

Health Outcomes

Health outcomes were self-reported on a standardized questionnaire given at base-line and at every follow-up visit [34,35].

Other Covariates

Standardized questionnaires were also administered to obtain sociodemographic da-ta including education, financial adequacy, comorbidities, and social support [34,35]. Social vulnerability was defined as either reporting financial inadequacy or lacking social support [14]. Financial inadequacy was deemed if participants reported inadequate financial resources to pay for expenses [14]. Lacking social support includes participants who do not maintain social contact with friends or relatives and lack confidant [14].

Statistical Analysis

Out of 743 eligible participants, 301 were pre-frail and 39 were frail at baseline. Our primary objective was to find independent associations of the 5 Intrinsic Capacity (IC) do-mains for "frail/pre-frail" vs. "robust" groups. This was a secondary

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analysis of data from the IPPT-S cohort, and was thus not guided by a prior sample size calculation. However, we adhered to recommendations on having at least 10 events per predictor variable (EPV) in multivariable logistic regression models [40-43]. We had 9 clinically meaningful variables to account for in the multivariable model and hence we needed at least 9*10 = 90 pre-frail/frail patients in the data. In our data, prevalence of "pre-frail/frail" group was 340 participants. All socio-demographics and frailty related data was presented based on baseline and 1 year frailty status. Continuous and categorical variables were summarized as mean (standard deviation) [range] and frequency (percentage) respectively.

Preliminary analysis with Analysis of Variance (ANOVA) and chi-square were done to investigate possible associations between the demographic factors (age, sex, social vulnerability, comorbidities) and the 3 different baseline frailty status groups. Subsequently, univariate logistic regressions of Frail/Prefrail against Robust at baseline were done to investigate possible associations between age, sex, social vulnerability, comorbidities and frailty status. Quantitative association was expressed as OR with 95% confidence interval (95%CI).

To explore associations between each of the IC domains and baseline frailty status, multivariable logistic regressions were performed, each adjusted for other IC domains, age, sex, social vulnerability, comorbidities. Model was fit for binary outcomes Prefrail plus Frail as an outcome group with reference to Robust. Subsequently, ordinal logistic regression of the 5 IC domains with baseline frailty status represented by Robust, Prefrail, and Frail, was performed to obtain the beta-coefficients used to generate the Weighted Compo-site IC Score.

This score was then calculated for all participants. The discriminant capability of this weighted score model on baseline frailty status (frail vs. robust and prefrail vs. robust), 1 year frailty progression, frailty-related health outcomes such as falls and hospitalization were verified through Receiving Operating Characteristic (ROC) analysis. A cumulative ROC analysis was also used to test the discriminant capability of the weighted score model in differentiating robust vs. prefrail vs. frail status [44].

All tests were two sided and P<0.05 was considered statistically significant for all tests. Analysis was conducted using IBM SPSS Version 26.

Results

Sample Characteristics

Seven hundred and forty-three (743) participants completed all baseline evaluations for IC and frailty. Owing to the COVID-19 pandemic, participant follow-up was disrupted. 481 (65.1%) participants were contacted via telephone for questionnaire administration at 1-year follow-up, of whom only 170 had complete on-site physical fitness assessments and were included in the analysis for frailty progression.

The cohort of 743 is predominantly female with mean age of 67.4 (6.8) years old, mostly of Chinese ethnicity (87.3%). Baseline Fried frailty status was mostly robust (54.2%), followed by prefrail (40.5%) then frail (5.2%) (Table 1). Out of the socio-demographic variables listed in Table 1, significant differences (p<0.05) were present in age, sex, social vulnerability, comorbidities across the 3 different baseline frailty status groups. There were also significant associations (p<0.05) of these factors with frailty status when comparing between Frail/Prefrail and Robust groups. There was no significant difference in age and sex, but there was a difference in base-line frailty status between those that completed follow-up versus those who did not, with less than expected follow-ups from those who were frail, prefrail and more from those who were robust, p =0.003.

Table 1: Socio-Demographics and Frailty Status at Baseline.

Socio-demographics	Overall Cohort (N=743)	Frailty Status			p-value†††
		Robust: 403 (54.2%)	Prefrail 301 (40.5%)	Frail 39 (5.2%)	
Age	67.4 (6.8) [51-100]	65.9 (6.1) [53-84]	68.8 (7.1) [51-100]	72.0 (7.2) [55-86]	<0.001
Sex (Female), n (%)	562 (75.6)	327 (81.1)	217 (72.1)	18 (46.2)	<0.001
Ethnicity, n (%)					
Chinese	649 (87.3)	357 (88.6)	260 (86.4)	32 (82.1)	0.615
Indian	27 (3.6)	14 (3.5)	14 (4.7)	1 (2.6)	
Malay	58 (7.8)	31 (7.7)	25 (8.3)	6 (15.4)	
Others	9 (1.2)	1 (0.2)	2 (0.7)	0 (0.0)	
Socially Vulnerable†, n(%)	219 (29.5)	106 (26.3)	97 (32.3)	16 (41.0)	0.049
Number of Comorbidities††	1.02 (1.0) [0-5]	0.86 (1.0) [0-4]	1.16 (1.1) [0-5]	1.59 (1.2) [0-5]	<0.001

†Socially Vulnerable defined as either lacking confidant, social isolation, insufficient expenses.

††Represented as Mean (Standard Deviation) [Range].

†††P-values from Analysis of Variance (ANOVA) and chi-square analysis of sociodemographic fac-tors across different frailty groups.

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Independent Association of Intrinsic Capacity Domains with Baseline Frailty Status in Community Dwelling Older Adults

Whilst controlling for the other Intrinsic Capacity domains, age, sex, social vulnerabilities, comorbidities, older adults with deficits in the vitality domain were 3.31 times [aOR (adjusted Odds Ratio)=3.31, 95% CI 2.21-4.97, p<0.001] more likely to be prefrail/frail, as compared to those with no deficits in vitality. Furthermore, those with deficits in the locomotion domain were 4.79 (95% CI 2.90-7.89, p<0.001) times more likely to be prefrail/frail, as compared to those with no deficits in locomotion. Sensory (aOR=1.23, 95% CI 0.86-1.77, p=0.252), psychological (aOR=1.27, 95% CI 0.83-1.96, p=0.275), and cognitive domains (aOR=1.24, 95% CI 0.87-1.77, p=0.237) were not significantly associated with prefrailty/frailty (Table 2). In terms of sociodemographic covariates, females (aOR=0.557, 95% CI 0.377-0.821, p=0.003) were less likely, and older participants (aOR=1.04, 95% CI 1.01-1.06, p=0.01) were more likely to be prefrail/frail.

Table 2: Binary Logistic Regression of Frailty Status at Baseline with the 5 IC Domains.

Intrinsic Capacity Domain	Adjusted Odds Ratio (aOR)	95% CI	P Value
Vitality	3.31	2.21-4.97	<0.001
Locomotion	4.79	2.90-7.89	<0.001
Sensory	1.23	0.86-1.77	0.252
Psychology	1.27	0.83-1.96	0.275
Cognition	1.24	0.87-1.77	0.237

Model is fit for Prefrail and Frail with reference group Robust; Adjusted for the other 4.

Intrinsic Capacity Domains, age, gender, social vulnerabilities, comorbidities. CI: Confidence Interval.

A Weighted Composite IC Score and Its Performance in Identifying Baseline Frailty Status

Adjusted OR of vitality (aOR=3.19, 95% CI 2.22-4.57, p<0.001), locomotion (aOR=7.85, 95% CI 5.14-12.00, p<0.001), sensory (aOR=1.40, 95% CI 1.01-1.94, p=0.044) indicate the significantly increased risk of frailty if these domains were in deficit. In addition, standardized Beta-coefficients of 1.16, 2.06, 0.34, 0.37, 0.25 were obtained for vitality, locomotion, sensory, psychology, cognition, respectively, and intercept as -3.17 (Table 3). As a result, we derived this equation: Weighted Composite IC Score =-3.17+1.16xVitality+2.06xLocomotion+0.34xSensory+0.25xCognition+0.37xPsychological, with a score of 1 given to domains with no deficits in the respective domain and 0 given to those with deficits. The sample's Weighted Composite IC Score has a mean of 0.11 (1.04) and range of -3.17 to 1.01.

Table 3: Ordinal Logistic Regression of 5 IC Domains with Baseline Frailty Status.

Intrinsic Capacity Domain	Beta-Coefficient	Adjusted Odds Ratio	95% CI	P Value
Intercept (SE)	-3.17 (0.30)			
Vitality	1.16	3.19	2.22-4.57	<0.001
Locomotion	2.06	7.85	5.14-12.00	<0.001
Sensory	0.34	1.4	1.01-1.94	0.044
Psychology	0.37	1.45	0.99-2.13	0.059
Cognition	0.25	1.28	0.92-1.78	0.138

Note: Ordinal logistic regression is modelled for Frail. Variable is coded as Robust, Prefrail and Frail. SE: Standard error. CI: Confidence Interval.

The discriminant capability of this weighted score model was tested with ROC analysis performed for the following pairs of frailty status: frail vs. robust and prefrail vs. robust. In comparing frail vs. robust, Area Under Curve (AUC) of the weighted Composite IC was 0.87 (95% CI 0.82-0.93). Weighted Composite IC scores less than or equal to -0.40 as the optimal cut-off of "frail" status determined by ROC shows sensitivity of 89.7% (75.8%-97.1%), specificity of 85.1% (81.3% to 88.4%), Positive Predictive Value (PPV) of 36.8% (31.1% to 43.0 %) and Negative Predictive Value (NPV) of 98.9% (97.13% to 99.54%) (Table 4).

When comparing prefrail vs. robust, Area Under Curve (AUC) of the weighted Composite IC was 0.65 (95% CI 0.62-0.69). Weighted Composite IC scores greater than 0.30 as cut-off of "Robust" status determined by ROC revealed sensitivity of 54.5% (48.7% to 60.2%), specificity of 76.43% (72.0% to 80.5%), NPV of 69.2% (66.3% to 72.0%), and PPV of 63.3% (58.47% to 67.9%)

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(Table 4). Using a cumulative receiver operator characteristic (ROC) curve analysis [44] to differentiate robust vs. prefrail vs. frail, Area Under Curve (AUC) of the weighted Compo-site IC was 0.72. Weighted Composite IC scores robust, prefrail and frail were >0.30, -0.40 to 0.30, and <-0.40 respectively (Table 4).

Weighted Composite IC Score's Performance in Predicting Frailty Progression, Falls, and Hospitalization at 1 Year

Of the 743 participants, 170 had complete 5 IC domains and Fried Frailty phenotype data at follow-up, of which, 81.2% were non-progressors and 18.2% were progressors in frailty status (Table 5). The discriminant capability of this weighted score model for frailty progression and frailty-related health outcomes at 1 year were also tested with ROC analysis. Weighted Composite IC Score had an AUC of 0.66 (95% CI 0.54-0.78) in differentiating frailty progressors from non-progressors, 0.59 (95% CI 0.48-0.70) in prediction of hospitalization, and 0.53 (95% CI 0.38-0.69) in falls prediction (Table 6).

Table 4: ROC for Baseline Weighted Composite IC Score against Baseline Frailty Status.

Statistic	Value	95% CI
Comparing Frail vs. Robust		
Sensitivity	89.70%	75.8% to 97.1%
Specificity	85.10%	81.3% to 88.4%
Positive Likelihood Ratio	6.03	4.66 to 7.79
Negative Likelihood Ratio	0.12	0.05 to 0.31
Disease prevalence (*)	8.80%	6.4% to 11.9%
Positive Predictive Value (*)	36.80%	31.1% to 43.0%
Negative Predictive Value (*)	98.90%	97.1% to 99.5%
Accuracy (*)	85.50%	81.9% to 88.7%
AUC (95%CI)	0.87	0.82 to 0.93
Comparing Prefrail vs. Robust		
Sensitivity	54.50%	48.7% to 60.2%
Specificity	76.40%	72.0% to 80.5%
Positive Likelihood Ratio	2.31	1.89 to 2.83
Negative Likelihood Ratio	0.6	0.52 to 0.68
Disease prevalence (*)	42.80%	39.1% to 46.5%
Positive Predictive Value (*)	63.30%	58.5% to 67.9%
Negative Predictive Value (*)	69.20%	66.3% to 72.0%
Accuracy (*)	67.10%	63.4% to 70.5%
AUC (95%CI)	0.65	0.62 to 0.69

Table 5: Socio-demographics and Frailty Status of Non-Progressors and Progressors at 1 Year.

	Non-Progressors (n=139)	Progressors (n=31)
Frailty Status		
Baseline. n (%)	Robust: 86 (61.9)	Robust: 19 (61.3)
	Prefrail: 53 (38.1)	Prefrail: 10 (32.3)
	Frail: 0 (0)	Frail: 2 (6.5)
At 1 year, n (%)	Robust: 106 (76.3)	Prefrail: 26 (83.9)
	Prefrail: 33 (23.7)	Frail: 5 (16.1)
	Frail: 0 (0)	
Socio-demographics		
Sex (Female), n (%)	112 (80.6%)	23 (74.2%)
Age (years)*	66.2 (5.5) [54-80]	70.2 (6.6) [55-84]

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Ethnicity, n (%)	Chinese 120 (86.3)	Chinese 27 (87.1)
	Indian: 5 (3.6)	Indian: 1 (3.2)
	Malay: 12 (8.6)	Malay: 3 (9.7)
	Others: 2 (1.4)	Others: 0 (0)
Socially Vulnerable†, n(%)	36 (25.9%)	7 (22.6%)
Number of Comorbidities††	0.89 (1.0) [0-5]	1.03 (1.1) [0-5]

†Socially Vulnerable defined as either lacking confidant, social isolation, insufficient expenses; ††Represented as Mean (Standard Deviation) [Range]. *p<0.05.

Table 6: Area Under the Curve for Baseline Weighted Composite IC Score against Frailty Progression and Frailty Outcomes at 1 Year.

Outcomes	AUC	95% Confidence Interval
Frailty Progression	0.66	0.54 - 0.78
Hospitalizations	0.59	0.48 - 0.70
Falls	0.53	0.38-0.69

Discussion

Our findings are consistent with a previous study that inspired this project. Previous-ly, Tay et al. noted significant associations between each of locomotion, vitality, and psychological domains with baseline frailty status and frailty progression [14]. Cognition was only associated with frailty progression whilst sensory was not significantly associated with neither frailty status nor progression [14]. These results demonstrate differential contributions of the domains to frailty when separate logistic regressions were ran [14]. As it has been hypothesized that 5 domains operate at different levels with tight interdependencies between them [17], our study accounted for these relations by placing all domains in the same logistic regression model to control for these interdependencies and complementary relations, showing that with all other domains controlled, vitality and locomotion were significantly associated with frailty status, suggesting that perhaps the other do-mains may be acting secondarily in influencing frailty.

The significant findings are consistent with a hypothesized frailty syndrome frame-work that ties vitality and locomotion: poor muscle strength and sarcopenia limits mobility, thus disrupts balance between energy expenditure and nutritional intake, leading to further weight loss, disability, adverse health outcomes [37,45]. In an investigation of the impact of different combinations of IC domains on frailty risk, preserved capacity in loco-motion and vitality conferred the lowest risk for incident frailty [46]. Thus, programs that optimize IC with particular emphasis on nutrition and exercise can be recommended for the prevention of frailty.

Interestingly, locomotion had the greatest association between IC domains and frailty status. This differs from previous hypothesis of vitality as the major driver of IC, with previous path analysis studies showing the 4 remaining domains as "expressed capacities" of vitality, with indirect effects of vitality through the remaining domains in determining activities of daily living (ADLs)/instrumental activities of daily living (IADLs) as outcomes [17,47]. This discrepancy was not surprising, considering that the modified Fried Phenotype Criteria, which includes exhaustion, slow gait speed, weak grip strength, low body mass index (BMI<18.5kg/m^2), low physical activity, although widely used in the field of frailty, places great emphasis on physical fitness, mobility, and activity. Although we tried to circumvent this issue by avoiding the use of gait speed in locomotion measurement, and instead used the 6 Minute Walk Test which focuses on endurance [30,31], and the Short Physical Performance Battery (SPPB) which measures lower extremity physical function [27,48], it is still likely that there are some overlaps in measurement between these widely used metrics in locomotion and frailty, creating a stronger association statistically. Thus, future research using multidimensional frailty scales, such as the Frailty Index [49], and Clinical Frailty Scale (CFS) [49], may be considered to clarify the key determinant among the IC domains in influencing frailty status. Tay et al. previously showed significant associations between the psychological do-main and baseline frailty status and progression; and cognition with frailty progression [14], whereas our study showed no significant associations between the two domains and frailty. These inconsistencies are possibly due to a difference in analysis approach: previous, study examined individual domains in isolation, whereas we placed all domains in one model for the current study, leading to inadvertent adjustments of potential mediators. For example, it is known that sensory loss contributes to cognitive decline and depression, both risk factors of frailty, and shown as significant in our study [50,51].

In addition, cognitive decline and the development of frailty share biological risk factors representing vitality [52]. Relationships like these are modulated in our model, perhaps biasing the effect of domains towards null, consistent with what we would expect if the domains were interdependent. In illustration, earlier studies also yielded contradictory findings between individual domains on frailty status. While vitality was

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most strongly associated with incident frailty in a Chinese cohort [46], vitality (along with cognitive and sensory decline) was not a significant predictor of frailty status [12] despite the risk conferred by cumulative IC conditions. Future work can utilize approaches such as directed acyclic graphs to further develop causal models depicting relationships between IC domains, mediators, and frailty.

Although domains differentially modulate frailty, the complex dependencies between the 5 domains makes it unrealistic to consider each domain separately. Rather, IC should be viewed holistically as a composite of physical and mental reserves, indicating the multidimensional capacities of an individual. This is also consistent with the theory of ageing, in which IC is regarded as a determinant of physical resilience and an integrative indicator of one's physiological reserves and ability to withstand stressors [53]. Declines in IC is comparable to the disintegration and diminishing biological and physiological mechanisms as seen in the context of frailty [46,54]. Thus, the IC construct and its constituents provide a powerful tool to study and monitor frailty. The Weighted Composite IC Score in this study considers the differential contributions from each domain. We showed that this developed score had good discriminant ability especially in the identification of established frailty status, albeit poorer for prefrailty. By understanding each IC domain's underlying weightages and their reflection to a global measure score, our score can identify certain domains for personalized interventions and provide a metric for monitoring one's global reserves.

Previous studies have demonstrated associations between IC with frailty progression and frailty-related outcomes such as hospitalizations and falls [14,55,56]. However, our Weighted Composite IC Score did not adequately predict these outcomes at 1 year of follow-up, although it did predict frailty progression (AUC 0.66) and hospitalizations (AUC 0.59) at 1 year better than the pre-existing methods [14] of simple additive score (AUC 0.65, AUC 0.57 respectively). Further work with different samples and health outcomes is re-quired to validate this score to determine its application in clinical and research settings. A valid predictor Weighted IC Composite Score would be deemed useful in more accurately monitoring the multi-domain reserves and trajectories in older adults.

Strengths and Limitations

Main strengths of this study include delineating the differential contributions from each domain whilst considering IC as a wholistic concept consisting of interdependent factors. Furthermore, we proposed a way to calculate a Weighted Composite score; further work in validating this can provide a powerful tool in quantifying and monitoring IC in clinical and research settings.

We acknowledge some limitations in this study. Firstly, methodological biases eg. selection biases are prominent as our sample is mostly women (76%) and Asian (87%). We recognize that this limits our observations and thus generalizability of our results to Asian settings, specifically to female cohorts. Although we did adjust for sex when determining the independent associations of each IC domain with frailty status at baseline, it was not adjusted in subsequent analyses due to concerns of overfitting.

Secondly, the proposed Weighted Composite IC score serves as a good starting point in conceptualizing how one's global reserves reflect frailty status. Although it has been shown to reflect one's frailty status adequately and one's frailty progression and hospitalizations at 1 year better than existing methods [14], there are still some limitations and space for future work. In particular, our sample size of 743 with smaller number of frail events (n=39) are not robust for running ordinal logistic regression and developing a representative Weighted Composite IC Score [57,58]. In addition, due to COVID-19 re-strictions, our response rate at 1 year follow-up was 22.8%, meaning that 77.2% of our initial participants, especially those who were prefrail and frail to begin with, were lost to follow-up. We recognize that the lack of sufficient longitudinal data to test the Weighted Composite IC Score limits our ability to draw conclusions to its ability in predicting frailty progression, falls and hospitalization. Thus, future work with bigger cohorts with longitudinal data available would be necessary to test its applicability. Furthermore, a vast amount of clinical data would need to be collected to calculate the score. Although possible in research settings, its applicability in daily clinical practice is limited. In the clinical realm, perhaps the score would be most useful as a monitoring tool that works in conjunction with community-based measurement stations like IPPT-S available. Trajectories of the scores after measurements can then be monitored by physicians and allied health members to facilitate healthy ageing. Nevertheless, we recognize that there are still major gaps for future research in creating, validating, and applying such a score that could potentially be powerful in reflecting one's reserves and deficits.

Thirdly, measurements of IC domains have always been debatable across studies due to the wide array of sub-domains that constitute each domain and lack of consensus in selecting representative subdomains and their measurements. Although we have chosen tests and cut-off's that are widely used and validated [22,59,60], it's possible that we could have excluded certain metrics. Particularly, vitality and locomotion are domains that are conceptually complex and difficult to measure, sparking much debate in their operationalization [29,61]. Vitality is usually understood as one's underlying physiologic reserves and the capacity to maintain homeostasis with balance of energy intake and expenditure [5,62]. WHO's initial work of the Integrated Care for Older People (ICOPE) program recommended nutrition as a

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primary indicator that could be measured by assessments such as mini-nutritional assessment [8]. Then, measures for physiological reserves and biological age such as the handgrip strength and biomarkers related to biomolecular mechanisms of ageing were used in studies [22,47]. Recently, a supplement from Age and Ageing summarizing the landscape of IC measurements stated fatiguability as the primary indicator because it is feasible to quantify, measure, and reflects energy and metabolism [61]. We ended up choosing nutrition as it was suggested by WHO's ICOPE programme as vitality's primary indicator and its influence in the biology of aging that alters energy metabolism and homeostasis [8,47]. We employed anthropometrics due to its role as vitality indicator in multiple studies and their ability to reflect one's underlying energy and metabolism [22,60,63]. We excluded fatiguability because it is overlapping with our exhaustion measures of our outcome variable frailty.

Locomotion is also a challenging domain to define as it encompasses muscle strength, power, function, and balance, with a variety of assessments that measures each attribute [29,64]. In our study, we utilized SPPB consisting of sit to stand, balance, gait speed, often used fully or partially in studies to measure multiple attributes of locomotion [22,29]. For endurance, we utilized 6MWT as it is the only tool identified in the supplement review with validity and reliability [29]. Although systematic reviews also included other tests such as Timed Up and Go (TUG), Balance Evaluation Systems Test (BESTest), our measures represent different components of the locomotion domain whilst minimizing the overlap between these measures and frailty metrics [29]. As there are many tools available with no definite consensus of a set of superior measures for each domain, the pro-posed weightages and equation for Weighted Composite IC Score are likely only applicable if the domains are measured by the respective tools used in our study.

Lastly, instead of objective observational metrics, face-to-face or phone interview administration of standardized questionnaires were used to obtain certain information. Specifically, social vulnerability was defined by self-reported financial inadequacy in paying for expenses or lacking social support. Health outcomes such as presence/absence of falls and hospitalization in the past year were also self-reported retrospectively. We recognize that answers gathered in such manner could be quite subjective and open to recall bias, thus posing as limitations of the study.

Conclusion

In conclusion, IC deficits in older adults can precede frailty and its adverse outcomes. Whilst controlling for potential interactions between the 5 domains, this study explored the associations of each IC domain with frailty. Monitoring and interventions targeted towards nutrition, body composition, mobility, physical training should be prioritized to protect against frailty and its progression. Furthermore, we proposed a Weighted Composite IC Score that is associated with one's global reserves to facilitate healthy ageing, in-spiring our future efforts in validation and application.

Author Contributions

Conceptualization, Isabelle Chiao Han Sung, Yee-Sien Ng and Laura Tay; Methodology, Isabelle Chiao Han Sung, Rehena Sultana, Yee-Sien Ng and Laura Tay; Software, Rehena Sultana; Formal analysis, Isabelle Chiao Han Sung and Rehena Sultana; Investigation, Isa-belle Chiao Han Sung, Yee-Sien Ng, Ee-Ling Tay, Shi Min Mah and Laura Tay; Resources, Yee-Sien Ng and Laura Tay; Data curation, Yee-Sien Ng, Ee-Ling Tay, Shi Min Mah and Laura Tay; Writing – original draft, Isabelle Chiao Han Sung; Writing – review & editing, Isabelle Chiao Han Sung, Re-hena Sultana, Yee-Sien Ng, Ee-Ling Tay, Shi Min Mah and Laura Tay; Supervision, Yee-Sien Ng and Laura Tay; Project administration, Yee-Sien Ng and Laura Tay; Funding acquisition, Yee-Sien Ng and Laura Tay.

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Ethical Standards

Study was approved on 16/04/2018 by Sing Health Institutional Review Board (2018/2115). All participants provided written informed consent prior to recruitment.

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