

The Impact of Intrinsic Capacity on Adverse Outcomes in Older Hospitalized Patients: A One-Year Follow-Up Study

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Keywords

Older · Hospitalized patients · Intrinsic capacity · Disability · Mortality

Abstract

Background: Intrinsic capacity (IC) is a novel view focusing on healthy aging. The effect of IC on adverse outcomes in older hospitalized Chinese adults is rarely studied. **Objectives:** This study focused on investigating the impact of IC domains on the adverse health outcomes including new activities of daily living (ADL) dependency, new instrumental activities of daily living (IADL) dependency, and mortality over a 1-year follow-up. **Methods:** In a retrospective observational population-based study, a total of 329 older hospitalized patients from Zhejiang Hospital in China were enrolled and completed 1-year follow-up. The 5 domains of IC including cognition, locomotion, sensory, vitality, and psychological capacity were assessed at admission. The IC composite score was calculated based on these domains, and the higher IC composite score indicated the greater amount of functional capacities reserved. Multivariate logistic regression models were used to explore the association between

IC at baseline and 1-year adverse outcomes. **Results:** During the 1-year follow-up, 69 patients (22.5%) experienced new ADL dependency, 103 patients (33.6%) suffered from new IADL dependency, and 22 patients (6.7%) died. After adjusting for age, sex, education level, comorbidities, and polypharmacy, low Mini-Mental State Examination (MMSE) scores at admission predicted 1-year new ADL dependency (odds ratio [OR] = 2.31, 95% confidence interval [CI]: 1.12–4.78) and new IADL dependency (OR = 2.15, 95% CI: 1.14–4.04) among older hospitalized patients, but no significance was obtained between IC domains and mortality. Higher IC composite score at admission was associated with decreased risks of 1-year new ADL dependency (OR = 0.53, 95% CI: 0.40–0.70) and new IADL dependency (OR = 0.76, 95% CI: 0.61–0.95), and 1-year mortality (OR = 0.48, 95% CI: 0.31–0.74) after adjustment for the possible confounders. **Conclusions:** Loss of ICs at admission predicted adverse health outcomes including new ADL and IADL dependency and mortality 1 year after discharge among older hospitalized patients.

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Introduction

The estimated proportion of older population in China is expected to exceed >one-third of the total population by 2050 [1]. The great risks for older individuals accompanied by chronic diseases, polypharmacy, and age-related disability result in greater healthcare expenditure and increased caregiving burden arise [2, 3]. In this context, the World Health Organization (WHO) proposed the concept of healthy aging emphasizing on fostering and maintaining functional ability as a lifelong pursuit of their age [4, 5]. Functional ability not only depends on intrinsic capacity (IC), which is a composite of physical and mental capacities of an individual, but also depends on their environment and the interactions between them [6]. IC included 5 key domains: cognition, locomotion, sensory, vitality, and psychological capacity, which have been proven to be the most influential on the individuals' health status and health trajectory [7, 8]. In previous studies, each separate IC component has been reported to associate with adverse outcomes, including functional dependence, falls, and mortality in community-dwelling older adults [9–13]. And recently, a few studies have focused on these components together as IC composite concept in community-dwelling and nursing home older residents [14, 15]. The Healthy Older People Everyday (HOPE) study comprising 1,051 community-dwelling older adults revealed a combined effect of vision impairment, multimorbidity, and frailty on IC [14]. Another cohort study among Belgian nursing home residents showed that poor nutrition status and low balance performance, which composed of 2 domains of IC, predicted the incidence of 3-year mortality, and poor nutrition status also predicted 3-year autonomy decline [15]. To our best knowledge, no study addressed the effect of IC on adverse outcomes in older hospitalized Chinese adults who were discharged 1 year.

Hospitalization is a major cause of long-term disability in older adults that lasts for over 6 months [16–19]. Studies have shown that incidence of new-onset disability related to hospitalization ranged from 5 to 50% [20–22], which was closely linked to higher healthcare utilization [23], institutionalization [24, 25], and mortality [22, 26, 27]. In addition, older patients are particularly vulnerable and often experienced various losses of functional capacities even after discharge from hospital, increasing risks of poor post-discharge outcomes [28]. Such projections require early identifying loss of IC at admission, and integrated care models can be implemented to guide amenable strategies that can be taken to prevent and reverse

functional deterioration, thereby reducing care dependency and even the incidence of adverse health events. Therefore, this current study aimed to investigate the predictive value of IC domains and IC composite score at admission on new activities of daily living (ADL) and instrumental activities of daily living (IADL) dependence and mortality over 1-year follow-up in older hospitalized Chinese adults.

Methods

Participants

This is a retrospective observational population-based study of comprehensive geriatric assessment (CGA) for elderly inpatients in Zhejiang Hospital in China. A total of 532 potential participants were recruited from October 2014 to July 2018, and the 1-year follow-up ended in July 2019. The inclusion criteria were as follows: age ≥ 60 years, being mobile with or without walking aids, and ability to understand and communicate with the others. The exclusion criteria in the study were as follows: hospitalized in long-term care, unable to finish 1-year follow-up, and main data incomplete. This study was approved by the Medical Ethics Committee of Zhejiang Hospital (2013–25), and written informed consent was obtained from each participant.

Baseline Assessment

At baseline, demographic characteristics including age, sex, marital status (coded as married, divorce, widow, or single), level of education (categorized by high school level or below), and BMI (kg/m^2) were recorded. Physician-diagnosed chronic diseases were recorded based on the International Classification of Diseases, Tenth Revision (ICD-10) codes. Five chronic diseases or more in 1 person was considered to be comorbidities [29]. Polypharmacy was defined as those who took 5 or more oral prescription medications daily [30].

IC Assessment

The 5 domains of IC were composed of cognition, locomotion, sensory, vitality, and psychological capacity. Cognition was assessed by the Chinese version of Mini-Mental State Examination (MMSE) [31], and the cutoff value was set ≤ 24 indicating cognitive decline. Locomotion was evaluated by the balance subscale of Tinetti Performance-Oriented Mobility Assessment (B-POMA) [32] and 4-m gait speed test. B-POMA scores ≤ 11 indicated poor balance performance [33]. The participants were asked to walk 4 m twice as usual starting from an inactive standing position (walking aids or cane allowed); and the shorter time was recorded. A gait speed < 1.0 m/s was defined as low physical performance based on recommendation by the Asian Working Group for Sarcopenia (AWGS) [34]. The sensory domain was self-reported hearing and vision status, which were categorized as good or bad. Vitality was measured by dominant handgrip strength and nutritional status using the Short-Form Mini Nutritional Assessment (MNA-SF) [8, 35, 36]. The participants underwent 3 tests using a hand dynamometer in kilograms, and the maximum was recorded for the final analysis. Low muscle strength by handgrip strength was defined as a grip strength < 28 kg for male participants and < 18 kg for

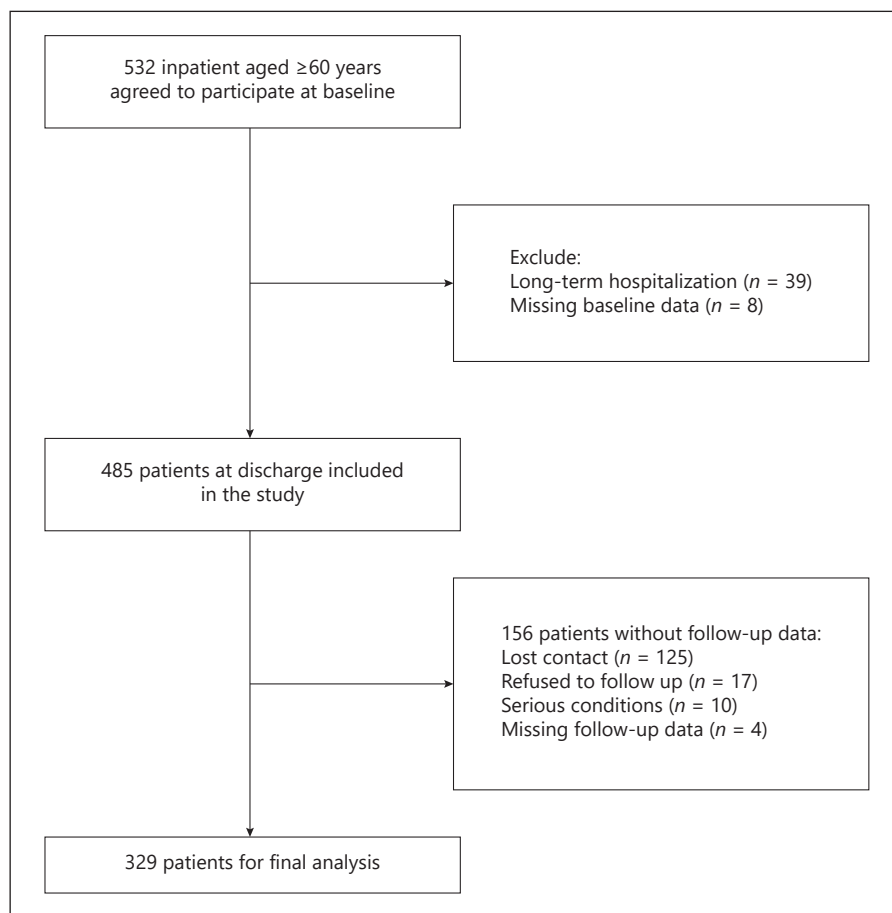


Fig. 1. Flowchart of patient selection.

female participants by AWGS recommendation [34]. The total MNA-SF score ranged from 0 to 14, and a score ≤ 11 indicated malnutrition risk. Psychological capacity was evaluated by assessing depressive symptoms using the 15-item Geriatric Depression Scale (GDS-15) [37]. The cutoff GDS-15 score ≥ 6 indicated worse psychological performance.

Any declines in each domain of IC was calculated as 0 and otherwise as 1. The total IC composite score summed the number of each normal domain and ranged from 0 to 5 in this study. The higher IC composite score indicated the greater amount of functional capacities reserved. All the assessments were implemented by qualified assessors.

Adverse Outcomes Assessment

ADL using the Barthel index [38] and IADL [39] were used to assess functional dependence; a decrease of at least 1 point in ADL during the follow-up was defined as new ADL dependency and so was new IADL dependency in this study. In addition, death was also recorded from the medical file. All the aforementioned adverse outcomes during the 1-year follow-up were recorded by face-to-face or telephone interviews.

Statistical Analysis

Data were analyzed using SPSS 18.0 software (SPSS, Chicago, IL, USA). Normally distributed continuous variables were present-

ed as means \pm standard deviations. Abnormally distributed continuous variables were presented as median and interquartile range, and categorical variables were expressed as numbers (percentages). Differences in the groups between baseline characteristics and IC domains were determined using the unpaired *t*-test; the χ^2 test; Fisher's exact test, if necessary; and the Mann-Whitney U-test, where appropriate. Furthermore, multivariate logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) were used to explore the effect of IC at baseline on 1-year adverse outcomes including new ADL and IADL dependency and mortality, when adjusting for age, sex, education level, comorbidities, and polypharmacy. A *p* value of <0.05 was defined as statistical significance.

Results

Enrollment and Total Sample Characteristics

Figure 1 presents the flowchart of patient selection. Among the included participants ($n = 329$), more than half of the participants were male aged ≥ 80 years. Comorbidities and polypharmacy were common in older adults, accounting for 66.3 and 53.2%, respectively.

Table 1. Characteristics of total sample

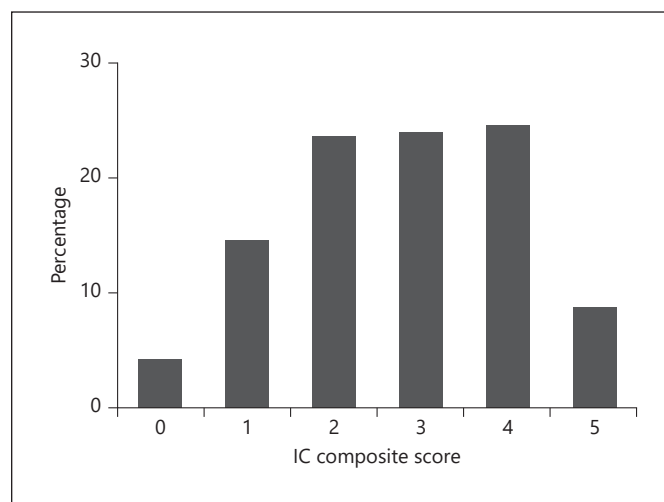
Variable	Total sample (n = 329)
Baseline characteristics, n (%)	
Age ≥80 years	175 (53.2)
Male	194 (59.0)
Married	254 (77.2)
High school or above	199 (60.5)
Comorbidities (≥5 diseases)	218 (66.3)
Polypharmacy (≥5 medications)	175 (53.2)
IC domains	
Cognition	
MMSE score ≤24, n (%)	102 (31.0)
Locomotion	
B-POMA score ≤11, n (%)	82 (24.9)
Gait speed <1.0 m/s, n (%)	192 (58.4)
Sensory	
Hearing impairment, n (%)	141 (42.9)
Vision impairment, n (%)	204 (62.0)
Vitality	
Handgrip strength <28 kg (male), 18 kg (female), n (%)	99 (30.1)
MNA-SF score ≤11, n (%)	107 (32.5)
Psychology	
GDS-15 score ≥6, n (%)	42 (12.8)
IC composite score, median (IQR)	3 (2–4)

IC, intrinsic capacity; MMSE, Mini-Mental State Examination; B-POMA, balance subscale of the Tinetti Performance-Oriented Mobility Assessment; MNA-SF, Short-Form Mini Nutritional Assessment; GDS-15, 15-item Geriatric Depression Scale; IQR, interquartile range.

The sensory and locomotion capacities declined more than psychological capacity in older hospitalized patients, and the characteristics of the total sample are further detailed in Table 1. The median IC composite score was 2 kinds of functional capacity losses. And the distribution of IC composite score is presented in Figure 2.

New ADL and IADL Dependency

Among the included patients, 69 patients (22.5%) experienced new ADL dependency and 103 patients (33.6%) suffered from new IADL dependency. As presented in Table 2, when comparing the main characteristics between older patients with new-onset ADL dependency and those without, we found that there were statistical differences in age, marital status, comorbidities, polypharmacy, MMSE scores, B-POMA scores, gait speed, vision impairment, handgrip strength, MNA-SF scores,

**Fig. 2.** Distribution of IC composite score. IC, intrinsic capacity.

GDS-15 scores, and IC composite scores (all $p < 0.05$). Older patients who experienced new-onset IADL dependency were older and had higher percentages of polypharmacy, lower MMSE scores, lower B-POMA scores, slower gait speed, worse handgrip strength, and lower IC composite scores (all $p < 0.05$), when compared with those who reserved IADL. Table 3 shows that low MMSE scores predicted 1-year new ADL dependency (OR = 2.31, 95% CI: 1.12–4.78) and new IADL dependency (OR = 2.15, 95% CI: 1.14–4.04) among older hospitalized patients after adjusting for the related potential confounders. Furthermore, we also found that the IC composite score was significantly associated with new ADL dependency (OR = 0.53, 95% CI: 0.40–0.70) and new IADL dependency (OR = 0.76, 95% CI: 0.61–0.95) (detailed in Table 4).

Mortality

Twenty-two patients (6.7%) died during the follow-up period. Table 2 shows that statistical differences between the deceased patients and the alive patients in age, MMSE scores, B-POMA scores, gait speed, handgrip strength, MNA-SF scores, and IC composite scores were obtained (all $p < 0.05$). The multivariate regression model is showed in Tables 3 and 4. No significant variables were associated with 1-year mortality ($p > 0.05$), but the IC composite score was significantly associated with 1-year mortality (OR = 0.48, 95% CI: 0.31–0.74) when adjusted the possible confounders.

Table 2. Comparing baseline characteristics and IC domains among patients with or without adverse health outcomes over 1-year follow-up

IC domain	New ADL dependency			New IADL dependency			Death		
	no (n = 238)	yes (n = 69)	p value	no (n = 204)	yes (n = 103)	p value	no (n = 307)	yes (n = 22)	p value
<i>Baseline characteristics, n (%)</i>									
Age ≥80 years	94 (39.5)	62 (89.9)	<0.001	76 (37.3)	80 (77.7)	<0.001	156 (50.8)	19 (86.4)	0.001
Male	137 (57.6)	41 (59.4)	0.783	111 (54.4)	67 (65.0)	0.075	178 (58.0)	16 (72.7)	0.174
Married	191 (80.3)	45 (65.2)	0.009	162 (79.4)	74 (71.8)	0.138	236 (76.9)	18 (81.8)	0.593
High school or above	150 (63.0)	40 (58.0)	0.447	129 (63.2)	61 (59.2)	0.494	190 (61.9)	9 (40.9)	0.052
Comorbidities (≥5 diseases)	146 (61.3)	56 (81.2)	0.009	130 (63.7)	72 (69.9)	0.281	202 (65.8)	16 (72.7)	0.507
Polypharmacy (≥5 medications)	112 (47.1)	51 (73.9)	<0.001	97 (47.5)	66 (64.1)	0.006	163 (53.1)	12 (54.5)	0.895
<i>IC domains</i>									
<i>Cognition, n (%)</i>									
MMSE score ≤24	50 (21.0)	37 (53.6)	<0.001	40 (19.6)	47 (45.6)	<0.001	87 (28.3)	15 (68.2)	<0.001
<i>Locomotion, n (%)</i>									
B-POMA score ≤ 11	30 (12.6)	38 (55.1)	<0.001	27 (13.2)	41 (39.8)	<0.001	68 (22.1)	14 (63.6)	<0.001
Gait speed <1.0 m/s	111 (46.6)	60 (87.0)	<0.001	96 (47.1)	75 (72.8)	<0.001	171 (55.7)	21 (95.5)	<0.001
<i>Sensory, n (%)</i>									
Hearing impairment	100 (42.0)	34 (49.3)	0.284	87 (42.6)	47 (45.6)	0.619	134 (43.6)	7 (31.8)	0.279
Vision impairment	140 (58.8)	50 (72.5)	0.040	123 (60.3)	67 (65.0)	0.418	190 (61.9)	14 (63.6)	0.870
<i>Vitality, n (%)</i>									
Handgrip strength <28 kg (male), 18 kg (female)	42 (17.6)	41 (59.4)	<0.001	37 (18.1)	46 (44.7)	<0.001	83 (27.0)	16 (72.7)	<0.001
MNA-SF score ≤11	60 (25.2)	32 (46.4)	0.001	55 (27.0)	37 (35.9)	0.106	92 (30.0)	15 (68.2)	<0.001
<i>Psychology</i>									
GDS-15 score ≥6, n (%)	23 (9.7)	14 (20.3)	0.017	22 (10.8)	15 (14.6)	0.337	37 (12.1)	5 (22.7)	0.147*
IC Composite score, median (IQR)	3 (2–4)	2 (1–3)	<0.001	3 (2–4)	2 (1–3)	<0.001	3 (2–4)	2 (1–2)	<0.001

Significance difference $p < 0.05$ is shown in bold. IC, intrinsic capacity; MMSE, Mini-Mental State Examination; B-POMA, balance subscale of the Tinetti Performance-Oriented Mobility Assessment; MNA-SF, Short-Form Mini Nutritional Assessment; GDS-15, 15-item Geriatric Depression Scale; ADL, activities of daily living; IADL, instrumental activity of daily living; IQR, interquartile range. * Fisher's exact test.

Table 3. Associations of IC domains and adverse health outcomes over 1-year follow-up using multivariate regression model

IC domain	New ADL dependency		New IADL dependency		Mortality	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
<i>Cognition</i>						
MMSE score ≤24	2.31 (1.12, 4.78)	0.024	2.15 (1.14, 4.04)	0.018	1.98 (0.69, 5.66)	0.204
<i>Locomotion</i>						
B-POMA score ≤11	2.08 (0.94, 4.58)	0.070	1.66 (0.79, 3.50)	0.183	1.10 (0.33, 3.66)	0.871
Gait speed <1.0 m/s	1.81 (0.72, 4.55)	0.207	1.20 (0.61, 2.37)	0.590	5.85 (0.64, 53.78)	0.118
<i>Sensory</i>						
Hearing impairment	0.60 (0.30, 1.21)	0.152	0.63 (0.35, 1.13)	0.118	0.37 (0.13, 1.07)	0.065
Vision impairment	1.73 (0.85, 3.54)	0.132	1.12 (0.63, 1.97)	0.705	1.00 (0.36, 2.82)	0.997
<i>Vitality</i>						
Handgrip strength <28 kg (male), 18 kg (female)	2.06 (0.94, 4.48)	0.070	1.64 (0.81, 3.33)	0.173	2.76 (0.79, 9.66)	0.112
MNA-SF score ≤11	1.23 (0.59, 2.58)	0.575	0.76 (0.40, 1.44)	0.400	2.25 (0.74, 6.79)	0.151
<i>Psychology</i>						
GDS-15 score ≥6	1.26 (0.45, 3.49)	0.662	1.07 (0.43, 2.65)	0.882	0.83 (0.22, 3.12)	0.781

After adjusting age, sex, education level, comorbidities, and polypharmacy. Significance difference $p < 0.05$ is shown in bold. IC, intrinsic capacity; MMSE, Mini-Mental State Examination; B-POMA, balance subscale of the Tinetti Performance-Oriented Mobility Assessment; MNA-SF, Short-Form Mini Nutritional Assessment; GDS-15, 15-item Geriatric Depression Scale; ADL, activities of daily living; IADL, instrumental activity of daily living; OR, odds ratio; CI, confidence interval.

Table 4. Associations of IC composite score and adverse health outcomes over 1-year follow-up using multivariate regression model

	New ADL dependency		New IADL dependency		Mortality	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
IC composite score	0.53 (0.40, 0.70)	<0.001	0.76 (0.61, 0.95)	0.017	0.48 (0.31, 0.74)	0.001

Significance difference $p < 0.05$ is shown in bold. After adjusting for age, sex, education level, comorbidities, and polypharmacy. IC, intrinsic capacity; ADL, activities of daily living; IADL, instrumental activity of daily living; OR, odds ratio; CI, confidence interval.

Discussion

In the current study of 329 older hospitalized patients admitted to the geriatric department, cognitive decline at admission predicted new ADL and IADL dependency 1-year after hospitalization. Moreover, higher IC composite score at admission was associated with lower incidence of 1-year new ADL and IADL dependency, as well as mortality.

Our research contributes to the existing knowledge on the impact of IC on clinical outcomes in several aspects. On the one hand, no study has examined the association between each IC domains together and adverse clinical outcomes in older inpatients, and this issue has increasingly gained clinical attention. Our findings highlight that cognitive decline of IC domains at admission has a detrimental effect on new ADL and IADL dependency 1 year after discharge in older hospitalized patients. It is in accordance with previous studies, which showed that cognitive decline at admission and during hospitalization was associated with functional disability after discharge for a long-term period [40–42]. Impaired cognitive performance at admission was a limitation on routine functional recovery of basic ADL and IADL tasks that require higher level cognitive processing [42]. Moreover, cognitive decline was proven to be a marker of underlying frailty characterized by increased vulnerability triggered by minor stressor events and further led to negative health outcomes [43, 44]. However, the association of IC domains and mortality failed to be confirmed in the current study. A cohort study among Belgian nursing home residents showed that poor nutrition status and low balance performance increased the incidence of 3-year mortality among nursing home residents [15]. Other studies have suggested that cognitive impairment was associated with increased mortality risk in community-dwelling older people [45, 46]. Our study was inconsistent with these, and the discrepant results were probably obtained due to the differences in study samples.

Hospitalized older adults experienced more acute events themselves and varied stressors from external and internal environment imbalance, affecting their limited functional capacities, deteriorating their social relationships, fostering isolation and depression, and further leading to adverse outcomes [28]. In addition, the study design, the follow-up duration, the living environment, and culture were also inconsistent.

On the other hand, considering that each IC domain does not exist in isolation but complements each other [7, 47], we integrated IC domains in the composite score, reflecting a composite of physical and mental capacities of the elderly. A higher IC composite score at admission was a protective factor for reducing 1-year adverse clinical outcomes including new ADL dependency, new IADL dependency, and mortality. Regardless of clinical phenotypes, shifting the focus from disease to IC has huge implications for clinical practice. IC is better understood in the context of an integrated care model which emphasizes on comprehensive and adequately targeted interventions, rather than mono-dimensional plan. Indeed, hospitalization and the transition from hospital to home are critical for older adults. Older patients often experienced loss of functional capacities due to the acute episode, the change of the living environments, and the interactions between them. Thus, it is important for older hospitalized patients to measure IC as early as possible and create and optimize comprehensive health intervention and care plans. Few recommendations of Integrated Care for Older People (ICOPE) guidelines are given as follows [48]: (1) for older adults with declining of physical capacity, multimodal exercise including progressive strength resistance training, balance, flexibility, and aerobic training can be recommended; (2) for older adults with malnutritional risk, oral supplemental nutrition with dietary advice can be offered; (3) for older adults with sensory deficits, hearing aids and comprehensive eye care are suggested; (4) for older adults with cognitive impairment, cognitive stimulation can be selected. Vellas

and colleagues [49] proposed 3 approaches to maintain cognitive capacity at different ages in community-dwelling older people (i.e., increasing IC cognitive reserve in 45–70 years, preserving cognitive functions in ≥ 70 years, and restoring cognitive functions, upon the diagnosis of mild cognitive impairment, cognitive frailty, or prodromal late onset dementia). (5) For older adults with depressive symptoms, brief and structured psychological interventions can be recommended. However, the details of frequency, intensity, and duration of the interventions have not been determined. Further longitudinal prospective studies in our specific older samples should be performed to determine intervention strategies in order to preserve and improve IC both in hospital and after discharge.

Apart from the abovementioned recommended interventions, some research studies pointed to the fact that low-grade inflammation (chronically raised C-reactive protein), hyperhomocysteinemia, and allostatic load integrated with 10 physiological parameters were associated with impairment on the combined IC levels [50, 51]. These revealed that changes in some biomarkers could modify the disabling process of an older individual. For example, correcting inflammation status and reducing high homocysteine levels and the abnormal blood pressure may improve IC and thus decrease the incidence of adverse clinical outcomes. Although the evidence is from older community-dwelling individuals, it also provides information that could be applied to IC management of older patients returning to the community after discharge. Integrating various patient characteristics including disease; physical, mental, living environment, and care needs; IC management during hospitalization; or the transition to the community needs further in-depth longitudinal studies [52].

The strengths should be mentioned in our study. This is the first study to specifically examine the predictive value of IC domains in clinical outcomes in a hospital setting, both in the IC domain and composite IC score. Data from CGA database of our geriatric hospital can represent the elderly population in East China. Moreover, a professionally trained CGA team for older inpatients is organized, and therefore, the validity and consistency of the evaluations can be guaranteed. However, our study also had some limitations. First, a relatively short follow-up time in 1 center cannot represent the Chinese hospitalized patients; thus, the generalization of our findings could not be applied to other clinical settings. Second, the IC domains were used according to ICOPE guidelines, but some of the recommended assessment tools were ad-

justed to other validated tools. In addition to self-reported sensory deficit and depression symptoms, other adjusted tools such as balance scale are objectively measured. This should not have a significant influence on the IC construct, but the result may be easily affected by situation and the judgment of the assessors. Third, we only focused on the baseline IC and did not explore whether the change of IC from baseline to follow-up or whether transitions in IC were associated with increased risk of adverse health outcomes.

Conclusion

Our study indicated that loss of ICs at admission predicted adverse health outcomes including new ADL dependence, new IADL dependence, and mortality 1 year from discharge. Our findings revealed that continuous assessment of IC is of increasing importance in the hospitalized older patients, and interventions to preserve and improve IC in those populations are critical to reduce adverse health events and promote healthy aging.

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Statement of Ethics

The Ethics Committee of Zhejiang Hospital approved this study (2013–25), and each participant signed written informed consent. Our research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

X.Z., S.S., and X.C. contributed to conceptualization and methodology. X.Z. and S.S. analyzed the data and wrote the original draft. L.X. and Y.Y. contributed to data collection. Y.W., L.C., H.G., and J.Z. participated in functional assessment. All the authors contributed to implement and revise the manuscript.

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