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Association between chronological age and geriatric assessment identified impairments: findings from the CARE registry

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Abstract

Background: NCCN guidelines recommend that older adults with cancer undergo a geriatric assessment (GA), when possible, to provide a comprehensive health appraisal to guide interventions and appropriate treatment selection. However, the association of age with GA-identified impairments (GA impairments) remains understudied and the appropriate age cut-off for employing the GA remains unknown.

Patients and Methods: We designed a cross-sectional study utilizing the Cancer and Aging Resilience Evaluation (CARE) registry of older adults with cancer. We included adults ≥60y with a diagnosis of gastrointestinal (GI) malignancy who underwent a patient-reported GA prior to their initial consultation at the GI oncology clinic. We noted the presence of GA impairments and frailty using Rockwood's deficit accumulation approach. We studied the relation between chronologic age and GA impairments/ frailty using Spearman's rank correlation and chi-squared tests of trend.

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Author Contributions:

SG and GRW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: SG, GRW

Acquisition, analysis, or interpretation of data: SG, GRW

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Results: We identified 455 eligible older adults ≥60y with GI malignancies with a median age of 68y (range 64-74y), with colorectal (33%) and pancreatic (24%) being the most common cancer type. The correlation between chronologic age and the number of geriatric impairments was weak and did not reach statistical significance (Spearman's rho 0.07, p value 0.16). Further, the prevalence of domain-specific impairments or frailty was comparable across the three age groups (60-64y, 65-74y, ≥75y), with the exception of comorbidity burden. Notably, 61% of patients, aged 60-64y had ≥2 GA impairments and 35% had evidence of frailty, which was comparable to patients 65-74y (66% and 36% respectively) and ≥75y (70% and 40% respectively).

Conclusions: The use of chronologic age alone to identify which patients may benefit from GA is problematic. Future studies should identify screening tools that may identify patients at high risk of frailty and GA impairments.

Background

Up to 60% of all new cancer diagnoses and 70% of all cancer related deaths occur among adults aged 65 or more.[1] Older adults with cancer are at high risk of treatment related toxicity and inferior survival, yet neither chronologic age nor clinician assessed performance status adequately captures this vulnerability.[2] A geriatric assessment (GA) is a multidimensional tool to uncover this vulnerability or "frailty" and predicts the risk of morbidity and mortality among older adults with cancer.[3–5] A growing body of literature show that GA can predict chemotherapy related toxicity[5,6] as well as mortality[4], guide clinical decision-making[7] and improve patient satisfaction[8] among older adults with cancer. Specifically among gastrointestinal cancers, GA has been shown to predict post-surgical complications among older adults with colorectal cancer[9], gastroesophageal[10] and hepatocellular carcinoma[11], chemotherapy related toxicity[12], as well as short- and long-term mortality[13]. Given these substantial benefits, the American Society of Clinical Oncology (ASCO)[14] and the National Comprehensive Care Network (NCCN) guidelines[15] currently recommend that all older adults with cancer undergo a GA.

However, the association between chronologic age and GA impairments and frailty remains understudied. Furthermore, ASCO recommends GA among all older adults with cancer over the age of 65 years (y), yet, the rationale for this age cut-off remains unclear. Because, patients with cancer patients are known to undergo accelerated aging through multiple mechanisms[16], extrapolating from the age-cutoff used in general population may be inaccurate. In this study, we examined the association between chronologic age and GA-identified impairments and frailty among adults ≥60y with gastrointestinal (GI) malignancies.

Methods

Study Population:

Using participants from the University of Alabama at Birmingham (UAB) Cancer & Aging Resilience Evaluation (CARE) Study, an ongoing prospective registry enrolling older adults (≥60y) undergoing cancer care at UAB Hospitals and Clinics[17,18], we identified patients diagnosed with a GI malignancy presenting for an initial consultation to our medical

oncology clinic. We chose 60y of age as criteria for enrollment in this registry given recognition of the uncertainty of the "right" age cutoff and to allow for meaningful age-related sub-analyses such as the current study.[19] The Institutional Review Board of UAB (IRB-300000092) approved this study.

Geriatric Assessment:

We conducted patient-reported GAs as previously described (Table S1).[17,18] Our GA comprised of the following domains; functional status, comorbidity, cognition, mental health status, nutrition, social support and health related quality of life, consistent with recommendations from the International Society of Geriatric Oncology.[3] We assessed functional status using the OARS instrumental activities of daily living (IADL)[20], OARS activities of daily living (ADL)[20], patient-reported ECOG performance status[21] and number of falls within the last 6 months.[22] Nutritional status was evaluated using an abridged version of patient generated subjective global assessment (PG-SGA).[23] Comorbidity assessment was done using number of medications[24] and OARS comorbidity assessment.[20,25] We assessed social support using MOS Social Support Survey[26], mental health status using PROMIS Anxiety and PROMIS Depression tool[27,28]. Meanwhile, cognition was evaluated PROMIS Cognitive function tool[29]. Lastly, health-related quality of life was examined using the PROMIS 10-item global health tool[30]. The geriatric was completed by the patient. However, if the patient has any vision issues, a member of the study personnel or a primary caregiver could ask the patient the GA questions.

GA Impairments:

Based on the above GA evaluation, we classified patients as having GA impairment if they met ≥2 of the following criteria[31]: one or more falls in the last 6 months; significant limitation in walking one block; impairment in ≥2 IADL; any ADL impairment; significant weight loss (3% in 3 months or 6% within 6 months); presence of four or more comorbidities; poor social support for physical activity; significant interference in social activity; presence of anxiety (T-score ≥60) or depression (T-score ≥60); cognitive impairment (T-score ≤60) and polypharmacy (≥9 medications).

Frailty Index:

We constructed a frailty index (hereafter known as the CARE Frailty Index) using the principle of deficit accumulation approach originally described by Rockwood et al[32], and following the standard procedures outlined by Searle et al.[33] Similar methods have been used by Guerard et al[4] and Cohen et al[34] to construct Frailty Indices that have been shown to be predictive of chemotherapy toxicity[34] as well as all-cause mortality[4] among older adults with cancer. We selected 44 GA variables from the CARE questionnaire, each of which captured a health deficit, and recoded responses using the convention that '0" indicated the absence of the deficit and '1' indicated the presence of deficit, for variables that included a single intermediate response (e.g. 'sometimes' or 'maybe'), we used an additional value of '0.5'. We then combined these individual scores into an aggregate frailty score reflecting the overall proportion of deficits (range 0-1), where 0 =no deficit present and 1=all 44 deficits present. We then categorized patients as robust (0-0.2), pre-frail (0.2-0.35) and frail (>0.35), as previously described[33]. In case of missing response data, we required that responses to at

least 30 items be present to construct a valid frailty index. An index constructed with at least 30 variables has been previously shown to be sufficiently accurate for predicting adverse outcomes among older adults.[35] We provide additional details regarding our definition for GA impairment and Frailty Index in the Supplement.

Statistical Analysis:

We compared baseline characteristics between the three age groups (age 60-64y, 65-74y and ≥75y) using appropriate bivariate statistical tests, i.e Analysis of Variance/Kruskal Wallis for continuous variables and Chi-squared test/Fisher's exact test for categorical variables depending on their underlying distribution. To measure the correlation between the number of geriatric impairments (a ranked variable) and chronologic age (continuous variable), we used Spearman's rank correlation co-efficient and tested the alternative hypothesis that the Spearman's rho was significantly different from zero. We compared the difference in proportion of various GA impairments and frailty categories among increasing age groups (age 60-64y, 65-74y and ≥75y) using chi-squared tests of trend. To evaluate the difference between number of GA impairments across the three age groups, we used a non-parametric extension of Wilcoxon rank-sum test.[36] All statistical tests were two sided and the level of significance was chosen as 0.05. We used STATA 13.0 (STATACorp LLC, College Station, TX) for all statistical analysis.

Results

Of the 523 consecutive adults ≥60y with gastrointestinal malignancy seen for initial consultation at UAB medical oncology clinic between 9/2017 and 10/2019, 455 (87%) enrolled in CARE registry and underwent GA (Figure S1). Of these, 367 (80%) had not started any systemic therapy, whereas the remaining (29%) had previously received treatment elsewhere. The median age of the entire cohort at the time of GA was 68y (IQR 64-74); 55% were males, and 72% non-Hispanic whites. Overall, 28% of the 455 patients were aged 60-64y, 47% were 65-74y and 25% were ≥75y. Common cancer types included colorectal (33%) and pancreatic (24%); 46% had stage IV disease. The demographic and clinical characteristics were similar across the three age groups, with the exception of marital status and cancer stage, as summarized in Table 1. Patients enrolled in the CARE registry had similar age, gender, cancer stage, with the exception of a higher proportion of non-responders among patients with hepatobiliary and pancreatic cancer, as compared to non-participants (Table S2)

Relationship between chronologic age and Geriatric Impairments:

There was no significant correlation between chronologic age and number of geriatric impairments (Spearman's rho 0.07, p value 0.16). Notably, even in the age group 60-64y, 61.4% of patients had GA impairments. This was not significantly different as compared to patients between 65-75y (66.2%) and ≥75y (70.5%) (*P value* .11). We found similar rates of impairments in IADL, ADL, nutritional status, falls, cognitive, anxiety, depression, polypharmacy, and patient-reported ECOG performance status across the age groups. However, there was higher comorbidity burden (≥3) in the older group (39%, 56% and 56% among 60-64y, 65-74y and ≥75y respectively, *P value* <.01) (Table 2). The increased

comorbidity burden in the older age groups was mainly driven by a higher proportion of patients reporting arthritis, hypertension and glaucoma (Table S3)

Relationship between chronologic age and Frailty:

Overall, 37% of the cohort were frail (N=108), whereas 30% (N=128) were pre-frail and 33% (N=143) had robust frailty status. Patients who were frail, vs those who were pre-frail or robust, were more likely to have a worse ECOG performance status ≥2 (68% vs 26% vs 4% respectively; *P* value <.001) and a higher cancer stage (52% vs 42% vs 42% respectively; *P* value .03), but did not differ significantly by treatment status (22% vs 20% vs 16% were already on treatment respectively; *P* value .44).

We then compared the rates of frailty categories across the different age groups. Notably, 26% and 35% of patients had evidence of prefrail and frail status in the 60-64 age group. This was not significantly different as compared to the proportion of patients with prefrail and frail in the 65-75y (30% and 36% respectively) and ≥75y (33% and 40% respectively) (*P* value .45).

Discussion

In this study comprising of an unselected cohort of older adults ≥60y with GI malignancies, we found no significant relationship between chronologic age and the presence of geriatric impairments or frailty. Furthermore, we found comparable prevalence of GA impairments and frailty in the 60-64y age group as compared to those 65 years and above, suggesting that the traditional cutoff of 65 years for conducting comprehensive geriatric assessment may not be accurate and even patients younger than 65y could benefit from GA evaluation.

There is no universal agreement on the age at which a person becomes old. In the US, age ≥65y is generally considered the chronologic definition of an older adult, similar to what is used for Medicare eligibility. Accordingly, consensus recommendations for GA from ASCO as well as the International Society of Geriatric Oncology (SIOG) use 65y as the age cutoff.[3,14,15] However, emerging evidence suggests cancer diagnosis and/or treatment can accelerate the human aging process through multiple mechanisms including DNA damage, induction of ageing related biological pathways such as telmoeraase activity, DNA hyper methylation and stem cell exhaustion.[16] Hence, the age cutoffs assumed for the general population may not apply to cancer patients. We postulate that this phenomenon may account for the high prevalence of GA impairments in our cohort <65y.

In a prior study, Aleixo *et al* reported the prevalence of GA impairments among patients younger than 65y with early stage breast cancer. Patients aged 50-64y had a high prevalence of falls in past 6 months (15%), abnormal timed up and go test >14 seconds (12%) and impaired IADL (17%). However, patients 50-64y comprised <10% of the study population and were derived from exercise intervention trials and compared to patients ≥65y derived from a prospective registry, thus raising a possibility of selection bias.[19] In comparison, our entire cohort includes unselected patients from a cancer registry who underwent initial consultation at the GI oncology clinic. However, we report similar findings, with comparable rates of GA impairments and frailty among patients in the 60-65y age group.

Limitations of our study include being a single institution study limited to GI malignancies; our findings may not be generalizable to other settings/populations. The reason for limiting to GI malignancies was to eliminate the possibility of selection bias as mentioned before. Nevertheless, we recognize that our cohort is still quite diverse and there may be substantial variation in the proportion of patients with GA impairment and frailty within individual cancer types and cancer stages. Almost half of our patients had stage IV disease, which may explain the high rate of GA impairments in our study. Notably, another study among patients with early stage breast cancer reported similar findings.[19] All patients who underwent GA evaluation did so at the time of initial contact with the UAB health system. Consequently, not all patients who presented for an initial appointment were previously untreated and about 20% had already cancer therapy at another facility. Furthermore, by limiting our sample to patients completing GA at their initial visit, we may have excluded patients with severe illness requiring hospitalization for urgent treatment or hospice care, such as those with more aggressive malignancies including hepatobiliary and pancreatic cancers. This may have potentially biased our findings. We did not have data on treatment related toxicity, treatment discontinuation, or healthcare utilization, which need to be explored in future studies.

To conclude, our study adds to the growing body of evidence that chronologic age is an imperfect marker of presence of GA impairment and frailty. Furthermore, GA impairments are seen even among adults younger than 65y, and GA may aid in the clinical management of even younger populations than previously considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Distribution of baseline demographic and clinical characteristics among patients of different age groups

Variable	60-64 y	65-74 y	≥75 y	*P* value
N	128	215	112	
Age, median (IQR)	62 (61-63)	69 (66-71)	79 (77-81)	<.001
Sex				.16
- Male	77 (60.2%)	122 (56.7%)	54 (48.2%)	
- Female	51 (39.8%)	93 (43.3%)	58 (51.2%)	
Race				.25
- White/Caucasian	91 (71.1%)	147 (68.4%)	90 (80.4%)	
- Black/African-American	35 (27.3%)	63 (29.3%)	21 (18.8%)	
- Other	2 (1.6%)	4 (1.9%)	0 (0%)	
- Unknown	0 (0%)	1 (0.5%)	1 (0.9%)	
Education				.90
- Less than high school	24 (18.8%)	34 (15.8%)	14 (12.5%)	
- high school graduate	29 (22.7%)	59 (27.4%)	29 (25.9%)	
- Associate/Bachelors	58 (45.3%)	91 (42.3%)	53 (47.3%)	
- Advanced Degree	12 (9.4%)	19 (8.8%)	13 (11.6%)	
- Unknown	5 (3.9%)	12 (5.6%)	3 (2.7%)	
Marital Status				.01
- Single	14 (10.9%)	15 (7%)	2 (1.8%)	
- W/D/S	23 (18.0%)	52 (24.2%)	44 (39.3%)	
- Married	86 (67.2%)	138 (64.2%)	62 (55.4%)	
- Unknown	5 (3.9%)	10 (4.7%)	4 (3.6%)	
Cancer Type				.91
- Colorectal	41 (32.0%)	65 (30.2%)	43 (38.4%)	
- Pancreatic	28 (21.9%)	56 (26.0%)	24 (21.4%)	
- Hepatobiliary	23 (18.0%)	40 (18.6%)	17 (15.2%)	
- Gastroesophageal	14 (10.9%)	22 (10.2%)	11 (9.8%)	
- Others	22 (17.2%)	32 (14.9%)	17 (15.2%)	
Cancer Stage				.05
- Stage I	9 (7.0%)	15 (7.0%)	10 (8.9%)	
- Stage II	17 (13.3%)	36 (16.7%)	33 (29.5%)	
- Stage III	39 (30.5%)	58 (27.0%)	25 (22.3%)	
- Stage IV	63 (49.2%)	102 (47.4%)	42 (37.5%)	
- Unknown	0 (0%)	4 (1.9%)	2 (1.8%)	
Treatment Status				.27
- Pre-Treatment	101 (78.3%)	170 (79.1%)	96 (85.7%)	

Variable	60-64 y	65-74 y	≥75 y	*P* value
- During Treatment	27 (21.7%)	45 (20.9%)	16 (14.3%)	

* Others include anal cancer (n=10), gastrointestinal stromal tumor (n=14), appendicular cancer (n=3), neuroendocrine carcinoma (n=39) and gastrointestinal cancer not otherwise stratified (n=5)

Table 2:

Comparison of overall and domain specific geriatric impairment and frailty among older adults of different age group.

Variable[#]	60-64y	65-74 y	≥75 y	*P* value[*]
N	119	199	104	
GA Impairment ≥2	78 (61.4%)	141 (66.2%)	79 (70.5%)	0.33
GA Impairment Count (0-13), median (IQR)	2 (1-4)	2 (1-5)	3 (1-6)	0.11
Frailty Score, median (IQR)	0.26 (0.13-0.41)	0.28 (0.15-0.40)	0.28 (0.17-0.48)	0.29
Frailty Category				0.45
- Robust	46 (38.2%)	70 (34.0%)	29 (26.6%)	
- Prefrail	33 (26.8%)	62 (30.1%)	36 (33.0%)	
- Frail	43 (35.0%)	74 (35.9%)	44 (40.4%)	
IADL Impairment ≥1	60 (47.2%)	111 (52.1%)	66 (58.9%)	0.20
ADL Impairment ≥1	26 (20.5%)	42 (19.7%)	27 (24.1%)	0.64
ECOG Performance Status ≥2	40 (33.6%)	65 (25.3%)	29 (27.1%)	0.61
≥1 Falls in 6 months	24 (18.9%)	37 (17.6%)	27 (24.1%)	0.34
Malnutrition	55 (43.3%)	103 (48.4%)	56 (50%)	0.54
Cognitive Impairment	11 (8.7%)	12 (5.6%)	9 (8.0%)	0.54
Anxiety	23 (18.1%)	44 (20.7%)	17 (15.2%)	0.50
Depression	19 (15.0%)	26 (12.2%)	15 (13.4%)	0.75
≥3 Comorbidities	48 (39.0%)	112 (56.3%)	59 (55.7%)	0.006
≥9 Medications	23 (19.0%)	50 (25.3%)	29 (27.1%)	0.29

GA, Geriatric Impairment; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; ECOG, Eastern Co-operative Oncology Group.

N reflects number of patients with available data to calculate the number of GA impairments. Patients were required to have non-missing information on at least 11 domains (85%) to have a valid result.

[*] Represents unadjusted *P* values. Additional sensitivity analyses were done accounting for marital support and cancer stage (Mantel-Haenszel test using marital support and cancer stage as stratifying variables in case of categorical variables, Poisson and linear regression for GA Impairment count and Frailty Score respectively, controlling for marital support and cancer stage), however the results remained unchanged (results not shown)

[#] Separate pairwise comparisons were conducted between age group 60-64y vs 65-74y and 60-64y vs ≥75y, with overall similar findings with the exception of higher comorbidity burden in the higher age group (results not shown).