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Prospective validation of the Cancer Ageing Research Group (CARG) score in geriatric patients undergoing curative intent chemotherapy: A simple assay to predict clinically relevant toxicity in the elderly

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Title – **Prospective validation of the Cancer Ageing Research Group (CARG) score in geriatric patients undergoing curative intent chemotherapy: A simple assay to predict clinically relevant toxicity in the elderly**

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Running title –CARG score in older Indian cancer patients undergoing curative-intent chemotherapy

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Abstract:

Importance:

The Cancer Aging Research Group (CARG) toxicity score is used to assess toxicity risk in geriatric patients receiving chemotherapy.

Objective:

The primary aim was to validate the CARG score in geriatric patients treated with curative intent chemotherapy in predicting Grade 3-5 toxicities.

Design:

This was a longitudinal prospective observational study

Setting:

Tata Memorial Hospital, Mumbai, India, a tertiary cancer care referral centre.

Participants:

Patients age >=65 with gastrointestinal, breast or gynaecological stage I-III cancers being planned for curative intent chemotherapy. A total of 270 patients were required for accrual in the study.

Exposure(s):

Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk).

Main Outcome(s) and Measure(s):

The primary endpoint of the study was to evaluate whether the CARG risk score predicted for grade 3-5 toxicities.

Results:

The study cohort of 270 patients had a mean age of 69 years (65-83), with the most common cancers being gastrointestinal (79%). Fifty-two percent of patients had at-least one grade 3-5 toxicity. The risk of toxicity was increased with increasing risk score (42% low, 51% medium, 79% high risk; P < .001). There was no association between either ECOG PS (p=0.69) or age adjusted Charlson Comorbidity Index (p=0.79) risk categories and grade 3-5 chemotherapy toxicity.

Conclusions and Relevance:

The current study validates the CARG risk score in predicting for grade 3-5 toxicities in geriatric oncology patients receiving curative intent chemotherapy and can be considered as standard of care before planning chemotherapy in every elderly patient.

Key words – CARG risk; Hurria score, curative, ECOG PS, Charlson Comorbidity Index, chemotoxicity

Strengths and limitations of the study:

- The CARG risk score is a simple tool comprising easily available clinical information.
- This is a prospective study to assess CARG risk score in elderly patients treated with curative intent to predict for grade 3-5 toxicities.
- CARG score performed better than traditional indices such as the age adjusted Charlson Comorbidity Index and ECOG PS.
- The results suggest that the CARG score is valid in the studied population and can be routinely used in clinical practice.
- This study does not include palliative patients and mainly GI cancer patients were recruited.

Manuscript :

Introduction

Older adult patients (age >=65 years) with cancer represent a growing proportion of patients in community clinical practice, primarily due to increasing life-spans as well as medical progress contributing to decreased morbidity and mortality from other causes (1). Elderly patients comprise anywhere between 20% to 60% in community oncology practice, with variances based on access to cancer care, disease stage and centre specific management strategies (2,3).

The age adjusted Charlson Comorbidity Index (ACCI) and ECOG Performance status (PS) amongst others have often been used to quantify risks and predict for outcomes in older adults with cancer, but there is limited data for correlation between these indices and treatment related side effects (4–6). The Cancer Aging Research Group (CARG) risk score, developed by Hurria and colleagues, is a an easy to use tool that predicts for significant chemotherapy related toxicities (grade 3- grade 5) in older North American adults >/= 65 years starting on chemotherapy (7,8). Based on their training samples and subsequent validation studies, the investigators clearly identified low, mid and high-risk groups predicting for increasing rates of grade 3-5 toxicities (low risk: 30%, intermediate risk: 52%, high risk: 83%) with statistical significance (P<0.001). The CARG risk score has been studies validated in other countries and in specific tumor sites to varying degrees (9,10).

In older adults being treated with curative intent chemotherapy, there is the possibility of treating oncologists using standard doses to maximize outcomes, despite patient related indicators suggesting a requirement for lower doses. This is a unique scenario where further information on risks and benefits would allow for informed clinical decision making on doses and drugs to be used. As patients with all stages of cancer were included in the CARG

studies, the ambiguity with regard to its usage in patients being treated with potentially curative intent lends itself to re-examination.

With this background, the investigators conductive a longitudinal prospective study with the primary aim of validating the CARG risk score in Indian older cancer patients treated with curative intent chemotherapy (neoadjuvant or/and adjuvant chemotherapy). Secondary and exploratory objectives included correlation of the age adjusted Charlson Comorbidity Index (ACCI) and physician measured ECOG PS with grade 3-5 toxicities as well as an estimation of grade 1 and grade 2 toxicities and their correlation with the CARG risk score.

Materials and methods

Patient selection and design

The study was designed as a longitudinal prospective observational study to validate the CARG risk score in predicting chemotherapy toxicity risk in elderly patients. The study was conducted at the Tata Memorial Hospital and enrolled patients aged>=65 years, chemotherapy naïve, with a histological diagnosis of gastrointestinal, breast or gynaecological cancer, stage I-III disease and planned for neoadjuvant or adjuvant systemic chemotherapy as a potentially curative treatment option.

The study was designed by investigators from the Department of Medical Oncology of the Tata Memorial Hospital and was approved by the ethics committee (IEC/1019/1716/001). The study was registered at Clinical trial registry of India (CTRI/2016/10/007357). Written informed consent was obtained from all patients before inclusion in the study.

Patient and public involvement:

There was no public or patient involvement in design, conduct or results declaration of the study.

Study procedures

Data regarding tumor type and stage, pre-treatment laboratory values, and chemotherapy regimen were recorded. All patients underwent standard pre-chemotherapy work up, including evaluation of end organ function. Patients were planned for chemotherapy by treating oncologist (with an assessment of ECOG PS and ACCI), who was blinded to the risk score. A study coordinator calculated the CARG risk score for patients enrolled in the study (7) . Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk), with division of the scores into low risk (0-5 points), intermediate risk (6 to 9 points) and high risk (10-19 points) as per the classification in the original study by Hurria et al (7). One modification of the original CARG risk score which was used in the current study was the measurement of 'Walking 1 block'. The concept of measuring distances by a block is not prevalent in India and hence, a distance of 100 metres in the immediate vicinity of the hospital was measured and patients were scored on their ability to walk the same. The chemotherapy dosing for the first cycle of chemotherapy was categorized as 'standard' if 100% doses were planned and 'dose reduced' if any dose below 100% was used. The decision for dose modifications was based on assessment by treating oncologist. Besides CARG risk score, the age adjusted Charlson's Comorbidity Index (ACCI) was calculated for all patients as part of standard assessment of older adults with cancer. A cut-off of 4 points (<=4 and >4) was used to differentiate between low and high CCI scores (11). Patients were followed from beginning till the end of chemotherapy course. Toxicities were captured prospectively at all clinical visits (by treating oncologist and study coordinator) and graded as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Decision on relatedness of toxicity to chemotherapy was made by treating physician. Blood values were captured as grade 1 to 5 toxicity if they met the criteria

on the date of scheduled chemotherapy or at the time the patient was seeking attention because of chemotherapy related toxicities.

Outcomes

The primary outcome of the study was the occurrence of any grade 3-5 chemotherapy related toxicity over the course of planned treatment and its association with the CARG risk score. The planned secondary endpoints of the study were the correlation of ACCI and ECOG PS with grade 3-5 chemotherapy related toxicity. Occurrence of any grade 1-2 chemotherapy related toxicity and its correlation with CARG risk score was an exploratory aspect of the study.

Statistical analysis

Descriptive analyses were performed to enumerate patient, tumor, treatment characteristics, CARG risk scores and ACCI. The incidence of grade 3 to grade 5 toxicities were calculated and compared between CARG risk groups, and ECOG PS cohorts by using the chi-square test. Sample size was calculated based on cumulative incidence of 20 % of grade 3-grade 5 toxicities in elderly patients with ECOG PS 0/1 and controlled or absent comorbidities as opposed to 36% in elderly patients with ECOG PS 2 with or without multiple uncontrolled comorbidities among patients receiving perioperative chemotherapy at Tata Memorial center for breast, gastrointestinal and gynaecological cancers. A power of 80% and alpha of 5% with 1 sided assumption was required with estimated sample size required being 246 patients. Assuming an attrition rate of 10%, a total of 270 patients were required for enrolment in the study. Chi square test was performed to test the association of the CARG risk score, PS, and ACCI with G 3-5 toxicities and for association of CARG risk score with grade 1-2 toxicities. The predictive ability of the CARG risk score was evaluated by calculating receiver-

operating characteristic (ROC) curves and calculating the area under the curve (also known as C-statistic). ROC curves were also calculated for ECOG PS and ACCI. All analyses were performed using SPSS version 25. All tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Patient and treatment characteristics

The study completed accrual of 270 patients, with mean age of patients being 69 years (range:65-83), 121 (45%) female patients and 212 patients (79%) having gastrointestinal cancers. For purposes of comparison, data from the seminal CARG study by Hurria et al is provided for comparison (table 1)

Chemotherapy toxicity

At least one grade 3 to 5 toxicity was seen in 140 patients (52%), with 119 (44%) having grade 3, 22 (8%) having grade 4, and 11(4%) grade 5 toxicities. Grade 3-5 haematological and non-haematological toxicities occurred in 60 patients (22%) and 120 (45%) patients respectively. Common haematological toxicities were neutropenia in 26 (10%) and febrile neutropenia in 17 (6%) patients, while common non-haematological toxicities were infections, fatigue and diarrhoea in 54 (20%), 24 (9%) and 23 (9%) patients respectively (table 2).

The incidence of grade 1 to grade 2 toxicities are listed in supplementary table 2.

CARG risk score and correlation with toxicity

The median overall CARG risk score was 6 (range, 0 to 19). Of the 270 patients, 72 (27%), 164 (61%) and 34 (13%) were classified as low, intermediate and high risk, respectively (table 1). Grade 3-5 toxicities were seen in 30(42%), 83 (51%) and 27 (79%) patients with

low, intermediate and high-risk score. There was a significant difference in toxicity amongst the risk groups (p<0.001) (figure 1 and table 2). The odds of a patient classified as low risk having a grade 3-5 toxicity as compared to patient with intermediate risk was 0.61 (95% CI: 0.47-0.81), while the odds of a patient classified as high risk having a grade 3-5 toxicity as compared to patient with intermediate risk was 3.31 (95% CI:1.58-6.94). Area under the ROC curve for the predictive model in the current cohort was 0.63 (95% CI: 0.57-0.7). The correlation of individual components of the CARG risk score with grade 3-5 toxicities is enumerated in supplementary table 1.

Grade 1-2 toxicities were seen in 61(86%), 144(88%) and 29 (85%) patients with low, intermediate and high-risk score. There was no significant difference in toxicity amongst the CARG risk groups (p=0.79).

Association of grade 3-5 toxicity with Age adjusted Charlson Comorbidity Index (ACCI) and ECOG PS

The median ACCI was 5. A CCI<=4 was seen in 111 patients (41%), while 159 patients (59%) had a CCI>=4. There was no significant difference in toxicities amongst both groups of patients (p=0.7) (figure 1 and table 3). The ROC of the model with CCI (as a continuous variable) was 0.48 (95% CI: 0.41-0.55), which was lower than the ROC of the CARG risk score model, 0.63.

ECOG PS was 0, 1 and 2 in 9(3%), 221(82%) and 40 (15%) patients, respectively. There was no significant difference in toxicities amongst both groups of patients (p=0.69) (figure 1 and table 3). The ROC of the model with ECOG PS (as a continuous variable) was 0.52 (95% CI: 0.45-0.59), which was lower than the ROC of the CARG risk score model, 0.63.

Discussion

This study validates the CARG risk score in older Indian patients receiving curative-intent chemotherapy for stage I-III gastrointestinal, breast and gynaecological cancers, though the association between rates of severe chemotherapy toxicity and CARG risk groups as being discriminatory was modest (AU-ROC 0.63). No association was found between ECOG PS and burden of comorbidities as measured by the ACCI with severe chemotherapy related toxicities.

There is a significant knowledge gap in terms of how older patients in general and older patients with cancer fare in the Indian scenario. Limited data suggests no defined care structure for older patients with cancer in India as well as only low-moderate awareness and use of geriatric assessment in older patients with cancer (3,12) . Available evidence from India suggests that 98% of older adult cancer patients have vulnerabilities in at least one geriatric domain, though the specific vulnerabilities appear to differ from previously published data (13). Such a high and differential vulnerability profile in these patients suggests that they may have a different incidence of toxicities with standard chemotherapy regimens. With such a background, it was essential to evaluate the validity of the CARG risk score before routine advocation in older adult patients.

There are some important differences between the populations of the current study and the seminal CARG study. The current study had only patients with stage I-III disease, while the CARG study had 38% with non-metastatic disease. Other relevant differences between the cohorts include a younger mean age (69 vs. 73 years), lesser comorbidities (46% with no comorbidities vs. 10% with no comorbidities), and better performance on a number of individual variables in the CARG risk score (better hearing, lesser number of falls, better social activity and effort tolerance). There were also a lower proportion of patients with high risk score in the current study (13% vs. 22%). These differences indicate that patients in the

current study were a well preserved and presumably fitter group of patients with lesser disease burden and potential for toxicities.

Despite the differences in patient cohorts in terms of baseline characteristics, the current study in validated the Cancer Aging Research Group (CARG) risk score in predicting grade 3 to grade 5 chemotherapy related toxicities. The low, intermediate and high risk CARG groups predicted for increasing incidences of grade 3-5 toxicities with statistical significance. The odds ratios between individual risk groups for predicting grade 3-5 toxicity was also statistically significant, highlighting the differential capability of the risk score. An unanswered component of the CARG risk assessment was whether it correlated with grade 1-2 toxicities. Previous studies by Moth et al estimating grade 1 and grade 2 toxicities as toxicity burden have not shown a correlation with the CARG risk score (14). This is possibly due to the near universal occurrence of such toxicities in patients receiving chemotherapy. A similar trend was seen in the current study wherein an increasing risk score did not predict for an increased risk of grade 1-2 toxicities. Additionally, in comparison to the predictive capacity of the CARG risk score, the Charlson Comorbidity Index and ECOG PS based risk groups did not predict for incidences of toxicity in the study. These results highlight certain salient points in the study, Firstly, the CARG risk score can be used with confidence in the Indian population to predict for grade 3-5 toxicity. The CARG risk score was evaluated only in a North American elderly adult cohort initially and the current study provides validation for the score in the Indian context. Secondly, despite being a better-preserved cohort in comparison to the population in the seminal study as well as having only patients on curative intent therapy, a high proportion of patients across risk groups developed grade 3-5 toxicity which may be life-threatening. Thus, it is imperative to carefully assess the trade-off between objectives such as survival and downstaging versus potentially life-threatening toxicities while planning curative intent chemotherapy in older adult patients. Thirdly, the area under

the ROC for the current study was 0.63 and is lower in comparison to the original study (0.72), though very similar to the results of the validation study (0.65) by the CARG group (8). Though this indicates a modest discriminatory capability for the CARG risk score in the current study, it is probably also reflective of the true value of the score in prediction of severe chemotherapy related toxicities. Smaller studies by Australian investigators have also previously commented on this lack of discriminatory value with the CARG risk score (14). Finally, using a global assessment score such as ECOG PS or only one aspect of an assessment profile such as comorbidity status (as in the case of ACCI) would not accurately capture the heterogeneity of the older adult population. This is reflected in the inadequacy of ECOG PS and ACCI in predicting for toxicities and hence, these indices should only be used in conjunction with other indices as measures of assessment in older adults with cancer (15,16).

Certain strengths of the current study need to be highlighted. The prospective collection of toxicity data removes any recall bias that may lead to underestimation of the same. The assessment in patients undergoing curative intent treatment only is novel and lays stress on the conundrum faced by oncologists when balancing risks and benefits of using potentially aggressive chemotherapy regimens in the neoadjuvant or adjuvant setting. The results will allow patients and oncologists to discuss options with evidentiary basis for expected toxicities when treatment regimens are considered. By validating the CARG risk score in an Indian population, the study provides further evidence for the use of the score across geographical regions.

There are certain limitations to this study. This is a single centre study and the results may not be generalizable to practice across India. There is an under-representation of non-gastrointestinal cancers and this may hamper the generalization of the study results to all solid tumors. Additionally, other common solid tumors like lung cancers, head and neck

cancers and genitourinary cancers have not been evaluated in this study. The rate of grade 3-5 toxicities was much higher than planned as per baseline statistical considerations – this may relate to the preponderance of GI cancers in the study population, besides other differences in baseline characteristics of the patient cohorts as has been previously discussed. Additionally, while information with regard to correlation of the CARG risk score with grade 1-2 toxicities has been provided, the study was not statistically powered to provide an answer for the same. We also do not have information on patient related outcomes in the study.

Going forward, future directions with regard to the CARG risk assessment include developing paradigms for the degree of dose modifications required in patients based on the score. Patients preferences with regard to tumor related endpoints versus toxicity limiting QOL based on toxicity risk assessment can be explored in trials, especially in the advanced cancer setting. Non-chemotherapeutic systemic treatment options like targeted therapy and immunotherapy can be assessed by the risk score for predicting toxicity.

In conclusion, the current study validates the CARG risk score in predicting for grade 3-5 toxicities in Indian older adult cancer patients receiving curative intent chemotherapy. The score contributes to informed clinical decision making with regard to planning treatment and expectation of toxicity in this cohort of patients. Additionally, indices such as ECOG PS and Charlson Comorbidity Index are inadequate to predict for toxicities and should only be used along with other measures to predict for chemotherapy related toxicities.

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Figure legends:

Figure 1- CARG (A) vs. (B) ACCI vs. (C) ECOG PS predict Grade 3 to 5 toxicity

Tables

Table 1 - Baseline characteristics of patients

Characteristic	Current study Number (%) (n=270)	CARG training cohort (n=500)
Mean age in years (range)	69 (65-83)	73 (65-91)
Gender • Female • Male	 121 (45) 149 (55)	 281 (56) 219 (44)
Comorbidities • Hypertension • Diabetes mellitus • Coronary artery disease • Chronic kidney disease	 114 (42) 71 (26) 12 (4) 3 (1)	 52% - 20% -
Number of comorbidities • 0 • 1 • >=2	 125 (46) 95 (35) 50 (19)	 10% - -
Cancer stage • Stage I-III	 270 (100)	 191 (38)
Undergone resection	210 (78)	-
ECOG performance status (clinician assessed) • 0/1 • 2	 230 (85) 40 (15)	 402 (80) * 86 (17) **

Factors assessed in CARG		
• Age ≥ 72 years	60 (22)	270 (54)
• Cancer type GI or GU	212 (79)	185 (37)
• Chemotherapy dosing, standard dose	205 (76)	380 (76)
• No. of chemotherapy drugs, polychemotherapy	194 (72)	351 (70)
• Haemoglobin < 11 g/dL (male), < 10 g/dL (female)	99 (37)	62 (12)
• Creatinine clearance < 34 mL/min	5 (2)	44 (9)
• Hearing, fair or worse	19 (7)	123 (25)
• No. of falls in last 6 months, 1 or more	18 (7)	91 (18)
• IADL: Taking medications, with some help/unable	29 (11)	39 (8)
• MOS: Walking 1 block, somewhat limited/limited a lot	17 (6)	109 (22)
• MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	18 (7)	218 (44)
Median overall risk score	6	7
Risk stratification		
• Low risk (0-5 points)	72 (27)	128 (26)
• Intermediate risk (6-9 points)	164 (61)	227 (45)
• High risk (10-19 points)	34 (13)	109 (22)
Age adjusted Charlson's Comorbidity Index		
• <=4	111(41)	-
• >4	159(59)	-

*equivalent to KPS>=80; ** equivalent to KPS 60-70

Table 2 – Treatment related Grade 3 – grade 5 toxicities

Toxicity type	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Haematological			
Anaemia	14 (5)	0	0
Neutropenia	18 (7)	8(3)	0
Thrombocytopenia	6 (2)	1 (0.4)	0
Febrile neutropenia	12 (4)	2 (0.7)	3(1)
Cumulative haematological	46 (17)	11 (4)	3(1)
Non-haematological			
Diarrhoea	16 (6)	4 (2)	3(1) *
Vomiting	12 (4)	1(0.4)	1(0.3) **
Mucositis	10 (4)	0	
Constipation	1 (0.4)	0	
Hand-foot-syndrome	1 (0.4)	-	
Neuropathy	3 (1)	-	
Infection with normal ANC	47 (17)	7(3)	
Hyponatremia	8 (3)	2 (0.7)	
Fatigue	24 (9)	-	
Sudden cardiac death			4(1)
Cumulative non-haematological	99(37)	13(5)	8(3)
Cumulative (all toxicities)	119(44)	22(8)	11(4)

*All 3 patients developed dehydration with resulting acute renal failure. **Patient developed grade 4 vomiting with irreversible grade 4 hyponatremia resulting in death

Table 3 - Ability of CARG Risk Score Versus Physician assessed ECOG PS Versus Age adjusted Charlson's Comorbidity Index (ACCI) to Predict Grade 3-5 Chemotherapy Toxicity

Risk Stratification	No toxicity		Toxicity		p value
	Number	%	Number	%	
CARG risk score • Low • Intermediate • High	 42 81 7	 58 49 21	 30 83 27	 42 51 79	0.001
Physician assessed ECOG PS • 0 • 1 • 2	 5 108 17	 56 49 43	 4 113 23	 44 51 57	0.69
Age adjusted Charlson's Comorbidity Index • <=4 • >4	 55 75	 50 47	 56 84	 50 53	0.7

Figure 1 – Ability of CARG risk score (A) versus (B) Age adjusted Charlson Comorbidity Index (ACCI) versus (C) ECOG Performance Status Index to predict Grade 3 to 5 chemotherapy toxicity.

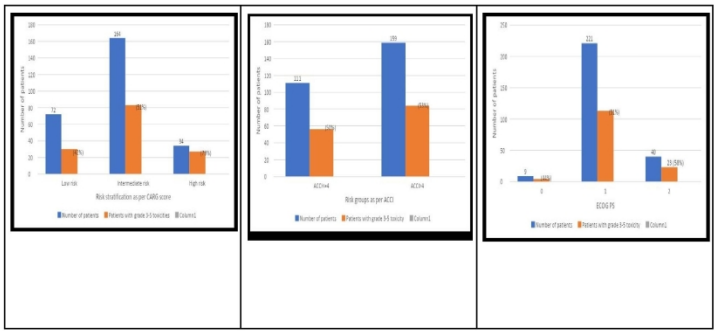

Figure 1- CARG (A) vs. (B) ACCI vs. (C) ECOG PS predict Grade 3 to 5 toxicity

215x279mm (300 x 300 DPI)

Supplementary table 1 – Treatment- related Grade 1 – grade 2 toxicities

Toxicity type	Grade 1/2 toxicities (%)
Haematological	
Anaemia	148(55)
Neutropenia	52(19)
Cumulative haematological	160(59)
Non-haematological	
Diarrhoea	131(49)
Vomiting	140(52)
Mucositis	57(21)
Constipation	41(15)
Hand-foot-syndrome	59(22)
Neuropathy	75(28)
Hyponatremia	17(6)
Fatigue	197(73)
Cumulative non-haematological	230(85)
Cumulative (all toxicities)	234(87)

Supplementary table 2 - Ability of individual factors in the CARG risk score to predict for Grade 3 to 5 toxicities

Risk factor	Prevalence		Toxicity		p value	OR (95% CI)
	Number	%	Number	%		
Age >=72 years	60	22	34	57	0.4	1.28 (0.72-2.29)
Cancer type (GI or GU)	212	79	116	55	0.07	1.71 (0.95-3.08)
Chemotherapy dosing, standard dose	201	74	101	50	0.37	0.77 (0.45-1.35)
Polychemotherapy	194	72	106	55	0.14	1.48 (0.87-2.54)
Haemoglobin <11gm% (male), <10gm% (female)	99	37	65	66	0.001	2.45(1.47-4.09)
Creatinine clearance <34ml/min	5	2	3	60	0.71	1.4(0.23-8.52)
Hearing, fair or worse	19	7	10	53	0.94	1.03(0.41-2.63)
No. of falls in last 6 months, >=1	18	7	10	56	0.75	1.17(0.45-3.07)
IADL, taking medications, with some help/unable	29	11	17	59	0.44	1.336 (0.62-2.97)
MOS, walking 1 block equivalent, somewhat limited/limited a lot	17	6	11	65	0.27	1.76 (0.63-4.91)
MOS, decreased social activity because of physical/emotional health, limited at least sometimes	18	7	12	67	0.19	1.94(0.71-5.32)

Precis

The CARG risk score was studied prospectively in older adult cancer patients being treated with curative intent and accurately predicts for grade 3-5 toxicities. The score can be incorporated into clinical decision making for older adults with cancer, and performed better than traditional indices such as the age adjusted Charlson Comorbidity Index and ECOG PS.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	9
Objectives	3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			13

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Prospective validation of the Cancer Ageing Research Group (CARG) score in geriatric patients undergoing curative intent chemotherapy: A simple assay to predict clinically relevant toxicity in the elderly

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Title – **Prospective validation of the Cancer Ageing Research Group (CARG) score in geriatric patients undergoing curative intent chemotherapy: A simple assay to predict clinically relevant toxicity in the elderly**

TITLE PAGE

Running title –CARG score in older Indian cancer patients undergoing curative-intent chemotherapy

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1. Dr. Vikas Ostwal

Author contribution - Conception and design, analysis and interpretation of data, drafting of manuscript, Final approval of the submitted version.

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Author contribution - Conception and design, analysis and interpretation of data, drafting of manuscript, Final approval of the submitted version.

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Author contribution - Conception and design, analysis and interpretation of data, drafting of manuscript, Final approval of the submitted version.

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1. Name of the Ethics committee: Institutional Ethics committee, Tata Memorial Centre, Parel, Mumbai.
2. IEC approval ID: IEC/1019/1716/001
3. The participants gave informed consent before taking part in the study.

Word count: 3398 (excluding abstract and references)

Data Availability statement: Data are available upon reasonable request

Abstract:

Importance:

The Cancer Aging Research Group (CARG) toxicity score is used to assess toxicity risk in geriatric patients receiving chemotherapy.

Objective:

The primary aim was to validate the CARG score in geriatric patients treated with curative intent chemotherapy in predicting Grade 3-5 toxicities.

Design:

This was a longitudinal prospective observational study

Setting:

Tata Memorial Hospital, Mumbai, India, a tertiary cancer care referral centre.

Participants:

Patients age >=65 with gastrointestinal, breast or gynaecological stage I-III cancers being planned for curative intent chemotherapy. A total of 270 patients were required for accrual in the study.

Exposure(s):

Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk).

Main Outcome(s) and Measure(s):

The primary endpoint of the study was to evaluate whether the CARG risk score predicted for grade 3-5 toxicities.

Results:

The study cohort of 270 patients had a mean age of 69 years (65-83), with the most common cancers being gastrointestinal (79%). Fifty-two percent of patients had at-least one grade 3-5 toxicity. The risk of toxicity was increased with increasing risk score (42% low, 51% medium, 79% high risk; P < .001). There was no association between either ECOG PS (p=0.69) or age adjusted Charlson Comorbidity Index (p=0.79) risk categories and grade 3-5 chemotherapy toxicity.

Conclusions and Relevance:

The current study validates the CARG risk score in predicting for grade 3-5 toxicities in geriatric oncology patients receiving curative intent chemotherapy and can be considered as standard of care before planning chemotherapy in every elderly patient.

Key words – CARG risk; Hurria score, curative, ECOG PS, Charlson Comorbidity Index, chemotoxicity

Strengths and limitations of the study:

- The CARG risk score is a simple tool comprising easily available clinical information.
- This is a prospective study to assess CARG risk score in elderly patients treated with curative intent to predict for grade 3-5 toxicities.
- CARG score performed better than traditional indices such as the age adjusted Charlson Comorbidity Index and ECOG PS.
- The results suggest that the CARG score is valid in the studied population and can be routinely used in clinical practice.
- This study does not include palliative patients and mainly GI cancer patients were recruited.

Manuscript:

Introduction

Older adult patients (age >=65 years) with cancer represent a growing proportion of patients in community clinical practice, primarily due to increasing life-spans as well as medical

progress contributing to decreased morbidity and mortality from other causes (1). Elderly patients comprise anywhere between 20% to 60% in community oncology practice, with variances based on access to cancer care, disease stage and centre specific management strategies (2,3).

The age adjusted Charlson Comorbidity Index (ACCI) and ECOG Performance status (PS) amongst others have often been used to quantify risks and predict for outcomes in older adults with cancer, but there is limited data for correlation between these indices and treatment related side effects (4–6). The Cancer Aging Research Group (CARG) risk score, developed by Hurria and colleagues, is an easy-to-use tool that predicts for significant chemotherapy related toxicities (grade 3- grade 5) in older North American adults >/= 65 years starting on chemotherapy (7,8). Based on their training samples and subsequent validation studies, the investigators clearly identified low, mid and high-risk groups predicting for increasing rates of grade 3-5 toxicities (low risk: 30%, intermediate risk: 52%, high risk: 83%) with statistical significance (P<0.001). The CARG risk score has been validated in other countries and in specific tumor sites to varying degrees (9,10).

In older adults being treated with curative intent chemotherapy, there is the possibility of treating oncologists using standard doses to maximize outcomes, despite patient related indicators suggesting a requirement for lower doses. This is a unique scenario where further information on risks and benefits would allow for informed clinical decision making on doses and drugs to be used. As patients with all stages of cancer were included in the CARG studies, the ambiguity with regard to its usage in patients being treated with potentially curative intent lends itself to re-examination.

With this background, the investigators conducted a longitudinal prospective study with the primary aim of validating the CARG risk score in Indian older cancer patients treated with

curative intent chemotherapy (neoadjuvant or/and adjuvant chemotherapy). Secondary and objectives included correlation of the age adjusted Charlson Comorbidity Index (ACCI) and physician measured ECOG PS with grade 3-5 toxicities. An exploratory component of the study involved an estimation of grade 1 and grade 2 toxicities and their correlation with the CARG risk score.

Materials and methods

Patient selection and design

The study was designed as a longitudinal prospective observational study to validate the CARG risk score in predicting chemotherapy toxicity risk in elderly patients. The study was conducted at the Tata Memorial Hospital and enrolled consecutive patients aged>=65 years, chemotherapy naïve, with a histological diagnosis of gastrointestinal, breast or gynecological cancer, stage I-III disease and planned for neoadjuvant or adjuvant systemic chemotherapy as a potentially curative treatment option.

The study was designed by investigators from the Department of Medical Oncology of the Tata Memorial Hospital and was approved by the ethics committee (IEC/1019/1716/001). The study was registered at Clinical trial registry of India (CTRI/2016/10/007357). Written informed consent was obtained from all patients before inclusion in the study.

Patient and public involvement:

There was no public or patient involvement in design, conduct or results declaration of the study.

Study procedures

Data regarding tumor type and stage, pre-treatment laboratory values, and chemotherapy regimen were recorded. All patients underwent standard pre-chemotherapy work up, including evaluation of end organ function. Patients were planned for chemotherapy by treating oncologist (with an assessment of ECOG PS and ACCI), who was blinded to the risk score. A trained medical doctor calculated the CARG risk score for patients enrolled in the study. The assessment of the score by the trained medical doctor was independently reviewed by an oncologist who was not part of the treating team (7) . Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk), with division of the scores into low risk (0-5 points), intermediate risk (6 to 9 points) and high risk (10-19 points) as per the classification in the original study by Hurria et al (7). One modification of the original CARG risk score which was used in the current study was the measurement of 'Walking 1 block'. The concept of measuring distances by a block is not prevalent in India and hence, a distance of 100 meters in the immediate vicinity of the hospital was measured and patients were scored on their ability to walk the same. The chemotherapy dosing for the first cycle of chemotherapy was categorized as 'standard' if 100% doses were planned and 'dose reduced' if any dose below 100% was used. The decision for dose modifications, whether initial or subsequent, was based on assessment by treating oncologist. Besides CARG risk score, the age adjusted Charlson's Comorbidity Index (ACCI) was calculated for all patients as part of standard assessment of older adults with cancer. A cut-off of 4 points (<=4 and >4) was used to differentiate between low and high CCI scores (11). Patients were followed from beginning till the end of chemotherapy course across all cycles of therapy, though occurrence of a single grade 3-4 toxicity was considered as an endpoint for the purpose of toxicity calculation in the study. Toxicities were captured prospectively at all clinical visits (by treating oncologist and trained medical doctor) and graded as per National Cancer Institute

Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Decision on relatedness of toxicity to chemotherapy was made by treating physician. Laboratory values were captured as grade 1 to 5 toxicity if they met the criteria on the date of scheduled chemotherapy or when patient was seeking attention because of treatment related toxicities.

Outcomes

The primary outcome of the study was the occurrence of any grade 3-5 chemotherapy related toxicity over the course of planned treatment and its association with the CARG risk score. The planned secondary endpoints of the study were the correlation of ACCI and ECOG PS with grade 3-5 chemotherapy related toxicity. Occurrence of any grade 1-2 chemotherapy related toxicity and its correlation with CARG risk score was an exploratory aspect of the study.

Statistical analysis

Descriptive analyses were performed to enumerate patient, tumor, treatment characteristics, CARG risk scores and ACCI. The incidence of grade 3 to grade 5 toxicities were calculated and compared between CARG risk groups, and ECOG PS cohorts by using the chi-square test. The CARG risk score is not routinely used in clinical practice in our institution and we did not have baseline data for the same for the purpose of sample size calculation . We conducted an internal audit of elderly patients with breast, gastrointestinal and gynecological cancers receiving curative intent chemotherapy in our hospital and found a 20 % incidence of grade 3-grade 5 toxicities in elderly patients with ECOG PS 0/1 and controlled or absent comorbidities (surrogate for “low risk) as opposed to 36% in elderly patients with ECOG PS 2 with or without multiple uncontrolled comorbidities (surrogate for “ high risk”). Extrapolating these results, a power of 80% and alpha of 5% with 1 sided assumption was

required with an estimated sample size required being 246 patients. Assuming an attrition rate of 10%, a total of 270 patients were required for enrolment in the study. Chi square test was performed to test the association of the CARG risk score, PS, and ACCI with G 3-5 toxicities and for association of CARG risk score with grade 1-2 toxicities as well dose modifications. The predictive ability of the CARG risk score was evaluated by calculating receiver-operating characteristic (ROC) curves and calculating the area under the curve (also known as C-statistic). ROC curves were also calculated for ECOG PS and ACCI. All analyses were performed using SPSS version 25. All tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Patient and treatment characteristics

The study completed accrual of 270 patients, with mean age of patients being 69 years (range:65-83), 121 (45%) female patients and 212 patients (79%) having gastrointestinal cancers. For purposes of comparison, data from the seminal CARG study by Hurria et al is provided for comparison (table 1). Details of chemotherapeutic regimens are presented in supplementary table 1.

Chemotherapy toxicity

At least one grade 3 to 5 toxicity was seen in 140 patients (52%), with 119 (44%) having grade 3, 22 (8%) having grade 4, and 11(4%) grade 5 toxicities. Grade 3-5 haematological and non-haematological toxicities occurred in 60 patients (22%) and 120 (45%) patients respectively. Common haematological toxicities were neutropenia in 26 (10%) and febrile neutropenia in 17 (6%) patients, while common non-haematological toxicities were infections, fatigue and diarrhoea in 54 (20%), 24 (9%) and 23 (9%) patients respectively (table 2).

The incidence of grade 1 to grade 2 toxicities are listed in supplementary table 2.

Correlation of CARG score with toxicity and dose modifications

The median overall CARG risk score was 6 (range, 0 to 19). Of the 270 patients, 72 (27%), 164 (61%) and 34 (13%) were classified as low, intermediate and high risk, respectively (table 1). Grade 3-5 toxicities were seen in 30(42%), 83 (51%) and 27 (79%) patients with low, intermediate and high-risk score. There was a significant difference in toxicity amongst the risk groups ($p<0.001$) (figure 1 and table 2). The odds of a patient classified as intermediate risk having a grade 3-5 toxicity as compared to patient with low risk was 1.64 (95% CI: 1.23-2.13), while the odds of a patient classified as high risk having a grade 3-5 toxicity as compared to patient with low risk was 7.58 (95% CI:2.61-21.73). Area under the ROC curve for the predictive model in the current cohort was 0.63 (95% CI: 0.57-0.7). The correlation of individual components of the CARG risk score with grade 3-5 toxicities is enumerated in supplementary table 3.

Grade 1-2 toxicities were seen in 61(86%), 144(88%) and 29 (85%) patients with low, intermediate and high-risk score. There was no significant difference in toxicity amongst the CARG risk groups ($p=0.79$).

The incidence of grade 2 peripheral neuropathy and grade 2 hand-foot-syndrome (HFS) are separately reported as these are specifically associated with diminished function. The incidence of grade 2 neuropathy was seen in 5 (7%), 11 (7%) and 2 (6%) patients in the low, intermediate and high-risk categories, respectively. There was no significant difference in grade 2 neuropathy amongst the CARG risk groups ($p=0.97$). The incidence of grade 2 HFS was seen in 5 (7%), 18 (11%) and 2 (6%) patients in the low, intermediate and high-risk categories, respectively. There was no significant difference in grade 2 HFS amongst the CARG risk groups ($p=0.47$)

Upfront dose modifications in chemotherapy regimens were performed in 65 patients (24%). Subsequent dose reductions were made in 89 patients (33%). On further analysis, these subsequent dose modifications were made in 18 (25%), 59 (36%) and 12 (35%) patients in the low, intermediate and high-risk categories, respectively. The differences in proportion of dose modifications were not statistically significant between the 3 groups (p=0.244).

Association of grade 3-5 toxicity with Age adjusted Charlson Comorbidity Index (ACCI) and ECOG PS

The median ACCI was 5. A CCI<=4 was seen in 111 patients (41%), while 159 patients (59%) had a CCI>=4. There was no significant difference in toxicities amongst both groups of patients (p=0.7) (figure 1 and table 3). The ROC of the model with CCI (as a continuous variable) was 0.48 (95% CI: 0.41-0.55), which was lower than the ROC of the CARG risk score model, 0.63.

ECOG PS was 0, 1 and 2 in 9(3%), 221(82%) and 40 (15%) patients, respectively. There was no significant difference in toxicities amongst both groups of patients (p=0.69) (figure 1 and table 3). The ROC of the model with ECOG PS (as a continuous variable) was 0.52 (95% CI: 0.45-0.59), which was lower than the ROC of the CARG risk score model, 0.63.

Discussion

This study validates the CARG risk score in older Indian patients receiving curative-intent chemotherapy for stage I-III gastrointestinal, breast and gynecological cancers, though the association between rates of severe chemotherapy toxicity and CARG risk groups as being discriminatory was modest (AU-ROC 0.63). No association was found between ECOG PS and burden of comorbidities as measured by the ACCI with severe chemotherapy related toxicities.

There is a significant knowledge gap in terms of how older patients in general and older patients with cancer fare in the Indian scenario. Limited data suggests no defined care structure for older patients with cancer in India as well as only low-moderate awareness and use of geriatric assessment in older patients with cancer (3,12) . Available evidence from India suggests that 98% of older adult cancer patients have vulnerabilities in at least one geriatric domain, though the specific vulnerabilities appear to differ from previously published data (13). Such a high and differential vulnerability profile in these patients suggests that they may have a different incidence of toxicities with standard chemotherapy regimens. With such a background, it was essential to evaluate the validity of the CARG risk score before routine advocation in older adult patients.

There are some important differences between the populations of the current study and the seminal CARG study. The current study had only patients with stage I-III disease, while the CARG study had 38% with non-metastatic disease. Other relevant differences between the cohorts include a younger mean age (69 vs. 73 years), lesser comorbidities (46% with no comorbidities vs. 10% with no comorbidities), and better performance on a number of individual variables in the CARG risk score (better hearing, lesser number of falls, better social activity and effort tolerance). There were also a lower proportion of patients with high-risk score in the current study (13% vs. 22%). These differences, coupled with lack of patients with metastatic disease in the study cohort, indicate that patients in the current study were a well preserved and presumably fitter group of patients with lesser disease burden and potential for toxicities.

Despite the differences in patient cohorts in terms of baseline characteristics, the current study validated the Cancer Aging Research Group (CARG) risk score in predicting grade 3 to grade 5 chemotherapy related toxicities. The low, intermediate and high risk CARG groups predicted for increasing incidences of grade 3-5 toxicities with statistical significance. The

odds ratios between individual risk groups for predicting grade 3-5 toxicity was also statistically significant, highlighting the differential capability of the risk score. An unanswered component of the CARG risk assessment was whether it correlated with grade 1-2 toxicities. Previous studies by Moth et al estimating grade 1 and grade 2 toxicities as toxicity burden have not shown a correlation with the CARG risk score (14). This is possibly due to the near universal occurrence of such toxicities in patients receiving chemotherapy. A similar trend was seen in the current study wherein an increasing risk score did not predict for an increased risk of grade 1-2 toxicities. Additionally, in comparison to the predictive capacity of the CARG risk score, the Charlson Comorbidity Index and ECOG PS based risk groups did not predict for incidences of toxicity in the study. These results highlight certain salient points in the study, Firstly, the CARG risk score can be used with confidence in the Indian population to predict for grade 3-5 toxicity. The CARG risk score was evaluated only in a North American elderly adult cohort initially and the current study provides validation for the score in the Indian context. Secondly, despite being a better-preserved cohort in comparison to the population in the seminal study as well as having only patients on curative intent therapy, a high proportion of patients across risk groups developed grade 3-5 toxicity which may be life-threatening. Thus, it is imperative to carefully assess the trade-off between objectives such as survival and downstaging versus potentially life-threatening toxicities while planning curative intent chemotherapy in older adult patients. Thirdly, the area under the ROC for the current study was 0.63 and is lower in comparison to the original study (0.72), though very similar to the results of the validation study (0.65) by the CARG group (8). Though this indicates a modest discriminatory capability for the CARG risk score in the current study, it is probably also reflective of the true value of the score in prediction of severe chemotherapy related toxicities. Smaller studies by Australian investigators have also previously commented on this lack of discriminatory value with the CARG risk score (14).

Finally, using a global assessment score such as ECOG PS or only one aspect of an assessment profile such as comorbidity status (as in the case of ACCI) would not accurately capture the heterogeneity of the older adult population. This is reflected in the inadequacy of ECOG PS and ACCI in predicting for toxicities and hence, these indices should only be used in conjunction with other indices as measures of assessment in older adults with cancer (15,16).

We also attempted to correlate the CARG risk scores with the necessity for further dose reductions during chemotherapy. There were no statistically significant differences between the risk groups in terms of requirement for subsequent dose modifications post initiation of therapy. This can partially be explained by the fact that a high proportion of patients (24%) underwent initial dose reductions when planned for therapy by the treating physicians who were blinded to the CARG risk score. Such an upfront dose reduction may have masked any possible correlation between the risk scores and need for dose modifications during chemotherapy.

Certain strengths of the current study need to be highlighted. The prospective collection of toxicity data removes any recall bias that may lead to underestimation of the same. The assessment in patients undergoing curative intent treatment only is novel and lays stress on the conundrum faced by oncologists when balancing risks and benefits of using potentially aggressive chemotherapy regimens in the neoadjuvant or adjuvant setting. The results will allow patients and oncologists to discuss options with evidentiary basis for expected toxicities when treatment regimens are considered. By validating the CARG risk score in an Indian population, the study provides further evidence for the use of the score across geographical regions.

There are certain limitations to this study. This is a single centre study and the results may not be generalizable to practice across India. There is an under-representation of non-gastrointestinal cancers and this may hamper the generalization of the study results to all solid tumors. Additionally, other common solid tumors like lung cancers, head and neck cancers and genitourinary cancers have not been evaluated in this study. The rate of grade 3-5 toxicities was much higher than planned as per baseline statistical considerations – this may relate to the preponderance of GI cancers in the study population, besides other differences in baseline characteristics of the patient cohorts as has been previously discussed. Additionally, while information with regard to correlation of the CARG risk score with grade 1-2 toxicities has been provided, the relevance of this is limited due to the fact that almost all patients on systemic therapy develop some grade 1 or 2 toxicity. Again, the CARG score was developed to predict for grade 3-5 toxicities, not grade 1-2 toxicities and thus, the inability to differentially predict for Grade 1-2 in the current study is not surprising . We also do not have information on patient related outcomes in the study.

Going forward, future directions with regard to the CARG risk assessment include developing paradigms for the degree of dose modifications required in patients based on the score. Patients preferences with regard to tumor related endpoints versus toxicity limiting QOL based on toxicity risk assessment can be explored in trials, especially in the advanced cancer setting. Non-chemotherapeutic systemic treatment options like targeted therapy and immunotherapy can be assessed by the risk score for predicting toxicity. Based on the current study, we plan to use the CARG score routinely in our hospital as well plan prospective studies utilizing the score to estimate dose modifications in relation to risk assessment by the score.

In conclusion, the current study validates the CARG risk score in predicting for grade 3-5 toxicities in Indian older adult cancer patients receiving curative intent chemotherapy. The

score contributes to informed clinical decision making with regard to planning treatment and expectation of toxicity in this cohort of patients. Additionally, indices such as ECOG PS and Charlson Comorbidity Index are inadequate to predict for toxicities and should only be used along with other measures to predict for chemotherapy related toxicities.

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Figure legends:

Figure 1- CARG (A) vs. (B) ACCI vs. (C) ECOG PS predict Grade 3 to 5 toxicity

Tables

Table 1 - Baseline characteristics of patients

Characteristic	Current study Number (%) (n=270)	CARG training cohort (n=500)
Mean age in years (range)	69 (65-83)	73 (65-91)
Gender • Female • Male	 121 (45) 149 (55)	 281 (56) 219 (44)

Comorbidities • Hypertension • Diabetes mellitus • Coronary artery disease • Chronic kidney disease	 114 (42) 71 (26) 12 (4) 3 (1)	 52% - 20% -
Number of comorbidities • 0 • 1 • >=2	 125 (46) 95 (35) 50 (19)	 10% - -
Cancer stage • Stage I-III	 270 (100)	 191 (38)
Undergone resection	210 (78)	-
ECOG performance status (clinician assessed) • 0/1 • 2	 230 (85) 40 (15)	 402 (80) * 86 (17) **
Factors assessed in CARG • Age ≥ 72 years • Cancer type GI or GU • Chemotherapy dosing, standard dose • No. of chemotherapy drugs, polychemotherapy • Hemoglobin < 11 g/dL (male), < 10 g/dL (female) • Creatinine clearance < 34 mL/min • Hearing, fair or worse • No. of falls in last 6 months, 1 or more • IADL: Taking medications, with some help/unable • MOS: Walking 1 block, somewhat limited/limited a lot • MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	 60 (22) 212 (79) 205 (76) 194 (72) 99 (37) 5 (2) 19 (7) 18 (7) 29 (11) 17 (6) 18 (7)	 270 (54) 185 (37) 380 (76) 351 (70) 62 (12) 44 (9) 123 (25) 91 (18) 39 (8) 109 (22) 218 (44)
Median overall risk score Risk stratification • Low risk (0-5 points) • Intermediate risk (6-9 points) • High risk (10-19 points)	6 72 (27) 164 (61) 34 (13)	7 128 (26) 227 (45) 109 (22)
Age adjusted Charlson's Comorbidity Index • <=4 • >4	 111(41) 159(59)	 - -

*equivalent to KPS>=80; ** equivalent to KPS 60-70

Table 2 – Treatment related Grade 3 – grade 5 toxicities

Toxicity type	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Haematological			
Anemia	14 (5)	0	0
Neutropenia	18 (7)	8(3)	0
Thrombocytopenia	6 (2)	1 (0.4)	0
Febrile neutropenia	12 (4)	2 (0.7)	3(1)
Cumulative haematological	46 (17)	11 (4)	3(1)
Non-haematological			
Diarrhoea	16 (6)	4 (2)	3(1) *
Vomiting	12 (4)	1(0.4)	1(0.3) **
Mucositis	10 (4)	0	
Constipation	1 (0.4)	0	
Hand-foot-syndrome	1 (0.4)	-	

Neuropathy	3 (1)	-	
Infection with normal ANC	47 (17)	7(3)	
Hyponatremia	8 (3)	2 (0.7)	
Fatigue	24 (9)	-	
Sudden cardiac death			4(1)
Cumulative non-haematological	99(37)	13(5)	8(3)
Cumulative (all toxicities)	119(44)	22(8)	11(4)

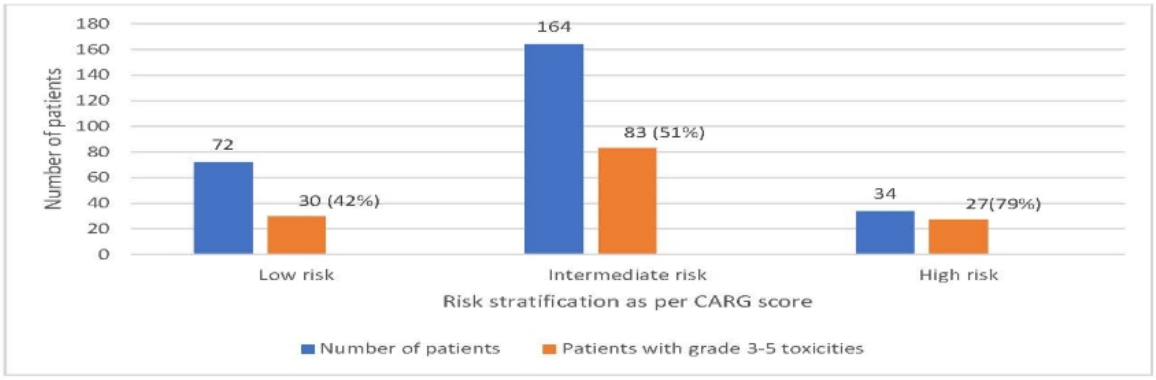
*All 3 patients developed dehydration with resulting acute renal failure. **Patient developed grade 4 vomiting with irreversible grade 4 hyponatremia resulting in death

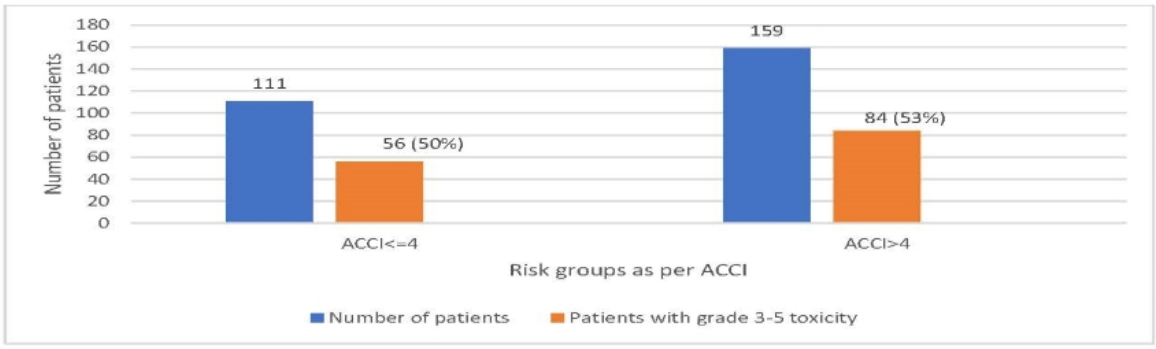
Table 3 - Ability of CARG Risk Score Versus Physician assessed ECOG PS Versus Age adjusted Charlson's Comorbidity Index (ACCI) to Predict Grade 3-5 Chemotherapy Toxicity

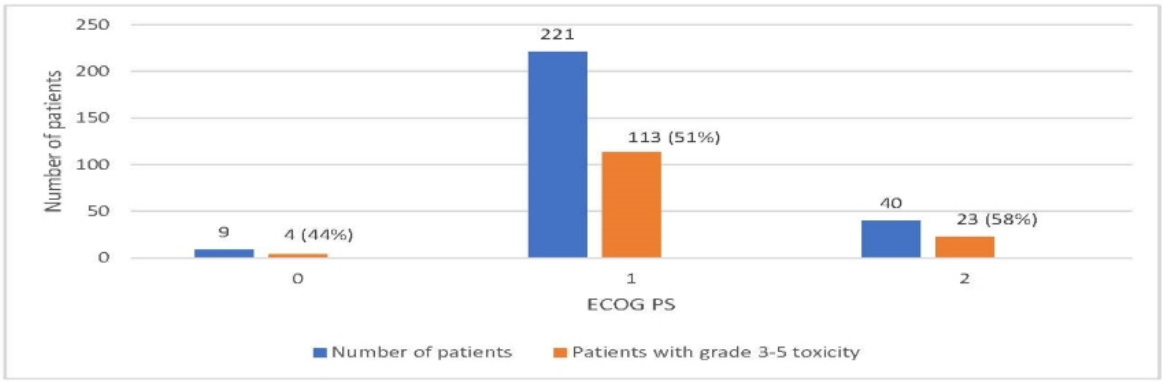
Risk Stratification	No toxicity		Toxicity		p value
	Number	%	Number	%	
CARG risk score • Low • Intermediate • High	 42 81 7	 58 49 21	 30 83 27	 42 51 79	0.001
Physician assessed ECOG PS • 0 • 1 • 2	 5 108 17	 56 49 43	 4 113 23	 44 51 57	0.69

Age adjusted Charlson's Comorbidity Index • <=4 • >4	 55 75	 50 47	 56 84	 50 53	0.7

Figure 1 – Ability of CARG risk score (A) versus (B) Age adjusted Charlson Comorbidity Index (ACCI) versus (C) ECOG Performance Status Index to predict Grade 3 to 5 chemotherapy toxicity.







Supplementary table 1 – Details of chemotherapy

Chemotherapy regimens	Number (percentage)
Platinum containing regimens	**159(59)**
Oxaliplatin containing regimens	123 (46)
• Docetaxel-Oxaliplatin- 5 -fluorouracil	50 (19)
• Capecitabine-Oxaliplatin	26 (10)
• 5-fluorouracil - leucovorin-oxaliplatin	33 (12)
• 5-fluorouracil - leucovorin-oxaliplatin-irinotecan	1 (0.4)
• Epirubicin- Capecitabine-Oxaliplatin	10 (4)
• Gemcitabine-Oxaliplatin	2 (1)
• Epirubicin- Oxaliplatin - 5-fluorouracil	1 (0.4)
Cisplatin containing regimens	19(7)
• Gemcitabine-Cisplatin	19 (7)
Carboplatin containing regimens	17 (6)
• Paclitaxel- Carboplatin	6 (2)
• Carboplatin monotherapy	11 (4)
Non-Platinum containing regimens	**111(41)**
• Epirubicin – Cyclophosphamide	9 (3)
• Adriamycin – Cyclophosphamide	19 (7)
• Docetaxel – Cyclophosphamide	1 (0.4)
• Cyclophosphamide-methotrexate – 5-fluorouracil	1 (0.4)
• 5-fluorouracil/leucovorin monotherapy	10 (4)
• Capecitabine monotherapy	25 (9)
• Gemcitabine monotherapy	26 (10)
• Paclitaxel - Trastuzumab	9 (3)
• Paclitaxel monotherapy	3 (1)
• Docetaxel - 5-fluorouracil	5 (2)
• Gemcitabine- nab-Paclitaxel	2 (1)
• Gemcitabine Capecitabine	1 (0.4)
Chemotherapy timing	
• Neoadjuvant	5 (2)

• Adjuvant	178 (66)
• Perioperative (neoadjuvant and adjuvant)	87 (32)

Supplementary table 2 – Treatment- related Grade 1 – grade 2 toxicities

Toxicity type	Grade 1/2 toxicities (%)
Hematological	
Anemia	148(55)
Neutropenia	52(19)
Cumulative hematological	160(59)
Non-hematological	
Diarrhoea	131(49)
Vomiting	140(52)
Mucositis	57(21)
Constipation	41(15)
Hand-foot-syndrome	59(22)
Neuropathy	75(28)
Hyponatremia	17(6)
Fatigue	197(73)
Cumulative non-hematological	230(85)
Cumulative (all toxicities)	234(87)

Supplementary table 3 - Ability of individual factors in the CARG risk score to predict for Grade 3 to 5 toxicities

Risk factor	Prevalence		Toxicity		p value	OR (95% CI)
	Number	%	Number	%		
Age >=72 years	60	22	34	57	0.4	1.28 (0.72-2.29)
Cancer type (GI or GU)	212	79	116	55	0.07	1.71 (0.95-3.08)
Chemotherapy dosing, standard dose	201	74	101	50	0.37	0.77 (0.45-1.35)
Polychemotherapy	194	72	106	55	0.14	1.48 (0.87-2.54)
Hemoglobin <11gm% (male), <10gm% (female)	99	37	65	66	0.001	2.45(1.47-4.09)
Creatinine clearance <34ml/min	5	2	3	60	0.71	1.4(0.23-8.52)
Hearing, fair or worse	19	7	10	53	0.94	1.03(0.41-2.63)
No. of falls in last 6 months, >=1	18	7	10	56	0.75	1.17(0.45-3.07)
IADL, taking medications, with some help/unable	29	11	17	59	0.44	1.336 (0.62-2.97)
MOS, walking 1 block equivalent, somewhat limited/limited a lot	17	6	11	65	0.27	1.76 (0.63-4.91)
MOS, decreased social activity because of physical/emotional health, limited at least sometimes	18	7	12	67	0.19	1.94(0.71-5.32)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	9
Objectives	3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			13

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Secondary Subject Heading:	Oncology, Pharmacology and therapeutics, Medical management, Geriatric medicine, Health services research
Keywords:	CHEMOTHERAPY, Adult oncology < ONCOLOGY, Gynaecological oncology < ONCOLOGY, Gastrointestinal tumours < ONCOLOGY, Breast tumours < ONCOLOGY, Adverse events < THERAPEUTICS

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Title – **Cancer Ageing Research Group (CARG) score in older adults undergoing curative intent chemotherapy: A prospective cohort study**

TITLE PAGE

Running title –CARG score in older Indian cancer patients undergoing curative-intent chemotherapy

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1. Name of the Ethics committee: Institutional Ethics committee, Tata Memorial Centre, Parel, Mumbai.

2. IEC approval ID: IEC/1019/1716/001

3. The participants gave informed consent before taking part in the study.

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Data Availability statement: Data are available upon reasonable request

Abstract:

Importance:

The Cancer Aging Research Group (CARG) toxicity score is used to assess toxicity risk in geriatric patients receiving chemotherapy.

Objective:

The primary aim was to validate the CARG score in geriatric patients treated with curative intent chemotherapy in predicting Grade 3-5 toxicities.

Design:

This was a longitudinal prospective observational study

Setting:

Tata Memorial Hospital, Mumbai, India, a tertiary cancer care referral centre.

Participants:

Patients age >=65 with gastrointestinal, breast or gynaecological stage I-III cancers being planned for curative intent chemotherapy. A total of 270 patients were required for accrual in the study.

Exposure(s):

Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk).

Main Outcome(s) and Measure(s):

The primary endpoint of the study was to evaluate whether the CARG risk score predicted for grade 3-5 toxicities.

Results:

The study cohort of 270 patients had a mean age of 69 years (65-83), with the most common cancers being gastrointestinal (79%). Fifty-two percent of patients had at-least one grade 3-5 toxicity. The risk of toxicity was increased with increasing risk score (42% low, 51% medium, 79% high risk; P < .001). There was no association between either ECOG PS (p=0.69) or age adjusted Charlson Comorbidity Index (p=0.79) risk categories and grade 3-5 chemotherapy toxicity.

Conclusions and Relevance:

The current study validates the CARG risk score in predicting for grade 3-5 toxicities in geriatric oncology patients receiving curative intent chemotherapy and can be considered as standard of care before planning chemotherapy in every elderly patient.

Key words – CARG risk; Hurria score, curative, ECOG PS, Charlson Comorbidity Index, chemotoxicity

Strengths and limitations of the study:

- The CARG risk score is a simple tool comprising easily available clinical information.
- This is a prospective study to assess CARG risk score in elderly patients treated with curative intent to predict for grade 3-5 toxicities.
- CARG score performed better than traditional indices such as the age adjusted Charlson Comorbidity Index and ECOG PS.
- The results suggest that the CARG score is valid in the studied population and can be routinely used in clinical practice.
- This study does not include palliative patients and mainly GI cancer patients were recruited.

Manuscript:

Introduction

Older adult patients (age >=65 years) with cancer represent a growing proportion of patients in community clinical practice, primarily due to increasing life-spans as well as medical progress contributing to decreased morbidity and mortality from other causes (1). Elderly patients comprise anywhere between 20% to 60% in community oncology practice, with variances based on access to cancer care, disease stage and centre specific management strategies (2,3).

The age adjusted Charlson Comorbidity Index (ACCI) and ECOG Performance status (PS) amongst others have often been used to quantify risks and predict for outcomes in older adults with cancer, but there is limited data for correlation between these indices and treatment related side effects (4–6). The Cancer Aging Research Group (CARG) risk score, developed by Hurria and colleagues, is an easy-to-use tool that predicts for significant chemotherapy related toxicities (grade 3- grade 5) in older North American adults >/= 65 years starting on chemotherapy (7,8). Based on their training samples and subsequent validation studies, the investigators clearly identified low, mid and high-risk groups predicting for increasing rates of grade 3-5 toxicities (low risk: 30%, intermediate risk: 52%, high risk: 83%) with statistical significance (P<0.001). The CARG risk score has been validated in other countries and in specific tumor sites to varying degrees (9,10).

In older adults being treated with curative intent chemotherapy, there is the possibility of treating oncologists using standard doses to maximize outcomes, despite patient related indicators suggesting a requirement for lower doses. This is a unique scenario where further information on risks and benefits would allow for informed clinical decision making on doses and drugs to be used. As patients with all stages of cancer were included in the CARG studies, the ambiguity with regard to its usage in patients being treated with potentially curative intent lends itself to re-examination.

With this background, the investigators conducted a longitudinal prospective study with the primary aim of validating the CARG risk score in Indian older cancer patients treated with curative intent chemotherapy (neoadjuvant or/and adjuvant chemotherapy). Secondary and objectives included correlation of the age adjusted Charlson Comorbidity Index (ACCI) and physician measured ECOG PS with grade 3-5 toxicities. An exploratory component of the study involved an estimation of grade 1 and grade 2 toxicities and their correlation with the CARG risk score.

Materials and methods

Patient selection and design

The study was designed as a longitudinal prospective observational study to validate the CARG risk score in predicting chemotherapy toxicity risk in elderly patients. The study was conducted at the Tata Memorial Hospital and enrolled consecutive patients aged>=65 years, chemotherapy naïve, with a histological diagnosis of gastrointestinal, breast or gynecological cancer, stage I-III disease and planned for neoadjuvant or adjuvant systemic chemotherapy as a potentially curative treatment option.

The study was designed by investigators from the Department of Medical Oncology of the Tata Memorial Hospital and was approved by the ethics committee (IEC/1019/1716/001). The study was registered at Clinical trial registry of India (CTRI/2016/10/007357). Written informed consent was obtained from all patients before inclusion in the study.

Patient and public involvement:

There was no public or patient involvement in design, conduct or results declaration of the study.

Study procedures

Data regarding tumor type and stage, pre-treatment laboratory values, and chemotherapy regimen were recorded. All patients underwent standard pre-chemotherapy work up, including evaluation of end organ function. Patients were planned for chemotherapy by treating oncologist (with an assessment of ECOG PS and ACCI), who was blinded to the risk score. A trained medical doctor calculated the CARG risk score for patients enrolled in the study. The assessment of the score by the trained medical doctor was independently reviewed by an oncologist who was not part of the treating team (7) . Total risk score ranged from 0 (lowest toxicity risk) to 19 (highest toxicity risk), with division of the scores into low risk (0-5 points), intermediate risk (6 to 9 points) and high risk (10-19 points) as per the classification in the original study by Hurria et al (7). One modification of the original CARG risk score which was used in the current study was the measurement of 'Walking 1 block'. The concept of measuring distances by a block is not prevalent in India and hence, a distance of 100 meters in the immediate vicinity of the hospital was measured and patients were scored on their ability to walk the same. The chemotherapy dosing for the first cycle of chemotherapy was categorized as 'standard' if 100% doses were planned and 'dose reduced' if any dose below 100% was used. The decision for dose modifications, whether initial or subsequent, was based on assessment by treating oncologist. Besides CARG risk score, the age adjusted Charlson's Comorbidity Index (ACCI) was calculated for all patients as part of standard assessment of older adults with cancer. A cut-off of 4 points (<=4 and >4) was used to differentiate between low and high CCI scores (11). Patients were followed from beginning till the end of chemotherapy course across all cycles of therapy, though occurrence of a single grade 3-4 toxicity was considered as an endpoint for the purpose of toxicity calculation in the study. Toxicities were captured prospectively at all clinical visits (by treating oncologist and trained medical doctor) and graded as per National Cancer Institute

Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Decision on relatedness of toxicity to chemotherapy was made by treating physician. Laboratory values were captured as grade 1 to 5 toxicity if they met the criteria on the date of scheduled chemotherapy or when patient was seeking attention because of treatment related toxicities.

Outcomes

The primary outcome of the study was the occurrence of any grade 3-5 chemotherapy related toxicity over the course of planned treatment and its association with the CARG risk score. The planned secondary endpoints of the study were the correlation of ACCI and ECOG PS with grade 3-5 chemotherapy related toxicity. Occurrence of any grade 1-2 chemotherapy related toxicity and its correlation with CARG risk score was an exploratory aspect of the study.

Statistical analysis

Descriptive analyses were performed to enumerate patient, tumor, treatment characteristics, CARG risk scores and ACCI. The incidence of grade 3 to grade 5 toxicities were calculated and compared between CARG risk groups, and ECOG PS cohorts by using the chi-square test. The CARG risk score is not routinely used in clinical practice in our institution and we did not have baseline data for the same for the purpose of sample size calculation . We conducted an internal audit of elderly patients with breast, gastrointestinal and gynecological cancers receiving curative intent chemotherapy in our hospital and found a 20 % incidence of grade 3-grade 5 toxicities in elderly patients with ECOG PS 0/1 and controlled or absent comorbidities (surrogate for “low risk) as opposed to 36% in elderly patients with ECOG PS 2 with or without multiple uncontrolled comorbidities (surrogate for “ high risk”). Extrapolating these results, a power of 80% and alpha of 5% with 1 sided assumption was

required with an estimated sample size required being 246 patients. Assuming an attrition rate of 10%, a total of 270 patients were required for enrolment in the study. Chi square test was performed to test the association of the CARG risk score, PS, and ACCI with G 3-5 toxicities and for association of CARG risk score with grade 1-2 toxicities as well dose modifications. The predictive ability of the CARG risk score was evaluated by calculating receiver-operating characteristic (ROC) curves and calculating the area under the curve (also known as C-statistic). ROC curves were also calculated for ECOG PS and ACCI. All analyses were performed using SPSS version 25. All tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Patient and treatment characteristics

The study completed accrual of 270 patients, with mean age of patients being 69 years (range:65-83), 121 (45%) female patients and 212 patients (79%) having gastrointestinal cancers. For purposes of comparison, data from the seminal CARG study by Hurria et al is provided for comparison (table 1). Details of chemotherapeutic regimens are presented in supplementary table 1.

Chemotherapy toxicity

At least one grade 3 to 5 toxicity was seen in 140 patients (52%), with 119 (44%) having grade 3, 22 (8%) having grade 4, and 11(4%) grade 5 toxicities. Grade 3-5 haematological and non-haematological toxicities occurred in 60 patients (22%) and 120 (45%) patients respectively. Common haematological toxicities were neutropenia in 26 (10%) and febrile neutropenia in 17 (6%) patients, while common non-haematological toxicities were infections, fatigue and diarrhoea in 54 (20%), 24 (9%) and 23 (9%) patients respectively (table 2).

The incidence of grade 1 to grade 2 toxicities are listed in supplementary table 2.

Correlation of CARG score with toxicity and dose modifications

The median overall CARG risk score was 6 (range, 0 to 19). Of the 270 patients, 72 (27%), 164 (61%) and 34 (13%) were classified as low, intermediate and high risk, respectively (table 1). Grade 3-5 toxicities were seen in 30(42%), 83 (51%) and 27 (79%) patients with low, intermediate and high-risk score. There was a significant difference in toxicity amongst the risk groups ($p<0.001$) (figure 1 and table 2). The odds of a patient classified as intermediate risk having a grade 3-5 toxicity as compared to patient with low risk was 1.64 (95% CI: 1.23-2.13), while the odds of a patient classified as high risk having a grade 3-5 toxicity as compared to patient with low risk was 7.58 (95% CI:2.61-21.73). Area under the ROC curve for the predictive model in the current cohort was 0.63 (95% CI: 0.57-0.7). The correlation of individual components of the CARG risk score with grade 3-5 toxicities is enumerated in supplementary table 3.

Grade 1-2 toxicities were seen in 61(86%), 144(88%) and 29 (85%) patients with low, intermediate and high-risk score. There was no significant difference in toxicity amongst the CARG risk groups ($p=0.79$).

The incidence of grade 2 peripheral neuropathy and grade 2 hand-foot-syndrome (HFS) are separately reported as these are specifically associated with diminished function. The incidence of grade 2 neuropathy was seen in 5 (7%), 11 (7%) and 2 (6%) patients in the low, intermediate and high-risk categories, respectively. There was no significant difference in grade 2 neuropathy amongst the CARG risk groups ($p=0.97$). The incidence of grade 2 HFS was seen in 5 (7%), 18 (11%) and 2 (6%) patients in the low, intermediate and high-risk categories, respectively. There was no significant difference in grade 2 HFS amongst the CARG risk groups ($p=0.47$)

Upfront dose modifications in chemotherapy regimens were performed in 65 patients (24%). Subsequent dose reductions were made in 89 patients (33%). On further analysis, these subsequent dose modifications were made in 18 (25%), 59 (36%) and 12 (35%) patients in the low, intermediate and high-risk categories, respectively. The differences in proportion of dose modifications were not statistically significant between the 3 groups (p=0.244).

Association of grade 3-5 toxicity with Age adjusted Charlson Comorbidity Index (ACCI) and ECOG PS

The median ACCI was 5. A CCI<=4 was seen in 111 patients (41%), while 159 patients (59%) had a CCI>=4. There was no significant difference in toxicities amongst both groups of patients (p=0.7) (figure 1 and table 3). The ROC of the model with CCI (as a continuous variable) was 0.48 (95% CI: 0.41-0.55), which was lower than the ROC of the CARG risk score model, 0.63.

ECOG PS was 0, 1 and 2 in 9(3%), 221(82%) and 40 (15%) patients, respectively. There was no significant difference in toxicities amongst both groups of patients (p=0.69) (figure 1 and table 3). The ROC of the model with ECOG PS (as a continuous variable) was 0.52 (95% CI: 0.45-0.59), which was lower than the ROC of the CARG risk score model, 0.63.

Discussion

This study validates the CARG risk score in older Indian patients receiving curative-intent chemotherapy for stage I-III gastrointestinal, breast and gynecological cancers, though the association between rates of severe chemotherapy toxicity and CARG risk groups as being discriminatory was modest (AU-ROC 0.63). No association was found between ECOG PS and burden of comorbidities as measured by the ACCI with severe chemotherapy related toxicities.

There is a significant knowledge gap in terms of how older patients in general and older patients with cancer fare in the Indian scenario. Limited data suggests no defined care structure for older patients with cancer in India as well as only low-moderate awareness and use of geriatric assessment in older patients with cancer (3,12) . Available evidence from India suggests that 98% of older adult cancer patients have vulnerabilities in at least one geriatric domain, though the specific vulnerabilities appear to differ from previously published data (13). Such a high and differential vulnerability profile in these patients suggests that they may have a different incidence of toxicities with standard chemotherapy regimens. With such a background, it was essential to evaluate the validity of the CARG risk score before routine advocation in older adult patients.

There are some important differences between the populations of the current study and the seminal CARG study. The current study had only patients with stage I-III disease, while the CARG study had 38% with non-metastatic disease. Other relevant differences between the cohorts include a younger mean age (69 vs. 73 years), lesser comorbidities (46% with no comorbidities vs. 10% with no comorbidities), and better performance on a number of individual variables in the CARG risk score (better hearing, lesser number of falls, better social activity and effort tolerance). There were also a lower proportion of patients with high-risk score in the current study (13% vs. 22%). These differences, coupled with lack of patients with metastatic disease in the study cohort, indicate that patients in the current study were a well preserved and presumably fitter group of patients with lesser disease burden and potential for toxicities.

Despite the differences in patient cohorts in terms of baseline characteristics, the current study validated the Cancer Aging Research Group (CARG) risk score in predicting grade 3 to grade 5 chemotherapy related toxicities. The low, intermediate and high risk CARG groups predicted for increasing incidences of grade 3-5 toxicities with statistical significance. The

odds ratios between individual risk groups for predicting grade 3-5 toxicity was also statistically significant, highlighting the differential capability of the risk score. An unanswered component of the CARG risk assessment was whether it correlated with grade 1-2 toxicities. Previous studies by Moth et al estimating grade 1 and grade 2 toxicities as toxicity burden have not shown a correlation with the CARG risk score (14). This is possibly due to the near universal occurrence of such toxicities in patients receiving chemotherapy. A similar trend was seen in the current study wherein an increasing risk score did not predict for an increased risk of grade 1-2 toxicities. Additionally, in comparison to the predictive capacity of the CARG risk score, the Charlson Comorbidity Index and ECOG PS based risk groups did not predict for incidences of toxicity in the study. These results highlight certain salient points in the study, Firstly, the CARG risk score can be used with confidence in the Indian population to predict for grade 3-5 toxicity. The CARG risk score was evaluated only in a North American elderly adult cohort initially and the current study provides validation for the score in the Indian context. Secondly, despite being a better-preserved cohort in comparison to the population in the seminal study as well as having only patients on curative intent therapy, a high proportion of patients across risk groups developed grade 3-5 toxicity which may be life-threatening. Thus, it is imperative to carefully assess the trade-off between objectives such as survival and downstaging versus potentially life-threatening toxicities while planning curative intent chemotherapy in older adult patients. Thirdly, the area under the ROC for the current study was 0.63 and is lower in comparison to the original study (0.72), though very similar to the results of the validation study (0.65) by the CARG group (8). Though this indicates a modest discriminatory capability for the CARG risk score in the current study, it is probably also reflective of the true value of the score in prediction of severe chemotherapy related toxicities. Smaller studies by Australian investigators have also previously commented on this lack of discriminatory value with the CARG risk score (14).

Finally, using a global assessment score such as ECOG PS or only one aspect of an assessment profile such as comorbidity status (as in the case of ACCI) would not accurately capture the heterogeneity of the older adult population. This is reflected in the inadequacy of ECOG PS and ACCI in predicting for toxicities and hence, these indices should only be used in conjunction with other indices as measures of assessment in older adults with cancer (15,16).

We also attempted to correlate the CARG risk scores with the necessity for further dose reductions during chemotherapy. There were no statistically significant differences between the risk groups in terms of requirement for subsequent dose modifications post initiation of therapy. This can partially be explained by the fact that a high proportion of patients (24%) underwent initial dose reductions when planned for therapy by the treating physicians who were blinded to the CARG risk score. Such an upfront dose reduction may have masked any possible correlation between the risk scores and need for dose modifications during chemotherapy.

Certain strengths of the current study need to be highlighted. The prospective collection of toxicity data removes any recall bias that may lead to underestimation of the same. The assessment in patients undergoing curative intent treatment only is novel and lays stress on the conundrum faced by oncologists when balancing risks and benefits of using potentially aggressive chemotherapy regimens in the neoadjuvant or adjuvant setting. The results will allow patients and oncologists to discuss options with evidentiary basis for expected toxicities when treatment regimens are considered. By validating the CARG risk score in an Indian population, the study provides further evidence for the use of the score across geographical regions.

There are certain limitations to this study. This is a single centre study and the results may not be generalizable to practice across India. There is an under-representation of non-gastrointestinal cancers and this may hamper the generalization of the study results to all solid tumors. Additionally, other common solid tumors like lung cancers, head and neck cancers and genitourinary cancers have not been evaluated in this study. The rate of grade 3-5 toxicities was much higher than planned as per baseline statistical considerations – this may relate to the preponderance of GI cancers in the study population, besides other differences in baseline characteristics of the patient cohorts as has been previously discussed. Additionally, while information with regard to correlation of the CARG risk score with grade 1-2 toxicities has been provided, the relevance of this is limited due to the fact that almost all patients on systemic therapy develop some grade 1 or 2 toxicity. Again, the CARG score was developed to predict for grade 3-5 toxicities, not grade 1-2 toxicities and thus, the inability to differentially predict for Grade 1-2 in the current study is not surprising . We also do not have information on patient related outcomes in the study.

Going forward, future directions with regard to the CARG risk assessment include developing paradigms for the degree of dose modifications required in patients based on the score. Patients preferences with regard to tumor related endpoints versus toxicity limiting QOL based on toxicity risk assessment can be explored in trials, especially in the advanced cancer setting. Non-chemotherapeutic systemic treatment options like targeted therapy and immunotherapy can be assessed by the risk score for predicting toxicity. Based on the current study, we plan to use the CARG score routinely in our hospital as well plan prospective studies utilizing the score to estimate dose modifications in relation to risk assessment by the score.

In conclusion, the current study validates the CARG risk score in predicting for grade 3-5 toxicities in Indian older adult cancer patients receiving curative intent chemotherapy. The

score contributes to informed clinical decision making with regard to planning treatment and expectation of toxicity in this cohort of patients. Additionally, indices such as ECOG PS and Charlson Comorbidity Index are inadequate to predict for toxicities and should only be used along with other measures to predict for chemotherapy related toxicities.

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Figure legends:

Figure 1- CARG (A) vs. (B) ACCI vs. (C) ECOG PS predict Grade 3 to 5 toxicity

Tables

Table 1 - Baseline characteristics of patients

Characteristic	Current study Number (%) (n=270)	CARG training cohort (n=500)
Mean age in years (range)	69 (65-83)	73 (65-91)
Gender • Female • Male	 121 (45) 149 (55)	 281 (56) 219 (44)

Comorbidities • Hypertension • Diabetes mellitus • Coronary artery disease • Chronic kidney disease	 114 (42) 71 (26) 12 (4) 3 (1)	 52% - 20% -
Number of comorbidities • 0 • 1 • >=2	 125 (46) 95 (35) 50 (19)	 10% - -
Cancer stage • Stage I-III	 270 (100)	 191 (38)
Undergone resection	210 (78)	-
ECOG performance status (clinician assessed) • 0/1 • 2	 230 (85) 40 (15)	 402 (80) * 86 (17) **
Factors assessed in CARG • Age ≥ 72 years • Cancer type GI or GU • Chemotherapy dosing, standard dose • No. of chemotherapy drugs, polychemotherapy • Hemoglobin < 11 g/dL (male), < 10 g/dL (female) • Creatinine clearance < 34 mL/min • Hearing, fair or worse • No. of falls in last 6 months, 1 or more • IADL: Taking medications, with some help/unable • MOS: Walking 1 block, somewhat limited/limited a lot • MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	 60 (22) 212 (79) 205 (76) 194 (72) 99 (37) 5 (2) 19 (7) 18 (7) 29 (11) 17 (6) 18 (7)	 270 (54) 185 (37) 380 (76) 351 (70) 62 (12) 44 (9) 123 (25) 91 (18) 39 (8) 109 (22) 218 (44)
Median overall risk score Risk stratification • Low risk (0-5 points) • Intermediate risk (6-9 points) • High risk (10-19 points)	6 72 (27) 164 (61) 34 (13)	7 128 (26) 227 (45) 109 (22)
Age adjusted Charlson's Comorbidity Index • <=4 • >4	 111(41) 159(59)	 - -

*equivalent to KPS>=80; ** equivalent to KPS 60-70

Table 2 – Treatment related Grade 3 – grade 5 toxicities

Toxicity type	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Haematological			
Anemia	14 (5)	0	0
Neutropenia	18 (7)	8(3)	0
Thrombocytopenia	6 (2)	1 (0.4)	0
Febrile neutropenia	12 (4)	2 (0.7)	3(1)
Cumulative haematological	46 (17)	11 (4)	3(1)
Non-haematological			
Diarrhoea	16 (6)	4 (2)	3(1) *
Vomiting	12 (4)	1(0.4)	1(0.3) **
Mucositis	10 (4)	0	
Constipation	1 (0.4)	0	
Hand-foot-syndrome	1 (0.4)	-	

Neuropathy	3 (1)	-	
Infection with normal ANC	47 (17)	7(3)	
Hyponatremia	8 (3)	2 (0.7)	
Fatigue	24 (9)	-	
Sudden cardiac death			4(1)
Cumulative non-haematological	99(37)	13(5)	8(3)
Cumulative (all toxicities)	119(44)	22(8)	11(4)

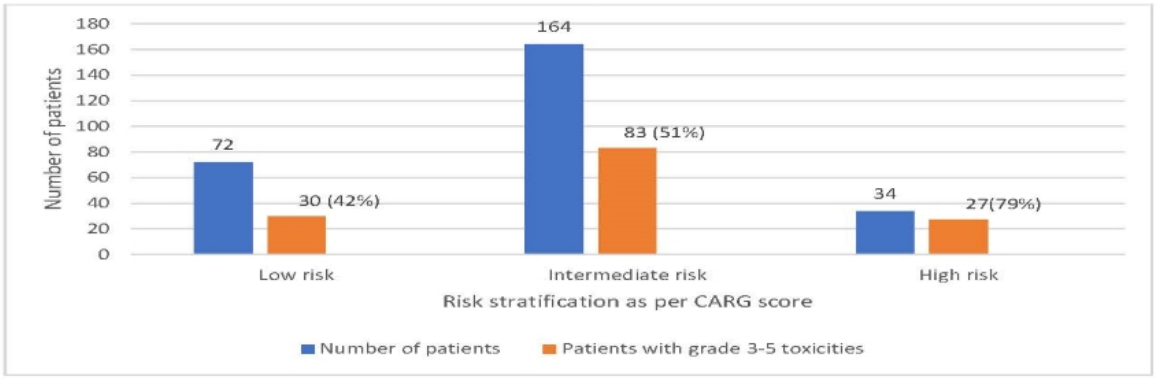
*All 3 patients developed dehydration with resulting acute renal failure. **Patient developed grade 4 vomiting with irreversible grade 4 hyponatremia resulting in death

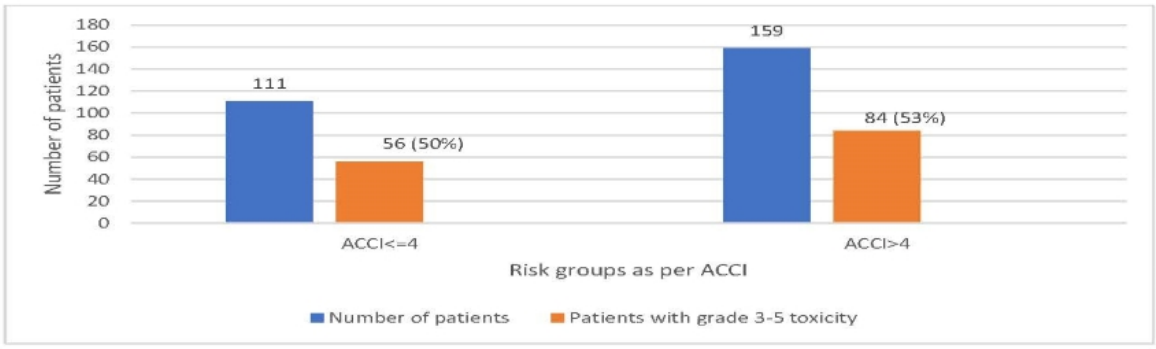
Table 3 - Ability of CARG Risk Score Versus Physician assessed ECOG PS Versus Age adjusted Charlson's Comorbidity Index (ACCI) to Predict Grade 3-5 Chemotherapy Toxicity

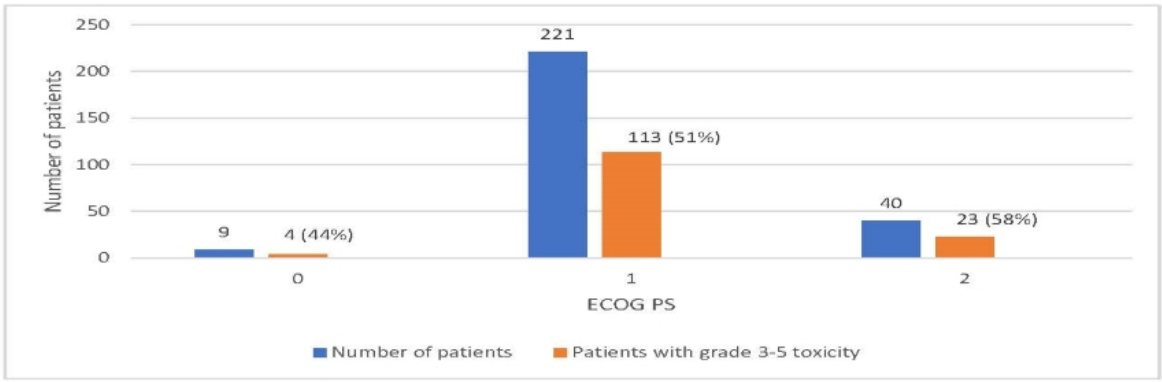
Risk Stratification	No toxicity		Toxicity		p value
	Number	%	Number	%	
CARG risk score • Low • Intermediate • High	 42 81 7	 58 49 21	 30 83 27	 42 51 79	0.001
Physician assessed ECOG PS • 0 • 1 • 2	 5 108 17	 56 49 43	 4 113 23	 44 51 57	0.69

Age adjusted Charlson's Comorbidity Index • <=4 • >4	 55 75	 50 47	 56 84	 50 53	0.7

Figure 1 – Ability of CARG risk score (A) versus (B) Age adjusted Charlson Comorbidity Index (ACCI) versus (C) ECOG Performance Status Index to predict Grade 3 to 5 chemotherapy toxicity.







Supplementary table 1 – Details of chemotherapy

Chemotherapy regimens	Number (percentage)
Platinum containing regimens	**159(59)**
Oxaliplatin containing regimens	123 (46)
• Docetaxel-Oxaliplatin- 5 -fluorouracil	50 (19)
• Capecitabine-Oxaliplatin	26 (10)
• 5-fluorouracil - leucovorin-oxaliplatin	33 (12)
• 5-fluorouracil - leucovorin-oxaliplatin-irinotecan	1 (0.4)
• Epirubicin- Capecitabine-Oxaliplatin	10 (4)
• Gemcitabine-Oxaliplatin	2 (1)
• Epirubicin- Oxaliplatin - 5-fluorouracil	1 (0.4)
Cisplatin containing regimens	19(7)
• Gemcitabine-Cisplatin	19 (7)
Carboplatin containing regimens	17 (6)
• Paclitaxel- Carboplatin	6 (2)
• Carboplatin monotherapy	11 (4)
Non-Platinum containing regimens	**111(41)**
• Epirubicin – Cyclophosphamide	9 (3)
• Adriamycin – Cyclophosphamide	19 (7)
• Docetaxel – Cyclophosphamide	1 (0.4)
• Cyclophosphamide-methotrexate – 5-fluorouracil	1 (0.4)
• 5-fluorouracil/leucovorin monotherapy	10 (4)
• Capecitabine monotherapy	25 (9)
• Gemcitabine monotherapy	26 (10)
• Paclitaxel - Trastuzumab	9 (3)
• Paclitaxel monotherapy	3 (1)
• Docetaxel - 5-fluorouracil	5 (2)
• Gemcitabine- nab-Paclitaxel	2 (1)
• Gemcitabine Capecitabine	1 (0.4)
Chemotherapy timing	
• Neoadjuvant	5 (2)

• Adjuvant	178 (66)
• Perioperative (neoadjuvant and adjuvant)	87 (32)

Supplementary table 2 – Treatment- related Grade 1 – grade 2 toxicities

Toxicity type	Grade 1/2 toxicities (%)
Hematological	
Anemia	148(55)
Neutropenia	52(19)
Cumulative hematological	160(59)
Non-hematological	
Diarrhoea	131(49)
Vomiting	140(52)
Mucositis	57(21)
Constipation	41(15)
Hand-foot-syndrome	59(22)
Neuropathy	75(28)
Hyponatremia	17(6)
Fatigue	197(73)
Cumulative non-hematological	230(85)
Cumulative (all toxicities)	234(87)

Supplementary table 3 - Ability of individual factors in the CARG risk score to predict for Grade 3 to 5 toxicities

Risk factor	Prevalence		Toxicity		p value	OR (95% CI)
	Number	%	Number	%		
Age >=72 years	60	22	34	57	0.4	1.28 (0.72-2.29)
Cancer type (GI or GU)	212	79	116	55	0.07	1.71 (0.95-3.08)
Chemotherapy dosing, standard dose	201	74	101	50	0.37	0.77 (0.45-1.35)
Polychemotherapy	194	72	106	55	0.14	1.48 (0.87-2.54)
Hemoglobin <11gm% (male), <10gm% (female)	99	37	65	66	0.001	2.45(1.47-4.09)
Creatinine clearance <34ml/min	5	2	3	60	0.71	1.4(0.23-8.52)
Hearing, fair or worse	19	7	10	53	0.94	1.03(0.41-2.63)
No. of falls in last 6 months, >=1	18	7	10	56	0.75	1.17(0.45-3.07)
IADL, taking medications, with some help/unable	29	11	17	59	0.44	1.336 (0.62-2.97)
MOS, walking 1 block equivalent, somewhat limited/limited a lot	17	6	11	65	0.27	1.76 (0.63-4.91)
MOS, decreased social activity because of physical/emotional health, limited at least sometimes	18	7	12	67	0.19	1.94(0.71-5.32)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	9
Objectives	3	State specific objectives, including any prespecified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			13

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	13
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13
		(b) Indicate number of participants with missing data for each variable of interest	13
		(c) Summarise follow-up time (eg, average and total amount)	13
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	5

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.