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UK national observational cohort study investigating Tolerance of Anti-cancer Systemic Therapy in the Elderly: the TOASTIE study

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ABSTRACT

Objective The Cancer and Aging Research Group (CARG) score was developed to predict severe chemotherapy-induced toxicity risk in older adults; validation study results have varied. The Tolerance of Anti-cancer Systemic Therapy in the Elderly study sought to evaluate the CARG score prospectively in a chemotherapy-naïve UK population.

Methods and analysis This multicentre, prospective, observational study recruited patients aged ≥65 years commencing first-line chemotherapy for any solid organ malignancy or setting. Baseline demographics and established frailty measures were recorded. Follow-up data including toxicity and hospital admissions were collected retrospectively. Baseline CARG score predictive ability was assessed.

Results 339 patients were recruited from 19 centres; median age 73 years (range 65–92), 51.9% male and 54.9% gastrointestinal primary. At baseline, 85% of patients were of Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1, with median Rockwood Clinical Frailty Scale (CFS) 3 (range 0–8). 314 (92.6%) patients had follow-up data; 69 (22.3%) patients experienced Common Terminology for Cancer Adverse Events grade ≥3 toxicity and 84 (27%) required hospital admission during treatment.
Increasing CARG risk groups had increased grade ≥3 toxicity (low 19.6%, medium 22.2%, high 28.2%); however, this was non-significant with no evidence of robust predictive performance. Predictive performance of CFS and ECOG PS was superior to CARG. Importantly, patient and clinician perceptions of toxicity risk differed significantly.

Conclusions In older UK patients with cancer commencing chemotherapy, baseline frailty was prevalent. CARG score did not robustly discriminate or predict high-grade toxicity risk. ECOG and CFS showed superior, although limited, ability to predict and discriminate. This study highlights the need for the development of tools that better predict toxicity in this population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Older adults are at greater risk of chemotherapy toxicity.

WHAT THIS STUDY ADDS

⇒ This is the first prospective study to investigate the ability of the Cancer and Aging Research Group (CARG) score to predict chemotherapy toxicity in a UK population; CARG score was not able to robustly predict population or individual risk of toxicity.
⇒ Frailty is prevalent in a UK older adult population with cancer commencing chemotherapy.
⇒ Patients and doctors' perception of risk from chemotherapy shows poor correlation even after an informed consent discussion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More research is needed to develop improved predictive tools and explore the consent process.

INTRODUCTION

There is a global epidemic of older adults with cancer.[1] Ageing is associated with increasing comorbidity and frailty,[2] both of which have been shown to result in inferior oncological outcomes.[3 4] International consensus from the American Society of Clinical Oncology (ASCO), International Society of Geriatric Oncology (SIOG), National Comprehensive Cancer Network (NCCN) and UK national guidance recommends the inclusion of geriatric and frailty assessment in the care of older adults with cancer.[5–9] Despite this, frailty assessment is not routinely performed in an oncology setting in the UK. Consequently, the exact prevalence of comorbidity and extent of frailty in our older cancer

population is unknown; however, available data suggest both the global prevalence and consequences of frailty are significant.[4]

There are complex challenges to achieving shared decision-making and truly informed consent when treating older adults with cancer. In this patient population, one of the main goals is to avoid both overtreatment and undertreatment, both of which can result in poorer cancer outcomes.[10]

The mismatch between real-world and trial populations means that we lack age-attuned data to inform decision-making adequately.[11] The lack of detailed assessment of frailty in the oncology setting can result in an inaccurate clinical assessment of the risk of treatment toxicity.[12–15] In addition, there is evidence of discordance between patient and clinician perception of the risk of treatment toxicity following consultation.[16] This is important as there is an increasing body of evidence, including from the UK, that older adults with cancer value other factors such as functional independence and social interaction over length of life when considering treatment options.[17–19] These factors can be significantly impacted by treatment-related toxicity.

Despite an increase in the availability and use of novel therapies such as immune checkpoint inhibitors and tyrosine kinase inhibitors, chemotherapy remains the backbone of therapy for most cancers. When evaluating the risk versus benefit of treatment, it remains difficult to accurately predict who will develop treatment toxicity. This takes on added importance when treating an older adult.

Two chemotherapy prediction tools that have been studied are the Cancer and Aging Research Group (CARG) score and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score.[20 21] The CARG score[21] is a concise tool consisting of 11 variables that can be completed with the patient in clinic.

The CARG score was initially developed in the USA and has subsequently been adapted to include tumour-specific factors relating to breast cancer.[22] Subsequent external validation studies have had mixed results.[15 23–26] It is possible that the variation in the utility of CARG by geographical region may be due to differences in thresholds of patient selection for chemotherapy and variation in treatments delivered, coupled to the availability of support networks.

To date, despite being recommended for use by the ASCO,[5] the CARG score has not been evaluated prospectively in a UK population. If validated, the CARG score could provide a useful tool in everyday practice to improve the process of patient assessment and consent, and this has been highlighted in the recently published UK guideline on assessing older adults with cancer.[8]

In this manuscript, we present prospective, observational data from an older UK population being assessed for and undergoing first-line chemotherapy for any solid tumour indication. We describe the demographics of the population seen, explore clinician and patient perceptions of toxicity risk and assess the ability of the CARG score to predict the risk of severe toxicity.

METHODS

This was a UK multicentre, prospective, observational study (non-randomised) which recruited patients aged 65 years and older who were commencing first-line neoadjuvant, adjuvant or palliative chemotherapy for a solid organ malignancy with a prognosis of more than 3 months. Patients receiving concomitant additional anticancer agents (eg, immune checkpoint inhibitors and tyrosine kinase inhibitors) were excluded. A full list of inclusion and exclusion criteria can be found in the online supplemental materials and the trial protocol is available online.[27]

Outcome measures

Primary outcome

- To validate the CARG score's ability to predict Common Terminology for Cancer Adverse Events (CTCAE) v5 grade 3–5 toxicity in patients aged ≥65 years who were receiving first-line chemotherapy in the UK National Health Service (NHS).

Secondary outcomes

- Describe the prevalence of frailty in patients aged ≥65 years commencing first-line chemotherapy in the UK.
- Demonstrate the feasibility of implementing frailty assessment in routine practice.
- Describe patient and clinician perception of toxicity risk associated with chemotherapy.

Study procedures

At baseline, each patient had detailed frailty screening parameters recorded. These included Rockwood Clinical Frailty Scale (CFS), Geriatric-8 (G8), Charlson Comorbidity Index (CCI) and an EQ-5D visual analogue scale quality of life score. These were recorded following the initial oncology appointment so as not to influence decision-making. Participants were then assessed during treatment as per local standard of care. G8 and CARG scores were calculated following submission of demographic data. Time to complete the CARG score assessment was taken from the beginning to ask patients questions to completion of recording the required data.

Treatment toxicity was assessed according to CTCAE v5 and was recorded on either paper or electronic notes prior to, and during, each chemotherapy cycle. Details of toxicity and hospital admissions were obtained retrospectively from the medical records. Only CTCAE v5 grade 3 or above toxicities were recorded.

To quantify clinician perception of risk, they were asked 'how likely do you think this patient will experience significant CTCAE grade 3 or more toxicity?', and required to classify this risk as unlikely, not very likely, quite likely or very likely, in addition to providing a continuous score (0-100% risk of severe toxicity). For assessment of patient

perception of risk, patients were asked: 'How likely do you think it is, that a side effect from chemotherapy will cause you to have to stay in hospital for one night or longer or have to stop treatment?' Patients were then, like clinicians, asked to classify this risk as: unlikely, not very likely, quite likely, very likely, as well as providing a continuous score with the scale: 0, meaning 'I think it definitely won't happen to me' and 100, meaning 'I think I will definitely need to stop treatment or stay hospital at some point during my treatment'.

Sample size and statistical analysis

The study planned to recruit 500 patients using centres which are part of the National Oncology Trainees Collaborative for Healthcare Research network.[28] The sample size calculation was made based on precision as opposed to power as is typical for interventional studies. Further details can be found in the published study protocol.[27]

The CARG score was calculated from 11 prechemotherapy variables (online supplemental table 1).[21] A chemotherapy dose reduction at baseline was counted as reduced dose for calculation. Patients were categorised into low-risk (0–5), intermediate-risk (6–9) and high-risk (10–19) groups. Observed grade ≥3 toxicity rates between groups were compared using a χ^2 test of proportions. The validity of the model was analysed by composing receiver operating characteristic curves and calculating the area under the curve (AUC; c-statistic) for the CARG score. A descriptive analysis of the prevalence of frailty in the population and the feasibility of implementing frailty assessment was performed. All analysis was performed using R V.4.2.3.

RESULTS

The population

365 patients were consented from 19 sites across the UK (online supplemental table 2) between December 2020 and December 2022. 339 were subsequently eligible for inclusion (figure 1); 9 had missing baseline demographics, 2 did not meet the age criteria, 12 had treatment including a non-chemotherapy agent and 3 were ineligible for other reasons.

Demographics

The demographics of the recruited population are shown in table 1. The median age was 73 years (range 65–92), and 51.9% were male. The primary tumour groups were gastrointestinal (gastro-oesophageal 25.7%, hepato-pancreato-biliary 7.3%, lower gastrointestinal 21.9%). A smaller number of patients with gynaecological, urological, lung and breast cancers were included. The recruited population also represented an advanced stage; 29.4% were tumour, node, metastases (TNM) stage 3 and 37.6% TNM stage 4.

59.1% of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 at baseline. The median Rockwood CFS was 3 (range 0–8), with 86.6% of patients having a Rockwood CFS of 1–4. Karnofsky Performance Status data were missing for 50.1% of

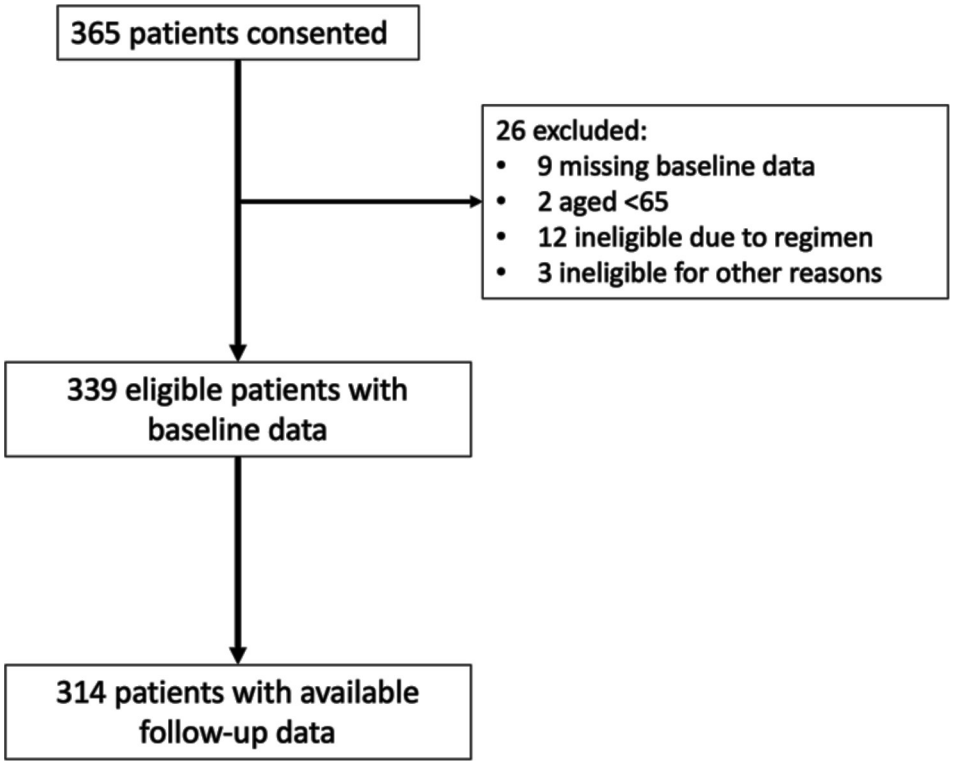

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram of patient recruitment to the Tolerance of Anticancer Systemic Therapy in the Elderly (TOASTIE) study.

Table 1 Baseline demographics of the recruited patient population in the TOASTIE study according to age group

	65–75 (n=225)	>75 (n=114)	Overall (n=339)
Age at time of clinic visit			
Mean (SD)	70.1 (2.88)	78.5 (3.50)	72.9 (5.01)
Median (min, max)	70.0 (65.0, 74.0)	78.0 (75.0, 92.0)	73.0 (65.0, 92.0)
Sex			
Female	110 (48.9%)	53 (46.5%)	163 (48.1%)
Male	115 (51.1%)	61 (53.5%)	176 (51.9%)
ECOG PS			
0	84 (37.3%)	30 (26.3%)	114 (33.6%)
1	111 (49.3%)	64 (56.1%)	175 (51.6%)
2+	26 (11.6%)	17 (14.9%)	43 (12.7%)
Missing	4 (1.8%)	3 (2.6%)	7 (2.1%)
KPS			
90–100	55 (24.4%)	14 (12.3%)	69 (20.4%)
70–80	45 (20.0%)	37 (32.5%)	82 (24.2%)
50–60	11 (4.9%)	4 (3.5%)	15 (4.4%)
50 or less	2 (0.9%)	2 (1.8%)	4 (1.2%)
Unknown	112 (49.7%)	57 (50.0%)	169 (49.9%)
Rockwood CFS			
1	53 (23.6%)	18 (15.8%)	71 (20.9%)
2	60 (26.7%)	19 (16.7%)	79 (23.3%)
3	61 (27.1%)	31 (27.2%)	92 (27.1%)
4	28 (12.4%)	23 (20.2%)	51 (15.0%)
5+	10 (4.4%)	13 (11.4%)	23 (6.8%)
Unknown	13 (5.8%)	10 (8.8%)	23 (6.8%)
Geriatric-8 score			
≤14	133 (59.1%)	75 (65.8%)	208 (61.4%)
>14	19 (8.4%)	8 (7.0%)	27 (8.0%)
Unknown	73 (32.4%)	31 (27.2%)	104 (30.6%)
BMI			
Mean (SD)	27.2 (5.4)	26.5 (4.2)	26.9 (5.1)
Median (min, max)	26.9 (14.4, 51.4)	26.3 (16.6, 37.9)	26.6 (14.4, 51.4)
Missing	2 (0.9%)	2 (1.8%)	4 (1.2%)
Number of comorbidities			
Mean (SD)	1.37 (1.48)	1.78 (1.79)	1.50 (1.60)
Median (min, max)	1.00 (0, 7.00)	1.00 (0, 7.00)	1.00 (0, 7.00)
Missing	1 (0.4%)	1 (0.9%)	2 (0.6%)
Charlson Comorbidity Index			
Mean (SD)	6.26 (2.50)	7.07 (2.43)	6.53 (2.50)
Median (min, max)	5.00 (2.00, 12.0)	6.00 (3.00, 12.0)	6.00 (2.00, 12.0)
Number of regular medications			
Mean (SD)	3.46 (2.73)	4.65 (3.22)	3.86 (2.95)
Median (min, max)	3.00 (0, 15.0)	4.00 (0, 14.0)	3.00 (0, 15.0)
Missing	1 (0.4%)	1 (0.9%)	2 (0.6%)
Smoking status			
Current	23 (10.2%)	4 (3.5%)	27 (8.0%)

Continued

Table 1 Continued

	65–75 (n=225)	>75 (n=114)	Overall (n=339)
Ex	69 (30.7%)	48 (42.1%)	117 (34.5%)
Never	63 (28.0%)	35 (30.7%)	98 (28.9%)
Missing	70 (31.1%)	27 (23.7%)	97 (28.6%)
Marital status			
Single	26 (11.6%)	13 (11.4%)	39 (11.5%)
Married/has a partner	112 (49.8%)	56 (49.1%)	168 (49.6%)
Widow/widower	11 (4.9%)	15 (13.2%)	26 (7.7%)
Divorced	6 (2.7%)	3 (2.6%)	9 (2.7%)
Missing	70 (31.1%)	27 (23.7%)	97 (28.6%)
Home status			
Alone	33 (14.7%)	27 (23.7%)	60 (17.7%)
With partner/family	117 (52.0%)	56 (49.1%)	173 (51.0%)
Carer	4 (1.8%)	4 (3.5%)	8 (2.4%)
Missing	71 (31.5%)	27 (23.7%)	98 (28.9%)

Data are mean (SD), median (range) or n (%).
BMI, body mass index; CFS, Clinical Frailty Scale; ECOG PS, Eastern Cooperative Oncology Group Performance Status; KPS, Karnofsky Performance Status; TOASTIE, Tolerance of Anti-cancer Systemic Therapy in the Elderly.

patients; however, in the available data, the median was 80 (range 30–100). Baseline G8 score was available for 235 patients; median was 12 (range 6–16) (online supplemental figure 1), with 208 (88.5%) having a score of 14 or less.

The median number of comorbidities was 1 (range 0–7), the median number of regular medications was 3 (range 0–15) and the median CCI score was 6 (range 2–12). Further details regarding the prevalence of comorbidity can be found in online supplemental table 3. From the available data, 59.5% were current smokers or ex-smokers, 69.4% were married or had a partner and 24.8% lived alone.

Baseline clinician decisions

Chemotherapy was planned to be administered in the neoadjuvant setting for 96 (28.3%) patients, adjuvant for 78 (23.0%) patients and palliative for 165 (48.7%) patients (table 2). The chemotherapy regimens planned in the cohort are shown in online supplemental table 4; 40 (11.7%) were monotherapy, 244 were doublet (70.8%) and 59 (17.4%) were triplet. Only 21 (6.2%) patients had a formal baseline frailty assessment, performed as routine standard of care, at their oncology appointment, and CARG toxicity risk assessment was performed at baseline for 36 (10.6%) patients. For the remaining patients, the CARG score was calculated retrospectively as per protocol.

Follow-up data were available and complete for 314 (92.6%) patients who were planned to receive chemotherapy. There was a baseline dose reduction in 124 (39.5%) cases. The reasons for dose reduction are detailed in table 3; CARG score was not given as the main reason for reduction in any of the patients. Patients were more likely to get a dose reduction at baseline if they were ECOG PS 2 or more (64.1%) compared with ECOG PS 0 (31.2%) or PS 1 (39.2%).

Clinician/patient perception of risk

Clinician's perceived risk of grade ≥3 toxicity was available for 303 (89.4%) patients. Of these, 43 (14.2%) patients were felt by clinicians to be at low risk, 155 (51.2%) to be at low-medium risk, 97 (32.0%) to be at medium-high risk and 8 (2.6%) to be at high risk. There was a good agreement between the clinician-attributed categorical risk group and the simultaneously completed clinician percentage risk of toxicity for the same patient (online supplemental figure 2).

291 patients had a patient quantified risk (recorded following their oncology appointment) alongside an associated independent clinician-documented risk assessment. Patients were more likely to think they had a lower risk of serious chemotherapy toxicity (low risk defined as a perceived risk less than 25%) than clinicians (60.8% vs 37.5%, p<0.001). Likewise, clinicians were more likely to think patients were at a high risk of toxicity (defined as greater than 50% risk) than patients (21.3% vs 6.5%, p=0.016). Overall, there was poor correlation between the clinician and patient perceptions of risk (Pearson r=0.258, p<0.001) (online supplemental figure 3), and paired t-test demonstrated a significant difference (p<0.001).

Treatment experience

The median number of complete chemotherapy cycles received was 4 (range 1–16). Of the 314 patients, 83 (26.4%) required at least one dose delay and 123 (39.2%) did not complete the planned number of cycles. The

Table 2 Cancer and treatment intent in recruited population to the TOASTIE study

	65–75 (n=225)	>75 (n=114)	Overall (n=339)
Primary site			
Upper GI	59 (26.2%)	28 (24.6%)	87 (25.7%)
HPB	17 (7.6%)	8 (7.0%)	25 (7.4%)
Lower GI	51 (22.7%)	24 (21.1%)	75 (22.1%)
Gynaecological	35 (15.6%)	14 (12.3%)	49 (14.5%)
Lung	9 (4.0%)	14 (12.3%)	23 (6.8%)
Breast	20 (8.9%)	9 (7.9%)	29 (8.6%)
Urology	24 (10.7%)	10 (8.8%)	34 (10.0%)
Other	10 (4.4%)	7 (6.1%)	17 (5.0%)
TNM stage			
1	8 (3.6%)	6 (5.3%)	14 (4.1%)
2	34 (15.1%)	15 (13.2%)	49 (14.5%)
3	69 (30.7%)	32 (28.1%)	101 (29.8%)
4	82 (36.4%)	43 (37.7%)	125 (36.9%)
Missing	32 (14.2%)	18 (15.8%)	50 (14.8%)
Chemotherapy intent			
Neoadjuvant	69 (30.7%)	27 (23.7%)	96 (28.3%)
Adjuvant	52 (23.1%)	26 (22.8%)	78 (23.0%)
Palliative	104 (46.2%)	61 (53.5%)	165 (48.7%)
Planned regimen			
Monotherapy	21 (9.3%)	19 (16.7%)	40 (11.8%)
Doublet	160 (71.1%)	80 (70.2%)	240 (70.8%)
Triplet	44 (19.6%)	15 (13.2%)	59 (17.4%)

GI, gastrointestinal; HPB, hepato-pancreato-biliary; TNM, tumour, node, metastases; TOASTIE, Tolerance of Anti-cancer Systemic Therapy in the Elderly.

reasons documented for early cessation were progressive disease (34, 27.6%), toxicity (60, 48.8%), patient choice (17, 13.8%), other reasons (5, 4.1%) and unknown (8, 6.5%). Those who had a baseline dose reduction had a higher chance of early cessation (51.6% vs 31.1%, p<0.001)—this was mainly due to progressive disease.

Table 3 Documented reason for dose reduction at baseline in the TOASTIE trial

	Overall (n=124)
Reason for dose reduction	
Clinician intuition	39 (31.5%)
Age	31 (25.0%)
ECOG PS	23 (18.5%)
Comorbidity	17 (13.7%)
Haematological/biochemistry	9 (7.3%)
DYPD result	5 (4.0%)

DYPD, dihydropyrimidine dehydrogenase deficiency; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TOASTIE, Tolerance of Anti-cancer Systemic Therapy in the Elderly.

One or more grade ≥3 CTCAE toxicities were documented for 70 (22.3%) patients, and 84 (26.8%) patients had at least one hospital admission during the study time period. Patients who developed grade ≥3 toxicity were older than those who did not (median 74 years vs 72 years, p<0.001); however, there was no difference in toxicity according to treatment intent (p=0.993) (online supplemental table 5).

CARG predictive ability

Within the population with follow-up data, the baseline CARG score could be calculated for 313 (99.7%) patients; grade ≥3 toxicity was 22.4% in this population. The median time to complete the CARG score was 5 min (range 0.5–20 min). The distribution of the CARG scores is shown in online supplemental figure 4; median score was 6 (range 1–14), with 107 (34.3%) patients deemed to be low risk, 167 (53.2%) medium risk and 39 (12.5%) high risk.

Increasing categorical CARG risk group was not associated with a statistically significant increased risk of toxicity (table 4); low risk 19.6%, medium risk 22.3% and high risk 28.2%, p=0.746. The AUC for continuous CARG score was 0.577 (95% CI 0.499 to 0.663).

Table 4 Grade ≥3 toxicity rates according to CARG toxicity risk group

	Low risk (n=107)	Medium risk (n=167)	High risk (n=39)	Overall (n=312)*	P value
Grade ≥3 toxicity					
No	86 (80.4%)	130 (77.8%)	28 (71.8%)	243 (77.9%)	0.746
Yes	21 (19.6%)	37 (22.2%)	11 (28.2%)	69 (22.1%)	

*1 patient from the cohort with available follow-up data did not have a CARG available.
CARG, Cancer and Aging Research Group.

For ECOG PS, 306 patients were available for analysis. Rates of grade ≥3 toxicity were 15.6% vs 24.7% vs 35.9% for ECOG PS 0, 1 and 2+, respectively, p=0.063 (online supplemental table 6). The AUC for ECOG PS was 0.616 (95% CI 0.527 to 0.699). For Rockwood CFS, 289 patients were available for analysis. Those with a CFS 1–3 had statistically significantly fewer high-grade toxicities than those with a CFS of 4 or more (19.7% vs 36.4%, p=0.02) (online supplemental table 7). The impact was even greater for those with a CFS 5 or more, where grade ≥3 toxicity rate was 45% vs 21.9% in those with CFS 1–4 (online supplemental table 8). The AUC for CFS was 0.605 (95% CI 0.526 to 0.688). For the G8 score, 198 patients had data available for analysis; of these, 41 patients had a grade ≥3 toxicity. The rate of grade ≥3 toxicity in those with a G8 score of ≥15 was 16.7% vs 21.3% in those with a G8 score of 14 or less, p=0.873. The AUC for continuous G8 score was 0.5918 (95% CI 0.500 to 0.688).

DISCUSSION

The cancer population worldwide is ageing.[1] Despite this, the availability of age-attuned oncology data is limited, which makes treatment decisions, particularly surrounding the risk of treatment toxicity, ever more challenging. In this manuscript, we present the results of a UK-wide prospective observational study in a population of older adults with solid malignancy who are chemotherapy naïve and receiving first-line chemotherapy. We report baseline demographics, pre-existing comorbidity, frailty and treatment toxicity outcomes. We evaluate both patient and clinician perceptions of risk of serious chemotherapy toxicity and look at their concordance. We also investigate the utility of the CARG score as a toxicity prediction tool in our population.

The median age of our population was 73 years, in keeping with the median age at diagnosis of many solid organ tumours in the UK, and the large proportion of patients with ECOG PS 1 or more is typical of real-world experience.[4 29] The types of tumours represented and the predominance of tumours of the gastrointestinal tract (55.2%) reflect the current first-line treatment choices in these tumour sites, despite an evolving paradigm of multitarget precision therapy in cancer.

We have established that in those older adults being assessed for and subsequently receiving chemotherapy, frailty is both prevalent and wide ranging, with the median Rockwood CFS (known to be prognostic across a range of tumour groups) of 3 (but with a range of 1–8). This range of CFS scores corroborates the breadth of fitness of older UK patients being treated with systemic therapy.[30] The G8 frailty screening tool results further support this; of those with an available score, 88.5% had a score of 14 or less and would thus warrant a comprehensive geriatric assessment and targeted intervention—something which is only available in a small number of UK centres[17 31 32] but has been shown to improve outcomes.[33–35] These data are supported by a systematic review which investigated the prevalence of prefrailty and frailty in an older cancer population.[4]

In keeping with the age of the population, the majority of patients had at least one comorbidity at diagnosis,[36] and the median number of regular medications was 3 (range 0–15). This is lower than previous reports but may reflect a fitter population which is undergoing treatment or an earlier stage of disease and thus reduced need for symptom control.[37]

Despite international guidelines at the time of the study development, which have since been updated, recommending frailty screening and the use of toxicity prediction tools in the decision-making process for older adults with cancer, this was rarely done. Importantly, we found that the CARG was feasible to perform within an NHS oncology clinic appointment. Within the UK, this is especially relevant given the recent publication of the UK Joint Collegiate Council for Oncology (JCCO) guidelines on implementing frailty assessment and management in oncology services.[8]

Analysis of CARG score in the cohort revealed a lower proportion of higher risk patients than in the landmark paper[21]—12.5% vs 20.4%. Despite this, the median risk score in our cohort was 6, similar to the median of 7 (range 0–19) reported by Hurria *et al*. The difference in risk groups may be a result of several factors. For example, differences in primary tumour site; 29% of patients had lung cancer in Hurria *et al*'s study, a cohort known to have a high degree of frailty,[38] compared with 6.8% in this study. In addition, there were differences in disease stage, for example, 61% were stage 4 in Hurria *et al*'s study compared with 36% in this study. There is also likely to be variations in practice between countries, such as different thresholds to treat older and/or frailer patients and preferences for combination therapy over monotherapy. Furthermore, only 71% of patients were receiving first-line treatment in Hurria *et al*'s study, and

prior systemic anticancer therapy is known to be a risk factor for additional toxicity.

When considering subsequent toxicity, the rate of grade ≥3 toxicity in our study was lower, 22.1% vs 53% in Hurria *et al*'s study. The factors mentioned above, in addition to higher baseline dose reductions in our study (39.5% vs 24%), that may have contributed to differences in the CARG risk group could also have contributed to the difference in toxicity rates. In addition, unlike Hurria *et al*, biochemical abnormalities were not collected within TOASTIE, and it is also known that older adults in the UK are less likely to receive systemic therapy.[39] We must also acknowledge that supportive medications, for example, granulocyte colony-stimulating factor (G-CSF) and antiemetics, are likely to have improved over the last decade alongside the availability of acute oncology services within the UK, which enable early access to oncology services even for low-grade toxicity.

On analysis, the categorical CARG risk groups did not appear to be able to stratify patients in a clinically meaningful way, with those in the low-risk group having a grade ≥3 toxicity rate of 19.6% compared with 22.3% and 28.2% in the medium and high-risk groups, respectively. Our data, therefore, do not support the use of the CARG score as a robust toxicity prediction tool in an older UK population.

As CARG score was unable to robustly discriminate or predict risk of high-grade toxicity, we investigated the predictive ability of the more commonly used clinical assessment tools Rockwood CFS and ECOG PS as toxicity prediction tools. Within our cohort, both appeared to have improved utility over CARG, in particular when using a CFS of 4 or ECOG PS of 2 as a cut-point. Both CFS and ECOG PS demonstrated increasing population-level risk of toxicity as fitness decreased, supporting the ongoing use of both in clinical practice to help shape the discussion around management options and decision-making. However, we must acknowledge the limited ability of the tools to predict robustly the risk of individualised treatment toxicity.

Regarding the consenting process and communication with older adults, we looked to investigate whether perceptions of risk of toxicity following an oncology consultation differed between individual patients and their clinicians. Despite clinicians deeming patients to be at high risk, the patient often perceived this not to be the case, indicating that clinician's perceived risk of toxicity for the patient may not have been accurately conveyed. This finding has been observed previously[16] and supports the need for further research relating to the consenting process for treatment. The CARG score could be a useful tool in this setting for helping to open and shape a discussion around treatment risk.

Our study has several strengths. This is the first multicentre study in the UK to prospectively report the demographics and pre-existing frailty of a real-world cohort of patients across a range of solid organ tumours. It provides a large dataset with detail relating to baseline assessment across multiple geriatric domains. It is also the first prospective study to investigate the use of the CARG score to predict chemotherapy treatment toxicity in a UK older adult population with cancer. The study was run by practising oncologists (consultants and registrars), with the data for the frailty scores collected in real time during routine new patient consultations. In addition, we have established that it is feasible to implement frailty screening tools within a time-constrained NHS oncology clinic environment. This has relevance following the release of the aforementioned UK JCCO guidelines regarding frailty assessment and management of older adults with cancer.[8]

However, we must acknowledge certain limitations, the first being that the recruitment target of 500 patients was not reached. The main reasons for this were the COVID-19 pandemic, meaning fewer cancer diagnoses and less cytotoxic chemotherapy being delivered,[40] and the approval of new first-line regimens in many tumour types which moved away from chemotherapy only regimens. Both of these factors occurred following the planning and opening of the study. The study also does not account for patients receiving combination modality treatment or immunotherapy, nor does it explore whether interventions based on frailty assessment resulted in improved patient outcomes. In addition, the retrospective nature of data capture relating to toxicity may partly explain the observed lower rates of toxicity compared with the original CARG development paper. Despite this, however, the study still provides valuable insight into the role of CARG and other frailty assessment tools in a UK clinical setting.

In summary, this study has highlighted the current lack of routine frailty assessment in an older UK cancer population and strengthens the need to build on the recently published UK guidance on the topic.[8] This is particularly important given the prevalence of frailty in our population receiving chemotherapy and the predictive ability of the Rockwood CFS. While the CARG score does not appear to perform well in an unselected UK population, that does not mean it does not have a role, potentially with refinement, in specific tumour groups, as has been done with the CARG-Breast Cancer in breast cancer.[22] We need to avoid both overtreatment and undertreatment, and this study highlights the need to bring frailty assessment earlier in the patient pathway, which may help influence management decisions at all stages.

As the UK geriatric oncology community moves forward, we need to think how we can better facilitate the clinical implementation of geriatric assessment in routine clinical practice and build on the findings of this study to drive future research. One of the key elements of this will relate to education, which we know is lacking in the UK[13] and is a top priority of SIOG.[41] This is especially important given the clear randomised controlled trial evidence demonstrating the benefits of geriatric assessment-driven interventions—therefore, should we move away from creating prognostic tools and focus efforts on providing a comprehensive geriatric assessment for all older adults? We feel

this is necessary to provide truly personalised precision care to our older adults with cancer.

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