**Background**

In the advent of novel targeted therapy and immunotherapy survival of patients with incurable solid tumours is improving with researchers forecasting the odds of long-term survivorship to be 46.7% greater by 2040 (1). Unsurprisingly, with the introduction of new therapies the rates of critical illness in cancer patients is also increasing, with a UK population-based observational study indicating 5% of all cancer patients will require critical care (CC) admission within the first 2 years of diagnosis (2). Consequently, clinical scenarios in which patients with incurable solid tumours require CC support are occurring more frequently.

Research examining predictors of CC survival in patients with cancer has, however, generated inconsistent results. Moreover, research fails to separate patients with curable and incurable disease, or haematological and solid-tumours making it difficult to apply these data to patients specifically with incurable solid malignancy (3-7). Research has also been criticised, particularly in view of the physical and psychologically traumatic nature of CC, for reporting only short-term CC outcome data (8-10). Researchers have previously indicated that assessment of longer-term survival, functional status and return to anti-cancer therapies (ACT) are vital in assessing the appropriateness of CC admission in this patient group (11).

Current prognostic tools which aim to predict CC survival, such as APACHE II, also remain unvalidated in this patient group. Furthermore, their outputs are based on data only available within the first 24 hours of CC admission and as such are not able to support decision making at the time of escalation (12).

Consequently, decisions to admit patients with incurable solid tumour to CC in the UK are based on clinician experience. CC admission discussions can lead to conflict due to differences in opinions held by oncologists and intensivists (13) and the greater likelihood of refusal by intensivists based on a cancer diagnosis alone (14, 15).

CREDIT (Cancer Related Escalations for ITu) is a UK multi-centre retrospective study which aims to understand which patients with incurable solid tumour survive CC with maintained functional status enabling reinstitution of anti-cancer therapy. Using these outcome measures, physiological and biochemical parameters available to clinicians at the time of escalation we propose a CREDIT score able to discern those likely to survive with a sufficiently maintained functional status to enable further ACT.

**Methods**

**Study Design**

This was a national multicentre retrospective observational cohort study. Patients were included across ten centres via the National Oncology Trainee Collaborative For Healthcare Research (NOTCH) Collaborative Group network. The study population comprised of patients with incurable locally advanced or metastatic solid cancer, who had an unplanned CC admission between January 2018 and December 2019. The study was conducted and is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (16).

The primary aim was to assess the relationship between patient demographic, treatment, physiological and biochemical characteristics and key outcomes following CC admission. This included currently used CC risk assessment scores such as the APACHE, SOFA and SAPS2 scoring systems and their associated modified versions.

The three clinical outcomes assessed were:

1. Survival six months after CC admission
2. Return to anticancer therapy (ACT)
3. ECOG PS greater than 2

The main purpose of the study was to build a bespoke score for an advanced cancer population to help better predict these three key outcomes, and therefore allow improved risk stratification regarding escalation to CC. This score would be called the *Cancer Related Escalation Decisions for ITU* (CREDIT) score.

**Ethical Considerations**

As this was a retrospective observational study ethical approval was not required. The lead centre obtained local Caldicott guardian approval to conduct the study, and to handle pseudo-anonymised data from other sites. To enrol in the study, the other centres were then required to also gain their own Caldicott approval to submit their data to the lead centre for central curation and analysis. Caldicott review ensures that standardly collected data is used legally, ethically and appropriately, and that confidentiality is maintained.

**Participants**

373 patients with advanced solid cancer admitted to CC were eligible for analysis. Each centre was required to perform a search via their local CC to formulate a list. The following inclusion and exclusion criteria were then applied:

Inclusion criteria:

* A histological diagnosis of locally advanced or metastatic cancer
* Emergency Admission to Critical Care (level II and III) between the dates of 01/01/2018 and 31/12/2019
* Patients with oligo-metastatic disease treated with either SABR or surgery should only be included where the treatment intent is palliative. For example solitary lung metastasis from colon cancer.
* Age > 16 years at diagnosis

Exclusion criteria:

* No histological diagnosis of solid tumour
* Patients with oligo-metastatic disease treated with SABR or surgery where treatment intent is considered radical. For example solitary liver metastasis in colon cancer.
* De novo presentation with incurable malignancy
* Haematological malignancy (unless concurrent with solid organ malignancy)
* Radically treatable disease
* Elective admission, post planned surgical intervention

Data including patient demographics, treatment details, physiological and biochemical parameters and clinical outcomes were extracted from electronic case records. Data was collected locally and then pseudo-anonymised and curated in Excel at the lead centre.

**Statistical Analysis**

Statistical analysis was conducted in R v4.2.2, with a p<0.05 considered statistically significant. Initially, a univariate logistic regression was performed for all the scoring systems, and their associated modified scoring systems against all three clinical outcomes previously described. The univariate logistic regression was then repeated with the individual variables that comprised the best performing scoring systems based on the OR and p value.

Next, to identify independent predictors of the three clinical outcomes we took all variables that were statistically significant for any of the clinical outcomes from the univariate regression. Variables with obvious correlations were discarded, with the most significant variables kept in the model. A multivariate logistic regression model for each of the clinical outcomes was then built using the final variable list, and independent predictors for any of the clinical outcomes were taken forward. Variance Inflation Factor (VIF) scores were calculated to assess for multicollinearity in the multivariate analysis (VIF=1 indicates no multicollinearity present, 1-5 indicates weak presence of multicollinearity, >5 indicates strong multicollinearity present).

Once the independent predictors were identified, the CREDIT scoring system was built using these variables and a score was retrospectively applied to each patient. All scoring systems were also split into categories (0, 1 and 2) based on median values for the clinical outcomes. The Kaplan-Meier survival method was used to assess 2-year OS across all scoring systems via the categorical data. Continuous data was used to assess the ability to predict Return to ACT and ECOG PS >2 by the scoring systems.

ROC analysis to generate curves with AUROC scores (C-statistic) were then planned to assess the performance of the CREDIT score compared to the other scoring systems across the clinical outcomes. To perform this analysis, the dataset was split into 80% training and 20% testing cohorts. This analysis was performed using the whole dataset including missing data, and then with a clean dataset omitting missing data. The clean dataset was too small for this analysis to be robust, with considerable variation in results compared to the whole dataset, and therefore it was decided that ROC analysis was not reliable enough to allow proper comparisons.

**Machine Learning Algorithm**

As a second method of validating the CREDIT score, machine learning was employed

**Results**

**Study Population**

<Figure 1 here>

**Demographics and Clinical Outcomes**

Table 1 displays the patient demographics. Median age was 64 (IQR 55 - 72) and 52% of patients were male. The median BMI was 26 (IQR 22.2 - 29.4) and 82% of patients were ECOG PS 0/1 on referral to Oncology. On admission to hospital, 49% were ECOG PS 0/1 and 51% were ECOG PS 2 or higher. The median Charlson Comorbidity Index (CCI) was 8 (IQR 7 - 9). The most common malignancies in the study were Urology (18%), Breast (16%), Lower Gastrointestinal (12%), Lung (12%), Gynaecological (9.7%) and Upper Gastrointestinal (8.1%).

All modified scoring systems were better predictors of the clinical outcomes than their original versions via univariate analysis. There was a reasonable amount of missing data across the cohort, particularly for some of the scoring systems. Missing values were not imputed as this was not felt to be representative. 89% of patients survived CC, with a median stay of 2.5 days (IQR 1 - 5). Of the patients who survived CC, the median survival time was 112 days (IQR 17 - 570). Regarding the patients who were discharged home successfully, the median survival time at home was 136 days (IQR 18 - 899). 69% of patients discharged home were ECOG PS 0/1/2, with 31% ECOG PS 3/4. 36% went on to have further oncological treatment and, of all patients regardless of CC survival, 64% survived up to six months following CC admission. Figure 1 shows the Kaplan-Meier survival curve for overall survival (OS) for the cohort, with a median survival time of 83 days displayed.

<Table 1 here>

<Figure 2 here>

**Building the CREDIT Score**

To identify independent predictors of the clinical outcomes in the cohort, univariate regression analysis using logistic regression for each clinical outcome was employed. First, this was performed for all three scoring systems and their modified versions. The results of this are available in the Supplemental Table 1. The modified versions of the scoring systems performed as well as, and in some cases, better than the original versions. Coupled with the superiority of the modified versions in the initial univariate analysis, and the prior evidence of their superior predictive power combined with enhanced simplicity (17-20), the modified scoring systems were taken forward to the next step of the analysis.

A second univariate logistic regression analysis was performed for all variables that make up the modified scoring systems, including some variables relevant to Oncology, not present in the scoring systems (e.g. CCI, ECOG PS etc) with a focus on parameters that are calculated prior to CC admission (and therefore have utility as a decision tool). The results of this analysis are available in the Supplemental Table 2.

Finally, a multivariate regression analysis was built via logistic regression for the clinical outcomes, and a separate cox proportional hazards model for overall survival (OS), to identify the independent predictors suitable to be used to build the CREDIT score. 290 patients with complete data were included in the multivariate analysis (78% of the cohort). Any statistically significant variables from the second regression analysis were considered for inclusion. Obvious correlates were discarded and once the models were run, VIF scores were calculated. The VIF scores were all <1.8 indicating that multicollinearity was likely not present. The multivariate analysis, available in Table 2, revealed eight independent predictors of the clinical outcomes. These variables were taken forward to formulate the CREDIT score, displayed in Table 3. Missing data was given a value of 0 for purposes of building the score, rather than being imputed. As missing data was minimal for the independent predictors, this was felt to be the best approach.

<Table 2 here>

<Table 3 here>

**Validating the CREDIT Score**

To validate the utility of the CREDIT score, we retrospectively applied a score to each patient in the cohort. Where missing data was present a score of 0 was added to the final CREDIT score. Missing data was kept to a minimum as above (Table 3). All scoring systems were also split into 3 categories with increasing risk (0, 1 and 2) based on the univariate analysis, and the median values associated with the clinical outcomes.

Due to missing data across the scoring systems, ROC analysis was felt to be unreliable to provide robust comparisons particularly when the datasets were split into smaller training and test cohorts.

Therefore, we employed Kaplan-Meier survival analysis to compare the CREDIT score with the other scoring systems’ ability to predict 2-year OS. The categorical data was used for the Kaplan-Meier survival analysis. The results are available on Figure 3, with the CREDIT score being the only score able to predict survival (p=0.0018).

Continuous data was used to allow comparison between the CREDIT score, and the other scoring systems, to assess the predictive ability for Return to ACT and ECOG PS >2. The results of this analysis are available in Figure 4 and Figure 5, with the CREDIT score again displaying the best ability to predict Return to ACT (p<0.001) and ECOG PS >2 (p<0.0001).

<Figure 3 here>

<Figure 4 here>

<Figure 5 here>

**Machine Learning**

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