Use of the Rockwood Clinical Frailty Scale in patients with advanced hepatopancreaticobiliary malignancies

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**ABSTRACT**

**Background:** Co-existing frailty in older patients with hepatopancreaticobiliary (HPB) malignancies is common. This study assessed the relationship between the Rockwood Clinical Frailty scale (CFS) and systemic anti-cancer therapy dose intensity (SACT-DI) and overall survival (OS) in patients with advanced HPB malignancies.

**Research design and methods:** CFS was assessed prospectively for consecutive patients with newly diagnosed advanced HPB malignancy (The Christie; Sep-2019 to June-2020). Mann-Whitney U test assessed association between CFS, ECOG Performance Status (ECOG PS), and SACT-DI and Spearman's rank assessed the association between ECOG PS, age, and frailty. Survival analysis was performed using Kaplan-Meier and Cox regression.

**Results:** Two hundred patients met inclusion criteria. SACT-DI was higher in Group-1 (not frail) (CFS 1–3)(median = 61\%) than Group-2 (vulnerable/mildly frail) (CFS 4–5)(median = 25.1\%), \( p < 0.001 \). Median OS was shorter in frail and pre-frail patients (HR 2.3(95\%CI 1.8–2.9), \( p < 0.001 \)). On multivariable analysis, both CFS (HR 1.5–1.9(95\%CI 1.2–1.9), \( p = 0.002 \)) and ECOG PS (HR 1.9 (95\%CI 1.6–2.3), \( p < 0.001 \)) were independent prognostic factors for OS.

**Conclusion:** Frailty assessments, in addition to ECOG PS, may identify patients that will benefit from systemic therapy and are both independent prognostic factors for OS.

1. Introduction

Hepatopancreaticobiliary (HPB) malignancies are rare, comprising pancreatic ductal adenocarcinoma (PDAC), biliary tract cancer (BTC), and hepatocellular carcinoma (HCC). Hepatopancreaticobiliary malignancies are typically a disease of the elderly and with an aging population, cancer is increasingly prevalent in this age group, with more than one-third of cancer diagnoses in patients aged over 70 years [1]. Elderly patients are a heterogeneous group, who vary significantly in functional status, co-morbidities, and general health [2]. Older patients (commonly defined as those reaching retirement age: \( \geq 65 \) years) are often underrepresented in clinical trials and as a result can be undertreated and can have poorer outcomes than their younger counterparts [3,4]. Increased risk of adverse outcomes in these patients can potentially be attributed to underlying frailty [1].

Co-existing frailty in patients with HPB malignancies is common. Frailty is characterized by an increased vulnerability to stressors, due to reduced physiological reserve, and is associated with adverse outcomes, such as poor tolerance to systemic therapy and increased risk of mortality [5]. Although frailty can increase with age, it is considered to be a distinct concept and has been found to be a better predictor of patient outcomes than chronological age in patients undergoing surgery for ovarian cancer, and a strong predictor of mortality and therapeutic toxicity in lung cancer [6,7].

Patients with advanced HPB malignancies have a dismal prognosis and the benefit of treatment (which can consist of chemotherapy, targeted therapy, immunotherapy, or chemoradiotherapy) is modest [8,9]. The aim of systemic anticancer therapy (SACT) in these patients is to achieve temporary tumor control, symptom palliation, and improvement in survival. With a median survival of 8–12 months with SACT, it is important that treatment decisions are made in the context of this timeframe; with an emphasis on improving symptoms, reducing toxicity and maintaining quality of life. Robust frailty assessments are recognized as important tools to help aid clinical decision making and identify patients at greatest risk of morbidity from systemic therapy. The Rockwood Clinical Frailty score (CFS), a 9-point Clinical Frailty Scale, validated for people aged 65 years or older, has been used to predict mortality and inpatient length of stay [10,11]. The CFS was traditionally developed to be used in the acute medicine setting and has not been widely validated in oncology [12]. Increased knowledge and assessment of frailty in this setting, through the routine use of CFS in patients with advanced HPB malignancies, could be a valuable tool for doctors.
malignancies, may help identify patients more likely to benefit from systemic therapy. This study aimed to assess the impact of frailty on systemic therapy dose intensity (SACT-DI) and survival in patients with advanced HPB malignancies and how these findings may support treatment decision making.

2. Methods

2.1. Population

This was a single site retrospective review of consecutive patients with newly diagnosed HPB malignancies referred to the tertiary referral cancer center, The Christie NHS Foundation Trust, between September 2019 and June 2020. Eligible patients had a histological diagnosis of HPB malignancy (PDAC, BTC, and HCC), documented CFS at baseline, and were not amenable to curative surgery. Through review of electronic case records, data were collected on patient demographics, tumor type, Eastern Cooperative Oncology Group performance status (ECOG PS), CFS, treatment (best supportive care, surveillance or systemic therapy), systemic anti-cancer therapy dose intensity (SACT-DI), and survival. This study was approved by the internal review board at The Christie NHS Foundation Trust; the Clinical Audit Committee (reference 2595).

2.2. Rockwood Clinical Frailty Scale

The Rockwood Clinical Frailty Scale (Table 1) was scored at baseline for all patients by the treating physician. The score range on a scale from 1 to 9, with 1 being very fit, 2 well, 3 managing well, 4 vulnerable, 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail, and 9 terminally ill. On review, patients were subsequently categorized into three groups based on their frailty score, as described in recent studies assessing frailty in elderly hospitalized patients [13,14]. Group 1 were defined as not frail (CFS 1–3), Group 2 were vulnerable/mildly frail (CFS 4–5), and Group 3 had significant frailty (CFS6-9).

2.3. Systemic anti-cancer therapy dose intensity

Systemic therapy was identified through the electronic prescribing system. Patients included were those treated with first-line palliative chemotherapy as standard of care or on a clinical trial. Systematic therapy dose intensity (SACT-DI) was calculated for all patients as a percentage of treatment received over a total of 6 months. Those who stopped treatment due to toxicity, had dose reductions, or died during treatment were included and SACT-DI was calculated up to the last dose received, or total reduced dose, as percentage of the intended full dose over 6 months.

2.4. Statistics

Statistical analysis was performed using SPSS Statistics 28 (IBM Corp, Armonk, New York). Mann-Whitney U test was used to assess the association between CFS, ECOG PS and median SACT-DI. Spearman’s rank was used to assess whether there was a significant association between ECOG PS and frailty and the relationship between age and frailty. Overall survival (OS) was calculated from date of diagnosis to date of death or date of last contact, for patients presumed alive; patients who were alive at time of analysis were censored at time of last follow-up. Kaplan Meier survival analysis and Cox regression was performed to assess OS by frailty group and ECOG PS. Multivariable analysis adjusted for age, gender, primary site, ECOG-PS and CFS score. A two-sided p value of <0.05 was considered statistically significant. Data was last updated on 2/09/2021.

3. Results

3.1. Demographics

Between September 2019 and June 2020, there were 298 patients referred to The Christie NHS Foundation Trust with a new diagnosis of a HPB malignancy. Of these, 200 met inclusion criteria (Figure 1) The median age of patients was 70.4 years, 65.5% of patients were ≥65 years and 58% were male. Pancreatic cancer made up 61.5% of cases, biliary tract 28.5%, and hepatocellular carcinoma 10%. The majority of patients were classed as not frail (62%) and 34.5% of patients received best supportive care alone. At the time of analysis, 74% of patients had died. Patient demographics and CFS scores are illustrated in Table 2.

3.2. Frailty

Twenty percent of patients were frail (CFS ≥ 5) in the group and 18% were pre-frail (CFS 4). There was no significant relationship between frailty (CFS) and age (p = 0.263). There was a strong

Table 1. Rockwood Clinical Frailty Scale.

| Score | Frailty Description |
|-------|---------------------|
| 1     | Very Fit Robust, energetic, motivated, exercise regularly |
| 2     | Well No active disease symptoms, active very occasionally |
| 3     | Managing well Medical problems well controlled, not regularly active |
| 4     | Vulnerable Symptoms limit activities, independent, ‘slowed up’ |
| 5     | Mildly frail Require help with high order ADLs i.e. finance, transport |
| 6     | Moderately frail Require help with all outside activities and house chores |
| 7     | Severely frail Completely dependent for personal care |
| 8     | Very severely frail Completely dependent, approaching the end of life |
| 9     | Terminally ill Completely dependent, life expectancy < 6 months |

Adapted from The Clinical Frailty Scale (CFS) version 2.0 [11] ADLs: activities of daily living.

Figure 1. Consort diagram of included and excluded patients HPB: Hepatopancreaticobiliary, CFS: clinical frailty scale.
association between CFS and ECOG PS, with frail patients having a worse PS (r = 0.74, p = 0.01). Frailty and pre-frailty (CFS group 2 and 3) was equally prevalent in those aged 65 years and over (39%) compared to patients under 65 years (36%).

3.3. Systemic therapy

Systemic therapy was received by 61.5% of patients. Patients with pancreatic cancer (n = 69) were treated with single agent gemcitabine (n = 17, 24.6%), gemcitabine and capecitabine (n = 20, 29%) gemcitabine and nab-paclitaxel (n = 9, 13%) or 5-fluorouracil, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) (n = 17, 24.6%). Patients with BTC (n = 40) were treated with cisplatin and gemcitabine (n = 22, 55%) or single agent gemcitabine (n = 7, 17.6%) and those with HCC (n = 14) were managed with sorafenib (n = 13, 93%). First-line atezolizumab with bevacizumab was not approved at time of patient inclusion [15]. Fourteen percent of patients received treatment via a clinical trial. Table 3 shows the breakdown of treatment according to CFS, with fewer vulnerable/mildly frail patients receiving intense chemotherapy regimens (i.e. FOLFIRINOX) or inclusion in a clinical trial, than those who were not frail.

3.4. Survival

Of the 200 patients followed up, 148 (74%) had died at the time of analysis. Patients who were not frail had a longer OS than those who were frail (CFS ≥ 5) or prefrail (CFS 4) (Figure 3). Median OS in patients in CFS G1 was 7.4 months (95%CI 6.3–8.5), CFS G2: 3.5 months (95%CI 1.6–5.3) and CFS G3: 1.5 months (95%CI 0.2–1.1) (HR 2.3(95%CI 1.8–2.9), p < 0.001).

Patients with a good performance status, generally had a longer OS than patients with a poor ECOG PS (Figure 4). Median OS for patients with ECOG PS 0 was 9.7 months (95% CI 8.3–11.1), 1: 7.6 months (95%CI 6.6–8.5), ≥ 2.2 months (95% CI 1.3–3.0), 3: 1.2 months (95%CI 0.7–1.6) 4: 1.5 months (95%CI 0–3.6)(HR 2.1(95%CI 1.8–2.5) p < 0.001).

The univariate analysis found that age, gender and primary site had no significant impact on OS (Table 4) ECOG PS and CFS were identified to be prognostic factors for OS and were included in the multivariable analysis. On multivariable analysis, both CFS (HR 1.5-(95%CI 1.2–1.9), p = 0.002) and ECOG PS (HR 1.9 (95%CI 1.6–2.3), p < 0.001) remained independent prognostic factors for OS.

4. Discussion

This study investigated the association of CFS with outcomes in patients with advanced HPB malignancy in a ‘real world’ large tertiary cancer center.

Frailty or pre-frailty is common in patients with HPB malignancies, present in 38% of all patients, and is similar for those classified as ‘elderly’ (aged 65 years and over) or ‘young’ (under 65 years). This is in keeping with other studies, which have shown that frailty exists in younger adults and that frailty is common in patients with cancer, with more than 50% of older patients with cancer classified as frail or pre-frail [1,16]. There are several underlying disease processes that can contribute to or worsen frailty in patients with HPB malignancies; pancreatic exocrine insufficiency (PEI), diabetes mellitus, biliary and duodenal obstruction, and liver cirrhosis. These can lead to anorexia and malnutrition, fatigue, weight loss, sarcopenia, and

| Table 2. Patient demographics. |
| n | % |
|---|---|
| Age | | |
| <65 | 69 | 34.5 |
| ≥65 years | 131 | 65.5 |
| Gender | | |
| Male | 116 | 58.0 |
| Female | 84 | 42.0 |
| ECOG PS | | |
| 0 | 22 | 13.5 |
| 1 | 87 | 43.5 |
| 2 | 57 | 28.5 |
| 3 | 27 | 13.5 |
| 4 | 2 | 1.0 |
| Treatment | | |
| Systemic therapy | 123 | 61.5 |
| Surveillance | 8 | 4.0 |
| Best supportive Care | 69 | 34.5 |
| CFS group | | |
| 1 Not frail-(CFS 1–3) | 124 | 62.0 |
| 2 Vulnerable/mildly frail-(CFS 4–5) | 51 | 25.5 |
| 3 Moderately/severely frail-(CFS 6–9): | 25 | 12.5 |

| Table 3. Systemic therapy received according to clinical frailty scale group. |
| CFS Group | Treatment | n (%) |
|---|---|---|
| 1Not frail-(CFS 1–3) | FOLFIRINOX | 17 (17.5) |
| | Gemcitabine nab-paclitaxel | 7 (7.2) |
| | Gemcitabine + Capecitabine | 15 (15.5) |
| | Gemcitabine | 15 (15.5) |
| | Cisplatin + Gemcitabine | 19 (19.6) |
| | Sorafenib | 9 (9.3) |
| Clinical trial | 15 (15.5) |
| 2Vulnerable/mildly frail-(CFS 4–5) | FOLFIRINOX | 0 |
| | Gem nab-paclitaxel | 2 (8) |
| | Gemcitabine + Capecitabine | 5 (20) |
| | Gemcitabine | 9 (36) |
| | Cisplatin + Gemcitabine | 3 (12) |
| | Sorafenib | 4 (16) |
| Clinical trial | 2 (8) |

CFS: clinical frailty scale, FOLFIRINOX: 5-fluorouracil, folinic acid, irinotecan and oxaliplatin.
infection which can all affect tolerance to treatment and survival [17].

The results demonstrate that patients who are frail or pre-frail receive less chemotherapy overall. The included patients in CFS group 2 received a median dose intensity of 25% and would have received only modest benefit from systemic therapy. None of the patients in CFS group 3 (moderately to severely frail, CFS ≥ 6) received treatment. The CFS score was discriminatory in determining SACT-DI between groups, and may, therefore, be a more useful clinical decision aid when determining which regimens patients should receive or whether frail patients should receive treatment at all [18]. This has been reported in advanced gastroesophageal cancer, where baseline geriatric assessment has been used to optimize chemotherapy dosing in older and/or frail patients [19]. In the GO2 Phase 3 trial, patients were allocated to oxaliplatin/capecitabine at 3 different dose levels, or best supportive care based on their baseline geriatric assessment. Overall Treatment Utility (OTU) was assessed, looking at efficacy, toxicity, quality of life, and acceptability. The study found that the lowest dose produced less toxicity, without significantly affecting cancer control, and that baseline geriatric assessment could help predict the utility of chemotherapy.

Studies have demonstrated that frailty is not fixed and may be prevented, slowed or even reversed with appropriate interventions [20,21]. Patients in CFS group 2 who are vulnerable or mildly frail should receive additional specialist support to help optimize them prior to therapy. This has been studied in stage II–IV colorectal cancer where vulnerable patients ≥70 years (determined through the use of the Geriatric 8 screening...
tool), receiving adjuvant or first-line palliative chemotherapy were randomized 1:1 to Comprehensive Geriatric Assessment (CGA) -based interventions or standard care [22]. Interventions included rationalization of medication, nutritional therapy and physiotherapy. This study reported that more patients who received intervention were able to complete planned chemotherapy, without further dose reductions or delays compared to the control group (45% vs. 28%, \( p = 0.0366 \)), and was most noticeable in patients receiving treatment in the adjuvant setting. Prehabilitation before surgical resection has been shown to reduce frailty, prevent nutritional deterioration and shorten hospital stay in patients with HPB malignancies [23,24]. Interventions such as nutritional optimization (including management of glucose, diet and PEI) and exercise therapy to manage sarcopenia may also benefit patients in the palliative setting. It is acknowledged that CFS has only been validated for patients aged 65 years or older. However, there have been some studies that have shown that CFS is useful in predicting prognosis, discharge destination, and patient outcomes in patients under 65 [25,26]. In addition, no significant relationship between age and frailty (\( p = 0.263 \)) was found in this study. This suggests that all patients receiving systemic therapy should be assessed for frailty and not only those aged 65 years and older. A study of treatment-naive patients with stage IV non-small cell lung cancer (NSCLC) found that frailty was independently associated with toxicity with grade 3–5 toxicity in cycle 1, when adjusted for age, body surface area, and comorbidity score (Odds ratio 7.0; 95% CI 1.1–44.6) [27].

Most studies assessing frailty in patients with cancer have only included older patients aged over 70 [28–30]. It is important to recognize that biologically frail younger patients may also require additional support and clinical trials should report on frailty for all ages, as it can help evaluate the generalizability to clinical practice.

In the current patient group, frail and pre-frail patients with advanced HPB malignancies had a shorter OS and frailty was independently prognostic for OS. These findings support results from studies in other tumor sites, which have reported that worse frailty scores are prognostic for mortality in patients with lung cancer (HR = 1.57, 95% CI 1.32–1.87), survival post-surgery for colorectal cancer (HR = 3.6, 95% CI 2.3–5.5, \( p < 0.01 \)) and increased risk of death for newly diagnosed myeloma (HR 1.159; 95% CI, 1.080 – 1.244; \( p < 0.001 \)) [7,31,32]. Most studies in patients with HPB malignancies have assessed the relationship between frailty and post-operative outcomes after surgery and have used various measures of frailty such as sarcopenia, the modified frailty index (mFI) and the comprehensive geriatric assessment [33]. Further study is needed to define frailty consistently in patients with advanced HPB malignancies and to correlate this with patient outcomes.

The strengths of this study are the inclusion of consecutive patients seen at a tertiary referral center and that CFS was assessed prospectively at baseline review. It is acknowledged that this study is limited by the heterogeneity of the population included (multiple tumor sites, but all with similar prognoses in the advanced setting, in the time frame studied, when treated with the then available systemic therapies). The use of the Rockwood CFS provides a more detailed functional assessment that can be more discriminatory than ECOG PS; however, it is a subjective measure of frailty, and there is likely to be variability in assessment amongst clinicians. Hand grip strength and gait speed are objective measures that have been shown to measure frailty and predict patient outcomes in hematological malignancies [34]. A more detailed assessment, such as the CGA, that accounts for medical, functional

**Figure 4.** Kaplan–Meier Analysis of overall survival according to ECOG performance status.

**Table 4.** Univariate and multivariate analysis.

|                  | Univariate analysis | Multivariable analysis |
|------------------|---------------------|------------------------|
| Age (Under 65 ≥ 65) | \( p = 0.666 \)    | N/A                    |
| Gender           | \( p = 0.666 \)    | N/A                    |
| Primary site     | \( p = 0.83 \)     | N/A                    |
| ECOG PS          | \( p < 0.001 \)    | \( p < 0.001 \)        |
| CFS              | \( p < 0.001 \)    | \( p = 0.002 \)        |

ECOG PS: eastern cooperative oncology group performance status, CFS: clinical frailty scale, N/A: not applicable.
and social limitations of frail patients, which can identify reversible issues can also be a more useful measure of frailty \[35\]. This however, can be time and resource consuming and may not be practical in a busy outpatient setting.

Future study should assess patients prospectively and consider interventions, such as exercise therapy, diet and nutrition optimization and early input from specialists such as geriatricians, physiotherapists and pharmacists, for those at highest risk of toxicity \[36\]. In addition, it would be useful to investigate how many patients who are deemed not frail at baseline develop frailty following systemic therapy, in order to identify ‘at risk’ groups. This data has been reported in patients with stage I–IIIIC breast cancer, where the mean frailty score increases post-chemotherapy compared to baseline, \(p < 0.01\) \[37\].

There are very few trials currently underway that assess frailty and outcomes in patients with advanced HPB malignancies. NCT04602026 will identify frail patients prior to undergoing surgery for pancreatic, liver or gastric cancer. Patients identified as frail will be allocated to a standard of care arm or a comprehensive rehabilitation arm, where they undergo a physical therapy consultation and complete home exercises 3 days per week. To our knowledge, there are no ongoing trials assessing frailty in patients with advanced HPB malignancies.

5. Conclusion

Routine frailty assessment in all patients with advanced HPB malignancies is feasible. Frailty is common in patients with advanced HPB malignancies, including those aged under 65 years. Patients who are frail or pre-frail receive a lower dose intensity of chemotherapy and those with CFS \(\geq 4\) may not benefit from SACT and should be carefully assessed for suitability. Frailty assessments may be an additional discriminatory tool, with ECOG PS, in identifying patients that will benefit from systemic therapy. Clinical Frailty Scale and ECOG PS are both prognostic factors for survival in patients with advanced HPB malignancies. Frailty assessments should be used in conjunction with ECOG PS to guide treatment decisions and identify patients who would benefit from optimization prior to systemic therapy. Future trials should report on patient frailty in addition to age, to help guide clinical decision making in the real world clinical setting.

Author contributions statement

D Shah: data collection, statistical analysis and manuscript writing
ZA Kapacee: data collection, manuscript review and revision of intellectual content, proof-reading
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MG McNamara: manuscript review and revision of intellectual content, proof-reading, and approval of the final version of manuscript.

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JW Valle has served in a consultant/advisory role for Agios, AstraZeneca, Delcath Systems, Keocyt, Genoscience Pharma, Incyte, Ipsen, Merck, Mundipharma EDO, Novartis, PCI Biotech, Pfizer, Pieris Pharmaceuticals, QED, and Wren Laboratories; has served on the speakers’ bureau for Imaging Equipment Limited, Ipsen, Novartis, Nucana; and has received travel grants from Celgene and Nucana.
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