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Brief Communication

The Limitations of Frailty Assessment Tools in ANCA-Associated Vasculitis

L. Floyd[1,2], L. Byrne[3], A.D. Morris[2], A.C. Nixon[1,2], A. Dhaygude[1,2]

1. Division of Cardiovascular Sciences, University of Manchester, United Kingdom; 2. Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; 3. University of Manchester, Medical School, United Kingdom.

Corresponding Author: Dr Lauren Floyd, Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Royal Preston Hospital, Sharoe Green Lane, Preston, PR2 9HT, UK, Phone +44-1772524629 / E-mail: Lauren.Floyd@lthtr.nhs.uk.

Abstract

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) can be associated with a high burden of morbidity and mortality in an ageing population. It is increasingly recognised that individualised management is needed. Few studies have looked specifically at frailty related outcomes in AAV and a gap remains in understanding the application of frailty assessment tools in these patients. We carried out a single centre, cohort study between 2017 to 2022. Forty-one patients who had newly diagnosed or relapsing AAV and aged ≥65 years were included. The Clinical Frailty Scale (CFS) score at presentation was assessed by health care practitioners and interval CFS scores were carried out a minimum of 6 weeks from diagnosis. The aim was to determine if patients living with frailty had worse outcomes or if their perceived frailty improved with immunosuppressive treatment. The median CFS at diagnosis was 4 (vulnerable) and this remained at follow up. There was no significant interval change in CFS (P=0.16) suggesting that the patients did not become frailer and instead there was a tendency towards improved frailty scores at re-assessment. There was no significant difference in end stage kidney disease between those with higher (>5) or lower (≤5) CFS (P=1.0), although crude mortality was higher among those with an initial CFS >5 (P=0.03). Overall, we demonstrated that CFS has limitations in determining patients that may be frail as a result of disease burden with the potential to improve with treatment and clinicians should be mindful of this when making decisions relating to management.

Key words: ANCA, clinical frailty score, frailty, glomerulonephritis, vasculitis.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a multi-system autoimmune condition that typically presents around 65 years of age (1). Due to its relapsing, remitting nature AAV can be associated with a high burden of morbidity and mortality in an ageing population. Over recent years, advances in immunotherapies have allowed for a more tailored approach to management, with an emphasis of steroid sparing regimes especially in the context of increasing age and co-morbidities (2–4).

Studies have shown that regardless of age, frailty in patients with rheumatological diseases is highly prevalent and this is due to the burden of chronic inflammation, malnutrition, impairment of physical activity due to musculoskeletal and neurological involvement, as well high levels of pain and fatigue leading to adverse quality of life outcomes (5–7). In AAV specifically, the disease process can be aggressive with a variety of clinical features and presentations. Patients tend to have a prodrome of illness which can affect their renal function, mobility, physiological reserve and cognition (8, 9). It can therefore be hard for clinicians to determine and distinguish the degree of reversible disease burden on initial assessment and to what degree any active disease may account for perceived frailty at presentation. However, despite patients presenting in older age with cumulating co-morbidities, few studies have looked specifically at frailty related outcomes in the AAV population and a gap remains in understanding the application of frailty assessment tools in such patients. We carried out a small study looking at the Clinical Frailty Scale (CFS) (10) at presentation and how this changed following remission induction treatment, to determine if patients living with frailty had worse outcomes or if their perceived frailty improved with immunosuppressive treatment.

Methods

Participants & Study Design

A single centre cohort study was carried out between July 2017 and June 2022. All patients included had newly diagnosed or relapsing AAV in accordance with the Chapel Hill consensus (11), aged 65 years and over and had a documented CFS (10) at the time of diagnosis. Patients with secondary vasculitis and those with less than 3 month follow up data were excluded. The following data were collected retrospectively from the time of diagnosis; demographics, clinical presentation, immunotherapy, patient outcomes (mortality and end stage kidney disease (ESKD)), time to remission and further hospital admissions. This retrospective review of care delivered at our centre met the criteria for service evaluation and formal ethical approval from a research ethics committee was not required.

Clinical Frailty Scale Scores

CFS scores at presentation were documented prospectively on electronic health records. The assessments were performed by independent health care practitioners as part of standard local practice when patients aged ≥65 years are admitted to hospital. In the cases of patients who were not admitted to hospital at presentation or where the CFS was not recorded, GP records were used. Patients without a documented CFS at presentation were not included.

Interval CFS scores were carried out a minimum of 6 weeks

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from diagnosis. Patients who had further hospital admissions underwent repeat CFS assessment by independent health care practitioners in hospital. For those not readmitted to hospital, GP records were reviewed or where the GP records were not updated, patients were assessed in clinic or over the telephone by a medical professional.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables are shown as proportions. Several statistical tests were applied, including the Wilcoxon-signed rank test: the interval change in central tendency for the CFS; the result was verified by application of the paired-samples t-test to the data under natural logarithmic and square-root transformations. Kendall's τB and Mann–Whitney U-test were used for correlation between the baseline CFS and hospital readmissions and mortality respectively. Fisher's exact test was applied for group differences and the logrank test for survival curves for all-cause mortality. Results were considered statistically significant at a threshold of P=0.05. Analyses were performed using JASP v0.16.2 and IBM SPSS Statistics 28.0.1.

Results

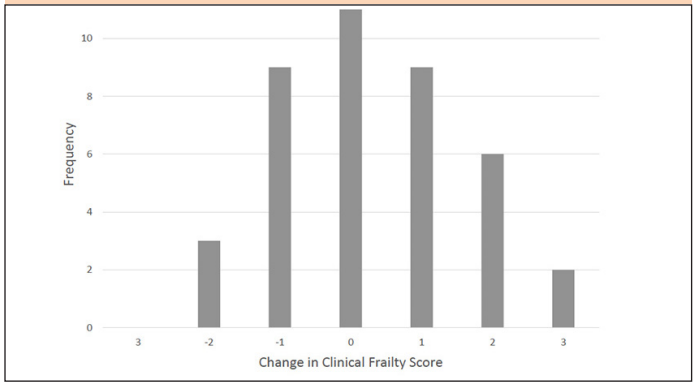
A total of forty-one patients aged 65 years and over with new or relapsing AAV were included. The mean age was 75 ± 6.17 years. Initial CFS assessments were performed on admission by independent health care practitioners in the majority of cases (n= 38, 92.7%). In the remaining three cases the scores were documented on electronic health records by GPs who had assessed the patient's frailty status within one month of presentation.

Follow up CFS scores were prospectively recorded; twelve patients had a repeated hospital admission, 4 patients had GP assessments and 24 patients had assessments in the outpatient clinic setting. One patient died prior to an interval CFS assessment and was excluded from data analysis. The median time between the initial and repeated CFS was 280 days (IQR 215-532). With the exception of one patient, all those included received standard remission induction therapy with cyclophosphamide and/or rituximab in addition to glucocorticoids.

The median CFS at diagnosis was 4 (IQR 3-5), which is classed as 'vulnerable', and this remained the predominant score at follow up. Five patients died during the follow up period and the median CFS in these patients was 5, classified as 'Mildly frail'. The median time from diagnosis to death was 18 months (IQR 8-21 months). Two patients died from infection, one from congestive cardiac failure and for two patients the cause of death was unknown. Crude mortality was higher among those with an initial CFS >5 compared to those with a CFS of ≤5 (P=0.03) and this was also seen when using CFS ≤4 vs CFS >4 as a cut off (P=0.04).

In seventeen cases (42.5%) the CFS actually improved with some patients going from a CFS of 6 (moderately frail) to 3 (managing well), (shown in Fig. 1). Among these patients, all were treated with immunosuppression; five patients received cyclophosphamide monotherapy, six received rituximab monotherapy, six received dual therapy with both cyclophosphamide and rituximab and 76.5% (n=13) received intravenous methylprednisolone alongside oral glucocorticoids. Eleven patients had the same CFS at repeat assessment and in 12 patients (30%) the CFS deteriorated from presentation. Twenty-one patients had a further hospital admission following diagnosis, with 10 patients having multiple admissions. When looking at each admission individually (n=35) the commonest cause of admission was infection (n=12, 34.2%) and cardiovascular events (n=4, 11,4%). There was no significant monotonic correlation between CFS and hospital readmissions (P=0.38).

Figure 1. Shows a histogram of the change in scores from baseline with the largest distribution round zero and a proportion of patient's clinical frailty scores improving



When applying statistical analysis to determine any significant interval change in the median CFS, the change was not statistically significant (P=0.16) suggesting that the patients did not become substantially frailer with follow-up and instead there was a tendency towards improved frailty measures at the point of re-assessment. There was no significant difference in ESKD at the end of the study between those with higher (>5) or lower CFS (≤ 5) (P=1.0).

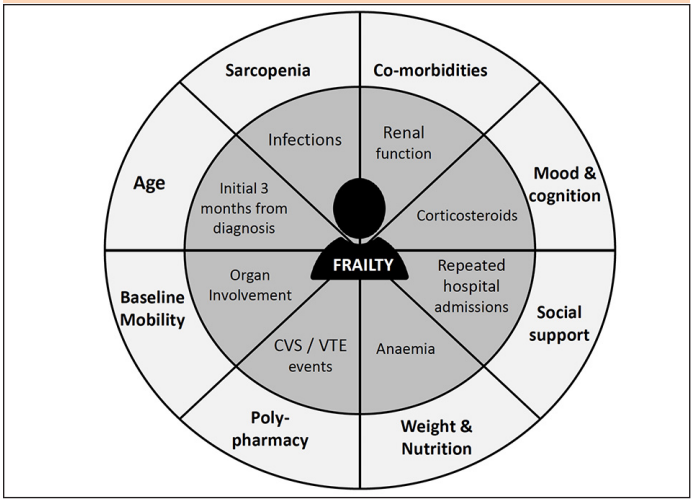
Discussion

Overall, our findings demonstrate that the assessment of clinical frailty in AAV is complex and not straight forward (shown in Fig. 2). Patients may present 'frail' as a result of significant disease burden, which has the potential to improve with appropriate treatment. Repeated assessments of clinical frailty are seldom done in the outpatient setting and determining change in functional status and physiological reserve is challenging. In the majority of cases presented in our cohort, the CFS stayed the same or improved from initial assessment, highlighting the need for repeated measures to aid management.

Whilst there is evidence to support the use of CFS as an assessment tool in a variety of diseases, including chronic and end stage kidney disease (12, 13), its utility in determining disease burden and frailty of patients with multifaceted, autoimmune inflammatory disease remains limited. Few studies have used CFS to assess outcomes in AAV. McGovern et al (3) applied retrospective CFS to a cohort of AAV patients

and showed that age and CFS were associated with increased mortality. Furthermore, the implication of immunosuppressive treatment, in particular glucocorticoids have been related to poor outcomes, especially in the first 3 months from diagnosis (14–16). Despite this, studies such as Morris et al (17) demonstrates that older aged patients treated with immunosuppressive therapy had favourable mortality outcomes compared to those who received less aggressive treatment (17, 18). Our study further supports this given all patients that had improved CFS (n=17) were treated with immunosuppression and over three quarters received intravenous glucocorticoid treatment at presentation This suggests that despite increasing age and frailty at assessment, the perceived risks associated with immunotherapy are likely outweighed by the benefits of adequate treatment.

Figure 2. Shows the multiple factors that contribute to frailty in patients presenting with AAV. The inner circle demonstrates disease contributing factors and the outer circle represents factors that contribute to frailty prior to diagnosis



AAV; Anti neutrophil cytoplasmic antibody (ANCA) associated vasculitis, CVS; cardiovascular system, VTE; venous thromboembolism

CFS is a useful assessment in patients aged over 65 years (10) but has potential limitations. The CFS is a brief frailty screening tool that summarises a healthcare professional's subjective assessment of frailty status. It is possible that frailty measures that are a more objective assessment of physical frailty, such as the Frailty Phenotype (which includes walking speed and grip strength measurement) (19), are more predictive of adverse outcomes in this setting. That being said, the CFS has good diagnostic accuracy for frailty in the advanced CKD setting when using Frailty Phenotype as the reference standard (13). Regardless, we hypothesise that frailty measures will be vulnerable to the same issues, specifically the ability to differentiate frailty, the age-associated decline in multiple physiological systems (20), from AAV disease burden that is amenable to specific disease therapy.

We also recognise the limitations of this study, including the small sample size. Follow up CFS assessments were performed using different methods with no standardised interval period which may be a confounder.

In conclusion, we recommend caution when determining treatment practices based solely on frailty assessments and the CFS. Based on the current available evidence, we propose that immunosuppressive therapy should be considered even in patients who are considered frail with high CFS scores. The use of other functional assessment tools to determine the patients physiological reserve, disease burden and degree of glucocorticoid toxicity should be considered, alongside a multi-disciplinary approach involving primary care. More work is needed to fully assess the role of frailty measures in patients with AAV, so as to improve outcomes and prevent over or under treatment.

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Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Ethical standard: This study met the criteria for service evaluation and ethical approval was not required.

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