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Moving upstream in the frailty trajectory

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Frailty is a condition characterised by loss of biological reserves and vulnerability to a range of adverse outcomes[1, 2].The cumulative deficit and phenotype models of frailty are internationally established and validated, but both models mainly use performance-based or clinical and functional assessments to identify frailty[3, 4]. This approach provides an important framework around which to understand frailty, but consideration of frailty from a physiological approach may enable improved precision of diagnosis, including identification of subclinical frailty, allowing future upstream targeting of interventions. Efforts to identify subclinical frailty from a biological perspective are aligned with a life course approach to frailty[5], which may enable investigation of clustering of characteristics at different life stages, and help shape future health policy.

In this issue, Blodgett and colleagues report the development and validation of a 23-item frailty index (FI-lab) assembled using markers to measure loss of biological reserve across physiological systems [6]. Their approach was based on the cumulative deficit frailty model and used commonly measured laboratory tests (such as serum sodium and vitamin D), pulse and blood pressure readings collected in a large prospective cohort study involving 3369 male participants.

The investigators tested the predictive validity and discrimination of the FI-lab for a range of adverse outcomes including care home admission, mortality, healthcare use, medication use, fractures, falls and a self-rated summary health questionnaire. The assessment of a broader range of outcomes, including those that impact on quality of life and independence as key priorities for older people, is welcome in frailty research, where a focus on all-cause mortality as a core outcome is too narrow [7-9] The choice is also pragmatic given the context of sub-clinical frailty, where all-cause mortality may be a remote outcome.

The investigators also compared the FI-lab to a clinically based frailty index (FI-clin) and assessed whether the FI-lab improved predictive validity and discrimination when combined with the FI-clin. FI-lab scores were higher in the population, compared with the clinical FI, and the population distributions were different. These findings are consistent with the notion of sub-clinical frailty as an intermediate step linking cellular mechanisms of ageing to clinically detectable deficits. The FI-lab predicted increased risk of care home admission, mortality, healthcare use, medication use and poor self-rated health. Increased risk of these outcomes and risk of falls and fractures were also identified by the FI-clin. A key finding of the study was that the predicted risk of these outcomes was increased when the FI-lab and FI-clin were combined.

C statistic estimates were reported by the authors for the range of outcomes measures. These estimates assess how well the frailty models discriminate between people who do and don't experience an outcome such as care home admission, falls or death, by rank-ordering cases and non-cases. A score of 1 is conventionally used to indicate perfect discrimination, with a score of 0.5 identifying no discrimination. The authors report estimates of between 0.6 to 0.7 for the FI-lab, suggesting moderate discrimination, and 0.7 to 0.8 for the FI-clin, indicating good discrimination. It is important to recognise that it is very unlikely that estimates approaching perfect discrimination will be achieved when investigating outcomes that are subject to a degree of random chance, such as mortality and care home admission. This is particularly pertinent in population-based studies, where most people are at low risk of these outcomes [7]. The c statistic estimates did not increase appreciably when

the FI-lab was combined with the FI-clin. However, this is a well-recognised limitation of c statistic estimates [10], and should not necessarily detract from the improvements in predicted risk that were observed when the measures were combined.

The findings have a number of possible implications for clinical practice. One key advantage of applying the cumulative deficit model of frailty to laboratory data is that the individual variables are not weighted. This means that implementation of an FI-lab in routine clinical practice is more straightforward, as a complicated algorithm is not required. Furthermore, the use of commonly available and inexpensive laboratory tests is welcome as many of the variables are already routinely collected in primary or secondary care. A simple, inexpensive method of identifying subclinical frailty is attractive, particularly in a primary care or non-specialist setting, and the added value of combining laboratory data with a clinical assessment has potential clinical utility.

However, the findings should be applied with a degree of caution. Identification of subclinical frailty may enable targeting of upstream interventions at an individual and population level, but treatments based on laboratory measures to identify sub-clinical frailty have not yet been evaluated, so clinical and cost-effectiveness is uncertain. Furthermore, the FI-lab is likely to provide information on risk prediction, rather than provide the clinical information required for constructing care plans based on individual problems and predicaments.

So what are the next steps? The study used data from a large prospective cohort study recruiting younger men (age range 40 to 79), and confirmation of the validity of the approach in representative older populations recruiting men and women is relevant. Investigation of the use of laboratory data measured as part of routine health care would enable preliminary testing of the approach in a clinical context. An electronic frailty index (eFI) that has been developed and validated using routine primary care electronic health record data is available in the UK (ref Clegg Age Ageing 2016 (in press)) and inclusion of an FI-lab alongside the eFI may increase predictive validity, but would require initial testing.

In the search for interventions to stabilise or improve frailty, the identification of subclinical frailty offers much opportunity, but many unanswered questions remain. The core advantage of identifying subclinical frailty and combining laboratory measures with a clinical assessment is likely to be improved targeting of interventions to improve outcomes across the frailty spectrum. A key strength of the continuous nature of the frailty index from both a laboratory and clinical perspective is that it may enable better targeting based on well-defined cut-points that accurately predict risk of outcomes. The precise cut-points are likely to vary depending on the particular intervention and outcome, so first require careful testing. However, this investigation is warranted because development and evaluation of targeted models of care based on individual frailty has considerable potential to improve the health and quality of life of older people living with frailty.

CoI: AC has led the development and validation of an electronic frailty index using routine primary care electronic health record data, based on the cumulative deficit model of frailty.

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