Association of a modified laboratory frailty index with adverse outcomes in geriatric rehabilitation inpatients: RESORT

Lihuan Guan a, Cheng Hwee Soh a, Esmee M. Reijnierse a,b, Wen Kwang Lim a, Andrea B. Maier a,c,d,e,*

a Department of Medicine and Aged Care, @AgeMelbourne, The Royal Melbourne Hospital, The University of Melbourne, Victoria, Australia
b Department of Rehabilitation Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, The Netherlands
c Faculty of Behavioural and Movement Sciences, Department of Human Movement Sciences, @AgeAmsterdam, Vrije Universiteit, Amsterdam Movement Sciences, Amsterdam, the Netherlands
d Centre for Healthy Longevity, @AgeSingapore, National University Health System, Singapore
e Healthy Longevity Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, @AgeSingapore, National University Health System, Singapore

ARTICLE INFO

Keywords:
Frailty
Laboratories
Institutionalization
Mortality
Rehabilitation

ABSTRACT

A higher number of laboratory measurements is associated with mortality in patients admitted to hospital, but is not part of the frailty index based on laboratory tests (FI-Lab). This study aimed to modify the FI-Lab (mFI-Lab) by accounting for the number of laboratory measurements and compare its validity to predict institutionalization and mortality at three-month post-discharge with the clinical frailty scale (CFS) in geriatric rehabilitation inpatients. In 1819 patients (median age 83.3 [77.6–88.3], 56.6% female), a higher FI-Lab was not associated with institutionalization but a higher risk of mortality. A higher mFI-Lab was associated with lower odds of institutionalization but a higher risk of mortality. A higher CFS was associated with institutionalization and higher mortality. The Akaike information criterion value was lowest for the CFS, followed by the mFI-Lab and the FI-Lab. The CFS is better than the mFI-Lab predicting short-term adverse outcomes in geriatric rehabilitation inpatients. When using laboratory data to estimate frailty, the mFI-Lab rather than the FI-Lab should be used.

1. Introduction

Frailty is a multifactorial state defined as vulnerable resolutions in response to physiological stressful events (Fried et al., 2004), which is associated with adverse health outcomes such as falls, disability, hospitalization, institutionalization and mortality (Clegg et al., 2013; Lee et al., 2010). The reported prevalence of frailty ranged from 32.5% to 87.1% in hospitalized older adults depending on the applied frailty criteria (Chong et al., 2017; Hao et al., 2019b; Joosten et al., 2014). The clinical frailty scale (CFS) is one of the commonly used frailty measures based on clinical judgement and has been shown to predict various adverse outcomes (Church et al., 2020). Assessing frailty is essential to identify vulnerable patients and help in clinical decisions making processes (Abbasi et al., 2018).

A frailty index (FI) comprised of routinely measured laboratory tests, the FI-Lab, was developed in community-dwelling older adults and is defined as the proportion of abnormal results from the total of measured tests (Howlett et al., 2014). With readily available laboratory tests data in electronic medical records, frailty by the FI-lab could be assessed in an easy, objective, and standardized way. A higher FI-Lab has been associated with falls (Blodgett et al., 2016), frequent doctor visits (Blodgett et al., 2016), more medication use (Blodgett et al., 2016), poor self-reported health (Blodgett et al., 2016) and mortality (Blodgett et al., 2017, 2016; Hao et al., 2019a; Howlett et al., 2014) in community-dwelling populations; with longer in-hospital stay, readmissions, institutionalization, and mortality in acutely hospitalized older patients (Ellis et al., 2020); and with mortality in institutionalized older adults (Rockwood et al., 2015; Yang et al., 2016). However, the association between the FI-Lab and adverse outcomes remains unknown in geriatric rehabilitation inpatients who are admitted to a post-acute...
rehabilitation setting for functional recovery (Achterberg et al., 2019). The use of the FI-Lab at geriatric rehabilitation admission might be helpful for risk stratification of adverse health outcomes and discharge planning. Moreover, the presence of laboratory tests itself, which has shown to be associated with mortality in patients admitted to hospital (Agniel et al., 2018), is not included in the existing FI-Lab.

The aims of this study were to (1) develop a modified FI-Lab (mFI-Lab) based on the proportion of measurements (measured ratio) and abnormal results (FI-Lab), (2) investigate the associations of the mFI-Lab and its components (measured ratio and FI-Lab) with functional decline, institutionalization and mortality at three-month post-discharge and (3) compare the predictive validity of the mFI-Lab with the FI-Lab and CFS among geriatric rehabilitation inpatients.

2. Methods

2.1. Study design

RESORRing health of acutely unwell adultTs (RESORT) is an observational, prospective, and longitudinal study including a total of 1890 geriatric rehabilitation inpatients admitted to the Royal Melbourne Hospital (Melbourne, Victoria, Australia) from 16th October 2017 and discharged until 18th March 2020. Patients were excluded if they were receiving palliative care at admission or were unable to consent and had no nominated proxy. Written informed consent was obtained from each patient or their designated proxy if patients were unable to consent themselves (e.g., due to severe dementia, delirium). Patients deceased in hospital were excluded in the current study (n = 71). This study was approved by the Melbourne Health Human Research Ethics Committee (No.: HREC/16/MH/346) and conducted in line with the Declaration of Helsinki (2013) and the National Statement on Ethical Conduct in Human Research (Anderson, 2011).

2.2. Data collection

A comprehensive geriatric assessment (CGA) was conducted within 48 h of admission to geriatric rehabilitation. Age and sex were extracted from medical records. Living status data was collected via a questionnaire completed by patients themselves and/or their carer. If the questionnaire was not completed, data on living status was extracted from medical records. The primary reasons for hospital admission were extracted from medical records and classified into musculoskeletal, neurological, cardiovascular, respiratory, infections, gastrointestinal, psychiatric and other diseases. Malnutrition risk was assessed using the malnutrition screening tool (MST) which consists of two questions with a total score of 5, higher scores indicating higher risk of malnutrition (Ferguson et al., 1999). Physical performance was assessed using the short physical performance battery (SPPB) which consists of standing balance tests, a four-meter walk test and the timed chair stand test, with total scoring ranging from 0 to 12 points (Guralnik et al., 1994). A higher SPPB score indicates better physical performance. Frailty status was assessed by the CFS with scores from 1 (very fit) to 9 (terminally ill) based on clinical judgement (Rockwood et al., 2005). The Katz activities of daily living (ADL) index scoring from 0 to 6 (Katz et al., 1963) and the Lawton and Brody scale instrumental activities of daily living (IADL) scoring from 0 to 8 (Lawton and Brody, 1969) were performed to assess self-management functional ability. Lower scores indicate higher dependency. The ADL and IADL at two weeks prior to hospital admission was also collected via the questionnaire or extracted from medical records if the questionnaire was not completed. Comorbidity was evaluated by the Charlson comorbidity index (CCI) with scoring from 0 to 37. Higher score represents greater comorbidity burden (Charlson et al., 1987). The hospital anxiety and depression scale (HADS) was used to assess anxiety and depressive symptoms and consists of anxiety and depression subscales with scoring from 0 to 21 for each subscale (Zigmond and Snaith, 1983). Scores of ≥ 11 points out of 21 on either subscale denote anxiety or depressive symptoms. Cognitive impairment was defined by a dementia diagnosis or an abnormal score on the standardised mini-mental state examination (sMMSE) < 24 points out of 30 (Folstein et al., 1975) or a Montreal cognitive assessment (MoCA) < 26 points out of 30 (Nasreddine et al., 2005) or a Rowland universal dementia assessment scale (RUDAS) < 23 points out of 30 (Storey et al., 2004). The prevalence of specific diseases including cardiovascular disease (myocardial infarction, heart failure, hypertension, stroke), renal impairment (renal calculi, acute and chronic renal impairment), diabetes, osteoporosis, delirium, chronic obstructive pulmonary disease were consolidated from data extracted from medical records and CCI. The number of medications used and length of stay in acute and geriatric rehabilitation was extracted from medical records.

2.3. Measured ratio, FI-Lab and mFI-Lab

Laboratory tests were measured based on clinical indication and performed at the Royal Melbourne Hospital pathology laboratories. Laboratory tests undertaken seven days before and after geriatric rehabilitation admission were included to create the mFI-Lab. If a laboratory variable was measured repeatedly, the test undertaken at the time closest to the geriatric rehabilitation admission time was included. Based on pathology data availability, a total of 77 laboratory test variables were included to calculate the mFI-Lab, covering a range of organ systems and functional parameters including haematology, electrolytes, liver, renal, inflammation, coagulation, metabolic, thyroid, cardiac and lung. Laboratory test variables were excluded if they were measured in less than 1% of inpatients. The list of included variables is presented in Table 1 with normal ranges and frequency of measurements.

The measured ratio was defined as the number of measured laboratory test variables divided by the total included number of laboratory test variables for each patient. For example, if a patient had 25 variables measured out of the total included 77 laboratory test variables, the measured ratio for this patient would be 0.32 (25/77). The FI-Lab was defined as the number of abnormal variables (out of the reference range) divided by the total measured variables for each patient (Howlett et al., 2014). For example, if the same patient had 10 abnormal variables out of the measured 25 laboratory test variables, the FI-Lab value for this patient would be 0.40 (10/25). The measured ratio and FI-Lab were expressed as continuous variables (per 0.1-unit higher) and dichotomized by respective median value. Low measured ratio (< median of the measured ratio) or low FI-Lab (< median of the FI-Lab) was set as the reference group. The mFI-Lab was expressed as a continuous variable calculated as the FI-Lab divided by the measured ratio (per 0.1-unit higher) and also a categorized variable created based on the dichotomized measured ratio and the dichotomized FI-Lab by their respective median values. Patients were classified into four mFI-Lab groups: high measured ratio (≥ median) and high FI-Lab (≥ median), high measured ratio (≥ median) and low FI-Lab (< median), low measured ratio (< median) and high FI-Lab (≥ median), and low measured ratio (< median) and low FI-Lab (< median).

2.4. Outcomes

The ADL, IADL and institutionalization at three-month post-discharge was collected via phone-call by trained researchers or extracted from medical records. Lower ADL or IADL at three-month post-discharge than that at two weeks prior to hospital admission was defined as functional decline. Patients were excluded from the functional decline analyses if they had missing ADL or IADL data at two weeks prior to hospital admission or three-month follow-up (n = 469). The incidence of institutionalization was defined as a new admission to a residential care institution at three-month post discharge from geriatric rehabilitation wards (Pacifico et al., 2021). Patients were excluded from the institutionalization analyses, if they were admitted from an institution (n = 51), had missing follow-up data (n = 127) or were deceased at
### Table 1
Normal ranges and frequency of included pathology variables measured in 1819 geriatric rehabilitation inpatients.

| Laboratory variables | Frequency n (%) | Normal range |
|-----------------------|-----------------|--------------|
| **Blood sample**      |                 |              |
| White cell count, × 10^9/L | 1806 (99.3) | 4.0-11.0 | 4.0-11.0 |
| Lymphocytes, × 10^9/L | 1806 (99.3) | 1.2-4.0 | 1.2-4.0 |
| Neutrophils, × 10^9/L | 1806 (99.3) | 2.0-8.0 | 2.0-8.0 |
| Basophils, × 10^9/L | 1806 (99.3) | 0.0-0.1 | 0.0-0.1 |
| Eosinophils, × 10^9/L | 1806 (99.3) | 0.0-0.5 | 0.0-0.5 |
| Monocytes, × 10^9/L | 1806 (99.3) | 0.1-1.0 | 0.1-1.0 |
| Platelet count, × 10^12/L | 1806 (99.3) | 140-400 | 140-400 |
| Red blood cell count, × 10^12/L | 1806 (99.3) | 4.5-5.7 | 3.8-5.1 |
| Haemoglobin, g/L | 1806 (99.3) | 130-170 | 115-150 |
| Haematocrit | 1806 (99.3) | 0.40-0.50 | 0.35-0.45 |
| MCH, pg | 1806 (99.3) | 27.0-33.0 | 27.0-33.0 |
| MCHC, g/L | 1806 (99.3) | 310-360 | 310-360 |
| MCV, fL | 1806 (99.3) | 80.0-96.0 | 80.0-96.0 |
| RDW, % | 1806 (99.3) | 11.0-15.0 | 11.0-15.0 |
| Urea, mmol/L | 1804 (99.2) | 3.2-7.4 | 2.5-6.7 |
| Creatinine, µmol/L | 1804 (99.2) | 60-110 | 45-90 |
| eGFR, ml/min/1.73 m² | 1804 (99.2) | > 90 | > 90 |
| Sodium, mmol/L | 1761 (96.8) | 135-145 | 135-145 |
| Potassium, mmol/L | 1761 (96.8) | 3.5-5.2 | 3.5-5.2 |
| Chloride, mmol/L | 1761 (96.8) | 95-110 | 95-110 |
| Bicarbonate, mmol/L | 1761 (96.8) | 22-32 | 22-32 |
| Albumin, g/L | 1751 (96.3) | 35-50 | 35-50 |
| MPV, fL | 1745 (95.9) | 7.4-10.4 | 7.4-10.4 |
| Calcium, mmol/L | 1722 (94.7) | 2.1-2.6 | 2.1-2.6 |
| Magnesium, mmol/L | 1689 (92.8) | 0.7-1.1 | 0.7-1.1 |
| Phosphate, mmol/L | 1688 (92.8) | 0.75-1.50 | 0.75-1.50 |
| Total protein, g/L | 1426 (78.4) | 60-80 | 60-80 |
| Bilirubin, µmol/L | 1418 (78.0) | < 21 | < 21 |
| ALT, IU/L | 1418 (78.0) | < 40 | < 35 |
| ALP, IU/L | 1418 (78.0) | 30-110 | 30-110 |
| AST, IU/L | 1412 (77.6) | < 35 | < 30 |
| GGT, IU/L | 1411 (77.6) | < 65 | < 37 |
| **Laboratory variables** | **Frequency n (%)** | **Normal range** |
| Globulin, g/L | 1387 (76.3) | 25-40 | 25-40 |
| CRP, mg/L | 1230 (67.6) | < 5 | < 5 |
| TSH, mU/L | 936 (51.5) | 0.35-4.94 | 0.35-4.94 |

---

### Table 1 (continued)

| Laboratory variables | Frequency n (%) | Normal range |
|-----------------------|-----------------|--------------|
| **Blood gas panel** |                 |              |
| pH | 631 (34.7) | Arterial: 7.35-7.45 | Arterial: 7.35-7.45 |
| pCO₂, mmHg | 631 (34.7) | Arterial: 35-45 | Arterial: 35-45 |
| pCO₂, mmHg | 631 (34.7) | Venous: 30-50 | Venous: 30-50 |
| Lactate, mmol/L | 631 (34.7) | Arterial: 0.2-1.8 | Arterial: 0.2-1.8 |
| Bicarbonate, mmol/L | 631 (34.7) | Venous: 22-32 | Venous: 22-32 |

| **Laboratory variables** | **Frequency n (%)** | **Normal range** |
|-------------------------|---------------------|------------------|
| Base excess, mmol/L | 631 (34.7) | Arterial: –3 to 3 | Arterial: –3 to 3 |
| MetHb, % | 347 (19.1) | Venous: 0.1-1.4 | Venous: 0.1-1.4 |
| COHb, % | 347 (19.1) | Arterial: 0.5-1.5 | Arterial: 0.5-1.5 |

| **Urine sample** | | |
|------------------|------------------|------------------|
| Leucocytes, × 10^6/L | 886 (48.7) | < 2 | < 2 |
| Erythrocytes, × 10^6/L | 886 (48.7) | < 13 | < 13 |
| Epithelial cells, presence | 870 (47.8) | Negative | Negative |
| Protein, presence | 823 (45.2) | Negative | Negative |
| Glucose, presence | 823 (45.2) | Negative | Negative |
| Blood, presence | 823 (45.2) | Negative | Negative |
| Specific gravity | 823 (45.2) | 1-1.03 | 1-1.03 |
| Ketones, presence | 795 (43.7) | Negative | Negative |
| Bilirubin, presence | 795 (43.7) | Negative | Negative |
| Nitrates, presence | 795 (43.7) | Negative | Negative |
| Urobilinogen, presence | 795 (43.7) | Normal | Normal |
| Leucocyte esterases, presence | 794 (43.7) | Negative | Negative |

Abbreviations: ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; APTT: Activated partial thromboplastin time; COHb: Carboxyhemoglobin; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; ESR: Erythrocyte sedimentation rate; GGT: Gamma glutamyl transferase; Haemoglobin; HbTrop 1; High sensitivity Troponin I; INR: International normalised ratio; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; MetHb: Methemoglobin; MPV: Mean platelet volume; pCO2: Partial pressure of carbon dioxide; pO2: Partial pressure of oxygen; PT: Prothrombin time; RDW: Red blood cell distribution width; TSH: Thyroid stimulating hormone.
Mechanisms of Ageing and Development 203 (2022) 111648

4

three-month follow-up (n = 133), leaving 1517 patients for the analyses (n = 9 nursing home residents died during three-month follow-up). Mortality data was obtained from the Registry of Births, Deaths and Marriages Victoria and extracted from medical records (Pacífico et al., 2021). The time to death was calculated from the discharge from geriatric rehabilitation to the date of the follow-up phone call.

2.5. Statistical analysis

The characteristics of patients at geriatric rehabilitation admission were described using medians with interquartile ranges (IQR) for skewed distributed continuous variables and numbers with percentages for categorical variables. The associations of the measured ratio, FI-Lab, mFI-Lab and CFS with functional decline and institutionalization were evaluated by multiple logistic regression analyses and expressed as odds ratios (OR) with 95% confidence intervals (CI). Cox regression was performed to investigate the associations of the measured ratio, FI-Lab, mFI-Lab and CFS with three-month mortality, expressed as hazard ratios (HR) with 95% CIs. Two models were used: a crude model and a model adjusted for age, sex, CCI score and primary reasons for hospital admission. The goodness of model fit was evaluated by the Akaike information criterion (AIC). A p-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using the statistical package for the social sciences (SPSS) 26.0 (IBM Corp, Armonk, NY, USA). Figures were plotted using Prism GraphPad 6.0 (GraphPad Software Incorporated, San Diego, CA, USA).

3. Results

3.1. Characteristics of patients

A total of 1819 patients were included with a median age of 83.3 years (IQR: 77.6–88.3), 56.6% were female and 47.7% of the patients were admitted to hospital due to musculoskeletal diseases. Patients had a median MST score of 1 point (IQR: 0–2), a median SPPB score of 1 point (IQR: 0–4), a median CFS of 6 points (IQR: 5–7), a median ADL score of 2 points (IQR: 1–3), a median IADL score of 1 point (IQR: 0–2) and a median CCI score of 2 points (IQR: 1–4). The median length of stay in acute hospitalization was 7.2 days (IQR: 4.0–12.5) and 19.9 days (IQR: 13.1–30.9) in geriatric rehabilitation. The median measured ratio was 0.58 (IQR: 0.47–0.70), the median FI-Lab was 0.31 (IQR: 0.23–0.38) and the median mFI-Lab was 0.51 (IQR: 0.38–0.68) (Table 2). The histograms of the measured ratio, FI-Lab and mFI-Lab are shown in Supplementary Fig. S1.

3.2. Associations between frailty measures with functional decline

Functional decline at three-month post-discharge was present in 78.6% of patients (n = 1061/1350). The measured ratio, FI-Lab, and mFI-Lab were not associated with functional decline in the crude and adjusted model (Table 3, Fig. 1A). A higher CFS (per 1-unit higher) was associated with functional decline in the crude and adjusted model (adjusted OR: 1.11, 95% CI: 1.02–1.20, p = 0.013). The FI-Lab was not associated with institutionalization. A higher mFI-Lab (per 0.1-unit higher) was associated with lower odds of institutionalization in the crude and adjusted model (adjusted OR: 0.93, 95% CI: 0.89–0.98, p = 0.009). A higher CFS (per 1-unit higher) was associated with higher odds of institutionalization in the crude and adjusted model (adjusted OR: 1.41, 95% CI: 1.26–1.58, p < 0.001) (Table 3).

Table 2

| Characteristic of patients | n | Total (n = 1819) |
|----------------------------|---|----------------|
| Age, years                 | 1819 | 83.3 [77.6–88.3] |
| Female, n (%)              | 1819 | 1029 (56.6) |
| Living alone, n (%)        | 1814 | 772 (42.6) |
| Nursing home residence, n (%) | 1819 | 51 (2.8) |
| Primary reasons for hospital admission, n (%) | 1819 |
| Musculoskeletal            | 1061/1350 | 868 (47.7) |
| Neurological               | 277 (15.2) |
| Cardiovascular             | 146 (8.0) |
| Respiratory                | 125 (6.9) |
| Infection                  | 110 (6.0) |
| Gastrointestinal           | 99 (5.4) |
| Psychiatry                 | 77 (4.2) |
| Other                      | 117 (6.4) |
| MST, score                 | 1792 | 1 (0–2) |
| SPPB, score                | 1722 | 1 (0–4) |
| Clinical frailty scale, score | 1651 | 6 (5–7) |
| Katz ADL, score            | 1801 | 2 (1–3) |
| Lawton and Brody Scale IADL, score | 1802 | 1 (0–2) |
| Charlson comorbidity index, score | 1819 | 2 (1–4) |
| Anxiety symptoms, n (%)    | 1208 | 279 (23.1) |
| Depressive symptoms, n (%) | 1228 | 332 (27.0) |
| Cognitive impairment, n (%) | 1819 | 1184 (65.1) |
| Cardiovascular disease, n (%) | 1819 | 1537 (84.5) |
| Renal impairment, n (%)    | 1819 | 700 (38.5) |
| Diabetes, n (%)            | 1819 | 655 (36.0) |
| Stroke, n (%)              | 1819 | 598 (32.9) |
| Osteoporosis, n (%)        | 1819 | 535 (29.4) |
| Delirium, n (%)            | 1819 | 424 (23.3) |
| Chronic obstructive pulmonary disease, n (%) | 1819 | 317 (17.4) |
| Medication count           | 1819 | 9 (7–12) |
| LOS in acute               | 1765 | 7.2 (4.0–12.5) |
| LOS in geriatric rehabilitation | 1819 | 19.9 (13.1–30.9) |
| Measured ratioa            | 1819 | 0.58 (0.47–0.70) |
| FI-Labb                    | 1810 | 0.31 (0.23–0.38) |
| mFI-Labc                   | 1810 | 0.51 (0.38–0.68) |
| Functional decline, n (%)  | 1350 | 1061 (78.6) |
| Incidence of institutionalization, n (%) | 1517 | 384 (25.3) |
| Three-month mortality, n (%) | 1819 | 133 (7.3) |

Data are presented as median [IQR] unless otherwise indicated. Abbreviations: MST: Malnutrition screening tool; SPPB: Short physical performance battery; ADL: Activities of daily living; IADL: Instrumental activities of daily living; LOS: Length of stay; FI-Lab: Frailty index based on abnormal laboratory tests; mFI-Lab: The modified frailty index based on abnormal laboratory tests.

3.3. Associations between frailty measures with institutionalization

The incidence of institutionalization at three-month post-discharge was 25.3% (n = 384/1517). A higher measured ratio (per 0.1-unit higher) was associated with institutionalization in the crude and adjusted model (adjusted OR: 1.14, 95% CI: 1.03–1.26, p = 0.015) and showed a trend in the adjusted model (adjusted OR: 1.11, 95% CI: 1.00–1.24, p = 0.051) (Table 3). A higher mFI-Lab (per 0.1-unit higher) was associated with lower odds of institutionalization in the crude and adjusted model (adjusted OR: 0.93, 95% CI: 0.89–0.98, p = 0.009). A higher CFS (per 1-unit higher) was associated with higher odds of institutionalization in the crude and adjusted model (adjusted OR: 1.32, 95% CI: 1.11–1.58, p < 0.002; adjusted OR: 1.11, 95% CI: 1.06–1.15, p < 0.001). A higher CFS (per 1-unit higher) was associated with higher

3.4. Associations between frailty measures with mortality

The mortality rate at three-month post-discharge was 7.3% (n = 133/1819). A higher measured ratio (per 0.1-unit higher) was associated with lower three-month mortality in the crude and adjusted model (adjusted HR: 0.87, 95% CI: 0.77–0.97, p = 0.015). Higher FI-Lab and mFI-Lab (per 0.1-unit higher) were associated with higher three-month mortality in the crude and adjusted model (adjusted HR: 1.32, 95% CI: 1.11–1.58, p < 0.002; adjusted HR: 1.11, 95% CI: 1.06–1.15, p < 0.001). A higher CFS (per 1-unit higher) was associated with higher
three-month mortality (adjusted HR: 1.37, 95% CI: 1.15–1.62, p < 0.001) (Table 3). A measured ratio above median level was not associated with mortality. The FI-Lab above median level was associated with higher mortality (adjusted HR: 1.58, 95% CI: 1.08–2.30, p = 0.018) (Table 3, Fig. 1C). In the mFI-Lab group analysis, a low measured ratio and low FI-Lab (adjusted HR: 2.08, 95% CI: 1.14–3.79, p = 0.016), high measured ratio and high FI-Lab (adjusted HR: 2.35, 95% CI: 1.33–4.16, p = 0.003), and low measured ratio and high FI-Lab (adjusted HR: 2.33, 95% CI: 1.31–4.15, p = 0.004) was associated with higher three-month mortality compared to a high measured ratio and low FI-Lab (Table 3, Fig. 1C).

3.5. Goodness of model fit

The AIC values were lower for the adjusted models than the crude models and lowest for the CFS. The AIC value of adjusted model that included the mFI-Lab was lower than the FI-Lab for both institutionalization and mortality outcomes (Table 4).

4. Discussion

Frailty index derived from abnormal laboratory tests was modified (mFI-Lab) to account for the number of laboratory variables measured. The measured ratio, FI-Lab, and mFI-Lab were not associated with functional decline. A high measured ratio, but not the FI-Lab, was associated with institutionalization. Lower measured ratio, higher FI-Lab and higher mFI-Lab were all associated with higher three-month mortality. The model fit of the mFI-Lab was better than the FI-Lab but worse than the CFS.

Conflicting results have been found on the association between the FI-Lab and institutionalization (Blodgett et al., 2016; Heikkila et al., 2021). The FI-Lab based on the abnormality of 23 items including common laboratory tests, blood pressure and pulse pressure was associated with institutionalization in community-dwelling men during a six-year follow-up period (Blodgett et al., 2016). Another FI-Lab created from 14 common laboratory tests was not associated with institutionalization in community-dwelling older adults during ten- and eighteen-year follow-ups (Heikkila et al., 2021). In the present study, a higher measured ratio but not the FI-Lab was associated with institutionalization at three-month follow-up among geriatric rehabilitation inpatients. The negative association between the mFI-Lab and institutionalization might be dominated by the measured ratio component. Institutionalization is a multi-faceted outcome which might be more related to functional decline and cognitive impairment as well as the shortage of social support or severe caregiver’s burden (Hébert et al., 2001; Luppa et al., 2010) rather than biological abnormalities as revealed by the FI-Lab. Indeed, the association between the mFI-Lab and functional decline was not found in this study. Laboratory tests are measured more frequently when patients experience poor health conditions which would attract more attention to be treated and cared (Hripcsak et al., 2015). Therefore, the measured ratio was associated with institutionalization instead of combined with the FI-Lab as the mFI-Lab.

Previously, the FI-Lab was constructed by the proportion of abnormal results and requires at least 60% or 70% or 80% of variables measured in each individual (Ellis et al., 2020; Jager et al., 2019; Klausen et al., 2017; Ritt et al., 2017). Participants with more laboratory variables measured were selected in these studies, whereas the presence of measurements itself, which might have prognostic information, was not taken into account. However, the result that a higher measured ratio was associated with lower mortality was in contrast to the study which showed that the presence of laboratory tests, regardless of the results, was associated with a higher risk of mortality in inpatients and outpatients with an included age range from 0 to 89 years (Agni et al.,...
Each additional laboratory test raises potential health concerns and further increases the risk of adverse outcomes (Agniel et al., 2018; Hripcsak et al., 2015). The geriatric rehabilitation population who had a median age of 83.3 years old and multi-morbid conditions in the present study was a different population from the previous study (Agniel et al., 2018). These geriatric patients admitted to post-acute rehabilitation wards were medically stable with aims to restore functional and autonomy abilities (Achterberg et al., 2019). More tests measured might be helpful to monitor the patients’ medical conditions so that clinicians could make better treatment strategies. However, the laboratory tests should be ordered when necessary. On the other hand, the finding that a higher FI-Lab was associated with higher mortality was consistent with previous studies in acutely admitted older adults (Ellis et al., 2020; Klausen et al., 2017) or hospitalized patients admitted to geriatric wards (Jager et al., 2019; Ritt et al., 2017). The abnormalities in laboratory tests might reflect adverse health conditions and dysfunction in organ systems which contribute to the risk of mortality.

This is the first study to integrate the number of laboratory variables...
measured into a frailty index based on abnormal laboratory tests and investigate its association with adverse outcomes in geriatric rehabilitation inpatients. The model fit of the mFI-Lab was better than the FI-Lab for institutionalization and mortality outcomes, whereas the CFS showed a lower AIC than the mFI-Lab. The application of the mFI-Lab was not limited to the patients with a certain number of variables measured. Moreover, more precise estimates were obtained with more deficits included in a frailty index (Searle et al., 2008). A total of 77 laboratory variables were included in the mFI-Lab, accounting for a wide range of organ system functions and health. Furthermore, the included laboratory tests are easily and objectively measured as part of routine clinical care, which makes the implementation of the mFI-Lab feasible. A limitation of this study is that the median values of the measured ratio and FI-Lab used as cut-offs in the mFI-Lab might not be generalizable to other populations.

5. Conclusions

In conclusion, among geriatric rehabilitation inpatients, the frailty index based on laboratory tests was not associated with functional decline. Higher proportion of measurements but not abnormal laboratory test results was associated with institutionalization. The mFI-Lab and its components (proportion of measured and abnormal laboratory variables) were associated with mortality. In the mFI-Lab group analysis, patients with high measured ratio and low FI-Lab had the lowest risk of mortality. The proportion of measurements should be considered when laboratory tests are used to assess frailty. The CFS is a better predictor than the mFI-Lab for short-term adverse outcomes in geriatric rehabilitation inpatients. Further studies are needed to investigate the association of the mFI-Lab with long-term outcomes and evaluate its predictive ability compared to other frailty measures.

Funding sources

This work was supported by an unrestricted grant of the University of Melbourne received by Prof. Andrea B. Maier and the Medical Research Future Fund (MRFF) provided by the Melbourne Academic Centre for Health (MACH). Lihuan Guan has received a China Scholarship Council - University of Melbourne PhD Scholarship.

Conflict of Interest

All authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgments

All authors thank the multidisciplinary team members of the Royal Park Campus, the Royal Melbourne Hospital in their involvement in the RESORT study for their clinical work and the @AgeMelbourne team for their role in the data collection. The authors would also like to thank the Department of Pathology, the Royal Melbourne Hospital for assessing the pathology data. The study was funded by an unrestricted grant of the University of Melbourne, Australia and the Medical Research Future Fund by the Melbourne Academic Centre for Health, Australia.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mad.2022.111648.

References

Abbasi, M., Rolfsen, D., Khera, A.S., Darabovskaja, J., Dent, E., Xia, L., 2018. Identification and management of frailty in the primary care setting. CMAJ 190, E1134–E1140.
Achterberg, W.P., Cameron, I.D., Bauer, J.M., Schols, J.M., 2019. Geriatric REHABILITATION-STATE OF THE ART AND FUTURE Priorities. J. Am. Med Dir. Assoc. 20, 396–398.
Aguiar, D., Kobane, I., Weber, G.M., 2018. Biases in electronic health record data due to processes within the healthcare system: retrospective observational study. BMJ 361, k1479.
Anderson, W., 2011, National Statement on Ethical Conduct in Human Research.
Blodgett, J.M., Theou, O., Howlett, S.E., Rockwood, K., 2017. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. Geroncology 39, 447–455.
Blodgett, J.M., Theou, O., Howlett, S.E., Wu, F.C., Rockwood, K., 2016. A frailty index based on laboratory deficits in community-dwelling men predicted their risk of adverse health outcomes. Age Ageing 45, 463–468.
Charlson, M.E., Pompei, P., Ales, K.L., MacKenzie, C.R., 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chronic Dis. 40, 373–383.
Chong, F., Ho, E., Baldevara-Llego, J., Chan, M., Wu, L., Tay, L., 2017. Frailty and Risk of Adverse Outcomes in Hospitalized Older Adults: A Comparison of Different Frailty Measures. J. Am. Med. Dir. Assoc. 18, 638 e637–638 e611.
Church, S., Rogers, E., Rockwood, K., Theou, O., 2020. A scoping review of the Clinical Frailty Scale. BMC Geriatr. 20, 393.
Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. Lancet 381, 752–762.
Ellis, H.L., Wan, B., Yeung, M., Rather, A., Mannan, I., Bond, C., Harvey, C., Raja, N., Dutay-Magni, P., Rockwood, K., Davis, D., Searle, S.D., 2020. Complementing chronic frailty assessment at hospital admission with an electronic frailty index (FI-Laboratory) comprising routine blood test results. CMAJ 192, E3–E8.
Ferguson, M., Capra, S., Bauer, J., Banko, M., 1999. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. Nutrition 15, 458–464.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res 12, 189–198.
Fried, L.P., Ferrucci, L., Darer, J., Williamson, J.D., Anderson, G., 2001. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J. Gerontol. A Biol. Sci. Med Sci. 56, 255–263.
Guralnik, J.M., Simonsick, E.M., Ferrucci, L., Glynn, R.J., Berkman, L.F., Blazer, D.G., Scherr, P.A., Wallace, R.B., 1994. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J. Gerontol. 49, M85–M94.
Hao, Q., Sun, X., Yang, M., Dong, B., Dong, B., Wei, Y., 2019a. Prediction of mortality in Chinese very old people through the frailty index based on routine laboratory data. Sci. Rep. 9, 221.
Hao, Q., Zhou, L., Dong, B., Yang, M., Dong, B., Weil, Y., 2019b. The role of frailty in predicting mortality and readmission in older adults in acute care wards: a prospective study. Sci. Rep. 9, 1207.
Hebert, R., Dubois, M.-F., Wolfson, C., Chambers, L., Cohen, C., 2001. Factors associated with long-term institutionalization of older people with dementia: data from the Canadian Study of Health and Aging. J. Gerontol. A Biol. Sci. Med Sci. 56, M693–M699.
Heikkila, E., Salminen, M., Viljanen, A., Katajajärvi, T., Koirula, M.K., Paakkari, K., Isonho, R., Kivela, S.L., Vihinen, M., Loponen, M., Vahlberg, T., Viikari, L., Ihaia, K., 2021. A practical laboratory index to predict institutionalization and mortality - an 18-year population-based follow-up study. BMC Geriatr. 21, 1, 139.

Table 4: Goodness of model fit for analyzing the associations of the measured ratio, FI-Lab, mFI-Lab and CFS with institutionalization and mortality.

| AIC | Institutionalization | Mortality |
| --- | --- | --- |
| Crude model | Measured ratio | 1716.665 | 1971.957 |
|  | FI-Lab | 1713.472 | 1927.288 |
|  | mFI-Lab | 1708.712 | 1925.244 |
|  | CFS | 1524.765 | 1754.363 |
| Adjusted model | Measured ratio | 1716.879 | 1940.496 |
|  | FI-Lab | 1711.804 | 1903.953 |
|  | mFI-Lab | 1706.008 | 1899.551 |
|  | CFS | 1496.960 | 1722.379 |

Adjusted model: adjusted for age, sex, CCI score and primary reasons for hospital admission.

Abbreviations: AIC: Akaike information criterion; FI-Lab: Frailty index based on abnormal laboratory tests; mFI-lab: Modified frailty index based on laboratory tests; CFS: Clinical frailty scale; CCI: Charlson comorbidity index.
Howlett, S.E., Rockwood, M.R., Mitnitski, A., Rockwood, K., 2014. Standard laboratory tests to identify older adults at increased risk of death. BMC Med 12, 171.

Hripcsak, G., Albers, D.J., Perotte, A., 2015. Parameterizing time in electronic health record studies. J. Am. Med Inf. Assoc. 22, 794–804.

Jager, J., Sieber, C.C., Gassmann, K.G., Ritt, M., 2019. Changes of a frailty index based on common blood and urine tests during a hospital stay on geriatric wards predict 6-month and 1-year mortality in older people. Clin. Inter. Aging 14, 473–484.

Jønsten, E., Demouynck, M., Detryner, E., Milisen, K., 2014. Prevalence of frailty and its ability to predict in hospital delirium, falls, and 6-month mortality in hospitalized older patients. BMC Geriatr. 14, 1–9.

Katz, S., Ford, A.B., Moskowitz, R.W., Jackson, B.A., Jaffe, M.W., 1963. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. JAMA 185, 914–919.

Klausen, H.H., Petersen, J., Randholm, T., Juel-Larsen, H.G., Tavenier, J., Eugen-Olsen, J., Andersen, O., 2017. Association between routine laboratory tests and long-term mortality among acutely admitted older medical patients: a cohort study. BMC Geriatr. 17, 62.

Lawton, M.P., Brody, E.M., 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 9, 179–186.

Lee, D.H., Buth, K.J., Martin, B.J., Yip, A.M., Hirsch, G.M., 2010. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation 121, 973–978.

Luppa, M., Luck, T., Weyerer, S., Konig, H.H., Brahler, E., Riedel-Heller, S.G., 2010. Prediction of institutionalization in the elderly. A systematic review. Age Ageing 39, 31–38.

Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699.

Pacifico, J., Reijnierse, E.M., Lim, W.K., Maier, A.B., 2021. The Association between Sarcopenia as a Comorbid Disease and Incidence of Institutionalisation and Mortality in Geriatric Rehabilitation Inpatients: RESORting health of acutely unwell adults (RESORT). Gerontology 1–11.

Ritt, M., Jager, J., Ritt, J.J., Sieber, C.C., Gassmann, K.G., 2017. Operationalizing a frailty index using routine blood and urine tests. Clin. Inter. Aging 12, 1029–1040.

Rockwood, K., McMillan, M., Mitnitski, A., Howlett, S.E., 2015. A Frailty Index Based on Common Laboratory Tests in Comparison With a Clinical Frailty Index for Older Adults in Long-Term Care Facilities. J. Am. Med Dir. Assoc. 16, 842–847.

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D.B., McDowell, I., Mitnitski, A., 2005. A global clinical measure of fitness and frailty in elderly people. CMAJ 173, 489–495.

Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M., Rockwood, K., 2008. A standard procedure for creating a frailty index. BMC Geriatr. 8, 24.

Storony, J.E., Rowland, J.T., Basic, D., Conforti, D.A., Dickson, H.G., 2004. The Rowland Universal Dementia Assessment Scale (RUDAS): a multicultural cognitive assessment scale. Int Psychogeriatr. 16, 13–31.

Yang, M., Zhuo, Y., Hu, X., Xie, L., 2018. Predictive validity of two frailty tools for mortality in Chinese nursing home residents: frailty index based on common laboratory tests (FI-Lab) versus FRAIL-NH. Aging Clin. Exp. Res 30, 1445–1452.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.