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SYSTEMATIC REVIEW

The frailty index based on laboratory test data as a tool to investigate the impact of frailty on health outcomes: a systematic review and meta-analysis

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Abstract

The frailty index (FI) quantifies frailty as deficit accumulation. It has been adapted to employ laboratory test data (FI-Lab). Our objective was to systematically review and meta-analyse the FI-Lab's ability to predict mortality. Secondary objectives were to review the FI-Lab's association with adverse health outcomes and whether FI-Lab scores differed between the sexes. A systematic literature search was carried out using six online databases to identify studies that measured the FI-Lab in humans. Hazard ratios (HRs) were combined in a meta-analysis to create a pooled risk estimate for mortality. Of the 1,201 papers identified, spanning January 2010 until 11 July 2022, 38 were included. FI-Lab scores per 0.01 unit increase predicted mortality overall (HR = 1.04; 95% confidence interval (CI) = 1.03–1.05) and for studies with a mean age of 81+ years (HR = 1.04; 95% CI = 1.03–1.05). The quality of evidence for these meta-analyses are moderate and high, respectively. Further, higher FI-Lab scores were associated with more frequent adverse health outcomes. Sex differences in FI-Lab scores varied, with no consistent indication of a sex effect. The FI-Lab is associated with mortality and with a variety of adverse health outcomes. No consistent sex differences in FI-Lab scores were observed, with several studies in disagreement. Notably, these conclusions were most relevant to older (65+ years old) individuals; further evidence in younger people is needed in both clinical and population representative studies.

Keywords: sex differences, gerontology, frailty, frailty index-lab (FI-Lab), systematic review, older people

Key Points

- An FI based on laboratory measures relates to mortality risk in a variety of populations.
- Frailty scores using an FI based on laboratory measures relate to higher risks for diverse adverse health events.
- Sex differences may not be as prominent in frailty indices based on laboratory measures compared to clinical frailty indices.

Introduction

The frailty index (FI) is an instrument used to quantify frailty and is based on a deficit accumulation model [1]. To achieve this end, various clinical health measures across physiological systems are assessed dichotomously either as deficient or not, which are then summed and divided by the total number of assessments. This yields a score ranging from 0 (no deficits) to 1 (all deficits). The resultant FI score is a macroscopic variable that reflects the state of an individual's health irrespective of how chronologically old they are, sometimes referred to as 'biological age' [2]. In this way, the FI reduces dozens of dimensions into a single variable [1].

A clinical FI is often constructed from a comprehensive geriatric assessment [3–6]. A more recent FI method constructs an FI using laboratory data (FI-Lab), which employs laboratory data to substitute for, or complement the count of deficits [6, 7]. Laboratory derived components are employed as non-arbitrary physiologic measures that count as deficits when deviating from an acceptable range. The first FI-Lab was in a murine ageing model [8], although not presented as such. In 2014, Howlett et al. [7] developed the first formal FI-Lab using standard laboratory tests in humans. This approach has subsequently been used in various human ageing studies, as reviewed here. The FI-Lab can be calculated readily, and its components can usually be obtained from commonly measured hospital tests. Indeed, basing an FI-Lab on routinely collected data was part of its inception [7]. Thus, operationalising standard laboratory data into an FI-Lab may be a convenient and accessible way to assess frailty in a clinical setting. The subsequent FI-Lab score could then be used as a screening tool, as has been suggested [9].

Likely due to its relatively recent origins, we found no systematic reviews or meta-analyses that focus on the FI-Lab. To summarise the available evidence on the FI-Lab, we performed a systematic review and meta-analysis on studies involving the FI-Lab. Our primary objective was to assess the relationship between the FI-Lab and mortality in humans. Secondary objectives were to assess the FI-Lab in relation to other adverse health outcomes and to examine sex differences in FI-Lab scores.

Methods

PRISMA guidelines

This systematic review and meta-analysis followed the PRISMA 2020 guidelines. The protocol was published on Open Science Framework. The most recent protocol is publicly available at: https://doi.org/10.17605/OSF.IO/2ASF9. All amendments are dated and explained in the protocol. The PRISMA 2020 checklist for this systematic review and meta-analysis is available (Supplemental Appendix A).

Data source and search strategy

Three electronic literature searches were conducted in July 2020, May 2021 and July 2022 by author D.G.S. Papers published in English from January 2010–11 July 2022 were searched for on electronic databases (PubMed, CINAHL, MEDLINE, EMBASED, Scopus, Web of Science and AgeLine). Specifically, we searched for ((‘Frailty Index’ AND Laboratory) OR (FI-LAB AND Frailty)) using Boolean-based terms. The searches were full text unless there were over 500 results from a single database.

Inclusion criteria:

- FI of at least 10 measures (below which the FI is unstable) [10, 11], where 70% of the deficits measured must be laboratory data, defined as any non-arbitrary diagnostic measure including clinical measures (e.g. hemodynamic measures).

Exclusion criteria:

- Papers were excluded if they were case studies, reviews, conference reports/presentations/abstracts, opinion pieces or unpublished data.

Data collection and management

Author D.G.S. compiled a list of articles from all databases, removed duplicates and completed a primary screening. Subsequently, any two of authors D.G.S., S.E.H. and B.M.C. independently screened the remaining article titles and abstracts. Reviewer S.E.H. or S.S.H. arbitrated conflicts in screening; inconsistencies were resolved by discussion. For studies that calculated hazard ratios (HRs) using multiple models, the following model/follow-up criteria were used to select the HR in order of priority: age-adjusted, sex-adjusted and closest to 1-year follow-up time. For studies that calculated the FI-Lab with varying deficit numbers, the HR for the FI-Lab using the most items measured was used for the meta-analysis. HRs were collected at the 0.01 or 0.1 decimal place but were always reported at the 0.01 level.

Subgroupings

Three subgroupings were created to categorise papers based on their findings, including mortality, adverse health outcomes and sex differences. Subgroup inclusion criteria and sorting of studies are depicted in Supplemental Figure 1. All papers were considered for subgroup analysis; however, three studies [12–14] did not fit any of the criteria and were not included in further subgroup analysis. The ‘mortality’ subgroup was further divided for dichotomous statistical comparisons considering study populations and design, including sample size, sex, mean age, items measured and follow-up time (Supplemental Figure 2). Sub-subgroup analyses were exploratory, and credibility was assessed using related criteria (Supplemental Table 1) [15].

Risk of bias and certainty of evidence

Risk of bias assessment used a modified Newcastle-Ottawa scale (Supplemental Appendix B). Studies were excluded from the mortality meta-analysis if they had four or fewer ‘stars’ across all categories (Supplemental Table 2). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scale was used to determine the certainty of evidence. A detailed description of the publication bias assessment and certainty of evidence can be found in the Supplemental Data.

Statistics

The inverse variance method was used to calculate effects using log-transformed HRs based on a 0.01 FI-Lab unit change. Study heterogeneity was assessed using cautious

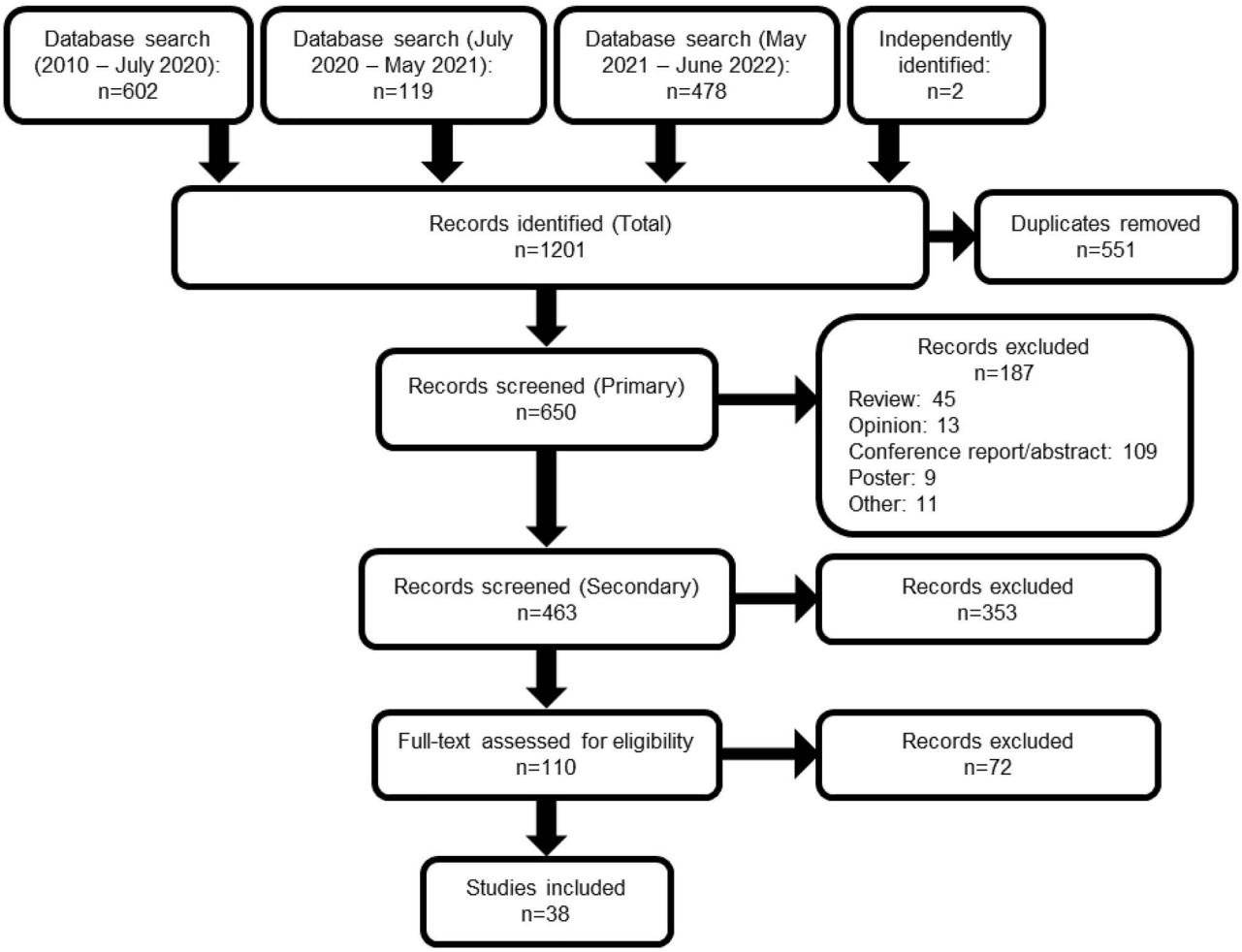

Figure 1. Search and screening results flow diagram of systematic review.

interpretation of the I^2 test statistic, given the narrow confidence intervals (CIs) of the HRs [16]. If heterogeneity was present, study populations were assessed using a random effects model rather than a fixed effects model. Detailed descriptions of the statistical approach can be found in the Supplemental Data.

Results

Search and selection

Three systematic searches across seven electronic databases (PubMed, CINAHL, MEDLINE, EMBASE, Scopus, Web of Science and AgeLine) identified 1,201 articles for the systematic review. The searches occurred in July 2020, May 2021 and July 2022. Figure 1 depicts the screening process.

Characteristics of studies

Of 38 studies (Table 1), the first was published in 2014 [7] and 15 were published since 2021. Studies came about equally from Asia-Pacific (seven from China [17–23]; four from Australia [12, 13, 24, 25], four from South Korea [26–29] and one from Northern Taiwan [14]), Europe [30–40] and North America (six from the USA [41–46] and six from Canada [7, 9, 46–49]). The sample sizes ranged from 14 clinical trial participants [44] to 25,253 in a retrospective analysis of a Canadian national cohort [49]. The mean age range was from 49.4 years [42] to 101.3 years [38]; four studies did not disclose a mean age of participants [13, 21, 34, 43]. The average percent female population across all studies was 47.0%.

Follow-up periods ranged from 1 month [44] to 18 years [32]. Four studies included multiple follow-up periods [13, 32, 33, 37]; 2 studies were cross-sectional with mortality follow-up [42, 43]; 11 were cohort studies [19, 20, 23–25, 36, 38, 39, 41, 47, 49] and 1 was a retrospective observational study [17].

The number of items measured per FI-Lab ranged from 14 deficits [32] to 77 deficits [24, 25]. The average number of deficits across the 37 reporting studies was 30.1 (±13.2 as standard deviation). The items measured varied across studies and have been summarised in Supplemental Figure 3 and Supplemental Table 3. Of the items used, 93% were from blood/urine tests and 7% were from physical measures

Table 1. Summary of study characteristics of 38 included studies in the systematic review

Author	Study details/location	Number of participants	Female (%)	Age (mean) (range)	Follow-up period	Number of items in FI-Lab	Acquisition of FI-Lab data
Arosio et al., 2022	Centenarians Northern Italy	65	70.8	101.3 ≥100	–	42	Blood tests from another study
Bello et al., 2018	World Trade Center Health Program NY, USA	7,346	16.7	51.0 40–85	–	33	Blood tests from another study
Blodgett et al., 2016	European Male Ageing Study Europe	Initial: 3,369 At follow-up: 2,933	0.0	60.2 40–79	4.4 years	23	Blood tests from another study
Blodgett et al., 2017	National Health and Nutritional Examination Survey (NHANES) USA	8,888	51.7	49.4 ≥20	–	32	Blood tests from another study
Blodgett et al., 2019	NHANES USA	8,898	51.7	≥20	–	32	Blood tests from another study
Blodgett et al., 2022	Canadian Longitudinal Study on Ageing Canada	25,253	51.8	45–85	–	23	Blood tests from another study
Chao et al., 2020	Northern Taiwan	33	55.0	69.5	2–3 years	LFI-1: 23 LFI-2: 32	Pre-dialysis blood test
Cheung et al., 2017	Canada	221	47.5	76.8 ≥65	–	23	Routine hospital admissions blood test
Ellis et al., 2020	UK	1,580	55.3	84.8	21 months	27	Routine hospital admissions blood test
Engvig et al., 2022	Norway	195	63	86.3 75–100	19.3 months	14	Routine hospital admissions blood test
Gu et al., 2021	China	154	29.2	79.7	–	23	Blood tests from medical records
Guan et al., 2022	Restoring Health of Acutely Unwell Adults (RESORT) Melbourne, Australia	1,819	56.6	83.3 (median) 77.6–88.3	3 months	77	Routine hospital admissions blood test
Hao et al., 2019	Project of Longevity and Ageing Sichuan Province, China	736	67.5	93.6 90–108	4 years	22	Blood tests to assess FI-Lab
Heikkila et al., 2021	Leito, Finland	1,153	58.0	73.6 64–100	10 and 18 years	14	Blood tests from another study
Howlett et al., 2014	Canadian Study of Health and Aging (CSHA) Canada	Initial: 1,013 Follow-up: 986	60.7	81.1 ≥65	5 years	23	Blood tests from another study
Huang et al., 2022	Western China	627	39.23	80 (median) ≥60	–	44	Routine blood test
Jäger et al., 2019	Erlangen, Germany	Initial: 500 Follow-up: 494	67.4	82.8	6 months and 1 year	21	Routine blood test at study admission
Justice et al., 2019	Texas, USA	14	14.3	70.8 55–85	1 month	34	Routine blood test
Kim CH et al., 2022	Seoul, South Korea	508	22.2	67.3	18.2 months	32	Pre-operative blood test
Kim Y et al., 2022	Seoul, South Korea	9,015	34.5	72.3	34.7 months	32	Pre-operative blood test
King et al., 2017	Duke Established Populations for Epidemiological Studies of the Elderly NC, USA	1,740	67.0	78.0 65–105	14 years	28	Blood tests from another study
Klausen et al., 2017	Hvidovre, Denmark	4,005	49.7	≥65	3 years	17	Routine hospital admissions blood test
Lim et al., 2022	South Korea	896	22	66	1 month	30	Pre-operative blood test
Ma, Liu et al., 2018	Rugao Longevity and Ageing Study (RuLas) Jiangsu Province, China	1,463	57.8	77.4 70–84	–	23	–
Ma, Cai et al., 2018	RuLas Jiangsu Province, China	1,780	52.8	77.0 70–87	–	23	Blood tests from another study
McMillan et al., 2021	Alberta, Canada	143	12	57.7 50–79	–	29	Routine blood test
Mitnitski et al., 2015	Newcastle 85+ Study Newcastle, UK	777	60.9	85.5 ≥85	7 years	40	Blood tests to assess FI-Lab
Naimimohasses et al., 2022	Dublin, Ireland	109	50.5	56	–	35	Routine blood test for study
Nixon et al., 2019	UK	90	50.0	69.0	–	27	–
Reid et al., 2022	Melbourne, Australia	214	69.2	84.7	–	27	–
Ritt et al., 2017	Erlangen, Germany	Initial: 306 1-year follow-up: 304	67.6	82.9	6 months and 1 year	23	Routine blood test at study admission
Rockwood et al., 2015	CSHA Canada	595	67.9	82.7	6 years	23	Blood tests from another study
Soh et al., 2022	RESORT Melbourne, Australia	1,819	56.5	83.3 (median) 77.5–88.3	1 year	77	Routine hospital admissions blood test
Sohn et al., 2019	South Korea	154	49.3	78.7	40 months	32	–
Stubbings et al., 2021	Multiple cohorts USA and Canada	9,854	Varied	Varied	5 years	Varied	Blood tests from another study
Theou et al., 2016	South Australia, Victoria, New South Wales	53 6-month follow-up: 44 1-year follow-up: 36	-	≥65	3 months, 6 months and 1 year	22	–
Wang et al., 2019	Chengdu, China	1,020	28.6	65 (median) ≥60	3.9 years	44	Routine blood test
Yang et al., 2019	Chengdu, China	329	68.1	85.2	1 year	30	Blood tests to assess FI-Lab

Table 2. Summary of findings with GRADE.

Outcomes	Results	No of participants (Studies) Follow-up range	Quality of the evidence (GRADE)[e]
Mortality (meta-analysis)	HR: 1.04 (1.03–1.05) for 0.01 change in FI-Lab	11,032 (11 studies) 6 months–7 years	⊕⊕⊕⊖ **MODERATE** Due to indirectness[a]
Mortality (meta-analysis—81+ years of age)	HR: 1.04 (1.03–1.05) for 0.01 change in FI-Lab for age 81+ years old	7,079 (9 studies) 6 months–7 years	⊕⊕⊕⊕ **HIGH**
Mortality (whole subgroup)	High FI-Lab scores were associated with increased risk of mortality in all studies	69,691 (23 studies) 6 months–18 years	⊕⊕⊕⊖ **MODERATE** Due to indirectness[a]
Adverse health outcomes	High FI-Lab scores were associated with increased risk of at least one adverse health outcome in 94% of studies	36,526 (18 studies) 1 month–18 years	⊕⊕⊕⊖ **MODERATE** Due to indirectness[b]
Sex differences	No clear association between FI-Lab and sex was found across all studies; 5 studies found no sex difference in FI-Lab scores, 3 found higher FI-Lab scores in males, 2 found higher FI-Lab scores in females and 1 found an age dependent sex effect	48,274 (13 studies) N/A	⊕⊖⊖⊖ **VERY LOW** Due to indirectness[a] Risk of bias[c] Inconsistency[d]

[a]The studies are not wholly representative of our target age range of 20+ years. [b]The studies are not wholly representative of our target age range of 20+ years. Each study identified a different adverse outcome. [c]Risk of bias due to studies including men and women but not reporting sex-based analyses. [d]Inconsistency in results across studies. More evidence is needed to make conclusions about sex differences. [e]Scores out of 4. ⊕ indicates a point. ⊖ indicates the absence of a point.

(especially vital signs; e.g. blood pressure, heart rate and oxygen saturation).

Normal ranges for FI-Lab items were sourced from other works in 10 studies [7, 9, 17, 19, 20, 28, 34, 42, 43]. Henry, 1991 [50] was most cited, while values from other works, such as Blodgett et al., 2015 [51]; Jones et al., 2012 [52] and Pickering et al., 2005 [53], were each used a few times. Six studies used local hospital ranges [21, 31, 39–41, 48] and two calculated their own ranges [35, 38]. The rest of the studies did not provide the source of the normal ranges for the FI-Lab.

Blood test data were acquired (Table 1) from previous studies in 12 of the FI-Lab papers, which were often following large cohorts [30, 42, 43]. Thirteen studies used blood test values obtained upon hospital admission or from routine blood tests [21, 23–25, 31, 33, 34, 37, 39, 40, 44, 47, 48]. Four studies used pre-operative data [14, 27–29], while only three took blood tests specifically to measure the FI-Lab [18, 22, 35].

Certainty of evidence

Risk of bias was assessed using a modified eight-item Newcastle-Ottawa scale (Appendix B). The GRADE approach was used to assess the quality of evidence for each of the subgroups. Mortality was also assessed separately in studies with a mean age of 81+ years subgroup due to greater availability of data in this age bracket. Evidence per subgroup ranged from very low to high (Table 2).

The FI-Lab as a predictor of mortality

Higher FI-Lab scores related to increased mortality risk in all included studies (Table 3). The relationship with mortality was assessed by a meta-analysis of studies that reported a HR based on a continuous 0.01 increase in FI-Lab scores. These effect sizes were heterogenous, as indicated by the I^2 (Figure 2A), although this is expected and not concerning when including larger studies with narrow CIs [16]. Egger's ($P = 0.2414$) and Begg-Mazumdar's ($P = 0.1857$) tests for funnel plot asymmetry did not show significant risk of publication bias (Supplemental Figure 4A–C). The possibility of different true effect sizes between studies due to differing populations and FI-Labs supported the use of a random effects model for the meta-analysis.

Using a random effects model, the FI-Lab predicted mortality across all ages (Figure 2A). When only studies with a mean age of 81+ years were included, the GRADE score increased from moderate to high, while the HR remained equivalent. Additionally, a subgroup analysis was performed that separated studies at a mean age of 80 years. The mean age (or median when mean was not available) of a study and the HR per 0.01 unit increase in FI-Lab scores were not significantly related (Figure 2A). We also separated studies by follow-up time (>/<2 years); shorter follow-up times yielded a non-significantly higher HR (Figure 2B).

The number of FI-Lab items assessed (< or >25) had no effect on the mortality risk (Figure 2C). Likewise, the proportion who were community dwelling (Supplemental Figure 5A), the sample size (Supplemental Figure 5B) and percent female sex (data not shown) or age or sex adjustment (data not shown) demonstrated no significant differences between groups. Each mortality subgroup analysis demonstrated high heterogeneity, save for the community dwelling group that only included two studies. All exploratory subgroup analyses were considered to have very low credibility for subgroup interactions (Supplemental Table 1).

Table 3. Subgroup summary data from studies included in each subgroup in the systematic review.

Mortality		
Study	Mortality HRs (95% CI)	Conclusions
Blodgett et al., 2016	1.04 (1.03–1.06) 0.01 change in FI-Lab score Adjustments: age	High FI-Lab scores associated with mortality
Blodgett et al., 2017	1.63, 2.59, 3.62, 6.35 Groupings: 0.1–0.2, 0.2–.03, 0.3–0.4, >0.4 Adjustments: age, sex	High FI-Lab scores associated with mortality
Blodgett et al., 2022	OR: 1.05 (1.04–1.06) 0.01 change in FI-Lab score Adjustments: age, sex	High FI-Lab scores associated with mortality
Ellis et al., 2020	Unadjusted: 1.51 (1.43–1.60) Adjusted: 1.45 (1.37–1.54) change in FI-Lab score Adjustments: age, sex, clinical frailty score, dementia, delirium, falls, residence at admission	High FI-Lab scores associated with mortality Higher mortality risk in females
Engvig et al., 2022	Unadjusted: 1.04 (1.02–1.05) Adjusted: 1.03 (1.00–1.05) 0.01 change in FI-Lab score Adjustments: age, ward placement, CCI, CFS, NEWS2	High FI-Lab scores associated with mortality in older medical inpatients
Gu et al., 2021	OR: 8.705 (3.646–20.782) Ranked FI-Lab scores	High FI-Lab scores predict in-hospital mortality in AECOPD patients
Guan et al., 2022	Unadjusted: 1.44 (1.23–1.70) Adjusted: 1.32 (1.11–1.58) 0.1 change in FI-Lab score Adjustments: age, sex, CCI, primary reason for hospital admission	High FI-Lab scores associated with mortality in geriatric rehabilitation inpatients
Hao et al., 2019	1.33 (1.09–1.63) Adjustments: age, sex, educational levels	Higher frailty proportions in mortality group 53.4% rate of 4-year mortality
Heikkila et al., 2021	1.69–3.75 Groupings: ≤0.08, 0.09–0.42, ≥0.43 Adjustments: age, sex	High FI-Lab scores predict increase in mortality
Howlett et al., 2014	(1.02–1.04) 0.01 change in FI-Lab score Adjustments: age, sex	High FI-Lab scores associated with mortality
Huang et al., 2022	Unadjusted: 2.955 (2.172–4.021); 4.997 (3.656–6.831) Adjusted: 2.173 (1.576–2.996); 2.877 (2.026–4.083) Groupings: <0.2 (ref), 0.2–0.35, >0.35 Adjustments: age, sex, smoking history, drinking history, state of consciousness, diabetes, hypertension, CHD, COPD, tumour, stroke history, dementia, respiratory failure, septic shock	High FI-Lab scores associated with mortality in older community-acquired pneumonia patients
Jäger et al., 2019	1.066 (1.051–1.081) 0.01 change in FI-Lab score Adjustments: age, sex	High FI-Lab scores associated with increased mortality rates for 6 months and 1 year after hospital readmission
Kim CH et al., 2022	1.042 (1.010–1.076) Groupings: 0.32 cut-off in FI-Lab score Adjustments: age, EuroSCORE II, peripheral vascular disease	High FI-Lab scores predict in-hospital mortality in patients after coronary artery bypass grafting
Kim Y et al., 2022	1.75 (1.49–2.06); 4.29 (3.41–5.40) Groupings: <0.25 (ref); 0.25–0.4; >0.4 Adjustments: age, sex, number of co-morbidities, operating room duration, cancer stage	High FI-Lab scores associated with mortality in older surgical patients with cancer
Klausen et al., 2017	1.94 (1.57–2.40); 2.84 (2.31–3.49); 3.66 (3.00–4.48) Quartiles: 1 (ref); 2; 3; 4 Adjustments: age	Post-discharge mortality associated with FI-Lab scores

(Continued)

Table 3. Continued.

Mortality

Study	Mortality HRs (95% CI)	Conclusions
Mitnitski et al., 2015	1.05 (1.04–1.07) 0.01 change in FI-Lab score Adjustments: sex	FI-Lab scores strongly associated with mortality
Ritt et al., 2017	1.071 (1.05–1.093) 0.01 change in FI-Lab score Adjustments: age, sex	FI-Lab scores predict 6-month and 1-year mortality risk
Rockwood et al., 2015	1.016 (1.007–1.025) 0.01 change in FI-Lab score Adjustments: age, sex	High FI-Lab scores associated with mortality
Soh et al., 2022	Unadjusted: 1.351 (1.195–1.528) Adjusted: 1.180 (1.037–1.343) 0.1 change in FI-Lab score Adjustments: age, sex, CCI	High FI-Lab scores associated with 1-year mortality in geriatric rehabilitation inpatients
Sohn et al., 2019	1.075 (1.040–1.111) Unadjusted	High FI-Lab scores associated with early mortality in SAVR patients
Stubbings et al., 2021	–	A quantile FI improves the predictive value of the FI-Lab
Wang et al., 2019	1.02 (1.01–1.03) 0.01 change in FI-Lab score Adjustments: age, sex	FI-Lab scores can predict mortality in lung cancer patients
Yang et al., 2019	1.07 (1.05–1.09) 0.01 change in FI-Lab score Adjustments: age, sex	FI-Lab scores can predict 1-year mortality

Adverse health outcomes

Study	Risk of adverse outcome	Conclusions
Bello et al., 2018	OR: 1.06 (1.027–1.086) for short-term memory problems OR measured per deficit in FI-Lab	FI-Lab scores are inversely associated with mental and physical health
Blodgett et al., 2016	OR: 1.02 (1.00–1.04); 1.03 (1.02–1.04); 1.04 (1.02–1.05); 1.03 (1.02–1.05); 1.00 (0.99–1.02); 1.01 (1.00–1.02) for institutionalisation, frequency of doctor visits, high number of medications, poor self-reported health, fractures and falls, respectively 0.01 change in FI-Lab	High FI-Lab scores are associated with institutionalisation, frequent doctor visits, high number of medications, poor self-reported health and falls
Blodgett et al., 2019	OR: 1.46 (1.39–1.54); 1.41 (1.32–1.50); 1.35 (1.29–1.42) for self-reported health, ADL disability and heath care use 0.10 change in FI-Lab score	High FI-Lab scores are associated with poor self-reported health, ADL disability and health care use
Cheung et al., 2017	OR: 0.8 (0.3–1.8); 1.6 (0.7–3.7) for adverse discharge destination Groupings: FI-Lab between 0.25–0.4 versus <0.25 and FI-Lab >0.4 versus <0.25 Adjustments: age, total number of co-morbidities and ISS	Severe frailty based on the FI-Lab was not associated with adverse outcomes
Ellis et al., 2020	Unadjusted OR: 1.61 (1.54–1.69); 1.40 (1.29–1.53); 1.20 (1.12–1.28) Adjusted OR: 1.47 (1.41–1.54); 1.39 (1.27–1.52); 1.18 (1.11–1.26) 0.10 change in FI-Lab score For inpatient days with follow-up as offset, discharge to a higher level of care and readmission, respectively	FI-Lab scores are associated with adverse outcomes, rates of hospital readmission and discharge location
Guan et al., 2022	Unadjusted OR: 0.98 (0.87–1.11); 0.96 (0.86–1.07) Adjusted OR: 0.98 (0.86–1.12); 1.00 (0.88–1.12) 0.10 change in FI-Lab score Adjustments: age, sex CCI, primary reason for hospital admission For functional decline and institutionalisation, respectively	FI-Lab scores are associated with functional decline and institutionalisation in geriatric rehabilitation inpatients
Heikkila et al., 2021	–	Laboratory index scores do not significantly predict institutionalisation

(Continued)

Table 3. Continued.

Mortality

Study	Mortality HRs (95% CI)	Conclusions
Huang et al., 2022	Unadjusted OR-respiratory failure: 3.797 (2.101–6.862); 6.113 (3.358–11.128) Unadjusted OR-septic shock: 4.385 (2.101–9.148); 16.8 (8.272–34.119) Adjusted OR-respiratory failure: 3.326 (1.799–6.15); 5.353 (2.835–10.107) Adjusted OR-septic shock: 3.701 (1.736–7.889); 12.713 (6.112–26.445) Groupings: <0.2 (ref), 0.2–0.35, ≥0.35 Adjustments: age, sex, BMI, smoking history, drinking history, state of consciousness, diabetes, hypertension, CHD, COPD, tumour, stroke history, dementia	FI-Lab scores are associated with respiratory failure and septic shock in older community-acquired pneumonia patients
Justice et al., 2019	–	FI-Lab scores are associated with pro-inflammatory cytokines
Kim CH et al., 2022	OR: 1.02 (1.002–1.039); 1.06 (1.014–1.039); 1.09 (1.032–1.152) Cut-off: 0.32 FI-Lab score For atrial fibrillation, acute kidney injury and reoperation for bleeding, respectively	FI-Lab scores associated with atrial fibrillation, acute kidney injury and reoperation for bleeding following coronary artery bypass grafting
Kim Y et al., 2022	OR-readmission within 30 days of surgery: 1.20 (1.04–1.38); 1.49 (1.12–1.98) OR-ICU admission within 30 days of surgery: 1.70 (1.47–1.97); 3.58 (2.77–4.63) Groupings: <0.25 (ref), 0.25–0.4, >0.4 Adjustments: age, sex number of co-morbidity, operating room duration, cancer stage	FI-Lab scores associated with longer length of stay, readmission after surgery and post-operative ICU admission in older surgical patients with cancer
Lim et al., 2022	OR: 1.51 (0.76–2.99); 2.58 (1.15–5.80) Groupings: <0.25 (ref), 0.25–0.4, >0.4 For readmission within 30 days	FI-Lab scores associated with longer length of hospital stay, ICU stay and hospital readmission in patients undergoing coronary artery bypass graft surgery
Ma, Cai et al., 2018	Unadjusted OR: 1.33 (1.07–1.64) Adjusted OR: 1.33 (1.08–1.65) 0.10 change in FI-Lab score Adjustments: age groups and gender For QTc interval	FI-Lab scores are associated with QTc prolongation
McMillan et al., 2021	–	FI-Lab scores inversely associated with fluency, fine motor skills and attention/concentration
Naimimohasses et al., 2022	–	FI-Lab scores increased with severity of non-alcoholic fatty liver disease
Nixon et al., 2019	–	FI-Lab scores are associated with worsening kidney function in CKD patients
Sohn et al., 2019	–	FI-Lab scores are associated with short- and long-term outcomes after SAVR in older patients
Wang et al., 2019	Unadjusted OR: 1.83 (1.25–2.67); 3.19 (1.67–6.09) Adjusted OR: 1.85 (1.26–2.72); 3.19 (1.67–6.12) Groupings: <0.2 versus 0.2–0.35 and < 0.2 versus >0.35 Adjustments: age, sex, occupation, health insurance, BMI, pack-years of cigarettes and drinking history For all adverse reactions	FI-Lab scores are associated with uncontrolled diseases FI-Lab scores can predict adverse outcomes in cancer patients

Sex differences

Study	Conclusions
Arosio et al., 2022	No sex differences in FI-Lab scores
Bello et al., 2018	Higher FI-Lab scores in males
Blodgett et al., 2019	Higher FI-Lab scores in females aged 20–39, males aged 60+ years
Blodgett et al., 2022	No sex differences in FI-Lab mortality HRs
Cheung et al., 2017	No sex differences in FI-Lab scores
Hao et al., 2019	Higher FI-Lab scores in males
Huang et al., 2022	No sex difference in FI-Lab scores
King et al., 2017	Higher FI-Lab scores in males
Lim et al., 2022	No sex difference in FI-Lab scores
Ma, Liu et al., 2018	No sex difference in FI-Lab scores
McMillan et al., 2021	Sex did not confound the association between FI-Lab and cognition
Mitnitski et al., 2015	Higher FI-Lab scores in females
Naimimohasses et al., 2022	Higher FI-Lab scores in females

Note: CCI, Charlson Co-morbidity Index; CFS, clinical FI; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ISS, injury severity score; NEWS2, new early warning score 2; OR, odds ratio; QTc, corrected QT interval.

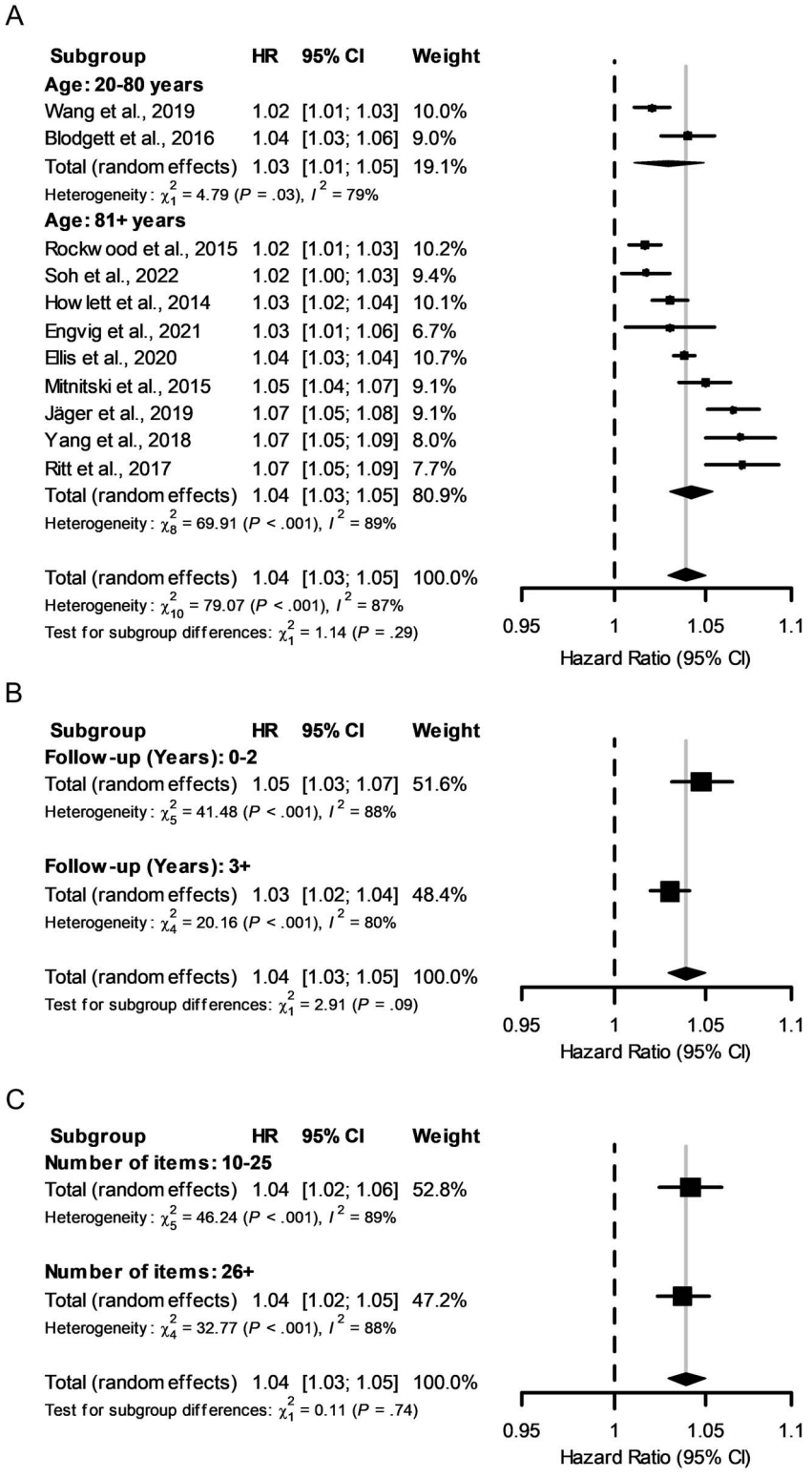

Figure 2. Forest plots of mortality risk by HR according to a 0.01 increase in frailty measured by the FI-Lab. All forest plots used HRs from all studies included in the mortality subgroup meta-analysis. Data are presented on a $\log_{10}$ scale, the dashed-vertical line represents no effect, and the solid-vertical line indicates the overall effect of all studies. (A) HR for all studies in the mortality subgroup. The mean age analysis is also represented with the respective effects of each age grouping. (B) Analysis separated by follow-up time. (C) Analysis separated by number of items measured.

Adverse health outcomes

Eighteen studies investigated the relationship between FI-Lab scores and adverse health outcomes (Table 3). Of these, 16 showed that FI-Lab scores were related to adverse health outcomes. The FI-Lab predicted adverse events both in a general population (e.g. Blodgett and colleagues [30, 43]) and in clinical groups (e.g. cancer patients [21] and chronic kidney disease patients [36]). Variations in statistical approaches to risk assessment, participant demographics and events makes comparing risks difficult between studies. However, two studies used similar FI-Labs and risk assessment methods by binning FI-Lab scores into low (<0.25), medium (0.25–0.4) and higher (>0.4) scores and adjusting for age and sex in either cancer surgery patients [28] or coronary artery bypass surgery patients [29]. The odds ratio of readmission to hospital within 30 days for high FI-Lab scores compared to low scores had overlapping CIs (1.15–5.80 versus 1.12–1.98). However, cardiac surgery participants with high FI-Lab scores stayed 2.20 days longer in hospital than those with low FI-Lab scores [29], whereas those who underwent cancer resection surgery and had high scores stayed 9.45 days longer than those with low scores [28]. Thus, even when FI-Labs are similarly constructed, measured risks may differ based on the population.

Sex differences in FI-Lab scores

Of 13 studies that assessed how FI-Lab scores differ by sex, 3 concluded that men had higher FI-Lab scores than women [18, 41, 45], while 2 concluded that women had higher FI-Lab scores than men [35, 40]. Five studies observed no sex differences in FI-Lab scores [19, 23, 29, 38, 47]. One study [43] concluded that FI-Lab scores were higher in women aged 20–39 but were higher in men aged 60+ years.

Discussion

This systematic review of the FI-Lab, which was introduced in 2014, identified 38 studies that used this assessment.

Mortality and adverse health outcomes

Our meta-analysis of the FI-Lab as a predictor of mortality in humans combined the HR per 0.01 change in FI-Lab scores across 11 studies. A 0.01 change in FI-Lab score is roughly equivalent to a person gaining a quarter of a deficit, if 25 items were measured (or 1 deficit in 100 measures). Consequently, as in the overall deficit accumulation FI, a small change in risk is expected for a 0.01 change and becomes larger when more deficits are present. Meta-analysis of 11 studies predicting mortality from an FI-Lab yielded an effect size as a HR of 1.04 (95% CI = 1.03–1.05) per 0.01 increase in the FI score. Interestingly, this effect size is nearly identical to a meta-analysis of clinical FIs, which sometimes included some laboratory measures, to predict mortality, where the comparable HR was 1.04 (95% CI = 1.03–1.04; [54]). Together, this suggests that the FI-Lab can predict mortality, and under some circumstances, this effect may be comparable to FIs not incorporating laboratory measures.

The relationship between the FI and mortality appears to hold in older adults. Our review did not identify much research using younger adults. One study suggested the prognostic value of an FI-Lab is not as strong a predictor of mortality in younger adults compared to older adults [42]. The improved predictive value in older adults might make sense, given the original criteria FIs are based upon [10], which suggests that deficits should increase with age and should cover a range of systems. As suggested by Blodgett and colleagues [42], investigating the FI-Lab's relationship with adverse health outcomes in younger people, instead of mortality, may be more fruitful. The current state of evidence cannot answer this question, however.

Despite most study populations having a mean age of 81+ years, the lack of association between mean age and HR at the 0.01 level using weighted means is intriguing. At the least, this suggests an FI-Lab predicts mortality similarly for older populations, such as those analysed here. In addition, the fact that the FI-Lab was associated with incident mortality in both presentative population samples and in clinical/institutional samples suggests that it is a useful tool for diverse health populations.

We also examined how the number of deficits measured per FI-Lab affected its relationship with mortality, which demonstrated no differences in HRs for studies using 20–25 items versus those with 26–77 items. This supports the notion that the number and exact items measured are not important when comparing between samples as long as they are ample enough and relate to a variety of physiological systems [10]. Sample size also did not seem to affect the FI-Lab's ability to predict mortality, suggesting that the included studies were powered appropriately.

Regarding non-fatal health issues, every study showed that the FI-Lab was associated with adverse health outcomes, except institutionalisation in one study [32] and adverse discharge destination in another [47]. It is unknown if this trend holds up to most adverse health outcomes, but it is intriguing to think of the FI-Lab serving as a robust holistic health risk metric for non-fatal health issues.

Sex differences in the FI-Lab

There was no clear indication of a sex difference in FI-Lab score between sexes. Three of 11 studies that evaluated sex differences concluded that men have higher FI-Lab scores than women, while 2 found the opposite and another 5 found no difference. Notably, Bello and colleagues [41] found an age-frailty interaction, where women were frailer at younger ages but then became less frail compared to men at older ages. These findings are inconsistent with the male–female health survival paradox, which suggests that women have increased frailty, but they are more resilient than men and live longer [55, 56]. With the FI-Lab, there is no clear indication of a sex effect, so the paradox is not present. More dedicated studies, with less heterogeneity, are needed

to establish whether there is a bona fide sex difference when using an FI-Lab. Whether the answer agrees with the male–female health survival paradox is unknown, although current evidence suggests it does not. Further, it will be important to identify whether the relationship between mortality and the FI-Lab is equal between men and women.

FI-Lab components

The deficits that make up the FI-Lab distinguish it from FIs based on clinical assessments. While both these tools function similarly, the FI-Lab is likely easier to automate and looks at frailty from a different perspective. In fact, the FI-Lab was able to improve the predictive power of a clinical FI through their combination or addition to a proportional hazard model [9]. Even so, it is not clear whether this simply reflects the nature of the additional items, or that more items typically make for more informative FIs, especially after age 65 [11]. Standard laboratory tests can be core measures used to create an FI-Lab, as was suggested [7], which operationalizes routinely collected data.

Quality of evidence

From the outset, we decided to focus on breadth for this systematic review and meta-analysis. This style has inherent benefits and limitations. We were able to collect all available information on the FI-Lab. However, the studies were quite diverse in nature, ranging widely in study populations. Our quality of evidence table, assessed by GRADE, reflects the evolving literature and our broad inclusion criteria. Our meta-analysis for the overall mortality subgroup included moderate-quality evidence due to the distribution of ages across studies. This portion of the meta-analysis lost quality because we sought to examine the FI-Lab's association with mortality in adults for all ages of $\geq$20 years. However, the papers we identified mostly included older adults. In this way, the quality of evidence improved by reframing our question to older adults, but it identified that little is known about how the FI-Lab works in younger adults.

Conclusions

This systematic review and meta-analysis suggest that FI-Labs, made of diverse deficits, predict mortality and other adverse health outcomes in a variety of populations. FI-Lab scores did not show a consistent difference between sexes. This does not align with what is found with clinical FIs, which typically find females to be frailer [56].

Future research utilising an FI-Lab may benefit from investigating the relationship between frailty in younger populations and the subsequent health status changes. Additionally, there is emerging evidence that a more granular approach to health variable categorisation (i.e. a non-binary quantile approach) using an FI-Lab improves the model's accuracy [46] relative to dichotomizing variables. Both avenues deserve further attention.

Declaration of Conflicts of Interest: K.R. is supported by the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research. K.R. has asserted copyright of the Clinical Frailty Scale through Dalhousie University's Industry, Liaison and Innovation Office. Use is free for education, research and not-for-profit health care. Users agree not to change or commercialise the scale. In addition to academic and hospital appointments, K.R. is the co-founder of Ardea Outcomes, which (as DGI Clinical), in the last 3 years, has contracts with pharma and device manufacturers (Danone, Hollister, INmune, Novartis and Takeda) on individualised outcome measurement. In 2020, he attended an advisory board meeting with Nutricia on dementia and chaired a Scientific Workshop & Technical Review Panel on frailty for the Singapore National Research Foundation. He is an associate director of the Canadian Consortium on Neurodegenerataion in Aging, itself funded by the Canadian Institutes for Health Research, the Alzheimer Society of Canada and several other charities. Otherwise, the authors do not declare any competing interests.

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Data Availability: The data underlying this article will be shared on reasonable request to the corresponding author.

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