Title: Development, validation and performance of laboratory frailty indices: A scoping review

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ABSTRACT

Introduction: Frailty is a syndrome characterised by decline in functional ability and increasing vulnerability to disease and associated with adverse outcomes. Several established methods exist for assessing frailty. This scoping review aims to characterise the development and validation of frailty indices based on laboratory test results (FI-Lab) and to assess their utility.

Methods: Studies were included in the review if they included data concerning the development and/or testing an FI-Lab using the deficit accumulation method. Studies were identified using PubMed/MEDLINE, Embase (Elsevier), OpenGrey and Google Scholar from 2010 to 2021. Two reviewers independently screened all abstracts, and those that met the inclusion criteria were reviewed in detail. Data extracted included details about the study characteristics, number, type and coding of laboratory variables included, validation, and outcomes. A narrative synthesis of the available evidence was adopted.

Results: The search yielded 915 articles, of which 29 studies were included. In general, 89% of studies were conducted after 2016 and 51% in a hospital-based setting. The number of variables included in FI-Labs ranged from 13 to 77, and 51% included some non-laboratory variables in their indices, with pulse and blood pressure being the most frequent. The validity of FI-Lab was demonstrated through change with age, correlation with established frailty indices and association with adverse health outcomes. The most frequent outcome studied was mortality (79% of the studies), with FI-Lab associated with increased mortality in all but one. Other outcomes studied included self-reported health, institutionalisation, and activities of daily living. The effect of combining the FI-Lab with a non-laboratory-based FI was assessed in 7 studies with a marginal increase in predictive ability.

Conclusion: Frailty indices constructed based on the assessment of laboratory variables, appear to be a valid measure of frailty and robust to the choice of variables included.

Introduction

Frailty is a syndrome characterised by a decline in functional ability and increasing vulnerability to disease and is linked with a range of adverse health outcomes, including mortality, falls, fractures and institutionalisation (Walston et al., 2006; Clegg et al., 2013). Several tools have been developed to assess frailty. One of the most widely used is the Frailty Index (FI), which is based on the identification and accumulation of clinically detectable health deficits across multiple systems (Mitnitski et al., 2001). The deficits are typically signs, symptoms, disease conditions, or functional impairments, and included if they are associated with health, increase with age, are not saturated too early with age, and cover a range of physiologic systems (Searle et al., 2008).

The deficits which contribute to the frailty index are ultimately a consequence of proximal damage at the organ, tissue and cellular levels. Some cellular/tissue biomarkers may be captured also by laboratory measurements used in clinical practice. Considered individually, these biomarkers may show a weak relationship with ageing and frailty. However, research suggests that combining laboratory biomarkers may be linked with adverse outcomes of ageing. Using data from the Canadian Study of Health and ageing, Rockwood and colleagues developed a laboratory-based frailty index (FI-Lab) based on characterising the proportion of a range of laboratory tests which are abnormal (Howlett et al., 2014). The FI-Lab included 21 laboratory deficits plus also systolic and diastolic blood pressure, and in an analysis of 1013 participants was associated with an increased risk of death (Howlett et al., 2014). Since then, several research studies have been published describing the development of, and or use of laboratory-based frailty indices (Blodgett et al., 2016; Blodgett et al., 2017; Yang et al., 2018). There are, however, differences in these studies in terms of the number and type of

laboratory variables included in the indices, the setting and age of subjects included, how they have been validated and their association with adverse outcomes.

The broad aim of this scoping review was to characterise the development, validation and utility of currently published FI-Lab indices. Specific review questions include: i) which, and how many, laboratory test variables have been used to construct FI-Lab indices? ii) what (if any) other variables had been combined with laboratory tests in the development of FI-Lab indices? iii) what approaches / principles have been used to define thresholds for laboratory tests to be included in FI-Lab indices? iv) how have the published FI-Lab indices been validated? v) what adverse health outcomes have been associated with FI-Lab indices? vi) how do FI-Lab indices compare with other frailty tools concerning predicting adverse outcomes? vii) is there evidence that combining information from an FI-Lab index and other frailty measures increases performance?

Methods

Protocol and registration

The scoping review was conducted following the JBI methodology for scoping reviews (Peters et al., 2021) and drafted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) (Tricco et al., 2018). The research protocol was registered with the Open Science Framework Registries on 17 March 2022 and can be assessed at https://osf.io/aq2vp/.

Eligibility criteria

Studies were included in the review if, i) they included data concerning the development of a frailty index using laboratory test data where the laboratory data comprised the majority of

the constituted index, or, they included data concerning the validation/performance of such an index, ii) they were original research studies, iii) included adults over 18 years.

Search methods and information sources

We searched PubMed/MEDLINE, and Embase (Elsevier) for published articles, and OpenGrey and Google Scholar for unpublished/grey literature from 2010 to February 2022. An initial limited search of MEDLINE was undertaken to identify articles on the topic and keywords in the titles and abstracts of relevant articles. These keywords were used to develop a comprehensive search strategy for PubMed/MEDLINE, and Embase (Elsevier). The search strategy, including all identified keywords and index terms, was adapted for each included database and/or information source. The reference lists of all studies which ultimately fulfilled the inclusion criteria were screened for additional studies. A manual search using the same free text terms was also performed in Google Scholar and OpenGrey. The full search strategy is outlined in Supplemetary Table 1.

Search strategy

Following the formal search, all identified citations were collated and uploaded into Rayyan (Ouzzani et al., 2016). Duplicate articles were removed. Two independent reviewers (FH and AM) screened the titles and abstracts for assessment against the inclusion criteria, and those which did not fulfil the criteria were excluded. The same reviewers then reviewed the full text of the remaining articles to confirm eligibility. Reasons for exclusion were recorded and reported. Any disagreements were resolved through discussion, with arbitration if needed by a third reviewer (TO).

Data extraction

Data were extracted from the articles which met the inclusion criteria using a data extraction tool developed by the reviewers (FH and AM). The extracted data included details about the study design, setting, subject recruitment, subject characteristics, and the laboratory and nonlaboratory variables used to construct the index. We also included the information on the threshold values used to define the laboratory deficits; how the index was developed, including weighting (if any) of variables; how the derived FI-Lab was validated; outcomes considered and whether the derived index was associated with these health outcomes. Finally, the information regarding whether the FI-Lab had been used in combination with other established frailty measures was included. Any disagreement during the data extraction between reviewers was resolved through discussion.

Data synthesis

As this was a scoping review, we adopted a narrative method for data synthesis. We characterised the included studies by their design, setting and subject characteristics. We characterised the laboratory and nonlaboratory variables used and the approach to defining thresholds for these variables. We also looked at how the published FI-Lab indices were validated, what adverse health outcomes have been associated with the indices, and how the FI-Lab indices compare with other frailty tools in predicting adverse outcomes. Finally, we looked at whether combining information from an FI-Lab index and other frailty measures increased the performance of the tools.

Results

Search strategy

The database search identified 1155 records. An additional five records were identified through hand-searching the references of the identified studies. After duplicate records were

removed, 915 records remained and were included in the screening stage. After title and abstract screening 98 articles remained, of which 29 met the inclusion criteria at full text review and were included for further review and data extraction (Fig. 1).

Study characteristics

An overview of the characteristics of the included studies is presented in Table 1. Amongst the 29 included studies, just over half (15/29) were conducted in hospital settings, 12 in the community and 2 in long-term care facilities. The majority of studies were conducted in China (7/29), the US (6/29), the UK (3/29) and Canada (3/29) and most were published after 2016 (26/29). The number of participants ranged from 33 to 49,004, and all of the studies included both men and women, except for one, which included men only (Blodgett et al., 2016). Most studies (23/29) were longitudinal and most used the FI-Lab to predict the risk of adverse health outcomes and compare it with other frailty scales. The adopted statistical technique by most of the included studies (19/29) for examining this was Cox's modelling (Howlett et al., 2014; Blodgett et al., 2016; Blodgett et al., 2017; Yang et al., 2018; Mitnitski et al., 2015; Ritt et al., 2017; Jäger et al., 2019; Ellis et al., 2020; Engvig et al., 2021; Guan et al., 2022; Hao et al., 2019; Heikkilä et al., 2021; Jin et al., 2021; Klausen et al., 2017; King et al., 2017; Rockwood et al., 2015; Soh et al., 2022; Sohn et al., 2019; Wang et al., 2019). Details of the individual studies are presented in Table 2.

Laboratory test variables

The 29 studies included data on the development or assessment of 29 FI-Lab indices (one study included two laboratory-based indices (Chao et al., 2020), and two studies used the same index (Guan et al., 2022; Soh et al., 2022)). The mean, median and interquartile range of the number of deficits included in the FI-Lab indices were 26.9, 23 and 22–31),

respectively. A total of 148 different laboratory variables were used to construct the FI-Lab indices. The ten most common tests included were Haemoglobin and Albumin (28/29), Creatinine (27/29), Glucose (23/29), Sodium (22/29), Platelets and uric acid (20/29), and Alkaline phosphatase, C-reactive protein and mean corpuscular volume (18/29). The full list of laboratory test variables is presented in Supplementary file 2.

Non-laboratory variables

Fifteen of the 29 FI-Lab indices included non-laboratory variables. The mean, median and interquartile range of the number of nonlaboratory deficits included in the 15 FI-Lab indices were 3.6, 4 and 2–5, respectively. The most frequent non-laboratory deficits were systolic blood pressure (15/29), diastolic blood pressure (14/29), pulse (8/29), pulse pressure (7/29), mean arterial pressure (4/29) and body mass index (BMI) (2/30). The mean, median and interquartile range of the number of non-laboratory deficits included in each of the FI-Lab indices were 1.8, 2 and 0–4, respectively. The full list of non-laboratory variables is presented in Supplementary file 3.

Thresholds for defining 'deficits'

All of the included studies defined threshold for defining 'deficits' based on normal laboratory reference ranges, apart from one study that used empirical cut points, chosen to achieve the best separation of mortality survival curves between people with and without the deficit by minimising the P-value of the log-rank test (Mitnitski et al., 2015).

Validity

Howlett (2014), in her original paper, showed that a derived FI-Lab shared similar properties as other FIs, including an increase with age, a skewed distribution, and an increased risk of

death (Howlett et al., 2014). It was also correlated with an existing frailty index (CSHA-FI). In most published studies, the FI-Lab has been validated using similar approaches. Thus many studies have looked at the change in FI with age (Blodgett et al., 2016; Blodgett et al., 2017; Yang et al., 2018; Ellis et al., 2020; King et al., 2017; Rockwood et al., 2015; Bello et al., 2018; Blodgett et al., 2019), and also gender differences - higher in men than in women (Ritt et al., 2017; Hao et al., 2019; Jin et al., 2021; King et al., 2017); however it is worth noting that, some studies found the FI-lab score did not significantly differ between women and men (Mitnitski et al., 2015; Wang et al., 2019; T Ma et al., 2018; Cheung et al., 2017). Many studies looked at the correlation between the FI-Lab and other frailty indices based on self-reported items (Blodgett et al., 2017), clinical deficits (Blodgett et al., 2016; Mitnitski et al., 2015; Rockwood et al., 2015) and comprehensive assessments (Howlett et al., 2014; Ritt et al., 2017), or the correlation with other frailty measures, including the Frailty Phenotype (Ritt et al., 2017; Nixon et al., 2019) and the Clinical Frailty Scale (CFS) (range of correlation coefficients: 0.16 to 0.49) (Ritt et al., 2017; Ellis et al., 2020; Engvig et al., 2021). Most publications also looked at predicting adverse health outcomes, including mortality, as outlined below. To our knowledge, none of the studies included an assessment of the test-retest reliability of the FI-Lab.

Health outcomes associated with FI-Lab indices (Predictive validity)

The association between the derived FI-Lab with one or more health outcomes was assessed in 27 studies. The most frequent outcome was mortality, with an increasing FI-Lab associated with increased mortality in 22 of 23 FI-LABs which included mortality as an outcome. The only index that did not exhibit increased risk mortality was one of the two indices that were used in Chao, et al. (Chao et al., 2020). It is worth noting that this one of the smallest studies (n = 33) and included patients with significant comorbidity (end stage renal disease). The

follow period for the included studies varied: up to one year (Yang et al., 2018; Ritt et al., 2017; Jäger et al., 2019; Engvig et al., 2021; Guan et al., 2022; Soh et al., 2022; Wang et al., 2019), between 1 and 5 years (Blodgett et al., 2016; Ellis et al., 2020; Hao et al., 2019; Jin et al., 2021; Klausen et al., 2017; Chao et al., 2020; Gu et al., 2021; Blodgett et al., 2021), between 6 and 10 years (Howlett et al., 2014; Blodgett et al., 2017; Mitnitski et al., 2015; Rockwood et al., 2015), and more than 10 years (Heikkil¨a et al., 2021; King et al., 2017; Sohn et al., 2019). Increasing FI-Lab was associated with poor self-reported health in 3 of the 3 studies which looked at his, activities of daily living in 2 of 3, and institutionalisation in 1 of 3. Other health outcomes considered (in a smaller number of studies) are shown in Fig. 2.

Predictive performance of FI-Lab indices compared with other frailty tools

Six studies compared the performance of the FI-Lab and other nonlaboratory frailty index instruments in predicting mortality, including a frailty index based on self-reported items (Blodgett et al., 2017), clinical deficits (Blodgett et al., 2016; Mitnitski et al., 2015; Rockwood et al., 2015) and comprehensive assessments (Howlett et al., 2014; Ritt et al., 2017). The non-laboratory indices were generally better at predicting mortality, though the difference was relatively small in some of these studies. A non-laboratory index was also better at predicting poor self-reported health and health care use (29).

The FI-Lab was compared other frailty tools which are not based on deficits accumulation approach. FI-Lab was compared to the frailty phenotype, rule-based frailty definition (Ritt et al., 2017) and FRAIL-NH in predicting mortality (Yang et al., 2018). In terms of the comparison with the Clinical Frail Scale (CFS), two studies found that both the FI-Lab and CFS were associated with adverse outcomes, including mortality (Ellis et al., 2020; Engvig et al., 2021), three studies compared the performance of FI-Lab and CFS in predicting mortality (Ritt et al., 2017; Guan et al., 2022; Soh et al., 2022), and one study compared the

performance in predicting adverse discharge destinations in geriatric trauma patients (Cheung et al., 2017). The FI-LAB was superior to the frailty phenotype, rule-based frailty definition and FRAIL-NH in predicting mortality. On the other hand, CFS was superior to the FI-LAB in predicting mortality and adverse discharge destinations.

Combining FI-Lab and other frailty measures

In seven studies, the FI-Lab was combined with a non-laboratory frailty index by combining the deficits from both and dividing by the total number of deficits to produce a 'combined' FI (Searle et al., 2008). In the majority of these, combining the FI-Lab with other frailty indices, including the FI-SR (Blodgett et al., 2017; Blodgett et al., 2019), FI-Clin (Blodgett et al., 2016; Mitnitski et al., 2015; Rockwood et al., 2015), FI-CSHA (Howlett et al., 2014) and FI-CGA (Ritt et al., 2017), resulted in a small improvement in prediction of death (Howlett et al., 2014; Blodgett et al., 2016; Blodgett et al., 2017; Mitnitski et al., 2015; Ritt et al., 2017; Rockwood et al., 2015), self-rated health and health care use (Blodgett et al., 2019) compared to either of the individual indices. The improvement, however, as evidenced by either an increase in the Area Under the Curve (AUC) in receiver operating characteristics (ROC, (Howlett et al., 2014; Blodgett et al., 2016; Blodgett et al., 2017; Mitnitski et al., 2015; Ritt et al., 2017)), or effect size (hazard ratio or odds ratio) (Rockwood et al., 2015; Blodgett et al., 2019) was relatively small in magnitude, see Table 3.

Discussion

In this scoping review, we identified 29 studies which described the development of and use of FI-Lab indices. Various blood tests accounted for most of the variables used for constructing the FI-Lab, and a few studies used urine tests. Half of the studies included some nonlaboratory variables. In all but one of the studies, the threshold for defining deficits for

inclusion was based on normal laboratory reference ranges. In most studies, validity was assessed by looking at change with age, distribution, correlation with established frailty indices and association with adverse health outcomes. The most frequent outcome studied was mortality (23 studies), with the FI-Lab associated with increased mortality in all but one. Other outcomes studied included self-reported health, institutionalisation, and activities of daily living. The effect of combining the FI-Lab with a non-laboratory-based FI was assessed in 7 studies with a marginal increase in predictive ability.

In most of the studies reviewed, the FI-Lab indices were significantly correlated with other Frailty indices (correlation coefficients range 0.16 to 0.49), increased with age and were associated with mortality suggesting they are related. The correlation coefficients however were relatively weak, suggesting that although related they may be capturing different concepts (Blodgett et al., 2016). It seems plausible that, as has been suggested by Mitinski (2015) and Blodgett (2016) that this may because subclinical deficits (which may be captured by the laboratory measurements and are linked with adverse outcomes) precede the clinically evident health deficits which are captured by the clinical-FIs (Blodgett et al., 2016; Mitnitski et al., 2015).

The majority of publications derived the FI-Lab using the approach used for other FIs, as the proportion of the laboratory variables studied were abnormal and scaled from zero to 1. Two publications from Australia based on the same population used a different approach to create a modified FI-Lab (mFI-Lab). The mFI-Lab was created by dividing the FI-Lab by the "measured ratio," which was defined as the proportion of possible laboratory test variables that were measured in a patient (thus for example if out of a total of 50 tests, if a patient had 30 measured, this would result in a measured ratio of 0.6 (30/50). The purpose of creating the mFI-Lab was to account for the number of measurements and to potentially provide

prognostic information for each patient (Guan et al., 2022; Soh et al., 2022). The authors found that the modified mFI-Lab was associated with lower odds of institutionalisation and a higher risk of mortality at 3 and 12 months (17,24). The strength of the association (hazard ratio) was greater for the FI-Lab than the mFI-Lab though for the analysis of mortality at 3 months model fit (Akaike information criterion) was slightly better for the mFI-Lab.

Several of the studies categorised the presence of frailty using an FI-Lab based on threshold values of the index though there was variation in the thresholds used. Some used an FI-Lab cut-point of 0.21 (Hao et al., 2019; Jin et al., 2021), and others a value of 0.25 (Bello et al., 2018; Cheung et al., 2017) for defining frailty. Others categorised participants as robust, pre-frail and frail using different cut-points (King et al., 2017; Wang et al., 2019), while others used different categorisation approaches and cut-points (Blodgett et al., 2016; Mitnitski et al., 2015; Engvig et al., 2021; Chao et al., 2020; Gu et al., 2021).

While almost all identified studies relied on laboratory reference ranges for assigning threshold for dichotomising deficits of the FI-Lab, the reference ranges differed based on the country, settings, data source and clinical laboratory sources. Recent studies highlight that using laboratory reference values for laboratory variables has limitations; as they were originally assigned for guiding diagnosis or treatment, they might not be the best measure for health, and also many laboratory deficits do not even have established diagnostic thresholds (Stubbings et al., 2020; Stubbings et al., 2021). However, the fact that the consistency in predicting adverse outcomes points to robustness in the development of the FI-Lab.

Other limitations are related to the fact that assigning deficits for the FI-Lab is based on dichotomising continuous variables (blood tests scores), which can lead to loss of information and statistical power, and also leads to sensitivity due to small variations around the cut-off point, in which participants who have scores close to the thresholds may show great

variability concerning acquiring the deficit (Stubbings et al., 2020; Stubbings et al., 2021; Altman & Royston, 2006). In a novel approach Stubbings and colleagues (Stubbings et al., 2020; Altman & Royston, 2006) explored a ‘‘quantile’’ methodology for the generic treatment of biomarker data that allowed construction of an FI without pre-existing medical knowledge (i.e. risk thresholds) of the included biomarkers. Using data from established cohorts including National Health and Nutrition Examination Study (NHANES), the Canadian Study of Health and ageing (CSHA) and the English Longitudinal Study of ageing (ELSA) the authors showed that the quantile approach performs as well as, or even slightly better than, established methods which used diagnostic thresholds including prediction of 5 year mortality.

Studies included in the review have been drawn from different geographic regions including North America, China and Europe, and also different settings including population samples and hospital-based samples. It is possible that differences in the populations studied and also health settings may potentially influence performance including for example the strength of associations between the derived Lab-FIs and adverse outcomes.

Even though the discriminative ability of FI-Lab was comparable to other frailty indices in the included studies, the AUCs of the FI-Lab indices were lower compared to frailty indices based on self-report and clinical deficits. This may possibly be due to the ‘sub-clinical’ nature of the deficits or the fact that most laboratory-based frailty indices have tended to include fewer included variables to build the index compared to other frailty indices (Blodgett et al., 2017). A previous study demonstrated that having a larger number of variables included increases frailty index predictive ability (Gobbens & van Assen, 2012). Evidence from a theoretical network model demonstrated that the predictive ability of the FI increases monotonically with a higher number of deficits included in the index (Mitnitski et al., 2017).

This could also explain the increased predictive ability of frailty indices that combine laboratory-based and other indices.

This review highlights the increased interest in the development and use of FI-Lab indices over recent years. Most of the research has focused on examining associations between the FI-Lab and mortality. There is relatively less data about whether the FI-Lab is associated with other adverse outcomes for including falls, fractures and hospital admissions for which further research is needed. By targeting subclinical deficits, the FI-Lab tool has the potential to identify individuals who are transitioning to frailty at an early stage. Early identification of individuals at risk of frailty could potentially facilitate targeting interventions to reduce the risk and longer-term adverse outcomes linked with frailty and improving older people's health and quality of life.

More than half of the studies included non-laboratory variables in the FI-lab indices. While the insensitivity to the number and type of included deficits of the Frailty index is one of its key characteristics, the effect of including non-laboratory variables on the characteristics and the predictive ability of the FI-lab remains unclear and for which further research is needed.

In conclusion, frailty indices constructed based on the assessment of laboratory variables, appear to be a valid approach to the measurement of frailty and robust to the choice of variables included. The ability of such indices to predict adverse health outcomes highlights their potential utility as a research tool and also clinical care.

Availability of data and materials

Data sharing is not applicable to this study as no datasets were generated for analysed during the current study.

Authors contributions

FH, CT and TWO devised the research study. FH and AM performed the systematic review and extracted data. FH analysed the data and prepared the initial draft. AM, CT and TWO critically reviewed, edited, and prepared the final draft. All authors read and approved the final manuscript.

Supplementary information

Supplementary file 1: Scoping review search strategy

Supplementary file 2: Full list of FI-Lab variables

Supplementary file 3: Full list of FI-Lab non laboratory variables

CRediT authorship contribution statement

Faisal F. Hakeem: Conceptualization, Methodology, Formal analysis, Writing – original draft. Asri Maharani: Methodology, Formal analysis, Writing – review & editing. Chris Todd: Methodology, Supervision, Writing – review & editing. Terence W O'Neill: Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2023.104995.

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Tables:

Table 1: Study characteristics stratified by study setting

		All	Hospital	Community	Long-term care
Articles n (%)		29 (100)	15 (51.7)	12 (41.3)	2 (6.8)
Year n (%)	2016+	26 (89.6)	15 (100)	10 (83.3)	1 (50)
	2010-2015	3 (10.3)	0	2 (16.6)	1 (50)
Language	English	29 (100)	15 (51.7)	12 (41.3)	2 (6.8)
Country	UK	3 (10.3)	2 (13.3)	1 (8.3)	0 (0)
	USA	6 (20.6)	1 (6.6)	5 (41.6)	0 (0)
	Canada	3 (10.3)	1 (6.6)	1 (8.3)	1 (50)
	Germany	2 (6.8)	2 (13.3)	0 (0)	0 (0)
	China	7 (24.1)	3 (20)	3 (20)	1 (50)
	Norway	1 (3.4)	1 (6.6)	0 (0)	0 (0)
	Finland	1 (3.4)	0 (0)	1 (8.3)	0 (0)
	Denmark	1 (3.4)	1 (6.6)	0 (0)	0 (0)
	South Korea	1 (3.4)	1 (6.6)	0 (0)	0 (0)
	Taiwan	1 (3.4)	1 (6.6)	0 (0)	0 (0)
	Australia	2 (6.8)	2 (13.3)	0 (0)	0 (0)
	Multi-countries	1 (3.4)	0 (0)	1 (8.3)	0 (0)
Number of participants	Range	33 - 49,004	33 – 10,253	736 – 49,004	329 - 675
Age groups	≥18	6 (20.7)	3 (20)	3 (25)	0 (0)
	≥40	3 (10.3)	1 (6.6)	2 (16.6)	0 (0)
	≥60	18 (62.2)	11 (73.3)	5 (41.6)	2 (100)
	≥85	2 (6.8)	0 (0)	2 (16.6)	0 (0)
Females %	# of articles reporting	28 (96.5)	15 (100)	12 (100)	1 (50)
	Range	0 - 69.3	28.3 – 67.6	0 - 69.3	68.1
Study design	Longitudinal	23 (79.3)	14 (93.3)	7 (58.3)	2 (100)
	Cross-sectional	6 (20.7)	1 (6.6)	5 (41.6)	0 (0)

Table 2: Detailed characteristics of the included studies in the scoping review

	First author	*Year*	*Study design*	*Setting*	*country*	*Type of participants*	*Number of participants*	*Age*	*Females%*	*Number of deficits*	*number and type of lab deficits*	*Number and type of non-lab deficits*	*Lab or routine physical?*
1	Blodgett (Blodgett et al., 2021)	2021	Cross-sectional, prospective study	Community-dwelling	US	Community-dwelling	49004	>20	51.8%	19	16 Blood tests	3	Both
2	Almanzar (Almanzar et al.. 2019)	2019	Retrospective	Hospital	USA	Admitted to hospital	10253	≥18	52.3%	16	16 Blood test	None	Laboratory only
3	Blodgett (Blodgett et al., 2019)	2019	Cross-sectional	Community-dwelling	USA	Community-dwelling		≥20	51.7%	32	27	5	Both
4	Blodgett (Blodgett et al., 2017)	2017	Prospective cohort (1-year follow-up)	Community-dwelling	US	Community-dwelling	8888	>20	51.7%	32	27	5	Both
5	Bello (Bello et al., 2018)	2018	Cross-sectional	Community-dwelling	USA	Community-dwelling	7364	≥40	16.7%	33	28 blood tests	3	Both
6	Klausen (Klausen et al., 2017)	2017	Prospective cohort (3-year follow-up)	Hospital	Denmark	Acutely admitted medical patients	4005	≥65	57.50%	17	17 blood tests	None	Laboratory only
7	Jin (Jin et al., 2021)	2021	Prospective cohort	Hospital	China	Cancer patients	2959	>20	43.4%	22	22 blood tests	None	Laboratory only
8	Blodgett (Blodgett et al., 2016)	2016	Prospective cohort study (4.4 ± 0.3 (mean ± SD) years follow-up)	Community-dwelling	Multiple countries	Community	2933	40-79	0	23	21 blood tests	2	Both
9	Ellis (Ellis et al., 2020)	2020	Prospective cohort	Hospital	UK	Admitted to hospital		84.8 ± 14.0	53.3%	27	27 blood tests	None	Laboratory only

10	Soh (Soh et al., 2022)	2022	Prospective cohort	Hospital	Australia	Geriatric rehabilitation inpatients	1819	≥70	56.6%	77	77 blood, gas, and urine	None	Laboratory only
11	Guan (Guan et al., 2022)	2022	Prospective cohort	Hospital	Australia	Geriatric rehabilitation inpatients	1819	≥70	56.60%	77	77 blood, gas, and urine	None	Laboratory only
12	Ma (Ma et al., 2020)	2018	Cross-sectional	Community-dwelling	China	Community-dwelling	1780	≥70	52.8%	23	19 Blood tests	3	Both
13	King (King et al., 2017)	2107	Cross-sectional longitudinal study	Community-dwelling	USA	Community-dwelling	1740	≥65	65.2%	28	28 blood tests	None	Laboratory only
14	Ma (ma et al., 2018)	2018	Cross-sectional	Community-dwelling	China	Community-dwelling	1463	≥70	57.8%	23	20 blood tests	3	Both
15	Heikkilä (Heikkilä et al., 2021)	2021	Prospective study with 10- and 18-year follow-ups	Community-dwelling	Finland	Community-dwelling	1153	≥60	58%	14	14 blood tests	None	Laboratory only
16	Wang (Wang et al., 2019)	2019	Retrospective cohort	Hospital	China	Hospital-based	1020	≥60	28.3%	44	44 blood test	None	Laboratory only
17	Howlett (Howlett et al., 2014)	2014	Prospective cohort study (6 years follow-up)	Community-dwelling	Canada	Community-dwelling	1013	≥65	69.3%	23	21 blood tests	2	Both
18	Mitnitski (Mitnitski et al., 2015)	2015	Prospective cohort (7-year follow-up)	Community-dwelling	UK	Community-dwelling	777	≥85	60.9%	40	40	None	Laboratory only
19	Hao (Hao et al., 2019)	2019	Prospective cohort (4-year follow-up)	Community-dwelling	China	Community-dwelling	736	≥90	67.5%	22	22 Blood tests	None	Laboratory only
20	Rockwood (Rockwood et al., 2015)	2015	Prospective cohort study (6 years follow-up)	Long-term care residents	Canada	Long-term care residents	675	≥65	Not reported	23	21 blood tests	2	Both

21	Jager (Jager etal., 2019)	2019	Prospective cohort	Hospital	Germany	Hospitalized in the geriatric wards	500	>=65	67%	21	20 blood tests and urine tests	None	Laboratory only
22	Yang (Yang et al., 2018)	2018	Prospective cohort (1-year follow-up)	Nursing homes	China	Nursing home residents	329	Mean 85.2 (3.4)	68.1%	30	30 blood tests	None	Laboratory only
23	Ritt (Ritt et al., 2017)	2017	Prospective cohort (1-year follow-up)	Hospital	Germany	Hospitalized	306	≥65	67.6%	23	23 (22 blood and one urine)	None	Laboratory only
24	Cheung (Cheung et al., 2017)	2017	Retrospective cohort (4-year)	Hospital	Canada	Patients to admitted to the trauma service	266	≥65	47.5%	23	20	3	Both
25	Engvig (Engvig er al., 2021)	2021	Prospective cohort	Hospital	Norway	Admitted to hospital	195	≥ 75	63%	14	14 blood tests	None	Laboratory only
26	Gu (Gu et al., 2021)	2021	Retrospective cohort	Hospital	China	Admitted to hospital	154	≥60	30%	23	21 routine blood tests	2	Both
27	Sohn (Sohn et al., 2019)	2019	Prospective cohort	Hospital	South Korea	Patients underwent primary surgical aortic valve replacement	154	≥75	49.3%	32	28 blood tests	4	Both
28	Nixon (Nixon et al., 2019)	2019	Cross-sectional	Hospital	UK	Patients with CKD G4-5D	90	Mean 68 (±13)	50%	27	25 blood tests	2	Both
29	Chao (Chao et al., 2020)	2020	Prospective cohort	Hospital	Taiwan	ESRD patients receiving chronic haemodialysis	33	>20	55%	23	19 blood tests	4	Both

Table 3: Combining FI-Lab with other frailty indices

First Author/ Year	Metric	FI-LAB	Other frailty Measure	Combined index
Howlett 2014 (5)	AUC ROC (Mortality)	0.71	0.72 FI-CSHA (Comprehensive assessment)	0.74
Mitntski 2015 (12)	AUC ROC (Mortality)	0.68	0.71 FI-CD (Clinical deficits)	0.76
Bloddget-2016 (6)	AUC ROC (Mortality)	0.70	0.79 FI-Clin (Clinical deficits)	0.81
Ritt 2017(13)	AUC ROC (Mortality)	0.76	0.80 FI-CGA (Comprehensive assessment)	0.83
Blodgett 2017 (7)	AUC ROC (Mortality)	0.72	0.82 FI-SR (Self-reported items)	0.83
Rockwood 2015 (23)	Mortality (HR)	1.02 (1.01-1.03)	1.03 (1.02 – 1.04). FI-Clinical-LTC (Clinical deficits)	1.04 (1.03-1.05)
Blodgett 2019 (29)	Self-reported Health (OR)	1.46 (1.39-1.54)	2.55 (2.40-2.71) FI-SR (Self-reported items)	2.83 (2.63-3.04)
	Health care use (OR)	1.35 (1.29-1.42)	2.15 (2.02-2.27) FI-SR (Self-reported items)	2.36 (2.21-2.52)

AUC: Area Under the Curve, ROC: receiver operating characteristic curves, HR: Hazard ratio, OR: Odds ratio

FI-CSHA: the Canadian Study of Health and Aging frailty index, FI-CD: Clinical deficit frailty index, FI-Clin: Clinical frailty index, FI-CGA: frailty index based on comprehensive geriatric assessment, FI-SR: frailty index based on Self-reported items, FI-Clinical-LTC: clinical frailty-index for long-term care

Figures:

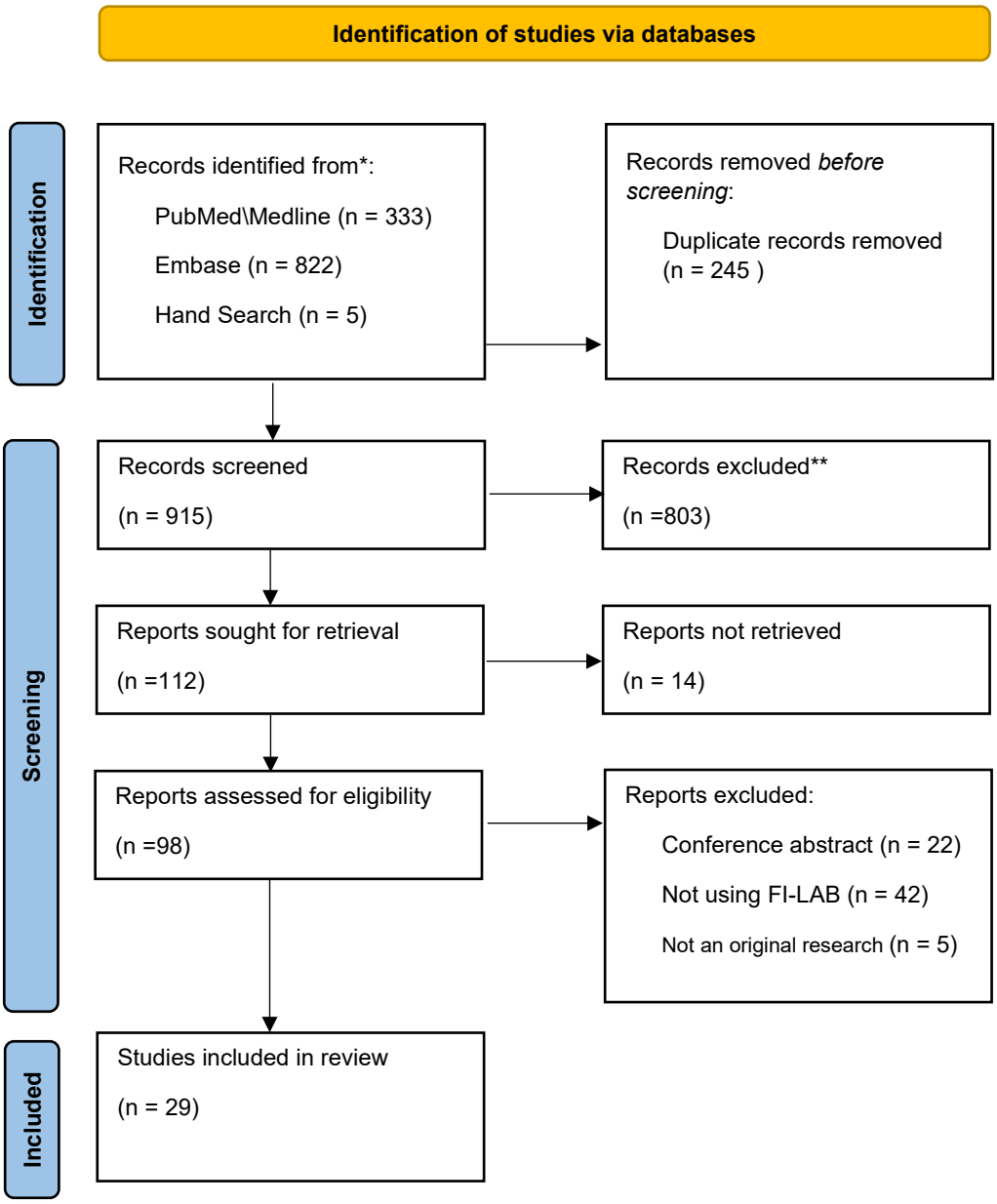

Figure 1: Flow chart for the scoping review process

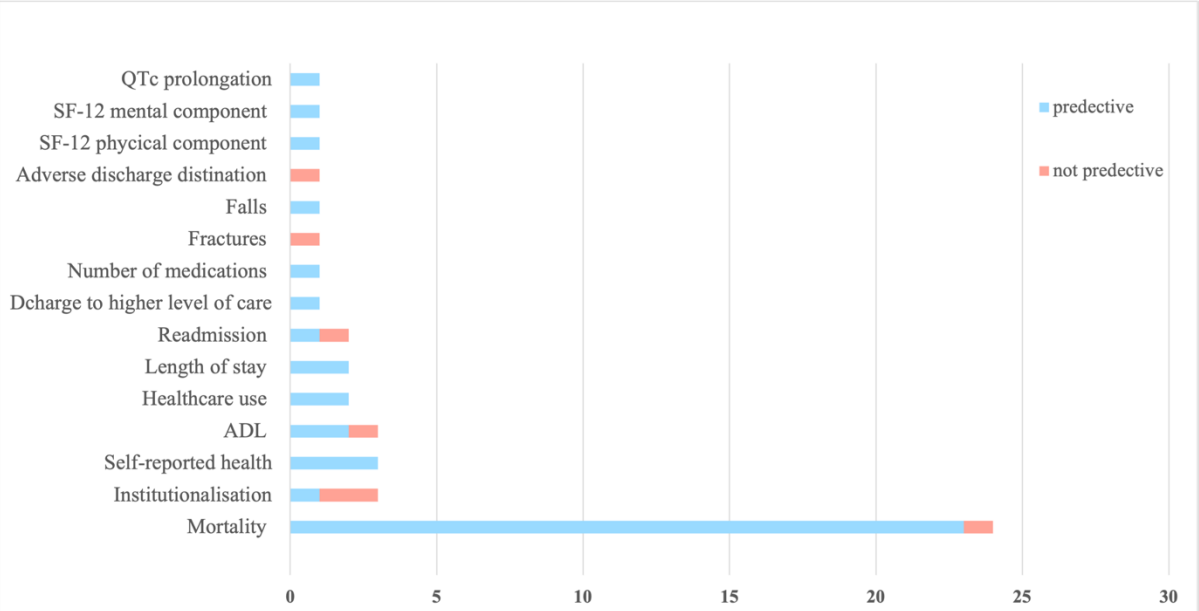

Figure 2: Association of FI-LAB with adverse outcomes