Development and validation of a modified Frailty Risk Index as a predictor of mortality in rural elderly people

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ABSTRACT

Background. Frailty is a reversible age-related condition characterised by declines across multiple physiologic systems and associated with an increased risk of mortality or unplanned hospitalisation. We developed and validated a new frailty index that is easy to apply in elderly people in rural India and has predictive accuracy for all-cause mortality at 6 and 12 months.

Methods. 1000 participants aged >60 years who were admitted to a geriatric unit of a rural hospital for screening or treatment of any illness were recruited for development and validation of the Frailty Index in Rural Elderly – Mental status, Activities of daily living, Depression, and Events (FIRE-MADE), which combines the Cumulative Deficits Model and the Comprehensive Geriatric Assessment Model and takes into account of four domains: physical, cognitive, psychosocial, and functional.

Results. The FIRE-MADE score increased with age and was higher in men than in women. Higher FIRE-MADE score was associated with higher rates of mortality and unplanned hospitalisation. In multivariable analysis, predictors for mortality were Mini-Mental State Examination, activities of daily living, ischaemic heart disease, history of stroke, and polypharmacy. In Kaplan-Meier survival analysis, 4.9%, 7.1%, and 16.7% of participants with mild (FIRE-MADE score, 0.3-0.4), moderate (0.5-0.6), and severe (>0.7) frailty died at the end of 1 year. The cut-off values for mortality and unplanned hospitalisation were 0.32 and 0.27, respectively, with the area under the receiver operating characteristic curve for the severity being 0.883 and 0.794, respectively. Compared with the Longitudinal Aging Study Amsterdam frailty index score in predicting mortality and unplanned hospitalisation, the FIRE-MADE score had positive predictive values of 88.89% and 88.89%, respectively, and negative predictive values of 65.93% and 41.10%, respectively. Association between the two indices was strong.

Conclusions. FIRE-MADE is easy to apply in clinical practice as a screening tool to detect frailty in elderly people in rural India.

Key words: Frail elderly; Hospitalization; Mortality

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INTRODUCTION

Frailty is a reversible age-related condition characterised by declines across multiple physiologic systems and associated with an increased risk of mortality or unplanned hospitalisation. The term 'frail' is intended to identify vulnerable elderly people at high risk of falls, disability, hospitalisation, and mortality. Nonetheless, frailty is not synonymous with age or disease. It is a geriatric syndrome and involves excess healthcare costs from consultations, polypharmacy, and hospitalisation.¹ Frailty confers loss of independence in activities of daily living and death when exposed to stress. Nonetheless, physical frailty is potentially reversible.¹⁻³

Numerous definitions and assessment tools for frailty have been developed. The Fried Frailty Phenotype Framework has been commonly used and extensively validated,² but it is considered not readily applicable in primary care practice.^{4,5} It measures only five variables: weight loss, exhaustion, grip strength, walking speed, and physical activity.² The presence of any three variables is defined as frailty (0=non-frail, 1-2=pre-frail, and 3-5=frail).² Dichotomisation on continuous scales (grip strength, walking speed, and physical activity) is done retrospectively according to the lowest 12th percentile rule, with further stratifications. This requires expertise in statistics and a reference sample, which is not easy for primary care practitioners.⁶

Owing to the ageing population and rising healthcare costs, health promotion and disability prevention is emphasised.^{6,7} To provide early intervention and/or multidisciplinary management at the primary care level, it is important to identify at-risk elderly people based on frailty, which fits well with the physical and psychosocial model.⁸ However, appropriate frailty metrics for primary care are lacking, and general practitioners are in need of easy instruments for frailty.⁹

The Cumulative Deficit Model identifies frailty based on variables (such as symptoms, signs, diseases, disabilities, and abnormal laboratory values) collectively referred to as deficits.¹⁰ The original model has 92 variables, but this can be reduced to 30 without loss of predictive validity.^{11,12} A frailty index is calculated based on the presence or absence of each variable as a proportion of the total. The criteria for variable inclusion in the frailty index are: (1) biologically plausible; (2) accumulates with age; and (3) does not saturate too early (ie, the prevalence of the deficit does not reach 100% before older age).¹³⁻¹⁵

In India, there are >100 million elderly people who often have comorbidities that are often neglected; 10% of them are admitted to hospital each year.^{16,17} This study aimed to develop and validate the Frailty Index in Rural Elderly – Mental status, Activities of daily living, Depression, and Events (FIRE-MADE)

FIGURE 1. Flowchart of the study

to identify predictors of frailty to predict all-cause mortality and unplanned hospitalisation in rural elderly people, with an aim of health promotion and disability prevention.

MATERIALS AND METHODS

This study was approved by the ethics committee of the Jawahar Lal Nehru Medical College (DMIMS (DU)/IEC/2014-15/859). Written informed consent was obtained from each participant. This longitudinal observational study was carried out from January 2015 to December 2017, with participants followed up at 6 and 12 months. 1000 elderly people aged >60 years who were admitted to our hospital for screening and treatment of any illness were recruited and randomly allocated to either the development cohort (n=900) or the validation cohort (n=100). Both cohorts had same study protocol (**FIGURE 1**). The sample size was calculated based on the study by Hoogendijk et al,¹⁸ in which the prevalence of frailty was 23.9%. For $p=0.239$, the number of subjects required was 900 with a power of 88%.

Development of FIRE-MADE

The Cumulative Deficits Model and the Comprehensive Geriatric Assessment Model were incorporated to form four domains: physical, cognitive, psychosocial, and functional.^{19,20} The physical domain incorporated health-related deficits (stroke, diabetes, heart attack) were taken from the Cumulative Deficits Model, whereas the cognitive, psychosocial (emotional), and functional (activities of daily living) domains were taken from the Comprehensive Geriatric Assessment Model. Based on literature review and clinical relevance, we identified 10 parameters for development of FIRE-MADE: (1) mental status, (2) activities of daily living, (3) depression, and events like (4) polypharmacy, (5) diabetes mellitus, (6) ischaemic heart disease, (7) chronic obstructive pulmonary disease / asthma, (8) stroke, (9) cancer, (10) others. Presence or absence of each parameter was indicated by 1 or 0 [**TABLE 1**].

For internal (content) validation, feedbacks were taken from experts. Each item was tested for its association with mortality using univariate analysis.

TABLE 1
Parameters of Frailty Index in Rural Elderly – Mental status, Activities of daily living, Depression, and Events

Parameter	Score
Mini-Mental State Examination score of <27 (impaired)	No=0, Yes=1
Help needed with activities of daily living score	
Feeding	No=0, Yes=1
Dressing	No=0, Yes=1
Bathing	No=0, Yes=1
Going to toilet	No=0, Yes=1
Urinary continence	No=0, Yes=1
Transferring	No=0, Yes=1
Geriatric Depression Scale score of >5	No=0, Yes=1
Events	
Polypharmacy	No=0, Yes=1
Diabetes mellitus	No=0, Yes=1
Ischaemic heart disease	No=0, Yes=1
Chronic obstructive pulmonary disease / asthma	No=0, Yes=1
Stroke	No=0, Yes=1
Cancer	No=0, Yes=1
Others	No=0, Yes=1

Multivariate logistic regression analysis was used to determine predictors of mortality after adjusting for confounders such as age, sex, education, and blood pressure. The predictors of mortality were then included in FIRE-MADE.

The FIRE-MADE score was calculated for each participant by summing the number of deficit parameters and dividing the total number of parameters ($n=10$). Based on the 32-item Longitudinal Aging Study Amsterdam (LASA) instrument,²¹ the cut-off value of 0.25 was used and four groups were devised: fit (<0.25), mild frailty ($0.3-0.4$), moderate frailty ($0.5-0.6$), and severe frailty (>0.7). The four groups were tested for the predictive validity in terms of mortality and unplanned hospitalisation. Hazard ratios (HR) for mortality and unplanned hospitalisation at 6 and 12 months were estimated. Kaplan-Meier survival analysis was performed using the log-rank test to compare the survival pattern of different frailty groups. Receiver operating characteristic (ROC) curve was used to determine the cut-off value of the FIRE-MADE score for mortality and unplanned hospitalisation. These cut-off values were then validated in the validation cohort.

Validation of FIRE-MADE

For testing the predictive validity of FIRE-MADE, Kaplan-Meier curves for mortality and unplanned hospitalisation were plotted for the two risk groups (fit and frail) of the validation cohort, based on the cut-off values devised from the development cohort.

In addition, the validation cohort was retrospectively assessed (based on records) with the LASA frailty index,²¹ which has four functional domains: physical, cognitive, emotional, and social functioning. The LASA frailty index has been

validated for use as external reference as a predictor of mortality. Prognostic score calculation and classification of the risk groups (fit and frail) were repeated in the validation cohort using ROC curves. FIRE-MADE was compared with the LASA frailty index to determine the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy.

Parameters of FIRE-MADE

Data collected included socio-demographics (age, sex, education), the presence of diabetes, chronic obstructive pulmonary disease/asthma, stroke, cancers, polypharmacy, cardiac diseases (ischaemic heart disease), other conditions (arthritis, fall, incontinence), and medications used in the past year. Polypharmacy was defined as the use of ≥ 5 medications with different anatomic therapeutic chemical classifications over the past 6 months.¹⁶ Depressive symptoms was measured using the Geriatric Depression Scale short version,^{22,23} with a score of >5 indicating a clinically significant level of depressive symptoms. Cognitive function was evaluated using the Hindi adaptation of the Mini-Mental State Examination (MMSE),²⁴ with a score of <27 indicating cognitive impairment. Functional dependency was assessed using self-reported difficulty and requiring help on basic activities of daily living.²⁵ Hospitalisation was based on patients' self-report and confirmed by hospital discharge ticket or prescription tickets. Mortality was confirmed by telephonic contact with relatives or registers of the municipalities where respondents were living.

Statistical analysis

Statistical analysis was performed using Epi Info 7.2.2.2. Chi-squared test was used to determine association of different parameters. Z-test was used for comparison of proportions, and t-test was used

TABLE 2
Scores of Frailty Index in Rural Elderly – Mental status, Activities of daily living, Depression, and Events

Age group, y	Overall (n=900)	Men (n=468)	Women (n=432)	p Value
60-65	0.30 $\pm$ 0.15 (n=423)	0.30 $\pm$ 0.18 (n=162)	0.31 $\pm$ 0.13 (n=261)	0.45
66-70	0.35 $\pm$ 0.17 (n=297)	0.34 $\pm$ 0.15 (n=162)	0.37 $\pm$ 0.20 (n=135)	<0.01
71-75	0.48 $\pm$ 0.21 (n=144)	0.49 $\pm$ 0.20 (n=117)	0.43 $\pm$ 0.26 (n=27)	<0.001
>75	0.62 $\pm$ 0.23 (n=36)	0.56 $\pm$ 0.24 (n=27)	0.80 $\pm$ 0.01 (n=9)	<0.001
Total	0.36 $\pm$ 0.19	0.37 $\pm$ 0.20	0.35 $\pm$ 0.18	0.38
One-way ANOVA (F value, p value)	$F_{3,896}=62.12$, $p<0.0001$	$F_{3,464}=36.96$, $p<0.0001$	$F_{3,428}=29.34$, $p<0.0001$	

TABLE 3
Multivariate logistic regression for predictors of mortality

Variables	Regression coefficient (β)	p Value	Exp(β) [odds ratio (95% CI)]
Mini-Mental State Examination	4.594	0.001	8.862 (3.308-19.327)
Activities of daily living	1.339	0.041	3.815 (1.010-16.162)
Depression	0.124	0.788	1.132 (0.457-2.808)
Ischaemic heart disease	-2.179	0.001	4.020 (1.041-3.309)
Chronic obstructive pulmonary disease	-0.782	0.071	0.457 (0.195-1.071)
Diabetes	0.637	0.226	1.892 (0.674-5.308)
History of stroke	2.055	0.003	7.807 (2.001-30.469)
Polypharmacy	3.689	0.001	39.994 (12.622-126.726)
Cancer	-0.411	0.386	0.663 (0.261-1.681)
Other comorbidities	-0.133	0.783	0.875 (0.339-2.262)
Constant	-10.265	0.001	0.001

for comparison of means. Multiple logistic regression analysis was used to determine predictors of frailty after adjusting for confounders, with odds ratio (OR) and 95% confidence interval (CI) calculated. One-way analysis of variance (ANOVA) followed by Tukey test was used to compare more than two means at a time. ROC analysis was used to determine the cut-off values for mortality and unplanned hospitalisation. Kaplan-Meier survival analysis by log-rank test was used to compare the survival pattern of different risk groups. Sensitivity, specificity, positive and negative predictive values were calculated. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 1000 participants aged 60 to 85 (mean, 67.11; median, 66; standard deviation, 5.11) years, 47% were aged 60-65 years, 33% were aged 66-70 years, 16% were aged 71-75 years, and 4% were aged >75 years ($p<0.05$).

In the development cohort, the FIRE-MADE score increased with age and was higher in men than in women (both $p<0.0001$, one-way ANOVA, **TABLE 2**). The prevalence of FIRE-MADE score of ≥ 0.25 was associated with age and was higher in men than in women (both $p<0.0001$, Chi-squared test). Higher FIRE-MADE score was associated with higher rates of mortality and unplanned hospitalisation (both $p<0.0001$, Chi-squared test).

In multivariable analysis, after adjusting for

confounders, predictors for mortality were MMSE (OR=8.86, 95% CI=3.30-19.32, $p=0.0001$), activities of daily living (OR=3.81, 95% CI=1.01-16.16, $p=0.041$), ischaemic heart disease (OR=4.02, 95% CI=1.04-3.31, $p=0.001$), history of stroke (OR=7.80, 95% CI=2.00-30.46, $p=0.003$), and polypharmacy (OR=39.99, 95% CI=12.62-126.72, $p=0.001$) [**TABLE 3**].

In Kaplan-Meier survival analysis, 4.9%, 7.1%, and 16.7% of participants with mild (FIRE-MADE score, 0.3-0.4), moderate (0.5-0.6), and severe (>0.7) frailty died at the end of 1 year. The survival rate decreased with increased FIRE-MADE score (**FIGURE 2**). Different risk groups had different survival patterns (log-rank=218.54, $p<0.000$). The cut-off

FIGURE 2. Kaplan-Meier survival curves for fit and mild, moderate, and severe frailty groups based on the Frailty Index in Rural Elderly – Mental status, Activities of daily living, Depression, and Events

FIGURE 3. The cut-off values for (a) mortality and (b) unplanned hospitalisation were 0.32 and 0.27, respectively, with the area under the receiver operating characteristic curve for the severity being 0.883 and 0.794, respectively.

FIGURE 4. Kaplan-Meier survival curve for mortality with a cut-off value of 0.32

values for mortality and unplanned hospitalisation were 0.32 and 0.27, respectively, and the areas under the ROC curve for the severity were 0.883 and 0.794, respectively (**FIGURE 3**).

In the validation cohort, the 1-year mortality pattern differed significantly in those with FIRE-MADE score of ≥ 0.32 or < 0.32 (log rank=96.33, $p < 0.001$, **FIGURE 4**). The unadjusted and adjusted Cox proportional hazard ratio for the cut-off value of 0.32 was 13.90 (95% CI=6.95-27.80, $p < 0.001$) and 9.77 (95% CI=4.82-19.80, $p < 0.001$), respectively. The unplanned hospitalisation pattern differed

significantly in those with FIRE-MADE score of ≥ 0.27 or < 0.27 (log rank=8.52, $p = 0.003$). The unadjusted and adjusted Cox proportional hazard ratio for the cut-off value of 0.27 was 0.22 (95% CI=0.06-0.73, $p = 0.013$) and 0.21 (95% CI=0.06-0.70, $p = 0.011$), respectively.

Compared with the LASA frailty index score, the FIRE-MADE score had a positive predictive value of 88.89% and 88.89%, and a negative predictive value of 65.93% and 41.10% in predicting mortality and unplanned hospitalisation, respectively (**TABLE 4**). Association between the two indices was strong.

DISCUSSION

FIRE-MADE with 10 health deficit items is easy to apply in rural India, taking into account of social, psychological, mental, treatment-related, and health deficits in affecting mortality and unplanned hospitalisation. Content validation included all the relevant items and excluded repeat items. Polypharmacy was not included in previous frailty indices such as the LASA frailty index, but we included polypharmacy in developing FIRE-MADE, because polypharmacy has been reported to be associated with frailty in elderly people.^{14,17,19-21,26,27} Construct validation of each item was performed using univariate and multivariate analyses, and predictors of frailty (MMSE, activities of daily living, ischaemic heart disease, history of stroke, and polypharmacy)

TABLE 4
Comparison of external validity of Frailty Index in Rural Elderly – Mental status, Activities of daily living, Depression, and Events (FIRE-MADE) with the Longitudinal Aging Study Amsterdam (LASA) frailty index

Outcome	Area under curve	Cut-off value	Diagnostic accuracy, %	Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
FIRE-MADE							
Mortality	0.883	0.32	68	20.51	98.36	88.89	65.93
Unplanned hospitalisation	0.794	0.27	54	35.32	90.91	88.89	41.10
LASA frailty index							
Mortality	0.948	0.34	69	21.05	98.39	88.89	67.03
Unplanned hospitalisation	0.833	0.31	73	50.00	96.00	92.59	65.75

were identified after adjusting for confounders. Although depression, chronic obstructive pulmonary disease, diabetes mellitus, cancer, and other comorbidities were not predictive of mortality, these items were kept in FIRE-MADE, as exclusion may affect the content validity. FIRE-MADE was used to classify frailty (fit, mild, moderate, and severe frailty) and then to predict mortality and unplanned hospitalisation at 6 and 12 months. ROC curves were constructed and areas under the ROC curve were calculated for the cut-off values of mortality (0.32) and unplanned hospitalisation (0.27). These cut-off values were validated in the validation cohort. This established the 'predictive validity' component of the 'criterion validity' of FIRE-MADE. The initial arbitrary cut-off value of 0.25 was close to the externally validated cut-off values. Criterion validity was established by assessing both 'concurrent validity' and 'predictive validity'. The 'concurrent validity' was assessed by comparing FIRE-MADE with the LASA frailty index for sensitivity, specificity, and positive and negative predictive values. Association between the two indices was strong.

One limitation of our study is that participants were recruited from only one tertiary centre in rural India. In addition, the follow-up duration was too short to conclude the cut-off value for risk stratification.

CONCLUSION

FIRE-MADE is easy to apply in clinical practice as a screening tool to detect frailty in elderly people in rural India.

DECLARATION

The authors have no conflict of interest to disclose.

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