Frailty defined by FRAIL scale as a predictor of mortality: A systematic review and meta-analysis

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ABSTRACT

Objectives: To conduct a systematic review of the literature on prospective cohort studies examining mortality risk according to frailty defined by FRAIL scale, and to perform a meta-analysis to synthesize the pooled risk estimates.

Design: Systematic review and meta-analysis.

Setting: Embase, Scopus, MEDLINE, CINAHL, and PsycINFO were systematically searched in January 2018. References of included studies were reviewed and a forward citation tracking was performed on relevant review papers for additional studies. Additional data necessary for a meta-analysis were requested to corresponding authors.

Participants: Community-dwelling middle-aged and older people.

Measurements: Mortality risk according frailty defined by FRAIL scale.

Results: After removing duplicates, there are 81 citations for title, abstract, and full-text screening. Eight studies were included in this review. Four studies calculated area under the receiver operating characteristic curve, which ranged from 0.54-0.70. A random-effects meta-analysis was conducted on three studies that provided adjusted hazard ratios (HR) of mortality risk according to three frailty groups (robust, prefrail, and frail) defined by FRAIL scale. Both frailty and prefrailty were significantly associated with higher mortality risk than robustness (pooled HR=3.53, 95%CI=1.66-7.49, p=0.001; pooled HR=1.75, 95%CI=1.14-270, p=0.01, respectively). No evidence of publication bias was observed.

Conclusion: This study demonstrated that FRAIL scale is a tool that can effectively identify frailty/prefrailty status, as well as quantify frailty status in a graded manner in relation to mortality risk. Although its feasibility is of note, not many studies are yet using this relatively new tool. More studies are warranted regarding mortality and other health outcomes.

Keywords: Frailty; FRAIL scale; Mortality; Systematic review; Meta-analysis.

INTRODUCTION

Frailty is a state of decreased physiological reserve and increased vulnerability to negative health outcomes.[1,2] Frailty is associated with falls,[3] fractures,[4] hospitalization,[5] institutionalization,[6] disabilities,[7] lower quality of life,[8] dementia,[9] and premature death.[10] Although there have been a numerous definitions and criteria proposed in the literature for determining frailty, consensus has yet to be reached.[1] The International Association of Nutrition and Aging Task Force proposed a new frailty tool, the FRAIL scale, based on five components: **F**atigue, **R**esistance (inability to climb stairs), **A**mbulation (inability to walk a certain distance), **I**llnesses, and **L**oss of weight.[11] FRAIL scale is a quick and simple questionnaire consisting of only five self-reported YES/NO items.[12] It does not require special equipment or measurements and therefore it can be administered by phone or mail. Since its publication in 2008,[11] this tool has been validated in various populations and has been increasingly used in clinical and research settings.[13] However, no meta-analysis has been found in the literature on associations between FRAIL scale and mortality. The aim of this study is to perform a systematic review and meta-analysis regarding frailty defined by FRAIL scale as a predictor of mortality.

METHOD

A protocol was developed according to the PRISMA statements[14] and registered at PROSPERO.[15] Embase, Scopus, MEDLINE, CINAHL, and PsychINFO were searched in March 2018 for studies published later than 2008, when the FRAIL scale was first published.[11,12] A combination of Medical Subjective Headings and text words related to FRAIL scale and mortality was used (available at the PROSPERO[15]). References in the included studies were reviewed, and forward citation tracking was performed for the papers advocating FRAIL scale[1,11,12] using Google Scholar. Any prospective studies that examined mortality risk according to FRAIL scale among general cohorts of community-dwelling middle-aged and older people were considered potentially eligible. Studies were assessed for methodological quality using the Newcastle-Ottawa scale.[16] Adequate quality studies were defined as those meeting $\geq$5 items out of nine. If the same cohort was used by multiple studies, the study with the largest sample size was included. A meta-analysis was conducted when three or more studies provided the same effect measures (hazard ratio (HR) or odds ratio (OR)) for all-cause mortality according to categories of robust, prefrail, and frail, which were defined as having 0, 1-2, and 3-5 items of FRAIL scale, respectively.[17] A random-effects meta-analysis was used due to expected high heterogeneity. Heterogeneity was measured using I^2 statistic. Publication bias was assessed by visually inspecting funnel plots. Subgroup and sensitivity analyses were also attempted if possible. All analyses were performed using Review Manager 5 (Cochrane Collaboration, Denmark).

RESULTS

Figure 1 is a flowchart of the literature search. A total of 189 citations were identified from five electronic databases and 3 studies were found from other sources. After removing 111 duplicates, 81 studies remained, among which eight studies were included in this review.[13,18-24] Study characteristics and findings were summarized in **Table 1**. All eight studies were considered to have adequate methodological quality based on the Newcastle-Ottawa scale (range=5-8).

Four studies calculated area under the receiver operating characteristic curve (AUC),[20-23] which ranged from 0.54-0.70, most of which were statistically significantly better than by chance. Five studies used Cox proportional hazard regression models and provided hazard ratios for mortality risk according to frailty status, which was categorized, based on the

FRAIL scale, into: 3 groups (0, 1-2, 3-5),[19,20] 5 groups (0, 1, 2, 3, 4-5),[13,24] or 2 groups (unknown cut-point).[18] Despite the different cut-points used, greater frailty status was significantly associated with higher mortality risks in a dose-response manner in all studies. Similar findings were shown by another study using OR.[21]

With additional data provided by the author on request,[18] a total of three studies (N=9273) were used for a meta-analysis.[18-20] As expected high degree of heterogeneity was observed (I^2=64-79%). **Figure 2** presents forest plots showing the both frailty and prefrailty were significantly associated with higher mortality risk than robustness (pooled HR=3.53, 95%CI=1.66-7.49, p=0.001; pooled HR=1.75, 95%CI=1.14-270, p=0.01, respectively). Obvious asymmetry was not observed in the funnel plots, which suggests no evidence of publication bias.

DISCUSSION

This systematic review identified eight original studies examining frailty defined by FRAIL scale and mortality among community-dwelling middle-aged and older people. The meta-analysis, which included 9273 individuals from three studies provided evidence of the significant association between FRAIL scale-defined frailty and higher mortality.

Currently, the most commonly used frailty definitions would include the frailty phenotype and the Frailty Index.[1] However, these two tools are time-consuming and practically infeasible in a busy clinical setting. The phenotypic approach requires performance measurements (gait speed and grip strength) and some calculation of lowest 20 percentile in the population examined.[25] The Frailty Index requires collecting a number of deficits, typically more than 30-40.[26] In contrast, FRAIL scale includes only five simple questions and can be administered in minimal time by busy clinicians, as well as other healthcare providers.[1,11,12]

FRAIL scale shares similarities with the frailty phenotype in that both use five criteria and can define robust, prefrail, and frail status as meeting 0, 1-2, and 3-5 criteria, respectively. A previous meta-analysis pooled 14 studies and showed that frail and prefrail individuals were at a significantly higher mortality risk than the robust (pooled HR=2.00, 95%CI=1.73-2.32; pooled HR=1.34, 95%CI=1.26-1.41, respectively),[27] which is in line with findings of the current study. It is not possible to compare magnitudes of the risk estimates because of the current study's wide confidence intervals resulting from the small number of the included studies.

This study is not without limitations. Partially because FRAIL scale was proposed relatively recently,[11,12] only a limited number of studies were included, especially for meta-analysis. This, in turn, hinders additional analyses, including sensitivity, subgroup, or meta-regression analyses. The whole process of systematic review was conducted by one investigator (GK), and some studies may have been missed.

Conclusion

This study demonstrated preliminary evidence that FRAIL scale is a promising tool that can effectively identify frailty/prefrailty status, as well as quantify frailty status in a graded manner in relation to mortality risk. Although its feasibility is of note, not many studies are yet using this relatively new tool. More studies are warranted regarding mortality and other health outcomes.

ACKNOWLEGMENT

Conflict of Interest

The author has no conflicts in the cover letter as well as in the manuscript, as noted above.

Author Contributions

Study concept and design: GK. Acquisition of data: GK. Analysis and interpretation of data: GK. Drafting the article: GK. Revising the article critically for important intellectual content: GK. Final approval of the version to be published: GK.

Sponsor's Role

None

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Table 1. Characteristics of the included studies examining FRAIL scale and mortality risk among community-dwelling middle-aged and older people.

Author/Year/Study	Location	Sample size	Female (%)	Age (range)	Follow-up period	Adjustment	Risk estimate HR/OR (95%CI)
Susanto 2018 ALSWH	Australia	8933	100%	-	16 years	age, BMI, education, income management, physical activity	0: ref 1: aHR=1.07 (0.83-1.37) 2: aHR=1.64 (1.19-2.27) 3: aHR=2.01 (1.29-8.23) 4-5: aHR=4.20 (2.14-8.23) 0-2: ref 3-5: aHR=2.01 (1.40-2.87)
Papachristou 2017 BRHS	UK	1615	0%	- (71-92)	3 years	age	0: ref 1-2: aHR=2.64 (1.11-6.28), p=0.0 3-5: aHR=7.60 (3.15-18.31), p<0.001
González 2016 MHAS	Mexico	4729	53.4%	≥60	2.4 years	age, gender, depressive symptoms, cognition, ADL	0: ref 1-2: aHR=1.25 (0.90-1.75), p=0.18 3-5: aHR=1.86 (1.21-2.88), p=0.005
Malmstrom 2014 AAH	US	779	-	(49-65)	9 years	age, gender	0: ref 1-2: aOR=1.45 (0.94-2.23), p=0.09 3-5: aOR=3.24 (1.62-6.47), p<0.001 AUC=0.57 (0.51-0.62)
Ravindrarajah 2013 EMAS	8 European countries*	2929	0%	59.9	4.3 years	age, center, smoking, partner status	0: ref 1-2: aHR=2.08 (1.47-2.95) 3-5: aHR=3.87 (2.25-6.66) AUC=0.66 (0.62-0.70)
Theou 2013 SHARE	11 European countries**	27527	54.8%	65.3 (50-104)	2 years 5 years	-	AUC=0.70 (0.67-0.72) AUC=0.67 (0.65-0.68)
Woo 2012	China	2000 2000	100% 0%	≥65	4 years	-	AUC=0.544 (0.492-0.597) AUC=0.543 (0.508-0.577)
Hyde 2010 HIMS	Australia	3616	0%	76.9 (70-88)	7 years	age, BMI, hypertension, dyslipidemia, diabetes, Charlson's index, smoking.	0:ref 1: aHR=1.38 (1.07-1.78), p=0.01 2: aHR=2.00 (1.53-2.63), p<0.001 3: aHR=2.27 (1.70-3.04), p<0.001 4-5: aHR=3.97 (2.89-5.45), p<0.001

AAH: African American Health
ALSWH: Australian Longitudinal Study on Women's Health
BRHS: British Regional Heart Study
EMAS: European Male Aging Study
HIMS: Health in Men Study
MHAS: Mexican Health and Aging Study
SHARE: Survey of Health, Ageing and Retirement in Europe
* Belgium, Estonia, Hungary, Italy, Poland, Spain, Sweden, UK.
** Italy, Belgium, Denkarm, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, Switzerland.

Figure 1. PRISMA Flow chart.

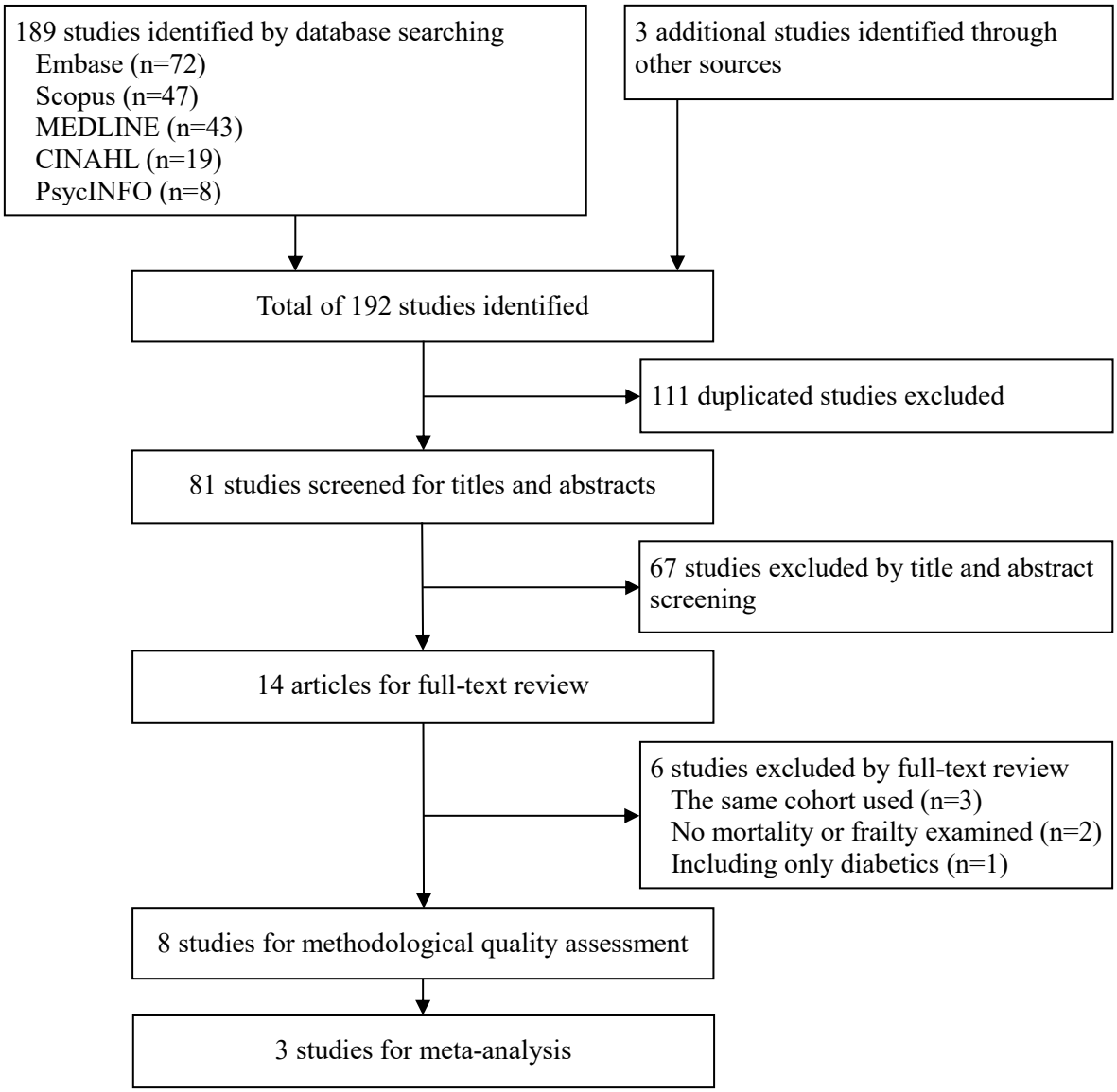

Figure 2. Forest plot of mortality risk according to frailty status based on FRAIL scale.