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Frailty as a predictor of adverse outcomes in hospitalized older adults: A systematic review and meta-analysis

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ABSTRACT

Frailty syndrome is prevalent among hospitalized older adults as are the occurrence of adverse outcomes. This systematic review and meta-analysis investigated whether frailty in older adults at hospital admission predicts adverse outcomes. Manual (ProQuest, conferences annals and references) and electronic searches (PUBMED, EMBASE, Web of Science, Lilacs, CINAHL, PsycINFO and Google Scholar) were performed. We included prospective studies of hospitalized older adults. Primary outcomes were functional decline at hospital discharge and mortality after discharge. Other data were considered secondary outcomes. Methodological quality was evaluated by the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Twenty-eight papers were included, corresponding to 19 cohorts (5 cohorts for functional decline and 16 for mortality), with moderate to good methodological quality. Being frail [RR: 1.32 (95%CI: 1.04; 1.67)] and pre-frail [RR: 1.51 (95%CI: 1.05; 2.17)] are risk factors for functional decline compared with being nonfrail. Frail individuals had a relative risk for in-hospital mortality and mortality in medium- and long-term compared to nonfrail (in-hospital RR: 8.20, medium RR: 9.49 and long RR: 7.94) and pre-frail (in-hospital RR: 3.19, medium RR: 3.31 and long RR: 3.72). The overall mortality risk in frail individuals is 3.49 and 2.14 times compared to nonfrail and pre-frail, respectively. Length of hospital stay was higher for frail older adults (13.5 days) compared with pre-frail (10.5 days) and nonfrail (8.3 days). Therefore, being frail at hospital admission is a risk factor for in-hospital mortality, long hospital stay, functional decline at hospital discharge, and mortality in the medium- and long-term.

1. Introduction

With the growth of the older population, there has been an increase in hospital admissions (Soong et al., 2015). During hospitalization, there are frequent occurrences of adverse outcomes, such as functional decline, mortality, delirium, falls (de Saint-Hubert et al., 2009d), pressure injuries, pneumonia and urinary infection (Bail et al., 2015). These outcomes may be due to the health problem that led to hospital admission or a consequence of hospitalization (Boyd et al., 2005). Hospitalized frail older adults are at increased risk of adverse outcomes compared with nonfrail individuals (Wou et al., 2013).

The prevalence of frailty in the hospital setting varies from 17.9% (Wou et al., 2013) to 40% (Joosten et al., 2014) using the criteria of the Cardiovascular Health Study (CHS). The frailty syndrome is characterized by a decline in functional reserve and resistance to stressors, leading to greater vulnerability to adverse outcomes (Fried et al., 2001). Hospitalized frail older adults are more likely to die after hospital discharge (Joosten et al., 2014; Kahlon et al., 2015) and to stay hospitalized for longer compared with nonfrail older adults (Evans et al., 2014).

For the older adult, hospital admission can be challenging due to the stress caused by their health status, bed restriction, the use of permanent catheters, polypharmacy and the interruption of their routine (Boyd et al., 2005). The costs of providing health care for the older adults continue to increase, which means it is important to reduce and control adverse outcomes in this population (Kawryshanker et al., 2014). However, there are difficulties in hospital practice, regarding adhering to clinical assessment models that identify predictors of adverse outcomes, due to the complexity of older adults care and barriers inherent to this setting (Hubbard et al., 2008; Kahlon et al., 2015).

Evaluations and interventions addressing older adults at risk of adverse outcomes have been shown to improve hospital care and

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reduce costs (Ellis et al., 2011). A systematic review on community-dwelling older adults verified that the frailty syndrome is a predictor of hospitalization, mortality, functional decline, falls and physical limitations (Vermeiren et al., 2016). However, these results can differ in relation to other populations in a state of greater vulnerability, such as hospitalized older adults (Vermeiren et al., 2016). Thus, it is important to investigate the impact of hospitalization on frail older adults, where these negative outcomes are even more frequent. This study used a systematic review and meta-analysis to analyze whether the frailty syndrome in hospitalized older adults is predictor of adverse outcomes. The results of this review could help promote early diagnosis of the frailty syndrome in the hospital setting, orientating prognoses, adequate behaviors toward frail older adults and the prevention of adverse outcomes.

2. Methods

2.1. Study design

This review was designed and reported following the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000), and registered on the PROSPERO website (CRD42018082742).

2.2. Search strategies

Electronic and manual searches were performed in December 2017 and updated in March 2019. The electronic search was performed in the following databases: PUBMED, EMBASE, Web of Science, Lilacs, CINAHL, PsycINFO and Google Scholar. The manual search was performed in the ProQuest (theses and dissertations), in the annals of International Congresses in the areas of Geriatrics/Gerontology/Frailty and in the lists of references of the eligible articles in the electronic search. Three thematic blocks of keywords were used: “Frailty”, “Prospective cohort study” and “Hospital”. In each block, the words were combined with the Boolean operator OR, and between the blocks, the operator AND (Appendix A.1). The search strategy was modified according to the specificities of each electronic database (Appendix A.2). No language limitation was applied; however, the date of publication was restricted to studies published from 2001 up to the present. This restriction is due to the emergence of the frailty phenotype in 2001 (Fried et al., 2001).

2.3. Eligibility criteria

The inclusion criteria for studies were: 1) prospective observational studies, 2) sample aged 60 years old or over, 3) therapeutic-hospital setting, and 4) assessment of the frailty syndrome upon hospital admission using a valid instrument (e.g. Fried criteria by the CHS, Edmonton Frail Scale, Clinical Frailty Scale-CFS, and others). The exclusion criteria eliminated studies that: 1) assessed frailty only using laboratory tests (e.g. albumin, creatinine and hemogram), 2) focused on patients with specific conditions (e.g. cancer, pre- and postoperative), 3) conducted in day hospital, 4) conducted in inpatient rehabilitation hospital, 5) conducted in the emergency room or intensive care unit, and 6) lacked the primary outcomes of this systematic review.

2.4. Study selection and data extraction

Selection of the studies was performed independently in two stages, by two researchers (A.I.L.C and S.B), and any discrepancies were resolved by a third researcher (N.A.R). Initially, the titles and abstracts of the studies were evaluated regarding the eligibility criteria, and near perfect agreement was obtained (Kappa = 0.850). During the second stage, the pre-selected studies were analyzed in their entirety (full text) to confirm their eligibility, with substantial agreement (Kappa = 0.798).

The studies selected were analyzed by two researchers (A.I.L.C and N.A.R) who used a form to extract data regarding the characteristics of the sample, study design (follow-up time), frailty assessment instrument, classification of frailty, and occurrence of adverse outcomes. The classification of frailty followed the groups proposed by the instruments used in the studies. Disagreements between the researchers concerning data extraction were resolved after discussion and consensus, with the assistance of a third researcher (S.B). When data was not available in the paper and/or doubts arose, we contacted authors by e-mail for clarification.

2.5. Outcomes

Functional decline at hospital discharge (evaluated by activities of daily living) and mortality after hospital discharge were used as primary outcome measures. Secondary outcome measures were all other adverse effects associated with frailty reported in the studies included in the review.

2.6. Methodological quality assessment

Two researchers (A.I.L.C and N.V) independently assessed each study for methodological quality according to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health, 2014). Discrepancies between the researchers were discussed and resolved with a third researcher (N.A.R). The instrument has 14 questions, each question is answered with an affirmative (yes), when the item evaluated is present with a one point score, or negative (no), when the item evaluated is absent, not determined (CD), not applicable (NA) or not reported (NR), with no punctuation, because it presents some kind of bias (National Institutes of Health, 2014). The instrument score ranges from zero to 14 points, the higher the score, the better the methodological quality of the study.

2.7. Synthesis and data analysis

Descriptive and critical analyzes were performed on the content of the studies. The meta-analysis was performed for the primary outcomes: functional decline at discharge and mortality after discharge in medium (5–6 months) and long-term (7–12 months). Meta-analysis was also performed for overall mortality (from the in-hospital to the very long follow-up), in-hospital mortality, and length of hospital stay. It was not possible to perform meta-analyzes for the primary outcomes short-term mortality (hospital stay up to 4 months) and very long-term mortality (over 2 years) due to lack of data, and for other secondary outcomes due to the heterogeneity of follow-up (falls and hospital readmissions) and insufficient data (cognitive alterations, pressure ulcer and discharge destination).

For meta-analyzes, comparison was made between frail and pre-frail and nonfrail older adults, and the nonfrail was also compared with pre-frail group. In studies that presented this classification of older adults (nonfrail, pre-frail and frail) the original categories were maintained. Studies that did not use this classification were reclassified. For the CFS the categories were reclassified as nonfrail, categories 1) very fit- 2) well- 3) managing well; pre-frail, category 4) vulnerable; and frail, categories 5) mildly frail- 6) moderately frail- 7) severely frail 8) very severely frail 9) terminally (Lewis et al., 2019). The Frailty Index (FI) was reclassified according to the cut-off points for nonfrail (FI < 0.35), pre-frail (FI: 0.35–0.45) and frail (FI ≥ 0.46) (Evans et al., 2014). For studies that used more than one instrument to classify frailty, we included the instrument most frequently used, i.e. that provided the largest data set.

For the outcomes of functional decline at discharge, overall mortality, mortality after hospitalization and in-hospital mortality, random effects models were applied, assuming heterogeneity between the studies, to calculate the relative risk (RR) and 95% confidence intervals

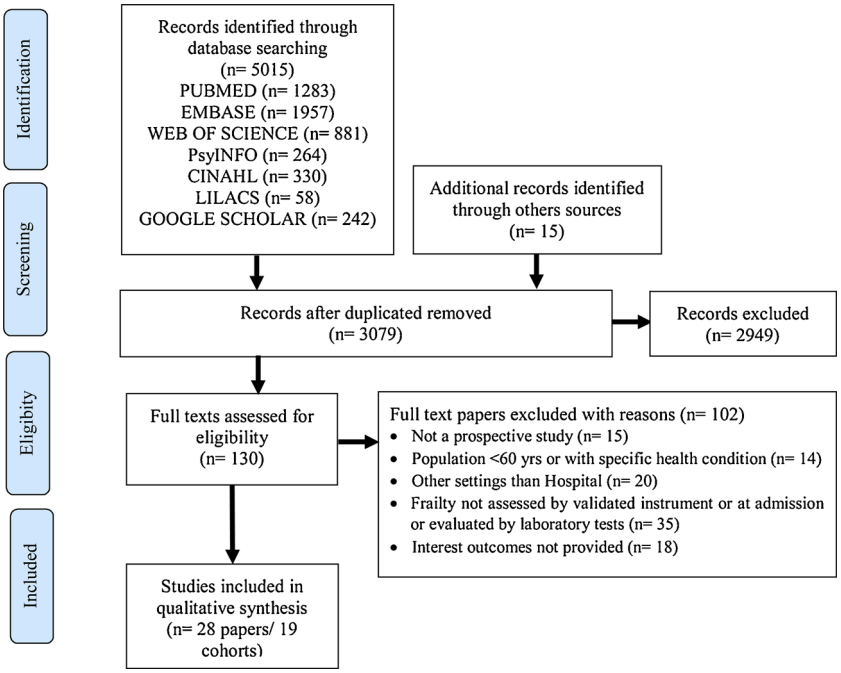

Fig. 1. Flowchart of the selection process of the studies.

(CI). For the meta-analysis of length of hospital stay, single-arm analysis was used, including studies that presented the mean and standard deviation (converted to standard error) of hospital stay in days, with subgroup analysis for the classification of frailty. The meta-analyses and forest plots were performed using RStudio® software.

3. Results

We found 5015 records using the electronic search strategies and 15 records by manual search. One hundred and thirty papers were selected for full reading (Fig. 1). Of these, 102 papers did not meet the inclusion criteria of this review (Appendix B).

The remaining 28 papers (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Carvalho et al., 2018; Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Evans et al., 2014; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Joosten et al., 2014; Pilotto et al., 2012; Ritt et al., 2016a,b, 2017, 2015) were included in the systematic review corresponding to 19 cohorts. Data from 14 cohorts each produced a single paper (Basile et al., 2019; Carvalho et al., 2018; Conroy and Dowsing, 2013; Dent and Perez-Zepeda, 2015; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Evans et al., 2014; García-Cruz and García-Peña, 2016; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Joosten et al., 2014; Pilotto et al., 2012). The other five cohorts originated more than one paper each, as follows: 1) Amblàs-Novellas et al (n = 2) (Amblàs-Novellas et al., 2017, 2018); 2) Chong et al (n = 2) (Chong et al., 2017, 2018); 3) Dent et al (n = 2) (Dent et al., 2013; Dent and Hoogendijk, 2014); 4) Hubbard et al (n = 4) (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017); and 5) Ritt et al (n = 4) (Ritt et al., 2016a,b, 2017, 2015). To avoid data overlapping, similar information presented in more than one paper referring to the same cohort was only used once.

3.1. Characteristics of the cohorts

Nineteen cohorts were included with a total number of older adults of 9655 with the sample varying from 80 (Dudzińska-Griszek et al., 2017) to 2033 (Pilotto et al., 2012) individuals. All the cohorts included individuals of both sexes, with majority of women (n = 5580). The mean age of the samples ranged from 70.5 (García-Cruz and García-Peña, 2016) to 89.4 (Chong et al., 2017, 2018) years old.

The cohorts came from general hospitals (n = 6) (Conroy and Dowsing, 2013; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Eeles et al., 2012; Pilotto et al., 2012; Ritt et al., 2016a,b, 2017, 2015), university hospitals (n = 7) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Carvalho et al., 2018; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Hao et al., 2019; Hernández-Luis et al., 2018), tertiary hospitals (n = 3) (Chong et al., 2017, 2018; Irina et al., 2018; Joosten et al., 2014), community hospital (n = 1) (Evans et al., 2014), specialty hospital (n = 1) (García-Cruz and García-Peña, 2016) and more than one type of hospital (secondary, tertiary, rural and university) (n = 1) (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017). The hospital units were: geriatric (n = 9) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dudzińska-Griszek et al., 2017; Hao et al., 2019; Joosten et al., 2014; Pilotto et al., 2012; Ritt et al., 2016a,b, 2017, 2015), general care (n = 2) (Hernández-Luis et al., 2018; Irina et al., 2018), acute care (n = 2) (Conroy and Dowsing, 2013; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) and mixed (geriatric and acute care) (n = 1) (Dent and Perez-Zepeda, 2015). Five studies (Carvalho et al., 2018; Dramé et al., 2011; Eeles et al., 2012; Evans et al., 2014; García-Cruz and García-Peña, 2016) did not specify the hospital unit in which data were collected.

Cohorts were followed in the short- (n = 8) (Carvalho et al., 2018; Conroy and Dowsing, 2013; Dent and Perez-Zepeda, 2015; Evans et al., 2014; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hernández-Luis et al., 2018; Pilotto et al., 2012), medium- (n = 4) (Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Joosten et al., 2014; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015), long- (n = 8) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Irina et al., 2018; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) and very long-term (n = 5) (Amblàs-Novellas

et al., 2017, 2018; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Hao et al., 2019; Hernández-Luis et al., 2018). The follow-up time after hospital discharge varied from 28 days (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) to 5 years (Eeles et al., 2012). Two cohorts were only followed during patient's hospital stay (Dent and Perez-Zepeda, 2015; García-Cruz and García-Peña, 2016) (Table 1).

3.2. Frailty evaluation

Assessment of the frailty syndrome was performed using 11 instruments. The instrument most used to identify frailty in the hospital setting was the FI (n = 11) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Eeles et al., 2012; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015). The total number of items that integrated the FI varied from 10 (Dent et al., 2013; Dent and Hoogendijk, 2014; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) to 56 (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) items. The difference in the number of items reflected the variation in the prevalence of frailty, which was 26% (FI 10 items) (Dent et al., 2013; Dent and Hoogendijk, 2014) to 92.5% (FI 25 items) (Amblàs-Novellas et al., 2017, 2018). Other instruments used in the assessment of frailty were the CHS (n = 7) (Carvalho et al., 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dudzińska-Griszek et al., 2017; García-Cruz and García-Peña, 2016; Hernández-Luis et al., 2018; Joosten et al., 2014; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015), the CFS (n = 4) (Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Hernández-Luis et al., 2018; Ritt et al., 2016a; b; Ritt et al., 2017, 2015), the Study of Osteoporotic Fracture (SOF) (n = 3) (Dent et al., 2013; Dent and Hoogendijk, 2014; Joosten et al., 2014; Pilotto et al., 2012) and the FRAIL scale (FRAIL) (n = 3) (Chong et al., 2017, 2018; Irina et al., 2018; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015). Several instruments were used only once: the Tilburg Frailty Indicator (Chong et al., 2017, 2018), Winograd's index (Dramé et al., 2011), Donini's index (Dramé et al., 2011), Schoevaerdt's index (Dramé et al., 2011), Multidimensional Prognostic Index (MPI) (Pilotto et al., 2012) and Canadian Study of Health and Aging rules-based frailty definition (CSHA-RBFD) (Ritt et al., 2016a). Twelve cohorts (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Carvalho et al., 2018; Conroy and Dowsing, 2013; Dent and Perez-Zepeda, 2015; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Evans et al., 2014; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Irina et al., 2018) were evaluated using a single instrument, while the remaining used two instruments (n = 2) (Hernández-Luis et al., 2018; Joosten et al., 2014), four instruments (n = 3) (Chong et al., 2017, 2018; Dramé et al., 2011; Pilotto et al., 2012), five instruments (n = 1) (Dent et al., 2013; Dent and Hoogendijk, 2014), and 11 instruments (n = 1) (Ritt et al., 2015).

The prevalence of frailty ranged from 25% (CSHA-RBFD) (Ritt et al., 2016a) to 97% (Donini's index) (Dramé et al., 2011), while pre-frailty

Table 1
Characteristics of the studies included in the systematic review.

Study	Characteristics of the sample (Local/ Mean age/ Sex)	Frailty assessment (Instrument/ Classification)	Time of Frailty assessment	Follow-up
Frailty Index (FI)				
Evans et al, 2014	Community Hospital n= 751 patients (84.0±5.5 yrs) ♀= 480 (60.7%) ♂= 271 (39.3%)	**Frailty Index Comprehensive Geriatric Assessment (FI-CGA):** 55 items - Nonfrail (<0.35): n= 205 (27.3%) - Pre-frail (0.35-0.45): n= 242 (32.2%) - Frail (0.46-0.55): n= 166 (22.1%) - Severely frail (>0.55): n= 138 (18.3%)	Within 48 hours of hospital admission	3 months
Amblàs-Novellas et al, 2017 **Amblàs-Novellas et al, 2018**	University Hospital- Acute Geriatric Ward n= 590 patients (86.3±5.6 yrs) ♀= 340 (57.5%) ♂= 250 (42.5%)	**Index Frailty- Valoración Integral Geriátrica (IF-VIG):** 25 items Ranking: 0 (absence of deficits) - 1 (presence of all deficits) - Nonfrail (<0.25): n= 44 (7.5%) - Frail (0.26-1): n= 546 (92.5%) IF-VIG: 0.43±0.15	Hospital admission	12 months 24 months
Dent and Perez-Zepeda, 2015	2 Hospitals (Internal Medicine wards and Geriatric unit) n= 254 patients (72.8±8.1 yrs) ♀= 135 (53%) ♂= 119 (47%)	**FI:** 40 items - Nonfrail (0–0.249): n= 104 (41%) - Frail (0.25–0.40): n= 91 (36%) - Severely frail (>0.40): n= 59 (23%) Mean (SD)= 0.31 (0.14)	Within 48 hours of hospital admission	Hospitalization period
Eeles et al, 2012	General Hospital n= 273 patients (82.3±7.5 yrs) ♀= 161 (58.9%) ♂= 112 (41.1%)	**FI:** 33 items - Nonfrail (<0.25): n= 162 (59.3%) - Frail (≥0.25): n= 111 (40.7%) Mean (SD): 0.24 (0.14)	Hospital admission	5 years after admission
Hubbard et al, 2015 **Hubbard et al, 2017** **Gordon et al, 2018** **Gregorevic et al, 2018**	11 Acute Care Hospitals (2 small secondary care centers, 2 rural hospitals, 4 metropolitan teaching facilities and 3 major tertiary referral centers). n= 1418 patients (81.0±6.8 yrs) ♀= 780 (55%) ♂= 638 (45%)	**FI Acute Care (FI-AC):** based on the INTER-RAI assessment system for acute care with 56 items - Nonfrail (<0.35): n= 884 (62.3%)* - Pre-frail (0.35-0.45): n= 304 (21.4%) - Frail (≥0.46): n= 230 (16.2%) Mean (SD), IQR= 0.32 (0.14), 0.22 to 0.41	Within 24 hours of hospital admission	28 days
Basile et al, 2019	University Hospital- Acute Geriatric Unit n= 156 patients (81.5±6.2 yrs) ♀= 93 (59.6%) ♂=63 (40.4%)	**FI:** 46 items > 0.25 = frail median FI at admission= 0.36 [IQR 0.31–0.40) - Admission FI median (IQR): 0.31 (0.19–0.44) - Discharge FI median (IQR): 0.29 (0.19–0.40) Statistically significant difference between the admission FI and the discharge FI (p = 0.04)	Within 24 hours of hospital admission	12 months
Hao et al, 2019	Center of Gerontology and Geriatrics n= 271 patients (81.1±6.6 yrs) ♀= 55 (20.3%) ♂=216 (79.7%)	**FI:** 36 items - Nonfrail (<0.25): n=138 (50.9%) - Frail (≥0.25): n= 133 (49.1%) Mean (SD): 0.26 (0.16) Median: 0.22	Within 48 hours of hospital admission	12 months 24 months 36 months
FI and others				

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Table 1 (*continued*)

Chong et al, 2017 **Chong et al, 2018**	Tertiary Hospital- Department of Geriatric Medicine n= 210 patients (89.4±4.6 yrs) ♀= 146 (69.5%) ♂= 64 (30.5%)	**FI:** 37 items - Nonfrail (<0.35): n= 59 (28.1%)* - Pre-frail (0.35-0.45): n= 31 (14.8%) - Frail (≥0.46): n= 120 (51.1%) **Frail Scale Status (FRAIL):** 5-point scale (range 0-5) - Nonfrail (0): n= 18 (8.6%)* - Pre-frail (1-2): n= 87 (41.4%) - Frail (≥3): n= 105 (50%) **Tilburg Frailty Indicator (TFI):** range 0-15 - Nonfrail (<5): n= 42 (20%) - Frail (≥5): n= 168 (80%) **Clinical Frailty Scale (CFS):** 7-point global assessment tool (range 1-7) - Nonfrail (1-3): n= 21 (10%)* - Pre-frail (4): n= 19 (9%) - Frail (5-7): n= 170 (81%)	Within 72 hours of hospital admission	6 months 12 months
Dent et al, 2014 **Dent and Hoogendijk, 2014**	Geriatric Evaluation and Management Unit n= 172 patients (85.2±6.4 yrs) ♀= 129 (72%) ♂= 43 (28%)	**FI of Cumulative Deficits (FI-CD):** 50 items - Nonfrail (<0.20): n= 11 (6%) - Pre-frail (0.20-0.45): n= 96 (56%) - Frail (>0.45): n= 65 (38%) **FI-CGA10:** 10 items (0-20 points) - Nonfrail: n= 18 (11%) - Pre-frail: n= 109 (63%) - Frail: n = 45 (26%) **Cardiovascular Health Study index (CHS):** range 0-5 components. - Nonfrail (0): n= 12 (7%) - Pre-frail (1-2 components): n= 64 (37%) - Frail (≥3 components): n= 96 (56%) **Study of Osteoporotic Fractures index (SOF index):** range 0-3 components. - Nonfrail (0): n= 6 (4%) - Pre-frail (1 component): n= 44 (26%) - Frail (≥2 components): n= 120 (70%) **FRAIL:** = 5-point scale (range 0-5). - Nonfrail: n= 3 (2%) - Pre-frail: n= 62 (36%) - Frail: n= 107 (62%)	Within 72 hours of hospital admission	6 months 12 months
Pilotto et al, 2012	20 Geriatric units n= 2033 patients (79.8±7.8 yrs) ♀= 1159 (57.0%) ♂= 874 (43.0%)	**FI-CD:** 32 items Mean (SD)= 10.3 (6.2) **FI-CGA10:** 10 items (0-20 points). - Mild (0-7): n= 1417 (69.7%) - Moderate (7-13): n= 593 (29.2%) - Severe frailty (>13): 23 (1.1%) **SOF index:** range 0-3 components. - Nonfrail (0): n= 686 (33.7%)	During the hospital stay	1 month 12 months

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ranged from 26% (SOF) (Dent et al., 2013; Dent and Hoogendijk, 2014) to 58.3% (CHS) (Joosten et al., 2014). Assessment of the frailty syndrome occurred within 24 h (n = 5) (Basile et al., 2019; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Irina et al., 2018; Joosten et al., 2014) up to one week (n = 1) (Dramé et al., 2011) after hospital admission. Five cohorts (Amblàs-Novellas et al., 2017, 2018; Conroy and Dowsing, 2013; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) had the assessment of frailty at hospital admission without specifying the exact time (Table 1).

3.3. Primary outcomes

Functional decline (difference between hospital admission and discharge) was assessed by in five cohorts (Carvalho et al., 2018; Chong et al., 2017, 2018; Dent and Perez-Zepeda, 2015; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017). The Katz index (n = 2) (Carvalho et al., 2018; Chong et al., 2017, 2018), the Barthel Scale (n = 1) (Dent and Perez-Zepeda, 2015), the Functional Independence Measure (FIM) (n = 1) (García-Cruz and García-Peña, 2016) and the daily life activities of interRAI-AC (n = 1) (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) were used for functional assessment. The functional decline in the general sample ranged from 7.1% (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) to 43.1% (Dent and Perez-Zepeda, 2015). For nonfrail older adults, functional decline varied from 0% (Carvalho et al., 2018) to 37% (Dent and Perez-Zepeda, 2015), while frail older adults from 8.5% (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) to 48% (Dent and Perez-Zepeda, 2015) (Table 2). Only one study reported a statistical association between functional decline in pre-frail older adults compared with nonfrail (Chong et al., 2017). Regarding prediction, only Hubbart et al (Hubbard et al., 2015, 2017) reported that an increment of 0.1 in the FI increased the chances of functional decline in older adults by 20% at hospital discharge.

Four (Carvalho et al., 2018; Chong et al., 2017, 2018; Dent and Perez-Zepeda, 2015; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) of the five studies (Carvalho et al., 2018; Chong et al., 2017, 2018; Dent and Perez-Zepeda, 2015; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) that assessed functional decline were included in the meta-analysis between nonfrailty and frailty, and three (Carvalho et al., 2018; Chong et al., 2017, 2018; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) studies for comparison with pre-frailty. The study that was excluded did not provide the number of older adults who showed functional decline by frailty classification (García-Cruz and García-Peña, 2016). Frail and pre-frail individuals show 1.32 times (95%CI: 1.04; 1.67; I^2 = 0%) and 1.51 times (95%CI: 1.05; 2.17; I^2 = 0%), respectively, more risk of developing functional decline during hospitalization compared with nonfrail individuals (Fig. 2). There was no difference on risk of functional decline between frail and pre-frail older adults (RR = 0.88; 95% CI: 0.62; 1.26; I^2 = 0%).

Mortality after hospital discharge was analyzed in 16 cohorts

Table 1 (*continued*)

		- Pre-frail (1 component): n= 804 (39.5%) - Frail (≥2 components): n= 543 (26.7%) **Multidimensional Prognostic Index (MPI):** 8 items (0-1 point): - Low risk (value <0.33): n= 851 (41.9%) - Moderate risk (0.34-0.66): n= 743 (36.5%) - Severe risk (>0.66): n= 439 (21.6%)		
Ritt et al, 2016a **Ritt et al, 2016b** **Ritt et al, 2017** **Ritt et al, 2015**	Geriatric wards n= 307 patients (89.0±4.2 yrs) ♀= 208 (67.7%) ♂= 99 (32.3%)	**CFS:** 9-point global assessment tool (range 1-9) - Very fit: n= 0 (0) - Well: n= 1 (0.3%) - Managing well: n= 18 (6.0%) - Vulnerable: n= 67 (21.8%) - Mildly frail: n= 76 (24.7%) - Moderately frail: n= 79 (25.7%) - Severely frail: n= 46 (15.0%) - Very severely frail n= 11 (3.5%) - Terminally ill: n= 9 (3.0%) **CHS modified:** 1-5 components - Nonfrail (0): n= 52 (16.9%) - Pre-frail (1–2 components): n= 122 (39.8%) - Frail (≥3 components): n= 133 (43.3%) **FI:** 50 items from 0 to 1 point. - FI (0-0.200): n= 29 (9.5%) - FI (0.201-0.400): n= 133 (43.6%) - FI (0.401-0.700): n= 143 (46.9%) **FI:** 41 items from 0 to 1 point. - FI 0-0.200: n= 56 (18.3%) - FI 0.200-0.400: n= 144 (47.2%) - FI 0.400-0.700: n= 105 (34.5%) **FI-CGA10:** 10 items - Nonfrail (<0.25): n= 64 (20.8%) - Frail (≥0.25): n= 243 (79.2%) **CSHA rules-based frailty definition:** 4-point scale (level 0 -fit- to level 3 -frail-) - Level 0 (fit): n= 93 (30.2%) - Level 1: n= 3 (0.9%) - Level 2: n= 132 (42.9%) - Level 3 (frail): n= 77 (25%) **FRAIL:** 5-point scale (range 0-5). - Nonfrail (0): n= 58 (19.0%) - Pre-frail (1-2 points): n= 139 (45.5%) - Frail (≥3): n= 108 (35.4%) **The fourteen-item FI-CGA:** 10 items +4 items comorbidity - Nonfrail (<0.25): n= 78 (25.4%) - Frail (≥0.25): n= 229 (74.6%) **FI-CGA-MIHD:** 50 items from 0 to 1 point.	Hospital admission	6 months 12 months

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(Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Joosten et al., 2014; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015), based on short- (n = 5) (Conroy and Dowsing, 2013; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hernández-Luis et al., 2018; Pilotto et al., 2012), medium- (n = 3) (Chong et al., 2017, 2018; Joosten et al., 2014; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) long- (n = 8) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Irina et al., 2018; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) and very long-term (n = 5) (Amblàs-Novellas et al., 2017, 2018; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Hao et al., 2019; Hernández-Luis et al., 2018) follow-up periods (Table 2).

In the short-term, the mortality rate ranged from 3.5% (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) in one month to 32.1% (Conroy and Dowsing, 2013) in three months. Five cohorts (Conroy and Dowsing, 2013; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hernández-Luis et al., 2018; Pilotto et al., 2012) showed that frailty predicted mortality in the short-term. In one month, the risk of death in the same sample ranged from 1.1-fold (FI—CD) to 2.4-fold higher (SOF) among frail older adults (Pilotto et al., 2012). For severely frail older adults, the risk varied from 4.5-fold (FI-CGA) to 7.7-fold (MPI) (Pilotto et al., 2012). For follow-up of 100 days, the chances mortality for frail older adults ranged from 2.6-fold (CFS) to 4.1-fold higher (CHS) in the same sample (Hernández-Luis et al., 2018). We were unable to perform a meta-analysis for this follow-up period, since of the five cohorts (Conroy and Dowsing, 2013; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hernández-Luis et al., 2018; Pilotto et al., 2012) in which this outcome was evaluated, two (Evans et al., 2014; Pilotto et al., 2012) did not present the number of deaths according to frailty classifications and one (Hernández-Luis et al., 2018) presented the number of deaths for nonfrail and pre-frail older adults as a single group.

In the medium-term (6 months), the overall mortality rate was 13.2% (Joosten et al., 2014) to 23% (Chong et al., 2017, 2018). Among nonfrail older adults, the mortality rate ranged from 0% [SOF (Joosten et al., 2014), FRAIL (Chong et al., 2017, 2018) CFS (Chong et al., 2017, 2018; Ritt et al., 2016a,b, 2015)] to 7.1% [TFI(Chong et al., 2017, 2018)], for pre-frail from 1.5% [CFS (Ritt et al., 2016a,b, 2015)] to 12% [SOF (Joosten et al., 2014)] and for frail older adults from 21% [CFS (Ritt et al., 2016a,b, 2015)] to 32.4% [FRAIL (Chong et al., 2017, 2018)]. The three cohorts (Chong et al., 2017, 2018; Joosten et al., 2014; Ritt et al., 2016a) in which this outcome was evaluated reported a relation with frailty, in which the chances of death for frail older adults increased 2.1-fold [TFI (Chong et al., 2017, 2018)] to 7.3-fold [CHS (Joosten et al., 2014)]. All the cohorts were included in the meta-analysis (Chong et al., 2017, 2018; Joosten et al., 2014; Ritt et al., 2016a), which showed that frailty increases the risk of death in the

Table 1 (*continued*)

		- Nonfrail (<0.25): n= 67 (21.8%) - Frail (≥0.25): n= 240 (78.2%)		
Cardiovascular Health Study index (CHS)				
Dudzińska-Griszek et a, 2017	Department of Geriatrics at University Hospital n= 80 patients (78.6±7.0 yrs) ♀= 55 (68.8%) ♂= 25 (31.2%)	**CHS:** range 0-5 components. - Nonfrail (0): n= 18 (22.5%) - Pre-frail (1-2 components): n= 30 (37.5%) - Frail (≥3 components): n= 32 (40%)	Hospital admission	24 months
Garcia-Cruz and Garcia-Pena, 2016	Specialty Hospital n= 133 patients (70.5 yrs) ♀= 70 (52.6%) ♂= 63 (47.4%)	**CHS:** range 0-5 components. - Nonfrail (0-2 components): n= 69 (51.9%) - Frail (≥3 components): n= 64 (48.1%)	Within the first 24 hours of hospital admission	Hospitalization period
Carvalho et al, 2018	University Hospital n= 99 patients (74.0±7.35 yrs) ♀= 40 (40.4%) ♂=59 (59.6%)	**CHS:** range 0-5 components. - Nonfrail (0): n= 8 (8.1%) - Pre-frail (1-2 components): n= 53 (53.5%) - Frail (≥3 components): n= 38 (38.4%)	Within 72 hours of hospital admission	30 days
CHS and others				
Hernandez-Luis et al, 2018	Internal Medicine Department at University Hospital n= 298 patients (76.6 yrs) ♀= 146 (49%) ♂= 152 (51%)	**CHS:** range 0-5 components. - Nonfrail- Pre-frail (0-2 components): n= 100 (33.6%) - Frail (≥3 components): n= 198 (66.4%) **CFS:** range 1-7 - Nonfrail- Mildly frail (1-5): n= 213 (71.4%) - Frail (6-7): n= 84 (28.6%)	2 days after hospital admission	Short-term 100 days Long-term 989 days
Joosten et al, 2014	Acute Geriatric Ward of a Tertiary Care Hospital n= 220 patients (83.5±5.1 yrs) ♀= 126 (57.2%) ♂= 94 (42.8%)	**CHS:** range 0-5 components. n= 220 patients - Nonfrail (0): n= 3 (1.5%) - Pre-frail (1-2 components): n= 129 (58.3%) - Frail (≥3 components): n= 88 (40%) **SOF index:** range 0-3 components. n= 204 patients - Nonfrail (0): n= 32 (16%) - Pre-frail (1 component): n= 104 (51.5%) - Frail (≥2 components): n= 66 (32.5%)	24 hours after hospital admission	6 months
Clinical Frailty Scale (CFS)				
Conroy and Dowsing, 2013	Acute Medical Units n= 905 patients (82.3 yrs) ♀= 525 (57.6%) ♂= 380 (42.4%)	**CFS:** range 1-7 - Nonfrail (1-3): n= 274 (30.4%)* - Pre-frail (4): n= 178 (19.6%) - Frail (5-7): n= 453 (50%)	Hospital admission	1 month 3 months
Others index				
Drame et al, 2011	9 University Hospitals n= 1306 patients (85.0±5.9 yrs) ♀= 849 (64.7%) ♂= 457 (35.3%)	**Winograd's index (n = 1098)** - Nonfrail: n= 14 (1.3 %) - Moderately frail: n= 929 (84.6 %) - Severely frail: n= 155 (14.1 %) **Donini's index (n = 1269)** - Nonfrail: n= 8 (0.6 %) - Moderately frail: n= 366 (28.8 %) - Severely frail: n= 895 (70.6%)	Within the first week of hospital stay	12 months
		Rockwood's index (n = 1293) - Nonfrail: n= 50 (3.9%) - Moderately frail: n= 1238 (95.7 %) - Severely frail: n= 5 (0.4%) **Schoevaerdt's index (n = 1228)** - Nonfrail: n= 122 (9.9%) - Moderately frail: n= 280 (22.8%) - Severely frail: n= 826 (67.3 %)		
Irina et al, 2018	Internal Medicine Department Tertiary Hospital n= 179 patients (72 yrs) ♀= 83 (46.4%) ♂= 96 (53.6%)	**FRAIL:** 5-point scale (range 0-5) - Nonfrail (0): n= 30 (16,7%) - Pre-frail (1-2): n= 77 (43,0%) - Frail (≥3): n= 72 (40,3%)	Within the first 24 hours of hospital admission	456 days

*Data provided by the authors via email.

CFS: Clinical Frailty Scale; CHS: Cardiovascular Health Study index CHSA: Canadian Study of Health and Aging rules based frailty definition; FI: Frailty Index; FI-CD: Frailty Index of Accumulative Deficits; FI-CGA: Frailty Index Comprehensive Geriatric Assessment; FI-CGA10D: Frailty Index Comprehensive Geriatric Assessment ten domains; FI-CGA10D + CM: Frailty Index Comprehensive Geriatric Assessment ten domains + co-morbidity; FI-CGA-MIHD: Frailty Index Comprehensive Geriatric Assessment multiple individual health deficits; FI-VIG: Index Frailty- Valoración Integral Geriátrica; FRAIL: Frail Scale Status; IQR: InterQuartile range; MPI: Multidimensional Prognostic Index; SOF: Study of Osteoporotic Fractures index; SD: standard deviation; TFI: Tilburg Frailty Indicator.

medium-term by 9.49 and 3.31 times, compared with nonfrail and pre-frail, respectively (Fig. 3). Analysis between nonfrail and pre-frail older adults indicated no difference between them in relation to risk of medium-term mortality (RR = 3.08; 95% CI: 0.54; 17.65; I^2 = 0%).

In the long-term, the mortality rate ranged from 11.1% (Irina et al., 2018) to 46.4% (Amblàs-Novellas et al., 2017, 2018). The mortality rate in 12 months of nonfrail older adults ranged from 0% [CFS (Chong et al., 2017, 2018; Ritt et al., 2016a, 2016b; Ritt et al., 2017); FI (Amblàs-Novellas et al., 2017, 2018); FRAIL (Irina et al., 2018)] to 11.9% [TFI (Chong et al., 2017, 2018)], among pre-frail from 1.5% [CFS (Ritt et al., 2016a, 2016b; Ritt et al., 2017)] to 24.2% [(CSHA-RBFD (Ritt et al., 2016a)], and among frail from 18% [FRAIL (Irina et al., 2018)] to 42.5% [FI (Chong et al., 2017, 2018)]. The eight cohorts (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Irina et al., 2018; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) in which this outcome was evaluated described an association with frailty, and in five cohorts frailty predicted mortality (Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Pilotto et al., 2012; Ritt et al., 2017), such that the chance of death in one year increase 2.4-fold (TFI) to 5.7-fold (CFS) in the same sample (Chong et al., 2017, 2018). Four (Amblàs-Novellas et al., 2017, 2018; Chong et al., 2017, 2018; Dramé et al., 2011; Ritt et al., 2016a, 2016b; Ritt et al., 2017) of the eight

cohorts (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Irina et al., 2018; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) were included in the meta-analysis to determine the differences between nonfrail and frail older adults. Two cohorts (Dent et al., 2013; Dent and Hoogendijk, 2014; Basile et al., 2019) were excluded for not providing data by frailty classification group, other (Pilotto et al., 2012) didn't report the number of individuals who suffered this event and one cohort (Irina et al., 2018) showed the long-term mortality data with in-hospital mortality. For analysis of pre-frail older adults, apart from the four cohorts (Dent et al., 2013; Dent and Hoogendijk, 2014; Basile et al., 2019; Pilotto et al., 2012; Irina et al., 2018) already excluded, one more cohort (Dramé et al., 2011) was removed from the analysis for not presenting data for this category. Frailty increases the risk of death in the long-term by 7.95 and 3.73 times, compared with nonfrail and pre-frail, respectively. And pre-frail individuals have a risk of 3.65 times of mortality in long-term compared to nonfrail (Fig. 3).

In very long-term follow-up, the mortality rates ranged from 12.5% (Dudzińska-Griszek et al., 2017) to 57.3%(Amblàs-Novellas et al., 2017, 2018) for 24 months, with the rates for nonfrail older adults ranging from 32.9% [FI (Amblàs-Novellas et al., 2017, 2018)] to 40% [CHS (Dudzińska-Griszek et al., 2017)] and frail from 60% [CHS (Dudzińska-Griszek et al., 2017)] to 63.7% [FI (Amblàs-Novellas et al., 2017, 2018)]. Four (Amblàs-Novellas et al., 2017, 2018; Eeles et al., 2012; Hao et al., 2019; Hernández-Luis et al., 2018) of the five cohorts (Amblàs-Novellas et al., 2017, 2018; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Hao et al., 2019; Hernández-Luis et al., 2018) in

Table 2
Results of individual studies regarding frailty syndrome as a predictor of functional decline at discharge and mortality at follow-up (primary outcomes).

Functional Decline				
Chong et al, 2017‡; Chong et al, 2018	**Dent and Perez-Zepeda, 2015**	**Garcia-Cruz and Garcia-Pena, 2016**	**Hubbart et al, 2015; Hubbard et al, 2017‡; Gordon et al, 2018; Gregorevic et al, 2018**	**Carvalho et al, 2018**
Katz Index decline: n= 58/ 202 (27.6%) **FI** - Nonfrail: n= 15/ 59 (25.4%) * - Pre-frail: n= 12/ 31 (38.7%) - Frail: n= 39/ 120 (32.5%) **FRAIL** - Nonfrail: n= 2/ 18 (11.1%) * - Pre-frail: n= 33/ 87 (37.9%) - Frail: n= 31/ 105 (29.5%) **TFI** - Nonfrail: n= 10/ 42 (23.8%) - Frail: n= 56/ 168 (30%) **CFS** - Nonfrail: n= 5/ 21 (22.5%) * - Pre-frail: n= 32/ 87 (36.7%) - Frail: n= 57/ 170 (33.5%) **Subgroup analysis (Non-frail - prefrail)** **FRAIL** - Nonfrail: n= 2/ 18 (11.1%) - Pre-frail: n= 32/ 87 (37.2%) No difference for FI or CFS. TFI was not evaluated as there is no cut-off score for pre-frail status.	**Barthel Scale decline (score drop ≥ 10% from admission):** n= 100/ 232 (43.1%) - Nonfrail: n= 37/ 100 (37%) - Frail: n= 40/ 84 (48%) - Severely frail: n= 23/ 48 (48%) AUC (95%CI)= 0.60 (0.53-0.67) Nonfrail vs frail/severely frail (<0.25 vs ≥0.25): Se= 63.0% Sp= 36.4% PPV= 45.0% NPV= 54.3% Non-frail/frail vs severely frail (≤0.4 vs >0.4): Se= 23.0% Sp= 81.1% PPV= 47.9% NPV= 58.2%	**Difference in Functional Independence Measure between baseline-discharge in Mean (SD)** - Nonfrail: n= -8.06 (9.64) (95%CI: -10.38to -5.74) - Frail: n= -21.18 (15.19) (95%CI: -24.97 to -17.38) Difference between groups: - 14.37 (14.19) (95%CI: -16.80 to -11.94) Simple linear regression analysis: - 23.56 (95%CI: -29.99 to -18.15) †Multiple linear regression analysis: - 17.27 (95%CI: -23.27 to -11.28) †Adjusted for all variables	**Discharge interRAI-AC ADL score on discharge compared to admission:** n= 96/ 1418 (7.1%) - Nonfrail: n= 53/ 868 (6.1%)* - Pre-frail: n= 26/ 289 (8.9%) - Frail: n= 17/ 198 (8.5%) **Associated with 0.1 FI increments:** †Adj OR (95%CI)= 1.20 (1.04–1.40) AUC (95%CI)= 0.58 (0.53–0.64) **FI>0.40:** Se= 28/ 96 (29%) Sp= 942/ 1.259 (75%) PPV= 28/ 345 (8%) NPV= 942/ 1.010 (93%) †Adjusted for age and sex	**Katz Index decline:** n= 18/ 99 (18.1%)* - Nonfrail: n= 0/ 8 (0%)* - Pre-frail: n= 11/ 53 (20.7%) - Frail: n= 7/ 38 (18.4%) **Bivariate Analysis (Before admission at end of follow-up)** -Pre-frail+Nonfrail: RR (95%CI)= 0.87 (0.81-1.00) -Frail: RR (95%CI)= 2.27 (1.30-3.97)

Mortality short-term				
Hubbart et al, 2015; Hubbard et al, 2017‡; Gordon et al, 2018‡; Gregorevic et al, 2018	**Pilotto et al, 2012**	**Evans et al, 2014**	**Conroy and Dowsing, 2013**	**Hernandez-Luis et al, 2018**
28 days post discharge: n= 47/ 1418 (3.5%) - Nonfrail: n= 15/ 863 (1.7%) * - Pre-frail: n= 14/ 288 (4.9%) - Frail: n= 18/ 194 (9.3%) **Associated with 0.1 FI increments:** †Adj OR (95%CI)= 1.66 (1.35-2.03) AUC (95%CI) = 0.71 (0.64-0.78) †Adjusted for age and sex **FI>0.40:** Se= 26/ 47 (67%) Sp= 986/ 1.298 (76%) PPV= 26/ 338 (8%) NPV= 986/ 1.007 (98%) †Adj HR (95%CI)= 1.83 (1.59-2.12) FI mean: 0.41 (0.18-0.69) OR (95%CI)= 1.66 (1.36-2.4) †Adjusted for age	**1 month:** n= 165/ 1927 (8.6%) **SOF** - Nonfrail: HR (95%CI)= 1.00 - Pre-frail: HR (95%CI)= 1.87 (1.27-2.76) - Frail HR (95%CI)= 2.42 (1.16-5.04) †Adj AUC (95%CI)= 0.63 (0.64-0.73) **FI-CD** HR (95%CI)= 1.13 (1.10-1.16) †Adj AUC (95%CI)= 0.73 (0.69-0.78) **FI-CGA** - Mild: HR (95%CI)= 1.00 - Moderate: HR (95%CI)= 2.92 (1.84–4.64) - Severe frailty: HR (95%CI)= 4.54 (1.68–12.24) †Adj AUC (95%CI)= 0.72 (0.68-0.77) **MPI** - Low risk: HR (95%CI)= 1.00 - Moderate risk: HR (95%CI)= 2.05 (1.40–3.00) - Severe risk: HR (95%CI)= 7.70 (5.73–10.34) †Adj AUC (95%CI) = 0.72 (0.69-0.75) †Adjusted for age and sex	**1 month**: n= 41/ 751 (5.4%) **3 months:** n= 44/ 751 (5.8%) **4 months:** n= 12/ 751 (1.59%) Risk of dying increased with each 0.01 increment in the FI- CGA: †Adj HR (95% CI)= 1.05 (1.04-1.07) †Adjusted for age and sex	**3 months:** n= 210/ 654 (32.1%) CFS and mortality risk: - Nonfrail: n= 55/ 274 (20%) * - Pre-frail: n= 39/ 178 (21.9%) - Frail: n= 116/ 453 (25.6%) †Adj OR (95%CI)= 1.4 (1.3-1.5) †Adjusted for age and sex	**100 days**: n= 46/ 298 (15.1%) **CHS** - Nonfrail-Pre-frail: n= 17/ 198 (8.6%) - Frail: n= 28/ 100 (28.0%) OR (95%CI)= 4.14 (2.14–9.02) **CFS** - Nonfrail-Mildly frail: n= 24/ 213 (11.3%) - Frail: n= 21/ 84 (25%) OR (95%CI)= 2.63 (1.37-5.04)

Mortality medium-term		
Chong et al, 2017; Chong et al, 2018‡	**Ritt et al, 2016a; Ritt et al, 2016b‡; Ritt et al, 2017; Ritt et al, 2015‡**	**Joosten et al, 2014**
6 months: n= 42/ 210 (23%) **FI** - Nonfrail: n= 1/ 59 (1.6%) *	**6 months:** n= 47/307 (15.3 %) **CFS-9** - Nonfrail (1-3): n= 0/ 19 (0%)	**6 months** **CHS:** n= 30/ 204 (14.7%) - Nonfrail + Pre-frail: n= 7/ 127 (5.5%)

(*continued on next page*)

Table 2 (*continued*)

- Pre-frail: n= 3/ 31 (9.6%) - Frail: n= 38/ 120 (31.6%) †Adj OR (95%CI): 3.68 (2.17-6.24) AUC (95%CI): 0.77 (0.70-0.84)	- Pre-frail (4): n= 1/ 67 (1.4%) - Frail (5-7): n= 29/ 199 (14.5%) AUC (95%CI)= 0.86 (0.80-0.92)	- Frail: n= 23/ 77 (30%) OR (95%CI)= 7.32 (2.95-18) †Adj OR (95%CI)= 4.68 (1.7-12.8)
FRAIL - Nonfrail: n= 0/ 18 (0%) * - Pre-frail: n= 8/ 87 (9.1%) - Frail: n= 34/ 105 (32.4%) †Adj OR (95%CI): 3.25 (1.97-5.36) AUC (95%CI): 0.75 (0.67-0.82)	**CHS modified** - Nonfrail: n= 1/ 52 (1.9%) - Pre-frail: n= 6/ 122 (4.9%) - Frail: n= 40/ 133 (30.1%) AUC (95%CI)= 0.75 (0.68-0.82)	**SOF index:** n= 25/ 189(13.2%) - Nonfrail n= 0/ 31 (0%) - Pre-frail: n= 12/ 99 (12%) - Frail: n= 13/ 59 (22%) OR (95%CI)= 2.75 (1.17-6.5) †Adj OR (95%CI)= 1.97 (0.75-5.2) †Adjusted for age, sex and others
TFI - Nonfrail: n= 3/ 42 (7.1%) - Frail: n= 39/ 168 (23.2%) †Adj OR (95%CI): 2.18 (1.43-3.32) AUC (95%CI): 0.67 (0.58-0.76)	**FI-CGA-10D** AUC (95%CI)= 0.76 (0.69-0.83)	
CFS - Nonfrail: n= 0/ 21 (0%) * - Pre-frail: n= 1/ 19 (5.1%) - Frail: n= 41/ 170 (24.1%) †Adj OR (95%CI): 4.37 (2.44-7.83) AUC (95%CI): 0.78 (0.70-0.85)	**FI-CGA-10D+CM** AUC (95%CI)= 0.83 (0.77-0.89)	
†Adjusted for age, sex and severity of Illness	**FI-CGA-MIHD** AUC (95%CI)= 0.83 (0.76-0.90)	

Mortality long-term

Chong et al, 2017; Chong et al, 2018‡	Ritt et al, 2016a‡; Ritt et al, 2016b; Ritt et al, 2017‡; Ritt et al, 2015	Amblàs-Novellas et al, 2017‡ Amblàs-Novellas et al, 2018‡	Dent et al, 2014; Dent and Hoogendijk 2014‡	Drame et al, 2011	Pilotto et al., 2012	Basile et al, 2019	Irina et al, 2018
12 months: n= 56/ 210 (30.6%) **FI** - Nonfrail: n= 3/ 59 (5%) * - Pre-frail: n= 3/ 31 (9.6%) - Frail: n= 51/ 120 (42.5%) †Adj OR (95%CI): 4.32 (2.60-7.20) AUC (95%CI): 0.79 (0.72-0.85) **FRAIL** - Nonfrail: n= 1/ 18 (5.5%) * - Pre-Frail: n= 13/87 (14.9%) - Frail: n= 43/ 105 (41.0%) †Adj OR (95%CI): 2.97 (1.90-4.65) AUC (95%CI): 0.73 (0.66-0.80) **TFI** - Nonfrail: n= 5/ 42 (11.9%) - Frail: n= 52/ 168 (31.0%) †Adj OR (95%CI): 2.40 (1.61-3.56) AUC (95%CI): 0.68 (0.61-0.76) **CFS** - Nonfrail: n= 0/ 21 (0%) * - Pre-frail: n= 1/ 19 (5.2%) - Frail: n= 56/ 170 (32.9%) †Adj OR (95%CI): 5.78 (3.19-10.48) AUC (95%CI): 0.79	**12 months:** n= 62/ 305 (20.3%) **CFS-9** - Nonfrail: n= 0/ 19 (0%) - Pre-frail: n= 1/ 67 (1.4%) - Frail (5-7): n= 29/ 199 (14.5%) AUC (95%CI)= 0.85 (0.80-0.90) **CFS-7** - Nonfrail: n= 0/ 19 (0%) - Pre-frail: n= 1/ 67 (0%) - Frail: n= 61/ 199 (30.6%) HR (95%CI)= 3.78 (2.68-5.35) AUC (95% CI)= 0.84 (0.78-0.89) **CHS modified** - Nonfrail: n= 2/ 52 (3.8%) - Pre-frail: n= 12/ 120 (10%) - Frail: n= 48/ 133 (36.1%) AUC (95%CI)= 0.72 (0.65–0.79) **50-item FI** - FI (0.001–0.100): n= 0/ 3 (0%) - FI (0.101–0.200): n= 0/ 26 (0%) - FI (0.201–0.300): n= 7/ 59 (11.9%) - FI (0.301–0.400): n= 6/ 74(8.1%) - FI (0.401–0.500): n= 11/ 72(15.3%) - FI (0.501–0.600):	**12 months:** n= 274/ 590 (46.7%) - FI-VIG:0-0.15: n= 0/ 22 (0%) - FI-VIG: 0.16-0.25: n= 1/73 (1.4%) - FI-VIG:0.26-0.35: n= 7/ 61 (11.4%) - FI-VIG:0.36-0.45: n= 48/161 (45.3%) - FI-VIG:0.46-0.55: n= 73/123 (70.7%) - FI-VIG:0.56-0.65: n= 45/120 (97.5%) - FI-VIG:0.66-1: n= 30/ 30 (100%) Correlation mortality and IF - VIG 12 months: r= 0.83 AUC (95%CI)= 0.90 (0.88-0.92)	**12 months:** n= 40/ 172 (23.2%) †Adj HR (95%CI)= 3.16(1.36–7.33) †Adjusted for age, sex and Charlson's Comorbity Index	**12 months:** n=445/ 1306 (34.1%) **Winograd** - Nonfrail: n= 1/ 14 (7%) - Moderately frail: n= 278/ 929 (30%) - Severely frail: n= 73/155 (47%) **Rockwood** - Nonfrail: n= 4/ 50 (8%) - Moderately frail: n = 436/ 1238 (35%)- Severely frail: n= 3/ 5 (60%) **Donini** - Nonfrail: n= 3/ 8(38%) - Moderately frail: n= 106/366 (29%) - Severely frail: n= 322/895 (36%) **Schoevaerdts** - Nonfrail: n= 10/ 122 (8%) - Moderately frail: n= 61/ 280 (22%) - Severely frail: n= 344/ 826 (42%)	**12 months:** n= 430/ 192 (24.9%) **SOF** - Nonfrail: HR= 1.00 - Pre-frail: HR (95%CI)= 1.67 (1.29-2.17) - Frail: HR (95%CI)= 2.45 (1.44–4.18) AUC (95%CI)= 0.69(0.67-0.72) **FI-CD** HR (95%CI)= 1.11 (1.09–1.13) AUC (95%CI)= 0.72 (0.70-0.76) **FI-CGA** - Mild: HR (95%CI)= 1.00 - Moderate: HR (95%CI)= 2.93 (2.25 3.83) - Severe frailty: HR (95%CI)= 4.18 (2.10–8.34) AUC (95%CI)= 0.72 (0.70-0.75) **MPI** - Low risk: HR (95%CI)= 1.00 - Moderate risk: HR (95%CI)= 2.00 (1.64- 2.45) - Severe risk: HR (95%CI)= 5.70 (4.49–7.22) AUC (95%CI)= 0.75 (0.72-0.78)	**12 months:** n= 45/ 149 (30.2%) - FI admission: †Adj OR (95%CI)= 5.5 (2.4–12.7) - FI discharge: †Adj OR (95%CI)= 3.7 (1.3–10.5) AUC (95%CI)= 0.827 (0.750–0.905) - Δ difference admission-discharge FI †Adj OR (95%CI)= 1.035 (1.006-1065) †Adjusted for age and sex	**456 days:** n= 20/ 179 (11.1%) - Nonfrail: n= 0/ 30 (0%)* - Pre-frail: n= 7/ 77 (9%) - Frail: n= 13/ 72 (18%) 456 days (included Hospital leght of hospital stay)

(*continued on next page*)

which this outcome was analyzed revealed a relation with frailty, in which the risk of death increased 2.0-fold (CHS) to 2.4-fold (CFS) in the same sample (Hernández-Luis et al., 2018) (Table 2). We were unable to perform a meta-analysis for this outcome, since three cohorts (Eeles et al., 2012; Hao et al., 2019; Hernández-Luis et al., 2018) presented distinct survival time data and follow-up periods, and another cohort (Dudzińska-Griszek et al., 2017) had the number of deaths for nonfrail and pre-frail adults as a single group.

The overall mortality risk (from the in-hospital to the very long-term follow-up) in frail individuals is 3.49 (95%CI: 2.09; 5.82; I^2 = 83%) and 2.14 (95%CI: 1.49; 3.05; I^2 = 76%) times, compared with nonfrail and pre-frail, respectively. Pre-frail individuals have 2.08 times (95%CI: 1.60; 2.68; I^2 = 12%) as high the risk of overall mortality compared to nonfrail (Appendix C).

3.4. Secondary outcomes

Seven additional adverse outcomes were identified: in-hospital mortality, cognitive alterations (cognitive decline and delirium), falls, pressure ulcer, length of hospital stay, hospital discharge, and hospital readmissions (Appendix D).

In-hospital mortality was analyzed in four cohorts (Basile et al., 2019; Chong et al., 2017, 2018; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014) and rates range from 3.9% (Chong et al., 2017, 2018) to 10.9% (Basile et al., 2019) in the sample. All the cohorts had a significant association between this outcome and frailty. One cohort (Chong et al., 2017, 2018) in which four instruments were used to evaluate frailty (FI, FRAIL, TFI and CFS), showed that frailty predicted this outcome through two instruments (FRAIL and CFS). The chances of in-hospital mortality for frail older

Table 2 (*continued*)

(0.73-0.86) †Adjusted for age, sex and severity of illness	n= 20/ 40(50%) - FI (0.601–0.700): n= 18/ 31(58.1%) AUC (95%CI)= 0.80 (0.74–0.86) **41-item FI** - FI 0: n= 0/ 0 (0%) - FI 0.001–0.100: n= 0/14 (0%) - FI 0.101–0.200: n= 1/42 (2.4%) - FI 0.201–0.300: n= 6/78 (7.7%) - FI 0.301–0.400: n= 10/ 66 (15.2%) - FI 0.401–0.500: n= 15/ 51 (29.4%) - FI 0.501–0.600: n= 19/ 34 (55.9%) - FI 0.601–0.700: n= 11/ 20 (55.0%) HR (95%CI): 1.95 (2.34-5.85) AUC (95%CI): 0.81 (0.75-0.86) **CSHA rules-based frailty definition** - Level 0 (fit): n= 3/ 93 (3.2%) - Level 1: n= 0/ 3 (0%) - Level 2: n= 32/ 132 (24.2%) - Level 3 (frail): n= 27/ 77 (35.1%) AUC (95%CI)= 0.70 (0.63– 0.76) **FRAIL** - Nonfrail: n= 1/ 58 (1.7%) - Pre-frail: n= 20/ 139 (14.4%) - Frail: n= 41/ 108 (38.0%) HR (95%CI): 3.70 (2.34-5.85) AUC (95%CI)= 0.72 (0.66-0.79) **Fourteen-item FI-CGA** - FI (0): n= 0/ 1(0%) - FI (0.001–0.100): n= 0/ 12 (0%) - FI (0.101–0.200): n= 0/ 39 (0%) - FI (0.201–0.300): n= 7/ 84 (8.3%) - FI (0.301–0.400): n= 16/ 74 (21.6%) - FI (0.401–0.500): n= 19/ 58 (32.8%) - FI (0.501–0.600): n= 8/ 21 (38.1%) - FI (0.601–0.700): = 11/ 15 (73.3%) - FI (0.701–0.800): n= 1/ 1 (100%) AUC (95%CI)= 0.80 (0.75–0.86)							
Mortality very long-term							
Amblàs-Novellas et al, 2017 **Amblàs-Novellas et al, 2018‡**	**Dudzińska-Griszek et al, 2017**	**Eeles et al, 2012**		**Hernandez-Luis et al, 2018**		**Hao et al, 2019**	
24 months: n= 338/ 589 (57.3%) - FI-VIG:0-0.15:n= 3/ 21 (13.6%) - FI-VIG:0.16-0.25: n= 12/ 73 (16.4%) - FI-VIG:0.26-0.35: n= 16/ 95 (26.2%) - FI-VIG:0.36-0.45: n= 73/ 127 (45.3%) - FI-VIG:0.46-0.55: n= 27/ 123 (70.7%) - FI-VIG:0.56-0.65: n= 117/ 120 (97.5%) - FI-VIG:0.66-1: n= 30/ 30 (100%) AUC (95%CI)= 0.85 (0.82-0.88)	**24 months:** n= 10/ 88 (12.5%) - Nonfrail + Pre-frail= 4/ 32 (40%)* - Frail= 6/ 56 (60%)	**Median survival 5 years** - Nonfrail: n= 1.368 days (95%CI: 1014-1722) - Frail: n= 207 days (95%CI: 88-326)		**Approximately 989 days**: n= 109/ 298 (36.5%) **CHS** Frail-Median survival: 742 days HR (95%CI)= 2.08 (1.43-3.04) **CFS** Frail- Median Survival: 566 days HR (95%CI)= 2.42 (1.65-3.55)		**36 months:** n= 58/ 271 (21.4%) -Nonfrail: n= 20/ 138 (14.5%) -Frail: n= 38/ 133 (28.6%) †Adj HR (95%CI)= 2.17 (1.26–3.76) †Adjusted for age, sex and education	

Statistically significant difference.

All the underline text are statiscally significant difference.

* Data provided by the authors via email.

┼ Adjusted.

‡ References correspond to the article the data was extracted from.

SD: standard deviation; CI: confidence interval; OR: Odds ratio; HR: Hazard ratio; RR: Risk ratio AUC: areas under curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value NPV: Negative predictive value.

ADL: activities of daily living; CFS: Clinical Frailty Scale; CHS: Cardiovascular Health Study index; CHSA: Canadian Study of Health and Aging rules based frailty definition; FI: Frailty Index; FI-CD: Frailty Index of Accumulative Deficits; FI-CGA: Frailty Index Comprehensive Geriatric Assessment; FI-CGA10D: Frailty Index Comprehensive Geriatric Assessment ten domains; FI-CGA10D + CM: Frailty Index Comprehensive Geriatric Assessment ten domains + comorbidity; FI-CGA-MIHD: Frailty Index Comprehensive Geriatric Assessment multiple individual health deficits; FI-VIG: Index Frailty- Valoración Integral Geriátrica; FRAIL: Frail Scale Status; MPI: Multidimensional Prognostic Index; SOF: Study of Osteoporotic Fractures index; TFI: Tilburg Frailty Indicator.

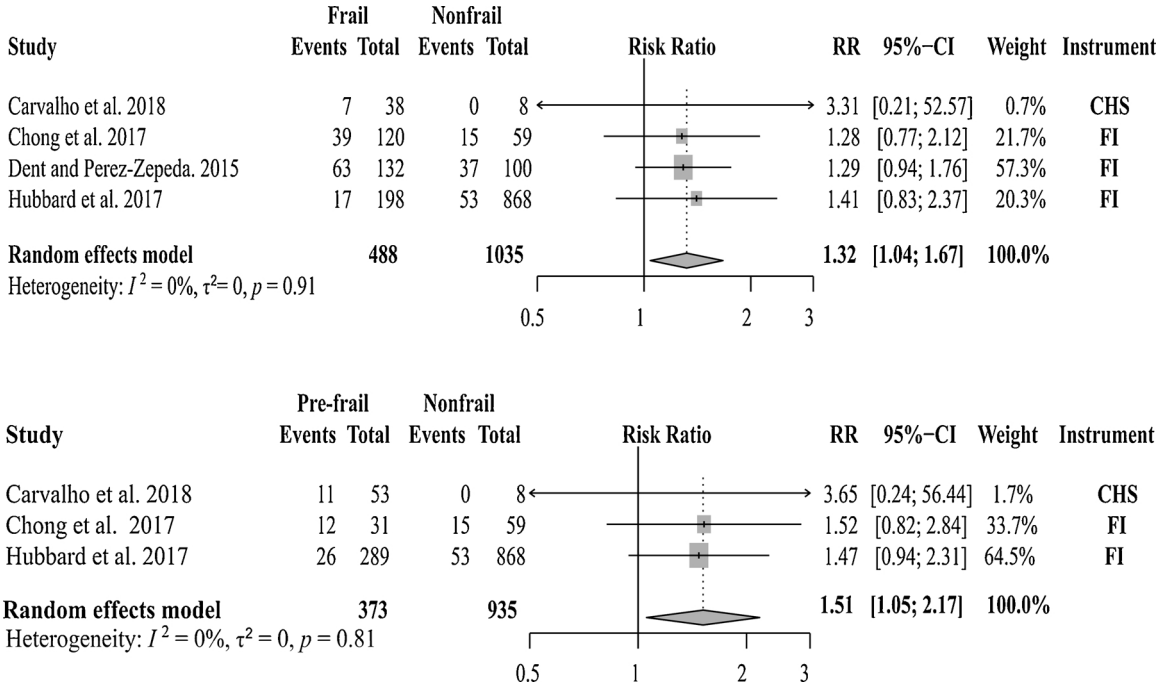

Fig. 2. Meta-analysis for risk of functional decline at hospital discharge in older adults regarding frailty status.

adults increased 3.6-fold (CFS) to 3.9-fold (FRAIL) compared to nonfrail older adults in the same sample (Chong et al., 2017, 2018). Three cohorts (Chong et al., 2017, 2018; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014) were included in the meta-analysis, which showed that frailty increases the risk of in-hospital death by 8.20 times and 3.20 times compared with nonfrailty and pre-frailty older adults, respectively (Appendix E.1). One cohort was excluded because it did not present mortality rate per group of frailty (Basile et al., 2019).We were unable to perform a meta-analysis for the nonfrail groups in relation to the pre-frail groups, since no death occurred in this period for these groups in two of the cohorts (Chong et al., 2017, 2018; Joosten et al., 2014).

Only in one cohort (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) pressure ulcers was evaluated, with an occurrence rate of 3.2%. An increment of 0.1 in the FI increased the chances of older adults developing pressure ulcers during hospitalization by 51% (Hubbard et al., 2017).

Three cohorts were evaluated for the occurrence of falls (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015). Evaluation of this outcome was performed during hospitalization (n = 2) (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014) and in the medium-term (6 months) (n = 1) (Ritt et al., 2016a, 2015). The rate of falls during hospitalization ranged from 5.9% (Hubbard et al., 2017) to 8.0% (Joosten et al., 2014) and the results of predicting falls varied among these cohorts (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014). The study by Hubbart et al (Hubbard et al., 2017) showed that an increment of 0.1 in the FI increased the chance of older adults falling during hospitalization by 29%, while Joosten et al (Joosten et al., 2014) reported that frailty determined by the SOF and CHS was unable to predict this outcome. The rate of falls in the medium-term in the general sample was 20.3% and no association between frailty and this outcome was observed in six months of follow-up using several instruments (Ritt et al., 2015).

Cognitive alterations were assessed regarding cognitive decline (n = 1) (Dramé et al., 2011) and delirium (n = 3) (Eeles et al., 2012; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014). The study that evaluated cognitive decline used the Mental State Mini Exam (MMSE), and reported no relation between frailty and long-term cognitive decline (12 months) (Dramé et al., 2011).The Confusion Assessment Method (CAM) (Joosten et al., 2014), the DSM-IV criteria (Eeles et al., 2012) and the interRAI delirium screen (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) were used to evaluate delirium at hospital stay. The rate of occurrence of delirium ranged from 23% (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) to 37.3% (Eeles et al., 2012) in the general sample. Two (Eeles et al., 2012; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) of the three studies evaluating this outcome showed that frail older adults presented significantly more episodes of delirium during hospitalization than nonfrail older adults.

The discharge destination of older adults was analyzed in five cohorts (Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017). The destinations evaluated in relation to frailty were: the community (n = 2) (Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017), post-acute care (ex: rehabilitation hospital) (n = 1) (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017), residential facility care (n = 1) (Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) and long-term care institutions (n = 2) (Chong et al., 2017, 2018; Dramé et al., 2011). Older adults returning to the community showed a lower mean in the FI (Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017). The chances of a frail older adult being discharged to a place where a greater level of health care was provided ranged from 1.9-fold (Hubbard et al., 2017) to 5-fold (Dent et al., 2013). Discharge destination to long-term institutions showed divergence among the findings of the studies (Chong et al., 2017, 2018; Dramé et al., 2011). In the study by Chong et al (Chong et al., 2017, 2018), no association was determined between frailty and this short-term outcome, while for Drame et al (Dramé et al., 2011) in the long-term (12 months), frailty was significantly associated with admission to long-term care institutions (Dramé et al., 2011).

The length of hospital stay was evaluated in eight cohorts (Basile et al., 2019; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Evans et al., 2014; Gordon et al., 2018; Gregorevic

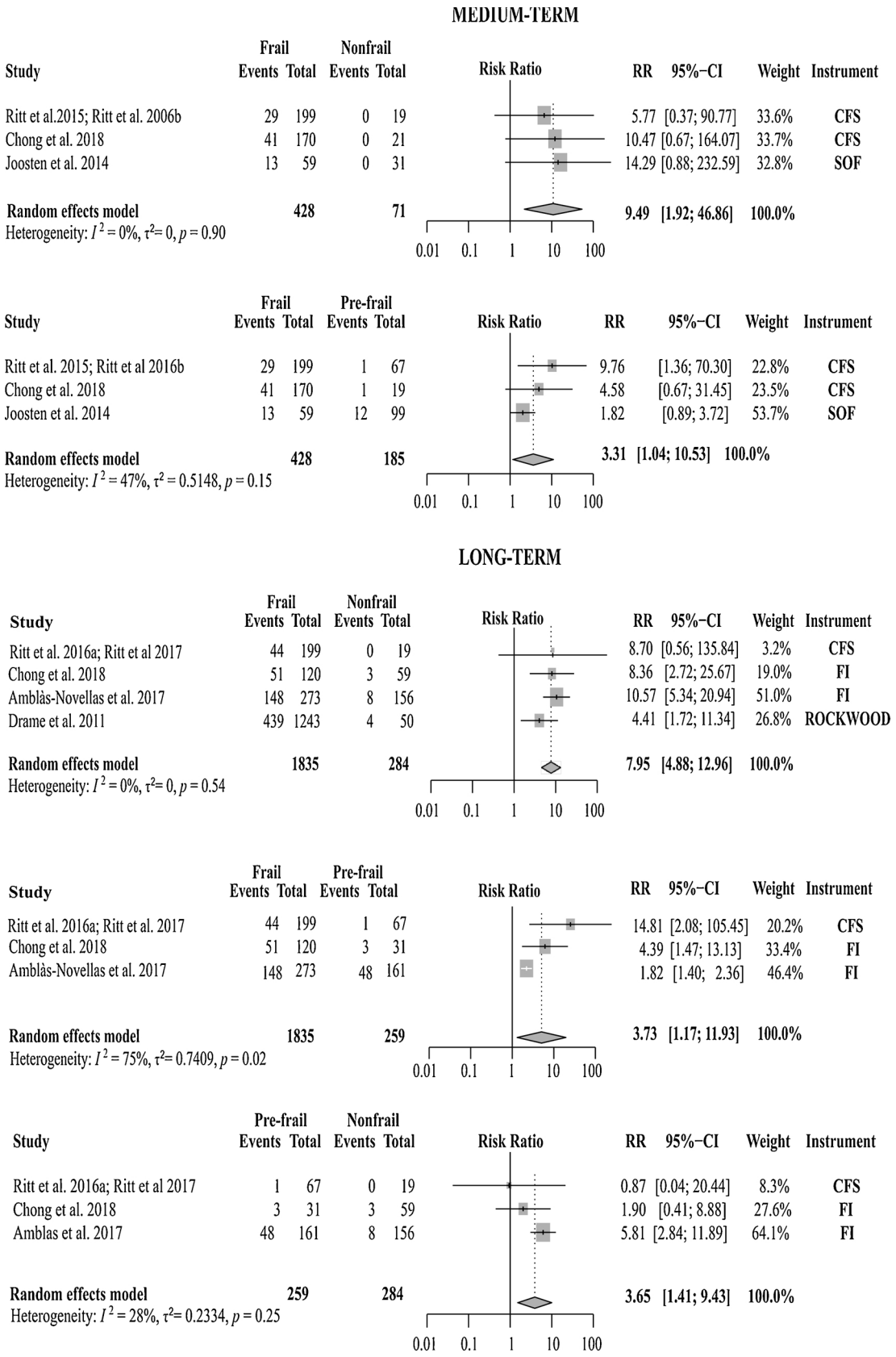

Fig. 3. Meta-analysis for risk of mortality after hospital discharge in medium and long-term in older adults regarding frailty status.

et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014). Overall, the mean length of hospital stay was 5.2 (Evans et al., 2014) to 9.6 (Gregorevic et al., 2018) days. The mean length of hospital stay ranged from 4.2 (Evans et al., 2014) to 12.2 (Joosten et al., 2014) days among nonfrail, and from 5.0 (Evans et al., 2014) to 17.9 (Joosten et al., 2014) days among frail older adults. In six cohorts (Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017) was founded a significant association between frailty and a longer hospital stay. Frailty was a predictor of this outcome in two cohorts (Dent et al., 2013; Dent and Hoogendijk, 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017), in which the chances of a frail older adult being hospitalized for longer was 2-fold (Dent et al., 2013; Dent and Hoogendijk, 2014) higher compared with nonfrail patients, and an increment of 0.1 in the FI increased the chances of older adults being hospitalized for longer periods by 29%(Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017). In the meta-analysis of the length of hospital stay, data from six cohorts (Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Dent and Perez-Zepeda, 2015; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014) were included for nonfrailty, five cohorts (Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014) for pre-frailty and four cohorts (Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Joosten et al., 2014) for frailty. The cohorts excluded (Basile et al., 2019; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Evans et al., 2014) from meta-analysis did not provide data by the group of frailty classification. In general, older adults were hospitalized for 10.5 days (95%CI: 8.82; 12.30), the length of hospital stay for frail older adults was statistically higher ($p = 0.001$) (13.5 days; 95%CI: 11.51; 15.63) compared with pre-frail older adults (10.5 days; 95%CI: 6.32; 14.73) and nonfrail (8.3 days; 95%CI: 6.40; 10.38) (Appendix E.2).

In six cohorts (Basile et al., 2019; Conroy and Dowsing, 2013; Dent et al., 2013; Dent and Hoogendijk, 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) was evaluated the relation between frailty and hospital readmission. The readmission rate in one month was 3.5% (Gregorevic et al., 2018) to 23.3% (Dent et al., 2013; Dent and Hoogendijk, 2014). In the short-term there was some divergence between the studies (Conroy and Dowsing, 2013; Dent and Hoogendijk, 2014; Gregorevic et al., 2018), while Dent and Hoogendijk (Dent and Hoogendijk, 2014) reported a significant association between frailty and one month of readmission (CHS), Gregorovick (FI) (Gregorevic et al., 2018), and Conroy and Dowsing (CFS) (Conroy and Dowsing, 2013) founded no relation for 28, 30 and 90-day follow-up, respectively. Two studies (Basile et al., 2019; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) evaluated this outcome in the medium term (6 months) and overall showed a 35% rate of hospital readmissions. However, in analyses by three different instruments (CFS, CHS and FI) only the CFS determined an association between frailty and readmissions (Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015). In very long term, using the FI, frailty increases 1.4 times the chance of hospital readmissions (Hao et al., 2019).

3.5. Methodological quality

Analysis of the methodological quality was performed for all 19 cohorts, the papers that corresponded to the same cohort were evaluated together. The scores ranged from 5 (n = 1) (Irina et al., 2018) to 11 (n = 4) (Conroy and Dowsing, 2013; Evans et al., 2014; García-Cruz and García-Peña, 2016; Pilotto et al., 2012) points (mean: 8.8 ± 1.7 / median: 9/ mode: 7, 9, 10 and 11). Most of the studies (94.7%) included in this review showed moderate to good methodological quality, demonstrating a low risk of bias.

The item evaluated in 100% of the studies was the exposure of interest prior to outcome. The items with the highest risk of bias among the studies were exposure assessed more than once (n = 18; 94.7%) (Amblàs-Novellas et al., 2017, 2018; Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Evans et al., 2014; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Joosten et al., 2014; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015), assessors blinded (n = 16; 84.2%) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Carvalho et al., 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Joosten et al., 2014; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015), sample size (n = 15; 78.9%) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Chong et al., 2017, 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Dramé et al., 2011; Dudzińska-Griszek et al., 2017; Eeles et al., 2012; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Joosten et al., 2014; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) and rate of eligible persons (n = 13; 68.4%) (Amblàs-Novellas et al., 2017, 2018; Basile et al., 2019; Carvalho et al., 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Dudzińska-Griszek et al., 2017; Evans et al., 2014; García-Cruz and García-Peña, 2016; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; Irina et al., 2018; Joosten et al., 2014; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) (Appendix F).

4. Discussion

This systematic review of 19 cohorts (28 papers) shows the high prevalence of frailty at hospital admission and numerous instruments are used in its identification. There is evidence that frailty is a risk factor for adverse outcomes, such as longer hospital stay, functional decline at discharge, and both in-hospital and medium- and long-term mortality in this population.

The assessment of frailty can be performed using subjective (self-reported measure), objective (directly measure) or mixed instruments (subjective and objective) (Buckinx et al., 2017). The range of instruments used by the studies in this review reflects the lack of consensus regarding the best instrument for assessing frailty (Sternberg et al., 2011; Van-Kan et al., 2008), particularly in the hospital setting. It is known that the assessment of frailty in the hospital setting is challenging due to the severity of the health status of hospitalized older adults and the routine of the setting (Boyd et al., 2005). The routine of hospital admission is often permeated by invasive procedures and examinations, as well as the use of probes and catheters, which often prevent objective testing. In addition, changes in the level of consciousness due to sedation, medications for pain control and delirium can limit subjective assessments. However, only with the implementation of frailty assessment at hospital admission we can prevent the emergence of new cases of frailty and the occurrence of adverse outcomes.

In this review, the most frequently used instrument for assessing frailty was the FI, that is an instrument based on items drawn from the Comprehensive Geriatric Assessment (AGA). The AGA is considered the gold standard for identifying frailty, because it involves a holistic and interdisciplinary view of the older adult (Practitioners, 2014). However, since it encompasses tests, scales and questionnaires from all dimensions of aging, it requires the expertise of the professionals involved in its application and time to collect the information, which makes it

difficult to use in certain therapeutic settings (Practitioners, 2014). Many hospitals already use the AGA in their routine, and thus the FI has become a good alternative for identifying the syndrome. However, it is necessary to transform the AGA components for the final calculation of the FI. This conversion requires more time and is not always done immediately after the conclusion of the AGA, which delays the early identification of cases of frailty. Moreover, this review showed that there is no agreement on which items or how many items should compose the FI and exposed the absence of standardization in cut-off scores or grades required to classify the degrees of frailty.

The diversity of instruments used in to evaluate the cohorts also reflects the large variation in the prevalence of frailty among hospitalized older adults that compose this review [25% (Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) to 97% (Dramé et al., 2011)]. The high prevalence of this syndrome in the hospital setting in relation to the other settings demonstrates the severity of this problem (Parker et al., 2006). It is worth emphasizing that these numbers may be even higher, considering that only one study (Basile et al., 2019) in this review evaluated frailty at more than one time point. These authors found that those older adults with lower FI at the admission had worsening of frailty status during the hospital stay (Basile et al., 2019). Studies that investigate the frailty syndrome at discharge and after hospitalization comparing to admission are necessary to identify the occurrence of transitions between the degrees of frailty (progression and reversion).

In this review, only eight cohorts (Carvalho et al., 2018; Dent et al., 2013; Dent and Hoogendijk, 2014; Evans et al., 2014; Irina et al., 2018; Joosten et al., 2014; Pilotto et al., 2012; Ritt et al., 2016a, 2016b; Ritt et al., 2017, 2015) classified older adults as pre-frail. We must consider the importance of identifying pre-frailty due to its high prevalence in the hospital setting, ranging from 9% (Chong et al., 2017, 2018) to 58.3% (Joosten et al., 2014), and its potential for reversion to the state of nonfrailty (Fairhall et al., 2015; Fried et al., 2001). During hospitalization, the identification of pre-frailty should be highlighted, since in this setting, older adults are more susceptible to evolving to frail than to nonfrail status. In the meta-analysis, we discovered that pre-frail older adults showed a lower risk of mortality and length of hospital stay than frail older adults. Thus, we must promote the early identification of pre-frail older adults and seek actions that aim to improve or maintain their health status.

Another variable that was poorly assessed was the primary outcome, functional decline during hospitalization. One possible reason for the lack of evaluation of this outcome is the difficulty in determining functional decline, since it requires evaluating all older adults at admission and discharge. We verified that in a mean of 10 days of hospital stay frail (RR: 1.32; 95%CI: 1.04–1.67) and pre-frail (RR: 1.51; 95%CI: 1.05–2.17) older adults are at higher risk of developing functional decline at discharge than nonfrail. A meta-analysis with community-dwelling older adults showed that frailty increases 1.6-fold (RR 95%CI: 1.46–1.77) the risk of functional decline in 60 months of follow-up (Vermeiren et al., 2016). Although both studies showed a quite similar risk, the time to develop functional decline was very different showing that the hospital environment can be very harm to these patients. Therefore, actions should be introduced by the hospital staff as soon as possible to prevent it. Frail older adults have low physiological reserves and when hospitalized they become more susceptible to functional decline (Martínez-Velilla et al., 2015). A systematic review revealed that functional decline after hospital discharge increases the level of care of older adults, which sometimes results in institutionalization (Kosse et al., 2013). Using exercise protocols during hospitalization is feasible and could favor the maintenance of functionality in older adults (Kosse et al., 2013; Martínez-Velilla et al., 2015).

Mortality was assessed by most of the studies included in this review. Besides its unquestionable relevance, another factor that contributes to the high frequency of mortality evaluation it is the practicality with which these data are collected in registries or through phone contact. Frailty alone increases the risk of mortality (Fried et al., 2001; Vermeiren et al., 2016) due to its pathophysiology (Fried et al., 2001). In a meta-analysis with community-dwelling older adults the risk for mortality in frail individuals was 2.10 (RR 95%CI: 1.38–3.19) on 0–12 months, 1.57 (RR 95%CI: 1.43–1.72) on 24–60 months and 2.14 (RR 95%CI: 1.60–2.87) on follow-up more than 60 months (Vermeiren et al., 2016). In a meta-analysis in the nursing home environment, frail individuals showed a higher rate mortality compared to those without frail in a follow-up period of less than one year (pooled HR: 2.67, 95% CI: 1.43–5.00) and of one year or more (pooled HR: 1.83, 95%CI: 1.52–2.21) (Zhang et al., 2019). However, when frail older adults are hospitalized, the risk are even higher as showed in our results. This increase is due to the risks inherent to hospitalization (immobilization, loss of muscle mass, functional decline) and the complications of the syndrome (Turner and Clegg, 2014). Protocols that prevent or delay the evolution of frailty should be developed to reduce these risks (Lin et al., 2016). It is worth emphasizing that we found no relation between short-term mortality and frailty. This could be due to the variation in follow-up time (28–100 days) between studies. In addition, in the short-term, older adults who survive hospitalization are still under the effect of the treatment administered during hospitalization and any worsening in their health status after discharge is more likely to lead to hospital readmission rather than death.

The length of hospital stay was an outcome evaluated in several cohorts, and 10.5 days was the overall average of hospital stay among older adults. This indicates that regardless of the degree of frailty older adults spend considerable time in hospital. European studies that assessed the average length of hospital stay among hospitalized older adults ranged from 5.45 (Van-Vliet et al., 2017) to 11.9 (Department of Health. London, 2016-17) days, and both studies address the risks of long-term hospitalization. It is known that the longer the hospital stay, the greater the number of complications and adverse outcomes associated with hospitalization are (Basic and Shanley, 2015) and the higher the costs of health care (Covinsky et al., 2011). In the meta-analysis, we verified that frail older adults remain hospitalized longer than nonfrail and pre-frail older adults. The fear of hospital readmission and early institutionalization may justify maintaining older adults in hospital longer (Gray and Dakin, 2011; Rose et al., 2014).

Other secondary outcomes were poorly evaluated by the studies, such that it was not possible to attribute any relation between these and frailty. Pressure ulcers (Schildmeijer et al., 2018; Schoonhoven et al., 2007), falls (Basic and Hartwell, 2015) and cognitive alterations (Ehlenbach et al., 2010) are frequent clinical outcomes among older adults during hospitalization. In addition, hospital readmissions and discharge destination are outcomes that provide information of the general health status of older adults at hospital discharge. Other outcomes, such as urinary tract infection and pneumonia, which despite being common in the hospital setting, were also not evaluated in any of the papers in this review. The identification of risk factors for these outcomes is necessary to improve the planning of care during hospitalization.

We verified that frail older adults show a higher risk of adverse outcomes (longer hospital stay, functional decline at discharge, and death) and we believe that these risks can be minimized by early identification of frailty at hospital admission and by the practice of specific prevention and treatment of older adults in this setting. There are guidelines (Practitioners, 2014; Turner and Clegg, 2014) of best practices aimed at community-dwelling frail older adults. However, these guidelines may not apply to hospitalized older adults, and more evidence is required to show which clinical practices (e.g. exercise protocols) are effective, feasible and safe in the hospital setting.

This review included a relevant number of studies with low risk of bias, which confirms the quality to our evidence. However, certain limitations should be highlighted, particularly the exclusion of studies that did not presented on data on the primary outcomes and, in reference to the meta-analysis, the exclusion of cohorts that had insufficient or heterogeneous data. Fifteen cohorts (Basile et al., 2019;

Carvalho et al., 2018; Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Dent et al., 2013; Dent and Hoogendijk, 2014; Dent and Perez-Zepeda, 2015; Dramé et al., 2011; Eeles et al., 2012; Evans et al., 2014; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2015, 2017; García-Cruz and García-Peña, 2016; Hao et al., 2019; Hernández-Luis et al., 2018; Irina et al., 2018; Pilotto et al., 2012) did not have the necessary data for meta-analysis and their authors were contacted by e-mail. Despite successive attempts only five authors (Carvalho et al., 2018; Chong et al., 2017, 2018; Conroy and Dowsing, 2013; Gordon et al., 2018; Gregorevic et al., 2018; Hubbard et al., 2008, 2015, 2017; Irina et al., 2018) responded to our requests. Another limitation is the results of this study are not applicable to populations of older adults hospitalized in emergency departments, intensive care units and, older adults with specific diseases.

5. Conclusion

This systematic review identified that there is a high prevalence of frailty at hospital admission and that this syndrome can be assessed by a wide variety of instruments. There is evidence that the frailty syndrome increases the risk of functional decline at discharge, mortality (overall, in-hospital, medium- and long-term) and length of hospital stay. By revealing the impact of frailty on the occurrence of adverse outcomes in the hospital setting, we hope to assist clinicians in recognizing these risks as early as possible and to guide their actions to avoid their occurrence.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.100960.

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