Aging and Disease
www.aginganddisease.org

Volume 11, Number 5; 1276-1290, October 2020
http://dx.doi.org/10.14336/AD.2019.1024

Review

Influence of Frailty on Outcome in Older Patients Undergoing Non-Cardiac Surgery – A Systematic Review and Meta-Analysis

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[Received August 7, 2019; Revised October 23, 2019; Accepted October 24, 2019]

ABSTRACT: Frailty is increasingly recognized as a better predictor of adverse postoperative events than chronological age. The objective of this review was to systematically evaluate the effect of frailty on postoperative morbidity and mortality. Studies were included if patients underwent non-cardiac surgery and if frailty was measured by a validated instrument using physical, cognitive and functional domains. A systematic search was performed using EMBASE, MEDLINE, Web of Science, CENTRAL and PubMed from 1990 – 2017. Methodological quality was assessed using an assessment tool for prognosis studies. Outcomes were 30-day mortality and complications, one-year mortality, postoperative delirium and discharge location. Meta-analyses using random effect models were performed and presented as pooled risk ratios with confidence intervals and prediction intervals. We included 56 studies involving 1.106.653 patients. Eleven frailty assessment tools were used. Frailty increases risk of 30-day mortality (31 studies, 673.387 patients, risk ratio 3.71 [95% CI 2.89-4.77] (PI 1.38-9.97; I2=95%) and 30-day complications (37 studies, 627.991 patients, RR 2.39 [95% CI 2.02-2.83). Risk of 1-year mortality was threefold higher (six studies, 341.769 patients, RR 3.40 [95% CI 2.42-4.77]). Four studies (N=438) reported on postoperative delirium. Meta-analysis showed a significant increased risk (RR 2.13 [95% CI 1.23-3.67). Finally, frail patients had a higher risk of institutionalization (10 studies, RR 2.30 [95% CI 1.81-2.92]). Frailty is strongly associated with risk of postoperative complications, delirium, institutionalization and mortality. Preoperative assessment of frailty can be used as a tool for patients and doctors to decide who benefits from surgery and who doesn't.

Key words: frailty, surgery, outcome, older patients, non-cardiac surgery

Life expectancy has increased with the focus on the quality of added life-years [1]. This prolonged life expectancy has created an increased demand for surgical care of the elderly [2, 3].

Several studies have described age as an independent risk factor for postoperative morbidity and mortality in both cardiac and non-cardiac surgery [4-7]. Advantages in operative techniques and perioperative management seem to improve outcome and multiple studies have even demonstrated an improved quality of life and enhancement of functional status after cardiac surgery in octogenarians [8-10]. Despite these improvements in perioperative care, postoperative adverse effects still remain more common in older patients when compared to

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the younger ones [5, 11]. Adequate risk assessment integrates surgical factors and factors that describe the biological status of the patient, rather than age alone, as age per se seems to be responsible for only a small increase in adverse events [3, 12].

Recently the concept of frailty has come into view [2]. Frailty can be defined as a clinically recognizable state of increased vulnerability resulting from aging-associated lack of physiological reserve and decline in function across multiple physiologic systems [13]. Focus on and optimization of frail patients can contribute to a reduced postoperative morbidity and thereby to better outcome in the older surgical population [2]. Globally, the World Health Organisation has recently developed recommendations on integrated care for older patients in order to maintain their physical and cognitive functions [14].

In order to adequately inform our patients of significant perioperative risks, additional information on frailty as a risk factor influencing postoperative outcome is essential. During the preoperative assessment, this information can guide the clinician in shared decision making on whether the older patient benefits from surgery or not. The aim of this study was to evaluate the predictive role of frailty on postoperative outcomes after non-cardiac surgery by conducting a systematic review and meta-analysis of literature.

METHODS

Search Strategy

A search of literature was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and MOOSE criteria [15]. The objective was to find all studies on frail patients undergoing non-cardiac surgery, correlating their age and its subsequent risk factors to postoperative morbidity and mortality. The systematic Internet based search was performed using EMBASE, MEDLINE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. Full electronic searches can be found in Supplementary Table. 1. In addition, we screened the reference section of all articles included in this review. The search was limited to original articles, human subjects and articles published from January 1990 – December 2017.

Publication selection

Two reviewers independently (EKMT and JMKvF) screened potentially relevant articles from the initial search, first by title and abstract and later on by full text. Any disagreements between the two reviewers were resolved by discussion and consensus with a third reviewer (SH). Studies were found eligible for inclusion if their subjects underwent non-cardiac surgery and if frailty was measured by a frailty instrument using at least physical, cognitive and functional domains. Also, the relationship between frailty and primary outcomes of 30-day mortality, or 30-day complications should be evaluated, with stratification of the outcome (frail versus non-frail). Studies were excluded if they were review articles, case reports, editorials or comments, or if full text was not available. Duplicate articles were removed during the initial search.

Data Extraction

The following data were gathered from eligible publications: publication date, study design, sample size, type of surgery, proportion of females, mean age, the frailty score and outcome. Outcome was measured by the following adverse events: 30-day mortality, 30-day complications, one-year mortality, manifestation of postoperative delirium (POD) and discharge to a specialized facility. 30-day complications are generally defined as suggested by the Clavien-Dindo classification system[16]; otherwise the authors should have predefined this outcome. Postoperative delirium was defined as a temporary state of confusion and diagnosis made with validated delirium screening tools or by a geriatric expert team [17]. Discharge destination was defined as “home”, or “not able to return home”. Furthermore, surgical procedures were categorised according to the ESC/ESA Guidelines [18] and divided into low-, intermediate- and high-risk procedures. Occasionally, the surgical risk category was documented as “mixed surgical population”. A subanalysis per surgery type was performed to better understand the effect of frailty according to the surgical risk category. Where absolute data were not presented in table or text and authors could not be reached, when possible, data were extracted from figures using WebPlotDigitizer (version, 2.6.8).

Assessment of quality and possible biases

Two reviewers performed assessment of quality. In case of disagreement a third reviewer was consulted. The quality assessment tool for prognosis studies as proposed by Hayden et al. was used for the appraisal of all included studies [19]. This tool focuses on six areas of potential bias; first *study participation* (i.e. the study sample represents the population of interest on key characteristics), second *study attrition* (i.e. whether the study was able to obtain a complete follow up), third *prognostic factor measurement* (i.e. a clear definition or description of the prognostic factor measured is provided), fourth *outcome measurement* (i.e. a clear definition of the outcome of interest), fifth *confounding measurement and account* (i.e. important potential confounders are appropriately accounted for) and sixth *analysis* (i.e. the statistical analysis is appropriate for the design of the study). After the evaluation of these six areas of potential bias, all studies were subsequently divided According to the Quality in Prognosis Study Tool into good (11 or 12 points), fair (9 or 10 points) and poor (< 9 points) quality.

Statistical methods

Numerical values reported by the studies were used for analysis. In some cases, further calculation was required for ascertaining outcomes. In the studies using the modified frailty index (mFI) patients were categorized into two groups: “not frail” (mFI < 0.27), or “frail” (mFI ≥ 0.27). The decision to divide patients into those categories was based on thresholds most commonly used to indicate the presence of frailty and was made before analysis. In the remaining studies, using ten different frailty instruments, outcome was also dichotomized according to predefined criteria as “not frail” or “frail”. Random effects models for meta-analysis were used because of the large expected heterogeneity in determinant and other study characteristics. The primary outcome measures 30-day mortality and 30-day complications were stratified by frailty score. Furthermore, a subanalysis per surgery type was performed to better understand the effect of frailty according to the surgical risk category. Effect estimates are presented as pooled risk ratios (RR) with 95% confidence intervals (CI’s). Robust meta-analytic conclusions of prognosis studies will be more appropriately signaled when prediction intervals are provided [20]. Thus, to further account for between-study heterogeneity, 95% prediction interval (PI) were also estimated, which evaluates the uncertainty of the effect that would be expected in a new study addressing the same association [21]. I^2 statistic was calculated, which is the percentage of variation across studies due to heterogeneity rather than random error. Since all reported outcomes were adverse events, a positive relative risk indicates that frailty is associated with worse patient outcome. A meta-regression analysis was carried out to assess the influence of the patient’s mean age (using mean or median age of the study populations as a proxy) on 30-day mortality. Finally, an additional sensitivity analysis was performed (excluding studies using ACS-NSQIP database) to circumvent the issue of possible duplicate cases and demonstrate the effect of frailty on postoperative outcome.

Data gathering and data analysis was performed using Excel (version 14.7.2) and Rstudio (version 1.1.463) respectively.

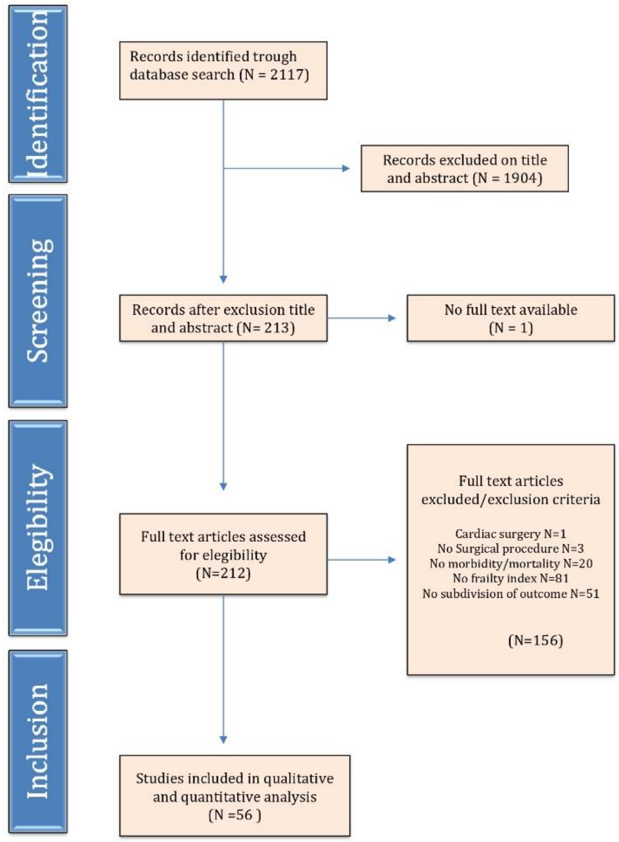

Figure 1. PRISMA flowchart for study selection. This flowchart depicts the flow of information trough different phases of the systematic research.

RESULTS

Initial literature search identified 2117 manuscripts as potentially relevant. Of these, 1904 were excluded due to unrelated research questions or study type. Full text was not available in one study; therefore 212 full text articles were thoroughly screened for eligibility. A total of 56 studies were found suitable for this systematic review. Figure 1 shows the search strategy flow chart.

Frailty assessment tools

A total of eleven different frailty assessment tools were used. The majority of studies (twenty-four) used the Modified Frailty Index (mFI), created by Saxton and Velanovich [22]. The mFI consists of eleven variables present in the Canadian Study on Health and Aging Frailty Index, as well as in the American College of Surgeons National Surgical Quality Improvement Program (ACS

NSQIP) dataset [23, 24]. Variations on the Fried Frailty Criteria [25] were used in eleven studies, where frailty was defined by identifying unintentional weight loss, exhaustion, low energy expenditure, low grip strength and slow walking speed. Frailty assessment tools were often based on comprehensive geriatric assessments, which can be derived from questionnaires or patient files, including the Frailty Index and the Groningen Frailty Indicator. Supplementary Fig. 2 provides a detailed description of all frailty assessment tools used in this review.

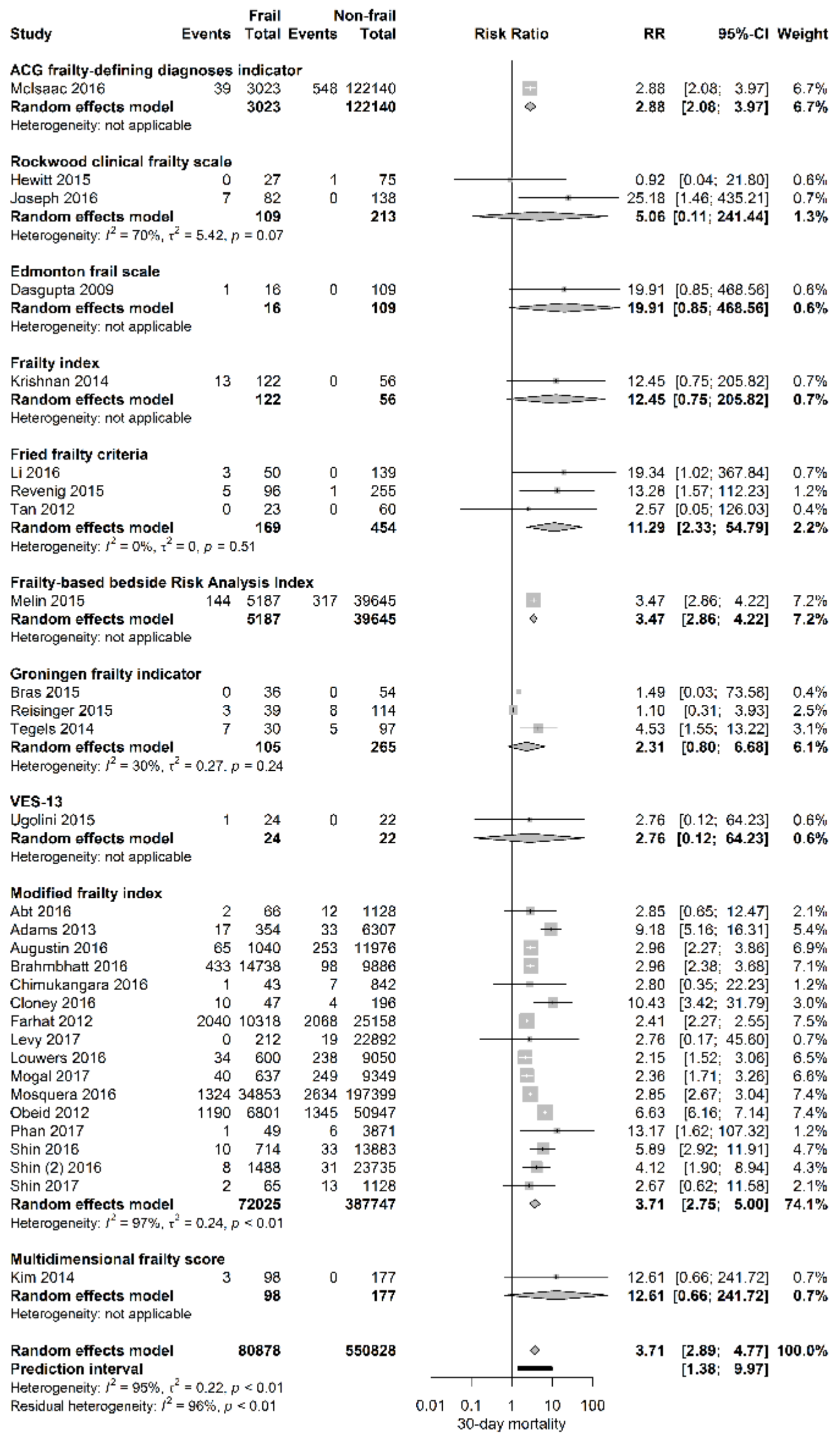

Figure 2. Forest plot 30-day mortality per frailty score. The number of events (deaths) and the total number of patients are shown for both frail and non-frail patients, stratified per frailty assessment tool.

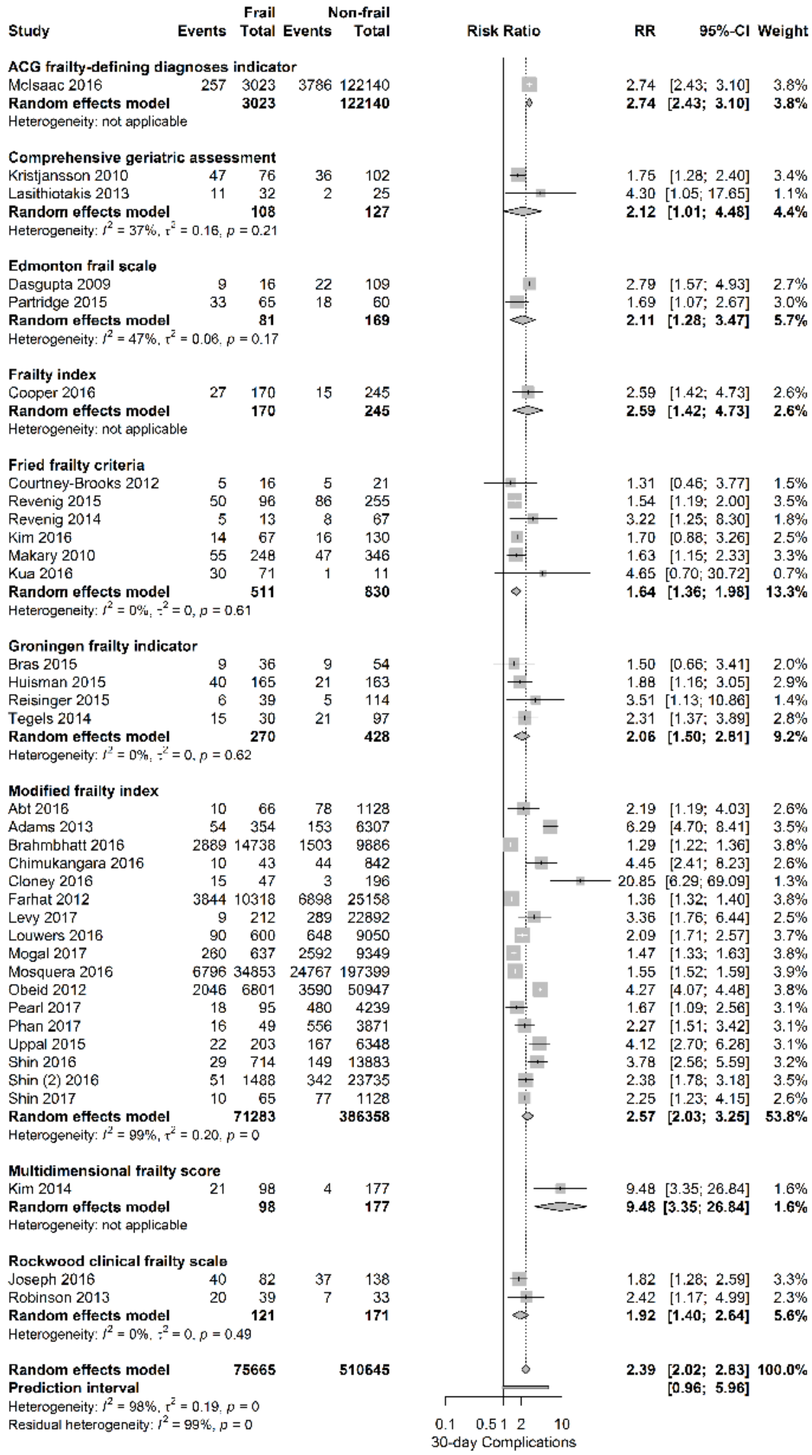

Figure 3. Forest plot postoperative complications per frailty score. The number of events (complications) and the total number of patients are shown for both frail and non-frail patients, stratified per frailty assessment tool.

Quality assessment

The quality assessment of the included studies is provided in Supplementary Fig. 3 and **table 1** provides a summary of our appraisal. Study participation was adequately described in 37 studies. The study attrition - referring to the response rate and attempts to collect information on patients who were lost to follow up - was adequately defined in 40 studies. Prognostic factors were clearly defined or described in most studies (86%). Ninety-one percent of studies provided a clear definition of the outcome of interest. When summarizing, 95% of all studies included were of at least fair quality, with more than half assessed as good quality.

Table 1. Study demographics and method of determining frailty.

Author	N	Setting	Period	Design	Type of surgery	Frailty score	Definition of complication	Quality
Abt	1193	Multicenter cohort study (NSQIP)	2006-2013	Prospective	Head and neck cancer surgery	Modified frailty index	CD 4	Good
Adams	6727	Multicenter cohort study (NSQIP)	2005-2010	Prospective	Head and neck cancer surgery	Modified frailty index	CD 4 or 5	Good
Arya	23027	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Vascular surgery (Open or EVAR)	Modified frailty index	CD 4	Good
Augustin	13020	Multicenter cohort study (NSQIP)	2005-2010	Prospective	Pancreatic resections	Modified frailty index	CD 4	Good
Brahmbhatt	24645	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Infrainguinal vascular surgery	Modified frailty index	CD 4	Good
Bras	90	Single-center cohort study	2008-2013	Retrospective	Surgery for head and neck cancer	Groningen frailty indicator	CD ≥ 2	Fair
Chappidi	2679	Multicenter cohort study (NSQIP)	2011-2013	Prospective	Radical cystectomy	Modified frailty index	CD 4 or 5	Good
Chimukangara	885	Multicenter cohort study (NSQIP)	2011-2013	Prospective	Paraesofageal hernia repair	Modified frailty index	CD ≥ 3	Fair
Cloney	243	Multicenter cohort study (NSQIP)	2000-2012	Prospective	Glioblastoma surgery	Modified frailty index	Complications (Glioma Outcomes Project System)	Fair
Cooper	415	Multicenter cohort study	2010-2013	Prospective	General and orthopedic surgery	Frailty phenotype; frailty index	Major complications	Fair
Courtney-Brooks	37	Single-center cohort study	2011	Prospective	Surgery for gynecologic cancer	Fried frailty criteria	Surgical complications (NSQIP)	Fair
Dale	76	Single-center cohort study	2007-2011	Prospective	Pancreaticoduodenectomy	4 (of 5) components of Fried frailty criteria; VES-13	CD ≥ 3	Fair
Dasgupta	125	Single-center cohort study	2002-2003	Prospective	Elective noncardiac surgery (82%) orthopedic)	Edmonton frail scale	Cardiac - / pulmonary comlications, POD	Fair
Farhat	35334	Multicenter cohort study (NSQIP)	2005-2009	Prospective	Emergency general surgery	Modified frailty index	Any complication (not mortality)	Fair
Flexman	52671	Multicenter cohort study (NSQIP)	2006-2012	Prospective	Spine surgery	Modified frailty index	Major complications	Good
Hewitt	102	Multicenter cohort study	2013	Prospective	Emergency general surgery	Rockwood clinical frailty scale	Not reported	Fair
Huisman	328	Multicenter cohort study	2008-2012	Prospective	Surgery for solid tumors	Groningen frailty indicator; VES-13	CD ≥ 3	Good
Joseph	220	Single-center cohort study	2012-2014	Prospective	Emergency general surgery	Rockwood clinical frailty scale	Surgical complications (NSQIP)	Fair
Kenig	184	Single-center cohort study	2013-2014	Prospective	Emergency abdominal surgery	VES-13, GFI; Rockwood; Balducci; TRST; Geriatric-8	Any complication (CD)	Fair
Kim	197	Single-center cohort study	2012-2014	Prospective	Elective noncardiac surgery	Fried frailty criteria	Surgical complications (NSQIP)	Good
Kim	275	Single-center cohort study	2011-2012	Prospective	Elective intermediate-risk or high-risk surgery	Multidimensional frailty score	Surgical complications (NSQIP)	Good
Krishnan	178	Single-center cohort study	2011	Prospective	Low trauma hip fracture surgery	Frailty index	Not reported	Poor

Kristjansson	178	Multicenter cohort study	2008-2011	Prospective	Elective surgery for colorectal cancer	Comprehensive geriatric assessment	CD ≥ 2	Good
Kua	82	Single-center cohort study	2013	Prospective	Hip fracture surgery	Edmonton frail scale; (modified) Fried frailty criteria	Any complication	Fair
Lascano	41681	Multicenter cohort study (NSQIP)	2005-2013	Prospective	Surgery for urologic cancer	Modified frailty index	CD 4	Good
Lasithiotakis	57	Single-center cohort study	2008-2011	Prospective	Elective laparoscopic cholecystectomy	Comprehensive geriatric assessment	Any complication	Poor
Leung	63	Single-center cohort study	2007	Prospective	Noncardiac surgery	Fried frailty criteria	Not reported	Fair
Levy	23104	Multicenter cohort study (NSQIP)	2008 to 2014	Prospective	Robot-assisted radical prostatectomy	Modified frailty index	CD 4	Good
Li	189	Single-center cohort study	Not reported	Prospective	Major intra-abdominal surgery	Fried frailty criteria	CD	Fair
Louwers	10300	Multicenter cohort study (NSQIP)	2005-2011	Prospective	Hepatectomy	Modified frailty index	CD 4	Good
Makary	594	Single-center cohort study	2005-2006	Prospective	Elective surgery	Fried frailty criteria	Surgical complications (NSQIP)	Good
McAdams-DeMarco	537	Single-center cohort study	2008-2013	Prospective	Kidney transplant surgery	Fried frailty criteria	Not reported	Fair
McIsaac	202811	Single-center cohort study	2002-2012	Retrospective	Major elective noncardiac surgery	ACG frailty-defining diagnoses indicator	Not reported	Good
McIsaac	125163	Single-center cohort study	2003-2012	Retrospective	Total joint arthroplasty	ACG frailty-defining diagnoses indicator	ICU-admission	Good
Melin	44832	Multicenter cohort study (NSQIP)	2005-2011	Prospective	Carotid endarterectomy	Frailty-based bedside Risk Analysis Index	Not reported	Fair
Mogal	9986	Multicenter cohort study (NSQIP)	2005–2012	Prospective	Pancreaticoduodenectomy	Modified frailty index	CD 3 or 4	Good
Mosquera	232352	Multicenter cohort study (NSQIP)	2005-2012	Prospective	elective high-risk surgery	Modified frailty index	Major and minor complications	Fair
Neuman	12979	Single-center cohort study	1992–2005	Retrospective	Elective colorectal cancer surgery	ACG frailty-defining diagnoses indicator	Readmission within 30 days	Fair
Obeid	58448	Multicenter cohort study (NSQIP)	2005–2009	Prospective	Laparoscopic and open colectomy	Modified frailty index	CD 4 or 5	Fair
Partridge	125	Single-center cohort study	2011	Prospective	Arterial vascular surgery	Edmonton frail scale	Composite postoperative complications	Fair
Pearl	4330	Multicenter cohort study (NSQIP)	2011-2014	Prospective	Radical cystectomy	Modified frailty index	Major in-hospital complications	Good
Phan	3920	Multicenter cohort study (NSQIP)	2010-2014	Prospective	Elective anterior lumbar interbody fusion (ALIF) surgery	Modified frailty index	Any complication	Good
Reisinger	159	Single-center cohort study	2010-2012	Prospective	Colorectal surgery	Groningen frailty indicator	Sepsis	Good
Revenig	351	Single-center cohort study	Not reported	Prospective	Major intra-abdominal surgery	Fried frailty criteria	CD 1-4	Fair
Revenig	80	Single-center cohort study	Not reported	Prospective	Intra-abdominal minimally invasive surgery	Fried frailty criteria	CD 1-4	Fair
Revenig	189	Single-center cohort study	Not reported	Prospective	Major intra-abdominal surgery	Fried frailty criteria	Any complication	Good
Robinson	72	Single-center cohort study	2007-2010	Prospective	Colorectal surgery	Rockwood clinical frailty scale	Any postoperative complication (VASQIP)	Fair
Shin	6148 ACDF;	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Cervical spine fusion; anterior cervical	Modified frailty index	CD 4	Good

	817 PCF				discectomy and fusion or posterior cervical fusion			
Shin	14583 THA; 25223 TKA	Multicenter cohort study (NSQIP)	2005-2012	Prospective	Total hip and knee arthroplasty	Modified frailty index	CD 4	Good
Suskind	95108	Multicenter cohort study (NSQIP)	2007-2013	Prospective	Common urological surgery	Modified frailty index	Major and minor complications	Good
Suskind	20794	Multicenter cohort study (NSQIP)	2011-2013	Prospective	Inpatient urological surgery	Modified frailty index	Not reported	Good
Tan	83	Multicenter cohort study	2008-2010	Prospective	Colorectal surgery	Fried frailty criteria	CD ≥ 2	Fair
Tegels	127	Single-center cohort study	2005-2012	Retrospective	Surgery for gastric cancer	Groningen frailty indicator	CD ≥ 3	Fair
Tsiouris	1940	Multicenter cohort study (NSQIP)	2005-2010	Prospective	Open lobectomy	Modified frailty index	CD 4	Good
Ugolini	46	Single-center cohort study	2009-2012	Prospective	Elective colorectal cancer surgery	Groningen frailty indicator; VES-13	Not reported	Poor
Uppal	6551	Multicenter cohort study (NSQIP)	2008-2011	Prospective	Surgery for gynecologic cancer	Modified frailty index	CD 4 and 5	Good

Abbreviations: CD = Cavien-Dindo classification of surgical complications; NSQIP = National Surgical Quality Improvement Program

Postoperative outcome predicted by frailty

Table 1 shows the details of study demographics and methods of frailty measurement. In the selected studies, fifty-one were of prospective design and sample size ranged from 37 – 232 352 patients. Gender distribution was reported in 93% of the studies with a proportion of females ranging from 0% in the study of Levy et al, describing a male population undergoing robot assisted radical prostatectomies, until 100% in the study of Courtney-Brooks et al, describing complications in elderly women undergoing gynecologic oncology surgery. Twenty-seven studies investigated the effect of frailty in oncological surgery (predominantly abdominal cancer surgery), four studies in vascular surgery, nine in orthopedic surgery, eleven in elective general surgery (predominantly intermediate - and high-risk surgery), four in emergency surgery and one study in transplant surgery. Thirty-one studies investigated the influence of frailty on 30-day mortality. Figure 2 shows a forest plot of this primary outcome with a pooled RR of 3.71 [95% CI 2.89-4.77] (PI 1.38-9.97; I2=95%) for frail patients compared to those who were not frail. The 95% prediction interval also showed exclusion of the null value.

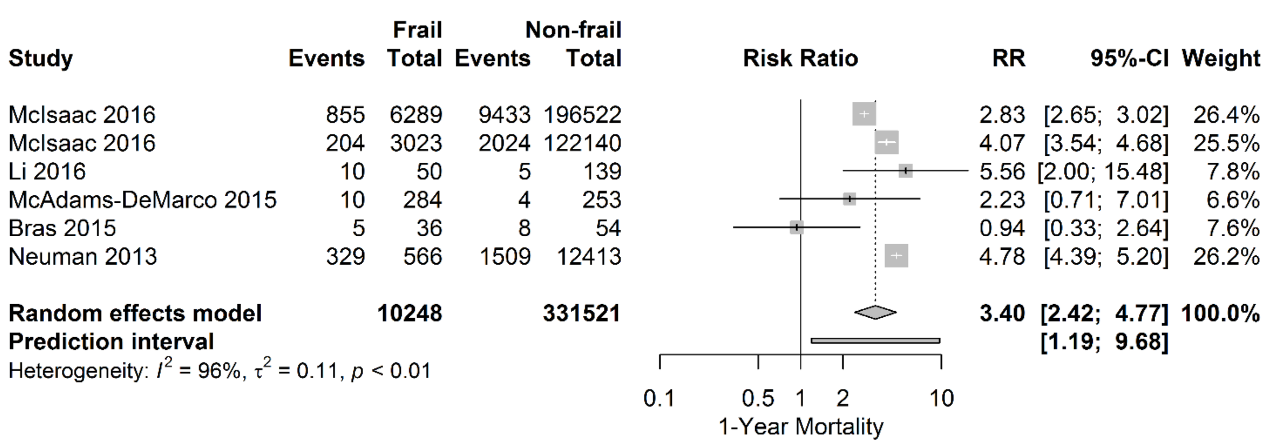

Figure 4. Forest plot 1-year mortality. The number of events (one-year mortality) and the total number of patients are depicted for frail and non-frail patients.

Stratified for frailty assessment tool, the association of frailty and 30-day mortality was observed according to the ACG frailty-defining diagnosis indicator, Fried frailty criteria, Frailty-based Risk Analysis Index and the Modified Frailty Index.

Figure 3 shows the relationship between frailty and the occurrence of postoperative complications, stratified for frailty assessment tool. This adverse outcome was evaluated in 37 papers. **Table 1** shows the predefined 30-day complications reported by the authors, in most cases defined as suggested by the Clavien-Dindo classification system. Overall, a positive relationship between frailty and 30-day complications with a pooled RR of 2.39 [95% CI 2.02-3.07] was observed (PI 0.96-5.69; I2=98%), regardless of the frailty score used.

Stratified per surgical risk category, pooled RR's for 30-day mortality were 2.75 [95% CI 2.48-3.05] for high-risk surgery (4 studies), RR 4.79 [95% CI 3.42-6.70] for intermediate-risk surgery (18 studies) and RR 3.06 [95% CI 2.35-3.97] for mixed surgical population (8 studies). The association of frailty and the primary outcome 30-day complications was also stratified per surgical risk category and again a positive relationship was observed with pooled RR's of 1.62 [95% CI 1.43 -1.82] for high-risk surgery (3 studies) and RR 2.94 [95% CI 2.44-3.54] for intermediate-risk surgery (24 studies).

Six studies investigated the association between frailty and one-year mortality (Fig. 4). In most of these studies, frailty increases the risk of one-year mortality with a pooled consequent risk ratio of 3.40 [95% CI 2.42-4.77], (PI 1.19- 9.68; I2=96%).

Figure 5 shows a forest plot**,** which summarizes the relationship between frailty and postoperative delirium. Four studies (438 patients) describe a positive relationship between frailty and POD with a pooled RR of 2.13 [95% CI 1.23-3.67], (PI 0.64- 7.05; I2=0%).

Figure 6 shows that frail patients seem to struggle to return to their own home, as these patients, described in ten studies (149 752 patients), have a twofold higher risk of being discharged to a specialized facility after surgery (RR 2.30 [95% CI 1.81-2.92]), (PI 1.06- 4.96; I2=92%). Just like in 30-day mortality and one-year mortality, the 95% prediction interval for postoperative discharge location showed exclusion of the null value.

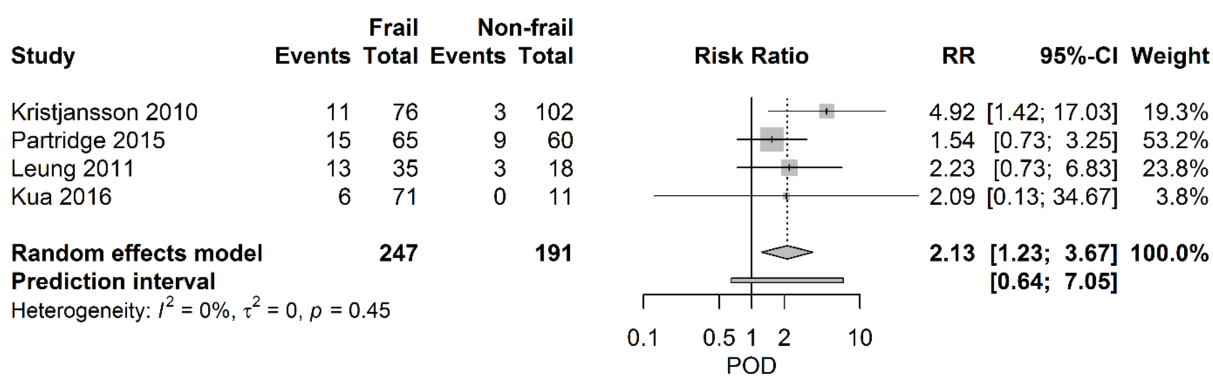

Figure 5. Forest plot postoperative delirium. The number of events (delirium) and the total number of patients are depicted for frail and non-frail patients.

A meta-regression analysis investigating showed no influence of age on primary outcome. Finally, to circumvent the issue of possible duplicate cases, the additional sensitivity analysis excluding studies using ACS-NSQIP database, showed an overall pooled RR of 3.62 [CI 95% 2.21-5.92] (PI 1.46-8.98; I2=14%) for 30-day mortality

DISCUSSION

Since life expectancy keeps rising, the number of frail patients being offered for surgical treatment will dramatically increase. Frail patients are vulnerable and may excessively decompensate after stressors such as surgery, because of their lack of physiological reserve [13].

In this systematic review and meta-analysis, we found frailty to be a strong predictor of post surgical complications, delirium, institutionalization and all-cause mortality. After reviewing fifty-six articles, 30-day mortality shows the strongest association with preoperative frailty with almost 4 times increased risk.

Our results are congruent with several other reviews investigating the effect of frailty on postoperative outcome. [26-30] However, most of the previous studies focused on specific age groups, specific types of surgery, or specific frailty assessment tool. Therefore, extrapolations to a heterogeneous group of elderly and multimorbid patients should be limited.

The strength of the present study is the extensiveness of the search, the inclusion of different validated frailty scores and the inclusion of different types of non-cardiac surgery, both elective and acute. The quality of this meta-analysis is dependent on the quality of the studies reviewed. Of all studies included 95% were of at least fair quality, with more than half assessed as good quality. Ninety-one percent of all studies were prospectively designed.

Recently, relevant developments have been made towards methodological frameworks, in order to improve the reliability and applicability of prediction studies [31]. Although the authors found improved reporting standards in the last decade, poor reporting and poor methods are still a topic of concern and likely to limit the reliability in this type of clinical research.

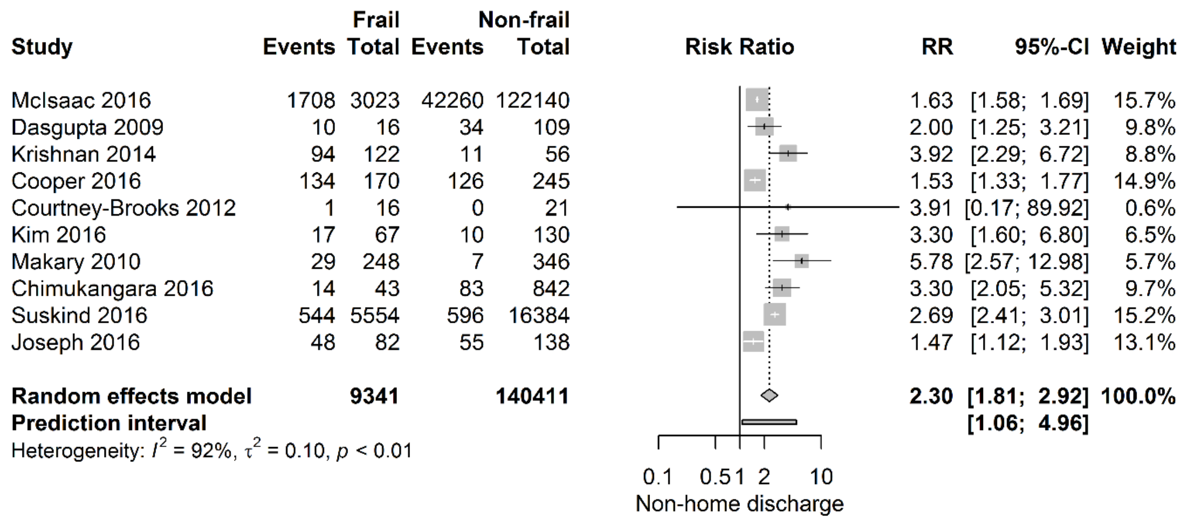

Figure 6. Forest plot discharge to specialized facility. The number of events (discharge to a specialized facility) and the total number of patients are depicted for frail and non-frail patients.

The studies in this review and meta-analysis describe eleven different frailty assessment tools. Moreover, the surgical procedures included could basically be divided into six different groups, which will have contributed to the heterogeneity. Heterogeneity, as assessed with I2, t2, Cochran's Q and prediction intervals, was estimated as a high degree of statistical heterogeneity. Importantly, the association between frailty and outcome seems robust throughout the reviewed articles regardless of the frailty assessment tool used. Furthermore, prediction intervals of 30-day mortality, one-year mortality and postoperative discharge location showed exclusion of the null value, which strengthens our findings.

A plausible explanation may be the fact that frailty was consistently measured by instruments using physical, cognitive and functional domains. Studies using only measurements of body composition or patients' phenotype, such as sarcopenia, hypoalbuminemia or cachexia were not included, as these studies did not use an established frailty assessment tool. The frailty instrument used in most studies was the modified frailty index (mFI), which has been validated as a reliable assessment tool in several studies [32-36]. It should be recommended that future studies focus on using a standardized, robust and validated frailty assessment tool, which is time-efficient and suitable for the medical staff to be conducted at patient's bedside.

Limitations of this study are those commonly seen with systematic reviews and meta-analysis. Hence, the results of this review and meta-analysis should be interpreted with caution. Besides the heterogeneity, another possible limitation is a variation among studies in the definition of discharge location. Despite these small differences, ten studies confirm that frail patients, when compared to healthier counterparts, struggle to return to their own home. Unfortunately, in many countries, availability of beds and nursing staff in specialized facilities are a topic of current concern. To overcome this limitation the need for rehabilitation or nursing home placement was defined as "not able to return home". Comparable heterogeneity was found within the definition of postoperative complications. Although most authors defined 30-day complications as suggested by the Clavien-Dindo classification system, others used the American College of Surgery National Surgical Quality Improvement Program definition, or other standardized complication definitions. It should be recommended that future studies in the area of frailty use a standardized postoperative complication definition as this might create a more accurate comparison. The International

Consortium for Health Outcomes Measurement (ICHOM) recently developed the first global standard set of outcome measures in older persons. Their effort towards standardization of outcome measures can possibly improve care pathways and quality of care [37].

Although we have performed an exhaustive literature search, the broad scope of our research question could have resulted in the omission of some studies.

Many studies in this systematic review and meta-analysis are observational registry studies, but several studies have derived their outcomes from clinical trials. Since many studies have used the ACS NSQIP database, there may be studies, which are double counted from the same cohort of patients. However, table 1 shows that most of these studies observed different subgroups of patients, as well as different timeframes and kinds of surgical specialisms. Additionally, the sensitivity analysis we have performed, excluding studies using ACS-NSQIP database, demonstrated a positive relationship between frailty and primary outcomes. Finally, subgroup analyses gave insight in the heterogeneity among the types of surgery and different frailty assessment tools, but this stratification has the drawback of small groups.

In a previous study we have found that the occurrence of postoperative complications is an important prognostic factor of late mortality [38]. Efforts to improve postoperative outcome have predominantly focused on enhanced recovery protocols and the improvement of surgical and anesthetic techniques [39, 40]. The concept of prehabilitation is a modern and proactive approach, based on the principle that structured exercise over a period of weeks leads to a better cardiovascular, respiratory and muscular condition. Optimization of patients' functional capacity may provide a physiological buffer and enables the patient to better withstand the stress of surgery [39, 41, 42].

Preoperative identification of frail patients provides an opportunity for prehabilitation, which subsequently may lead to reduced postoperative morbidity. Besides prehabilitation, regionalization in health care might improve surgical outcome in complex oncological surgery. Regionalization is about enabling appropriate allocation and integration of health resources, focusing on the local populations needs. Frail patients may benefit from high-volume hospitals with high-volume surgeons in so called centers of excellence [43].

This study demonstrates that the presence of preoperative frailty increases the risk of adverse outcome after non-cardiac surgery. It should be noted that heterogeneity of the frailty scores is high, but associations with postoperative outcome are robust. Frailty status should be considered to be part of the preoperative screening, at least in patients who seem to have a lack of physiological reserve. Identification of potentially reversible health deficits is important, as may provide an opportunity to optimize patients' clinical condition prior to surgery. Conversely, irreversible frailty should be taken most seriously, as it can guide both clinician and patient in their decision making on whether the patient benefits from surgery or not.

Acknowledgements

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Supplementary Materials

The Supplemenantry data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2019.1024.

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