The American Journal of Surgery 218 (2019) 393–400

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Impact of frailty on outcomes in surgical patients: A systematic review and meta-analysis

A.C. Panayi [a], A.R. Orkaby [b, c], D. Sakthivel [a], Y. Endo [d], D. Varon [e], D. Roh [a], D.P. Orgill [a], R.L. Neppl [f], H. Javedan [g], S. Bhasin [h], I. Sinha [a, *]

[a] Division of Plastic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[b] Geriatric Research, Education, and Clinical Center, VA Boston Healthcare System, Boston, MA, USA
[c] Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[d] Division of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[e] University of Michigan Medical School, Ann Arbor, MI, USA
[f] Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[g] Division of Gerontology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[h] Division of Endocrinology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Article history:
Received 13 September 2018
Received in revised form
1 November 2018
Accepted 15 November 2018

ABSTRACT

Importance: Age has historically been used to predict negative post-surgical outcomes. The concept of frailty was introduced to explain the discrepancies that exist between patients' chronological and physiological age. The efficacy of the modified frailty index (mFI) to predict surgical risk is not clear.
Objective: We sought to synthesize the current literature to quantify the impact of frailty as a prognostic indicator across all surgical specialties.
Data sources: Pubmed and Cochrane databases were screened from inception to 1 January 2018.
Study selection: Studies utilizing the modified Frailty Index (mFI) as a post-operative indicator of any type of surgery. The mFI was selected based on a preliminary search showing it to be the most commonly applied index in surgical cohorts.
Data extraction and synthesis: Articles were selected via a two-stage process undertaken by two reviewers (AP and DS). Statistical analysis was performed in Revman (Review manager V5.3). The random-effects model was used to calculate the Risk Ratios (RR).
Main outcome(s) and measure(s): The primary outcomes: post-operative complications, re-admission, re-operation, discharge to a skilled care facility, and mortality.
Results: This meta-analysis of 16 studies randomizes 683,487 patients, 444,885 frail, from gastrointestinal, vascular, orthopedic, urogenital, head and neck, emergency, neurological, oncological, cardiothoracic, as well as general surgery cohorts. Frail patients were more likely to experience complications (RR 1.48, 95%CI 1.35–1.61; $p < 0.001$), major complications (RR 2.03, 95%CI 1.26–3.29; $p = 0.004$), and wound complications (RR 1.52, 95%CI 1.47–1.57; $p < 0.001$). Furthermore, frail patients had higher risk of readmission (RR 1.61, 95%CI 1.44–1.80; $p < 0.001$) and discharge to skilled care (RR 2.15, 95%CI 1.92–2.40; $p < 0.001$). Notably, the risk of mortality was 4.19 times more likely in frail patients (95% CI 2.96–5.92; $p < 0.001$).
Conclusions: and Relevance: This study is the first to synthesize the evidence across multiple surgical specialties and demonstrates that the mFI is an underappreciated prognostic indicator that strongly correlates with the risk of post-surgical morbidity and mortality. This supports that formal incorporation of pre-operative frailty assessment improves surgical decision-making.

* Corresponding author. Division of Plastic Surgery Brigham and Women's Hospital, 75 Francis St. Boston, MA, 02115, USA.
E-mail address: isinha@bwh.harvard.edu (I. Sinha).

https://doi.org/10.1016/j.amjsurg.2018.11.020
0002-9610/

Introduction

The US population is aging with those over 65 years old projected to reach 88 million by 2050, representing a 105% increase from 2015.[1] As the elderly patient demographic grows, surgeons will more commonly operate on these patients, with studies showing that up to 30% of invasive procedures performed in Medicare beneficiaries occurring in the final year of life.[2] Although chronological age has historically been used to predict poor post-surgical outcomes, in recent years, the concept of frailty was introduced to reconcile the mismatch between a patient's chronological and physiological age.

The precise definition of frailty is an evolving one, but is generally recognized as a state of decreased physiologic reserve coupled with an increased vulnerability to stressors which leads to higher susceptibility to adverse health outcomes, disability, and death.[3] In general, frail individuals are those clinically characterized by an impairment in their nutrition, endurance, mobility, physical strength and muscle power, balance, and cognitive function.[4,5]

A frailty model, termed the Frailty Index (FI), proposed by Rockwood et al. supports that frailty is a multidimensional risk state characterized by the accumulation of various health-related deficits, whose severity is dependent on the number rather than the nature of each individual health deficit.[6,7] The model's variables capture multiple domains of health including cognitive dysfunction, functional limitation, psychosocial risk factors, geriatric syndromes, and medical co-morbidities.[8–10]

In 2011 Obeid et al. mapped the variables included in the FI against the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to propose the modified frailty index (mFI).[11] The mFI consists of 11 variables (Fig. 1). Each of these criteria corresponds to one point. The index is then calculated by adding all the applicable points and dividing by the total, that is 11. The majority of studies analyzing the impact of frailty in post-surgical outcomes utilize the mFI because it is based on easily identifiable patient characteristics that are relevant to surgical patients and which can be extracted using simple history taking and physical examination.

Studies have supported that frailty indices are an efficient and accurate way of identifying patients who are at higher risk of negative post-operative outcomes.[12] Recognizing the necessity for frailty assessment in surgical care, in 2012 the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and the American Geriatrics Society (AGS) conjointly proposed best practice preoperative guidelines that recommended formal assessment of frailty.[13]

In this review and meta-analysis we seek to summarize the currently available literature in order to quantify the strength of the mFI, and indirectly frailty, as a prognostic indicator of postoperative outcomes across all surgical specialties.

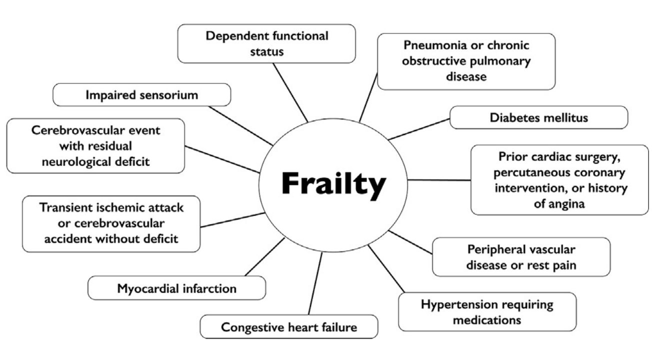

Fig. 1. The eleven mFI variables.

Patients and methods

Selection criteria

The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 was consulted to establish the review strategy.[14] The review was registered on the Research Registry UIN: reviewregistry472 (http://www.researchregistry.com). The PUBMED and Cochrane electronic databases were screened from inception to 1 January 2018 using the keywords: frailty, frail, mFI, Modified Frailty Index, surgery, and surgical (Supplemental Table 1). The syntax of each database determined the search format.

The inclusion criteria were limited to any prospective or retrospective studies including case-control studies, cohort studies, case series, and randomized controlled trials, reporting on surgical outcomes in frail patients, classified as such using the mFI. This index was selected as it is the most commonly investigated frailty index in surgical populations, enabling us to include the highest number of articles in our review. All surgical interventions and specialties were considered. Inclusion of generic terms like surgery increases the likelihood of the search strategy being comprehensive (Supplemental Table 2).

Articles were selected via a two-stage process undertaken by two reviewers (AP and DS). All data of identified studies were extracted into Microsoft Excel® 2017 (Microsoft, Redmond, WA, USA), followed by screening of the title and abstracts to select eligible studies. In the second stage the manuscript of eligible studies was assessed for inclusion. The last author was consulted to resolved inconsistency between the two reviewers (IS).

Quality assessment

The methodological quality of the studies was independently assessed by two reviewers (DS, YE) using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) guidelines.[15]

Statistical analysis

The Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUOROM) guidelines were consulted and the meta-analysis was performed in RevMan (Review manager V5.3).[16] The random-effects model was used to calculate the Risk Ratios (RR). Statistical heterogeneity was quantified using the I^2 and X^2 statistics with their corresponding P-values. Publication bias was assessed using funnel plots.

Subgroup analysis

Subgroup analyses were performed to investigate the difference in complication occurrence and mortality in non-frail and frail patients with mFI scores of 0.09, 0.18, 0.27, and >0.36.

Sensitivity analysis

Sensitivity analysis was performed to assess whether outcomes were altered when the analysis was restricted to higher quality studies and whether limiting the analysis to studies utilizing data prior to 2012 had any effect on results.

Results

Primary studies included in the literature review

A search of the PUBMED database resulted in 192 relevant articles and further search in the Cochrane database yielded no additional articles (Fig. 2). Of the 192 studies 88 studies were excluded based on the type of study, according to our exclusion criteria, and of the remaining 104 studies, seven were excluded based on their title, and 63 based on their abstract as they stratified frailty using indices other than the mFI. Full manuscripts were evaluated for 34 publications but only 16 fulfilled the entry criteria for the meta-analysis.[11,17–31] The 18 papers excluded from the meta-analysis did not provide the appropriate numerical data necessary for statistical analysis, but were included in the literature review.[32–49]

Main study characteristics and methodological quality assessment

Of the 34 included studies, only three were prospective (Table 1). All studies were case series and had a Level of Evidence (LoE) of 4 as defined by the Oxford Centre for Evidence-Based Medicine.[50] No randomized controlled trials were found. Numerical data for meta-analysis could be extracted from 16 studies, three of which focused on orthopedic, three on vascular, and six on gastrointestinal surgery. Seven of 16 studies were of *low* and six of *very low* quality on the GRADE scale. Three studies were deemed moderate quality based on their large effect according to GRADE

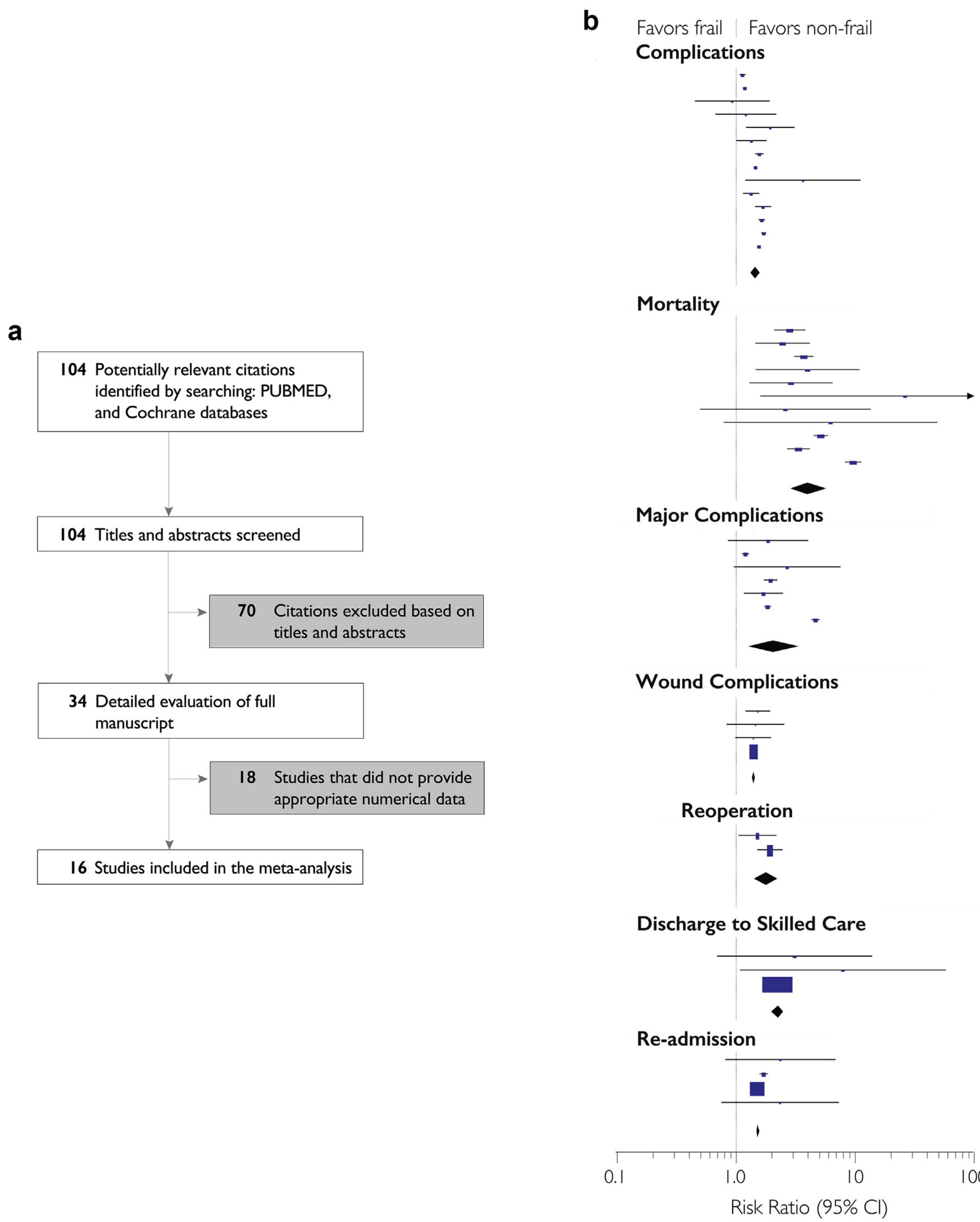

Fig. 2. The selection process of the studies included in the literature review and meta-analysis.

Table 1
Studies included in the literature review, organized by year of publication.

Study	Publication Year	Study Period	Country*	Type	Type of Surgery	Patients	Outcomes
Youngerman et al.	2018	2008–2012	USA	R	Neurosurgery	9149	Mort, Comp, Major Comp, LOS, DSC
Ali et al.	2017	2010	USA	R	Vascular	4704	Mort, Comp
Gani et al.	2017	2014	USA	R	Gastrointestinal	2714	Mort
Konstantinidis et al.	2017	2005–2014	USA	P	Gastrointestinal	1171	Mort, Major Comp
Levy et al.	2017	2008–2014	USA	R	Urogenital	23104	Mort, Major Comp
Mazzola et al.	2017	2015–2016	Italy	P	Gastrointestinal	76	Mort, Comp, Major Comp, LOS, RA, DSC
Mogal et al.	2017	2005–2012	USA	R	Gastrointestinal	9986	Mort, Comp, Major Comp
Park et al.	2017	2007–2012	USA	R	Oncology	846	Mort, Comp
Runner et al.	2017	2005–2014	USA	R	Orthopedic	90260	Mort, Major Comp, Wound Comp, RA
Seib et al.	2017	2016–2017	USA	R	General	140828	Comp, Major Comp
Vermillion et al.	2017	2005–2012	USA	R	Gastrointestinal	41455	Mort, Comp, Major Comp, LOS
Wachal et al.	2017	2006–2012	USA	R	Head and Neck	343	Comp, Major Comp, LOS, DSC
Wahl et al.	2017	2007–2014	USA	R	General	236957	Mort, Comp, RA
Wen et al.	2017	2006–2015	USA	R	Gastrointestinal	272	Comp, RA
Abt et al.	2016	2006–2013	USA	R	Head and Neck	1193	Mort, Major Comp, RA, RO
Ali et al.	2016	2006–2010	USA	R	Orthopedic	18294	Mort, Major Comp, Wound Comp
Arya et al.	2016	2011–2012	USA	R	Vascular	15843	Comp, DSC
Cloney et al.	2016	2000–2012	USA	R	Neurosurgery	243	Mort, Comp, LOS
Ehlert et al.	2016	2006–2012	USA	R	Vascular	72106	Mort, Major Comp
Flexman et al.	2016	2006–2012	Canada	R	Orthopedic	53080	Mort, Major Comp, LOS, DSC
Leven et al.	2016	2005–2012	USA	R	Orthopedic	1001	Mort, Comp, Wound Comp, RO
Mosquera et al.	2016	2005–2012	USA	R	Gastrointestinal	94811	Mort, Comp
Phan et al.	2016	2010–2014	USA	R	Orthopedic	3920	Mort, Comp, Wound Comp, RO
Brahmbhatt et al.	2015	2005–2012	USA	R	Vascular	24624	Mort, Comp, Major Comp, LOS
George et al.	2015	2008–2012	USA	R	Urogenital	66105	Mort, Major Comp, Wound Comp
Lascano et al.	2015	2005–2013	USA	R	Urogenital	41681	Mort, Major Comp
Tsiouris et al.	2015	2005–2010	Canada	P	Cardiothoracic	1940	Mort, Comp, Major Comp
Keller et al.	2014	2009–2012	USA	R	Gastrointestinal	859	Mort, Comp, RA, RO, LOS
Kolbe et al.	2014	2005–2012	USA	R	Gastrointestinal	104952	Mort, Major Comp
Adams et al.	2013	2005–2010	USA	R	Head and Neck	6727	Mort, Comp, Major Comp
Karam et al.	2013	2005–2008	USA	R	Vascular	67308	Mort, Comp, Wound Comp
Obeid et al.	2012	2005–2009	USA	R	Gastrointestinal	58448	Mort, Comp, Major Comp, Wound Comp
Farhat et al.	2011	2005–2009	USA	R	Emergency	35344	Mort, Comp, Wound Comp
Louwers et al.	2007	2005–2011	USA	R	Gastrointestinal	10300	Mort, Major Comp, LOS

*: Institution of lead author; R: retrospective; P: prospective; Mort: Mortality; Comp: Complications; RA: Readmission; RO: Reoperation; DSC: Discharge to skilled care; LOS: Length of hospital stay.

guidelines (Supplemental Table 3).

Definitions of frailty

Although the mFI was not proposed to be used as a dichotomous variable, for the purpose of this meta-analysis, a score of 0 was considered non-frail and a score greater than 0 was considered frail. This selection was made in order to include the highest number of studies possible, as there was large variation in the use of the mFI between studies.

Definitions of outcome measures

Complications were reported by 24 studies and were defined as any 30-day negative outcome other than death.[11,17–20,22–27,29–31,33,36,38,40,41,43,46–49] Complications were further subclassified into major complications and wound complications, with some studies focusing solely on these complications and not providing information on minor complications. Major complications were reported in 21 studies.[11,17–19,21,23–25,29,32–35,37,39,40,42,44–49] The majority of the studies defined major complications as Clavien-Dindo class IV complications, that is, complications that are life-threatening or require critical care management. This includes, but is not limited to, postsurgical myocardial infarction, pulmonary embolism, stroke, or coma.[11,18,19,21,25,29,32–35,39,40,42,44,45,47,48] Three studies defined major complications as Clavien-Dindo class > III complications[24,46,49] and two as class > II.[23,37] For the purpose of this review and meta-analysis, major complications were considered any Clavien-Dindo class > III complications. Wound complications were reported in eight studies.[11,22,26,27,34,36,39,40] Four of these defined wound complications as the occurrence of any superficial, deep, or organ space wound infection, or wound infections with dehiscence.[26,36,39] One study focused on wound infections with dehiscence.[27] Two papers looked at wound infections without further defining them[11,40] and one paper analyzed wound complications but did not specify what this outcome included.[22] Length of postoperative hospital stay was reported in nine studies which defined the length of stay in days.[19,20,23,29,37,41,45,48,49] Reoperation was reported in four studies and was defined as an unplanned return to the operating room.[22,26,32,41] Six studies looked at readmission defined as an unplanned re-admission to hospital within 30 days post-surgery.[23,27,30–32,41] Discharge to skilled care was reported in five studies, four of which defined it as discharge to a care facility rather than home[18,23,29,37] and one termed it unfavorable disposition, that is a discharge destination with a higher level of care than before admission.[48] Mortality was defined by 30 studies as death within 30 days of surgery.[11,17,19–22,24–27,29,30,33–49]

Results for the overall meta-analysis

Sixteen studies were included in the meta-analysis providing a total of 683,487 patients, of which 444,885 were frail. The results of the primary outcomes analysis are shown in Table 2. Frail patients were more likely to experience complications, including major and wound complications. Frail patients had a higher risk of readmission and reoperation and were more likely to be discharged to a skilled care facility. Most notably, the risk of mortality was 4.19

Table 2
Forest plots for primary outcomes in frail versus non-frail patients (see Fig. 2b).

Study	Frail		Non-frail		Weight	RR
	No.	Total	No.	Total	%	M – H Random, 95% CI
Complications						
Mogal et al. (2017)	2381	6157	1292	3829	10.3	1.15[1.09, 1.21]
Runner et al. (2017)	10444	66847	3051	23413	10.5	1.20[1.15, 1.24]
Mazzola et al. (2017)	11	41	10	35	1.3	0.94[0.45, 1.94]
Wen et al. (2017)	23	147	16	125	1.9	1.22[0.68, 2.21]
Wachal et al. (2017)	79	241	17	102	2.7	1.97[1.23, 3.15]
Ali et al. (2017)	376	4019	47	685	4.9	1.36[1.02, 1.83]
Seib et al. (2017)	1465	67793	992	73033	9.9	1.59[1.47, 1.72]
Mosquera et al. (2016)	15032	52304	8273	42507	10.7	1.48[1.44, 1.51]
Cloney et al. (2016)	49	198	3	45	0.6	3.71[1.21, 11.38]
Leven et al. (2016)	292	612	137	389	8.0	1.35[1.16, 1.59]
Phan et al. (2016)	347	1895	217	2025	8.0	1.71[1.46, 2.00]
Arya et al. (2016)	1626	5914	1638	9929	10.2	1.67[1.57, 1.77]
Brahmbatt et al. (2015)	4276	12738	1916	9886	10.4	1.73[1.65, 1.82]
Obeid et al. (2012)	11225	35818	4492	22630	10.6	1.58[0.53, 1.63]
Total (95% CI) $I^2 = 92\%$ ($P < 0.0001$)	**47626**	**254724**	**22101**	**1886333**	**100.0**	**1.48[1.35, 1.61]**
Mortality						
Mogal et al. (2017)	238	6157	51	3829	12.8	2.90[2.15, 3.92]
Runner et al. (2017)	115	66847	16	23413	10.7	2.53[1.50, 4.27]
Wahl et al. (2016)	1863	189706	122	47251	13.6	3.80[3.17, 4.57]
Ali et al. (2017)	96	4019	4	685	6.5	4.09[1.51, 11.80]
Konstantinidis et al. (2017)	17	455	9	716	8.1	2.97[1.34, 6.61]
Mazzola et al. (2017)	15	41	0	35	1.4	26.57[1.65, 428.63]
Phan et al. (2016)	5	1895	2	2025	3.4	2.67[0.52, 13.75]
Leven et al. (2016)	10	612	1	389	2.4	6.36[0.82, 49.46]
Mosquera et al. (2016)	1530	52304	236	42507	13.9	5.27[4.60, 6.04]
Brahmbatt et al. (2015)	433	12738	98	9886	13.4	3.43[2.76, 4.26]
Obeid et al. (2012)	2547	35818	164	22630	13.8	9.81[8.39, 11.48]
Total (95% CI) $I^2 = 91\%$ ($P < 0.0001$)	**6869**	**370232**	**703**	**153366**	**100.0**	**4.19[2.96, 5.92]**
Major Complications						
Mazzola et al. (2017)	15	41	7	35	11.4	1.83[0.84, 3.97]
Mogal et al. (2017)	1869	6157	983	3829	16.2	1.18[1.11, 1.26]
Wachal et al. (2017)	25	241	4	102	9.3	2.65[0.94, 7.41]
Seib et al. (2017)	622	67793	349	73033	16.0	1.92[1.68, 2.19]
Konstantinidis et al. (2017)	51	455	48	716	14.8	1.67[1.15, 2.44]
Brahmbatt et al. (2015)	2894	12738	1239	9886	16.2	1.81[1.71, 1.93]
Obeid et al. (2012)	5195	35818	718	22630	16.2	4.57[4.24, 4.93]
Total (95% CI) $I^2 = 99\%$ ($P = 0.004$)	**10671**	**1232431067′**	**3348**	**110231**	**100.0**	**2.03[1.26, 3.29]**
Wound Complications						
Runner et al. (2017)	236	66847	49	23413	1.2	1.69[1.24, 2.29]
Leven et al. (2016)	25	612	10	389	0.2	1.59[0.77, 3.27]
Phan et al. (2016)	45	1895	32	2025	0.6	1.50[0.96, 2.35]
Obeid et al. (2012)	8924	35818	3718	22630	98.0	1.52[1.47, 1.57]
Total (95% CI) $I^2 = 0\%$ ($P < 0.0001$)	**9230**	**105172′**	**3809**	**48457**	**100.0**	**1.52[1.47, 1.57]**
Reoperation						
Leven et al. (2016)	50	612	19	389	33.0	1.67[1.00, 2.79]
Phan et al. (2016)	103	1895	47	2025	67.0	2.34[1.67, 3.29]
Total (95% CI) $I^2 = 13\%$ ($P < 0.0001$)	**153**	**2507′**	**66**	**2414**	**100.0**	**2.10[1.54, 2.86]**
Discharge to Skilled Care						
Mazzola et al. (2017)	7	41	2	35	0.5	2.99[0.66, 13.46]
Wachal et al. (2017)	18	241	1	102	0.3	7.62[1.03, 56.31]
Arya et al. (2016)	659	5914	518	9929	99.2	2.14[1.91, 2.39]
Total (95% CI) $I^2 = 0\%$ ($P < 0.0001$)	**684**	**6196′**	**521**	**10066**	**100.0**	**2.15[1.92, 2.40]**
Re-admission						
Mazzola et al. (2017)	11	41	4	35	1.1	2.35[0.82, 6.72]
Runner et al. (2017)	3485	66847	714	23413	1.2	1.71[1.58, 1.85]
Wahl et al. (2016)	22540	189706	3722	47251	53.6	1.51[1.46, 1.56]
Wen et al. (2017)	11	147	4	125	1.0	2.34[0.76, 7.16]
Total (95% CI) $I^2 = 68\%$ ($P < 0.0001$)	**26047**	**256741′**	**4444**	**70824**	**100.0**	**1.61[1.44, 1.80]**

times more likely in frail patients. Complications, mortality and major complications had high heterogeneity, readmission had moderate heterogeneity, and wound complications, reoperation and discharge to skilled care had low heterogeneity. Funnel plots were asymmetric suggesting publication bias (Supplemental Fig. 1).

Subgroup analysis

Subgroup analysis for complication occurrence in the different mFI score classes was based on four studies,[11,22,27,28] three of which looked at more than 20,000 patients.[11,27,28] The occurrence of complications increased proportionally to the mFI score. Frail patients with a score of 0.36 or more, indicating a score of 4 points out of 11 (RR 2.08, 95% CI 1.50 to 2.87; $p < 0.001$) were more likely to develop surgical complications than patients with an mFI of 0.27, or 3 points, (RR 1.90, 95% CI 1.46 to 2.48; $p < 0.001$), 0.18, 2 points, (RR 1.52, 95% CI 1.29 to 1.80; $p < 0.001$), and 0.09, 1 point (RR 1.25, 95% CI 1.16 to 1.34; $p < 0.001$) undergoing surgery. Subgroup analysis for mortality was based on four studies.[11,22,27,31] Mortality was more likely to occur in frail patients with a score of 0.36 or more (RR 33.87, 95% CI 27.94 to 38.67; $p < 0.001$) than patients with an mFI of 0.27 (RR 14.84, 95% CI 6.84 to 32.20; $p < 0.001$), 0.18 (RR 5.70, 95% CI 2.36 to 13.75; $p < 0.001$), and 0.09 undergoing surgery (RR 2.88, 95% CI 1.52 to 5.45; $p = 0.001$; Supplemental Table 4). Subgroup analysis for the other primary outcomes could not be performed as the majority of papers did not provide data for each individual mFI score.

Sensitivity analysis

When performing the meta-analysis with data from the three studies deemed to be of moderate quality, again frail patients were more likely to experience complications (RR 1.41, 95% CI 1.20 to 1.65; $p < 0.0001$) and had a higher mortality rate (RR 3.82, 95% CI 1.87 to 7.79; $p = 0.0002$) (Supplemental Table 5) than non-frail patients.

Sensitivity analysis focusing on pre-2012 data could be performed for six of the primary outcomes (Supplemental Table 6). Frail patients were again more likely to experience complications (RR 1.50, 95% CI 1.37 to 1.65; $p < 0.001$),[11,17–20,22,24,25,29] major complications (RR 2.22, 95% CI 1.11 to 4.42; $p = 0.02$),[11,19,24,29] wound complications (RR 1.52, 95% CI 1.47 to 1.57; $p < 0.001$),[11,22] mortality (RR 4.78, 95% CI 3.00 to 7.62; $p < 0.001$),[11,17,19,22,24,25] and discharge to skilled care (RR 2.69, 95% CI 1.03 to 7.03; $p = 0.04$).[18,29]

Discussion

In this meta-analysis of 16 studies that used the mFI in surgical patients we found that frailty was associated with a higher rate of all-cause complications and mortality. This result held true across multiple surgical specialties. Studies have suggested that frail patients have reduced physical reserves and hence less ability to respond well to surgery.[51] In addition, frail patients often have multiple comorbidities which increase the risk for post-operative complications such as myocardial infarction and pulmonary embolism.[52] It should be noted that frailty is not simply a count of comorbidities and the mFI provides a more general picture of physical condition by including social, functional, and cognitive factors as well as comorbidities. Subgroup analysis showed that as the mFI increased so did the relative risk for complications. The higher rate of wound complications may be due to the fact that frail patients are more likely to have a low physiological reserve that can predispose to surgical wound complications such as infection.[37] In addition, studies have shown that frail patients have increased inflammation, possibly owing to higher levels of acute phase reactants and coagulation factors, including CRP, factor VIII and fibrinogen.[53] These factors may increase further following a major inflammatory stressor such as surgery and could account for the higher level of complications, particularly those associated with wound healing.[53]

The rate of reoperation was higher in frail patients as well, with only one of the four studies reporting a non-statistically significant increase.[26] By combining the data of this study in the meta-analysis a statistically significant difference between frail and non-frail patients was found. A higher rate of reoperation may be due to the higher rate of complications seen in frail patients, with one study reporting that a large percentage of reoperations was due to higher rates of wound infections seen with increasing mFI scores.[22]

Four of six studies reporting on readmission rates found that although this was more likely to occur in frail patients it was not found to be statistically significant.[23,30,32,41] The two studies with the highest number of patients showed that, in their analysis, readmission was strongly associated with mFI. As this studies were both included in the meta-analysis, along with two studies with a small number of patients, a statistically significant positive correlation was found between frailty and readmission.[27,31]

Three of four studies included in this review found that frail patients are statistically more likely to be discharged to a care facility.[18,29,37] The fourth study was limited by a small number of patients but was included in the meta-analysis which showed that frailty is a strong predictor for non-home discharge.[16] Flexman et al. analyzed the rate of discharge to a care facility as it correlates to the mFI using both an unadjusted and adjusted analysis. A higher mFI was first found to be a strong predictor of discharge to skilled care in an unadjusted analysis, which was followed by confirmation with an analysis which adjusted for pre-specified procedure and patient specific variables.[37] This increased rate of discharge to a care facility may be explained by the higher rate of complications seen in frail patients. Arya et al. used a stratified analysis to show that frailty was a strong positive predictor for non-home discharge, both independently but also in association with the occurrence of postoperative complications.[18] Specifically, they found that frail patients without complications were more likely to be discharged to a care facility than non-frail patients with no complications, with the lack of functional reserve in frail patients being the likely reason. Likewise, frail patients with complications had a higher risk of non-home discharge than non-frail patients with complications.[18]

Eight of the nine studies reporting on the length of stay found that a longer length of stay correlates with pre-operative frailty status.[19,20,29,37,41,45,48,49] The increased length of stay could be due to several factors, including the higher rate of complications but also the increased likelihood of discharge to a skilled care facility which can often delay discharge.

Interestingly, Farhat et al. found that post-operative mortality was strongly associated with frailty and using a multivariate analysis showed that mFI was better at predicting mortality than age or the ASA score.[36] Aging does not independently increase mortality, however, frailty with its associated comorbidities and deterioration of physical condition is more likely to be the cause of increase in surgical risk.[54]

Given the introduction of the NSQIP/AGS preoperative guidelines in 2012 we sought to perform a sensitivity analysis investigating whether the effect we were seeing from the retrospective studies was due to a secular trend caused by changes in preoperative selection of patients from 2012 to 2017. Elimination of all studies post-2012 did not affect our conclusions, highlighting that frail patients were still more likely to experience complications, discharge to skilled care and mortality.

It should be emphasized that frailty should not be considered an absolute contraindication for surgery. Rather, risk stratification through frailty assessment based on strict criteria provides the opportunity to optimize patients' physiology prior to surgery through pre-habilitation, such as nutrition and exercise regimes, as well as post-surgery through proper rehabilitation.

In addition, frailty assessment can enhance identification of patients who may require reoperation and discharge to a skilled care facility. This would allow for better planning, identification of adequate resources, and engagement of patient support systems, which may decrease the length of stay post-surgery.[52] The decision making of the patient would also be improved as a surgeon would be better able to inform the patient of their individual potential for surgical risk and benefit.

This review and meta-analyses was the first to synthesize the evidence of the effect of frailty on postoperative outcomes across surgical specialties, analyzing the most recent studies including 12 studies from 2017. A study protocol was not published a priori, however, this study follows the PRISMA guidelines.[55] The study is non-commercial and set strict inclusion and exclusion criteria. In addition, the GRADE criteria were used to assess the methodological quality of the studies, and a sensitivity analysis was performed to provide more robust conclusions.

This study carries limitations commonly seen with systematic reviews and meta-analyses. First, the quality of this meta-analysis is dependent on the quality of the studies it analyzes, all of which are non-randomized. Non-randomized studies carry inherent biases, including selection bias. All included studies are case series which tend to be perceived as lighter surgical research evidence because of several short-comings including having vague objectives and exaggerated conclusions. However, they carry relevance to a certain degree as proof of a potential cause-effect relationship.[56] Accepting the limitations of case series allows surgeons to learn from such evidence.[57] Furthermore, according to the GRADE criteria, 12 of 14 studies included in this meta-analyses were of low or very low quality. We sought to overcome this limitation by repeating the analysis using data solely from studies deemed to be of moderate quality. Last, the study is subject to publication bias as all but one study were conducted in the US and Canada. Adding to the publication bias is the fact that our criteria excluded studies that were unpublished and included only studies published in the English language. In addition, the funnel plots indicate a lack of studies showing no effect.

Based on this meta-analysis, the mFI is an underappreciated prognostic indicator that strongly correlates with higher risks of post-operative complications, longer hospitalization periods, greater rates of readmission, reoperation, and discharge to skilled care, as well as higher mortality. Despite not being a perfect measure, the mFI is easy to calculate and uses patient characteristics extracted during history taking and examination. This meta-analysis serves to highlight that the mFI is a powerful prognostic tool. Overall, identifying patients at risk prior to surgery can improve patient outcomes, discharge planning and post-operative support, and have long lasting financial benefits for the healthcare system. Prospective actions such as prehabilitation can improve the frailty status of surgical patients leading to better postoperative outcomes. This supports the formal incorporation of pre-operative frailty assessment using the mFI which has the potential to improve surgical risk stratification.

Keypoints

Question: Is the Modified Frailty Index (mFI) an effective tool for risk-stratifying surgical patients?

Findings: Based on this meta-analysis, the mFI strongly correlates with higher rates of post-operative complications, readmission, reoperation, discharge to skilled care, longer hospitalization periods, as well as greater rates of mortality.

Meaning: The mFI is an underappreciated prognostic indicator and formal incorporation of pre-operative frailty assessment using the mFI has the potential to improve surgical risk stratification.

Funding

This work is supported by the Boston Pepper Center NIA P30AG031679 (SB, IS) and NIA K76AG059996 (IS).

Financial disclosure statement

None of the authors have any conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.11.020.

References

1. Census Bureau. *Table 3. Projections of the Population by Sex and Selected Age Groups for the United States: 2015 to 2060*. Census Bureau; 2014. Available at: https://www2.census.gov/programs-surveys/popproj/tables/2014/2014-summary-tables/np2014-t3.xls. Accessed March 23, 2018.
2. Kwok AC, Semel ME, Lipsitz SR, et al. The intensity and variation of surgical care at the end of life: a retrospective cohort study. *Lancet*. 2011;378(9800):1408–1413.
3. Robinson T, Eiseman B, Wallace JI, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. *Ann Surg*. 2009;250(3):449–455.
4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–762.
5. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156.
6. Rockwood K, Fox RA, Stolee P, Robertson B, Beattie BL. Frailty in elderly people: an evolving concept. *CMAJ (Can Med Assoc J)*. 1994;150(4):489–495.
7. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ (Can Med Assoc J)*. 2005;173(5):489–495.
8. Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB, Walston JD. Interventions on frailty working group. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J Am Geriatr Soc*. 2004;52(4):625–634.
9. Mitnitski A, Xiaowei S, Skoog I, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. *J Am Geriatr Soc*. 2005;53(12):2184–5189.
10. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24.
11. Obeid NM, Azuh O, Reddy S. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. *J Trauma Acute Care Surg*. 2012;72:878–883.
12. McIsaac DI, Wong CA, Huang A, Moloo H, van Walraven C. Derivation and validation of a generalizable preoperative frailty index using population-based health administrative data. *Ann Surg*. 2018 Apr 18 [Epub ahead of print].
13. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF, American College of Surgeons National Surgical Quality Improvement Program; American Geriatrics Society. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the american College of surgeons national surgical quality improvement Program and the american geriatrics society. *J Am Coll Surg*. 2012;215(4):453–466.
14. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011] [Internet]. The Cochrane Collaboration*; 2011. Available at: http://handbook.cochrane.org/. Accessed March 2, 2018.
15. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926.
16. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses *Lancet*. 1999;354(9193):1896–1900.
17. Ali TZ, Lehman EB, Aziz F. Modified frailty index can Be used to predict adverse outcomes and mortality after lower extremity bypass surgery. *Ann Vasc Surg*. 2018;46:168–177.
18. Arya S, Long CA, Brahmbhatt R, et al. Preoperative frailty increases risk of

nonhome discharge after elective vascular surgery in home-dwelling patients. *Ann Vasc Surg*. 2016;35:19–29.

19. Brahmbhatt R, Brewster LP, Shafii S, et al. Gender and frailty predict poor outcomes in infrainguinal vascular surgery. *J Surg Res*. 2016;201(1):156–165.
20. Cloney M, D'Amico R, Lebovic J, et al. Frailty in geriatric glioblastoma patients: a predictor of operative morbidity and outcome. *World Neurosurg*. 2016;89: 362–367.
21. Konstantinidis IT, Chouliaras K, Levine EA, Lee B, Votanopoulos KI. Frailty correlates with postoperative mortality and major morbidity after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol*. 2017;24(13):3825–3830.
22. Leven DM, Lee NJ, Kothari P, et al. Frailty index is a significant predictor of complications and mortality after surgery for adult spinal deformity. *Spine*. 2016;41(23):E1394–E1401 (Phila Pa 1976).
23. Mazzola M, Bertoglio C, Boniardi M, et al. Frailty in major oncologic surgery of upper gastrointestinal tract: how to improve postoperative outcomes. *Eur J Surg Oncol*. 2017;43(8):1566–1571.
24. Mogal H, Vermilion SA, Dodson R, et al. Modified frailty index predicts morbidity and mortality after pancreaticoduodenectomy. *Ann Surg Oncol*. 2017 Jun;24(6):1714–1721.
25. Mosquera C, Spaniolas K, Fitzgerald TL. Impact of frailty on approach to colonic resection: laparoscopy vs open surgery. *World J Gastroenterol*. 2016;22(43): 9544–9553.
26. Phan K, Kim JS, Lee NJ, et al. Frailty is associated with morbidity in adults undergoing elective anterior lumbar interbody fusion (ALIF) surgery. *Spine J*. 2017;17(4):538–544.
27. Runner RP, Bellamy JL, Vu CCL, Erens GA, Schenker ML, Guild 3rd GN. Modified frailty index is an effective risk assessment tool in primary total knee arthroplasty. *J Arthroplasty*. 2017;32(9S):S177–S182.
28. Seib CD, Rochefort H, Chomsky-Higgins K, et al. Association of patient frailty with increased morbidity after common ambulatory general surgery operations. *JAMA Surg*. 2018;153(2):160–168.
29. Wachal B, Johnson M, Burchell A, et al. Association of modified frailty index score with perioperative risk for patients undergoing total laryngectomy. *JAMA Otolaryngol Head Neck Surg*. 2017;143(8):818–823.
30. Wen Y, Jabir MA, Dosokey EM, et al. Using modified frailty index to predict safe discharge within 48Hours of ileostomy closure. *Dis Colon Rectum*. 2017 Jan;60(1):76–80.
31. Wahl TS, Graham LA, Hawn MT, et al. Association of the modified frailty index with 30-day surgical readmission. *JAMA surgery*. 2017;152(8):749–757.
32. Abt NB, Richmon JD, Koch WM, Eisele DW, Agrawal N. Assessment of the predictive value of the modified frailty index for clavien-dindo grade IV critical care complications in major head and neck cancer operations. *JAMA Otolaryngol Head Neck Surg*. 2016;142(7):658–664.
33. Adams P, Ghanem T, Stachler R, Hall F, Velanovich V, Rubinfeld I. Frailty as a predictor of morbidity and mortality in inpatient head and neck surgery. *JAMA Otolaryngol Head Neck Surg*. 2013;139:783–789.
34. Ali R, Schwalb JM, Nerenz DR, Antoine HJ, Rubinfeld I. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery. *J Neurosurg Spine*. 2016;25(4):537–541.
35. Ehlert BA, Najafian A, Orion KC, Malas MB, Black 3rd JH, Abularrage CJ. Validation of a modified Frailty Index to predict mortality in vascular surgery patients. *J Vasc Surg*. 2016 Jun;63(6):1595–1601. e2.
36. Farhat JS, Velanovich V, Falyo AJ, et al. Are the frail destined to fail? Frailty index as predictor of surgical morbidity and mortality in the elderly. *J Trauma Acute Care Surg*. 2012;72(6):1526–1530.
37. Flexman AM, Charest-Morin R, Stobart L, Street J, Ryerson CJ. Frailty and postoperative outcomes in patients undergoing surgery for degenerative spine disease. *Spine J*. 2016 Nov;16(11):1315–1323.
38. Gani F, Cerullo M, Amini N, et al. Frailty as a risk predictor of morbidity and mortality following liver surgery. *J Gastrointest Surg*. 2017;21(5):822–830.
39. George EM, Burke WM, Hou JY, et al. Measurement and validation of frailty as a predictor of outcomes in women undergoing major gynaecological surgery. *BJOG*. 2016 Feb;123(3):455–461.
40. Karam J, Tsiouris A, Shepard A, Velanovich V, Rubinfeld I. Simplified frailty index to predict adverse outcomes and mortality in vascular surgery patients. *Ann Vasc Surg*. 2013 Oct;27(7):904–908.
41. Keller DS, Bankwitz B, Nobel T, Delaney CP. Using frailty to predict who will fail early discharge after laparoscopic colorectal surgery with an established recovery pathway. *Dis Colon Rectum*. 2014;57(3):337–342.
42. Kolbe N, Carlin AM, Bakey S, Louwers L, Horst M, Rubinfeld I. Assessing risk of critical care complications and mortality in the elective bariatric surgery population using a modified frailty index. *Obes Surg*. 2015 Aug;25(8): 1401–1407.
43. Lascano D, Pak JS, Kates M, et al. Validation of a frailty index in patients undergoing curative surgery for urologic malignancy and comparison with other risk stratification tools. *Urol Oncol*. 2015;33(10):426. e1–12.
44. Levy I, Finkelstein M, Bilal KH, Palese M. Modified frailty index associated with Clavien-Dindo IV complications in robot-assisted radical prostatectomies: a retrospective study. *Urol Oncol*. 2017;35(6):425–431.
45. Louwers L, Schnickel G, Rubinfeld I. Use of a simplified frailty index to predict Clavien 4 complications and mortality after hepatectomy: analysis of the National Surgical Quality Improvement Project database. *Am J Surg*. 2016;211(6): 1071–1076.
46. Park SJ, Bateni SB, Bold RJ, Kirane AR, Canter DJ, Canter RJ. The modified frailty index to predict morbidity and mortality for retroperitoneal sarcoma resections. *J Surg Res*. 2017 Sep;217:191–197.
47. Tsiouris A, Hammoud ZT, Velanovich V, Hodari A, Borgi J, Ilan Rubinfeld I. A modified frailty index to assess morbidity and mortality after lobectomy. *J Surg Res*. 2013 Jul;183(1):40–46.
48. Youngerman BE, Neugut AI, Yang J, Hershman DL, Wright JD, Bruce JN. The modified frailty index and 30-day adverse events in oncologic neurosurgery. *J Neuro Oncol*. 2018;136(1):197–206.
49. Vermillion SA, Hsu FC, Dorrell RD, Shen P, Clark CJ. Modified frailty index predicts postoperative outcomes in older gastrointestinal cancer patients. *J Surg Oncol*. 2017 Jun;115(8):997–1003.
50. *OCEBM Levels of Evidence Working Group the Oxford 2011 Levels of Evidence*. Oxford Centre for evidence-based medicine; 2011:5653. Available at: http://www.cebm.net/index.aspx?o=5653. Accessed March 23, 2018.
51. Shem Tov L, Matot I. Frailty and anesthesia. *Curr Opin Anaesthesiol*. 2017;30(3): 409–417.
52. Orkaby AR, Forman DE. Assessing risks and benefits of invasive cardiac procedures in patients with advanced multimorbidity. *Clin Geriatr Med*. 2016;32(2):359–371.
53. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med*. 2002;162: 2333–2341.
54. Kim KI, Park KH, Koo KH, Han HS, Kim CH. Comprehensive geriatric assessment can predict postoperative morbidity and mortality in elderly patients undergoing elective surgery. *Arch Gerontol Geriatr*. 2013;56:507–512.
55. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
56. Jenicek M. Clinical case reports and case series research in evaluating surgery. Part II. The content and form: uses of single clinical case reports and case series research in surgical specialties. *Med Sci Monit*. 2008;14(10):RA149–RA162.
57. Agha RA, Orgill DP. Evidence-based plastic surgery: its rise, importance, and a practical guide. *Aesthet Surg J*. 2016;36(3):366–371.