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Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery

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Background: Frailty is associated with poor prognosis, but the multitude of definitions and scales of assessment makes the impact on outcomes difficult to assess. The aim of this study was to quantify the effect of frailty on postoperative morbidity and mortality, and long-term mortality after major abdominal surgery, and to evaluate the performance of different frailty metrics.

Methods: An extended literature search was performed to retrieve all original articles investigating whether frailty could affect outcomes after elective major abdominal surgery in adult populations. All possible definitions of frailty were considered. A random-effects meta-analysis was carried out for all outcomes of interest. For postoperative morbidity and mortality, overall effect sizes were estimated as odds ratios (OR), whereas the hazard ratio (HR) was calculated for long-term mortality. The potential effect of the number of domains of the frailty indices was explored through meta-regression at moderator analysis.

Results: A total of 35 studies with 1153684 patients were analysed. Frailty was associated with a significantly increased risk of postoperative major morbidity (OR 2.56, 95 per cent c.i. 2.08 to 3.16), short-term mortality (OR 5.77, 4.41 to 7.55) and long-term mortality (HR 2.71, 1.63 to 4.49). All domains were significantly associated with the occurrence of postoperative major morbidity, with ORs ranging from 1.09 (1.00 to 1.18) for co-morbidity to 2.52 (1.32 to 4.80) for sarcopenia. No moderator effect was observed according to the number of frailty components.

Conclusion: Regardless of the definition and combination of domains, frailty was significantly associated with an increased risk of postoperative morbidity and mortality after major abdominal surgery.

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Introduction

One of the most challenging areas of surgery is accurate patient selection. Treatment decisions based on individual clinical judgement are subject to bias, and may result in inappropriate surgery and consequent adverse outcomes.

In the general population, there is a constant and growing demand for cure, with often unrealistic expectations. Strong patient motivation for surgery and a lack of standardized risk assessment may expose patients to excessive risk of major postoperative morbidity and mortality or poor long-term prognosis. Conversely, failure to offer surgery with curative intent to patients who are judged unfit based on generic and imprecise risk variables is unacceptable^{1,2}. Despite technical improvements and advances in perioperative care, major abdominal operations are still associated with a high rate of severe complications, long-term disability, and health and social costs³⁻⁷. Moreover, the likelihood of successfully rescuing patients from surgery-related morbidity is still unpredictable. Failure to rescue is defined as the probability of death after a major complication^{8,9}. Whether a patient is salvaged after a complication is a function of the care delivered by the hospital, and its resources and facilities, but mostly of patient resilience¹⁰. Failure to rescue frequently occurs in frail patients lacking the physiological reserve to survive major postoperative complications, even when treated with best available care. Frailty is a state of vulnerability to

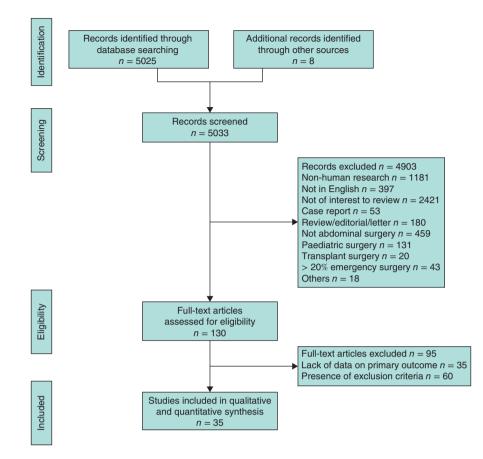


Fig. 1 PRISMA flow chart showing selection of articles for review

poor resolution of homeostasis following a stressor event. It develops as a consequence of cumulative decline across multiple physiological systems, and increases the risk of adverse events¹¹.

Recently, it has been suggested that chronological age and co-morbidity are inappropriate parameters to decide whether a patient should undergo a surgical procedure¹². On the contrary, frailty may reflect a more accurate and individualized parameter of 'biological age'¹³. Thus, frailty should not be considered as an exclusive state of ageing and may be detected in any person with limited functional reserve for several different reasons.

Different frailty scales have been applied to surgical cohorts, regardless of age, as a predictor of surgery-related morbidity and mortality, with consistent results^{14–16}. The multitude of definitions and scoring systems and the metric complexity that have been proposed in the surgical scenario, may limit routine assessment, and make it difficult to understand and decide whether it is valuable to incorporate frailty estimates into daily clinical practice.

The purpose of this study was to review the scoring methods used to evaluate frailty in surgical patients, and to

assess their ability to predict adverse clinical outcomes. In particular, the aim was to assess the global impact of frailty on postoperative morbidity and mortality, and long-term mortality in patients undergoing major abdominal operations, and to assess whether frailty metric predictive performance may differ based on the number of domains considered in the definition of frailty.

Methods

Study selection

An extended web search of the literature was performed in January 2017 by two authors. MEDLINE, Embase, PubMed, Cochrane and Scopus libraries were queried, and all papers analysing the potential impact of frailty among surgical patients, written in English and published from 1990, were considered for inclusion (*Table S1*, supporting information). The related articles function and the reference lists of the studies retrieved for full-text review were used to broaden the search. In the event of overlap of institutions, authors or patients, the most recent article was considered.

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Reference		No. of patients	Odds ratio	Weight (%)
Buettner <i>et al.</i> ²³		1326	2.28 (1.72, 3.01)) 4.56
Choi et al.24		281	8.51 (2.21, 32.79)) 1.62
Courtney–Brooks et al. ²⁶		37	8.33 (1.23, 56.67)	0.96
Erekson <i>et al.</i> ²⁸		22 114	6.97 (4.46, 10.89)) 4.06
George et al.29		66 105	2.02 (1.74, 2.34)) 4.85
Jones et al. ³¹		100	4.81 (1.32, 17.61)) 1.71
Kenig et al. ³²		75	4.10 (1.30, 9.60)) 2.33
Kim et al. ³³		275	1.17 (0.92, 1.49)	4.66
Kristjansson <i>et al</i> . ³⁴		178	7.58 (1.61, 35.68)) 1.33
Kuroki et al.35		122	0.75 (0.35, 1.58)) 3.04
Lascano et al. ³⁶		18 384	3.70 (2.87, 4.79)) 4.63
Levy et al. ³⁷		23 104	2.2 (1.71, 2.84)) 4.63
Makary et al.38		594	2.39 (1.39, 4.09)) 3.74
Mogal <i>et al</i> . ³⁹		9986	1.80 (1.53, 2.12)) 4.82
Obeid et al.41	□	58 448	6.02 (5.68, 6.39)) 4.95
Pearl et al.43		4329	1.52 (1.23, 1.88)) 4.73
Resinger et al.44		159	3.96 (1.14, 13.83)) 1.80
Revenig et al.45		214	2.07 (1.05, 4.08)) 3.27
Revenig et al. ⁴⁶		80	5.91 (1.25, 27.26)) 1.35
Revenig et al. ¹		351	2.14 (1.33, 3.44)) 3.95
Robinson et al. ¹²		72	3.77 (1.34, 10.57)	
Saxton and Velanovich ⁴⁷ (2)		226	1.37 (0.88, 2.13)	
Sur et al. ⁴⁸		100	4.72 (1.26, 17.71)	
Suskind et al.49	0	95 108	1.55 (1.48, 1.62)) 4.96
Tan <i>et al</i> . ⁵⁰		83	3.97 (1.42, 11.14)) 2.25
Tegels <i>et al</i> . ⁵¹		127	3.62 (1.53, 8.58)	
Uppal <i>et al.</i> ⁵² (1)		6551	2.33 (1.05, 5.19)) 2.88
Uppal <i>et al</i> . ⁵² (2)		6551	12.5 (4.47, 32.76)) 2.34
Velanovich et al.53 (1)		727 041	1.75 (1.73, 1.77)) 4.97
Velanovich et al.53 (2)		23 569	1.31 (1.21, 1.43)) 4.93
Overall: $P < 0.001$, $l^2 = 98.4\%$ 0.5	1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.1	- 10 65 690	2.56 (2.08, 3.16)) 100
Not frail	Frail			

Fig. 2 Forest plot of the effect of frailty on major postoperative morbidity. Odds ratios are shown with 95 per cent confidence intervals

Inclusion and exclusion criteria

All original articles investigating whether frailty could affect outcomes after elective major abdominal surgery in adult populations were included. Given the lack of a standard definition or consensus on the ideal frailty metric, all possible author descriptions for inclusion were considered, with no limitations on the number of items and domains used for frailty assessment.

Allocation to the frail or not-frail group reflected the definition provided by each author. Patients of intermediate frailty were included in the frail group.

Major abdominal surgery was defined as all gastrointestinal (colorectal, gastric, small bowel, hepatic, pancreatic resection), urological (nephrectomy, cystectomy, prostatectomy) and gynaecological (uterus and ovary resection, pelvic floor reconstruction) operations, undertaken for any indication. Studies focusing on vascular, cardiac, thoracic and transplant operations were excluded. Open and laparoscopic procedures were included. Emergency surgery was defined as any operation performed within 48 h of unplanned admission from the emergency department. Any study reporting both elective and emergency abdominal operations was included if at least 80 per cent of patients had an elective procedure.

Four authors evaluated the eligibility of the studies, which were included if they provided information on at least one of the three primary outcomes (postoperative morbidity, short-term and long-term mortality). Where studies reported a frailty metric tested in different cohorts (separate data sets for types of surgery), or tested more than one frailty metric in the same cohort of patients, the two groups were analysed as separate series. Review articles, opinion letters and case reports were not considered.

Outcomes of interest

The primary outcomes were 30-day major morbidity, defined according to the Clavien–Dindo classification¹⁷,

Table 1 Characteristics of studies included in the systematic review and meta-analysis

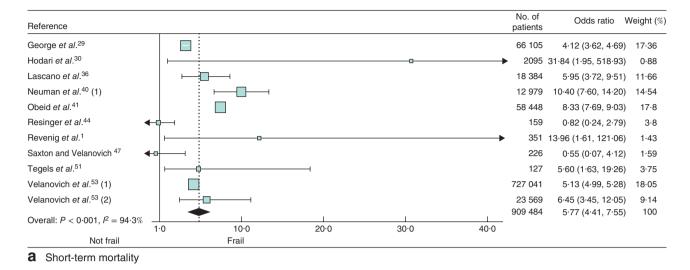
Defenses	Ocumbra	No. of	Age	Frail	Type of	No. of		Morbidity	Mortality
Reference	Country	patients	(years)*	(%)	operation	items	Domains†	definiton	definition
Amrock et al. ²² (1)	USA	76 106	74.4	n.r.	Lower GI	5	RDA; CO; NS; CF; A	NSQIP	30 days
Amrock <i>et al.</i> ²² (2)	USA	76 106	74.4	n.r.	Lower GI	3	CO; NS; A	NSQIP	30 days
Buettner et al. ²³ (1)	USA	1326	65	n.r.	Mixed GI	12	RDA; CO (10); CA	CDC III-IV	1 year
Buettner <i>et al.</i> ²³ (2)	USA	1326	65	30.0	Mixed GI	1	S	CDC III-IV	1 year
Choi et al.24	Korea	281	74.8	26.3	Mixed abdominal	9	S; RDA (2); CO; NS (2); CF (2); CA	NSQIP	n.r.
Cohan <i>et al.</i> ²⁵	USA	2493	n.r.	21.3	Lower GI	6	RDA; CO (4); NS	NSQIP	n.r.
Courtney-Brooks et al. ²⁶ ‡	USA	37	73	16	Gynaecological	5	PF; NS; DE; GS; W	NSQIP	n.r.
Dale <i>et al.</i> ²⁷ ‡	USA	76	67.3	n.r.	Upper GI	4	NS; DE; GS; W	CDC III-IV	n.r.
Erekson <i>et al.</i> ²⁸	USA	22 214	n.r.	0.54	Gynaecological	1	NS	Overall	n.r.
George et al. ²⁹	USA	66 105	n.r.	15.5	Gynaecological	11	RDA; CO (9); CF	CDC IV	30 days
Hodari <i>et al.</i> ³⁰	USA	2095	n.r.	n.r.	Upper GI	11	RDA; CO (10)	n.r.	30 days
Jones <i>et al.</i> ³¹	UK	100	68.6	15.0	Lower GI	1	S	n.r.	n.r.
Kenig <i>et al.</i> ³² ‡	Poland	75	75	8	Mixed GI	8	RDA (2); M; CO; NS; CF; DE; W	CDC III-IV	n.r.
Kim <i>et al.</i> ³³ ‡	Korea	275	75.4	35.6	Mixed abdominal	9	S; RDA (2); CO; NS (2); CF (2); CA	NSQIP	1 year
Kristjansson <i>et al.</i> ³⁴ ‡	Norway	178	76.6	42.7	Lower GI	7	RDA (2); M; CO; NS; CF; DE	CDC III-IV	n.r.
Kuroki <i>et al.</i> ³⁵	USA	122	65.9	50.0	Gynaecological	1	S	n.r.	n.r.
Lascano <i>et al.</i> ³⁶	USA	18 384	57.7	n.r.	Urological	15	RDA; CO (10); NS; CF (2); CA	CDC IV	30 days
Levy et al. ³⁷	USA	23 104	61.9	54.8	Urological	15	RDA; CO (10); NS; CF (2); CA	CDC IV	30 days
Makary et al. ³⁸ ‡	USA	594	72.8	10.4	Mixed GI	5	RDA; NS; DE; GS; W	NSQIP	n.r.
Mogal <i>et al.</i> ³⁹	USA	9986	64.1	6.4	Upper GI	11	RDA; CO (10);	CDC III-IV	30 days
Neuman <i>et al.</i> ⁴⁰ (1)	USA	12 979	84.4	4.3	Lower GI	5	CO; NS; W; F; O	n.r.	90 days
Neuman <i>et al.</i> ⁴⁰ (2)	USA	12 979	84.4	4.3	Lower GI	5	CO; NS; W; F; O	n.r.	1 year
Obeid <i>et al.</i> ⁴¹	USA	58 448	n.r.	12.8	Lower GI	11	RDA; CO (10)	CDC IV	30 days
Ommundsen <i>et al.</i> ⁴²	Norway	178	80	42.7	Lower GI	6	RDA; M; CO; NS; CF; DE	n.r.	1 year
Pearl <i>et al.</i> ⁴³	USA	4329	n.r.	67.2	Urological	11	RDA; CO (10)	n.r.	n.r.
Reisinger <i>et al.</i> ⁴⁴ ‡	The Netherlands	159	n.r.	25.8	Lower GI	7	RDA; PF; M; NS; CF; VH; DE	Sepsis	30 days
Revenig <i>et al.</i> ⁴⁵ ‡	USA	214	62	16	Mixed abdominal	5	PF; NS; DE; GS; W	Overall	n.r.
Revenig <i>et al.</i> ⁴⁶ ‡	USA	80	60.0	23.4	Mixed abdominal	5	PF; NS; DE; GS; W	CDC II-III-IV	n.r.
Revenig <i>et al.</i> 1‡	USA	351	63	27.3	Mixed abdominal	5	RDA; NS; DE; GS; W	n.r.	30 days
Robinson <i>et al.</i> ¹² ‡	USA	72	74	33	Lower GI	8	RDA; CO; NS; CF; W; A; F; O	VASQIP	n.r.
Saxton and Velanovich47 (1)	USA	226	61	n.r.	Mixed GI	70	CSHA	Overall	30 days
Saxton and Velanovich47 (2)	USA	226	61	n.r.	Mixed GI	70	CSHA	CDC II-III-IV	n.r.
Sur et al. ⁴⁸	USA	100	65.6	31.0	Upper GI	1	DE	NSQIP	n.r.
Suskind <i>et al.</i> ⁴⁹	USA	95 108	n.r.	21.5	Urological	11	RDA; CO (10)	NSQIP	n.r.
Tan e <i>t al.</i> 50‡	Japan	83	81.2	28	Lower GI	5	RDA; NS; DE; GS; W	CDC II-III-IV	n.r.
Tegels et al. ⁵¹ (1)	The Netherlands	127	69.8	23.6	Upper GI	7	RDA; PF; M; NS; CF; VH; DE	CDC III-IV	In hospital
Tegels et al. ⁵¹ (2)	The Netherlands	127	69.8	n.r.	Upper GI	7	RDA; PF; M; NS; CF; VH; DE	CDC III-IV	6 months
Uppal <i>et al.</i> ⁵² (1) and (2)§	USA	6551	n.r.	n.r.	Gynaecological	11	RDA; CO (10)	CDC III-IV	n.r.
Velanovich et al.53 (1)	USA	727 041	n.r.	n.r.	Mixed abdominal	11	RDA; CO (10)	Overall	30 days
Velanovich et al.53 (2)	USA	23 569	n.r.	n.r.	Gynaecological	11	RDA; CO (10)	Overall	30 days
Wagner et al.54	USA	518	72	25.1	Upper GI	1	S	n.r.	1 year
-									

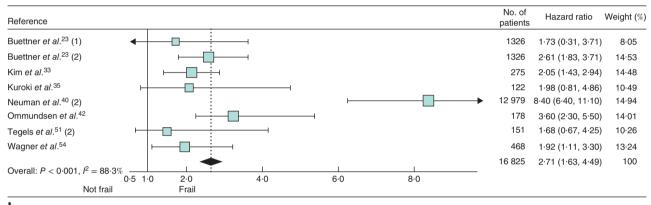
*Values are mean or median. †Values in parentheses are number of items used to create the domain. ‡Prospective studies; the others were retrospective. \$Uppal and colleagues⁵² considered two different scores for the same metric system, on the same population; morbidity outcomes are reported separately for the two scores. n.r., Not reported; GI, gastrointestinal; RDA, reduced daily activities; CO, co-morbidity; NS, nutritional status; CF, cognitive function; A, anaemia; NSQIP, National Surgical Quality Improvement Program; CA, cancer; CDC, Clavien–Dindo classification; S, sarcopenia; PF, physical fitness; DE, depression/exhaustion; GS, grip strength; W, walking test; M, medication; F, falls; O, others; VH, visual and hearing deficit; VASQIP, Veterans Affairs Surgical Quality Improvement Program; CSHA, Canadian Study of Health and Aging 70 Item Frailty Score.

or the National Surgical Quality Improvement Program (NSQIP)¹⁸ or the Veterans Affairs Surgical Quality Improvement Program (VASQIP)¹⁹ classification; short-term mortality, defined as death within 90 days after operation; and long-term mortality, defined as any death occurring before 1 year after surgery. Secondary outcomes were rates of hospital readmission and discharge to a location other than home.

Data collection

Data were extracted independently by four investigators; if there was disagreement, two impartial raters cross-checked the data. Data collected included: first author, country of origin, year of publication, type of surgery, rate of operations for cancer disease and/or emergency surgery, cohort samples, number and type of screening tools used to assess frailty, and outcome measures.





b Long-term mortality

Fig. 3 Forest plots of the effect of frailty on a short-term and b long-term mortality. Odds ratios and hazard ratios are shown with 95 per cent confidence intervals

Statistical analysis

A random-effects meta-analysis was performed for all outcomes of interest. Odds ratios (OR) were calculated for postoperative morbidity and mortality, and hazard ratios (HRs) for long-term mortality. P < 0.050 was considered statistically significant. The weights assigned to each study were computed according to the inverse of the variance. Heterogeneity was quantified using I^2 and τ^2 indices, and testing the null hypothesis that all studies shared a common effect size. Publication bias was assessed with Egger's test and funnel plots^{20,21}.

Subgroup analyses were carried out according to the type of surgery. The effects of age and the number of domains of the frailty indices on morbidity were explored through meta-regression and moderator analysis. Given the high variability in frailty assessment, the aim was to explore the predictive ability of each frailty domain on the primary outcomes, so random-effects meta-analyses were performed for each frailty item used in the scores. The effect sizes used were those reported for each specific score item in each study. If separate data for each item comprising the frailty score were not provided, the combined-effect score was used. Two different metaanalyses were performed with the first including all studies, and the second including only those for which the effect sizes were reported for each item individually.

Results

Study selection

Some 5033 titles were identified and 4903 were excluded. Some 130 full-text articles were examined and, after

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Reference	Reduced daily activity	Sarcopenia	Co-morbidities	Nutritional status	Cognitive function	Depression/ exhaustion	Walking test	No. of patients
Odds ratio								
Amrock et al. ²² (1)	2.08 (1.89, 2.32)	-	-	1.34 (1.28, 1.40)	1.21 (1.10, 1.43)	-	-	76 106
Amrock et al. ²² (2)	-	-	1.09 (1.00, 1.18)	1.45 (1.43, 1.58)	-	-	-	76 106
Buettner et al.23 (2)	-	2.28 (1.72, 3.01)	-	-	-	-	-	1326
Choi et al. ²⁴	3.66 (0.94, 14.20)	4.57 (1.98, 10.50)	1.27 (0.55, 2.89)	3.25 (1.42, 7.46)	3.01 (1.31, 6.90)	-	-	281
Dale et al.27	-	-	-	0.81 (0.29, 2.26)	-	4.04 (1.40, 11.80)	1.02 (0.50, 2.06)	76
Jones et al. ³¹	-	4.81 (1.32, 17.60)	-	-	-	-	-	100
Erekson et al.28	-	-	-	2.49 (1.48, 4.17)	-	-	-	22 214
Kenig et al. ³²	1.70 (0.50, 5.80)	-	1.20 (0.40, 3.50)	1.10 (0.40, 2.90)	1.70 (0.50, 5.80)	1.10 (0.20, 2.40)	3.60 (1.10, 13.40)	75
Kuroki <i>et al.</i> ³⁵	-	0.74 (0.35, 1.58)	-	-	-	-	-	122
Revenig et al. ¹	1.11 (0.59, 2.10)	-	-	1.90 (1.22, 2.96)	-	1.49 (0.94, 2.36)	1.63 (0.69, 3.86)	351
Sur et al. ⁴⁸	-	4.72 (1.26, 17.7)	-	-	-	3.70 (1.21, 1.71)	-	100
Overall	1.85 (1.29, 2.66)	2.52 (1.32, 4.80)	1.09 (1.00, 1.18)	1.45 (1.31, 1.62)	1.65 (0.89, 3.07)	2.13 (1.12, 4.06)	1.56 (0.82, 2.97)	
P (effect)	0.001	0.005	0.041	< 0.001	0.112	0.022	0.174	
l ² (%)	31.8	70.7	0	65.6	58.5	45.6	34.5	
P (heterogeneity)	0.220	0.008	0.923	0.008	0.090	0.028	0.217	
No. of patients	76 813	1929	76 462	175 209	76 462	602	502	

Table 2 Analysis of studies reporting the effect size for each item of the score in predicting major postoperative morbidity

Values in parentheses are 95 per cent confidence intervals.

exclusions based on abstract review, 35 studies were included in the analysis (*Fig. 1*).

Study characteristics and frailty assessment

No randomized trials were retrieved. Most studies were observational (23 of 35) with a total of 1 153 684 patients available for the analysis. Cohorts were composed of patients undergoing lower gastrointestinal (GI) surgery (10 studies), upper GI surgery (6), mixed GI surgery (4), gynae-cological surgery (6), urological surgery (4) and mixed abdominal surgery (6) (*Table 1*)^{1,1,2,2-54}.

Frailty was assessed through many combinations of different components, ranging from one to 70 items. The prevalence of frail patients ranged from 0.5 to 67.2 per cent. Most surgical procedures were performed for cancer; only four studies^{25,28,29,41} had fewer than half of the patients without malignancy.

Outcomes of interest

In analyses of all the included studies, frailty was associated with an increased risk of postoperative major morbidity (OR 2.56, 95 per cent c.i. 2.08 to 3.16); the I^2 value for heterogeneity was 98.4 per cent (*Fig. 2*). The OR for short-term mortality was 5.77 (4.41 to 7.55) (*Fig. 3a*) and the HR for long-term mortality was 2.71 (1.63 to 4.49) (*Fig. 3b*). Heterogeneity was high ($I^2 = 94.3$ per cent for short-term mortality and $I^2 = 88.3$ per cent for long-term mortality).

Only for major morbidity was the distribution of studies asymmetrical, although no significant publication bias was detected by Egger's linear regression test (P = 0.211, P = 0.666 and P = 0.143 for major morbidity, and shortand long-term mortality respectively) (*Fig. S1*, supporting information).

Subgroup and moderator analyses

To lower the potential bias related to different operations, a subgroup analysis was undertaken according to the type of surgery. The effect of frailty on major morbidity was confirmed across all specialties. Similarly, the association between frailty and the likelihood of death was confirmed for all types of surgery, except for mixed elective surgery (727 267 patients), where the effect on short-term mortality was no longer observed (OR 2·14, 95 per cent c.i. 0·25 to 18·12; P = 0.485) (*Table S2*, supporting information).

Because frailty may be related to ageing, moderator analysis was performed to adjust for potential differences in population ageing across the studies. No moderator effect of age on postoperative morbidity ($\beta = -0.08$, $\alpha = 0.01$, P = 0.503) or short-term mortality ($\beta = -0.29$, $\alpha = 0.03$, P = 0.426) was detected. On meta-regression, age modulated the effect of frailty on long-term mortality ($\beta = -3.38$, $\alpha = 0.06$, P = 0.021) (*Fig. S2*, supporting information).

No moderator effect on the primary outcomes was observed according to the number of frailty index components ($\beta = 1.06$, $\alpha = -0.01$, P = 0.215 for postoperative morbidity; $\beta = 2.17$, $\alpha = -0.04$, P = 0.172 for short-term mortality; $\beta = 0.75$, $\alpha = 0.04$, P = 0.419 for long-term mortality) (*Fig. S3*, supporting information).

The cumulative risk of readmission was significantly increased in frail patients (OR 3.78, 95 per cent c.i. 1.77 to 8.05; P = 0.001), whereas frailty was not significantly associated with discharge to a location other than home (OR 3.74, 0.81 to 17.30; P = 0.091) (*Fig. S4*, supporting information).

Frailty scores and domains

Ten studies reported data on the risk of morbidity for a single frailty domain. To analyse potential different effects on outcome prediction, several different meta-analyses were carried out for each frailty domain considered. All domains, except cognitive function and walking test, were significantly associated with the occurrence of major post-operative morbidity, with ORs ranging from 1.09 (95 per cent c.i. 1.00 to 1.18) for the presence of co-morbidities, to 2.52 (1.32 to 4.80) for sarcopenia (*Table 2*).

Comparable results were observed after adding studies to the meta-analyses that did not provide separate ORs for each frailty domain (*Fig. S5*, supporting information).

Discussion

This meta-analysis included data from 35 studies reporting over one million patients. Preoperative existence of a frailty condition was associated with more than double the risk of developing major postoperative morbidity, a six times higher risk of early postoperative mortality, and a threefold increase in long-term mortality compared with non-frail patients. This suggests that, in patients who are scheduled for major surgical interventions, frailty should always be assessed before deciding whether to, and how to, proceed.

Even more worrisome is the discrepancy between the rate of major morbidity and short-term mortality after surgery. Early deaths after elective operations are expected to be a consequence of major morbidity, related directly to the procedure, rather than as a consequence of the primary disease. A similar risk of short-term mortality and major morbidity would therefore be expected. It can be hypothesized that an underlying frailty condition may be responsible for failure to rescue after the occurrence of a major surgical complication^{8–10}. This issue should not be underestimated in the decision-making process when assessing possible alternatives to surgery.

A limitation of the present analysis is the high degree of heterogeneity of the studies for all primary outcomes. A possible explanation lies in the inclusion criteria applied to select studies, incorporating all studies reporting major abdominal operations, including gastrointestinal, urological and gynaecological or mixed procedures. However, on subgroup analysis frailty remained a risk factor for adverse outcomes across different surgical procedures. An additional potential source of heterogeneity was the variability in the definition of major postoperative morbidity, although all of the scores of complication severity have been validated extensively and are commonly accepted in the surgical community^{17–19}.

Another potential source of bias was ageing. In non-surgical cohorts, a clear correlation between prevalence of frailty and age has been reported⁵⁵. The meta-regression showed that age *per se* did not increase the risk of major postoperative morbidity and short-term mortality. This supports frailty as a marker of 'biological age' with more value than chronological age¹³. Conversely, ageing modulated the effect size of long-term mortality in meta-regression, suggesting that other factors contribute to long-term mortality.

The results of this meta-analysis should be interpreted with caution because of the variability in the definition of frailty across studies and the number of domains used to measure this condition. Frailty was assessed using 12 different definitions, which incorporated from one to 70 domains in different combinations. Nevertheless, the subgroup analysis of different domains, and the meta-regression on the number of items, showed that the risk estimates for each outcome remained similar after stratification. This suggests that complex methods to assess frailty are not superior to simple ones, and that each domain may have an independent weight in composing the overall risk. In this context, the present data do not support the superiority of one frailty definition nor the superiority of one domain over the others in the creation of frailty scales.

The ultimate risk metrics should be easy to measure, accurate, objective, reproducible, transferable, quick and cheap. Even the most accurate score may become unusable if too complex and time-consuming, thereby reducing its practicality. Feasibility is a function of the time, expertise and resources available in daily clinical practice; whether to apply comprehensive and inclusive frailty assessments or instead to use quick and easy screening tools may depend on many local variables, but should be taken into consideration in each healthcare organization.

A recent study⁵⁶ demonstrated that frail surgical patients consume significantly more healthcare resources after hospital discharge, including 30-day readmission, than non-frail patients. These results further corroborate the importance of providing a preoperative frailty evaluation in patients undergoing major surgery, as it is possible that

Frailty metrics in major abdominal surgery

the cost of readmissions and additional treatment may exceed the cost of frailty assessments.

The secondary endpoints of this study fully confirmed the above results. There was a higher rate of discharge to a location other than home and hospital readmission in frail patients.

Choosing the right treatment for the right patient is essential in achieving the best outcome⁵⁷. A question raised is how to use the finding that frailty is a risk factor for poor surgical outcome. It could be used to restrict access of frail patients to major surgery, although this is somewhat constraining given the increasing proportion of older and frail patients⁵⁸. It could enable more individual risk assessment, discussion and consent to take place, or indeed allow targeted preoperative optimization of patients. A recent commentary by Wick and Finlavson⁵⁹ challenges medical research to 'move from measurement to action', with the need to demonstrate that outcomes may be truly improved by modifying frailty components. Integrated care delivery models, such as enhanced recovery after surgery programmes, have already confirmed the possibility of significantly improving clinical and functional outcomes in elderly and high-risk patients⁶⁰⁻⁶². In this situation, despite limited evidence, prehabilitation programmes, including preoperative optimization of coexisting chronic disease therapy, nutritional status, physical function and physiological support⁶³⁻⁶⁵, may represent a more comprehensive and effective opportunity.

Regardless of the tools and combinations of domains used to create a frailty index, this condition is significantly associated with an increased risk of developing major complications, and of short- and long-term mortality after abdominal operations.

Disclosure

The authors declare no conflict of interest.

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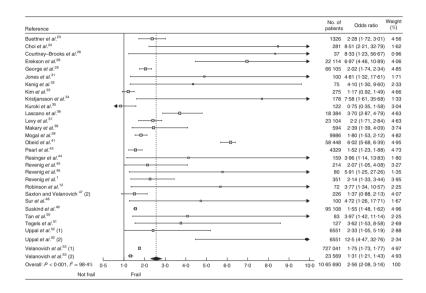
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Graphical Abstract

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We ran a random-effect meta-analysis to evaluare the effect of frailty on morbidity and postoperative mortality. A total of 35 studies with 1 135 300 patients were analysed. Frailty was associated with a significantly increased risk of postoperative major morbidity, short-term mortality and long-term mortality.