Systematic review and meta-analysis of the association between frailty and outcome in surgical patients

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ABSTRACT

INTRODUCTION Frailty is becoming increasingly prevalent in the elderly population although a lack of consensus regarding a clinical definition hampers comparison of clinical studies. More elderly patients are being assessed for surgical intervention but the effect of frailty on surgical related outcomes is still not clear.

METHODS A systematic literature search for studies prospectively reporting frailty and postoperative outcomes in patients undergoing surgical intervention was performed with data collated from a total of 12 studies. Random effects meta-analysis modelling was undertaken to estimate the association between frailty and mortality rates (in-hospital and one-year), length of hospital stay and the need for step-down care for further rehabilitation/nursing home placement.

RESULTS Frailty was associated with a higher in-hospital mortality rate (pooled odds ratio [OR]: 2.77, 95% confidence interval [CI]: 1.62–4.73), a higher one-year mortality rate (pooled OR: 1.99, 95% CI: 1.49–2.66), a longer hospital stay (pooled mean difference: 1.05 days, 95% CI: 0.02–2.07 days) and a higher discharge rate to further rehabilitation/step-down care (pooled OR: 5.71, 95% CI: 3.41–9.55).

CONCLUSIONS The presence of frailty in patients undergoing surgical intervention is associated with poorer outcomes with regard to mortality and return to independence. Further in-depth studies are required to identify factors that can be optimised to reduce the burden of frailty in surgical patients.

KEYWORDS

Frailty – Elderly – Postoperative outcomes – Mortality rates – Sarcopenia

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The aging population alongside technological advances in surgical and anaesthetic techniques present surgeons with increasing dilemmas as to whether to intervene on elderly patients with a number of surgical conditions in both the elective and emergency setting.^{1,2} It is well recognised that age is a predictor of poorer postoperative outcomes, which in turn predict poor long-term survival.^{3,4} Nevertheless, not all older patients have poor surgical outcomes. The concept of frailty is a recognised syndrome in the field of elderly medicine (although there is little consensus on its exact definition),^{5,6} and there is recognition of an overlap between frailty and other geriatric syndromes including sarcopenia.^{7,8} This lack of definition has resulted in a lack of consensus on the optimal method to determine frailty.⁹

Not all elderly patients have a frailty phenotype, which suggests that frailty is not an inevitable consequence of aging and as such, may be amenable to treatment. The presence of a frailty phenotype has potential significance in an elderly surgical population as perioperative frailty related interventions may improve outcomes. However, it

is essential to first determine what effect frailty has on the outcomes of commonly performed surgical procedures. The aim of this study was to estimate the association between frailty and adverse patient events in surgical patients using meta-analysis.

Methods

An electronic search was undertaken using the PubMed and MEDLINE® databases from 1 January 1980 to 1 October 2012. The search employed the terms ‘frailty’ and ‘sarcopenia’ combined with the terms ‘surgery’, ‘postoperative’ and ‘hospital discharge’. Abstracts of the citations identified by the search were scrutinised by two of the authors (KO and RN) to determine eligibility for inclusion in the analysis. Studies were deemed eligible if they were purely prospective studies, included surgically related outcomes (specifically mortality rates, complication rates, length of stay [LOS] and need for postoperative placement in rehabilitation facilities) and reported on at least 50 patients.

There is no widely accepted definition of frailty. Scores relating to functional or cognitive dependence, weight, muscle mass and co-morbid illness have been developed⁹ but these have not been widely adopted or standardised. It is therefore not yet possible to capture a frail population using one discrete definition. As a consequence, studies were eligible if they defined frailty objectively and had a comparator 'non-frail' group. Patients undergoing all forms of surgery (elective and emergency) except surgery for fractured neck of femur were included. Fractured neck of femur patients were excluded as the widespread involvement of orthogeriatricians could bias the comparability of these patients. Further references were found through scrutinised review of the bibliographies of selected articles to identify any articles missed by the searches.

Outcomes of the meta-analysis were 1-year mortality and early mortality (ie in-hospital mortality). For studies where in-hospital mortality was not reported, 30-day mortality or mortality 'following surgery' were used. Other outcome measures assessed were LOS and requirement for step-down rehabilitation placement. Overall and organ specific complication rates, where reported, are also summarised in this review.

Statistical analysis

All analyses were performed using the random effects model for meta-analysis, employing the DerSimonian and Laird method.¹⁰ The meta-analyses of binary outcomes (in-hospital and one-year mortality, need for rehabilitation) used study specific log odds ratios (comparing frail with non-frail patients) as outcome data, and the resulting pooled estimates and confidence intervals were converted to odds ratios (ORs). Since the binary outcomes were all adverse events, a positive OR indicated that frailty is associated with worse patient outcomes. The LOS meta-analysis used study specific mean differences of LOS as outcome data, where a positive mean difference indicated that frailty is associated with longer hospital stays.

All analyses used numerical values (eg percentages, counts, means) reported by the studies. In some circumstances, further calculations were needed to ascertain the outcome data but no values were obtained by attempting to read them from graphs. Twelve studies were deemed suitable for meta-analysis. Six studies provided outcome data for two distinct groups of patient groups ('frail' and 'non-frail' groups).^{11–16} One study provided outcome data for four groups but identified one of these groups as patients with sarcopenia;¹⁷ this group was used for frail data. The other five studies provided data for multiple patient groups and did not define a threshold to indicate frailty.^{18–22}

With the exception of the study by Sündermann *et al*,¹⁸ data from the frailest group of patients provided our frail outcome data and the other groups were combined to provide our non-frail outcome data. However, as the most frail group ('severely frail') in the study by Sündermann *et al* contained only 19 patients (9%) and also because the next most frail group consisted of 95 clearly frail ('moderately frail') patients (45%), it was decided to combine the

severely and moderately frail data to provide frail outcome data. This decision was made prior to performing the statistical analyses that follow.

In two studies, a single patient in the group of patients defined as being frail died.^{20,22} These single deaths are not included in the in-hospital mortality meta-analysis because the zero counts in the corresponding non-frail group would require artificial correction to include them in the random effects meta-analysis and the resulting normal approximation would be especially crude and could result in bias, especially for relatively small studies such as these.

The study by Makary *et al* provided mean lengths of hospital stay but did not report the associated standard deviations.²¹ This information is needed for the calculation of the within-study variance of the mean difference. As a result, the data for LOS from this study were not used. The 2011 study by Peng *et al* provided data on LOS stratified by sex.¹⁷ The pooled (across the two sexes) standard deviations for this study were therefore used to calculate the corresponding within-study variance.

The results from the meta-analyses are presented as pooled ORs (with 95% confidence intervals [CIs]) for in-hospital mortality, one-year mortality and the requirement for step-down rehabilitation. The pooled mean difference (with 95% CI) is presented for the LOS. I^2 statistics are also presented to describe the extent of the between-study heterogeneity. Other postoperative complications were investigated qualitatively.

Results

A total of 385 potentially relevant articles were identified (Fig 1), of which 12 met the inclusion requirements for our systematic review, corresponding to a total of 7,960 patients (Table 1). Of the 7,300 patients for whom sex was reported, 5,392 were men (73.9%). Of the twelve studies, one assessed patients undergoing elective non-cardiac surgery, four assessed patients undergoing cardiac surgery, six assessed patients undergoing gastrointestinal/hepatopancreaticobiliary surgery and one assessed patients undergoing open abdominal aortic aneurysm surgery (Table 1). The objective measures of frailty used in each study are documented in Table 1.

In-hospital/one-year mortality

In-hospital 30-day mortality was reported in 6 studies (Table 2).^{15–18} The pooled OR for the association between frailty and in-hospital mortality was 2.77 (95% CI: 1.62–4.73, $I^2=16\%$). One-year mortality rates were reported in five studies.^{11,13,17–19} The pooled OR for the association between frailty and one-year mortality was 1.99 (95% CI: 1.49–2.66, $I^2=0\%$).

Length of stay

Data for LOS were available in four studies.^{12,13,17,22} The pooled mean difference between the LOS for frail and non-frail patients was 1.05 days (95% CI: 0.02–2.07 days, $I^2=21\%$).

Need for step-down rehabilitation

Six studies reported on the need for step-down rehabilitation.^{12,15,16,20–22} The pooled OR was 5.71 (95% CI: 3.41–9.55, $I^2=61\%$).

Postoperative complications

Postoperative complication rates were presented in seven studies (Table 3).^{12–18} Owing to the limited amount of information available, meta-analyses were not performed using these data but some observations are briefly summarised here. In four studies, there were notable differences between frail and non-frail groups with the frail groups showing greater complication rates.^{14–17} The reverse was seen in two studies^{12,15} and one study was equivocal.²⁰

Discussion

The syndrome of frailty is common with an estimated prevalence in excess of 10% in community dwelling adults aged 65 years and over, and higher levels seen with increasing age and in women.²³ The issue of frailty has been brought to prominence in the UK with the National Confidential Enquiry into Patient Outcome and Death publication *An Age Old Problem*.²⁴ One of the principal recommendations was that co-morbidity, disability and frailty need to be recognised as markers of risk in the elderly. Our meta-analysis shows that following surgical intervention, frailty is associated with higher in-hospital and one-year mortality, longer length of hospital stay and increased requirement for step-down care to rehabilitation facilities or nursing homes.

Table 1 Study characteristics including methods of determining frailty, sex and details of surgical procedures in the 12 studies used in the systematic review

Study	Definition of frailty	Surgical procedure	Group	n	Male
van Vledder, 2012 ¹¹	Skeletal muscle mass on CT <41.1cm ² /m ² for women and <43.75cm ² /m ² for men	Hepatic surgery for colorectal liver metastasis	Frail	38	11
			Non-frail	158	109
Liefers, 2012 ¹²	Lumbar skeletal muscle index <38.5cm ² /m ² for women and 52.4cm ² /m ² for men	Primary colorectal resection	Frail	91	57
			Non-frail	143	18
Peng, 2012 ¹³	TPA (lowest quartile)	Pancreatic surgery	Frail	139	74
			Non-frail	418	222
Cervera, 2012 ¹⁴	The use of equipment or assistance from another person for any ADL, patients from nursing homes and patients receiving long-term dialysis or oxygen therapy	Elective CABG	Frail	318	316
			Non-frail	1,185	1,179

Afialo, 2010 ¹⁵	Time taken to walk 5m .6s or unable to perform walk test with a Fried frailty score >3	Cardiac surgery	Frail	60	34
			Non-frail	71	53
Lee, 2010 ¹⁶	Any impairment in ADL (Katz index) or ambulation, or a documented history of dementia	Elective/emergency cardiac surgery	Frail	157	96
			Non-frail	3,699	2,732
Peng, 2011 ¹⁷	TPA .500mm ² /m ²	Hepatic surgery for colorectal liver metastasis	Frail	41	8
			Non-frail	218	185
Sündermann, 2011 ¹⁸	Comprehensive assessment of frailty score .11. Two-part scoring system: a) deduced from the Fried criteria, b) measures of physical performance including balance tests and measures to assess body control	Elective cardiac surgery	Frail	114	
			Non-frail	99	
Lee, 2011 ¹⁹	TPA (lowest tertile)	Elective open AAA surgery	Frail	84	
			Non-frail	178	
Robinson, 2011 ²⁰	≥4 of: a) timed up and go >15s, b) dependence >1 ADL, c) Mini-Cog™ score <3, d) albumin <3.4g/dl, e) Charlson index >3, f) haematocrit <35%, g) >1 fall in last 6 months	Colectomy	Frail	23	
			Non-frail	37	
Makary, 2010 ²¹	A validated scale (0–5) including weakness, weight loss, exhaustion, low physical activity and slowed walking speed. Patients scoring 4–5 classified as frail.	Elective general surgery	Frail	62	36
			Non-frail	532	202
Dasgupta, 2009 ²²	Edmonton frail scale* 7	Elective non-cardiac surgery	Frail	16	36
			Non-frail		109

CT = computed tomography; TPA = total psoas area; ADL = activities of daily living; CABG = coronary artery bypass graft; AAA = abdominal aortic aneurysm
 *The Edmonton frail scale incorporates the domains of cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance, and is scored out of 17.

Frailty itself can be theoretically defined as a clinically recognisable syndrome of increased vulnerability as well as age associated decline in reserve and function.²⁵ In clinical practice, there is a lack of a standard definition²⁶ and this is reflected by the varying definitions of frailty used by the studies identified in this review. Fried *et al* defined frailty as meeting three of five phenotypic criteria indicating compromised physicality (eg slowed walking speed).²⁵ Peng *et al* diagnosed frailty as loss of psoas muscle mass on diagnostic imaging.¹⁷ A 2013 publication focusing on determining a definition did not reach consensus.²⁷

Although the precise definition of frailty is yet to be determined, the concept that it leads to poor outcome following surgery still stands. The studies included in this

review were heterogeneous in their study populations and definition of frailty but the effect of frailty (particularly on in-hospital and one-year mortality) was consistent.

The biological basis for the effect of frailty is yet to be fully understood, and may include changes at a cellular level (eg oxidative damage) and systemic changes associated with medical co-morbidities.^{25,28,29} Cumulative co-morbidity may lead to poor outcome as patients may develop complications directly related to their medical condition or they may simply have reduced physiological reserve.

Separating frailty from specific co-morbidities or disability is difficult, especially as many of the frailty scores incorporate co-morbid illness. In this review, there were too few

Table 2 In-hospital and one-year mortality rates for frail and non-frail populations from the eight studies that reported mortality as an outcome

Study	Frail patients			Non-frail patients		
	<i>n</i>	In-hospital mortality	1-year mortality	<i>n</i>	In-hospital mortality	1-year mortality
van Vledder, 2012 ¹¹	38		15.8%	158		3.8%
Peng, 2012 ¹³	139	0.7%	43.2%	418	0.5%	28.5%
Cervera, 2012 ¹⁴	318	0.9%		1,185	1.1%	
Afilalo, 2010 ¹⁵	60	10.0%		71	1.4%	
Lee, 2010 ¹⁶	157	14.6%		3,699	4.5%	
Peng, 2011 ¹⁷	41	2.4%	39.0%	218	0.5%	31.7%
Sündermann, 2011 ¹⁸	114	8.8%	16.7%	99	4.0%	7.1%
Lee, 2011 ¹⁹	84		14.3%	178		7.3%

AUC = area under the curve; CI = confidence interval; CRP = C-reactive protein

studies available and no patient specific data to attempt to fit meta-regression models, which can adjust for confounders in a very limited way. As such, from a statistical perspective, in the absence of randomisation, it is not possible to infer causation from the analyses. However, the strength of the measures of association, combined with the fact that patient frailty is such an obvious potential cause of adverse events, suggests that frailty is likely to be a strong predictor of poorer outcomes for all interventions despite these limitations.

A further statistical issue is that the in-hospital mortality rates were generally quite low, which reduces the accuracy of the normal approximations used in the corresponding meta-analysis. When determining longer-term mortality rates, the possibility of dropout needs to be considered. For studies that provided mortality rates at one year, dropout rates were ignored when calculating study specific log odds ratios and for studies that gave numbers at risk at one year, an assumption was made that all those no longer at risk had died, which again ignores the possibility of dropout. Given that the follow-up period was only one year and that only prospective studies were analysed, dropout is likely to be small.

There was variation between studies in defining need for rehabilitation or nursing home placement. Despite these subtle differences, the results from our review confirm that frail patients struggle to return to their own home after surgery. Surprisingly, there was only a difference of a single day in overall LOS between frail and non-frail patients. This may in part be due to the data coming from various healthcare systems (and the variation in availability of rehabilitation facilities) but it may also be explained by institutions keeping patients in hospital longer while home circumstances are optimised.

Conclusions

The results of this systematic review suggest that issues associated with frailty should be addressed to improve patient outcomes. An easily identifiable definition that is

applicable in clinical practice needs to be formulated and research to determine this must be undertaken. It is also essential to ascertain which specific aspects of the frailty phenotype bring about such poor outcomes. This may differ depending on the specific surgical population and pathology operated on, and it is the key to establishing how best to improve frailty in surgical patients. Irreversible frailty should be taken into account when deciding whether to proceed to surgical intervention and this may improve the process of informed consent. Conversely, the identification of potentially reversible components of frailty not only provides an opportunity for surgical optimisation but also has wider benefits, particularly in terms of social and health economic planning.

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