

Does frailty predict postoperative outcomes in geriatric patients receiving surgery for colorectal cancer? A systematic review and meta-analysis

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Abstract

Background Surgery remains the mainstay of colorectal cancer (CRC) and substantially reduces cancer-related morbidity and mortality. Preoperative assessment for frailty in geriatric patients is critically important in risk stratification and clinical decision-making. In this systematic review and meta-analysis, we aimed to quantitatively summarise the effect of frailty on postoperative outcomes in geriatric patients receiving surgery for CRC. Methods A systematic literature search was conducted in MEDLINE, Cochrane and EMBASE from inception to 30 April 2020. Fully published articles reporting risk estimate(s) of frailty on postoperative complication(s), readmission and/ or mortality in patients aged ≥ 65 years who received surgery for CRC were eligible for qualitative and quantitative analyses. Results Across 10 articles of 9 unique studies ($n = 69332$) that were eventually included in the systematic review and meta-analysis, overall prevalence of frailty was 23.0% (95% CI: 11–43%, $I^2 = 100\%$). Odds ratios (ORs) on overall and severe postoperative complications were respectively increased by 2.36- (95% CI: 1.66–3.35, $P < 0.01$; $I^2 = 12\%$) and 2.35-fold (95% CI: 1.30–4.27, $P < 0.01$; $I^2 = 72\%$) in frail patients compared to non-frail counterparts. On pooled analysis, frailty was significantly associated with an increased risk of postoperative readmission (OR:1.91; 95% CI: 1.35–2.70, $P < 0.01$; $I^2 = 6\%$). Whilst a significantly higher risk of frailty on mortality during 12 months after CRC surgery was observed (OR: 5.52; 95% CI:4.40–6.92, $P < 0.01$; $I^2 = 89\%$), the summary OR on 30-day/ inpatient mortality crossed the null line (OR: 1.65; 95% CI: 0.56–4.93, $P = 0.37$; $I^2 = 55\%$). Funnel plot and Duval-Tweedie's trim and fill test did not reveal significant publication bias. Conclusions In the studies reviewed, frailty appeared to be associated with increased risks for postoperative complications, readmission and mortality during 12 months in patients aged ≥ 65 years who received surgery for CRC. Nevertheless, no significant association between frailty and 30-day/ inpatient postoperative mortality was observed.

Background

In 2012, approximately 700,000 deaths from colorectal cancer (CRC) were recorded, making CRC the fourth leading cause of cancer death worldwide [1]. The incidence of CRC dramatically rises up to 1.8 million new cases annually due to a rapidly ageing population, shift in dietary patterns and reduction in physical activity [2]. The risk of CRC increases sharply with age. Individuals aged >60 years have an over 50-time higher risk of CRC compared to those younger than 40 years, contributing to 80% of cases diagnosed [3]. Comprehensive geriatric assessment is currently regarded as the gold standard to globally evaluate older adults' health status; however this assessment may not be feasible due to time constraints and lack of expertise. Screening for frailty is more practicable in routine clinical practice [4]. Given that surgery remains the mainstay of CRC and effectively decreases distant metastasis, local recurrence and cancer-related mortality, accurate evaluation on general health status and identification of frailty pre-operatively is of great importance in clinical decision-making [5]. Previously a meta-analysis has demonstrated comorbidity is associated with higher risks of overall and cancer-specific mortality [6]. However, the impact on postoperative outcomes in elderly patients with CRC has never been quantitatively examined by using formal frailty assessment instrument(s) [7]. Also, the underlying

mechanisms by which frailty confer a poorer prognosis need to be determined yet [8-10]. In this systematic review and meta-analysis, we aimed to summarize current evidence and quantitatively evaluate the effect of frailty on postoperative outcomes in geriatric patients receiving surgery for CRC.

Methods

Research question and eligibility criteria for literature search

The systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and the Meta-Analysis of observational studies in Epidemiology (MOOSE) guidelines [11, 12] (PRISMA checklist available in Additional file 1: Table S1). The study focused on the following research question: Does frailty predict clinical outcomes in patients who received surgery for CRC? Studies were included in the systematic review and meta-analysis when they met the following criteria: 1) Patients received surgery for CRC either for curative or palliative purpose; 2) Patients were aged 65 years or above; 3) Studies were conducted as case-control, cohort or nested design; 4) Formal frailty assessment instruments were utilized and assessed preoperatively; 5) Risk estimates on clinical outcomes including postoperative complication(s), readmission and/or mortality compared between frail and non-frail patients were expressed as either hazard ratio (HR) or odds ratio (OR); 6) Studies were published as full articles; 7) Studies were conducted in human population; 7) Articles were published in English. Studies were excluded if 1) Patients with CRC did not receive surgical therapy; 2) No formal frailty assessment was available in the articles; 3) Risk estimates compared between frail and non-frail patients were unavailable in the articles; 4) Studies were published as conference abstracts; 5) Studies were conducted in animals; 6) Articles were written in language(s) other than English.

Search strategy

Literature search through MEDLINE, Cochrane and EMBASE databases was systematically performed from inception to 30 Apr 2020 to identify studies that compared the risk estimates on clinical outcomes between frail and non-frail patients who received surgery for CRC. The following key Medical Subject Headings (MeSH) terms were used for literature search: 'frailty' OR 'frail' AND 'colorectal carcinoma' OR 'colorectal cancer' OR 'colorectal malignancy' OR 'bowel surgery' OR 'colectomy' OR 'colorectomy' OR 'colon resection' OR 'colorectal resection'. The identified records were independently scanned and assessed by two research investigators (XY & CX) to identify the eligible studies. Discrepancies between the two researchers were discussed and resolved by two senior researchers (JW & LY).

Data extraction

Information on study population, study design, frailty assessment instruments, prevalence rate of frailty, comorbidities, the American Society of Anesthesiologists Physical classification System (ASA classification), prevalence rates of postoperative complications, length of in-hospital stay, risk estimates on clinical outcomes including, postoperative complication(s) and mortality was extracted from the

eligible studies. The severity of complications was graded according to predefined criteria [13, 14]. When necessary, corresponding authors of the publications were contacted for either clarification of data redundancy or data recalculation for associated risk estimates.

Assessment of publication bias

Quality of study assessment was conducted using Newcastle-Ottawa Scale (NOS) for cohort studies for assessing risk of bias by two researchers (XY & CX) independently [15]. High-quality studies were graded when 7 or above out of 9 points were obtained using NOS. Discrepancies between the two authors were resolved by two senior researchers (JW & LY).

Statistical analysis

Meta-analyses were conducted using the inverse of variance method and random-effects models by assuming that the true value of the effect size of each study is sampled from a probability distribution rather than identical. Data from the same study and population were calculated only once based on the most recent available publication and/ or the largest sample size to avoid data redundancy [16, 17]. Forest plots were used to present the pooled estimates in graphical form. *P* values lower than 0.05 were regarded as statistically significant. Low heterogeneity was defined by using the Cochrane Q test with <25% of I^2 , while moderate and high heterogeneity were defined as <50% and $\geq 50\%$, respectively [18]. Egger's linear regression, Begg's rank correlation test and leave-one-out sensitivity analysis were further conducted to identify potential reason(s) for high heterogeneity (i.e. $I^2 \geq 50\%$) [19, 20].

Risk estimates from the models that adjusted for the maximum numbers of covariates were selected for data-analysis, where alternative adjusted estimates were available. When multivariate risk estimate was unavailable, univariate risk estimate was used instead. Indirect methods of extracting estimates were used, where risk effect was not directly reported in the publication [16, 21, 22]. The OR and 95% confidence interval (CI) were calculated. Funnel plot and Duval-Tweedie's trim and fill test were used to visually and quantitatively assess publication bias. Statistical analyses were performed by Review Manager Version 5.3 (Cochrane IMS, Copenhagen, Denmark) and R Version 4.0.0 (R Foundation for statistical Computing).

Results

Study selection

The initial search identified 2035 records, of which 1035, 165 and 835 were collected from MEDLINE, Cochrane and EMBASE, respectively (Figure 1). After 2025 records were excluded due to duplicates, reviews, conference abstracts and irrelevant contents, 10 articles of 9 unique studies were eventually included in the systematic review and meta-analysis.

Study characteristics

A total of 69332 patients (males: 50.9% (35240/69249) reported in 9 unique studies) who received surgery for CRC were eventually included in the systematic review and meta-analysis (Table 1). Seven articles of 6 studies [16, 17, 22-26] presented a prospective observational design reporting longitudinal data, while data from the remaining 3 studies were retrospectively analyzed [8, 21, 27]. Study characteristics including population, study design, sample size frailty assessment instrument and risk estimates were summarized in Table 1.

Frailty assessment instruments and prevalence rate of frailty in patients receiving CRC surgery

The overall prevalence of frailty derived from 9 unique studies was 26% (95% CI: 16–38%, $I^2 = 99\%$) (Table 2 & Figure 2A), whereas seven studies focusing on elective surgery showed a slightly lower pooled prevalence of frailty as 25% (95% CI: 14–41%, $I^2 = 100\%$) (Figure 2B). Notably, patients receiving elective operation accounted for 99.8% (68673/68750) as indicated in original studies (Table 1).

Impact of frailty on postoperative clinical outcomes

Postoperative complications

Six studies [17, 21, 22, 24, 26, 27] reported overall postoperative complications in comparison between frail and non-frail patients (Table 2). Forest plot showed that frailty was associated with an increased risk of postoperative complications (OR: 2.36, 95% CI: 1.66–3.35, $P < 0.01$; $I^2 = 12\%$) (Figure 3A). Similar result was observed in patients who underwent elective surgery (OR: 2.50, 95% CI: 1.72–3.63, $P < 0.01$; $I^2 = 15\%$) [17, 21, 24, 26] (Figure 3B). The pooled risk estimate of being frail on severe complications was increased by 2.35-fold (95% CI: 1.30–4.27, $P < 0.01$; $I^2 = 72\%$) compared to that of being non-frail [17, 23, 27] (Figure 3C). Subanalysis on elective surgery was summarized in 2 studies [17, 23], also revealing a significant association between frailty and severe complications (OR: 3.25; 95% CI: 2.00–5.28, $P < 0.01$; $I^2 = 0$) (Figure 3D). However, the summary risk of frailty on postoperative anastomotic leakage summarized in 4 studies was statistically non-significant (OR: 1.84 (95% CI: 0.98–3.46, $P > 0.05$, $I^2 = 0$) [17, 22-24] (Figure 3E).

Postoperative readmission

A total of 3 studies [17, 24, 27] reported risk estimate of frailty on postoperative readmission (Table 2), indicating an overall OR value of 1.91 (95% CI: 1.35–2.70, $I^2 = 6\%$) (Figure 4).

Postoperative mortality

A significant higher risk of frailty on mortality during 12 months after CRC surgery was observed in 5 studies (OR: 5.52; 95% CI: 4.40 – 6.92, $P < 0.01$), with a high heterogeneity identified ($I^2 = 89$) (Table 2 & Figure 5A). A subanalysis on elective surgery also revealed a significant association (OR: 5.66; 95% CI: 4.51 – 7.11, $P < 0.01$; $I^2 = 89\%$) (Figure 5B). While the summary OR on 30-day/ inpatient mortality crossed the null line (OR: 1.65; 95% CI: 0.56–4.93, $P = 0.37$; $I^2 = 55\%$) (Figure 5C), a 2.01-fold increased risk of

frailty was identified in subanalysis on elective surgery (OR: 2.01; 95% CI: 1.25–3.22, $P < 0.01$; $I^2 = 56\%$) (Figure 5D)

Two studies [16, 25] reported time-effect of frailty on mortality, suggesting frailty was associated with 3.33-fold increased HR of long-term mortality (95% CI: 2.21–5.01, $P < 0.01$; $I^2 = 0\%$) (Table 2 & Figure 5E).

Study quality and Publication bias

Assessment of study quality yielded the 10 articles were all scored ≥ 7 out of 9 points using NOS (Additional file 1: Table S2). On estimating prevalence of frailty, 66.7% (6/9) of the included studies fell outside the 95% CI of funnel plot control limits. We therefore proceeded to performing trim and fill test and found publication bias was trivial (adjusted prevalence of frailty: 34.3%; 95% CI: 20.58–51.27, $P < 0.01$; $I^2 = 99.8\%$) (Additional file 1: Figure S1). Egger's linear regression or Begg's rank correlation test did not reveal strong evidence of publication bias in prevalence of frailty (Egger's test: $P = 0.431$; Begg's test: $P = 0.532$).

Funnel plot, Egger's or Begg's test was not performed in the forest plot for pooled risk estimate of frailty on severe complications, 30-day/ inpatient or 1-year mortality due to small number of studies. When leave-one-out sensitivity analysis was performed, the overall prevalence of frailty did not significantly differ, indicating an acceptable robustness of pooled estimate (Additional file 1: Table S3). Nevertheless, the heterogeneity identified in OR of frailty on severe postoperative complications, 30-day/ inpatient mortality and mortality within one year was significantly diminished by the leave-one-out approach (Additional file 1: Tables S4–S6).

Discussion

Impact of frailty on postoperative outcomes in patients receiving surgery for CRC

To our knowledge, this study was first to systematically synthesize quantitative evidence and evaluate the effects of frailty on postoperative outcomes in patients who received surgery for CRC. The results showed that frailty negatively impacted postoperative complications by ~ 2.35 -fold. Slightly higher ORs were observed in patients receiving elective surgery. Moreover, frailty was associated with 1.91- and 6.16-fold increased risks of postoperative readmission and mortality during 12 months, whereas the effect of frailty on 30-day/ inpatient mortality reached statistical significance in patients who underwent elective surgery only.

Studies previously reported frailty was an independent factor in predicting postoperative complications, readmission and mortality in abdominal and cardiothoracic surgeries in older adults [28, 29]. Because aggressive treatment (e.g. curative surgery) contributes to dysregulation of systemic immune system, causing progressive organ damage and exacerbating decline in physiological reserve [21], identifying frail patients in elderly population is essentially crucial in decision-making and therapeutic options. Moreover, postoperative outcome(s) leading to prolonged inpatient stay incurs substantial additional costs of

medical care, and at the same time leading to poorer quality of life and increased risk of emergency readmission [30].

Several mechanisms potentially explain the association between frailty and postoperative adverse outcomes in patients undergoing surgery for CRC. First, frailty characterised by vulnerability and impaired physiological reserve is accompanied by up-regulation of inflammatory and proinflammatory cytokines (e.g. interleukin (IL)-6, C-reaction protein (CRP), tumour necrosis factor (TNF)- α , etc.), leading to the development of systemic inflammatory response [31]. This positive association between inflammatory markers and postoperative complications are particularly evident in occurrence of sepsis, anastomotic leakage and pulmonary insufficiency [32].

Second, frailty is frequently accompanied by the coexistence of multi-morbidity, being more frequent with increasing degrees of frailty [33]. However, while preoperative comorbidities and ASA classification are widely accepted as perioperative risk stratification tools and associated with higher risks of complications and mortality [34], the predictive value of frailty assessment instruments in conjunction with co-morbidity or perioperative complications on mortality is still limited in literature [35].

Third, increased risks of anemia, hypoalbuminemia and poor nutritional status associated with frailty have been well documented [36-38]. Condition of being anemic or malnourished directly prolonged postoperative recovery due to surgical complications (e.g. dehiscence, anastomotic leakage, surgical site infection, etc.) in colorectal and other major abdominal surgeries [39-41]. Nevertheless, the risk estimate on major surgical complications(s) such as anastomotic leakage and/or abscess formation crossed the line of null effects summarized from 4 studies in this study. There are many factors thought to affect anastomotic leakage following colorectal surgery. Evidence has showed general factors (e.g. advanced age, obesity, malnutrition, corticosteroid use, etc.), local factors (e.g. vascular flow insufficiency, infection, etc.) as well as technical and experience factors (e.g. tumour location, operative modalities (i.e. laparoscopic vs. open surgery), anastomotic tension, etc.) all influence the integrity of conduit and anastomotic healing [39, 42, 43]. Subanalyses on tumour site, operation modality, etc. were not performed in this study due to data insufficiency. The association between frailty and postoperative anastomotic leakage is yet to be investigated in future studies.

Fourth, reduction in muscle mass and mitochondrial enzyme activity exacerbated by curative operation in turn activates muscle inflammation and predisposes to frailty process [44]. Although pre-habilitation training effectively reduced morbidity and mortality after intra-abdominal cancer surgery [45], its role in improving postoperative muscle strength and functional capacity is yet to be determined. Furthermore, the degree of frailty severity fluctuating over time is rarely reported in CRC patients.

Fifth, altered composition of commensal microbiota, if present, potentiates the development of frailty and bowel oncogenicity [46, 47]. Although causal evidence showing interlinks between changes in gut microbial communities, frailty process and CRC formation is scarce, long-term alteration in gut microbiota after colorectal surgery may disturb skeletal muscle protein synthesis, resulting in muscle atrophy and attenuation [48].

Frailty assessment instruments and prevalence of frailty in patients receiving surgery for CRC

Frailty generally affects 12.8% of older individuals aged ≥ 60 years and is more prevalent in cancer patients [49-51]. In this systematic review and meta-analysis, we reported that preoperative prevalence rate of frailty in CRC patients aged ≥ 65 years was 26.0% (95% CI: 16–38% ranging from 4.4–52.2%) in 9 unique studies, with a very high level of heterogeneity identified. While dozens of frailty assessment instruments are used worldwide [52], no standard frailty index is specifically validated for CRC patients in predicting postoperative prognosis. Pandit *et al.* [21] recently proposed a modified frailty index (Colon Cancer Frailty Index (CCFI)) in conjunction of previously validated Canadian Study of Health and Aging Frailty Index (CSHA-FI) and two additional variables (i.e. anemia and weight loss), guiding the strategy on treatment options and complications [21, 53].

Another indicator of frailty is the cumulative deficit index, using clinical and/or laboratory variables and expressing the index as the number of abnormal variables over the total number of variables tested [54]. The predictive value of this index in evaluating complications and mortality reached ~ 0.70 after gastrointestinal tract surgery [55]. However, this index is more readily available for large-scale epidemiological data than in routine clinical practice. In contrast, magnitude of impairment of physiological reserve by objective/ semi-objective measures (i.e. muscle strength, gait speed, energy expenditure, etc.) is assessed in the Fried frailty phenotype. In this meta-analysis, only one study used Fried frailty phenotype [56]. More frequently, other frailty assessment instruments (e.g. Groningen Frailty Index (GFI), the John Hopkins' Adjusted Clinical Groups (ACG) definition of frailty, etc.) with multidimensional aspects (i.e. physical, functional and psychosocial domains) are currently used in CRC researches, in line with recommendations of the International Society of Geriatric Oncology (SIOG) suggesting that geriatric assessment (GA) incorporated with some initial screening tools (e.g. G8, VES-13, etc.) be assessed in CRC patients with ≥ 65 years of age who are candidates for surgical procedures [57], given that increasing age coupled with coexisting medical conditions and psychosocial issues makes therapeutic decision(s) more challenging.

Limitations of the study

There are several limitations in this systematic review and meta-analysis.

First, distribution of curative and palliative purpose that was only available in three of the included studies made it unable to in particular analyze the effect of frailty on mortality and other outcomes across the subgroups. Among patients with metastatic CRC, majority of the lesions are unresectable, despite that a few of them can still be amenable to curative resection of primary tumour and metastases. Palliative surgery is mainly reserved for these patients, which confers an operative mortality rate at 6–10% [58] and postoperative morbidity between 18–47% [59]. However, some of the studies reported that no significant association was observed between tumour stage and postoperative complication(s) [17]. Moreover, in multivariable analysis, frailty status remained to be an independent prognostic indicator after adjustment for TNM stage [16]. Second, only all-cause mortality was considered as a hard endpoint in this study. Non-cancer-specific mortality has been the main form of competing risk that occurs and

leads to biased results when applying survival analysis [60]. Competing risk nomograms has been established for gastrointestinal cancer diseases in the recent years in order that overall survival (OS) and cancer-specific survival (CSS) in patients with surgically resected tumours can be predicted [61, 62]. As far as we know, only two studies previously explored discrimination between physiologically fit and non-fit patients in cancer-related and non-cancer specific mortality after curative resection for CRC [63, 64]. However, neither of them predicted outcomes by utilizing formal frailty assessment instrument(s). Competing risk models including functional and nutritional factors will be critical in classifying geriatric patients according to their frailty status [63]. Third, as an important confounder affecting prognosis, emergency surgery was not absolutely eliminated in this study, although we attempted to subanalyze the patients who underwent elective surgery. The positive correlation between emergent surgical presentation and postoperative mortality in elderly patients undergoing CRC surgery was confirmed in previous studies [65, 66]. Given that an emergent surgical presentation in a senior patient frequently points at a diagnosis of bowel obstruction or perforation, these two conditions often indicate an advanced stage and carry a poor prognosis [65]. Also, it is unlikely that preoperative assessment and prehabilitation training can be implemented in these patients. Fourth, frailty assessment instruments were not uniformly assessed. Some studies mostly relied on physical components, while others used multidimensional approach, culminating in large variance in prevalence of frailty. Moreover, risk estimates were extracted directly or calculated indirectly from relatively small numbers of studies. Furthermore, univariate risk estimates were used in some of the studies when multivariate appraisals were unavailable in original publications.

Conclusions

Frailty is highly prevalent in geriatric patients receiving surgery for CRC. In the studies reviewed, frailty appeared to be associated with higher risks of postoperative complications, readmission and mortality during 12 months. Nevertheless, no significant association between frailty and 30-day/ inpatient postoperative mortality was observed.

Abbreviations

CRC: colorectal cancer; CI: confidence interval; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; MOOSE: the Meta-Analysis of observational studies in Epidemiology; HR: hazard ratio; MeSH: Medical Subject Headings; ASA: the American Society of Anesthesiologists; NOS: Newcastle-Ottawa Scale; NS: non-significant; LOS: length of stay; ISAR-HP: identification of Seniors at Risk for Hospitalised Patients; IL: interleukin; CRP: C-reaction protein; TNF: tumour necrosis factor; CCFI: Colorectal Cancer Frailty Index; CSHA-FI: Canadian Study of Health and Aging Frailty Index; GFI: Groningen Frailty Index; SIOG: the International Society of Geriatric Oncology; GA: geriatric assessment; OS: overall survival; CSS: cancer-specific survival.

Declarations

Ethics approval and consent to participate

Not declared.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed in the study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare they have no competing interests.

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Authors' contributions

XY, LY, JW participated in study concepts and design. XY, CX, LY and JW performed the literature search, data extraction and quality assessment. XY, CX, LX and QQ ran the statistical tests. XY and JW were the major contributors of the manuscript writing. CX, JC, LX, QQ, JH, LY participated in manuscript revision. All the authors read and approved the final manuscript.

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Tables

Table 1 Characteristics of the included studies.

Duration of recruitment	Study design	Sample size	Age (y)	Male gender (n, %)	ASA classification	Open surgery (n, %)	Purpose of surgery	Categories for surgery	Sites of CRC	Stage of CRC
Jan 2016- Dec 2018	Retrospective	1676	75 (69-81)	841, 50.2%	I-II: 23.6% III-IV: 76.4%	618, 36.9%	N/A	Both elective and non-elective; elective percentage: 79.3% (1329/1676)	N/A	Disseminated cancer: 9.5%
Jan 2011- Aug 2016	Prospective, observational	269	Frail: 80 (65-89); Non-frail: 68 (65-84)	167, 62.1%	N/A	99, 36.8%	Curative	Elective	N/A	Stage I-II: 70.6% Stage III-IV: 29.4%
2011	Retrospective	53652	Frail: 75.2±8.1; Non-frail: 75.1±7.3	28898, 53.9%	N/A	22288, 41.5%	N/A	Elective	N/A	N/A
May 2015- Aug 2016	Prospective, observational	139	77.7 (75.0-82.8)	76, 55%	I-II: 71%; III-V: 29% -	33, 24%	Curative	Elective	Colon: 82%; Rectum: 18%	Stage I: 24%; Stage II: 41%; Stage III: 35%.
Sep 2009- Jun 2012	Prospective, observational	46	80.52±6.68	24, 52.2%	N/A	24, 52.2%	N/A	Elective	N/A	N/A
Nov 2006- Jun 2008	Prospective, observational	178	70-79 Y: 89, 50% 80-89 Y: 79, 44% ≥90 Y: 10, 6%	76, 43%	N/A	118, 66%	N/A	Elective	Colon: 71%; Rectum: 29%	TNM stage 0: 5% I: 24%; II: 32%; III: 25%; IV: 12%; Unclassified: 2%
Jan 2010- May 2012	Prospective, observational	310 (of whom GFI score was assessed in 153 patients)	N/A	155, 50%	I: 5.5%; II: 70.6%; III: 20.0%; IV: 3.9%	277, 89.4%	N/A	Both elective and acute	Colon: 66.1%; Rectum: 33.9%.	N/A
1999-2005	Retrospective	12979	84.4±3.7	5003, 39%	N/A	N/A	Curative	Elective	N/A	N/A
Feb 2008- Apr 2010	Prospective, observational	83	81.2 (75-93)	N/A	I: 10.8%; II: 57.8%; III: 30.1%; IV: 1.2%	61, 73.5%	N/A	Elective	Colon: 26.5%; Rectum: 73.5%	N/A
Nov 2006- Jun 2008	Prospective, observational	178	79.6±5.7	76, 42.7%	N/A	118, 66%	N/A	Elective	Colon: 71%; Rectum: 29%	TNM stage 0: 5% I: 24%; II: 32%; III: 25%; IV: 12%; Unclassified: 2%

ASA, American Society of Anesthesiologists. GFI, Groningen Frailty Index. *Sample derived from the same cohort.

Table 2 Prevalence of frailty and clinical outcomes in patients receiving surgery for colorectal cancer.

Age of patients (years)	Frailty assessment instrument	Prevalence rate of frailty	Data and/ or risk estimates for clinical outcomes					
			LOS (days)	Readmission	Postoperative complications		Mortality	
					Overall	Severe	≤30-day/ inpatient	>30-day
≥65	mFI modified from frailty index	25% (423/1676)	1.05 (0.97-1.15), <i>P</i> >0.05	OR: 1.68 (95% CI: 1.20- 2.36)	N/A	OR: 1.51 (1.14- 2.00)	N/A	N/A
≥65	Clinical Frailty Scale	29% (78/269)	Median: frail vs. non-frail: 13 (7-64) vs.10 (6-61), <i>P</i> <0.01)	N/A	N/A	OR: 3.42 (95% CI: 1.62-7.29)	N/A	N/A
≥65	Colon Cancer Frailty Index (CCFI)	34.0% (18241/53652)	Median: frail vs. non-frail: 8.9 vs. 7.2, <i>P</i> <0.01	N/A	OR: 1.8 (95% CI: 1.1-2.9)	N/A	OR: 1.2 (95%: 0.9-1.6)	N/A
>70	G8 ≤14+ISAR-HP ≥2	14.6% (20/137) [#]	Mean: frail vs. non-frail: 8.6±4.2 vs. 8.7±7.1, <i>P</i> >0.05)	OR: 3.4 (1.1-11.0)	OR: 2.4 (95% CI: 1.1-5.4)	N/A	OR: 6.7 (95% CI: 1.3-36.0)	OR: 9.5 (95% C: 1.9-47.4)
≥70	Groningen Frailty Index	52.2% (24/46)	N/A	N/A	N/A	N/A	N/A	HR: 2.265 (95% CI: 0.836-6.136)
≥70	Comprehensive Geriatric Assessment	42.7% (76/178)	N/A	N/A	N/A	N/A	N/A	HR: 3.6 (95% CI: 2.3-5.5); 1-year survival rate: frail vs. non-frail: 80% vs. 92% 5-year survival rate: frail vs. non-frail: 24% vs. 66%
≥70	Groningen Frailty Indicator	25.5% (39/153)	Mean: 11±0.6	N/A		N/A	OR: 0.68 (95% CI: 0.09-5.45)	N/A
≥80	The Johns Hopkins' Adjusted Clinical Groups case-mix system	4.4% (571/12979)	Median: 9 (2-165)	N/A	N/A	N/A	OR: 10.4 (95% CI: 7.6-14.2)	OR: 8.4 (95% CI: 6.4-11.1)
≥75	Fried frailty phenotype	27.7% (23/83)	N/A	N/A	Overall complication rate: frail vs. non-frail: 47.8% vs. 18.3%)	N/A	N/A	N/A
≥70	Comprehensive Geriatric Assessment	42.7% (76/178)	N/A	OR: 2.80 (1.06-7.41)	Overall complication rate: frail vs.intermediate vs. fit: 76% vs.48% vs. 48%	Severe complication rate: 62% vs.36% vs. 33%	N/A	N/A

*Sample derived from the same cohort. [#]G8 and ISAR-HP were derived from 137 of 139 patients. LOS, length of stay; OR, odds ratio; HR, hazard ratio. ISAR-HP, Identification of Seniors at Risk for Hospitalised Patients.

Figures

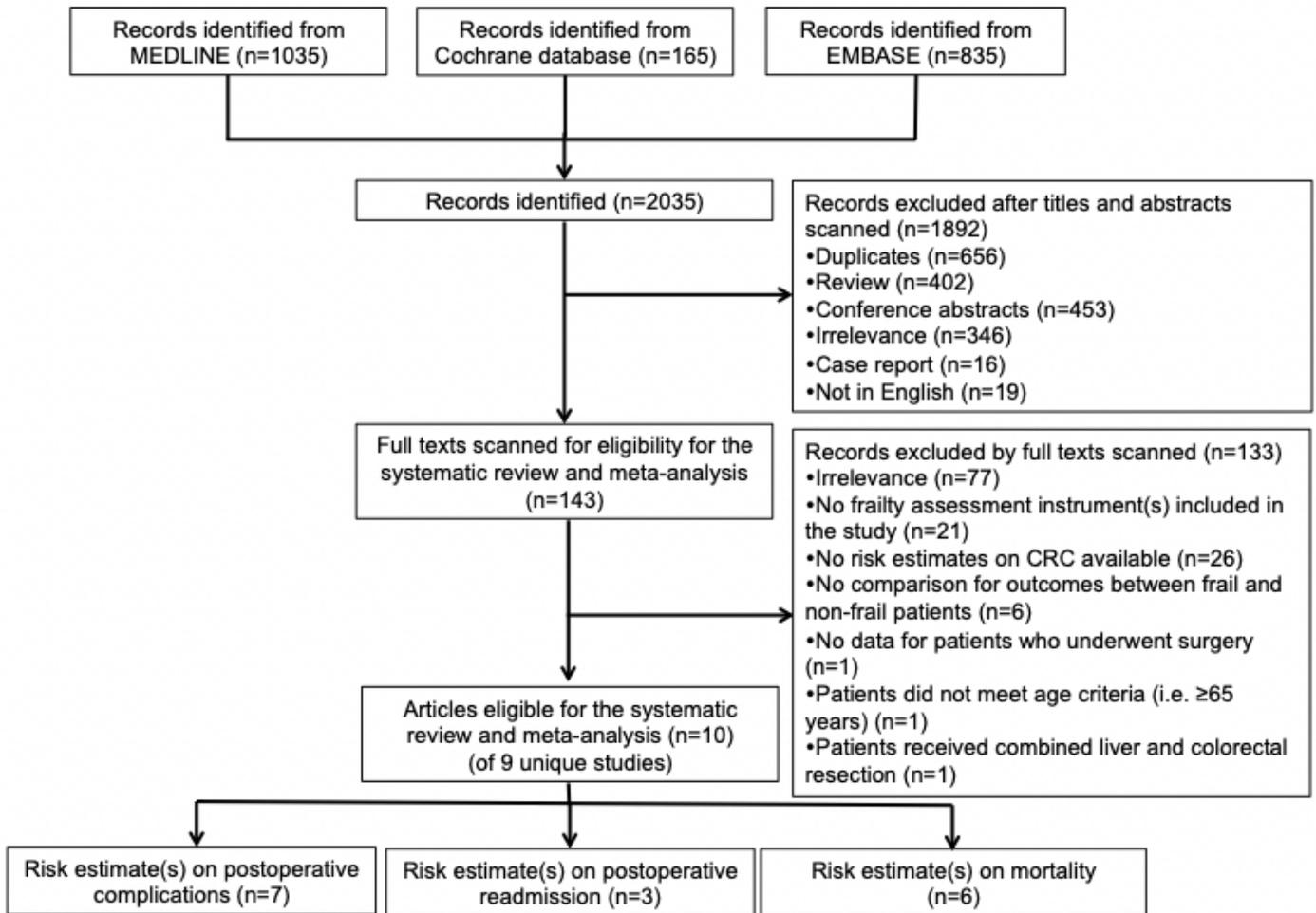
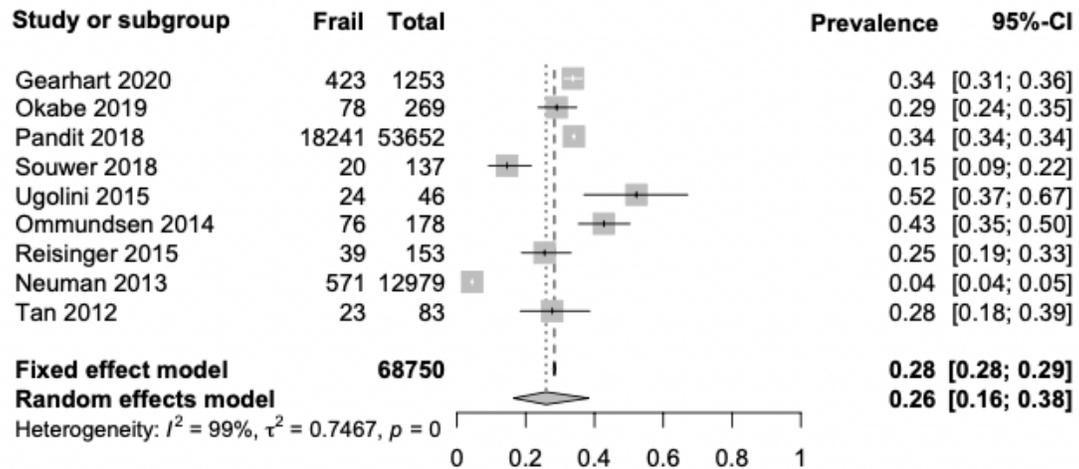
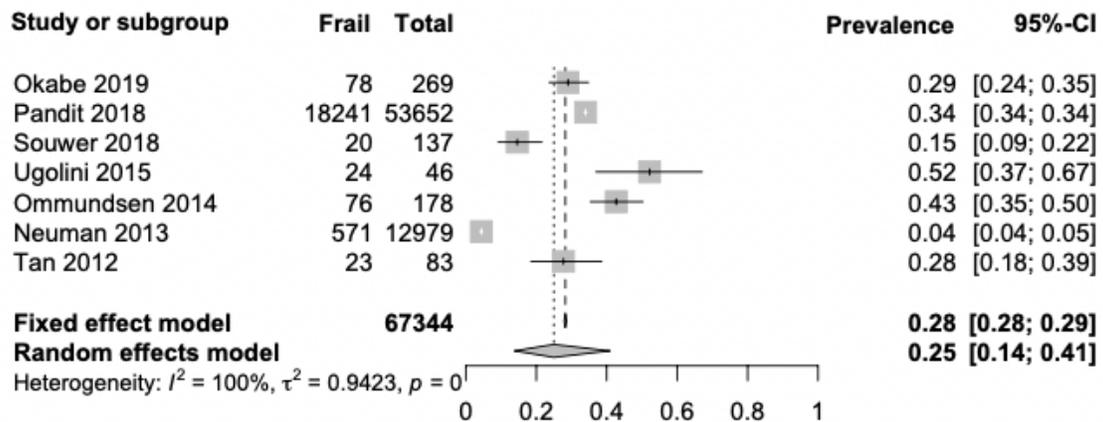
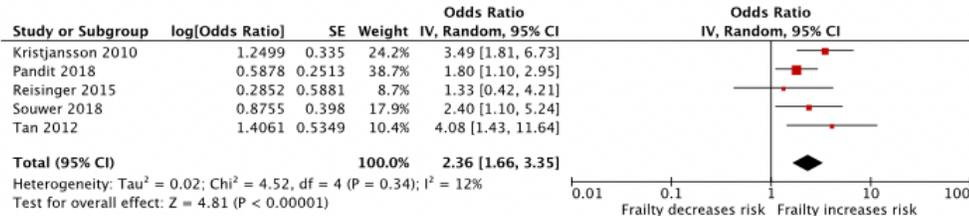
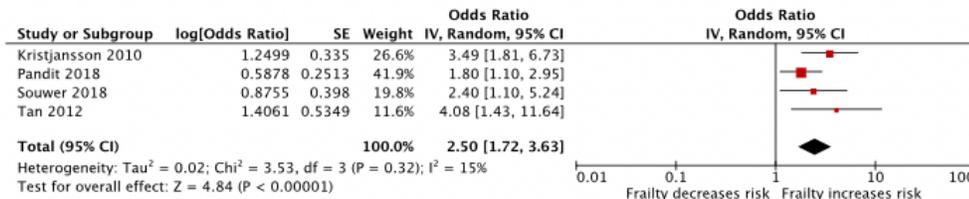
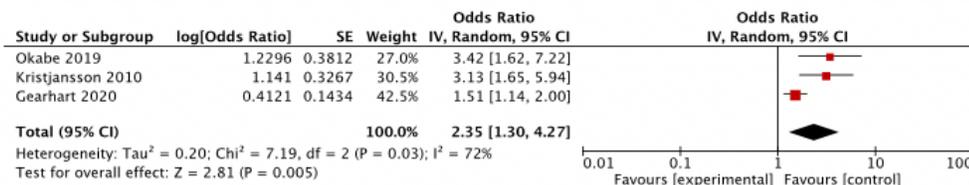
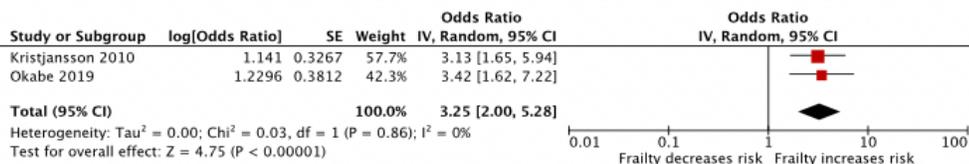
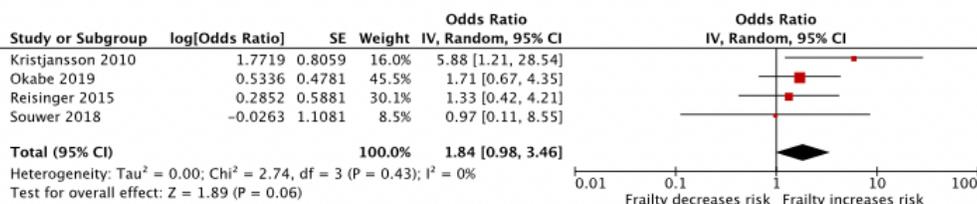


Figure 1

Flow diagram on study identification and selection.

A**B****Figure 2**

Forest plot on prevalence of frailty in patients receiving surgery for CRC. (A) Overall prevalence of frailty in 9 unique studies. (B) Pooled prevalence of frailty in 7 studies focusing on elective surgery.

A**Overall postoperative complications****B****Overall complications after elective surgery****C****Severe postoperative complications****D****Severe complications after elective surgery****E****Anastomotic leakage****Figure 3**

Effects of frailty on postoperative complications. (A) Pooled analysis on overall postoperative complications. (B) Effect of frailty on complications after elective surgery. (C) Three studies included in meta-analysis on severe complications. (D) Subanalysis on severe complications after elective surgery. (E) Summary OR on postoperative anastomotic leakage derived from 4 studies.

Postoperative readmission

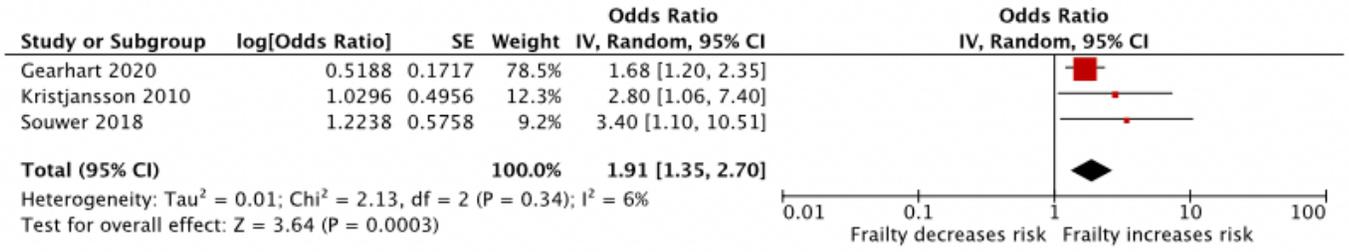
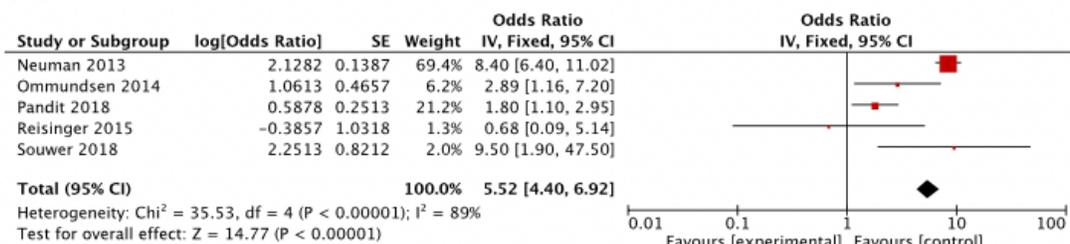
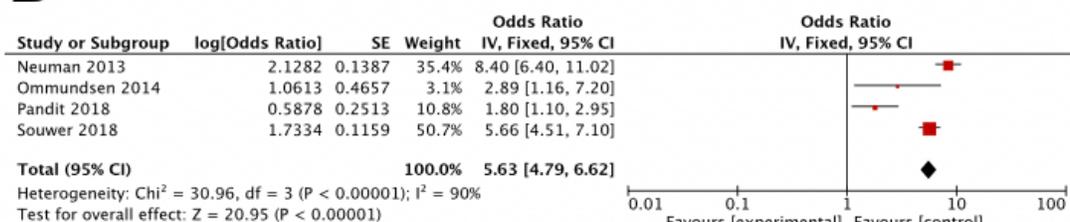
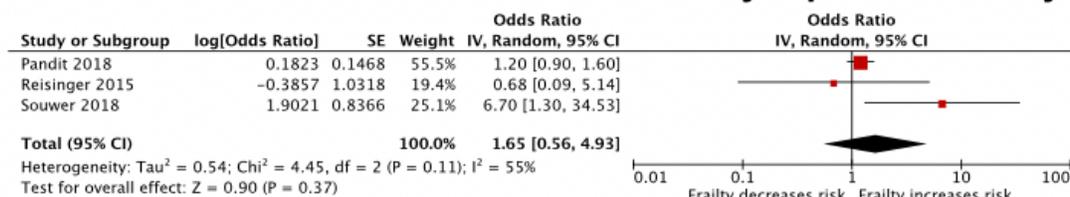
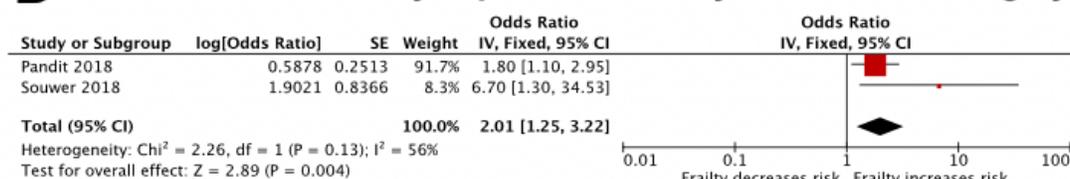
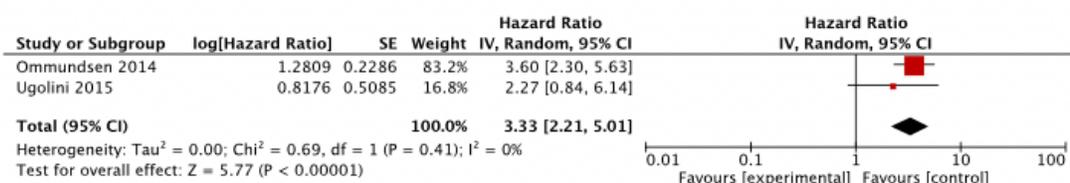


Figure 4

Forest plot for risk estimates of frailty on postoperative readmission

A**Postoperative Mortality during 12 months****B****Mortality during 12 months after elective surgery****C****30-day/ inpatient mortality****D****30-day/ inpatient mortality after elective surgery****E****Mortality in time-to-event analysis****Figure 5**

Forest plots on risk effects of frailty on mortality. (A) Three studies on 30-day/ inpatient postoperative mortality. (B) Subanalysis on 30-day mortality after elective surgery. (C) Risk effects of frailty on postoperative mortality during 12 months. (D) Subanalysis on mortality during 12 months after elective surgery. (E) Mortality in time-to event analysis available in 2 studies.

Supplementary Files

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