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Original Article

Association of preoperative frailty with short- and long-term outcomes after hepatic resection for elderly patients with hepatocellular carcinoma: multicentre analysis

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Abstract

Background: The growing demand for surgical resection in elderly patients with hepatocellular carcinoma highlights the need to understand the impact of preoperative frailty on surgical outcomes. The aim of this multicentre cohort study was to investigate the association between frailty and short- and long-term outcomes after hepatic resection among elderly patients with hepatocellular carcinoma.

Methods: A multicentre analysis was conducted on elderly patients with hepatocellular carcinoma (aged greater than or equal to 70 years) who underwent curative-intent resection at ten Chinese hospitals from 2012 to 2021. Frailty was assessed using the Clinical Frailty Scale (with frailty defined as a Clinical Frailty Scale score greater than or equal to 5). The primary outcomes were overall survival and recurrence-free survival; secondary outcomes encompassed postoperative 30-day morbidity and mortality, and 90-day mortality. The outcomes between patients with and without preoperative frailty were compared.

Results: Of the 488 elderly patients, 148 (30.3%) were considered frail. Frail patients experienced significantly higher 30-day morbidity (68.9% (102 of 148) *versus* 43.2% (147 of 340)), 30-day mortality (4.1% (6 of 148) *versus* 0.6% (2 of 340)), and 90-day mortality (6.1% (9 of 148) *versus* 0.9% (3 of 340)) compared with non-frail patients (all $P < 0.010$). During a median follow-up of 37.7 (interquartile range 20.4–57.8) months, frail patients demonstrated significantly worse median overall survival (41.6 (95% c.i. 32.0 to 51.2) *versus* 69.7 (95% c.i. 55.6 to 83.8) months) and recurrence-free survival (27.6 (95% c.i. 23.1 to 32.1) *versus* 42.7 (95% c.i. 34.6 to 50.8) months) compared with non-frail patients (both $P < 0.010$). Multivariable Cox regression analysis revealed frailty as an independent risk factor for decreased overall survival (HR 1.61; $P = 0.001$) and decreased recurrence-free survival (HR 1.32; $P = 0.028$).

Conclusion: Frailty is significantly associated with adverse short-term and long-term outcomes after resection in elderly patients with hepatocellular carcinoma. The findings suggest that frailty assessment should be incorporated into perioperative and postoperative evaluation for elderly patients undergoing hepatocellular carcinoma resection.

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Introduction

Hepatocellular carcinoma (HCC) has a high incidence in China, accounting for almost half of the global cases[1,2]. Hepatic resection remains one of the main curative treatment options for HCC, especially for patients with preserved liver function and localized tumours[3]. Treatment decisions for elderly patients with HCC are often challenging due to concerns about age-related physiological changes, co-morbidities, and the potential risk for postoperative complications[4,5].

Frailty is a multidimensional geriatric syndrome characterized by a decline in physiological reserve and increased vulnerability to stressors, leading to adverse health outcomes[6,7]. As previously demonstrated, frail patients with malignant tumours are at increased risk of postoperative complications, chemotherapy intolerance, disease progression, and death[8]. Frailty could influence surgical outcomes in the elderly population, as it is associated with increased morbidity, mortality, and functional decline after major surgery[8–14]. Various tools have been developed to assess frailty, including the Clinical Frailty Scale (CFS), which evaluates an individual's frailty status based on their physical, cognitive, and social functioning[15,16].

Despite the increasing demand for hepatic resection in elderly HCC patients, the impact of preoperative frailty on surgical outcomes remains poorly understood. The aim of this multicentre cohort study was to identify the effect of preoperative frailty, assessed using the CFS, on short-term and long-term outcomes after hepatic resection for elderly HCC patients.

Methods

Study design and patient cohort

This multicentre cohort study focused on elderly patients (aged 70 years or older) who underwent curative-intent hepatic resection for HCC at ten hepatobiliary centres in China from January 2012 to December 2021. The participating centres were: Eastern Hepatobiliary Surgery Hospital, First Hospital of Jilin University, Shandong Provincial Qianfoshan Hospital, Mengchao Hepatobiliary Hospital, Fourth Hospital of Harbin, Ziyang First People's Hospital, Fuyang People's Hospital, Liuyang People's Hospital, Pu'er People's Hospital, and First Affiliated Hospital of Harbin Medical University. Ethical approval was granted by the respective ethics committees of each centre and the study adhered to the Declaration of Helsinki. All patients signed the corresponding informed consent before surgery.

The study included patients who were aged greater than or equal to 70 years, had a pathologically confirmed HCC diagnosis, had a curative resection with a microscopically clear margin (R0 resection), and had clinical and follow-up data that were available. Patients with a combined HCC-cholangiocarcinoma or a recurrent HCC diagnosis or submitted to a prior anti-HCC treatment (for example transcatheter arterial chemoembolization (TACE), portal vein embolization, and associating liver partition and portal vein ligation for staged hepatectomy) before surgery or an R1 or R2 resection or without complete data were excluded. Data censoring occurred on 31 December 2022.

Preoperative assessment

Liver function was assessed through serum biochemistry and Child–Pugh grade, where Child–Pugh grade C was deemed a contraindication for HCC resection. Preoperative cardiovascular evaluation was standardized across all participating institutions[17] and, for patients aged greater than or equal to 60 years, routine evaluations included a thorough medical history, physical examination, 12-lead electrocardiogram, echocardiography, and pulmonary function tests. Additional tests, such as cardiopulmonary exercise testing (CPET) or anaerobic threshold (AT) determination, were not routinely performed. Resection criteria remained consistent throughout the study interval, encompassing the number of resectable tumours, the presence or absence of gross tumour thrombus, and sufficient liver function reserve, defined as Child–Pugh class A or selected B, and future liver remnant volume greater than 30% of total liver volume for non-cirrhotic patients or greater than 40% for cirrhotic patients[18,19].

The clinical characteristics of patients included: age, sex, co-morbidities, American Society of Anesthesiologists (ASA) grade, hepatitis B virus (HBV) infection status, hepatitis C virus (HCV) infection status, the presence of cirrhosis or portal hypertension, Child–Pugh grade, preoperative α-fetoprotein (AFP) levels, maximum tumour size, tumour number, the presence of macrovascular or microvascular invasion, satellite nodules, tumour differentiation, and tumour encapsulation. Co-morbidities encompassed hypertension, diabetes mellitus, chronic obstructive pulmonary disease, renal dysfunction, and cardiovascular disease. Cirrhosis was verified through histopathological examination. Portal hypertension was identified by the presence of either splenomegaly with reduced platelet count (less than 100×10^9/l) or oesophageal varices. Tumour encapsulation was defined based on pathological criteria, which was confirmed by the presence of a fibrous capsule completely surrounding the tumour tissue upon microscopic examination. Complete encapsulation was defined as the presence of an intact capsule surrounding the entire tumour circumference, whereas incomplete encapsulation was defined as partial or absent capsule formation. Operative variables included operative approach (open or laparoscopic), intraoperative blood loss, intraoperative blood transfusion, duration of operation, extent of hepatectomy (major or minor), type of resection (anatomical or non-anatomical), and resection margin status. Major hepatectomy was defined as a partial hepatectomy involving greater than or equal to three Couinaud liver segments, whereas minor hepatectomy was defined as a partial hepatectomy involving less than three Couinaud liver segments.

Frailty assessment

Frailty was assessed using the CFS, a nine-point scale that measures an individual's frailty by evaluating their physical, cognitive, and social functioning (*Table S1*)[15]. The CFS assessment was performed by the admission nurse as part of the standard preoperative evaluation protocol. The scale's standardized criteria and straightforward variables ensured consistent evaluation across all participating centres. Patients were classified into frail (CFS score greater than or equal to 5) and non-frail (CFS score less than 5) groups.

Surgical procedures and perioperative management

Surgical techniques and perioperative management were largely uniform across all participating centres, with resection criteria remaining consistent throughout the study interval[20,21]. Perihepatic ligaments and hepatic parenchyma were transected using a harmonic scalpel or a Cavitron ultrasonic surgical aspirator. Broad-spectrum antibiotics were intravenously administered for 1–3 days. Fresh frozen plasma or albumin was provided if plasma albumin levels were less than 30 g/l. Blood tests and serological liver function tests were conducted on postoperative days 1, 3, 5, and 7. All patients underwent chest X-ray examinations on postoperative day 3 and ultrasonography during the first week after resection. Blood transfusions were given to patients with haemoglobin levels less than 7 g/dl. If no complication occurred, drains were removed between postoperative days 2 and 4.

The follow-up comprised serum AFP measurements, ultrasonography, or contrast-enhanced CT or MRI of the abdomen once every 2 months for the initial 6 months, once every 3 months for the subsequent 18 months, and then once every 6 months at 2 years. Decisions regarding adjuvant TACE were made by multidisciplinary tumour boards at each institution, considering factors such as tumour characteristics, surgical outcomes, and patient performance status. Tumour recurrence was defined as the emergence of new intrahepatic or extrahepatic tumour nodules, with or without elevated serum AFP levels, and the presence of intrahepatic nodules displaying typical imaging features and characteristic HCC attributes on contrast-enhanced CT or MRI examination. Treatment for HCC recurrence was determined by the recurrence pattern, the remaining hepatic functional reserve, and the patient's overall condition.

Study outcomes

The primary outcomes were overall survival (OS) and recurrence-free survival (RFS) and the secondary outcomes included postoperative mortality and morbidity. OS was defined as the time from surgery to death or the last follow-up and RFS was defined as the time from surgery to either disease recurrence or death from any cause, whichever occurred first. Patients who remained alive without recurrence were censored at the last follow-up date. Deaths without documented recurrence were considered events rather than censored observations, as RFS requires patients to be both alive and disease-free. Postoperative mortality encompassed deaths occurring within both 30 and 90 days after surgery. Postoperative morbidity was graded according to the Clavien–Dindo classification, with Clavien–Dindo grades III–V indicating major morbidities[22].

Statistical analysis

Continuous variables are expressed as mean(s.d.) or median (interquartile range (i.q.r.)) and they were compared using Student's *t* test or the Mann–Whitney *U* test. Categorical variables are presented as *n* (%) and they were compared using the chi-squared test or Fisher's exact test, as appropriate. Survival curves were estimated using the Kaplan–Meier method and survival distributions between the frail and non-frail groups were compared using the log rank test. Univariable and multivariable Cox proportional hazards regression models were employed to identify factors associated with OS and RFS. Variables with $P < 0.100$ in the univariable analysis were included in the multivariable analysis. Results are reported as HRs with 95% confidence intervals. A two-sided $P < 0.050$ was considered statistically significant. All statistical analyses were conducted using SPSS® (IBM, Armonk, NY, USA; version 26.0).

Results

Patient characteristics

A total of 488 elderly HCC patients who underwent curative hepatic resection were included in the study, with 340 patients in the non-frail group and 148 patients in the frail group (*Fig. 1*). The median age of the cohort was 75 (i.q.r. 72–78) years and the median CFS score was 4 (i.q.r. 1–6) (*Table 1*). Significant differences were observed between the two groups with regard to age, co-morbidities, ASA grade, the presence of portal hypertension, Child–Pugh grade, maximum tumour size, tumour number, the presence of macrovascular invasion and satellite nodules, tumour differentiation, intraoperative blood loss, intraoperative blood transfusion, extent of hepatectomy, and resection margin status (all $P < 0.050$).

Short- and long-term outcomes

The postoperative 30-day overall, major, and minor morbidity rates in the frail group were 68.9% (102 of 148), 14.2% (21 of 148), and 54.7% (81 of 148) respectively, which were significantly higher compared with those in the non-frail group, which were 43.2% (147 of 340), 6.2% (21 of 340), and 37.0% (126 of 340) respectively (all $P < 0.01$) (*Table 1*). The frail group also exhibited higher 30-day mortality (4.1% (6 of 148) *versus* 0.6% (2 of 340); $P < 0.001$) and 90-day mortality (6.1% (9 of 148) *versus* 0.9% (3 of 340); $P < 0.001$) compared with the non-frail group.

After excluding 12 patients with early postoperative deaths (less than or equal to 90 days after surgery), 476 patients were included in the long-term outcome analysis, comprising 337 patients in the non-frail group and 139 patients in the frail group (*Table 2*). The median follow-up interval was 37.7 (i.q.r. 20.4–57.8) months. The median OS in the frail group was 41.6 (95% c.i. 32.0 to 51.2) months, which was significantly lower compared with that in the non-frail group (69.7 (95% c.i. 55.6 to 83.8) months; $P < 0.001$) (*Fig. 2*). The frail group also exhibited a poorer median RFS of 27.6 (95% c.i. 23.1 to 32.1) months compared with the non-frail group (42.7 (95% c.i. 34.6 to 50.8) months; $P = 0.002$) (*Fig. 3*).

Univariable and multivariable analyses for overall survival and recurrence-free survival

Frailty was found to be independently associated with both poorer OS (HR 1.61 (95% c.i. 1.22 to 2.13); $P = 0.001$) (*Table 3*) and poorer RFS (HR 1.32 (95% c.i. 1.03 to 1.70); $P = 0.028$) (*Table 4*). Other independent risk factors for poorer OS were Child–Pugh grade B, preoperative AFP level greater than 400 μg/l, multiple tumours, macrovascular or microvascular invasion, and intraoperative blood transfusion, whereas other independent risk factors for poorer RFS were tumour size greater than 5 cm, multiple tumours, macrovascular invasion, and intraoperative blood transfusion.

Discussion

Identifying frail patients at an increased risk of adverse outcomes may allow healthcare providers to implement targeted interventions, such as prehabilitation, optimization of medical co-morbidities, and enhanced recovery after surgery protocols, to minimize postoperative complications and improve long-term survival[5,23,24]. The present study demonstrates that preoperative frailty, assessed using the CFS, is significantly associated with worse short-term and long-term postoperative outcomes in elderly HCC patients.

Recent studies have demonstrated encouraging outcomes for hepatic resection in selected elderly HCC patients. Xing *et al.*[25] analysed 17 431 patients and found comparable survival outcomes between elderly and younger patients when proper patient selection was employed. Chen *et al.*[26] recently reported

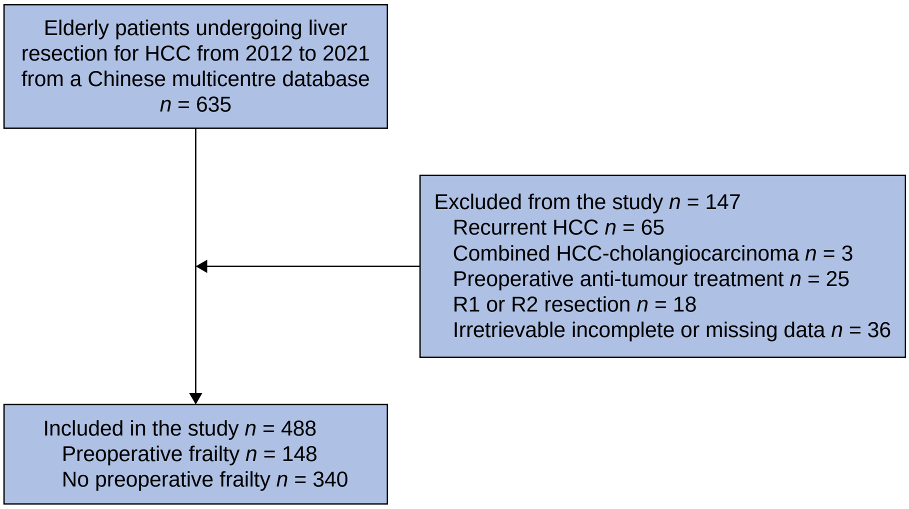

Fig. 1 Flow chart of the patient cohort

HCC, hepatocellular carcinoma.

Table 1 Clinical characteristics, operative variables, and short-term outcomes

	Non-frail group (*n* = 340)	Frail group (*n* = 148)	*P*
Clinical characteristics			
Age (years), mean(s.d.)	74.8(4.0)	76.3(4.7)	0.001
Male	275 (80.9)	111 (75.0)	0.148
Co-morbidities	166 (48.8)	94 (63.5)	0.001
ASA grade >II	120 (35.3)	77 (52.0)	0.001
Positive for HBV	293 (86.2)	129 (87.2)	0.886
Positive for HCV	20 (5.9)	13 (8.8)	0.244
Cirrhosis	242 (71.2)	111 (75.0)	0.441
Portal hypertension	89 (26.2)	54 (36.5)	0.023
Child–Pugh grade B	10 (2.9)	15 (10.1)	0.003
Preoperative AFP level >400 μg/l	93 (27.4)	53 (35.8)	0.068
Maximum tumour size (cm), mean(s.d.)	5.0(3.6)	5.9(4.1)	0.015
Multiple tumours	188 (55.3)	79 (53.4)	0.767
Macrovascular invasion	15 (4.4)	14 (9.5)	0.037
Microvascular invasion	105 (30.9)	48 (32.4)	0.751
Satellite nodules	35 (10.3)	33 (22.3)	0.001
Poor tumour differentiation	183 (53.8)	97 (65.5)	0.017
Incomplete tumour encapsulation	246 (72.4)	102 (68.9)	0.448
Operative variables			
Laparoscopic hepatectomy	138 (40.6)	52 (35.1)	0.268
Intraoperative blood loss (ml), median (i.q.r.)	225 (100–400)	375 (250–650)	0.008
Intraoperative blood transfusion	45 (13.2)	38 (25.7)	0.002
Major hepatectomy	59 (17.4)	38 (25.7)	0.037
Anatomical resection	199 (58.5)	87 (58.8)	0.958
Resection margin <1 cm	149 (43.8)	91 (61.5)	<0.001
Short-term outcomes			
Postoperative hospital stay, mean(s.d.)	10.1(6.6)	14.9(10.9)	<0.001
Postoperative 30-day mortality	2 (0.6)	6 (4.1)	0.011
Postoperative 90-day mortality	3 (0.9)	9 (6.1)	0.002
Postoperative 30-day morbidity	147 (43.2)	102 (68.9)	<0.001
Major morbidity	21 (6.2)	21 (14.2)	0.008
Minor morbidity	126 (37.0)	81 (54.7)	<0.001
Readmission within 30 days after discharge	5 (1.5)	16 (10.8)	<0.001

Values are *n* (%) unless otherwise indicated. ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; i.q.r., interquartile range.

successful outcomes for major hepatectomy in elderly patients with large HCC, showing that age alone should not be a contraindication for surgical resection. These findings align with the present results, suggesting that careful patient selection is more crucial than chronological age in determining surgical outcomes. The importance of frailty assessment in elderly patients undergoing surgery has been increasingly recognized in recent years[8,27–32]. Frailty is a multidimensional concept that reflects a decline in an individual's physiological reserve, increasing their vulnerability to adverse outcomes when faced with stressors, such as surgery[6,16,30,31,33,34]. The CFS is a simple and validated tool that measures an individual's frailty by evaluating their physical, cognitive, and social functioning[15,35]. In this study, 30.3% of the elderly patients undergoing hepatic resection for HCC were classified as frail, which is consistent with other surgical populations[12,36].

Table 2 Long-term outcomes

	Non-frail group ($n = 337$)	Frail group ($n = 139$)	*P*
Follow-up interval (months), mean(s.d.)	46.2(32.4)	36.4(25.0)	<0.001
Adjuvant TACE	73 (21.5)	25 (18.0)	0.367
Recurrence during the follow-up	131 (38.9)	53 (38.1)	0.918
Intrahepatic recurrence	98 (29.1)	40 (28.8)	0.947
Extrahepatic recurrence	10 (3.0)	5 (3.6)	0.774
Intrahepatic and extrahepatic recurrence	23 (6.8)	10 (7.2)	0.845
Reoperation for recurrence	11 (8.4)	3 (5.7)	0.760
Death during the follow-up	153 (45.4)	84 (60.4)	0.003
OS (months), median (95% c.i.)	69.7 (55.6,83.8)	41.6 (32.0,51.2)	<0.001
One-year OS rate (%)	90.7	86.2	
Three-year OS rate (%)	75.2	58.4	
Five-year OS rate (%)	55.2	36.8	
Median RFS (months), median (95% c.i.)	42.7 (34.6,50.8)	27.6 (23.1,32.1)	0.002
One-year RFS rate (%)	77.2	75.4	
Three-year RFS rate (%)	55.3	40.2	
Five-year RFS rate (%)	37.4	24.2	

Values are *n* (%) unless otherwise indicated. TACE, transcatheter arterial chemoembolization; OS, overall survival; RFS, recurrence-free survival.

In terms of short-term outcomes, the findings of the present study revealed that frail elderly patients had significantly higher 30-day morbidity and mortality rates compared with their non-frail counterparts, in line with previous studies analysing various types of surgery[16,31,34,37–40]. The increased vulnerability of frail patients to complications could be attributed to their diminished physiological reserve, as well as the presence of co-morbidities and impaired functional status[11,41,42]. Frailty has been associated with an increased risk of delirium, falls, and prolonged hospital stay, all of which can contribute to higher morbidity and mortality rates[43,44].

The present study demonstrated that frail elderly patients had significantly poorer OS and RFS after hepatic resection for HCC, in line with previous reports that have shown an association between frailty and worse oncological outcomes in patients undergoing surgery for various malignancies[45–49]. Several factors may explain the poorer long-term outcomes observed among the frail elderly patients in this study. Frail patients may have an increased susceptibility to the adverse effects of adjuvant therapy, leading to suboptimal treatment and worse oncological outcomes[50,51]. Frailty has been linked to a higher risk of developing postoperative complications, which could negatively impact long-term survival[52,53], and it is often associated with an increased risk of non-cancer-related mortality due to the presence of co-morbidities and diminished functional status[54,55].

Frailty assessment should be incorporated into the preoperative evaluation process to better stratify the risk of complications, to inform shared decision-making[56,57], and to develop perioperative management strategies for selected individual (such as prehabilitation, optimization of co-morbidities, and closer postoperative monitoring). Prehabilitation, which involves interventions aimed at

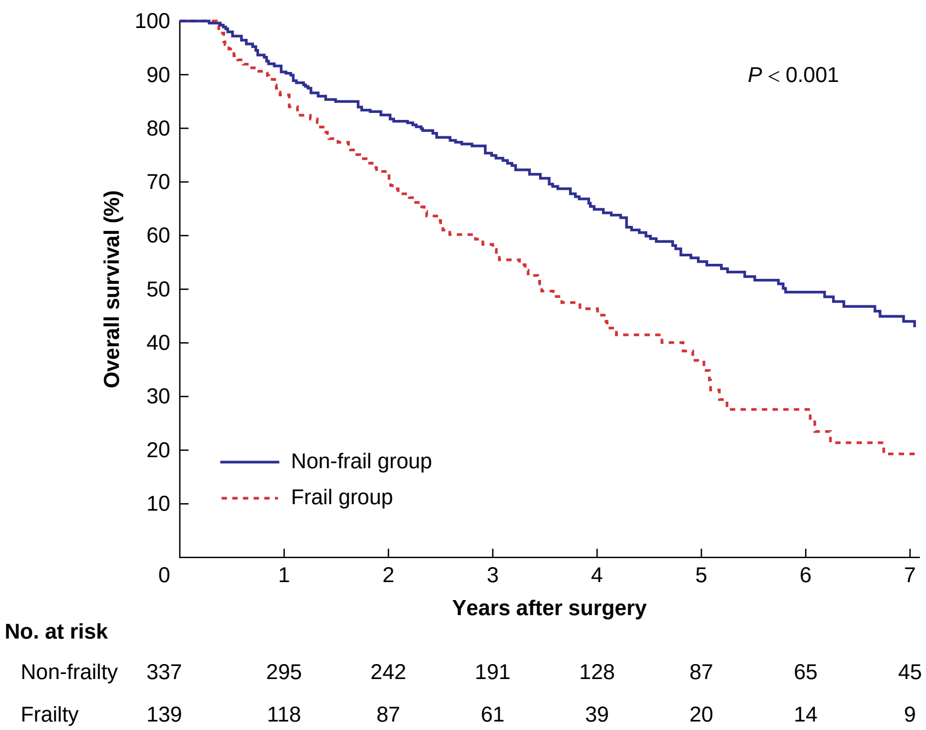

Fig. 2 Curves for comparison of cumulative incidence of overall survival between elderly patients with and without preoperative frailty ($P < 0.001$; calculated using the log rank test)

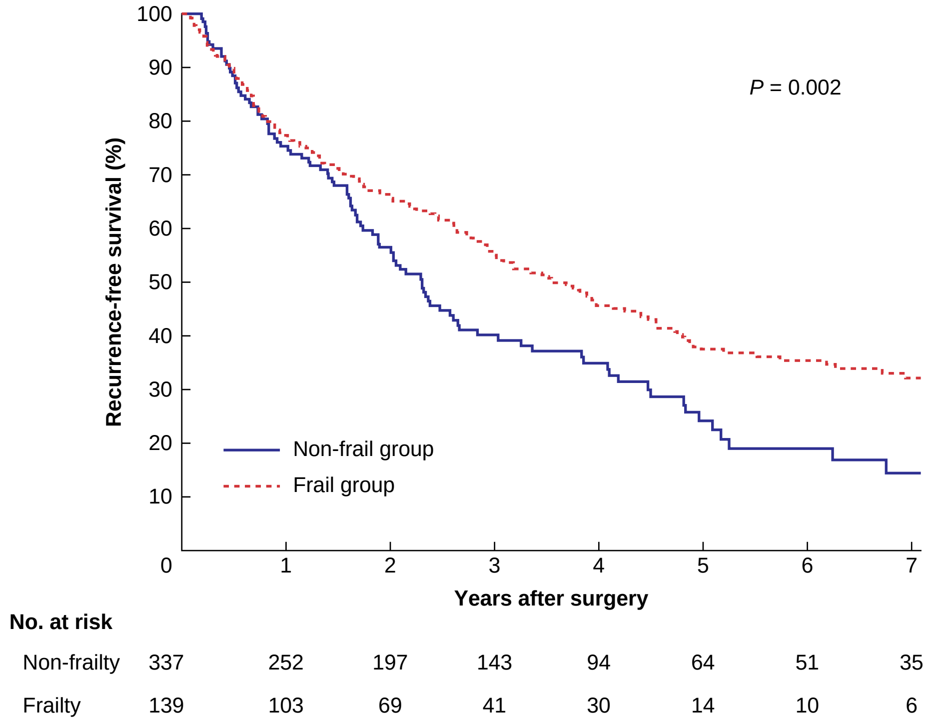

Fig. 3 Curves for comparison of cumulative incidence of recurrence-free survival between elderly patients with and without preoperative frailty (*P* = 0.002; calculated using the log rank test)

Table 3 Univariable and multivariable Cox regression analyses of risk factors associated with overall survival

Variable	HR comparison	Univariable HR (95% c.i.)	Univariable *P*	Multivariable HR (95% c.i.)	Multivariable *P*
Frailty status	Frailty *versus* non-frailty	1.78 (1.36,2.34)	<0.001*	1.61 (1.22,2.13)	0.001*
Age	≥80 years *versus* <80 years	1.01 (0.73,1.40)	0.949		
Sex	Male *versus* female	1.06 (0.77,1.46)	0.709		
Co-morbidities	Yes *versus* no	1.21 (0.89,1.64)	0.235		
ASA grade	>II *versus* ≤II	1.04 (0.80,1.35)	0.763		
Positive for HBV	Yes *versus* no	0.93 (0.66,1.32)	0.688		
Positive for HCV	Yes *versus* no	1.07 (0.69,1.67)	0.761		
Cirrhosis	Yes *versus* no	1.12 (0.83,1.51)	0.450		
Portal hypertension	Yes *versus* no	1.16 (0.89,1.52)	0.276		
Child–Pugh grade	B *versus* A	2.22 (1.33,3.70)	0.002*	1.75 (1.03,2.96)	0.038*
Preoperative AFP level	>400 μg/l *versus* ≤400 μg/l	1.36 (1.04,1.78)	0.024*	1.39 (1.06,1.83)	0.017*
Maximum tumour size	>5 cm *versus* ≤5 cm	1.38 (1.07,1.78)	0.014*	NA	0.218
Tumour number	Multiple *versus* solitary	1.54 (1.18,2.01)	0.001*	1.48 (1.12,1.94)	0.005*
Macrovascular invasion	Yes *versus* no	3.41 (2.17,5.36)	<0.001*	2.97 (1.86,4.72)	<0.001*
Microvascular invasion	Yes *versus* no	1.55 (1.17,2.04)	0.002*	1.44 (1.06,1.94)	0.018*
Satellite nodules	Yes *versus* no	2.02 (1.43,2.84)	<0.001*	NA	0.234
Poor tumour differentiation	Yes *versus* no	1.40 (1.08,1.83)	0.012*	NA	0.067
Tumour encapsulation	Incomplete *versus* complete	1.41 (1.05,1.90)	0.023*	NA	0.072
Operative approach	Open *versus* laparoscopic	0.95 (0.72,1.26)	0.724		
Intraoperative blood loss	>400 ml *versus* ≤400 ml	1.38 (0.92,2.06)	0.118		
Intraoperative blood transfusion	Yes *versus* no	2.09 (1.52,2.87)	<0.001*	1.67 (1.20,2.32)	0.002*
Extent of hepatectomy	Major *versus* minor	1.27 (0.93,1.74)	0.135		
Type of resection	Non-anatomical *versus* anatomical	0.92 (0.71,1.19)	0.526		
Resection margin	<1 cm *versus* ≥1 cm	1.06 (0.82,1.37)	0.655		
Adjuvant TACE	No *versus* yes	1.13 (0.92,1.39)	0.253		

*Statistically significant. ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, α-fetoprotein; NA, not available; TACE, transcatheter arterial chemoembolization.

improving a patient's physical, nutritional, and psychological status before surgery, has been shown to improve postoperative outcomes in various surgical populations[58–62].

This study has several limitations. The retrospective design could have introduced selection bias and limited the ability to control for confounding factors. Another limitation of this study was the use of the CFS to assess frailty. While the CFS is a valid measure of frailty, there are alternative frailty assessment tools that could be more suitable, such as the Frailty Index, the Fried Frailty Phenotype, and the Short Physical Performance

Table 4 Univariable and multivariable Cox regression analyses of risk factors associated with recurrence-free survival

Variable	HR comparison	Univariable HR (95% c.i.)	Univariable P	Multivariable HR (95% c.i.)	Multivariable P
Frailty status	Frailty *versus* non-frailty	1.46 (1.14,1.87)	0.002*	1.32 (1.03,1.70)	0.028*
Age	≥80 years *versus* <80 years	0.83 (0.61,1.12)	0.231		
Sex	Male *versus* female	1.21 (0.90,1.61)	0.205		
Co-morbidities	Yes *versus* no	1.08 (0.82,1.43)	0.561		
ASA grade	>II *versus* ≤II	1.12 (0.89,1.42)	0.330		
Positive for HBV	Yes *versus* no	1.08 (0.78,1.50)	0.630		
Positive for HCV	Yes *versus* no	1.00 (0.65,1.52)	0.985		
Cirrhosis	Yes *versus* no	1.18 (0.91,1.53)	0.222		
Portal hypertension	Yes *versus* no	1.09 (0.85,1.39)	0.503		
Child–Pugh grade	B *versus* A	1.68 (1.04,2.71)	0.034*	NA	0.278
Preoperative AFP level	>400 μg/l *versus* ≤400 μg/l	1.19 (0.93,1.52)	0.158		
Maximum tumour size	>5 cm *versus* ≤5 cm	1.52 (1.21,1.92)	<0.001*	1.31 (1.04,1.67)	0.024*
Tumour number	Multiple *versus* solitary	1.53 (1.21,1.94)	<0.001*	1.37 (1.08,1.74)	0.010*
Macrovascular invasion	Yes *versus* no	4.00 (2.61,6.13)	<0.001*	2.86 (1.83,4.46)	<0.001*
Microvascular invasion	Yes *versus* no	1.46 (1.14,1.86)	0.003*	NA	0.102
Satellite nodules	Yes *versus* no	1.80 (1.32,2.45)	<0.001*	NA	0.285
Poor tumour differentiation	Yes *versus* no	1.41 (1.11,1.78)	0.004*	NA	0.156
Tumour encapsulation	Incomplete *versus* complete	1.26 (0.98,1.64)	0.074*	NA	0.263
Operative approach	Open *versus* laparoscopic	1.19 (0.94,1.52)	0.150		
Intraoperative blood loss	>400 ml *versus* ≤400 ml	1.21 (0.96,1.57)	0.144		
Intraoperative blood transfusion	Yes *versus* no	1.84 (1.39,2.45)	<0.001*	1.51 (2.13,2.03)	0.006*
Extent of hepatectomy	Major *versus* minor	1.30 (0.98,1.71)	0.071*	NA	0.547
Type of resection	Non-anatomical *versus* anatomical	0.87 (0.69,1.10)	0.241		
Resection margin	<1 cm *versus* ≥1 cm	0.87 (0.69,1.09)	0.234		
Adjuvant TACE	No *versus* yes	1.14 (0.95,1.35)	0.154		

*Statistically significant. ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available; AFP, α-fetoprotein; TACE, transcatheter arterial chemoembolization.

Battery[6,15,63]. The generalizability of the findings of the present study could also be limited, as the study population was from ten Chinese hospitals; further research is needed to confirm the findings in more diverse patient populations and to explore the potential impact of cultural, socio-economic, and healthcare system-related factors on the relationship between frailty and surgical outcomes[64,65]. The findings of the present study do not directly inform the development of interventions to address frailty in elderly HCC patients. Further research is needed to identify effective strategies for preventing or mitigating frailty in elderly HCC patients, such as prehabilitation, optimization of co-morbidities, and individualized perioperative care plans[24,56].

Prospective studies are needed to validate the use of the CFS in preoperative risk stratification for elderly HCC patients. Interventional studies exploring the effectiveness of prehabilitation programmes in improving postoperative outcomes for frail patients should be conducted. The development and validation of HCC-specific frailty assessment tools that incorporate both general frailty measures and liver-specific factors could further refine risk prediction in this population. Studies investigating the impact of frailty on long-term quality of life and functional outcomes after HCC resection would provide valuable information for shared decision-making between clinicians and patients.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F *et al*. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;**66**:115–132
2. Yang T, Lu JH, Wu MC. Hepatocellular carcinoma in China. *BMJ* 2010;**340**:c1026
3. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;**69**:182–236
4. Oishi K, Itamoto T, Kohashi T, Matsugu Y, Nakahara H, Kitamoto M. Safety of hepatectomy for elderly patients with hepatocellular carcinoma. *World J Gastroenterol* 2014;**20**: 15028–15036
5. Zhao L-Y, Huo R-R, Xiang X, Torzilli G, Zheng M-H, Yang T *et al*. Hepatic resection for elderly patients with hepatocellular carcinoma: a systematic review of more than 17,000 patients. *Expert Rev Gastroenterol Hepatol* 2018;**12**:1059–1068
6. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–M156
7. Sternberg SA, Wershof Schwartz A, Karunananthan S, Bergman H, Mark Clarfield A. The identification of frailty: a systematic literature review. *J Am Geriatr Soc* 2011;**59**:2129–2138
8. Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin* 2017;**67**: 362–377
9. Sandini M, Pinotti E, Persico I, Picone D, Bellelli G, Gianotti L. Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery. *BJS Open* 2017;**1**:128–137
10. Beggs T, Sepehri A, Szwajcer A, Tangri N, Arora RC. Frailty and perioperative outcomes: a narrative review. *Can J Anaesth* 2015; **62**:143–157
11. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P *et al*. Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010;**210**:901–908
12. Kim S-W, Han H-S, Jung H-W, Kim K-I, Hwang DW, Kang S-B *et al*. Multidimensional frailty score for the prediction of postoperative mortality risk. *JAMA Surg* 2014;**149**:633–640
13. Lai JC, Shui AM, Duarte-Rojo A, Rahimi RS, Ganger DR, Verna EC *et al*. Association of frailty with health-related quality of life in liver transplant recipients. *JAMA Surg* 2023;**158**:130–138
14. Lai JC, Shui AM, Duarte-Rojo A, Ganger DR, Rahimi RS, Huang C-Y *et al*. Frailty, mortality, and health care utilization after liver transplantation: from the multicenter functional assessment in liver transplantation (FrAILT) study. *Hepatology* 2022;**75**:1471–1479
15. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;**173**:489–495
16. Le ST, Liu VX, Kipnis P, Zhang J, Peng PD, Cespedes Feliciano EM. Comparison of electronic frailty metrics for prediction of adverse outcomes of abdominal surgery. *JAMA Surg* 2022;**157**: e220172
17. Yang T, Zhang J, Lu JH, Yang GS, Wu MC, Yu WF. Risk factors influencing postoperative outcomes of major hepatic resection of hepatocellular carcinoma for patients with underlying liver diseases. *World J Surg* 2011;**35**:2073–2082
18. Yang SC, Liang L, Wang MD, Wang X-M, Gu L-H, Lin K-Y *et al*. Prospective validation of the Eastern Staging in predicting survival after surgical resection for patients with hepatocellular carcinoma: a multicenter study from China. *HPB (Oxford)* 2023; **25**:81–90
19. Yao L-Q, Chen Z-L, Feng Z-H, Diao Y-K, Li C, Sun H-Y *et al*. Clinical features of recurrence after hepatic resection for early-stage hepatocellular carcinoma and long-term survival outcomes of patients with recurrence: a multi-institutional analysis. *Ann Surg Oncol* 2022;**29**:4291–4303
20. Yang T, Lu J-H, Lau WY, Zhang Tian-Yi, Zhang H, Shen Y-N *et al*. Perioperative blood transfusion does not influence recurrence-free and overall survivals after curative resection for hepatocellular carcinoma: a propensity score matching analysis. *J Hepatol* 2016;**64**:583–593
21. Xu X-F, Xing H, Han J, Li Z-L, Lau W-Y, Zhou Y-H *et al*. Risk factors, patterns, and outcomes of late recurrence after liver resection for hepatocellular carcinoma: a multicenter study from China. *JAMA Surg* 2019;**154**:209–217
22. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;**240**: 205–213
23. Tzeng CW, Cooper AB, Vauthey JN, Curley SA, Aloia TA. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. *HPB (Oxford)* 2014;**16**:459–468
24. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. *Curr Opin Clin Nutr Metab Care* 2005;**8**:23–32
25. Xing H, Liang L, Wang H, Zhou Y-H, Pei Y-L, Li C *et al*. Multicenter analysis of long-term oncologic outcomes of hepatectomy for elderly patients with hepatocellular carcinoma. *HPB (Oxford)* 2020;**22**:1314–1323
26. Chen Z-L, Zhang C-W, Liang L, Wu H, Zhang W-G, Zeng Y-Y *et al*. Major hepatectomy in elderly patients with large hepatocellular carcinoma: a multicenter retrospective observational study. *Cancer Manag Res* 2020;**12**:5607–5618
27. Robinson TN, Walston JD, Brummel NE, Deiner S, Brown CH, Kennedy M *et al*. Frailty for surgeons: review of a National Institute on Aging conference on frailty for specialists. *J Am Coll Surg* 2015;**221**:1083–1092
28. McIsaac DI, Bryson GL, van Walraven C. Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: a population-based cohort study. *JAMA Surg* 2016;**151**:538–545
29. Hall DE, Arya S, Schmid KK, Blaser C, Carlson MA, Bailey TL *et al*. Development and initial validation of the Risk Analysis Index for measuring frailty in surgical populations. *JAMA Surg* 2017;**152**: 175–182
30. Wahl TS, Graham LA, Hawn MT, Richman J, Hollis RH, Jones CE *et al*. Association of the modified frailty index with 30-day surgical readmission. *JAMA Surg* 2017;**152**:749–757
31. Shinall MC JR, Arya S, Youk A, Varley P, Shah R, Massarweh NN *et al*. Association of preoperative patient frailty and operative stress with postoperative mortality. *JAMA Surg* 2020;**155**: e194620
32. Seib CD, Rochefort H, Chomsky-Higgins K, Gosnell JE, Suh I, Shen WT *et al*. Association of patient frailty with increased morbidity after common ambulatory general surgery operations. *JAMA Surg* 2018;**153**:160–168
33. Xue Q-L. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011;**27**:1–15
34. Shah R, Attwood K, Arya S, Hall DE, Johanning JM, Gabriel E *et al*. Association of frailty with failure to rescue after low-risk and high-risk inpatient surgery. *JAMA Surg* 2018;**153**:e180214
35. Bagshaw SM, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N *et al*. Association between frailty and short- and

long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ* 2014;**186**:E95–E102
36. Joseph B, Pandit V, Zangbar B, Kulvatunyou N, Hashmi A, Green DJ *et al.* Superiority of frailty over age in predicting outcomes among geriatric trauma patients: a prospective analysis. *JAMA Surg* 2014;**149**:766–772
37. Dasgupta M, Rolfson DB, Stolee P, Borrie MJ, Speechley M. Frailty is associated with postoperative complications in older adults with medical problems. *Arch Gerontol Geriatr* 2009;**48**:78–83
38. Robinson TN, Wu DS, Pointer L, Dunn CL, Cleveland Jr JC, Moss M. Simple frailty score predicts postoperative complications across surgical specialties. *Am J Surg* 2013;**206**:544–550
39. Partridge JS, Fuller M, Harari D, Taylor PR, Martin FC, Dhesi JK. Frailty and poor functional status are common in arterial vascular surgical patients and affect postoperative outcomes. *Int J Surg* 2015;**18**:57–63
40. 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
41. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004;**59**:255–263
42. Shinall MC JR, Youk A, Massarweh NN, Shireman PK, Arya S, George EL *et al.* Association of preoperative frailty and operative stress with mortality after elective vs emergency surgery. *JAMA Netw Open* 2020;**3**:e2010358
43. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;**383**:911–922
44. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *Br J Anaesth* 2009;**103**(Suppl 1):i41–i46
45. Aaldriks AA, Giltay EJ, Nortier JW, van der Geest LGM, Tanis BC, Ypma P *et al.* Prognostic significance of geriatric assessment in combination with laboratory parameters in elderly patients with aggressive non-Hodgkin lymphoma. *Leuk Lymphoma* 2015;**56**:927–935
46. Li JL, Henderson MA, Revenig LM, Sweeney JF, Kooby DA, Maithel SK *et al.* Frailty and one-year mortality in major intra-abdominal operations. *J Surg Res* 2016;**203**:507–512.e1
47. Wagner D, Büttner S, Kim Y, Gani F, Xu L, Margonis GA *et al.* Clinical and morphometric parameters of frailty for prediction of mortality following hepatopancreaticobiliary surgery in the elderly. *Br J Surg* 2016;**103**:e83–e92
48. Lee DU, Kwon J, Han J, Fan GH, Hastie DJ, Lee KJ *et al.* The clinical impact of frailty on the postoperative outcomes of patients undergoing gastrectomy for gastric cancer: a propensity-score matched database study. *Gastric Cancer* 2022;**25**:450–458
49. Ngo-Huang A, Holmes HM, des Bordes JKA, Parker NH, Fogelman D, Petzel MQB *et al.* Association between frailty syndrome and survival in patients with pancreatic adenocarcinoma. *Cancer Med* 2019;**8**:2867–2876
50. Extermann M, Boler I, Reich RR, Lyman GH, Brown RH, DeFelice J *et al.* Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. *Cancer* 2012;**118**:3377–3386
51. Mohile SG, Xian Y, Dale W, Fisher SG, Rodin M, Morrow G *et al.* Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. *J Natl Cancer Inst* 2009;**101**:1206–1215
52. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al.* The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009;**250**:187–196
53. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. *J Am Coll Surg* 2006;**203**:865–877
54. Hubbard RE, O'Mahony MS, Savva GM, Calver BL, Woodhouse KW. Inflammation and frailty measures in older people. *J Cell Mol Med* 2009;**13**:3103–3109
55. Hubbard RE, Searle SD, Mitnitski A, Rockwood K. Effect of smoking on the accumulation of deficits, frailty and survival in older adults: a secondary analysis from the Canadian Study of Health and Aging. *J Nutr Health Aging* 2009;**13**:468–472
56. Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. *Age Ageing* 2012;**41**:142–147
57. Farhat JS, Velanovich V, Falvo AJ, Horst HM, Swartz A, Patton JH *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**:1526–1530; discussion 1530–1531
58. Carli F, Scheede-Bergdahl C. Prehabilitation to enhance perioperative care. *Anesthesiol Clin* 2015;**33**:17–33
59. Topp R, Ditmyer M, King K, Doherty K, Hornyak J III. The effect of bed rest and potential of prehabilitation on patients in the intensive care unit. *AACN Clin Issues* 2002;**13**:263–276
60. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A *et al.* Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* 2014;**121**:937–947
61. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS *et al.* Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg Endosc* 2013;**27**:1072–1082
62. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil* 2013;**92**:715–727
63. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG *et al.* A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;**49**:M85–M94
64. Olsson T, Terent A, Lind L. Rapid Emergency Medicine score: a new prognostic tool for in-hospital mortality in nonsurgical emergency department patients. *J Intern Med* 2004;**255**:579–587
65. Leung JM, Dzankic S, Manku K, Yuan S. The prevalence and predictors of the use of alternative medicine in presurgical patients in five California hospitals. *Anesth Analg* 2001;**93**:1062–1068