The Prevalence of Frailty in Cancer Patients and Mortality Prediction With a Novel Frailty Index Based Clinical Algorithm-A Multicenter, Prospective, Observational Study

Xi Jin (jxfl007@zju.edu.cn)
Zhejiang University School of Medicine First Affiliated Hospital

Yue Ren
Zhejiang University School of Medicine First Affiliated Hospital

Li Shao
Zhejiang University School of Medicine First Affiliated Hospital

Zengqing Guo
Fujian Provincial Cancer Hospital

Chang Wang
Jilin University First Hospital

Ying He
Chongqing Medical University

Lan Zhou
Yunnan Cancer Hospital

Minghua Cong
University of the Chinese Academy of Sciences

Hu Ma
Affiliated Hospital of Zunyi Medical College

Wei Wang
First People's Hospital of Foshan

Chunling Zhou
Tumor Hospital of Harbin Medical University

Yongdong Feng
Huazhong University of Science and Technology

Yi Ba
Tianjin Tumor Hospital

Jianguo Gao
Zhejiang University School of Medicine First Affiliated Hospital

Miaomiao Lu
Zhejiang University School of Medicine First Affiliated Hospital

Mengmeng Zhang
Zhejiang University School of Medicine First Affiliated Hospital
Xuewei Gu
Zhejiang University School of Medicine First Affiliated Hospital
Chunhua Song
Zhengzhou University
Hongxia Xu
Third Military Medical University Daping Hospital and Research Institute of Surgery
Hanping Shi
Capital Medical University Affiliated Beijing Shijitan Hospital

---

Research

Keywords: cancer, Frailty, blood test, mortality

Posted Date: June 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-34820/v1

Abstract

Purpose To investigate the prediction capacity and status of frailty in Chinese cancer patients in national level, through establishing a novel prediction algorithm.

Methods The percentage of frailty in different ages, provinces and tumor type groups of Chinese cancer patients were revealed. The predictioncapacity of frailty on mortality of Chinese cancer patients was analyzed by FI-LAB that is composed of routine laboratory data from accessible blood test and calculated as the ratio of abnormal factors in 22 variables. Establishment of a novel algorithm MCP(mortality of cancer patients)to predict the five-year mortality in Chinese cancer patients was accomplished and its prediction capacity was tested in the training and validation sets using ROC analysis.

ResultsWe found that the increased risk of death in cancer patients can be successfully identified through FI-LAB. The univariable and multivariable Cox regression were used to evaluate the effect of frailty on death. In the 5-year follow-up, 20.6% of the 2959 participants (age = 55.8 ± 11.7 years; 43.5% female) were dead while the mean FI-LAB score in baseline was 0.23 (standard deviation = 0.13; range = 0 to 0.73).Frailty (after adjusting for gender, age, and other confounders) could be directly correlated with increased risk of death, with a hazard ratio of 12.67 (95% confidence interval CI: 7.19, 22.31) in comparison with those without frailty. In addition, MCP algorithm presented an area under the ROC (AUC) of 0.691 (95% CI: 0.659-0.684) and 0.648 (95% CI: 0.613-0.684) in the training and validation set, respectively.

Conclusion Frailty is common in cancer patients and FI-LAB has high prediction capacity on mortality. The MCP algorithm is a good supplement for frailty evaluation and mortality prediction in cancer patients.

Background

Frailty is an emerging global health burden, with major implications for clinical practice and public health. The prevalence of frailty is expected to rise alongside rapid growth in the ageing population(1). The course of frailty is characterized by a decline in functioning across multiple physiological systems, accompanied by an increased vulnerability to stressors, especially in cancer patients(2). The concept of frailty is increasingly being used in primary, acute, and specialist care. However, despite efforts over the past three decades, agreement on a standard procedure to identify frailty has not yet been achieved. During the conceptualization of frailty, three significant factors have remained consistent(3). First, frailty is multidimensional, with physical and psychosocial factors involved in its development. Second, although its prevalence does increase with age, frailty is an extreme consequence of the normal ageing process. Finally, frailty is a dynamic and fluctuatable status(3). Subjects with frailty have increased risks of adverse outcomes, including fall, hospitalization, and mortality(4) as well as individual burden, including impaired quality of life and loneliness(5). The prevalence of cancer and its related mortality

have been increasing in the last decades all over the world, becoming the leading cause of death since 2010 in China(6–8). Since malnutrition and even cachexia are often observed in the end stage of cancer, it is theoretically plausible that frailty is actively involved. Nevertheless, although the association between cancer and frailty has been summarized elsewhere(2, 9), these studies mainly focused on older patients while the frailty status in China and its prediction capacity in cancer mortality have been rarely reported.

Currently, the major obstacle for frailty study may be the shortage of global standardized assessment(10). The most widely used methods are based on frailty physical phenotype and frailty index, with various modifications in different studies(11). The physical phenotype is more subjective and usually applied in cohort studies(12) while frailty index is more objective and based on cumulative health-related deficits(13). Frailty index is defined as the number of deficits (out of the normal range of investigated parameters) in a patient divided by the sum of all investigated parameters. Therefore, the range of a frailty index is 0 to 1 with higher scores suggesting a greater frailty level. Except for well acknowledged hospital frailty index score(14), FI-LAB was developed from the Canadian Study of Health and Aging (CSHA) cohort based on 21 laboratory variables in older patents for death risk prediction(15). Several other studies confirmed that FI-LAB was practicable, valid and closely associated with frailty indexes based on complex, self-reported data for the prediction of mortality(16, 17). However, these studies only included 35 to 89 years old Caucasian individuals, where the association in the other stages of life and in cancer patients are still unclear.

Therefore, in this study, we carried out a multicenter, prospective, observational study based on the Chinese largest prospective oncology and nutrition study (INSCOC study) to investigate the frailty status of Chinese patients with different cancer types in different provinces using FI-LAB algorithm. The role of FI-LAB in predicting patients' mortality was also performed. Moreover, we successfully built a risk assessment algorithm comprising FI-LAB and other factors to predict mortality in Chinese patients with various cancers.

Methods

Participants and Ethics

In 2019, we collected data from a Chinese Society of Nutritional Oncology (CSNO) initiated clinical research project, the Investigation on Nutrition Status and Its Clinical Outcome of Common Cancers (INSCOC) starting from 2013. This observational, multi-center and hospital based prospective cohort study was registered with the Chinese Clinical Trial Registry (ChiCTR1800020329) and approved by local ethical committees of all the participant hospitals, with formal written consent from every patient. This study was carried out in accordance with the declaration of Helsikin. The primary outcome was the prevalence of frailty in Chinese patients with local regional, recurrent or metastatic cancers at different ages. The secondary outcome included the prediction capacity of nutrition status, physical performance and quality of life at admission on the overall cancer survival, the association between frailty and demographic characteristics and the establishment of a mortality prediction model based on FI- LAB.

All patients were recruited by clinical investigators in various departments of participating hospitals. Patients were diagnosed with one of the following 18 malignant tumors: lung cancer, gastric cancer, liver cancer, colorectal cancer, breast cancer, esophageal cancer, cervical cancer, endometrial cancer, nasopharyngeal carcinoma, malignant lymphoma, leukemia, pancreatic cancer, ovarian cancer, prostate cancer, bladder cancer, brain tumor, biliary tract malignant tumor and gastric stromal tumor. Medical records were supplied with the anatomical site according to the 10th edition of the International Classification of Disease (ICD-10). The inclusion criteria include > 13 year, tumor properly diagnosed by pathology and staged as local, metastatic and/or loco-regional relapse and with conscious. The exclusion criteria include hospitalized more than two times during our investigation, with organ transplantation, pregnant woman, diagnosed with human immuno-deficiency virus (HIV) infection and admitted to intensive care unit (ICU) at the beginning of recruitment.

Several co-existing diseases that may affect frail status were investigated at the admission to the hospital, including hepatic cirrhosis, chronic hepatitis, chronic pancreatitis, stroke, chronic obstructive pulmonary disease (COPD), myocardial infarction, diabetes, hypertension, coronary heart disease, anemia, hyperthyroidism, hypothyroidism, chronic nephrosis, dialysis treatment, osteoporosis, ulcerative colitis, Crohn's disease, chronic diseases of the biliary system, systemic lupus erythematosus and tuberculosis. For this analysis, participants lacking data of following time (22 cases) and age (4 cases) were excluded, finalizing a study sample of 2959 (male 1673; female 1286).

Frailty index-FI-LAB establishment based on lab variables

In this study, we constructed a frailty index-FI-LAB based on 22 lab variables from fasting blood sample. Variables were selected according to previous studies(15, 18), including counts of white blood cells, neutrophilic leukocytes, platelets, hematocrit, red blood cells, hemoglobin, the mean values of corpuscular volume, cell hemoglobin, and corpuscular hemoglobin concentrations (MCV, MCH, and MCHC, respectively), blood glucose, total and direct bilirubin (TBil and DBil, respectively), alanine transaminase (ALT), albumin (Alb), globulin (Glob), urea, creatinine (CREA), uric acid (URIC), cholesterol (CHOL), high-density and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively), and triglycerides (TG). Each variable was coded as either 1 or 0, with 1 indicating that the values exceeded the normal range or cut-offs (deficits), and 0 indicating that the values were within the normal range(19). FI-LAB is defined as the sum of all existing deficits from parameter divided by the sum of all considered parameters (here, 22). Theoretically, FI-LAB is a continuous variables between 0 to 1 for each given individual. In this study, established FI-LAB cut-points (0.21) were employed according to previous study(18, 19).

Data for mortality and other co-variables

Mortality data were collected till 2019 for all patients. The status of the patient was divided as survive and dead, where those loss of follow-up was defined as censored data. The time of death was recorded and the co-variables were recorded, including individual's age, gender and chronic disease using a general questionnaire through direct interview by well trained volunteers. All the reported chronic ailments were diagnosed by local certified physicians.

Statistical analysis

Descriptive statistics were used for baseline characteristics. The continuous or categorical variables were described using mean values, standard deviation (SD), numbers or percentages. For continuous and categorical variables, the differences between survival and frailty status (determined by FI-LAB) were evaluated by applying the unpaired Student's *t*-test and the chi-square test, respectively. We applied regression models of Cox proportional hazard to determine the hazard ration (HR) and its 95% confidence intervals (CI) of frailty, with a function of increased mortality represented by each parameter in FI-LAB and overall frailty status. Univariate and multivariate cox regression analyses were used to identify predictors of mortality. Factors significantly associated with mortality in the univariate analysis ($P < 0.05$) were tested for multicollinearity using linear regression. Factors were included in the algorithm if they remained significant in the multivariate analysis. Using these variables, a Cox regression based nomogram was developed to predict mortality in cancer patients. The discriminative power of the model was then evaluated based on discrimination and calibration. The predictive accuracy of the nomogram was validated using ROC and quantified by the area under the curve (AUC) and 95% confidence intervals (CIs). An AUC of 0.5 and 1.0 indicate no relationship and perfect concordance while an AUC > 0.75 is considered to have a relatively good discrimination. The SPSS version 22 (SPSS Inc., Chicago, IL, USA) and Prism 8 were applied for all statistical analyses and plots. The statistical significance was set as two-tailed P at < 0.05.

Results

Baseline characteristics of patients with different cancers and frailty

A total of 2959 patients with different cancers were included in this study, with mean age of 55.8 ± 11.7 years (ranging from 13 to 94 year) and female percentage of 43.5%. The participants' median, mean and maximum scores of FI-LAB were 0.227, 0.233, and 0.730, with 99th percentile score of 0.591. The overall prevalence of frailty was 55.2% (FI-LAB ≧ 0.21; 95% CI 53.4%-57.0%). Considering gender distribution, men had higher FI-LAB score compared with that of women (0.24 ± 0.13 vs. 0.23 ± 0.13; p = 0.007). As shown in Table 1, cancer patients with frailty had significantly older age, higher rate of male gender and levels of total cholesterol (TC), triglycerides (TG) and LDL-C as well as lower levels of HDL-C, serum uric acid (SUA) and BMI. Concerning co-existing diseases, cancer patients with frailty had significantly higher rates of hypertension, diabetes, anemia and chronic hepatitis. More importantly, the rate of death is nearly doubled in cancer patients with frailty than those without frailty (26.0% vs 14.3%, p < 0.001).

Table 1
Characteristics of the study population according to frailty assessed by FI-LAB

	Frailty		P value
	NO (n = 1352)	YES (n = 1607)	
Age (years)	55.0 ± 11.9	56.5 ± 11.6	< 0.001**
Male(%)	54.1	58.6	0.016*
BMI (kg/m2)	23.2 ± 3.3	22.8 ± 5.2	0.042*
Weight (kg)	62.0 ± 10.4	61.6 ± 15.4	0.319
Height (cm)	163.5 ± 7.8	164.0 ± 7.7	0.095
TG (mmol/l)	1.4 ± 1.0	1.6 ± 1.1	< 0.001**
TC (mmol/l)	4.7 ± 1.2	4.8 ± 1.6	0.012*
HDL-C(mmol/l)	1.3 ± 0.5	1.2 ± 0.5	< 0.001**
LDL-C (mmol/l)	2.9 ± 0.8	3.1 ± 1.0	< 0.001**
SUA (μmol/l)	314.6 ± 73.0	306.3 ± 95.8	0.008*
Hypertension (%)	5.8	10.4	0.002*
Diabetes (%)	14.9	19.3	< 0.001**
Cardiovascular disease	2.8	3.7	0.19
Anemia	0.5	2.2	< 0.001**
Chronic hepatitis	4.5	6.2	0.048*
Death (%)	14.3	26.0	< 0.001**

Data are the mean ± SD unless otherwise indicated. *P < 0.05, **P < 0.01. Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; TC, total cholesterol; TG, triglycerides; SD, standard deviation.

Frailty investigation in cancer patients categorized by province, age and tumor type

We investigated the incidence rate of frailty in cancer patients categorized by province, age and tumor type. The patients were mainly from Fujian province (total 1499, frailty incidence rate of 52.4%), Jilin province (total 1249, frailty incidence rate of 56.0%) and Chongqing city (total 105, frailty incidence rate of 48.6%), without significant difference of frailty among them ($X^2 = 4.8$, $p = 0.09$, Fig. 1A-B). The frailty incidence rate in different cancers was varied (Fig. 1C), including lung cancer of 55.9%, gastric cancer of 64.7%, liver cancer of 45.6%, breast cancer of 45.6%, esophageal cancer of 47.2%, cervical cancer of

64.4%, nasopharyngeal cancer of 37.3% and colonic cancer of 57.6% ($X2 = 86.3$, $p < 0.001$ among these groups). The frailty incidence was also differed by ages (Fig. 1D), including the teenager of 57.1%, the youth of 45.4%, the middle-age of 55.8% and the old-age of 59.0%. The chi-square test revealed significant differences of frailty incidence between youth and middle-age group ($X2 = 18.4$, $p < 0.001$) and between youth and old-age group ($X2 = 15.6$, $p < 0.001$).

Comparison between patients in death and survival group

The all-cause mortality of patients in this study was 20.6%. The subjects in death group were significantly older and frailer than those in survival group (58.3 ± 11.5 vs 55.0 ± 11.7, $p < 0.001$; 0.28 ± 0.14 vs 0.21 ± 0.12, $p < 0.001$). The death group had a higher proportion of frailty compared with that of the survival group (68.4% vs. 49.7%, $p < 0.001$). Patients from survival group had significantly higher TG, SUA, BMI and HDL-C levels than these from death group (23.3 ± 4.9 vs. 22.4 ± 3.57, $p < 0.001$; 1.3 ± 0.5 vs. 1.2 ± 0.6, $p < 0.001$). Table 2 showed the attributes of subjects according to the status of survival.

Table 2
Characteristics of cancer patients in survival and death group

	Status of survival		P value
	Survival (n = 1918)	Death (n = 611)	
Age (years)	55.0 ± 11.7	58.3 ± 11.5	< 0.001**
Male (%)	53.0	64.6	< 0.001**
BMI (kg/m2)	23.3 ± 4.9	22.4 ± 3.5	< 0.001**
Weight (kg)	62.1 ± 14.6	61.2 ± 11.2	0.147
Height (cm)	163.2 ± 7.8	165.2 ± 7.8	< 0.001**
TG (mmol/l)	1.6 ± 1.1	1.4 ± 0.9	0.007*
TC (mmol/l)	4.8 ± 1.4	4.7 ± 1.6	0.095
HDL-C(mmol/l)	1.3 ± 0.5	1.2 ± 0.6	< 0.001**
LDL-C (mmol/l)	3.0 ± 0.9	2.9 ± 0.9	0.123
SUA (μmol/l)	311.5 ± 81.7	301.3 ± 91.9	0.014*
Hypertension (%)	17.4	18.7	0.483
Diabetes (%)	8.0	9.3	0.312
Cardiovascular disease (%)	3.2	4.4	0.416
Anemia (%)	1.3	2.1	0.145
Chronic hepatitis (%)	5.5	5.7	0.85
Frailty (%)	49.7	68.4	< 0.001**

Prediction capacity of FI-LAB on 5 year mortality of cancer patients

The outcomes from the adjusted and unadjusted Cox regression models of frailty and mortality were presented in Table 3. Subjects with frailty had a highly significant increased risk of mortality compared with those without frailty (HR: 13.62, 95% CI: 7.77–23.87, P < 0.001). The model for Cox proportional hazard regression was quite stable (HR: 12.67, 95% CI: 7.19–22.31) after compensating for age, gender, BMI, hypertension, cardiovascular disease, anemia, diabetes, and chronic hepatitis. The cumulative death hazard and survival of the study population based on FI-LAB at baseline was presented in Fig. 2A, where the median survival time of patients with frailty was significantly shorter than patients without frailty (1010 days vs 1138 days, X^2 of Log Rank test = 33.2, p < 0.001; X^2 of Breslow test = 32.9, p < 0.001 and X^2 of Tarone-Ware = 36.4, p < 0.001). Although statistical analysis showed that most variables (neutrophilic

leukocytes, platelets, red blood cells, MCV, MCH, MCHC, blood glucose, TBil, DBil, ALT, Alb, Glob, CREA, URIC, CHOL, TG, HDL-C, and LDL-C) comprising FI-LAB did not increase the risk of five-year mortality, the levels of PLT, creatinine, ALT and LDL-C increased while hematocrit, hemoglobin, triglycerides, HDL-C and albumin decreased the risk of five-year mortality (Supplementary Table 1).

Table 3
Estimate of the accuracy of the FI-LAB on mortality, modeled with Cox regression

	No frailty	Frailty HR (95% CI)
Unadjusted model	1 (Reference)	13.62 (7.77,23.87)
Adjusted model 1a	1 (Reference)	12.20(6.95,21.45)
Adjusted model 2b	1 (Reference)	12.27 (6.97,21.55)
Adjusted model 3c	1 (Reference)	12.67(7.19,22.31)

aAdjusted for age, gender; bAdjusted for age, gender, BMI; cAdjusted for age, gender, BMI, hypertension, cardiovascular disease, anemia, diabetes, chronic hepatitis. Abbreviations: HR, hazard risk; CI, confidence interval.

Development of a novel mortality prediction algorithm based on FI-LAB

Based on FI-LAB and other factors independently associated with mortality, we developed a algorithm for predicting mortality in cancer patients (shown in Table 4). The algorithm MCP (the mortality of cancer patients) = 3.678*FI-LAB + 1.575*sex + 1.779*First TNM Staging. Patients were randomly divided into a training set (n = 966) and a validation set (n = 1963). A receiver operating characteristic (ROC) curve and a calibration plot were applied to assess the predictive value of MCP. The training set had significantly less men but more cardiovascular disease, anemia and chronic hepatitis as well as higher BMI, weight, TG, but lower LDL-C and SUA (Supplementary Table 2). The MCP algorithm presented a good accuracy of mortality prediction, with an AUC of 0.691 (95% CI: 0.656–0.726) and 0.648 (95% CI: 0.613–0.684) in the training and validation sets respectively (Fig. 2B). In this algorithm, frailty index played the most important role in accordance with the hazard ratio of frailty (HR: 13.62, 95% CI: 7.77–23.87, P < 0.001).

Table 4
Univariate analysis of factors predicting mortality in cancer patients

Variables	COX Univariate Analysis	
	B	P
Sex	-0.536	< 0.001**
Age	0.020	< 0.001**
Liver cirrhosis	-0.427	0.115
Chronic hepatitis	-0.257	0.141
Shock	-3.002	0.797
COPD	-0.370	0.603
Myocardia infarction	0.179	0.758
Diabetes	0.025	0.857
Hypertension	0.064	0.539
Cardiovascular disease	0.165	0.401
Anemia	0.159	0.572
Hyperthyroidism	-1.682	0.093
Hypothyroidism	-0.976	0.330
Chronic pancreatitis	0.910	0.199
Osteoporosis	-0.395	0.495
Ulcerative colitis	-1.212	0.087
Crohn Disease	-3.002	0.771
Biliary disease	0.031	0.857
Chronic kidney disease	1.227	0.084
Tuberculosis	-3.001	0.832
Tumor family history	-0.415	0.002*
Surgery	-0.311	0.022
Chemotherapy	0.346	< 0.001**
Radiotherapy	-0.598	< 0.001**
Heat therapy	0.292	0.477

Variables	COX Univariate Analysis	
	B	P
Targeted therapy	0.254	0.197
Immunotherapy	-0.330	0.078
Endocrine therapy	-1.195	0.017
Complication therapy	0.645	0.001*
Frailty index	2.622	< 0.001**
Height	0.016	0.002*
Weight	-0.014	< 0.001**
BMI	1.000	0.035*
Trauma	-1.294	0.010*
Gt 65 years	0.308	0.001*
Disease score	0.250	0.003*
Disease staging	0.323	< 0.001**
Life quality score	0.028	< 0.001**
Outcome after 30d	1.372	< 0.001**
Total hospital stay	-0.003	0.462
ICU stay	-0.398	0.011*
First TNM Staging	0.558	< 0.001**

Discussion

In this study, we firstly investigated the frailty status of 2959 cancer patients and performed subgroup analysis based on different tumor types, ages and provinces, which, as far as we know, is the largest sample size in this specific population. Previous meta analysis on the prevalence and outcomes of frailty in older cancer patients from 20 studies only included 2916 participants(9). Secondly, we, for the first time, evaluated the prediction capacity of frailty index (FI-LAB) on mortality in cancer patients. Finally, based on FI-LAB and other independent laboratory parameters, we developed a novel algorithm of MCP to predict the five-year mortality of cancer patients, reaching good ROC scored of 0.691 and 0.648 in the training and validation sets respectively. To sum up, we illustrated that the existence of frailty assessed by FI-LAB was linked to an increased risk of mortality and our novel developed algorithm MCP had good prediction capacity on 5-year mortality of cancer patients, calling for more attention on the diagnosis and treatment of frailty in cancer patients.

We also found that men were more susceptible to frailty than women, according to both FI-LAB score and frailty incidence, differing from most previous studies showing higher frailty rate in women than in men with self-reported frailty physical phenotype data(20–22). This phenomenon may be due to the fact that we enrolled cancer patients of different age levels while previous studies mainly focused on older people in community. However, since one study employing laboratory parameters to constitute the frailty index also found higher FI-LAB score in men than women among older patients(23), the methods used for assessing frailty may also contribute to such difference. It is well acknowledged that laboratory variables are more objective than health-related deficits from self-reported data(24), including biologically interconnected symptoms and signs (unintentional weight loss, low handgrip strength, slow working speed, low physical activity level and self-reported exhaustion)(25). It implied that FI-LAB showed greater advantage in evaluating the influence of frailty on cancer patient's mortality than other frailty assessment methods.

The prediction capacity of FI-LAB on mortality was similar between our study and others that included participants from 35 to 89 years old(15, 16). One study found that the association between FI-LAB and mortality was not statistically significant amongst 20–39 years group(16), in contrast with our finding of the significant association between youth and middle-age group as well as youth and old-age group. Several studies reported that aging increased the risk of frailty(26–28), since the escalating incidence of frailty with old age was associated with the mounting physiological dysregulation with ageing in a non-linear manner. When frailty is present, stress responses are highly dysregulated and there is high vulnerability to adverse outcomes(25, 29, 30). Weight loss has been incorporated in many frailty measures. However, it, indeed, is postulated to be a modifiable factor in frailty(31–33). In our study, the frailty cohort had smaller BMI (22.8 ± 5.2 vs 23.2 ± 3.3, $p = 0.042$) and the death cohort also had smaller BMI (22.4 ± 3.5 vs 23.3 ± 4.9, $p < 0.001$). This result was in accordance with the fact that frailty is a gradual, progressive process of deterioration which including weight loss(2).

Intriguingly, we found that the majority of variables that composed the FI-LAB did not increase the five-year mortality risk, except for PLT (HR: 1.001, 95% CI: 1.00-1.002), creatinine (HR 1.009; 95% CI: 1.006–1.013), ALT (HR: 1.002, 95% CI: 1.000-1.005) and LDL-C (HR: 1.002, 95% CI: 1.000-1.005). Some variables even decreased the five-year mortality risk, including hematocrit (HR: 0.952, 95% CI: 0.940–0.965), hemoglobin (HR: 0.990, 95% CI: 0.987–0.994), triglycerides (HR: 0.863, 95% CI: 0.790–0.954), HDL-C (HR: 1.120, 95% CI: 1.024–1.224) and albumin(HR:0.938, 95% CI: 0.925–0.950). Nevertheless, patients with frailty had a highly significant increased risk of mortality compared with subjects without frailty (HR: 13.62, 95% CI: 7.77–23.87, $P < 0.001$). The model for Cox proportional hazard regression was quite stable after compensating for age, gender, BMI and other confounders. These results are in accordance with the theory of health-related deficits as reflected by FI-LAB(16, 34). In clinical practice, we should raise awareness of the accumulation of these abnormal laboratory variables.

Our study has several limitations. First, though we had the largest number of 2959 subjects, the distribution was quite uneven in geography and tumor types, putting difficulty in generalizing our finding to national level. Second, we only enrolled hospitalized cancer patients, which may cause survival bias.

Third, other potential confounders, including income, education, exercise and other chronic diseases were not adjusted for analysis. Fourth, this study did not provide data involving grip strength, speed of walking and other subjects in frailty phenotype. However, the frailty phenotype and index are comparable, particularly when the cut-off point of a frailty index is set at 0.20–0.25(19, 35). Moreover, recent studies revealed that both the frailty index and frailty phenotype can predict the three-year mortality risk(36). Finally, the predictive accuracy of the novel MCP algorithm was not satisfactorily high, as an AUC of 0.691 (95% CI: 0.656–0.726) and 0.648 (95% CI: 0.613–0.684) in the training and validation set.

Despite of the above mentioned limitations, the novel MCP algorithm still had its unique and practical function. It could predict the five-year mortality of cancer patients and raised patients' awareness of frailty. Insight into risk factors could guide preventive strategies, in particular when these risk factors are potentially modifiable by specific interventions. For example, physical inactivity is recognized as one of the major contributing factors to frailty onset and progression, while physical exercise is known to preserve or improve frailty(37). In addition, many interventions for the clinical management of frailty are available, including changing lifestyle, physical activity, increasing nutritional intake, and deprescription of unnecessary medications(4, 37). However, more evidence based knowledge regarding the effective intervention strategy, the feasibility and cost- effectiveness of frailty is needed. Besides, since individuals with frailty are able to dynamically transit, it is important to have strategies for the delivery of care ranging across the continuum of frailty. The clinical care of cancer patients with frailty should also focus on maintaining functional independence and other personalcentered outcomes. The opportunities, challenges, and future directions we discussed give the hope that the next generation of frailty management would improve the health outcomes of cancer patients and promote the quality of care.

Conclusion

In conclusion, we have successfully developed a novel MCP algorithm based on simple routine examinations that was able to predict the five-year mortality of cancer patients. We also proved that frailty was linked to an increased risk of mortality than those of the non-frailty group. Further studies using external multi-institutional data sets are needed to confirm current model and prospective cohort studies are needed to confirm the association between frailty and mortality.

Abbreviations

COPD, chronic obstructive pulmonary disease; MCV, mean values of corpuscular volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentrations; TBil, total bilirubin; DBil, direct bilirubin; ALT, alanine transaminase; Alb, albumin; Glob, globulin; CREA, creatinine; URIC, uric acid; CHOL, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; Chol, cholesterol; TG, triglycerides; SD, standard deviation; MCP, the mortality of cancer patients; BMI, body mass index; SUA, serum uric acid; TC, total cholesterol; HR, hazard risk; CI, confidence interval; HGB, hemoglobin; HCT, hematocrit; BUN, blood urea nitrogen

Declarations

Acknowledgements

We thank all the patients and healthy providers participating in the largest prospective observational study on nutrition status and cancer outcomes initiated by Chinese Society of Nutritional Oncology (CSNO)-the Investigation on Nutrition Status and Its Clinical Outcome of Common Cancers (INSCOC).

Authors' contributions

XinJindeveloped the idea and designed this project. Yue Renand Li Shao assisted with data analysis and prepared the manuscript;Jianguo Gao and MiaomiaoLu edited the manuscript. Theother authors helped to collect data and prepared the manuscript.Chunhua Song*, Hongxia Xu* and Hanping Shi*supervised the whole process of this project.

Funding

The National Key Research and Development Program : The key technology of palliative care and nursing for cancer patients（2017YFC1309200）

Availability of data and materials

SupplementalTable (1–2) and associated figure legends are provided as supplemental material and are available online with the paper.

Ethics approval

This observational, multi-center and hospital based prospective cohort study was registered with the Chinese Clinical Trial Registry (ChiCTR1800020329) and approved by local ethical committees of all the participant hospitals, with formal written consent from every patient. This study was carried out in accordance with the declaration of Helsikin.

Consent for publication

All authors have given their consent for the publication of thisarticle.

Competing interests

None of the authors have any competing interests.

Author details

1, Department of Gastroenterology, The First Affiliated Hospital, School of Medicine, Zhejiang University

2, Institute of Translational Medicine, The Affiliated Hospital of Hangzhou Normal University

3, Department of Medical Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital

4, Cancer Center of the First Hospital of Jilin University

5, Department of Clinical Nutrition, Chongqing General Hospital

6, Department of Nutrition, Third Affiliated Hospital of Kunming Medical College, Tumor Hospital of Yunnan Province

7, Comprehensive Oncology Department, Cancer Hospital, Chinese Academy of Medical Sciences

8, Department of Oncology, Affiliated Hospital of Zunyi Medical University

9, Cancer center, The First People's Hospital of Foshan

10, Department of Clinical Nutrition, The Fourth Affiliated Hospital, Harbin Medical University

11, Department of Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

12, Department of Gastrointestinal Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer

13, Department of Epidemiology and Statistics, College of Public Health, Zhengzhou University

14, Department of Nutrition, Department of Nutrition, Daping Hospital &Research Institute of Surgery, Third Military Medical University

15, Department of Gastrointestinal Surgery/Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University/The 9th Clinical Medical College, Peking University

References

1. EO H, KE JA, P E. K, G O, LP F. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75.
2. CG E, MA B, AB J, SK M, K O VAM. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. Cancer J Clin. 2017;67(5):362–77.
3. M M-R, G B. Conceptualizations of frailty in relation to older adults. Journal of advanced nursing. 2003;44(1):58–68.
4. FC ED, R R-O MHBJW. JD W. Management of frailty: opportunities, challenges, and future directions. Lancet. 2019;394(10206):1376–86.
5. S I GK. S J, K W. Association between frailty and quality of life among community-dwelling older people: a systematic review and meta-analysis. J Epidemiol Commun Health. 2016;70(7):716–21.

6. RL S, Cancer statistics KDMAJ. 2020. CA: a cancer journal for clinicians. 2020;70(1):7–30.
7. RL S, Cancer statistics KDMAJ. 2016. CA: a cancer journal for clinicians. 2016;66(1):7–30.
8. W C, R Z, PD B, S Z, H Z, F B, et al. Cancer statistics in China, 2015. CA: a cancer journal for clinicians. 2016;66(2):115–32.
9. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol. 2015;26(6):1091–101.
10. E D, P K, EO H. Frailty measurement in research and clinical practice: A review. European journal of internal medicine. 2016;31:3–10.
11. Ferrat E, Paillaud E, Caillet P, Laurent M, Tournigand C, Lagrange JL, et al. Performance of Four Frailty Classifications in Older Patients With Cancer: Prospective Elderly Cancer Patients Cohort Study. J Clin Oncol. 2017;35(7):766–77.
12. Hurria A, Dale W, Mooney M, Rowland JH, Ballman KV, Cohen HJ, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol. 2014;32(24):2587-94.
13. SD S, EA AM, TM G. G, K R. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
14. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. Lancet. 2018;391(10132):1775–82.
15. SE H, MR R. A M, K R. Standard laboratory tests to identify older adults at increased risk of death. BMC Med. 2014;12:171.
16. JM B, O T. SE H, K R. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. GeroScience. 2017;39(4):447–55.
17. K R MM. A M, SE H. A Frailty Index Based on Common Laboratory Tests in Comparison With a Clinical Frailty Index for Older Adults in Long-Term Care Facilities. J Am Med Dir Assoc. 2015;16(10):842–7.
18. Q H. X S, M Y, B D, B D, Y W. Prediction of mortality in Chinese very old people through the frailty index based on routine laboratory data. Scientific reports. 2019;9(1):221.
19. M MH. R, C S, J B. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. Health reports. 2013;24(9):10–7.
20. EA S, KA H, TT F, FB H, F R-A, E L-G. Diet quality and risk of frailty among older women in the Nurses' Health Study. The American journal of clinical nutrition. 2020.
21. K B-R CLS, RR JHBB. K, R V, et al. Frailty in Older Adults: A Nationally Representative Profile in the United States. The journals of gerontology. Series A, Biological sciences and medical sciences. 2015;70(11):1427–34.
22. B S-E PC. J S, J J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. The journals of gerontology. Series A, Biological sciences and medical sciences. 2009;64(6):675–81.

23. JI MRJJ. R, CC S, KG G. Operationalizing a frailty index using routine blood and urine tests. Clin Interv Aging. 2017;12:1029–40.
24. O T, MD OC, BL K-K, AM OH. K R, RA K. Measuring frailty using self-report and test-based health measures. Age Ageing. 2015;44(3):471–7.
25. CL RV, K B-R SQLX. LP F. Stimulus-response paradigm for characterizing the loss of resilience in homeostatic regulation associated with frailty. Mech Ageing Dev. 2008;129(11):666–70.
26. Williams GR, Deal AM, Sanoff HK, Nyrop KA, Guerard EJ, Pergolotti M, et al. Frailty and health-related quality of life in older women with breast cancer. Support Care Cancer. 2019;27(7):2693–8.
27. Wang Y, Zhang R, Shen Y, Su L, Dong B, Hao Q. Prediction of chemotherapy adverse reactions and mortality in older patients with primary lung cancer through frailty index based on routine laboratory data. Clin Interv Aging. 2019;14:1187–97.
28. Overcash J, Cope DG, Van Cleave JH. Frailty in Older Adults: Assessment, Support, and Treatment Implications in Patients With Cancer. Clin J Oncol Nurs. 2018;22(6):8–18.
29. LP F, QL X. AR C, L F, P C, R V, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. The journals of gerontology. Series A, Biological sciences and medical sciences. 2009;64(10):1049–57.
30. AR C, QL X. LP F. Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging studies. The journals of gerontology. Series A, Biological sciences and medical sciences. 2009;64(2):243–8.
31. PJ EL S, E G, S R, S V, A J, et al. Frailty and diabetes status in older patients with cancer: impact on mortality in the ANCRAGE cohort. Aging clinical and experimental research. 2020.
32. Crow RS, Lohman MC, Titus AJ, Bruce ML, Mackenzie TA, Bartels SJ, et al. Mortality Risk Along the Frailty Spectrum: Data from the National Health and Nutrition Examination Survey 1999 to 2004. J Am Geriatr Soc. 2018;66(3):496–502.
33. Anderson JE, Seib CD, Campbell MJ. Association of Patient Frailty With Increased Risk of Complications After Adrenalectomy. JAMA Surg. 2018;153(10):966–7.
34. K R. Conceptual Models of Frailty: Accumulation of Deficits. The Canadian journal of cardiology. 2016;32(9):1046–50.
35. TK M, DK M. JE M. A comparison of four frailty models. J Am Geriatr Soc. 2014;62(4):721–6.
36. TA SK. G, R L, EL M, RGJ W. Discrimination ability of comorbidity, frailty, and subjective health to predict mortality in community-dwelling older people: Population based prospective cohort study. European journal of internal medicine. 2017;42:29–38.
37. JS M, DP F. D J, J N, N P, H D. Physical activity in older age: perspectives for healthy ageing and frailty. Biogerontology. 2016;17(3):567–80.

Figures

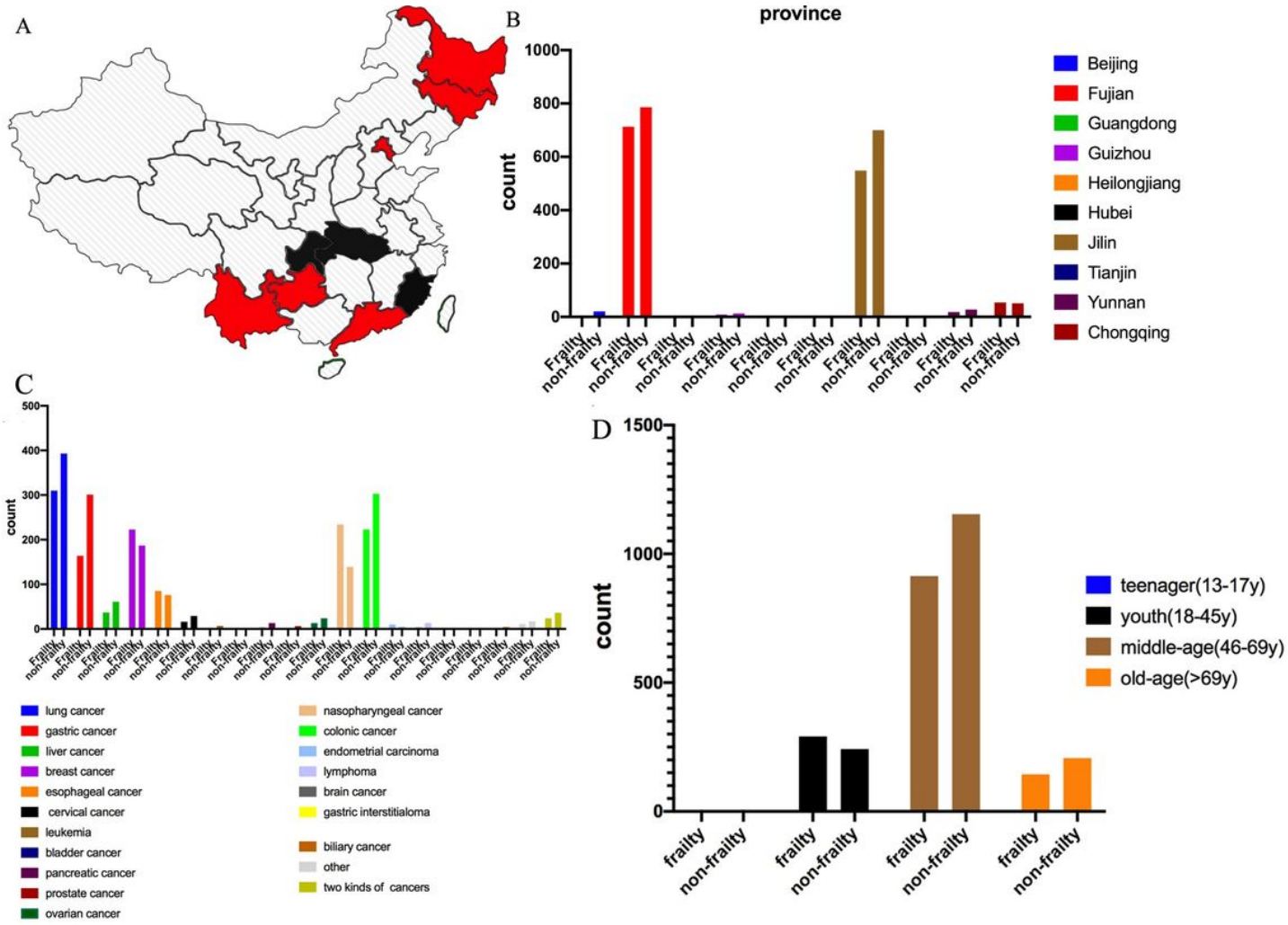

Figure 1

Cancer patients distribution in China (A) and the the number of patients with/without frailty in different provinces (B), cancers (C) and ages (D). In the Chinese map,the red color indicating incidence rate ≥50%， the black color indicating incidence rate ≤50% and the gray color indicating data not available.Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

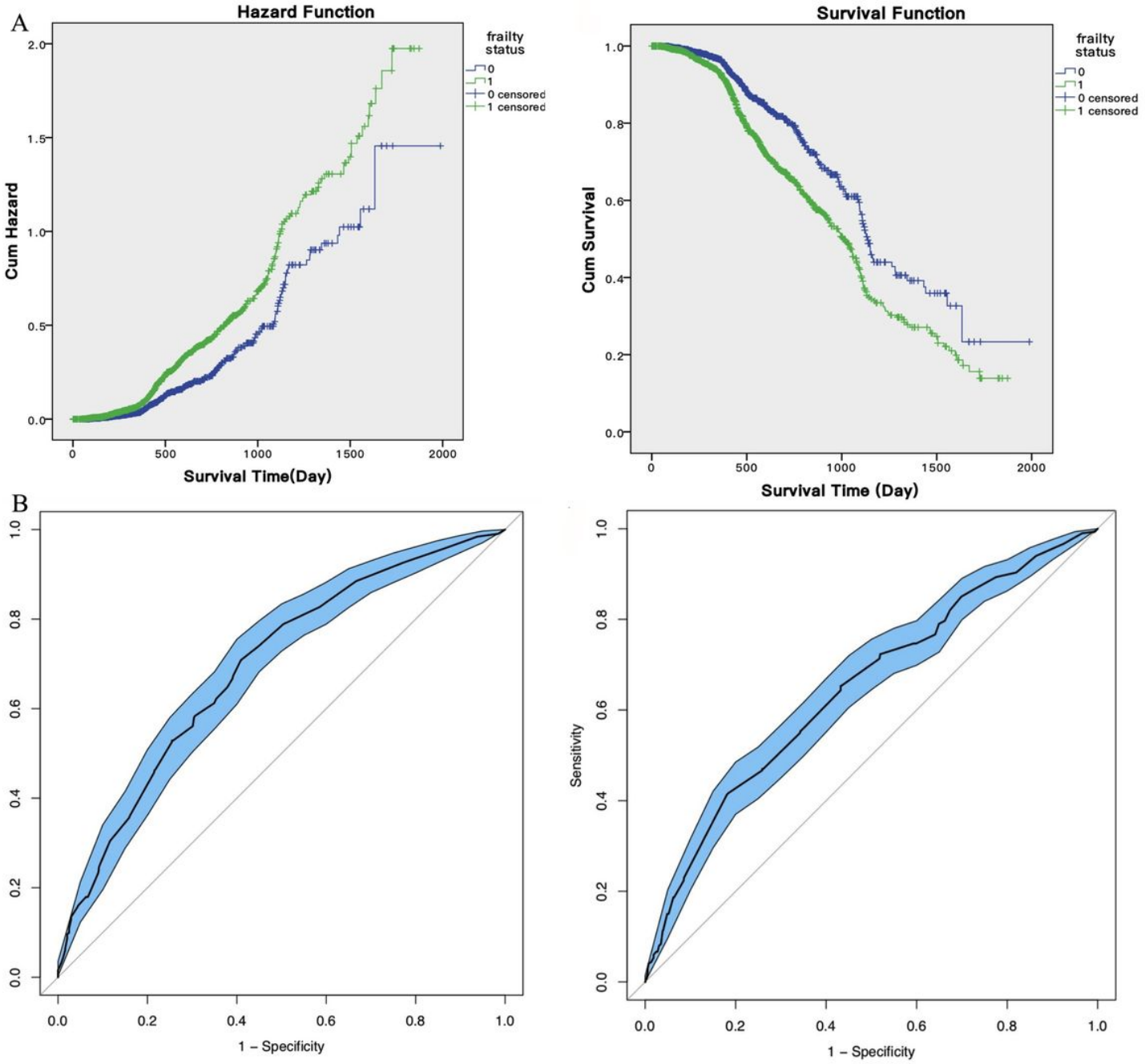

Figure 2

Effect of FI-LAB and MCP in mortality prediction of patients with various cancers. (A), Cumulative hazard of death (left panel) and survival (right panel) in the study population, according to frailty at baseline. (B), The ROC curve of training (left panel) and validation (right panel) set indicated good predictive accuracy of MCP on mortality of patients with various cancers. 0 indicated no frailty; 1 indicated frailty.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarytable.docx
- supplementarytable.docx