Predictive value of preoperative fried frailty phenotype assessment and serum biomarkers on the prognosis of elderly patients with femoral neck fracture under general anesthesia within 3 months after surgery

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Abstract

Background/aim: Femoral neck fracture (FNF) seriously harms the health of the

elderly and affects the long-term quality of life of the patients. The aim of this study was to determine whether preoperative FFP combined with serum FGFR3 and RUNX2 could better predict the prognosis of elderly patients with FNF at 3 months after surgery.

Materials and Methods: A total of 150 elderly patients with FNF (60-89 years old) were enrolled and divided into a non-frailty cohort and a frailty cohort based on preoperative Fried Frailty Phenotype (FFP) evaluation. The hip recovery of patients 3 months after surgery was evaluated using Harris hip score (HHS). Serum FGFR3 and RUNX2 levels were analyzed, and the relationship between HHS and serum FGFR3 and RUNX2 levels was evaluated. The specificity and sensitivity of FFP, serum FGFR3 and RUNX2 were evaluated by ROC curve before surgery. Potential prognostic factors were analyzed by multivariate Logistics logistic regression.

Results: Serum FGFR3 and RUNX2 levels were lower and hip recovery was poorer in the frailty cohort than in the non-frailty cohort ($p < 0.001$). Within 3 months after surgery, there were 12 deaths (17.6%) in the frailty cohort and 1 in the non-frailty cohort (1.2%) ($p < 0.001$). FFP assessment combined with serum FGFR3 and RUNX2 levels had a higher diagnostic significance. Readmission and preoperative frailty phenotype were independent factors affecting the prognosis of patients with FNF. HHS (> 70 scores) and higher levels of serum FGFR3 and RUNX2 cutoff values (7.85 ng/mL and 56.5 ng/mL) were protective factors for prognosis.

Conclusion: FFP assessment combined with serum FGFR3 and RUNX2 levels may help to evaluate the prognosis of elderly patients with FNF at 3 months after surgery.

Keywords: Fried frailty phenotype; femoral neck fracture; FGFR3; RUNX2; prognostic value

1. Introduction

Femoral neck fracture (FNF) poses a serious threat to the health of the elderly due to its high morbidity and mortality and causes a huge economic burden [1]. Elderly hip fractures are mainly related to osteoporosis, among which FNF is the most common [2]. As the global population continues to age, more than 1 million hip fractures are reported each year worldwide, with this number particularly high in developing countries. It has been reported that by 2050, there will be more than 4 million hip fractures worldwide, of which 1.5 million will occur in China [3], while another review reported that the mortality rate within one year of hip fractures in older adults may be between 14% and 58% [4]. At present, the common clinical methods for senile FNF are internal fixation, artificial femoral head replacement, hip replacement, etc [5, 6]. General anesthesia is usually operated in patients with FNF, but during the induction of general anesthesia, a variety of drugs are required, which will affect the respiratory and circulatory functions of patients, cause significant fluctuations in heart rate and blood pressure, increase cardiac load and work, and easily lead to cardiovascular adverse events such as tachycardia and hypotension [7, 8]. In addition, elderly patients are prone to hemodynamic fluctuations during surgery and anesthesia stimulation, affecting patient prognosis [9]. Therefore, preoperative prognostic evaluation is often carried out in

elderly patients to better guide clinical treatment, predict postoperative complications, and improve prognosis. Frailty is a state in which the human body is vulnerable to damage after experiencing stressful events due to the decline in the functional reserves of multiple systems [10]. Frailty assessment was first used to evaluate the physiological state and survival status of elderly people in communities, and frailty is an independent predictor of postoperative complications, prolonged hospital stay, death, and other adverse prognosis [11]. Fried Frailty Phenotype (FFP) is a classic method for frailty assessment. It is simple to operate and widely used in clinical and research studies. The scale takes frailty as a precursor state of clinical events and can independently predict adverse events so that preventive measures can be taken [12]. However, no studies have reported the predictive value of FFP in the 3-month prognosis of elderly patients with FNF under general anesthesia.

Fibroblast growth factor receptor 3 (FGFR3) is one of the four typical high-affinity receptors for FGF ligands [13]. FGFR3 in periosteal cells drives the transformation of cartilage into bone in bone repair [14]. Recombinant FGFR3 therapy restores the effective maturation of growth plate chondrocytes in bone and promotes bone growth in a dose-dependent manner [15].

Run-Related transcription factor 2 (RUNX2) is considered significant in the maturation of chondrocytes and can promote the transcription of various mineralization-related protein genes in osteocytes [16]. The homeostasis of bone tissue requires strict regulation of multiple signaling pathways, and Runx2-dependent bone

development or bone formation involves a complex regulatory cascade. It is reported that RUNX2 can improve the maintenance of the osteoblastic phenotype of mesenchymal stem cells and promote bone repair of femoral head necrosis [17].

The elderly have poor tolerance to anesthesia and surgery, and preoperative evaluation can effectively predict the prognosis and provide a basis for clinical treatment. Although poor prognosis in patients with FNF has been well documented, prognostic factors have not been thoroughly examined. Identifying which factors are associated with prognosis may help surgeons make treatment decisions and ultimately enhance care for patients with FNF. The objective of this study was to determine whether preoperative FFP combined with serum FGFR3 and RUNX2 could better predict the prognosis of elderly patients with FNF at 3 months after surgery.

2. Materials and methods

2.1. Research objects

All participants, including FNF patients and healthy controls, received informed consent. Inclusion criteria: ① FNF diagnosed by clinical and hip X-ray examination; ② ≥ 60 years old; ③ walk normally before fracture; ④ no cognitive dysfunction; ⑤ Surgery under general anesthesia.

Exclusion criteria: ① malignant tumors; ② Pathological hip fracture; ③ unwillingness to receive surgical treatment; ④ old hip fracture; (5) ipsilateral hip fracture history or surgical history; ⑥ Incomplete clinical data.

This was a central study in Shenzhen Longhua District People's Hospital, and data were collected prospectively. From December 2018 to December 2022, 150 patients with FNF were enrolled, with a mean age of 74 years (95% confidence interval [CI]: 63-85). The ASA score determines the patient's physical state before anesthesia and surgery. The patient ASA rating is assessed by the senior anesthesiologist responsible for the surgery, and the ASA score divides patients undergoing surgery into I (healthy patients), II (Patients with mild systemic disease), III (Patients with serious systemic disease who are not incapacitated), and IV (Patients with disabling systemic diseases). The duration of the procedure (in minutes), the estimated amount of surgical blood loss (in milliliters), and the length of the patient's hospital stay (in days) were recorded. The patients were followed up for 3 months after the surgery, and the incidence of all-cause readmission, total postoperative complications (postoperative infection, cardiovascular and cerebrovascular accidents, abnormal liver function, postoperative delirium, postoperative bleeding, lower extremity venous thrombosis, electrolyte disturbance, hypoproteinemia, etc.) and total mortality were recorded. Harris hip score (HHS) was performed on the hip function of the patients 3 months after surgery, including 4 items (pain, function, joint motion, and deformity), and was scored by two professional orthopedic surgeons. The mean value obtained was the hip performance score of the patients, and a score of less than 70 was classified as poor recovery. At the same time, 38 age - and gender-matched subjects were recruited as the control group.

2.2. Preoperative frailty assessment

Preoperative FFP assessment: (1) slow step: patients are instructed to walk 5 m at a normal speed; ② Decreased grip strength: the maximum grip strength of the patient's favorable hand was measured; (3) Low physical activity: Based on the International Physical Activity Questionnaire, the weekly metabolic equivalent did not reach 600 was considered to be low activity; Fatigue: the patients were asked about two items in the depression scale, "I feel it is difficult to do anything", "I can't get up to do things"; Low weight: unintentional weight loss of ≥ 5% in the past 1 year. Meeting three criteria is defined as frailty. This study stipulates that meeting any item of the above scale is recorded as level 1, two items are recorded as level 2, and the highest is level 5.

2.3. Blood sample collection

In control subjects, blood samples were collected during blood drawing for other specified medical reasons, such as anemia assessment or prior to elective surgery. Blood samples were taken from all subjects after fasting overnight and processed within 2 h. To obtain the serum, the blood was placed in an EDTA-free tube, and 10 mL sample was centrifuged at 1300 g at 4°C for 20 min. The serum was then equally divided into 0.5 mL tubes and stored at −80°C until analysis was performed.

2.4. Clinical features collection and laboratory testing

Clinical features and anthropometry during clinical visits or through review were recorded. Clinical information included gender, age, height, weight, and disease history.

Samples were tested by the Longhua District Maternity and Child Health Hospital’s central laboratory. Serum FGFR3 and RUNX2 were determined by ELISA

kits, purchased from RD Systems Inc. All samples were repeated in one assay to avoid Inter-assay variation. ELISA measured less than 3% intra-assay variation.

2.5. Data statistics

Data for subjects' clinical and anthropometric continuous variables were expressed as median (25^{th} and 75^{th} percentiles), while categorical variables were expressed as frequency (%). Enumeration data were measured by chi-square or Fisher exact test between groups. Measurement data were compared between two groups by Mann-Whitney U test, and between multiple groups by Kruskal-Wallis H test. The correlation between HHS and serum FGFR3 and RUNX2 levels was assessed by Spearman's correlation coefficient. Based on ROC curve, the predictive value of preoperative FFP assessment on patients' death, readmitted status, and hip recovery 3 months after surgery was determined. The area under the curve (AUC) was calculated, and the cutoff value was obtained by Youden. Univariate binary logistic regression was used to screen the prognostic factors. Multivariate logistic regression was used to analyze prognostic factors, including variables that showed statistical effects in univariate variables, to study the prognostic value of preoperative FFP assessment and serum FGFR3 and RUNX2 levels. A P-value below 0.05 was considered statistically significant. SPSS software 22.0 was employed for analysis, and GraphPad Prism 8.3.0 (GraphPad, San Diego, CA) for mapping.

3. Results

3.1. Baseline data and operative status of elderly patients with FNF

As shown in Table 1 summarizes the demographic data of a total of 150 elderly patients with FNF, most of whom were 110 women (73.3%) and 40 men (26.7%), with a median age of 67 years and a median body mass index (BMI) of 21.8 kg/m^2. Most patients had a Grade II or III ASA classification at baseline (78.0%). According to the preoperative FFP assessment method, we divided the patients into two categories: 82 cases (54.7%) of non-frailty and 68 cases (45.3%) of frailty.

We observed a significant difference in ASA classification between the two cohorts ($p = 0.005$), with 23 (33.8%) and 11 (16.2%) patients in grade III and IV, respectively. In addition, patient age, gender, BMI, and disease history did not differ between the two groups. As shown in Table 2, we did not find a difference in the duration of surgery and the amount of intraoperative blood loss between the non-frailty and frailty groups, and frailty patients had a longer hospital stay than the non-frailty group ($p = 0.013$), with a median of 17 days. In the total patient cohort, the 3-month readmission rate and complication rate were 24% and 28%, respectively, and the frailty cohort had a higher readmission rate and complication rate than the non-frailty cohort ($p < 0.001$, $p = 0.005$). Three months after surgery, the hip recovery of patients was assessed by HHS, and it was found that the majority of patients who were evaluated as frailty phenotype before surgery had poor recovery (58.8%) ($p < 0.001$). Notably, there were 12 deaths in the frailty cohort (17.6%) and only 1 in the non-frailty cohort (1.2%) within 3 months after surgery ($p < 0.001$). These results suggest that preoperative FFP assessment to

determine whether patients have frailty phenotype may have a certain guiding effect on postoperative readmission, complication rate, hip recovery, and 3-month risk of death.

3.2. Preoperative FFP assessment combined with serum FGFR3 and RUNX2 levels can effectively predict the prognosis of elderly patients with FNF 3 months after surgery

First, we compared serum FGFR3 and RUNX2 levels and found that serum FGFR3 and RUNX2 levels were higher in patients with FNF than in controls (As shown in Figure 1A, $p < 0.001$). There were significant differences in FGFR3 and RUNX2 levels between control, non-frailty, and frailty groups (As shown in Figure 1B; As shown in Table 3, $p < 0.001$, $p = 0.002$). Next, we analyzed HHS in the frailty versus non-frailty patient cohorts, with higher HHS 3 months after surgery in the non-frailty patients (As shown in Figure 2A, $p < 0.001$). In addition, Spearman's correlation analysis showed that HHS was positively correlated with serum FGFR3 and RUNX2 levels (As shown in Figure 2B and 2C, $r^2 = 0.5345$, $p < 0.001$; $r^2 = 0.5029$, $p < 0.001$). ROC curve and AUC (As shown in Figure 3) showed that preoperative FFP assessment, serum FGFR3 and RUNX2 levels had high diagnostic values for death (Figure 3A), readmission (Figure 3B), and hip recovery (Figure 3C) of patients. Among them, the AUC value of FFP combined with serum FGFR3 and RUNX2 levels was higher than that of FFP assessment or serum FGFR3 and RUNX2 levels. It suggested that FFP assessment combined with serum FGFR3 and RUNX2 levels had better diagnostic significance.

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The cutoff value of serum FGFR3 and RUNX2 obtained by Youden were calculated based on the patient ROC curve for stratification. To determine prognostic factors in elderly patients with FNF, multivariate binary Logistic regression analysis was performed (As shown in Figure 4), and variables showing significance in univariate analysis were used as covariates. Patient baseline characteristics, including age, gender, and BMI, were used as adjusting factors for regression analysis (Figure 4A). Readmission within 3 months after surgery and preoperative assessment of FFP were independent factors affecting the prognosis of patients. We did not observe postoperative complications as an independent prognostic factor. HHS (> 70 scores) and higher levels of serum FGFR3 and RUNX2 cutoff values (7.85 ng/mL and 56.5 ng/mL) were protective factors for prognosis (Figure 4B).

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4. Discussion

We investigated potential prognostic factors 3 months after surgery in elderly patients with FNF. The vast majority of patients who died 3 months after surgery had a Frailty Phenotype. The frailty phenotype assessed before surgery and the readmission rate within 3 months after surgery were independent factors affecting the prognosis of patients with FNF. HHS (more than 70 scores) and higher levels of serum FGFR3 and RUNX2 cutoff values (7.85 ng/mL and 56.5 ng/mL) were protective factors for prognosis. The incidence of postoperative complications is not an independent factor affecting prognosis.

In this analysis, elderly patients with FNF were selected as the investigation objects. Due to the global aging trend and the fact that FNF is a common fracture in the elderly population, it is of high socio-economic importance [18]. More studies have looked at the association between FNF and other diseases and the risk of death in older adults. For example, in patients with end-stage renal disease requiring dialysis, comorbidities and postoperative complications are factors contributing to the risk of readmission and death [19]. Patients with FNF combined with cancer or cardiovascular disease have an increased risk of death within 3 years [20]. In our study, however, we did not find differences in comorbidities (including hypertension, diabetes, cardiovascular and cerebrovascular disease, lung disease, and kidney disease) between the frailty and non-frailty FNF cohorts. ASA score, which is used to assess the overall physical fitness or disease of patients before surgery, is regarded as a scale to predict risk [21]. ASA score is associated with longer hospital stays and 30-day mortality in elderly patients with FNF [22]. Our results also showed that the frailty in preoperative FFP assessment was associated with a high ASA score. However, we did not observe an association between ASA scores and outcomes at 3 months after surgery in patients with FNF. In a study, Hirohisa et al. employed the FFP as a means to assess the relationship between frailty and postoperative complications in individuals with curative colorectal inflammation. The findings revealed a significant association between patients diagnosed with frailty and advanced age, severe postoperative complications, as well as an extended duration of hospitalization [23]. Similarly, our research results also show

that postoperative hospital stay, readmissions rate, total complication rate, and mortality were correlated with preoperative FFP. In addition, FFP can also distinguish well between death, readmission, and hip recovery in patients with FNF 3 months after surgery.

FGFR3 and RUNX2 have been investigated to promote the bone repair process [13, 24, 25]. Our study was the first to combine FFP with serum FGFR3 and RUNX2 to evaluate the prognosis of patients with FNF 3 months after surgery. The organs or tissues of the human body, including bones, initiate certain self-repair after injury, which is a natural process common to all living organisms [26]. As expected, serum FGFR3 and RUNX2 levels were higher in patients with FNF, and bone repair processes were present in vivo. Serum FGFR3 and RUNX2 levels were lower in the frailty cohort than in the non-frailty cohort. Although no significant difference in data was shown, the frailty cohort may be affected by age, body mass index, or other unknown diseases on a physiological basis that reduces the initiation of repair processes. HHS is a disease-specific health status scale often used to measure the outcome of total hip replacement [27]. Furthermore, the research conducted by Jasvinder et al. indicates that a diminished postoperative HHS score can serve as a predictive factor for the likelihood of revision following total hip replacement, thus signifying an unfavorable prognosis for patients [28]. Our study found that HHS was higher in the non-frailty cohort and that HHS in patients with FNF had a significant positive association with serum FGFR3 and RUNX2 levels. Furthermore, serum FGFR3 and RUNX2 levels were good

differentiators of death, readmission, and hip recovery 3 months after surgery in patients with FNF. Moreover, FFP combined with serum FGFR3 and RUNX2 levels had higher diagnostic significance. There is a prevailing belief that early intervention in the advancement of weakness yields greater success in impeding or reversing its progression, thereby significantly impacting the prognosis of the disease. In our study, Multivariate Logistic regression confirmed that readmission within 3 months after surgery and frailty phenotype were independent factors affecting the prognosis of patients with poor hip joints. HHS (> 70 scores) and higher levels of serum FGFR3 and RUNX2 cutoff values (7.85 ng/mL and 56.5 ng/mL) were protective factors for prognosis. In addition, postoperative complications were not an independent factor affecting prognosis.

5. Limitation

A limitation of our study is the relatively small cohort size, which may affect the validity of the statistical analysis. In addition, it is necessary to confirm the relationship between FFP assessment and serum FGFR3 and RUNX2 in other cohorts. In addition, more reasonable grouping should be further combined with other Frailty assessment methods, such as Frailty Index. Second, follow-up time is limited and longer studies are needed to confirm our findings.

6. Conclusion

Preoperative FFP assessment has a good predictive ability for postoperative adverse outcomes. FFP assessment and serum FGFR3 and RUNX2 levels were associated with prognosis in elderly patients with FNF. FFP combined with serum FGFR3 and RUNX2 to predict the prognosis of elderly patients with FNF could help clinicians identify patients with poor prognosis at an early stage and recommend better preoperative or postoperative care to minimize mortality and readmission.

Author's Contribution

Fu XU conceived and designed the study. Xin KUANG and BaoFeng CAO performed the research. Yang YUE provided help and edited the manuscript. Xin KUANG and BaoFeng CAO analyzed the data. Fu XU wrote the manuscript. Yang YUE reviewed and edited the manuscript. All authors contributed to editorial changes in the manuscript.

All authors read and approved the final manuscript.

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Competing interests

The authors have no conflicts of interest to declare.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Shenzhen Longhua District People's Hospital and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

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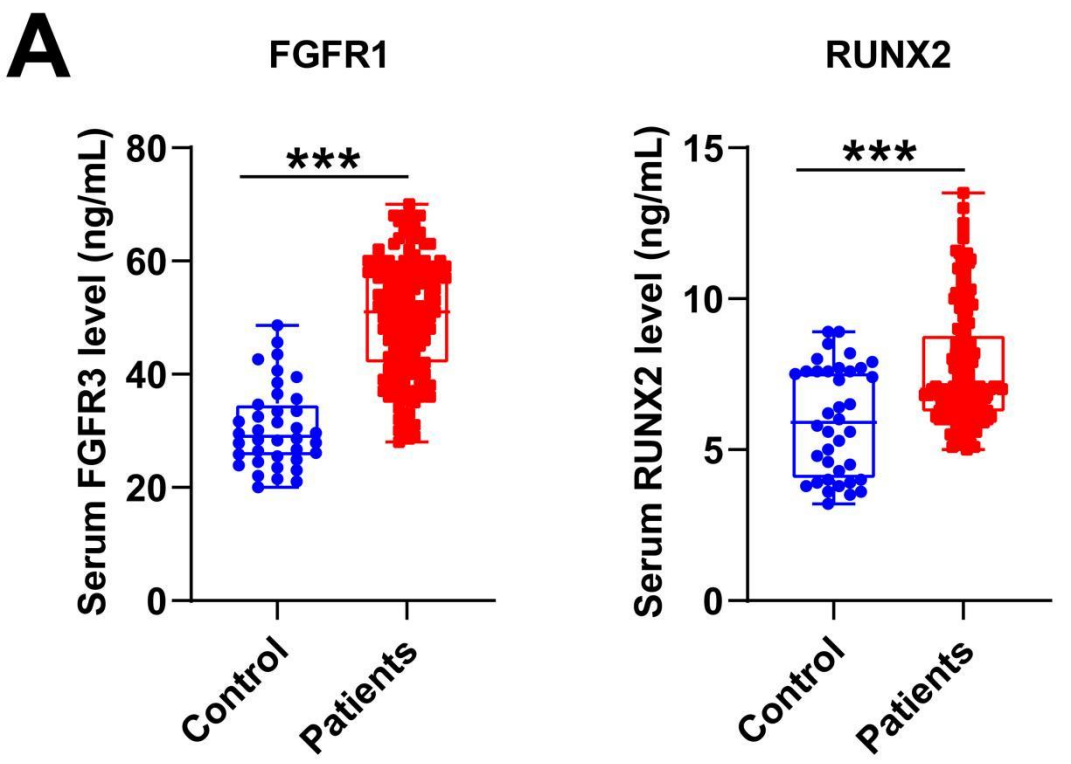
1 **Figures and Tables**



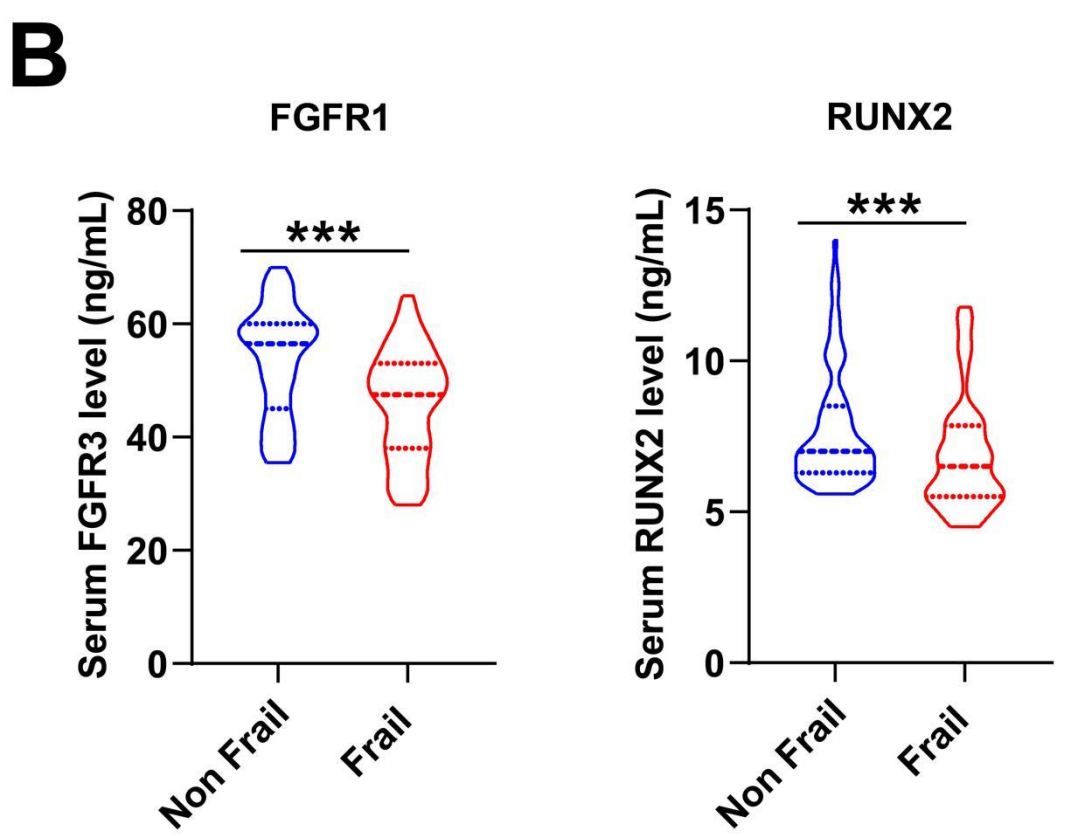


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Figure 1. (A) Comparison of healthy controls with elderly patients with FNF. (B) Comparison of non-frailty and frailty elderly patients with FNF. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

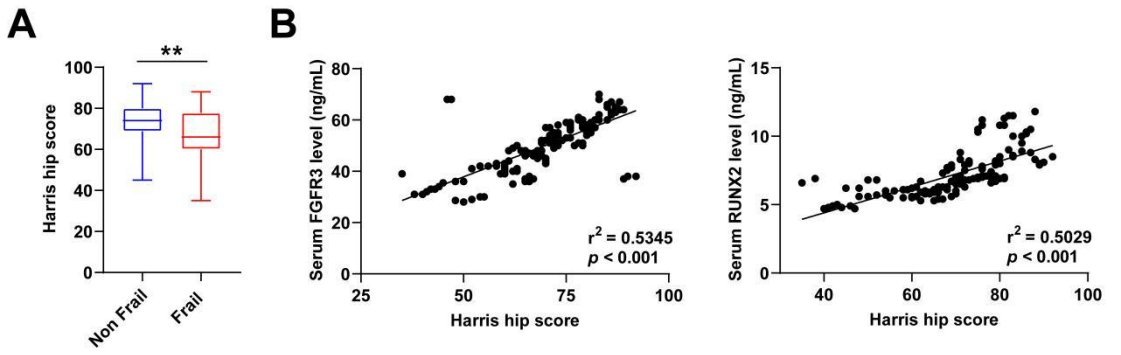

Figure 2. (A) HHS in patients with and without frailty. Spearman test was used to determine the correlation between HHS and serum (B) FGFR3 and (C) RUNX2 levels. Preoperative frailty and non-frailty HHS were evaluated by the Mann-Whitney U test. $p < 0.05$.

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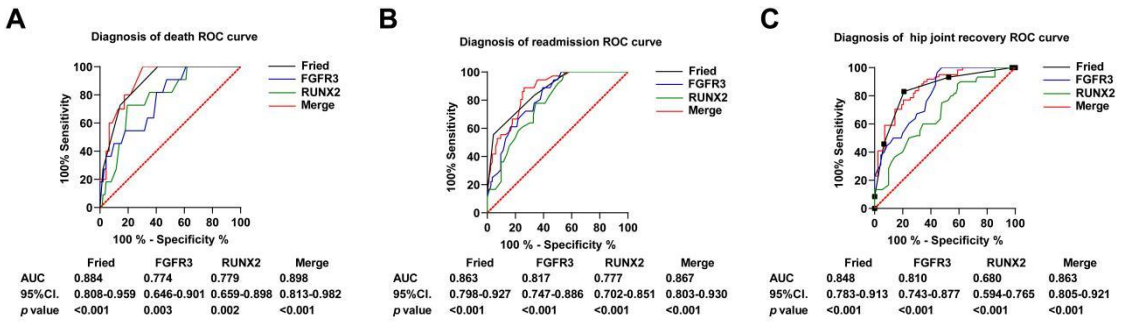

	Fried	FGFR3	RUNX2	Merge
AUC	0.884	0.774	0.779	0.898
95%CI.	0.808-0.959	0.646-0.901	0.659-0.898	0.813-0.982
p value	<0.001	0.003	0.002	<0.001

	Fried	FGFR3	RUNX2	Merge
AUC	0.863	0.817	0.777	0.867
95%CI.	0.798-0.927	0.747-0.886	0.702-0.851	0.803-0.930
p value	<0.001	<0.001	<0.001	<0.001

	Fried	FGFR3	RUNX2	Merge
AUC	0.848	0.810	0.680	0.863
95%CI.	0.783-0.913	0.743-0.877	0.594-0.765	0.805-0.921
p value	<0.001	<0.001	<0.001	<0.001

Figure 3. ROC curve of preoperative FFP combined with serum FGFR3 and RUNX2 levels to predict (A) death, (B) readmission and (C) hip function in elderly patients with FNF within 3 months after surgery. $p < 0.05$.

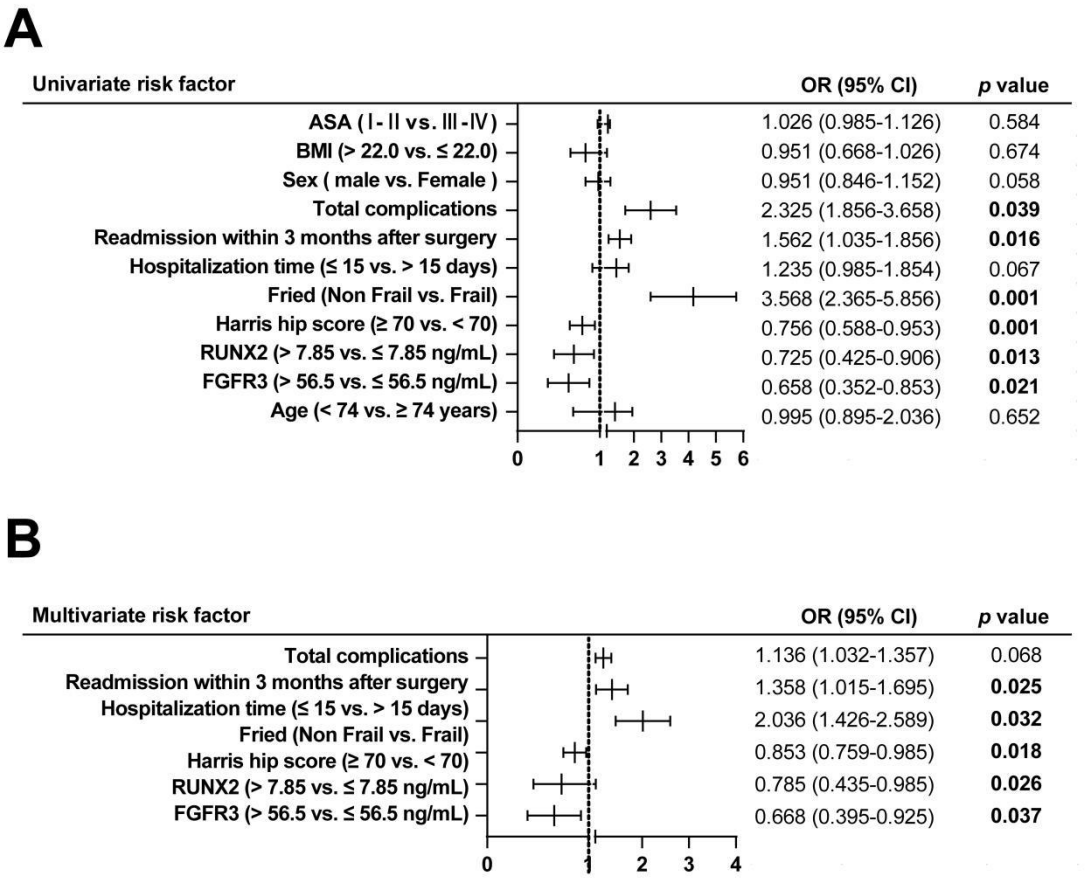

Figure 4. Variate analysis of univariate and multivariate analyses affecting hip functional recovery 3 months after surgery in elderly patients with FNF. $p < 0.05$.

Table 1 Demographic data of elderly patients with femoral neck fracture

Parameter (n%)	**Non Frail (n=82)**	**Frail (n=68)**	***p* value**
Age (years)	68 (62-86)	66 (62-84)	0.252
Sex (male/female)	20/62	20/48	0.489
BMI (kg/m^2)	22.3 (21.9-28.6)	21.5 (20.5-27.9)	0.686
ASA classification			

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I	8 (9.7)	2 (2.9)	
II	42 (51.2)	32 (47.1)	
III	30 (36.6)	23 (33.8)	0.012*
IV	2 (2.4)	11 (16.2)	
Medical history			
Hypertension	38 (46.3)	27 (39.7)	0.414
Diabetes mellitus	33 (40.2)	29 (42.6)	0.766
Coronary artery	13 (30.9)	19 (27.9)	0.072
Cerebrovascular	16 (19.5)	16 (23.5)	0.55
Lung disease	8 (9.7)	9 (13.2)	0.503
Kidney disease	3 (3.6)	6 (8.8)	0.185

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Data are expressed as the median (25^{th}, 75^{th} percentile) or number of cases (%). Enumeration data were evaluated by Chi-square or Fisher exact test, and measurement data were evaluated by Mann-Whitney U test to evaluate the demographics of elderly patients undergoing surgery for femoral neck fracture. *p value <0.05 is considered significant.

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Table 2 Comparison of surgical and postoperative outcomes of patients with Frailty Phenotype and non-frailty phenotype based on preoperative assessment of Fried Frailty Phenotype

Index (n%)	**Non Frail**	**Frail**	***p* value**

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	(n = 82)	(n = 68)	
Operation time (min)	79 (45-105)	82 (43-108)	0.728
Estimated Blood lose (ml)	52 (32-86)	50 (29-75)	0.056
Hospitalization time (d)	13 (6-20)	17 ((10-28)	0.013*
Readmission within 3 months	10 (12.2)	26 (38.2)	＜ 0.001*
Total complications	17 (20.7)	25 (36.8)	0.029*
Harris hip score			
recovered well (70-100)	62 (75.6)	28 (41.2)	＜ 0.001*
poor recovery (＜ 70)	20 (12.2)	40 (58.8)	
Death within 3 months after surgery	1 (1.2)	12 (17.6)	＜ 0.001*

Data are expressed as the median (25^{th}, 75^{th} percentile) or number of cases (%). Enumeration data were evaluated by Chi-square or Fisher exact test, and the measurement data were evaluated by Mann-Whitney U test. **p* value <0.05 is considered significant.

Table 3 Serum FGFR3 and RUNX2 levels

Index	Control (n=38)	Non Frail (n = 82)	Frail (n = 68)	*p* value
FGFR3 (ng/mL)	29.1 (25.6-34.3)	56.6 (45.3-60.0)	47.5 (38.0-53.0)	＜ 0.001*
RUNX2 (ng/mL)	5.9 (4.1-7.6)	7.0 (6.3-8.5)	6.5 (5.5-7.8)	0.002*

The Kruskal-Wallis H test performed data comparisons. **p* value <0.05 is considered

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significant.