CLINICAL ARTICLE

Mortality and Related Risk Factors of Fragile Hip Fracture

Pei-Wen Wang, MM[1#], Xue-Dong Yao, MB[1#], Hua-Feng Zhuang, MM[1], Yi-Zhong Li, MM[1], Hao Xu, MM[1],
Jin-Kuang Lin, MB[1], Wen-Ge Liu, MD[2] 🆔

[1]Department of Orthopaedic Surgery, The Second Affiliated Hospital, Fujian Medical University, Quanzhou and [2]Department of Orthopaedic
Surgery, The Affiliated Union Hospital, Fujian Medical University, Fuzhou, China

Abstract
Objective: To explore the mortality of patients with fragile hip fractures and assess the death-associated risk factors.

Methods: A total of 690 patients with osteoporotic hip fractures (age, 50–103 years) that were treated from January 2010 to December 2015 were enrolled and followed-up in this study and the clinical data were retrospectively collected. Three months, 1 year, and the total mortality were measured. Mortality-related risk factors were assessed including age, gender, surgery, the duration from injury to operation, pulmonary infection, and the number and type of complications. The mortality of each group was compared by chi-square test or corrected chi-square test for univariate analysis, and the factors with statistically significant mortality difference confirmed by univariate analysis were analyzed by binary logistic multivariate analysis.

Results: The 3-month mortality was 7.69%, the 1-year mortality was 15.60%, and the total mortality of the follow-up time was 24.06%. The 1-year and total mortality during the follow-up of the patients were higher in the >75-year-old group than those in the ≤75-year-old group ($p = 0.000$, respectively); were higher in the male patients than that in the female patients ($p = 0.042$; $p = 0.017$, respectively); were significantly lower in the operation group than that in the non-operation group ($p = 0.000$, respectively); were significantly lower in the patients that underwent the operation in ≤5 days than the patients that underwent the operation within >5 days ($p = 0.008$; $p = 0.000$, respectively); were significantly lower in patients with >2 kinds of combined medical diseases than those with ≥2 kinds of chronic diseases ($p = 0.000$, respectively); were significantly lower in patients receiving anti-osteoporosis treatment than in patients not receiving anti-osteoporosis treatment ($p = 0.000$, $p = 0.002$, respectively). Binary logistic regression analysis showed that the independent risk factors affecting mortality included advanced age >75-years-old (OR = 5.653, $p = 0.000$), male (OR = 1.998, $p = 0.001$), non-surgical treatment (OR = 9.909, $p = 0.000$), the number of combined medical diseases ≥2 (OR = 1.522, $p = 0.042$), and non-anti-osteoporosis treatment (OR = 1.796, $p = 0.002$).

Conclusion: Age, whether or not surgical treatment was performed, the number of medical diseases, and whether or not anti-osteoporosis treatment was performed were independent risk factors for 3-month and 1-year mortality in patients with fragile hip fractures.

Key words: fragile fractures; hip; mortality; risk factors; treatment

Address for correspondence Pei-Wen Wang, MM, Department of Orthopaedic Surgery, The Second Affiliated Hospital, Fujian Medical University, No. 34 of Zhongshan North Road, Licheng District, Quanzhou 362000, China Tel: +86 13959955252, Email: pwwdr123@sina.com; Wen-Ge Liu, MD, Department of Orthopaedic Surgery, The Affiliated Union Hospital, Fujian Medical University, No. 29 of Xinquan Street, Gulou District, Fuzhou 350001, China Tel: +86 13808551717, Email: wgl_2022@163.com
#These authors contributed equally to this study.
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DEATH RISK FACTORS OF FRAGILE HIP FRACTURE

Introduction

Approximately 1 million people suffer from hip fractures every year in China, most of them are elderly patients, and the incidence rate has increased visibly. From 2002–2006, the annual incidence of hip fractures increased by approximately 10%[1]. Fragile hip fracture is a worldwide public health concern, which causes great burden to the medical system. Since elderly patients often have underlying diseases before the injury, the risk of operation for hip fracture and the postoperative disability rate were high while the mortality rate after a fracture was also generally at a higher level[2-4]. Foreign research has reported that within 1 year after a hip fracture, 30% of patients died from various complications and 50% of them were disabled[5,6]. Compared with the healthy elderly population, the 1-year mortality after hip fracture increased by 27.2% in male patients and by 17.1% in female patients[7]. The risk of death after fragile hip fractures in the elderly population can last for 10 years[8]. Previous Chinese literature has also reported that 12%–20% of patients with a fragile hip fracture died within 1 year, 50% of them needed care from other people for daily living activities, and none of them recovered to the level before the fracture[9]. Currently, the treatment of fragile hip fractures mainly depends on surgery and conservative treatment. In general, tibial tubercle bone traction or lower extremity skin traction are used for conservative treatment. However, these treatment strategies require patients rest for a long-term time on the bed, which possibly leads to pulmonary infection, bedsores, urinary system infection, lower limb venous thrombosis, and other complications while significantly reducing the patients' quality of life. The fatality rate is high. Therefore, surgery remains the main treatment for hip fracture patients with fairly stable general conditions and patients that are tolerable to surgery. The main surgical methods are internal fixation and artificial joint replacement[10].

At present, many factors influencing the mortality of osteoporotic hip fracture have been reported in the literature, such as age, gender, treatment method, operation time, the American Society of Anesthesiologists (ASA) grade, number and type of combined medical diseases, post-injury complications, anti-osteoporosis treatment, and walking ability before the fracture[11,12]. Whether these factors affect the death of patients with fragile hip fracture is still debated. Some scholars have found that men have a major risk factor for mortality from fragile hip fractures[13,14]. However, other studies have shown that through multivariate analysis, there was no significant difference in the mortality rate of fragile hip fracture between men and women[11]. Moran et al.[15] advised that the delayed operation for more than 4 days after the fragile hip fracture would significantly increase mortality, while Vidal et al.[16] suggested that the time from injury to operation was not associated with high risk of mortality of patients with fragile hip fractures.

Since fragile hip fractures are a common cause of death in the elderly population, it is necessary to recognize the associated factors affecting the mortality of patients with fragile hip fractures. The present study explored the mortality of patients with fragile hip fractures during the follow-up period to analyze the risk factors for short-term mortality in fragile hip fracture patients.

Material and Methods

Inclusion and Exclusion Criteria

Inclusion criteria: (i) patients aged ≥50 years; (ii) patients with a fragile hip fracture and presumably most of them had a trivial fall before the fracture.

Exclusion criteria: (1) patients with severe violent trauma, such as traffic accident, falling from a high place, and high energy impact injury; (2) patients with a pathological fracture of the hip caused by primary or metastatic tumors.

General Information

From January 2010 to December 2015, 13,089 fracture patients were admitted to our hospital. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University. Written informed consent was obtained from all individual participants included in the study.

Anti-osteoporosis treatment include: (i) active vitamins, calcium agent + active vitamin D; (ii) calcitonin + calcium agent + vitamin D; (iii) bisphosphonate + calcium agent + vitamin D.

Surgical Methods

Surgical methods for femoral neck fractures include arthroplasty and internal fixation. Surgical methods for femoral intertrochanteric fractures include joint replacement and internal fixation.

Statistical Methods

Data were analyzed using statistical software SPSS 21.0 (USA). The mortality of each group was compared by chi-square test or corrected chi-square test for univariate analysis, and the factors with statistically significant mortality difference confirmed by univariate analysis were analyzed by binary logistic multivariate analysis. $p < 0.05$ was considered as statistically significant.

Results

General Information

A total of 1211 patients with a fragile hip fracture aged over 50 years old, among which 690 patients were followed up (56.98%), the age ranged within 50–103 years and the average age was 77.19 ± 10.38 years. Of the 690 patients, 234 cases were male, the average age was 75.27 ± 11.46 years and 456 patients were female, the average age was 79.52 ± 9.87 years. There were 335 cases of femoral neck fracture, including 275 cases of artificial joint replacement,

DEATH RISK FACTORS OF FRAGILE HIP FRACTURE

Item	Femoral neck fracture ($n = 335$)	Intertrochanteric fracture ($n = 355$)	Total (n)	Follow-up over 1 year (n, %)
TABLE 1 The general conditions of the 690 patients				
Gender				
Male	102	132	234	219 (93.59%)
Female	233	223	456	416 (91.23%)
Treatment measures				
Operative treatment	304	307	611	560 (91.65%)
Nonoperative treatment	34	45	79	75 (94.94%)
Combined medical diseases				
One kind	99	114	213	201 (94.37)
Two kinds	86	83	169	152 (89.94%)
Three or more kinds	32	27	59	49 (83.05%)
Cardiovascular disease	186	178	364	329 (90.38%)
Diabetes	42	50	92	86 (93.48%)
Cerebrovascular disease	51	47	98	87 (88.78%)
Respiratory disease	12	25	37	31 (83.78%)
Other medical diseases	21	22	43	37 (86.05%)
Lung infection	54	61	115	107 (93.04%)
Anti-osteoporosis	243	233	478	448 (93.72%)
Non-anti-osteoporosis treatment	92	122	212	187 (88.21%)
Age				
50–59 (years)	23	17	40	35 (87.50%)
60–69 (years)	58	41	99	93 (93.94%)
70–79 (years)	106	90	196	180 (91.84%)
80–89 (years)	121	165	286	262 (91.61%)
≥90 (years)	27	42	69	65 (94.20%)

26 cases of internal fixation, and 34 cases of non-operative treatment. There were 355 cases of intertrochanteric fracture of femur, including eight cases of arthroplasty, 302 cases of internal fixation, and 45 cases of non-operative treatment. The general conditions of these 690 patients are shown in Table 1.

There were 444 patients with cardiovascular disease, diabetes, cerebrovascular disease, chronic respiratory disease, and other medical diseases.

The follow-up duration for the 690 patients ranged between 7–52 months and the average duration was 28.53 ± 9.75 months. Within 3 months of the follow-up, 46 patients died and the mortality rate was 7.69% (46/690). Among the 635 patients who were followed up for more than 1 year, 99 patients died within 1 year and the mortality rate was 15.60% (99/635). A total of 166 deaths occurred during the follow-up period and the total mortality was 24.06% (166/690).

The Impact of Age on Mortality

The patients in this study were divided into two groups according to their ages: the ≤75-year-old group and the >75-year-old group. The 3-month, 1-year, and total mortality during the follow-up of the patients were higher in the >75-year-old group than those in the ≤75-year-old group. The differences in 1-year mortality and the total mortality during the follow-up period between the two groups were statistically significant ($p < 0.05$, Table 2).

The Impact of Gender on Mortality

The 3-month, 1-year, and total mortalities during the follow-up were higher in the male patients than in the female patients. The differences in 1-year mortality and the total mortality during the follow-up period between the two groups were statistically significant ($p < 0.05$, Table 2).

The Impact of Surgery on Mortality

The 3-month, 1-year, and total mortality during the follow-up period were significantly lower in the operation group than in the non-operation group, the differences between the two groups were statistically significant ($p < 0.05$, Table 2).

The Impact of Surgery Methods on Mortality

The total mortality of patients in the artificial joint replacement group at 3 months, 1 year, and follow-up period was slightly lower than that of patients in the internal fixation group, but there was no significant difference in mortality (all $p > 0.05$, table 2).

The Impact of the Interval from Injury to Surgery on Mortality

The 3-month, 1-year, and total mortality during the follow-up period were significantly lower in the patients that underwent the operation in ≤5 days than the patients that underwent the operation within >5 days, the differences between the two groups were statistically significant ($p < 0.05$, Table 2).

DEATH RISK FACTORS OF FRAGILE HIP FRACTURE

TABLE 2 Results of univariate analysis of single factor effect on mortality

Related factors	Total	Follow-up over 1 year (n)	3-month mortality (n, %)	χ^2	p	1-year mortality (n, %)	χ^2	p	Total mortality during follow-up (n, %)	χ^2	p
Age				1.705	0.192		21.243	0.000		37.705	0.000
≤75	221	203	6 (2.71)			12 (5.91)			21 (9.50)		
>75	469	432	40 (8.53)			87 (20.14)			145 (30.92)		
Gender				3.030	0.082		4.155	0.042		5.713	0.017
Male	234	219	21 (8.97)			43 (19.63)			69 (29.49)		
Female	456	416	25 (5.48)			56 (13.46)			97 (21.27)		
Treatment measures				72.246	0.000		132.467	0.000		102.53	0.000
Surgical treatment	611	559	23 (3.76)			53 (9.48)			112 (18.33)		
Non-surgical treatment	79	76	23 (29.11)			46 (60.52)			54 (71.05)		
Surgery methods				0.077	0.781		0.199	0.655		0.155	0.694
Joint replacement	283	256	10 (3.53)			23 (8.13)			50 (17.67)		
Internal fixation	328	303	13 (3.96)			30 (9.15)			62 (18.90)		
Time from the injury to the operation				3.880	0.049		7.013	0.008		13.974	0.000
≤5 days	225	198	4 (1.78)			10 (5.05)			24 (10.67)		
>5 days	386	361	19 (4.92)			43 (11.91)			88 (22.80)		
Lung infection				6.727	0.010		9.093	0.003		4.975	0.026
Yes	115	107	14 (12.17)			27 (25.23)			37 (32.17)		
NO	575	528	32 (5.57)			72 (13.64)			109 (22.43)		
Number of combined medical diseases				10.111	0.001		15.358	0.000		16.524	0.000
<2 kinds	462	434	21 (4.55)			51 (11.75)			97 (21.00)		
≥2 kinds	228	201	25 (10.96)			48 (23.88)			69 (30.26)		
Combined vascular disease				4.237	0.040		6.569	0.010		3.462	0.062
Yes	364	329	31 (8.52)			63 (19.15)			98 (26.92)		
No	326	306	15 (4.60)			36 (11.76)			68 (20.86)		
Combined diabetes				0.402	0.402		3.196	0.074		2.363	0.124
Yes	92	86	8 (8.70)			19 (22.09)			28 (30.43)		
No	598	549	38 (6.35)			80 (14.57)			138 (23.08)		
Combined cerebrovascular disease				0.411	0.521		0.209	0.648		0.132	0.717
Yes	98	87	8 (8.16)			15 (17.24)			25 (25.51)		
No	592	548	38 (6.42)			84 (15.33)			141 (23.82)		
Combined respiratory disease				2.946	0.086		4.475	0.034		2.626	0.105
Yes	37	31	5 (13.51)			9 (29.03)			13 (35.14)		
No	653	604	41 (6.28)			90 (14.90)			153 (23.43)		
Anti-osteoporosis				31.131	0.000		22.685	0.000		9.537	0.002
Yes	478	448	15 (3.14)			50 (11.16)			99 (20.71)		
No	212	187	31 (14.62)			49 (26.20)			67 (31.60)		

The Impact of Pulmonary Infection on Mortality

The 3-month, 1-year, and total mortality during the follow-up period were significantly higher in the patients with in-hospital pulmonary infection than in patients without pulmonary infection, the differences between the two groups were statistically significant ($p < 0.05$, Table 2).

The Impact of the Number of Combined Medical Diseases on Mortality

The 3-month, 1-year, and total mortality during the follow-up period were significantly lower in patients with >2 kinds of chronic diseases than those with ≥2 kinds of chronic diseases, the differences between the two groups were statistically significant ($p < 0.05$, Table 2).

TABLE 3 Multivariate analysis results of recent death risk of fragile hip fracture

Influence factor	β value	χ^2 value	p value	OR (95% CI)
Age	1.732	38.283	0.000	5.653 (3.266, 9.784)
Gender	0.692	10.844	0.001	1.998 (1.323, 3.017)
Surgical treatment or not	2.208	62.531	0.000	9.909 (5.263, 15.726)
Number of combined medical diseases	0.420	4.154	0.042	1.522 (1.016, 2.278)
Anti-osteoporosis treatment	0.586	9.975	0.002	1.796 (1.249, 2.584)

The Impact of the Types of Combined Medical Diseases on Mortality

The 3-month, 1-year, and total mortality during the follow-up period were higher in patients with cardiovascular diseases than in patients without cardiovascular diseases, the differences in the 3-month and 1-year mortalities between the two groups were statistically significant ($p < 0.05$, Table 2). The 3-month, 1-year, and total mortality during the follow-up period were higher in patients with respiratory diseases than in patients without respiratory diseases, but only the difference in 1-year mortality between the two groups was statistically significant ($p = 0.034$, Table 2). The differences in 3-month, 1-year, and total mortality during the follow-up period between patients with or without diabetes and between patients with or without cerebrovascular diseases were not statistically significant ($p > 0.05$, Table 2).

The Impact of Anti-Osteoporosis Treatment on Mortality

The 3-month, 1-year, and total mortality during the follow-up period were significantly lower in patients receiving anti-osteoporosis treatment than in patients not receiving anti-osteoporosis treatment, the differences between the two groups were statistically significant ($p < 0.05$, Table 2).

The Multivariate Analysis of Mortality

Using the factors with statistical significance in the univariate analysis as independent variables and the total mortality of patients in the follow-up period as dependent variables, the multivariate logistic regression analysis was conducted. The results revealed that advanced age >75-years-old (OR = 5.653, $p = 0.000$), male (OR = 1.998, $p = 0.001$), non-surgical treatment (OR = 9.909, $p = 0.000$), the number of combined medical diseases ≥2 (OR = 1.522, $p = 0.042$), and non-anti-osteoporosis treatment (OR = 1.796, $p = 0.002$) were independent risk factors for the short-term (1-year) mortality in patients with fragile hip fractures (Table 3).

Discussion

The Age Factor

The data in this study showed that in a population with an age over 50 years, with the increase in age, the incidence of hip fractures increased, and 70–89-years-old is the high incidence age of fragile hip fractures because of the decrease in activity and the number of cases reduced in the elderly aged over 90 years. The mortality of patients with fragile hip fractures increased with age. Previous studies also revealed that advanced age increased the 1-year mortality of hip fracture patients[7,17]. Statistical data in this study revealed that the 3-month, 1-year, and total mortality during the follow-up period of patients who were >75-years-old were higher than those in patients who were ≤75-years-old. Among the patients over 75 years, the 1-year mortality was 20.14%, and the total mortality during the follow-up period was as high as 30.92%. The difference was statistically significant compared with the patients with an age ≤75 years. The multivariate analysis also confirmed that age was an independent risk factor for short-term mortality in patients with fragile hip fractures.

The Gender Factor

Women are also more likely to develop hip fractures than men; in the present study, the ratio of male to female was 1:1.95. Previous studies have revealed that the male gender was a major risk factor for mortality from fragile hip fractures[13,14]. After the hip fracture occurs, the life expectancy of the elderly will be greatly reduced and the physical life of females was decreased by 4 years when compared with the life expectancy, while that of males was decreased by 5 years[18]. Kannegaard et al.[7] reported that compared with females, the average age of onset of fragile hip fractures was 4 years younger in males and mortality was significantly higher. However, some reports revealed that mortality in patients with fragile hip fractures was not related to gender[11,19]. This study revealed that when compared with females, the average age of onset of fragile hip fractures was 4.24 years younger in males, the 3-month, 1-year, and total mortality during the follow-up period were higher in males than in females, and the differences in the 1-year and total mortality during the follow-up period between males and females were statistically significant. This result suggests that although the incidence and age of onset of fragile hip fractures were lower in males, the mortality was higher in males than in females, and this was established by the multivariate analysis, showing that the male gender was an independent risk factor for short-term mortality in patients with fragile hip fractures. This is consistent with the findings of previous studies conducted by many scholars[13,14].

The Surgical Factors

The purpose of fragile hip fracture treatment is to allow patients to continue with painless activities and get out of bed to reduce the complications caused by long-term bed rest and reduce the fatality and disability rate. In the present study, the 3-month, 1-year, and total mortality during the follow-up period was 3.76%, 9.48%, and 18.33%, respectively, in the operation group and were far lower than in the non-operation group (29.11%, 60.52%, and 71.05%, respectively), the differences were statistically significant. It was also confirmed by multivariate analysis that the non-operative treatment was an independent risk factor for short-term mortality in patients with fragile hip fractures. This fully demonstrates that the operation treatment of fragile hip fracture has a significant positive effect.

Option of Operation Opportunity

The association between delayed surgery and mortality after fragile hip fractures in the elderly population remains a major issue[20,21]. Some scholars consider that the earlier the operation and even the emergency operation is performed, the better the effect is. Shiga et al.[22] reported that an operation completed at more than 48 h after the fragile hip fracture will increase the 1-month and 1-year mortality in patients. Some other scholars believe that the operation should not be performed in a rush and that there should be enough time to treat the internal diseases of the elderly patients before surgery. Preoperative preparation and evaluation should also be enhanced to reduce the risk of the operation and its success rate. Vidal et al.[16] showed in their studies that the time from injury to operation was not associated with the in-hospital and 1-year mortality after surgery while Kim et al.[23] showed that a delayed operation would not affect the postoperative complications of hip fractures. In the present study, all the patients had slight trauma and no obvious trauma. Some of the patients did not even realize that they had a fracture but were admitted to the hospital after the pain was not improved for 1–2 days. After admission, due to the advanced age of the patients, the hospital had no preoperative green channel for hip fractures, so preoperative preparations required 3–4 days. Therefore, in the present study, an interval from injury to the operation of 5 days was set as the grouping boundary. The researchers observed that although the 3-month, 1-year, and total mortality during the follow-up period were lower in patients with the interval from injury to the operation of ≤5 days than in patients with the interval from injury to the operation of >5 days, the differences were statistically significant. However, it was established by multivariate analysis that the interval from injury to operation was not an independent risk factor for short-term mortality in patients with fragile hip fractures. Therefore, the researchers considered that the selection of operation time for elderly patients with hip fractures should follow the principle of individualization and should be lengthily measured according to the patient's physical condition. Patients that can tolerate the operation should be operated on as early as possible to reduce the difficulties of bed rest while the patients with poor physical conditions should have enough time for the preoperative planning.

Preoperative Combined Medical Diseases

Elderly patients with hip fractures regularly have multiple internal diseases and poor organ compensatory function. Surgery will worsen the existing combined medical diseases and even lead to death. A previous study described that the mortality after hip fractures was associated with chronic diseases such as hypertension, diabetes, ischemic heart disease, and stroke[24]. Moran et al.[15] showed that the risk of death 30 days after surgery in patients with fragile hip fractures combined with internal diseases was 2.5 times higher than in patients without internal diseases. The findings of the present study are similar; of these 690 patients, 441 patients had various internal chronic diseases, up to 63.91%, of patients had two or more chronic diseases, the 3-month mortality was 10.96%, the 1-year mortality was 23.88%, and the total mortality was 30.26%. All the results were higher than the mortality of patients with <2 medical chronic diseases. In patients who had cardiovascular diseases or chronic respiratory system diseases before the operation, the mortality was also statistically and significantly increased. The multivariate analysis revealed that the number of internal diseases before the injury was an independent risk factor for short-term mortality in patients with fragile hip fractures. The treatment of medical diseases before surgery is directly associated with the success of the operation and the prognosis in patients. Therefore, after admission, patients should actively collaborate with the physician to treat their combined diseases and physicians should measure patients' tolerance to surgery to select a tolerable operation to reduce the mortality in elderly patients with fragile hip fractures.

Complications after Fractures

The incidence of difficulties after fragile hip fractures is high and the main complications include pulmonary infection, heart event, and deep vein thrombosis of the lower extremity, delirium, and cerebrovascular accidents. Fang et al.[25] consider that pulmonary infection and respiratory failure are frequently the main causes of death in these patients. In the present study, pulmonary infection occurred in 115 patients during hospitalization, 37 of them died during hospitalization and the follow-up period and the 3-month, 1-year, and total mortality during the follow-up period were significantly higher in patients with in-hospital pulmonary infection than in patients without in-hospital pulmonary infection; the differences were statistically significant. These findings indicate that in-hospital pulmonary infection is a significant risk factor for short-term mortality in patients with fragile hip fractures. However, given the interaction between various factors, the multivariate analysis showed that in-hospital pulmonary infection was not an independent risk factor for short-term mortality in patients with fragile hip fractures.

Anti-Osteoporosis Treatment

Anti-osteoporosis treatment has been confirmed to effectively reduce the risk of succeeding fractures and improves the functional outcome of hip fracture patients[26]. This leads to a hypothesis, that is, osteoporosis drug treatment can reduce the risk of death in patients with fragile hip fractures. Zoledronic acid has also been confirmed to significantly increase bone mineral density in the hip and lumbar spine, reduce the risk of new clinical fractures by 35%, and reduce the risk of death in patients with recurrent fractures within 3 years by 28%[27]. In the present study, it was also confirmed that anti-osteoporosis treatment (including bisphosphonates and non-bisphosphonates) was significantly related to a reduction in short-term mortality in fragile hip fractures. Furthermore, it was established by the multivariate analysis that the absence of anti-osteoporosis treatment was an independent risk factor for short-term mortality in patients with fragile hip fractures.

The Limitations

This retrospective study had several limitations. Firstly, only 56.98% of the hip fracture patients were followed-up successfully and this was a retrospective and not a randomized study. Moreover, the sample size of the non-operation group was relatively small, which should be expanded in future studies to further confirm the conclusion of this study. Secondly, the present study did not include all the aspects that may affect the prognosis of patients with fragile hip fractures, such as the patients' activity function before the injury, ASA score before surgery, and the surgeons' surgical skills. Thirdly, whether the basis for grouping the factors involved in this study was reasonable, for example, 75 years patient was set as the boundary of age and 5 days was set as the boundary of the interval from injury to operation, needs to be studied further.

Conclusion

In summary, the short-term mortality of elderly patients with fragile hip fractures is high. Death after the injury is the outcome of an interaction of many factors, but different influences have different impacts on mortality. In the present study, age, whether or not surgical treatment was performed, the number of medical diseases, and whether or not anti-osteoporosis treatment was performed had the greatest impact on mortality. These factors were independent risk factors for short-term mortality in patients with fragile hip fractures. Therefore, the short-term mortality of patients in the future can be reduced by vigorously addressing the internal diseases and operating on the patients as soon as possible.

Author Contributions

Pei-Wen Wang and Xue-Dong Yao been involved in drafting the manuscript and revising it critically for important intellectual content and conception and design; Hua-Feng Zhuang and Yi-Zhong Li made substantial contributions to acquisition and interpretation of data; Hao Xu and Jin-Kuang Lin analyzed the data; Wen-Ge Liu was responsible for supervision and correspondence; all authors given final approval of the version to be published.

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Conflict of Interest

The authors have no conflict of interest to declare.

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DEATH RISK FACTORS OF FRAGILE HIP FRACTURE

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