

Mortality Risk Assessment at the Admission in Patient With Proximal Femur Fractures: Electrolytes and Renal Function

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Abstract

In patients over 65y.o. who were surgically treated for a hip fracture, electrolytes have not been specifically studied as predictors of mortality. The main purpose of this study was to assess whether electrolytes and chronic kidney disease (CKD) stages, evaluated at admission, could represent a pre-operative prognostic factor in this population. Moreover, the role of epidemiological and clinical parameters was analyzed with and without a surgical timing stratification. This retrospective study included 746 patients. For each patient, their age, gender, fracture classification, Hb value, comorbidities, ASA class, chronic kidney disease, creatinine levels, electrolytes and surgical timing were collected. CKD-epi, MDRD, modified MDRD and BIS1 were used to obtain eGFR and CKD stages. All parameters were analyzed individually and in relation to the different surgical timing. Descriptive statistics, Chi-square test and survivability analysis with Kaplan Meier curve were used. In patients with a hip fracture non-significant association with increased mortality was shown for the following variables: Hb value, sodium values, calcium values, CKD stages and creatinine values. Otherwise altered kalemia was associated with a statistically significant increase in mortality as well as male gender, two or more comorbid medical conditions, advanced age (>75 years), higher ASA class. Surgery performed within 72h resulted in a statistically significant reduction in mortality at 6 months and, when performed in 24h-48h, a further reduction at 4 years. Age and ASA class statistically significant increased mortality regardless the surgical timing. Male patients operated after 48h from hospitalization were associated with a statistically significant increase in mortality rate. Two or more comorbidities were related to a statistically significant increased number of deaths when patients were treated after 96h. Altered kalemia values at hospitalization are associated with a statistically significant increase in mortality in patients operated after 72h from admission.

Keywords

hip fracture, mortality risk, electrolytes, kidney, mortality, basic research, fragility fractures, geriatric trauma, trauma surgery, geriatric medicine

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Introduction

Hip fractures are a common injury in the elderly and early surgical treatment has been one of the most important challenges in orthopedic surgery in the last decade. Current guidelines indicate that hip surgery should be performed within 48 hours from the injury to drastically reduce mortality and post-operative complications.¹⁻⁴ Furthermore, many studies suggest that different pre-operative factors are directly associated with higher mortality rates: male gender, clinical comorbidities, dementia, delirium, ASA classification and general anesthesia.⁵⁻⁷ Being aware of these mortality factors and their influence is fundamental in surgical decision-making. A delay in the

execution of surgery is often caused by management problems⁸⁻¹⁰ or the need to “optimize” the patients, reducing the risk of perioperative complications. However, in patients with multiple comorbidities, it is still unclear if clinical stabilization

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can bring benefits in terms of mortality risk reduction.¹¹⁻¹² Acute renal failure has been associated with increased mortality up to 1 year after surgery.¹³ Moreover, chronic kidney disease (CKD),¹⁴ as well as kidney dysfunction, evaluated with cystatin C,¹⁵ are likely risk factors for hip fractures. Despite these extensively evaluated conditions, there are only a few controversial analyses comparing kidney dysfunction and patient-reported outcomes. Furthermore, in elderly patients with a hip fracture, the role of electrolytes as factors related to mortality has not been fully investigated.¹⁶ The main purpose of this study was to assess whether electrolytes and chronic kidney disease (CKD) stages, evaluated at hospitalization, could be a pre-operative prognostic factor in patients over 65 with femur fracture. Moreover, the role of epidemiological and clinical parameters, also assessed at hospitalization, was analyzed with and without the surgical timing stratification. Guidelines indicate that an early surgery can lead to great improvements in patients' wellbeing. The study of these variables related to an increased mortality was made considering both independent factors and surgical timing related factors. The authors hypothesize that higher CKD stages could be associated with an increased post-operative mortality in these patients. No significant results were expected from the evaluation of electrolytes due to the attention in rebalancing and maintaining their normal values in the pre and post-surgical management. The results of the epidemiological and clinical parameters were expected to be in accordance with the literature.

Materials and Methods

A retrospective study was conducted on 746 patients over the age of 65 that presented with a proximal femoral fracture and were treated in our Orthopedic Department between 1st January 2013 and 31st December 2016. Each X-Ray was revised by 2 independent reviewers (G.E.V. and F.B.). In cases of disagreement, the senior author (L.C.) was consulted for the final decision. Periprosthetic fractures, fractures related to metastases/cancer, patients affected by at least another concomitant fracture, those who were under the age of 65 and those undergoing the dialysis, were excluded. For each patient, specific data were collected: age, gender, hip fracture classification, pre- and post-surgery hemoglobin (Hb) value, electrolytes, comorbid medical conditions, American Society of Anaesthesiologists (ASA) classification, chronic kidney disease, surgical timing. Of the 746 patients 660 of them had undergone surgery. The remaining 86 patients, based on a high intra and post-operative risk of death defined by the anesthesiology evaluation, refused the planned surgery and received non-surgical treatment. The operated patients were allocated into 3 age groups: 65-75 years, 76-85 years and over 86 years old. Fractures were classified according to the AO classification in AO/OTA 31A, 31B, 31C¹⁷ and to anatomic pattern in subcapital fractures, transcervical fractures, basicervical fractures, petrochanteric and inter/sub-trochanteric fractures. Hemoglobin values (1g/dl rate) were observed pre- and post-surgery, evaluating the gap (positive in

blood loss) as well as blood transfusions. Pre-operative electrolytes parameters were collected and reviewed for each patient. Sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) were divided into 3 ranges each according to the serum level of each parameter: hypocalcemia ($\text{Ca}^{2+} < 8.5$ mg/dl), normocalcemia ($8.5 < \text{Ca}^{2+} < 10.59$ mg/dl), and hypercalcemia ($\text{Ca}^{2+} > 10.6$ mg/dl); hypokalemia ($\text{K}^+ < 3.5$ mEq/L), normokalemia ($3.5 < \text{K}^+ < 5.19$ mEq/L), and hyperkalemia ($\text{K}^+ > 5.2$ mEq/L); hyponatremia ($\text{Na}^+ < 134.9$ mEq/L), normonatremia ($135 < \text{Na}^+ < 145.9$ mEq/L), hypernatremia ($\text{Na}^+ > 146$ mEq/L). All patients had pre-operative albumin levels $> 3,0$ g/dl and glycemia under control during surgery. However, no correction has been made for Ca^{2+} according to the albumin level. Creatinine levels were collected upon admission and used to obtain estimated glomerular filtration rate (eGFR) using the following equations: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD), modified MDRD, Berline Initiative Study (BIS1) [18-25]. At this point each patient has been classified in CKD stages: 1 (eGFR > 90 ml/min), 2 (eGFR 60-89 ml/min), 3 (eGFR 30-59 ml/min), 4 (eGFR 15-29 ml/min), 5 (eGFR 0-14 ml/min). To better evaluate the correlation with mortality, eGFR was also divided into 2 stages: eGFR > 60 ml/min; and eGFR < 60 ml/min. In most of the cases, surgery was performed as follows: displaced subcapital femoral neck fractures (< 80 years) underwent an uncemented total hip replacement; displaced subcapital femoral neck fractures (> 80 years) underwent a cemented hemiarthroplasty; inter/sub-trochanteric fractures were fixed with an intramedullary nail. According to guidelines, all patients underwent thromboprophylaxis and antibiotic prophylaxis based on their comorbidities and allergies. In each patient the electrolyte alterations, in particular Na^+ and K^+ , were carefully evaluated and, when necessary, these were restored to normal values before surgery. Therefore, these were monitored and kept in balance within normal ranges until discharge. The time between the trauma and the surgery was retrieved in each patient. Patients were divided according to surgical timing: within 24 hours, between 24 and 48 hours, between 48 and 72 hours, between 72 and 96 hours, after 96 hours. Comorbid medical conditions were evaluated, considering the anatomic district involved and the number of conditions. Patient survival was confirmed using the National TS Project (Health Insurance Card) and the NAR (Regional Health Registry Office) archive until 4th March 2017. These details were used to indicate the time that had passed since hospitalization. Lastly, the association between mortality and age, gender, type of fracture, Hb value, electrolytes, comorbid medical conditions and CKD stages were evaluated. These factors were analyzed individually and relating to the different surgical timings mentioned above.

Statistical Analysis

General analysis was carried out with mean and standard deviation, maximum and minimum values for continuous variables; absolute number and frequency distribution for categorical variables. Chi-square test was used for normally distributed

Table 1. Patient Population.

Total n° patient population	746		
Total n° deaths	251		
Gender	M: 189 (25.3%)	F: 557 (74.7%)	
Age	Min: 65	Average: 82	Max: 100
Operated patients	Yes: 660 (88.5%)		
Type of Fracture	Extra-capsular: 511 (68.5%)	Intra-capsular: 235 (31.5%)	

Table 2. Patient Population: Kidney Function.

	N° patients	Average	Min	Max
Kidney function				
Creatinine	694	1.13	0.38	8.99
eGFR (Treated)	648	60.85	4.79	106.27

Table 3. Increase in Mortality: CKD Stages Based on CKD-EPI Equation in Operated Patients.

CKD Stages	Total n° patients	N° treated patients	Deaths	Deaths %	Increase in mortality correlated to Stage I
Stage 1	65	60	15	25,0	
Stage 2	293	273	83	30,4	OR: 1.3105 (CI:0.69-2.48) p value >0.05
Stage 3	258	246	81	32,9	OR: 1.4727 (CI:0.78-2.79) p value >0.05
Stage 4	61	54	20	37,0	OR: 1.7647 (CI:0.79-3.94) p value >0.05
Stage 5	17	15	7	46,7	OR: 2.6250 (CI:0.81-8.46) p value >0.05
Total	694	648	206		
CKD Stages					Increase in mortality correlated to moderate stages
Moderate (Stages 1, 2, 3)		579	179	30,9	
Severe (Stages 4, 5)		69	27	39,1	OR: 1.4366 (CI:0.86-2.40) p value >0.05

Table 4. Increase in Mortality: CKD Stages Based on MDRD Equation in Operated Patients.

CKD Stages	N° patients	Deaths	Deaths %	Increase in mortality correlated to Stage I
Stage 1	153	45	29,4	
Stage 2	219	62	28,3	OR: 0.9478 (CI:0.60-1.49) p value >0.05
Stage 3	220	78	35,5	OR: 1.3183 (CI:0.85-2.06) p value >0.05
Stage 4	45	17	37,8	OR: 1.4571 (CI:0.73-2.92) p value >0.05
Stage 5	11	4	36,4	OR: 1.3714 (CI:0.38-4.92) p value >0.05
Total	648	206		
CKD Stages	N° patients	Deaths	Deaths %	Increase in mortality correlated to moderate stages
Moderate (Stages 1, 2, 3)	592	185	31,3	
Severe (Stages 4, 5)	56	21	37,5	OR: 1.32 (CI:0.75-2.33) p value >0.05

continuous data. A p-value < 0.05 was considered to be statistically significant. Survivability analysis were carried out with a Kaplan Meier curve. Data were collected using Microsoft Excel and statistical analysis was performed with XLSTAT program. Univariate analysis was used in this study.

Results

A total of 746 proximal femoral fractures were admitted to our hospital between 1st January 2013 and 31th December 2016 (Table 1). Creatinine was collected in 694 patients. The

eGFR was calculated with the CKD-EPI equation only in the 648 operated patients. The average value of eGFR was 60.85 ± 23.25 ml/min (Table 2). An increase in mortality was found in patient at CKD stages ≥ 2 compared to those at CKD stage 1, although the correlation was not statistically significant (Table 3). The same evaluation was conducted using MDRD, modified MDRD and BIS1 equations without any significant association being found (Tables 4, 5, and 6). An unreported calculation has also been made with simple creatinine levels and again no statistically significant difference was found.

Table 5. Increase in Mortality: CKD Stages Based on MDRD Modified Equation in Operated Patients.

CKD Stages	N° patients	Deaths	Deaths %	Increase in mortality correlated to Stage I
Stage 1	128	38	29,7	
Stage 2	207	60	29,0	OR: 0.9667 (CI:0.60-1.57) p value >0.05
Stage 3	249	84	33,7	OR: 1.2057 (CI:0.76-1.91) p value >0.05
Stage 4	50	17	34,0	OR: 1.2201 (CI:0.61-2.45) p value >0.05
Stage 5	14	7	50,0	OR: 2.3684 (CI:0.78-7.22) p value >0.05
Total	648	206		

CKD Stages	N° patients	Deaths	Deaths %	Increase in mortality correlated to moderate stages
Moderate (Stages 1, 2, 3)	584	182	31,2	
Severe (Stages 4, 5)	64	24	37,5	1.3253 (CI:0.76-2.26) p value >0.05

Table 6. Increase in Mortality: CKD Stages Based on BISI Equation in Operated Patients.

CKD Stages	N° patients	Deaths	Deaths %	Increase in mortality correlated to Stage I
Stage 1	28	7	25,0	
Stage 2	209	60	28,7	OR: 1.2081 (CI:0.49-2.99) p value >0.05
Stage 3	343	112	32,7	OR: 1.4545 (CI:0.60-3.52) p value >0.05
Stage 4	57	23	40,4	OR: 2.0294 (CI:0.74-5.55) p value >0.05
Stage 5	11	4	36,4	OR: 1.7143 (CI:0.39-7.66) p value >0.05
Total	648	206		

CKD Stages	N° patients	Deaths	Deaths %	Increase in mortality correlated to moderate stages
Moderate (Stages 1, 2, 3)	580	182	31,4	
Severe (Stages 4, 5)	68	27	39,7	OR: 1.4753 (CI:0.88-2.47) p value >0.05

Regarding the electrolytes' evaluation, Ca^{2+} was collected in 682 patients while Na^+ and K^+ was collected in 700 patients. As for the patients who had surgery, on the other hand, Ca^{2+} values were retrieved in 640 patients while Na^+ and K^+ values were retrieved in 653 patients. Altered levels of Na^+ and Ca^{2+} , related to normal values, did not show statistically significant correlation with increased mortality, both independently and relating to any surgical time. Hypokalemia (OR: 2.01; p value < 0.05) as well as hyperkalemia (OR: 2.48; p value < 0.05), when related to normokalemia, showed a correlation with an increased mortality (Tables 7 and 8). Altered levels of K^+ were studied in their correlation between surgical timing and mortality. Patients suffering from hyperkalemia with a surgery performed after 72 hours, compared to normokalemia value, showed a statistically significant increase in mortality (OR: 2.09, p value < 0.05). Hypokalemia assessed in relation to the surgical timing showed an increased risk of death without being statistically significant (Tables 9 and 10).

The dates of death were recorded until 4th March 2017. At that time, the death toll was 251 (33.65%), while 495 patients were still alive (66.35%). A cumulative survival rate was established with a Kaplan Meier curve in 30 days of $94.1\% \pm 0.009$; in six months of $80.7\% \pm 0.014$; in 1 year of $75.3\% \pm 0.016$; in 2 years of $69.6\% \pm 0.017$; in 3 years of $67.6\% \pm 0.017$ and in 4 years of $66.4\% \pm 0.017$. Among the patients who underwent surgery (660 patients, 88.5%), the death toll was 209 (31.7%).

Eighty-six patients (11.5%) received non-surgical treatment and 42 deaths of them were registered (48.8%). Based on the dates of hospitalization and surgery, patients were grouped according to their surgical timing. No statistically significant difference was noted in terms of mortality in patients treated within 24 hours of hospitalization compared to the others (OR: 0.24; p value > 0.05), although the test sample was small. Patients who underwent surgery before 48 h, compared to those operated later, showed a statistically significant reduction of mortality (OR: 0.67; p value < 0.05). This reduction in mortality was even more statistically significant in patients operated within 72 hours and 96 hours compared to patients treated later (p value < 0.05). In patients operated within 72 hours, compared to those treated subsequently, there was a reduction in mortality that was already evident six months after the hospitalization. Performing the surgical procedure before 48 hours, compared to the surgical timing window of 48-72 hours, further reduced the mortality at 4 years after the hospitalization (Table 10).

Evaluation of how ASA classification could have influenced mortality showed that patient with ASA class > 2, compared to $ASA \leq 2$, was associated with increased mortality (OR: 8.72, p value < 0.05 and OR: 26.04, p value < 0.05 for ASA 3 and 4 respectively). Furthermore, patients with ASA class 3 and 4, compared to those with a lower class, showed a statistically significant correlation with an increased mortality regardless of the surgical timing.

Table 7. Patient Population: Electrolytes Levels.

Electrolytes	N° patients	Average	Min	Max
Na+	700	138.98	110	163
K+	700	4.40	2.70	7.74
Ca2+	682	8.40	4.60	11.43

Table 8. Patient Population: Electrolytes Levels in Operated Patients.

Electrolytes	Total n° of patients			
Na+		Hypo	Normal values	Hyper
N° of patients	653	68	563	22
K+		Hypo	Normal values	Hyper
N° of patients	653	36	553	64
Ca2+		Hypo	Normal values	Hyper
N° of patients	640	369	269	2

Table 9. Increase in Mortality: Altered Levels of Electrolytes in Operated Patients.

Electrolytes	Altered levels < n.v.	Altered levels > n.v.
Na+	OR: 1.02 (CI:0.61-1.71) p value >0.05	OR: 1.43 (CI:0.66-3.12) p value >0.05
K+	OR: 2.01 (CI:1.03-3.91) p value <0.05	OR: 2.48 (CI:1.44-4.29) p value <0.05
Ca2+	OR: 1.35 (CI:0.96-1.90) p value >0.05	OR: 2.54 (CI:0.16-41.12) p value >0.05

Table 10. Increase in Mortality: Altered Kalemia Levels Correlated to Surgical Timing.

lperK+	Surgical timing	Increase in mortality
	< 48H	OR: 1.75 p value >0.05
	> 48H	OR: 2.60 p value <0.05
	< 72H	OR: 1.49 p value >0.05
	< 96H	OR: 2.09 p value <0.05
lperK	Surgical timing	Increase in mortality
	> 48H	OR: 2.01 p value >0.05
	< 72H	OR: 1.22 p value >0.05

Patients over 75 years of age, compared to patients between 65 and 75 years of age, had a statistically significant increase in mortality (OR: 2.27; p value < 0.05). A further evaluation was made by correlating this factor to the surgical timing. Patients older than 75 years, compared to those under 75, showed statistically significant correlation with an increased mortality regardless of the surgical timing.

Regarding the gender evaluation, females represented the 74.7% of the whole population and were therefore more affected by femur fracture than the male gender. However, the male gender recorded a statistically significant increase in mortality (OR: 1.93; p value < 0.05) both independently and relating to surgical timing in those patients operated after 48 hours when compared to the female gender (OR: 1.67; p value < 0.05).

Analysis of comorbidities and mortality indicate that patients with two or more comorbidities had a statistically

significant increase in mortality compared to those who had none (OR: 2.81; p value < 0.05). Furthermore, the correlation between patients with two or more comorbidities and surgery performed after 96 hours showed a statistically significant increase in mortality when compared to those who presented fewer comorbidities (OR: 2.97, p value < 0.05).

Fractures were identified and divided according to anatomic pattern as follows: 384 pertrochanteric fractures (51.4%), 155 subcapital fractures (20.8%), 80 transcervical fractures (10.7%), 74 basicervical fractures (9.9%) and 53 inter/subtrochanteric fractures (7.1%). Following a generic partition into lateral and medial fractures the correlation with an increased mortality rate was found to be not statistically significant (OR: 1.19; p value > 0.05).

Hemoglobin was evaluated in 660 patients with an average pre and post-surgery value of 10.95 ± 1.90 g/dl and 9.10 ± 1.68 g/dl respectively. The increase of mortality in patients with a pre-surgical value of Hb < 8 g/dl, compared to those with Hb \geq 8 g/dl, was not statistically significant (OR: 1.22; p value > 0.05). Moreover, patients with blood loss of \geq 5 g/dl between pre and post-surgery, compared to those with blood loss of <5 g/dl, still showed a non-statistically significant increase in mortality (OR: 0.97; p value > 0.05).

Discussion

The main finding of this study was that, based on admission tests, no significant association was observed between an increased risk of mortality in patients over 65-years of age who

Table 11. Mortality Correlation in Patients Treated Within 72 and 48 Hours.

Time from hospitalization (months)	Surgical timing <72 hours	Surgical timing <48 hours
1	OR: 0.81 (CI:0.39-1.70) p value >0.05	OR: 1.57 (CI:0.72-3.43) p value >0.05
6	OR: 0.65 (CI:0.44-0.98) p value <0.05	OR: 0.78 (CI:0.48-1.27) p value >0.05
12	OR: 0.61 (CI:0.42-0.89) p value <0.05	OR: 0.80 (CI:0.52-1.24) p value >0.05
24	OR: 0.59 (CI:0.42-0.82) p value <0.05	OR: 0.69 (CI:0.46-1.04) p value >0.05
36	OR: 0.58 (CI:0.42-0.81) p value <0.05	OR: 0.68 (CI:0.45-1.10) p value >0.05
48	OR: 0.58 (CI:0.42-0.81) p value <0.05	OR: 0.67 (CI:0.45-0.99) p value <0.05

were surgically treated for a proximal femur fracture and CKD stages ≥ 2 . The method used to evaluate the renal function was the CKD-EPI equation, which is considered the gold standard equation in staging CKD. However, the authors decided to use all the accepted equations to minimize possible error: BIS1, MDRD and modified MDRD.¹⁸⁻²⁵ Regardless of the equation used, no statistically significant association was identified between higher stages of impaired renal function and increased mortality. Furthermore, creatinine levels and subsequent CKD stages were not found to be a risk factor even when the increase in mortality was correlated with surgical timing. Therefore, in this patient population, due to the enormous clinical implications that CKD has, it is unclear what role this issue may play in determining mortality. In literature, there are only few studies where eGFR has been evaluated as a predictor of mortality in patients who have undergone surgery for hip fracture. Two studies, based on a multivariate statistical analysis, showed a correlation between CKD stage 4 (CKD-EPI equation) and higher mortality risk at 1 year.^{26,27} However, the overall mortality rate may vary with a longer follow-up. In fact, it is important to remember that an acute kidney injury following a hip fracture is common, directly associated with a worse outcome¹⁸ and is most likely to happen in patients with an already altered kidney function. An association between a CKD stage 4 or higher and mortality was also found in another study which is slightly different and based on a much smaller population of patients.²⁸ Three more studies also gave similar results but with a non-specifically treated population and using different follow-up, statistical analysis and eGFR equations.²⁹⁻³¹ Lastly, a study, based on a population of 88 over-70 patients, evidenced that the HUGE (Hematocrit, Urea, Gender) equation was an independent risk factor for mortality while no statistical correlation was found with eGFR calculated with Cockcroft-Gault, MDRD or CKD-EPI equations.³² The only recent meta-analysis on the subject reported a moderate evidence in CKD as a mortality risk factor in a population over 60 years of age.³³ Therefore, it remains doubtful whether CKD can be considered a risk factor in determining an increased mortality in this population of patients.

To our knowledge only one study has evaluated the role of electrolytes disorders as mortality risk factors in patient over 65 years of age treated for a proximal femur fracture. Lewis et al. has shown that patient with an increased serum urea value, creatinine value, potassium or sodium concentration as well

as an initial hyponatremia have an increased cumulative mortality. In particular, they found a strong correlation between the degree of uremia and mortality at 2 years. However, surgical timing was never specified or evaluated and patients affected by periprosthetic fractures were included in the study.¹⁶ Analyzing the electrolytes values in our study showed that most of the patients included in the present study presented with hypocalcemia (57.65%). This may suggest a fragile condition associated with an increased risk of fractures. On the other hand, a weak and non-statistically significant correlation with an increased mortality after surgery was found. When analyzing Na^+ imbalance, no association with increased mortality was observed. Differently, K^+ disorders showed a correlation with an increased mortality. Both hyper and hypokalemia alterations were found to be a relevant negative prognostic factor. However, when related to surgical timing, hypokalemia was not statistically significant associated with a higher mortality, while this factor was relevant in patients with hyperkalemia. Particularly, a significant increased mortality was found in those patients surgically treated after 72 hours from admission. In order to reduce mortality in patients with hyperkalemia, a surgical treatment within 72 hours was found to be the most appropriate indication. In the literature only two other studies have evaluated electrolytes as mortality risk factors in patients with hip fractures. However, none of them specifically analyzed patients who had undergone surgery. A study was strictly focused on in-hospital mortality.³⁴ and the other one evaluated the electrolytes as a generic presence/absence of fluid and electrolytes disorders in an age-related multivariate analysis.³⁵ Undoubtedly, it is certainly important to restore the electrolytes, especially the K^+ , to normal values before surgery. However, this study showed that K^+ alterations can be an indicator of the risk of mortality since admission and, nonetheless, should be a factor in planning the timing of the surgery to reduce the mortality risk.

Analyzing the cumulative survival curve obtained with the Kaplan Meier method, it was found that most patients with femoral neck fractures died in the first few months after hospitalization regardless of whether they were treated or not. An association between execution of the surgery and a decrease in mortality was found, so when possible, it is necessary to operate. As already evaluated by Simunovic et al.,⁴ it was observed that an early procedure reduces mortality and patients operated after 48 hours, compared to those treated before, had a higher

mortality rate and this association was statistically significant. Similarly, patients operated within 24 and 48 hours, compared to those treated later, benefited from the early surgical procedure with a significant decrease in mortality. This significant association with increased mortality was even more evident in those patients treated after 72 hours. In particular, no significant differences were found within the first months after surgery, while already at six months there was a clear decrease in mortality in patients operated within 72 hours compared to those treated later. This trend is maintained in the same population even at 1, 2, 3 and 4 years after surgery. In addition, patients treated within 48 hours benefited from a further reduction in mortality at 4 years. Therefore, it is strongly recommended operating within 48 hours and mandatory never to exceed 72 hours (Table 11). These findings confirm many other studies published in the literature that report an increase in mortality in patients operated more than 48-72 hours after the fracture.^{2,4,5,36-39}

In several studies, male gender, presence of comorbid medical conditions, advanced age and higher ASA classification are reported as negative prognostic factors after proximal femoral fractures.³⁸

A statistically significant association between male gender and increased mortality was also demonstrated in our study, in accordance with the literature.⁴⁰ However, a drastic reduction in mortality related to this factor has been shown in patients operated within 48 hours. Therefore, it can be assumed that in the case of two equal patients who differ only in gender, it may be appropriate to prioritize the planning of surgery for the male patient.

The analysis of comorbidities has shown that the presence of at least two comorbidities is significantly associated with an increase in mortality. Although it may be necessary or useful to delay surgery to clinically stabilize patients, excessive delay leads to a significant increase in mortality. It is advisable to operate on these patients within 96 hours from hospitalization to minimize the mortality rate.

The data showed that age is an important factor in the short, medium and long term. Patients older than 75 years, compared to younger ones, had a significant increase in the mortality rate, as also Moran CG et al. demonstrated.⁴⁰ Relating to surgical timing, older age (>75 years) resulted as a negative prognostic factor regardless of the surgical timing as also reported in a recent metanalysis.⁷

In accordance with the literature, ASA class has been an excellent predictor of mortality. A significant association with increased mortality was found for ASA classes 3 and 4 when compared to patients with a lower ASA class. Furthermore, as well as age, ASA class is a direct measure of mortality risk, regardless the surgical timing.

Lastly, our study showed that the anatomic type of femoral neck fracture does not affect mortality and neither did the difference between lateral and medial fractures. Similarly, pre and post-operative hemoglobin values were not relevant in determining patient outcomes.

This study has some limitations. A larger patient population could guarantee a higher statistical value and multiple

creatinine evaluations with cystatin C measurements would allow the use of more accurate equations for CKD staging. The study is based on single detection at hospitalization, which has always been compared with subsequent examinations to validate its truthfulness / accuracy, although this can still be a liability. Sodium levels can be altered not only by glycemia, which has always been evaluated and corrected, but also by other variables such as cholesterol/LDL that instead have not been considered. Univariate analysis was used, it could be useful to perform a multivariate analysis of the data in case of a larger sample size. Our study is also limited by its retrospective design. A longer clinical follow-up would increase the validity of the data and further prospective studies could serve to confirm the results.

In conclusion, this study has observed that, in patients older than 65 years with hip fracture, a surgical timing of less than 48-72 hours has been associated with a significant reduction in mortality. Evidence of that was already significant after six months from hospitalization, underlining the importance of operating within 72 hours to have a reduction of mortality risk at the short/medium term. A surgery performed within 24-48 hours, compared to one performed between 48 h and 72 hours, led to a further reduction in long-term mortality at 4 years. No significant association with a reduction or an increase in mortality was shown for the following variables: pre and post-surgery Hb values, post-surgery hemoglobin differential values, sodium values, calcium values, CKD stages and altered levels of creatinine at hospitalization. On the other hand, this study confirmed the correlation between male gender, older age (>75 years), altered kalemia, comorbid medical conditions, high ASA class and an increased mortality risk in older patients with hip fracture. Negative prognostic factors like age and ASA class did not influence mortality relating to surgical timing. Otherwise, male gender was associated with an increased mortality in patients operated after 48 hours from hospitalization. Patient and surgeon must be aware that altered kalemia values at hospitalization are significantly associated with an increase in mortality. To avoid this specific risk related to hyperkalemia, patients must be operated within 72 hours of admittance. Moreover, two or more comorbidities, compared to patients with not or with only one associated pathology, were related to an increased number of deaths when patients were treated after 96 hours.

List of abbreviation

ASA	American society of anaesthesiologist;
eGFR	estimated glomerular filtration rate;
CKD	chronic kidney disease;
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration;
MDRD	Modification of Diet in Renal Disease;
BIS1	Berline Initiative Study.

Authors' Note

The dataset analyzed during the current study are available from the corresponding author on reasonable request. GEV performed the literature research and drafted the manuscript. FB collected the data and derived the results. AC prepared the Tables. LC designed the study

and proofread the manuscript. All authors read and approved the final manuscript. All patients were informed about the study and gave their consent. All patients gave consent to publication.



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