

Impact of anticoagulants in elderly patients who suffer a hip fracture. Should we have a different approach?

Francisco Lotti¹, Cristina María Elizondo², Jorge Barla¹, Guido Carabelli¹, Maria Liliana Soruco¹, Bruno Rafael Boietti², Javier Alberto Benchimol³

¹Servicio de Ortopedia y Traumatología, Hospital Italiano de Buenos Aires, CABA, Argentina; ²Área de investigación en medicina Interna, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, CABA Argentina; ³Sección de Geriatria, Servicio de Clínica Médica, Hospital Italiano de Buenos Aires, CABA Argentina

Summary. *Introduction:* Hip fracture in the elderly is a frequent problem. Chronic treatment with anticoagulants is common in these patients and may delay surgery. *Objectives:* To compare time to surgery, hospital stay, in-hospital and 90 days complications between anticoagulated and non-anticoagulated groups. *Methods:* Retrospective cohort of >64 years-old patients with acute hip fracture. Period June-2014 to December 2019. We estimated crude and adjusted Odds Ratio (95%CI) for in-hospital complications with logistic regression model. We report the crude and adjusted Hazard Ratio for readmission and 90-days mortality with Cox proportional hazards model. *Results:* Of the 1058 patients, 123 (11%) were anticoagulated. Time to surgery was 26.4 hours (IIQ 13.9-48) in anticoagulated and 24 hours (IIQ 2.3-48) in non-anticoagulated, p 0.001. Hospital stay was 7 days (IIQ 5-9) in anticoagulated and 6 days (IIQ 5-10.5) in non-anticoagulated, p 0,000. In-hospital complications were 17 (14%) in anticoagulated and 81 (9%) in non-anticoagulated, p 0.064. The adjusted OR was 1.53 (95%CI 0.8-2.7) p 0.138. For 90-days readmission, the crude HR was 1.51 (95%CI 0.99-2.29) p 0.053 and the adjusted HR was 1.31 (95%CI 0.85-2.00) p0,09. For 90-days mortality, the crude HR was 0.80 (95%CI 0.45-1.43) p 0.464 and the adjusted HR was 0.70 (95% CI 0.39-1.25) p 0.239. *Discussion:* While we found differences between groups in time to surgery and hospital statistics these differences may not be clinically relevant. (www.actabiomedica.it)

Key words: hip fracture, elderly, anticoagulants

Introduction

Hip fracture is a frequent injury in elderly persons. Only in the United States, there are 250,000 new cases per year (1). This condition is associated with increased disability and mortality rate per year that can reach up to 36% (2). Hip fracture occurs in a comorbid, generally polymedicated, frail elderly population with greater probability of complications after the event (3-5).

In this context, a percentage of these patients are treated with anticoagulants. The proportion of patients who receive treatment with warfarin is approximately 10% (between 7.8% and 10.3%) (6-8). The most com-

mon indication for warfarin in this group is atrial fibrillation (83%), followed by thromboembolic disease (18%) and a mechanical heart valve (5%); in about 7% with multiple indications (9).

The time-to-surgery delays ranging from 12 to 62 hours among anticoagulated and non-anticoagulated patients with hip fracture (10-13). This leads to increased hospital stay. In some studies the increase is from 11 to 14 days (12) or from 5 to 8 days (14) of hospitalization, and to generate greater chances of both clinical complications (urinary tract infections, respiratory infections, loss of muscle mass and bedsores) and functional complications in the postoperative period (4, 5).

Regarding patients chronically medicated with anticoagulants who suffer a hip fracture, surgery is often delayed until the target International Normalized Ratio (INR) is achieved. In patients who have altered INR values, normalization of the values is expected to take between 96 and 115 hours (15). The British Society for Hematology recommends suspension of warfarin before the surgery and administration of vitamin K to accelerate INR decrease/correction. A value of 1.5 is required before hip surgery so that it can be safely performed (16-19).

We propose to explore the effect of being anticoagulated at the time of a hip fracture and its postoperative results.

Primary objective

To evaluate the association between usual prescription of anticoagulants and surgical delay, hospital stay and postoperative complications during hospitalization and after 3 months in patients with hip fracture included in the RIAFC of Hospital Italiano de Buenos Aires (HIBA).

Secondary objective

To describe outcomes according to the medication used for anticoagulation (acenocumarol, warfarin, enoxaparin and new oral anticoagulants).

Materials and methods

Study Design

A retrospective cohort study of patients with hip fracture was conducted using the RIAFC (20). Period June-2014 to December 2019.

Setting

HIBA is made up of two high-complexity university hospitals, with 679 inpatient beds, and about 42,300 inpatient discharges annually. The medical care provided to patients is centrally recorded in a computerized data repository, including a single electronic medical record per person (21).

Study Population

All patients older than 64 years with acute hip fracture that attended the HIBA were enrolled. Polytrauma, pathological, subtrochanteric, and periprosthetic fractures, or patients who refused to participate in the RIAFC were excluded. This study also excluded patients with acute fracture who were not operated by medical decision. The study patients was divided into two groups: anticoagulated patients (receiving oral or subcutaneous anticoagulation prior to the fracture) (Group A) and non-anticoagulated patients (Group NA).

Data Source:

Data were obtained from the RIAFC and electronic medical record.

Variables evaluated:

- *Demographic and Clinical Characteristics:* age, gender, comorbidities and clinical functional scales, such as Charlson Comorbidity Index, Parker Mobility Scale, Barthel and Lawton indexes.
- *Time to surgery:* time elapsed between hospital admission and definitive surgery, in hours.
- *Surgery Time:* duration of the definitive surgery, in minutes.
- *Nosocomial complications and complications at follow-up:* all the complications developed during surgery and during the first 3 post-operative months were recorded.
- *Days of hospitalization:* the number of hospitalization days, from admittance through the emergency unit to discharge from hospital.

Sampling:

Every patient included in the RIAFC were enrolled prospectively. Anticoagulation characteristics of all the patients were collected, and a standardized assessment of the follow-up at 3 months was conducted for the evaluation of complications.

Statistical Analysis:

Quantitative variables were described as means and standard deviations or median with its interquar-

tile interval according to distribution characteristics. Categorical variables were described as proportion. Comparisons of quantitative variables were carried out with t-test or Mann-Whitney test according to distribution characteristics. Comparisons between categorical variables were performed using the chi-squared or Fisher's test according to assumptions. The risk of complications associated with anticoagulant pretreatment was estimated with a regression logistics model, which was adjusted for potential confounding factors. Odds Ratios (ORs) were reported with 95% confidence intervals (95% CI). To assess the risk of complications at follow-up, a Cox proportional hazard model was used. Crude and adjusted odds ratios (ORs) with 95% confidence intervals are shown.

Results

There were a total of 1058 hip fractures during this period (Flow Chart of patients in figure 1). Eighty-five percent of the patients were female (95% CI 83.45% - 87.70%), with a median age of 86 years (interquartile range 81 - 90). Six hundred and fourteen (58.09%) were extracapsular hip fractures and 444 (41.99%) were

intracapsular hip fractures. One hundred and twenty-three patients were included in Group A (11.72% 95% CI, 9.77% -13,66%). The rest of the patients' characteristics are described in Table 1.

Comparison between anticoagulated and non-anticoagulated patients

The time between hospital admission and surgery measured in hours recorded a median of 24 hours (range of 3.08 - 48 hours). In the anticoagulated group, the time was two hours more than in the non-anticoagulated group. Global inpatient stay was a median of 6 days (range of 5-9). The stay in both groups was different. The anti-coagulated group recorded a median of one more day (see Table 2).

Seventeen (13.82%) and 81 (8.67%) nosocomial complications were recorded in Group A and Group NA, respectively ($p = 0.064$). Table 3 describes the nosocomial complications group, showing differences in the atrial fibrillation (AF) event in the anti-coagulated group and thromboembolic disease (TE) in the non-anticoagulated group.

The risk of nosocomial complication associated with the anticoagulated group had an OR of 1.69 (95% CI 0.96-2.96 $p = 0.066$). The OR adjusted for age, gender, CCI > 2, and frailty was 1.53 (95% CI 0.87-2.71 $p = 0.138$).

Five (4.07%) and 13 (1.41%) hospital deaths were recorded in the anticoagulated and non-anticoagulated groups, respectively ($p = 0.033$). The crude OR was 3.01 (95% CI 1.05-8.60 $p = 0.039$), while the OR adjusted for age, gender, Charlson Comorbidity Index (CCI) >2, and frailty was 2.46 (95% CI 0.84-7.17 $p = 0.099$).

In the follow-up at 90 days there was no difference between both groups with regard to readmissions. There were 27 (22.58%) and 145 (15.42%) readmissions in Group A and Group NA, respectively ($p = 0.069$).

The free estimate of readmission at 90 days was 75.08% (95% CI 66.15 - 81.97%) in the anticoagulated patients and 83.32% (95% CI 80.72 - 85.60%) in non-anticoagulated patients. Kaplan-Meier free estimate of readmission is shown in Figure 2. The crude OR for readmissions at 90 days was 1.51 (95% CI 0.99-2.29

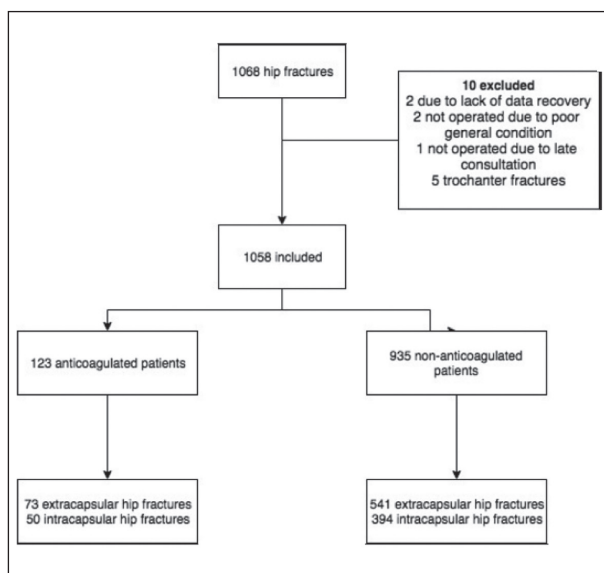


Figure 1. Flow chart of patients with hip fracture included in the Registry of Elderly with Hip Fracture during June-2014 to December 2019 period

Table 1. Baseline characteristics of hip fracture patients included in the Institutional Registry of Elderly with Hip Fracture according to anticoagulation group during June-2014 to December 2019 period (n = 1058)

Characteristics	Anticoagulated patients n=123	Non-anticoagulated patients n=935	p-value
Age*	87 (84-89.5)	85 (80- 90)	0.006
Female	84.68 (105)	85.76 (801)	0.747
Hypertension	87.90 (109)	76.85 (719)	0.005
Dementia	17.60 (22)	23.95 (223)	0.124
Kidney Failure	20.16 (25)	7.74 (72)	0.000
Chronic Lung Disease	8.87 (11)	7.52 (70)	0.595
Stroke	20.00 (25)	76.85 (83)	0.000
Diabetes	13.71 (17)	9.85 (92)	0.184
Depression	20.16 (25)	25.81 (240)	0.173
Atrial Fibrillation	67.94 (83)	8.26 (77)	0.000
Nursing Home	9.68 (12)	10.08 (107)	0.548
CCI ≥ 2	41.13 (51)	26.98 (252)	0.001
Barthel ADL-dependent (<100)	57.26 (71)	48.93 (457)	0.081
Lawton IADL-dependent (<8)	68.55 (85)	56.21 (525)	0.009
Canadian Frailty Scale >4	57.26 (71)	46.04 (430)	0.019
Polypharmacy (≥ 5 medications)	72.58 (90)	50 (467)	0.000
Intracapsular Fracture	40.32 (50)	42.12 (393)	0.703
Extracapsular Fracture	59.68 (73)	57.88 (541)	
Parker Basal*	6 (4-9)	7 (4-9)	0.014

*Median (interquartil range), percentage (n)

ADL: Activities Daily Living

IADL: Instrumental Activities Daily Living

CCI: Charlson Comorbidity Index

p = 0.053), and the HR adjusted for age, gender, CCI >2, frailty and nosocomial complication was 1.31 (95% CI, 0.85-2.00 p = 0.209).

In the follow-up at 90 days there was no difference between both groups with regard to survival. There were 13 (10.48%) and 121 (12.96%) deaths in groups A and NA, respectively. The survival rate was 91.73% (95% CI 85.18-95.46) and 95.00% (95% CI 93.35-96.26) for Group A and Group NA, respectively. Kaplan-Meier survival curve is shown in Figure 3.

The crude HR was 0.80 (95% CI 0.45-1.43 p = 0.464) for death associated with anticoagulation, and the HR adjusted for age, gender, CCI >2, frailty and

nosocomial complication was 0.70 (95% CI 0.39-1.25 p = 0.239).

Group A was mostly treated with Acenocoumarol 106 (85%) followed by Dabigatran 6 (4.80%), Enoxaparin 4 (4%), Warfarin 4 (3.2%) and Apixaban 2 (2.40%). INR of admission recorded a median of 2.23 (interquartile interval 1.56-3.01) and the pre-operative INR was 1.45 (interquartile interval 1.33-1.78).

Regarding the 123 fractures in Group A, only in 61 cases it was necessary to use some type of reversal: 43 (34.68%) with vitamin K, 5 (4%) with fresh frozen plasma, and 12 (9.6%) with clotting factors. In addition, we used a second reversal agent in 9 patients

Table 2. Nosocomial surgical characteristics of patients with hip fracture included in the Institutional Registry of Elderly with Hip Fracture according to anticoagulation group during June-2014 to December 2019 Period June-2014 to December 2019 (n = 1058)

Surgical Characteristics	Anticoagulated patients n=123	Non-anticoagulated patients n=935	p-value
Time to surgery from hospitalization (hours)*	26.3 (13.9-48)	24.0 (2.3-48)	0.001
Surgical time (minutes)*	41.5 (30-60)	50.0 (35-60)	0.015
Days of Hospitalization*	7.0 (5-10.5)	6.0 (5-9)	0.000
Red Blood Cell Transfusion	52.9 (65)	32.5 (300)	0.000
Post-operative Closed Unit	18.6 (23)	7.5 (70)	0.000

*Median (interquartil interval), percentage (n)

Table 3. Nosocomial complications of patients with hip fracture included in the Institutional Registry of Elderly with Hip Fracture according to anticoagulation group during June-2014 to December 2019 period (n = 98)

Nosocomial complication n=98	Anticoagulated patients n=17	Non-anticoagulated patients n=81	p-value
Infection	10 (50)	30 (37.0)	0.288
Acute Kidney Failure	2 (10)	16 (19.8)	0.514
Stroke	1 (5)	2 (2.47)	0.488
Acute Myocardial Infarction	1 (5)	1 (1.2)	0.358
Flare-up or New Atrial Fibrillation	7 (41.2)	10 (12.4)	0.004
Bleeding in Digestive Tract	2 (10)	2 (2.5)	0.175
Thromboembolic Disease	1 (5)	24 (29.7)	0.041
Prosthetic Loosening	-	2 (2.5)	-
Periprosthetic Fracture	-	-	-

n (percentage)

(4 with fresh frozen plasma and 5 with clotting factors).

The description of anticoagulant groups defined three groups of Acenocoumarol and Warfarin (Group 1), Enoxaparin (Group 2) and New Oral Anticoagulants (Group 3). There were no differences between time to surgery, requirement of transfusions or nosocomial complications among the different anticoagulant groups. These are described in Table 4.

Discussion

In our study, the total number of anticoagulated patients with hip fracture (11.72%) is similar to other reports that show figures from 7.8% to 10.3% (8). The mean age of our population is 87 years old, thus the anticoagulated patients are almost two years older than non-anticoagulated patients. In other publications the anticoagulated population with hip fracture was

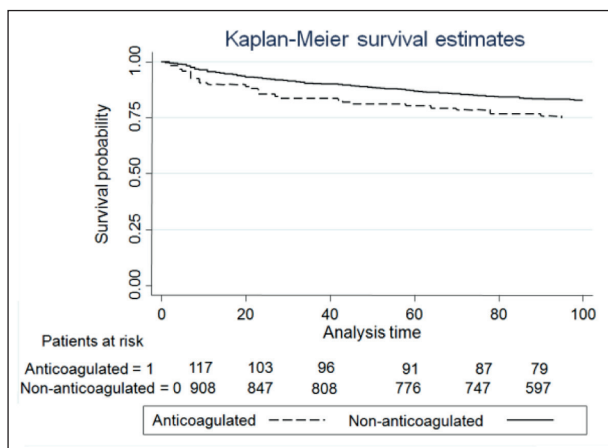


Figure 2. Kaplan Meier. Reinternation at 90 days of hip fracture patients included in the Institutional Registry of Elderly with Hip Fracture according to anticoagulation group during June-2014 to December 2019 period (n = 950)

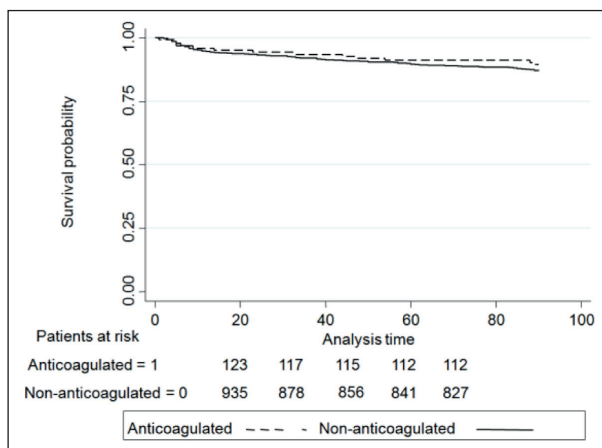


Figure 3. Kaplan Meier. Mortality at 90 days of hip fracture patients included in the Institutional Registry of Elderly with Hip Fracture according to anticoagulation group during June-2014 to December 2019 period (n = 950)

Table 4. Global and 90-day complication of patients with hip fracture included in the Institutional Registry of Elderly with Hip Fracture according to anticoagulant group during June-2014 to December 2019 period (n = 123)

Characteristics	Group 1 n=110	Group 2 n=4	Group 3 n=9	p-value
Time to surgery (hours)*	24 (13.7-48)	48 (0-48)	48 (26.7-72)	0.192
Stay (days)*	7 (5-11)	6 (5-6)	9 (6-9)	0.428
Nosocomial Complication	15.5 (17)	20 (1)	22.2 (2)	0.587
Inpatient Red Blood Cell Transfusion	54.1 (59)	60 (3)	33.3 (3)	0.512
Intensive Care Requirement	20 (22)	0	11.1 (1)	0.735

*Median (intercuartil interval)
Percentage (n)

younger and with less percentage of female patients (6, 14).

We have noticed no differences in the condition of geriatric frailty or in the place of residence between the two populations (anticoagulated vs. non-anticoagulated) under analysis. The anticoagulated population has greater blood vessel diseases (chronic kidney failure, stroke and atrial fibrillation) and greater Charlson Comorbidity Index. These findings could be demonstrating the frailty difference between both populations over the fact of anticoagulation as the only factor to be taken into account for decision making in terms of surgical intervention and post operative care.

The anticoagulant agents more frequently used in our series were vitamin K antagonists (88.2% Acenocoumarol and Warfarin). Although new anticoagulants are becoming more popular we were not able to find any difference due to the small number of patients under these drugs. This could relate to the contra indication for their use in this population (Chronic kidney failure as an example)

Time from admission to surgery and hospital stay between the two groups is statistically higher in the first group; however, we believe it is not clinically significant. These findings are in line with the study by Cohn et al (14), where the time of admission to sur-

gery (47 vs 30 hours) and hospital stay (8 vs 5 days) were evaluated and found to be statistically higher in the anticoagulated group. Even though more requirements of postsurgical care in critical care units and transfusion of red blood cells are demanded when both groups are compared, we found no differences in nosocomial complications.

The group of anticoagulated patients with hip fracture has not recorded more nosocomial complications. During the baseline analysis, this group recorded greater in-hospital mortality; however, after adjusting the value for Charlson score, frailty, and age, this significant difference disappears. Gleason et al (7), evaluated 84 fractures in anticoagulated patients reporting a mortality of 4.8%, similar to the percentage reported by Cohn et al (14) -4.34%. In our study, the anticoagulated group recorded similar in-hospital mortality while the non-anticoagulated group recorded a lower rate of in-hospital mortality, although this might be probably associated with comorbidities, since the difference in risk disappears after the rate is adjusted for confounding factors.

With regard to survival and readmissions at 3 months we found no difference between both groups.

In the group of anticoagulated patients, there were no differences between time to surgery, requirement of transfusions or nosocomial complications among the different anticoagulant groups.

Conclusion

Although we found differences between both groups with respect to time to surgery and hospital stay, these differences may not be clinically relevant for decision making. When we have to deal with a comorbid population in need of anticoagulation, the fact of being anticoagulated does not imply greater risk of complications or mortality after undergoing surgery for hip fracture.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. NHDS - National Hospital Discharge Survey Homepage [Internet]. 10 Jan 2018 [cited 10 May 2018]. Available: <http://www.cdc.gov/nchs/nhds/index.htm>
2. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int*. 2009;20: 1633-1650.
3. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive Impairment, Drug Use, and the Risk of Hip Fracture in Persons over 75 Years Old: A Community-based Prospective Study. *Am J Epidemiol*. 1998;148: 887-892.
4. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a Predictor of Surgical Outcomes in Older Patients. *J Am Coll Surg*. 2010;210: 901-908.
5. Wolinsky FD, Fitzgerald JF, Stump TE. The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. *Am J Public Health*. 1997;87: 398-403.
6. Eardley WGP, Macleod KE, Freeman H, Tate A. "Tiers of delay": warfarin, hip fractures, and target-driven care. *Geriatr Orthop Surg Rehabil*. 2014;5: 103-108.
7. Gleason LJ, Mendelson DA, Kates SL, Friedman SM. Anticoagulation management in individuals with hip fracture. *J Am Geriatr Soc*. 2014;62: 159-164.
8. Tran T, Delluc A, de Wit C, Petrich W, Le Gal G, Carrier M. The impact of oral anticoagulation on time to surgery in patients hospitalized with hip fracture. *Thromb Res*. 2015;136: 962-965.
9. Lawrence JE, Fountain DM, Cundall-Curry DJ, Carrothers AD. Do Patients Taking Warfarin Experience Delays to Theatre, Longer Hospital Stay, and Poorer Survival After Hip Fracture? *Clin Orthop Relat Res*. 2017;475: 273-279.
10. Bansal R, Watson DK. Surgical delay in acute admissions on warfarin: are we doing enough? *Int J Clin Pract*. 2005;59: 1283-1288.
11. Ashouri F, Al-Jundi W, Patel A, Mangwani J. Management of warfarin anticoagulation in patients with fractured neck of femur. *ISRN Hematol*. 2011;2011: 294628.
12. Ranhoff AH, Martinsen MI, Holvik K, Solheim LF. Use of Warfarin is Associated with Delay in Surgery for Hip Fracture in Older Patients. *Hosp Pract*. 2011;39: 37-40.
13. Bathia N, Malanga G. Ultrasound-guided aspiration and corticosteroid injection in the management of a paralabral ganglion cyst. *PM R*. 2009;1: 1041-1044.
14. Cohn MR, Levack AE, Trivedi NN, et al. The Hip Fracture Patient on Warfarin: Evaluating Blood Loss and Time to Surgery. *J Orthop Trauma*. 2017;31: 407-413.
15. White RH, Minton SM, Andya MD, Hutchinson R. Temporary reversal of anticoagulation using oral vitamin K. *J Thromb Thrombolysis*. 2000;10: 149-153.
16. Gidwani S, Davidson N, Trigkilidas D, Blick C, Harborne R, Maurice HD. The Detection of Patients with "Fragility Fractures" in Fracture Clinic - An Audit of Practice with Reference to Recent British Orthopaedic Association Guidelines. *Ann R Coll Surg Engl*. 2007;89: 147-150.
17. Al-Rashid M, Parker MJ. Anticoagulation management

- in hip fracture patients on warfarin. *Injury*. 2005;36: 1311-1315.
18. Kearon C, Hirsh J. Management of Anticoagulation before and after Elective Surgery. *N Engl J Med*. 1997;336: 1506-1511.
19. Jaffer AK, Brotman DJ, Chukwumerije N. When patients on warfarin need surgery. *Cleve Clin J Med*. 2003;70: 973-984.
20. Benchimol J, Fiorentini F, Elizondo CM, et al. Institutional Registry of Elderly Patients With Hip Fracture in a Community-Based Tertiary Care Hospital in Argentina (RIAFC). *Geriatr Orthop Surg Rehabil*. 2016;7: 121-125.
21. Website [Internet]. [cited 10 May 2018]. Available: (<https://www1.hospitalitaliano.org.ar/#!/home/hospital/seccion/20507>)

Received: 24 October 2019

Accepted: 10 December 2019

Correspondence:

Cristina María Elizondo

Calle Pte. Perón 4190,

AC1181, Ciudad Autónoma de Buenos Aires, Argentina.

E.mail: cristina.elizondo@hospitalitaliano.org.ar