Title: Mortality, Perioperative complications and surgical timelines in hip fracture patients: Comparison of the Spanish with the non-Spanish Cohort of the HIP ATTACK-1 trial

Authors: Ernesto Guerra-Farfán [a, b, c], Flavia K. Borges [d, e, f], Mohit Bhandari [g], Yaiza Garcia-Sanchez [a, h], Jorge H. Nuñez [c, i], Jaume Mestre-Torres [j], Jordi Tomas-Hernandez [a], Jordi Teixidor-Serra [a], Mariano Balaguer-Castro [k, l], Pablo Castillón [i], Alfred Dealbert [m], Julio De Caso Rodriguez [n], Hector J. Aguado [o], Enrique Guerado [p], Ekaterine Popova [n], Ana Claudia Tonelli [q], Kumar Balasubramanian [e], Jessica Vincent [e], Valerie Harvey [e], Etri Kocaqi [r], Gerard Slobogean [s] ,PJ Devereaux [e, f], HIP ATTACK-1 Investigators.

Institutional affiliation:

a. Department of Orthopaedic Surgery and Traumatology, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
b. Departament de Cirurgia, Universitat Autònoma de Barcelona, Barcelona, Spain.
c. Department of Orthopaedic Surgery and Traumatology, Artro-Esport, Centro Médico Teknon, Barcelona, Spain.
d. Department of Medicine, McMaster University, Hamilton, Ontario, Canada.
e. Population Health Research Institute, Hamilton, Ontario, Canada.
f. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada.
g. Department of Surgery, McMaster University, Hamilton, Ontario, Canada.
h. Department of Orthopaedic Surgery and Traumatology, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain
i. Department of Orthopaedic Surgery and Traumatology, University Hospital of Mutua de Terrassa, Terrassa, Barcelona, Spain.
j. Department of Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
k. Department of Orthopaedic Surgery and Traumatology, Parc Taulí Hospital Universitari, Sabadell, Barcelona, Spain.
l. Department of Orthopaedic Surgery and Traumatology, Hospital Clínic Barcelona, Barcelona, Spain.

m. Department of Orthopaedic Surgery and Traumatology, Consorci Sanitari Del Garraf, Barcelona, Spain.
n. Biomedical Research Institute, (IIB Sant Pau), Hospital de la Santa Creu i Sant Pau, Barcelona Spain.
o. Department of Orthopaedic Surgery and Traumatology, Hospital Clínico Universitario de Valladolid, Valladolid, Spain.
p. Department of Orthopaedic Surgery and Traumatology, Hospital Universitario Costal Del Sol, Medical School. University of Málaga, Marbella, Málaga, Spain.
q. Internal Medicine Service, Hospital de Clinicas de Porto Alegre (HCPA), Brazil.
r. Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada.
s. R Adams Cowley Shock Trauma (STC) at the University of Maryland Medical Center's Division of Orthopaedic Traumatology, Baltimore, US.

Corresponding author:

Yaiza Garcia-Sanchez

Department of Orthopaedic Surgery and Traumatology, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain

E-mail: yaiza.garcia@vhir.org

Telephone number: +34 934 89 34 88

Fax number: 934 89 30 00

ORCID: 0000-0003-0894-1721

ABSTRACT

Background: Hip fractures carry a substantial risk of complications and death. This study aimed to report the 90-day incidence of mortality, major perioperative complications and in-hospital timelines after a hip fracture in the Spanish HIP ATTACK-1 trial cohort, comparing with the non-Spanish cohort.

Methods: Prospective cohort study of Spanish patients nested in the HIP ATTACK-1 trial. The HIP ATTACK-1 was an international, randomized, controlled trial (17 countries, 69 hospitals, 7 in Spain, highest recruiting country). Patients were randomized to either accelerated surgery (goal of surgery within 6 hours of diagnosis) or standard care. Participants were ≥45 years of age who presented with a low-energy hip fracture requiring surgery.

Results: Among 534 patients in the Spanish cohort, 69 (12.9%) patients died at 90 days follow-up, compared to 225 (9.2%) in the non-Spanish cohort (p=0.009), mostly due to higher nonvascular related mortality. A composite of major postoperative complication occurred in 126 patients (23.6%). The most common perioperative complications were myocardial injury (189 patients, 35.4%), infection with no sepsis (86 patients, 16.1%) and perioperative delirium (84 patients, 15.7%); all these complication rates in Spain were significantly higher than the non-Spanish patients (29.2% p=0.005; 11.9% p=0.008 and 9.2% p<0.0001, respectively). Spanish cohort patients were older and had more comorbidities than the non-Spanish cohort, evidencing their greater frailty at baseline. Among Spanish patients, the median time from hip fracture diagnosis to surgery was 30.0 hours (IQR 21.1-53.9) in the standard-care group, with 68.8% of patients receiving surgery within 48 hours of diagnosis. This median time was lower in the non-Spanish cohort (22.8 hours, IQR 9.5-37.0), where 82.1% of patients were operated within 48 hours.

Conclusions: In the HIP ATTACK-1 trial, 1 in 8 patients died 90 days after a hip fracture in Spain. The most common complication after a hip fracture was myocardial injury, followed by infection and delirium. Spanish patients had worse outcomes than non-Spanish patients. Research needs to focus on new interventions such as accelerated surgery and perioperative troponin measurement with the appropriate investment of resources, to prevent and identify early these complications with a goal of improving mortality for this high-risk population.

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Level of evidence: II

Key words: Hip fracture; Surgical Procedure; Accelerated; Mortality; Perioperative Complications; Surgical Timelines; Medical Outcomes.

Introduction

Hip fractures primarily occur in the elderly population and present an ever-growing healthcare challenge. Hip fractures carry a substantial risk of major complications, including vascular, infectious, and neurocognitive deficits [1-4]. Mortality rates are unacceptably high, around 7-10% at 30 days, and 10-20% at 90 days [5,6]. In Spain, there are approximately 40,000 to 45,000 hip fractures per year, with an annual cost of >1,590 million euros and a loss of >7,200 quality-adjusted life-years [7,8]. Spain's elderly population continues to grow as life expectancy will exceed 85 years for both sexes by 2040 [9]. Moreover, as incidence of hip fractures increases with age, hip fractures and their associated complications are expected to continue rising for years to come. Therefore, a better understanding of perioperative complications and their impact is key for optimization and standardization of care.

In Spain, several registries and multicentre studies have previously reported incidence and complications of hip fractures. These results are briefly summarized in supplemental Table 1. Due to a lack of standardized monitoring, cardiovascular complications are frequently under reported. Despite this, cardiovascular complications were 5-fold more common than venous complications [10]. No single study has comprehensive reported vascular complications in a cohort of hip fracture patients who have had serial troponin measurements after surgery to identify perioperative myocardial injury, an important perioperative complication strongly associated with mortality [11]. Additionally, time to perform surgery is an important benchmark to reflect quality of care in this population. The International Fragility Fracture Network [12] recommends surgery should be facilitated within 48 hours of hip fracture. More recently, 2020 hip fracture European guidelines, proposed even faster timelines (i.e., 36 hours); however, guideline recommendations are generally slow to translate into clinical practice [13].

The HIP ATTACK-1 Trial was an internationally trial comparing accelerated surgery to standard care that systematically monitored and followed patients for complications after surgery. Spain was the highest recruiting country. We undertook analyses using the HIP ATTACK-1 data to inform timelines to surgery and outcomes for Spanish patients and to compare these results with the non-Spanish patients.

Materials and Methods

Design, source of study population and study procedure

Overall, the HIP ATTACK-1 trial recruited 2970 surgical hip fracture patients, in 69 hospitals in 17 countries. The HIP ATTACK-1 Spanish subgroup is a prospective cohort study of 534 patients recruited across 7 Spanish sites (supplemental Table 2). Detailed descriptions of the study design, recruitment strategy and methods have been previously reported [14]. Briefly, eligible patients were aged 45 years or older, diagnosed during regular working hours with low-energy mechanism hip fracture that required surgery, and provided informed consent. Exclusion criteria included receiving a therapeutic dose of an anticoagulant with no reversal agent; those with a peri-prosthetic, open fracture, or bilateral fracture; history of heparin-induced thrombocytopenia taking a therapeutic dose of vitamin K antagonist; requiring emergency surgery; refusing participation; or previously enrolled in the HIP ATTACK-1 trial. Recruitment ran between March 14, 2014, and May 24, 2019. All eligible patients were randomly assigned (1:1) to either accelerated surgery (i.e., goal of surgery within 6 hours of orthopedic diagnosis) or standard care (usual standard timelines to perform surgery accordingly to local practices in each site). All participants received the same structured follow-up including: daily troponin and creatinine measurements up to day 7 after randomization; delirium and pain assessment for the first 7 days post-randomization; daily follow-up for trial outcomes till hospital discharge, follow-up 30 days and 90 days post-randomization to determine if any trial outcomes occurred. A group of independent expert physicians with experience in perioperative care performed blinded adjudication of trial outcomes.

Data Collection

Data was collected at the time of admission, throughout hospitalization, and at 30- and 90-day follow-up post-randomization. Details about data collection procedure have been previously reported [14]. In summary, it included details of patients' baseline characteristics and acute or newly diagnosed medical conditions. In-hospital variables included main timelines (i.e., hip fracture to Emergency Room (ER) arrival, ER arrival to X-ray, X-ray to orthopaedic diagnosis, orthopedic diagnosis to medical clearance, orthopedic diagnosis to surgery start), proportion of patients with baseline troponin measurements pre-randomization (as per site discretion), and proportion of patients with baseline troponin elevation.

Incidences of primary, secondary, and tertiary outcomes (outlined below) were collected prospectively as per the previously outlined protocol [14].

Ethics

Before commencing recruitment, all sites obtained local ethical approval, and the relevant health authorities approved the protocol. All participants provided consent to participate before enrollment, either by direct permission, or via legal representative. The HIP ATTACK-1 Trial is registered at ClinicalTrials.gov (NCT02027896) [15].

Outcomes

The two co-primary outcomes were mortality and major perioperative complications (i.e., a composite of all causes of mortality, non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, and major bleeding) at 90 days post-randomization in the Spanish population, as well as their comparison with the non-Spanish cohort. In-hospital timelines were also included as a primary outcome. Secondary outcomes were vascular mortality, non-vascular mortality, myocardial injury after randomization not meeting the third universal definition of myocardial infarction [16], myocardial infarction, congestive heart failure, new clinically important atrial fibrillation, types of infection, major bleeding, life-threatening bleeding, delirium within 7 days post-randomization, pressure ulcer at discharge, stroke, proximal deep venous thrombosis and pulmonary embolism, as stated in the HIP ATTACK-1 Trial [10]. We also compared the mortality and complication rates between patients who performed open reduction and internal fixation versus patients who performed arthroplasty in the Spanish cohort. Overall vascular death was defined as any death with a vascular cause (i.e. deaths following a myocardial infarction, cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death was defined as any death due to a clearly documented non-vascular cause (e.g. infection, malignancy, trauma). Tertiary outcomes and definitions are available in the supplemental appendix 2 and supplemental table 3.

Statistical Analysis

Statistical analyses were performed in SAS® using version 9.4 and statistical significance was set at $p<0.05$. Descriptive statistics were used to describe the baseline, in-hospital characteristics and all primary, secondary, and tertiary binary outcomes that have an event date. Standard methods were applied to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Summaries of continuous variables and continuous outcomes included the number of subjects (N), mean, and standard deviation, median, 25th and 75th percentiles. The categorical data and categorical outcomes were presented as frequency distributions (N and %). Primary statistical analyses were based on adjudicators' decision. Event rates for the primary outcome in the Spanish group and for the non-Spanish cohort were estimated and plotted over time using Kaplan-Meier methodology and compared between the groups using log-rank test. For the primary composite outcomes (i.e., major perioperative complications) the cumulative incidence function (CIF) was utilized, which accounts for the competing risk, as per Fine and Gray. All efforts were made to collect complete data for all patients in the study. Missing data were treated as 'missing', and only observed values were used for analysis. All participants were censored on their last day of available contact during the study. All patients completed follow-up for the analysis of our primary endpoint (0% lost to follow-up).

Results

In total, 534 patients were enrolled in the Spanish cohort. Baseline characteristics and details of surgery are described in Table 1. Participants mean age was 83.9 years (SD 8.9), 390 (73%) were women, 301 (56.4%) needed help with activities of daily living (ADL), and 132 (24.7%) lived in a nursing home before their fracture. Hypertension (70.2%), dementia (30.9%), diabetes (23.8%), and osteoporosis (17.6%) before the fracture were the most common comorbidities. The most frequent types of fractures were intertrochanteric in 296 patients (55.4%) and femoral neck in 212 patients (39.7%). Open reduction and internal fixation in 341 patients (63.9%) and arthroplasty in 190 patients (35.6%) were the most prevalent surgical procedures. Fifteen new diagnosed medical conditions out of 534 participants (2.8%) were reported from hip fracture to randomization for the Spanish cohort, of which only 3 (<1%) were cardiac events (1 acute myocardial infarction with mechanical complication/ST elevation, 1 new acute congestive heart failure, and 1 new atrial fibrillation). Among the 244 patients in whom troponin was measured at hospital admission, 68 (27.9%) had an elevated baseline troponin.

The median time from hip fracture to hospital arrival was 1.6 hours (IQR 1.0-2.5) and ER arrival to diagnosis was 0.9 hours (IQR 0.6-1.3) in the Spanish cohort. The median time from hip fracture diagnosis to medical clearance was 2.9 hours (IQR 1.8-5.0) in the standard-care group of the Spanish cohort, in contrast to a median of 4.2 hours (IQR 2.0-15.0) for the standard-care group of the non-Spanish cohort. Among Spanish patients, the median time from hip fracture diagnosis to surgery start was 30.0 hours (IQR 21.1-53.9) for the standard-care group, with 68.8% of patients receiving surgery within 48 hours of diagnosis. For the standard-care group of the non-Spanish cohort, the median time from hip fracture diagnosis to surgery was lower, 22.8 hours (IQR 9.5-37.0), than in Spain, and 82.1% of patients were operated on within 48 hours from hip fracture diagnosis (Table 2).

Sixty-nine (12.9%) patients died at 90-day follow-up in the Spanish cohort, compared to 225 patients (9.2%) who died in the non-Spanish cohort (p=0.0098) (Figure 1). Among patients with baseline troponin elevation, 15/68 (22%) patients died within 90 days. The cause of death in Spanish patients was vascular (50.7%) and non-vascular mortality (49.3%). Non-vascular mortality accounted for more deaths in Spain than centres outside of Spain (6.4% vs 3.7%, p=0.0044) (Table 3). Infection was the most prevalent cause of non-vascular mortality, suffered by 20 of the deceased Spanish patients (29.0%) (Table 4).

A composite of major postoperative complication occurred in 126 patients (23.6%) in the Spanish cohort (Figure 2). The most common perioperative complications were myocardial injury (189 patients, 35.4%), followed by infection with no sepsis (86 patients, 16.1%) and perioperative delirium (84 patients, 15.7%). These three major complications were significantly higher in the Spanish population than in the non-Spanish cohort (29.2% p=0.0050, 11.9% p=0.0089 and 9.2% p<0.0001, respectively). The most common types of infection in the Spanish cohort were urinary tract infection (52 patients, 9.7%), upper respiratory tract infection (27 patients, 5.1%) and pneumonia (25 patients, 4.7%) (Supplemental Table 4). Additionally, more patients had sepsis, congestive heart failure and suffered a surgical site infection post-operatively in the Spanish cohort (7.1%, 3.9% and 3.0%, respectively) than in the non-Spanish group (4.2%, 1.7% and 1.5%, respectively) (p=0.0045, p=0.0010 and p=0.0154, respectively). At discharge, patients in the Spanish cohort developed more pressure ulcers (32 patients, 6.0%) as opposed to the non-Spanish patients (57 patients, 2.3%, p<0.0001) (Table 3). Mortality and complication rates were similar between

patients who performed open reduction and internal fixation versus patients who performed arthroplasty (Supplemental Table 5).

In Spain, at time of hospital discharge or at 30-day post-admission, one in three patients had a nursing home as a new residence (30.5%), while 11.7% of non-Spanish patients were newly admitted to a nursing home at that time. The first 3 days post hip fracture admission, lower percentage of Spanish patients had moderate to severe pain (>=3 out of 10 on pain scale) than the non-Spanish patients (Supplemental Table 6).

For tertiary clinical outcomes in the Spanish cohort, 66 patients (12.4%) required hospital readmission compared to 9.7% (237 patients) of patients in the non-Spanish cohort (p=0.08). Spanish population had 25 patients (4.7%) that required a hip re-operation, and 13 patients (2.4%) suffered a prosthetic hip dislocation. This was significantly different to the non-Spanish cohort with 46 patients (1.9%) needing a hip re-operation (p=0.0001) and 14 patients (0.6%) experienced a prosthetic hip dislocation (p<0.0001). Patients' first mobilization since surgery completion was 21.7 hours (IQR 18.3-37.9) in Spain, while non-Spanish patients were first mobilized at 19.4 hours (IQR 15.0-24.7) since the end of surgery. The median time from surgery to hospital discharge was 8.0 days (7.0- 11.0) in the Spanish cohort, one day longer than the median non-Spanish length of hospital stay (Supplemental Table 7 and 8).

Discussion

This is the first large prospective cohort study in the Spanish population, reporting in detail surgical timelines and the incidence of 90-day mortality and major perioperative complications after a hip fracture with prospective data collection, including active monitoring for perioperative myocardial injury. We observed that 1 in 8 patients died 90 days after a hip fracture in Spain. This is significantly higher than the HIP ATTACK-1 non-Spanish cohort, where 9.2% patients died at 90 days compared to 12.9% in Spain, mostly due to higher nonvascular mortality (6.4% versus 3.7%; p=0.0044).

We also found that, among 244 patients with an available troponin measurement at hospital arrival, 27.9% had a baseline myocardial injury, identified by a troponin elevation. However, only 3 patients presented to the hospital with new acute symptomatic cardiac conditions. The low incidence of new acute

symptomatic cardiac conditions at hospital presentation indicates that new cardiac events are unlikely to be the reason of the fall resulting in hip fracture in this cohort. Additionally, more than a third of patients (35.4%) experienced new myocardial injury after randomization. Myocardial injury was by far the most common perioperative complication [17], not reported in most hip fracture cohorts. The incidences of myocardial infarction and stroke in our cohort were comparable to previously reported rates [18]. Cardiovascular events were several times more common than venous events (only one patient had venous thromboembolism), likely due to early mobilization and adherence to standard venous thromboembolism prophylaxis. Thomas et al found that 1 in 8 orthopaedic patients had myocardial injury within 30 days after noncardiac surgery, and it was associated with a higher mortality rate regardless of symptoms [17]. In our study, 1 in 3 patients had myocardial injury within 90 days after randomization. Thomas' et al study included mostly elective surgeries, which explains the lower incidence of perioperative myocardial injuries, as compared with our cohort of acute hip fracture patients undergoing urgent surgery. Based on these results, perioperative troponin measurements should be assessed in all hip fracture patients because most myocardial injuries (>80%) are asymptomatic and would go undetected without routine measurements. Moreover, they carry a poor prognosis. In the HIP ATTACK-1 trial patients with preoperative troponin elevation had a 3-fold increase in mortality compared to patients presenting with normal troponin levels [10].

As for major postoperative complications, infection was the second most frequent complication, followed by perioperative delirium. 1 in 6 patients experienced an infection with no sepsis, and the most common types of infection were urinary tract infection (9.7%), upper respiratory tract infection (5.1%), and pneumonia (4.7%). Additionally, 7.1% of patients experienced an infection with sepsis. The rate of infection with sepsis and pneumonia was higher in our cohort than the 0.5% and 0.7%, respectively reported in a prospective cohort study by Blanco et al [18]. This discrepancy may be due to clinical definitions and parameters determined by our rigorous data collection methodology, which may result in a higher detection rate for several postoperative complications. In Spain, a significantly higher percentage of patients suffered infection with (7.1% vs 4.2%; $p = 0.0045$) and without sepsis (16.1% vs 11.9%; $p = 0.0089$), as well a surgical site infection (3% vs 1.5%; $p = 0.0154$), compared to the non-Spanish HIP ATTACK-1 population. Given that infection is the cause of approximately 59% of nonvascular mortality it could be the main factor responsible for the significant increase in this type of mortality compared to the non-Spanish cohort.

Although HIP ATTACK-1 trial had explicit eligibility criteria (e.g., included patients aged 45 years or older diagnosed during regular working hours with a low-energy mechanism hip fracture that required surgery) that were consistently used globally, the Spanish cohort had worse outcomes for almost all medical complications compared to the rest of the world. This difference may be explained by Spanish patients being older, having almost a 3-fold higher history of congestive heart failure, more than twice as much chronic atrial fibrillation, double the baseline incidence of dementia, and having 2 times more hypertension compared to non-Spanish patients. Spanish patients also had twice as many patients requiring assistance with ADLs at baseline, more use of a walking aid and a higher percentage from a nursing home than the non-Spanish cohort at the time of hospital admission. The Spanish hip fracture patient profile was much more medically and functionally frail than the non-Spanish cohort, which may have resulted in a greater number of medical complications and higher mortality at 90-day follow-up in the Spanish cohort. According to these circumstances, the implementation of strategies to reduce the incidence of postoperative complications and mortality such as expedited surgery to prevent delirium, urinary tract infections and moderate-to-severe pain, as well as having a faster mobilisation, standing and hospital discharge [10] are strongly recommended.

Timeline of hip fracture management in Spain has evolved over the last decade. Spanish National Hip Fracture Registry (RNFC) was established in 2017, the year in which only 40% of hip fractures were operated on in less than 48 hours (median, 62.6 [28.8–96.3] hours), practically double the surgical delay of any other available international established registries [19]. In 2019, the RNFC reported an improvement by almost 7% of Spanish patients operated on in the first 48 hours following a proposal of specific indicators of quality standards to improve healthcare for this type of patients [20-21]. However, this percentage continues to be considerably below the recommended timeframes. In our Spanish cohort, the median time from hip fracture diagnosis to surgery was 30.0 hours (IQR 21.1-53.9) in the standard care group, with 68.8% of patients receiving surgery within 48 hours of diagnosis. This rate was lower than the non-Spanish cohort (82.1%), but higher and far from the previous Spanish reports, which averaged 35-50% (Supplemental Table 1) [22-24]. Numerous clinical practice guidelines recommend surgery in the first 48 hours following a hip fracture to reduce in-hospital, 30-day and 1-year mortality, which is also endorsed by the Spanish Ministry of Health. The proportion of patients operated on within 48 hours from diagnosis in

the accelerated group of the Spanish cohort was 93.6%, comparable to the 93.0% achieved in the accelerated non-Spanish group. The predominant reason for surgical delay (>6 hours from hip diagnosis to surgery) in the accelerated care in Spain was operating room availability, rather than a medical reason to optimize the patient. These findings indicate that it is possible to expedite surgery and adhere to the evidence-based recommended timelines with the appropriate investment of resources by the healthcare system.

Lost to follow-up at 90 days for Spanish cohort was 0%. Our study had certain limitations. The Spanish sites that participated in the trial were selected after a site qualification visit and a detailed feasibility assessment; however, they may not be representative of practice in all community hospitals in Spain, due to the varying organizational and economic resources of each center. Most participants (92%) were recruited in the Catalonia region, precluding comparison with other parts of the country. There may be intra-hospital variability resulting from the unbalanced rate of patient inclusion between sites. Following the approach of HIP ATACK-1 trial, only patients diagnosed during regular working hours were included, which may influence the implementation of accelerated surgery in the hospitals.

In Spain, 1 in 8 patients died 90 days after a hip fracture. The most common complication after a hip fracture is myocardial injury, followed by infection and delirium. Research needs to focus on new interventions, early identification and prevention of these complications to improve mortality in this high-risk population.

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Tables and Figures

Table 1. Baseline characteristics and surgical details of the Spanish and non-Spanish cohorts.

Table 2. Timeline of hip fracture management in the Spanish cohort compared to the non-Spanish cohort.

Table 3. 90-day primary and secondary study outcomes in Spanish population compared to non-Spanish HIP ATTACK-1 cohort.

Table 4. Type of vascular and nonvascular mortality in the Spanish cohort.

Figure 1. Kaplan Meier estimates for the primary outcome Mortality of the Spanish and non-Spanish cohorts.

Figure 2. Kaplan Meier estimates for the primary outcome Composite of Major Complications of the Spanish and non-Spanish cohorts.

446 **Table 1.** Baseline characteristics and surgical details of the Spanish and non-Spanish cohorts
447

	Spanish Cohort n=534 (%)	Non-Spanish Cohort n=2436 (%)
Age (yrs)- Mean (SD)	83.9 (8.9)	77.6 (11.6)
Women	390 (73.0)	1663 (68.3)
Assistance with ADL	301 (56.4)	677 (27.8)
Use of walking aid	290 (54.3)	1006 (41.3)
Current nursing home residence	132 (24.7)	402 (16.5)
History of tobacco use	109 (20.4)	635 (26.1)
Total Pack Years - Mean (SD)	42.4 (29.4)	30.1 (26.5)
History before hip fracture		
Hypertension	375 (70.2)	1449 (59.5)
Dementia	165 (30.9)	357 (14.7)
Diabetes	127 (23.8)	526 (21.6)
Osteoporosis prior to Fracture	94 (17.6)	354 (14.5)
COPD	66 (12.4)	213 (8.7)
Congestive Heart Failure	64 (12.0)	119 (4.9)
Chronic Atrial Fibrillation	53 (9.9)	108 (4.4)
Previous Hip Fracture	50 (9.4)	165 (6.8)
Stroke	47 (8.8)	207 (8.5)
Active Cancer	39 (7.3)	104 (4.3)
Infection within 3 months	34 (6.4)	142 (5.8)
Myocardial infarction	32 (6.0)	198 (8.1)
Paroxysmal Atrial Fibrillation	27 (5.1)	61 (2.5)
Transient ischemic attack	26 (4.9)	115 (4.7)
Stable Angina	23 (4.3)	63 (2.6)
CABG or PCI	23 (4.3)	157 (6.4)
Peripheral Vascular Disease	20 (3.7)	77 (3.2)
Deep Vein Thrombosis	14 (2.6)	39 (1.6)
Aortic Stenosis	11 (2.1)	54 (2.2)
Unstable Angina	10 (1.9)	32 (1.3)
Pulmonary Embolus	8 (1.5)	17 (0.7)
Epilepsy	10 (1.9)	46 (1.9)
Subarachnoid hemorrhage	6 (1.1)	20 (0.8)
Renal Failure requiring Dialysis	6 (1.1)	16 (0.7)
Troponin measurement	244 (45.6)	1148 (47.1)
Elevated troponin	68 (27.9)	254 (22.1)
Type of fracture:		
Intertrochanteric	296 (55.4)	1245 (51.1)
Femoral Neck	212 (39.7)	1086 (44.6)
Subtrochanteric	30 (5.6)	134 (5.5)
Other	0 (0)	4 (0.1)
Type of hip surgery*:		
Open Reduction and Internal Fixation (ORIF)+:	341 (63.9)	1536 (63.1)
Cephalomedullary Nail	320 (59.9)	971 (39.9)
Sliding Hip Screw	9 (1.7)	405 (16.6)
Cannulated Screws	11 (2.1)	107 (4.4)
Arthroplasty	190 (35.6)	859 (35.3)
Hemi Arthroplasty	169 (31.6)	697 (28.6)
Total Arthroplasty	18 (3.4)	159 (6.5)
Other Implant Type	3 (0.6)	3 (0.1)
Other surgery	0 (0)	4 (0.2)
Type of anesthesia^:		
Neuroaxial (Spinal or epidural)	485 (90.8)	1446 (59.4)
General	34 (6.4)	882 (36.2)
General + Neuroaxial	13 (2.4)	71 (2.9)

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SD: Standard Deviation; ADL: Activities of daily living; COPD: chronic obstructive pulmonary disease; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention.

∫: Some patients had more than one type of fracture.
***:** Two Spanish patients died before surgery.
+: One Spanish patient was scheduled for ORIF but finally received conservative treatment in the operating room (no implant).
∧: For the non-Spanish Cohort: surgery data available n = 2399.

Table 2. Timeline of hip fracture management in the Spanish cohort compared to the non-Spanish cohort.

	Spanish Cohort						**Non-Spanish Cohort**					
	Overall		**Accelerated Care**		**Standard Care**		**Overall**		**Accelerated Care**		**Standard Care**	
	N	Median (Q1-Q3)	N	Median (Q1-Q3)	N	Median (Q1-Q3)	N	Median (Q1-Q3)	N	Median (Q1-Q3)	N	Median (Q1-Q3)
Participant randomized	534		**265**		**269**		2436		**1222**		**1214**	
Time fracture to ER arrival (hrs)	534	1.6 (1.0- 2.5)	265	1.6 (1.1- 2.5)	269	1.5 (1.0- 2.8)	2381	3.4 (1.5- 19.0)	1200	3.2 (1.4- 18.1)	1181	3.6 (1.6- 19.0)
Time ER arrival to X-Ray (hrs)	532	0.4 (0.2- 0.9)	265	0.4 (0.2- 0.9)	267	0.4 (0.3- 0.9)	2290	1.1 (0.5- 1.9)	1156	1.0 (0.5- 1.9)	1134	1.1 (0.5- 1.9)
Time X-Ray to fracture diagnosis (hrs)	534	0.3 (0.2- 0.7)	265	0.4 (0.2- 0.7)	269	0.3 (0.2- 0.6)	2415	0.8 (0.4- 1.8)	1215	0.8 (0.4- 1.8)	1200	0.8 (0.4- 1.8)
Time ER arrival to fracture diagnosis (hrs)	534	0.9 (0.6- 1.3)	265	0.9 (0.7- 1.3)	269	0.8 (0.5- 1.3)	2385	2.1 (1.0- 3.5)	1200	2.1 (1.1- 3.5)	1185	2.1 (1.0- 3.4)
Time fracture diagnosis to medical clearance (hrs)	534	2.2 (1.5- 3.8)	**265**	**1.8 (1.3- 2.7)**	**269**	**2.9 (1.8- 5.0)**	2340	2.7 (1.5- 6.2)	**1176**	**2.0 (1.3- 3.8)**	**1164**	**4.2 (2.0- 15.0)**
Time fracture diagnosis to surgery start (hrs)	532	10.7 (6.1- 31.8)	**264**	**6.3 (5.2- 9.2)**	**268**	**30.0 (21.1- 53.9)**	2396	9.4 (5.2- 25.9)	**1206**	**5.8 (4.3- 9.3)**	**1190**	**22.8 (9.5- 37.0)**
Time fracture diagnosis to surgery start (hrs) **>=48hrs**	99	18.5%	**16**	**6.0%**	**83**	**30.9%**	263	10.8%	**70**	**5.7%**	**193**	**15.9%**
Time fracture diagnosis to surgery start (hrs) **<48hrs**	433	81.1%	**248**	**93.6%**	**185**	**68.8%**	2133	87.6%	**1136**	**93.0%**	**997**	**82.1%**
Time surgery start to surgery completion	532	1.2 (0.8- 1.5)	264	1.2 (0.8- 1.5)	268	1.1 (0.8- 1.5)	2397	1.2 (0.8- 1.6)	1206	1.2 (0.8- 1.5)	1191	1.2 (0.8- 1.6)

ER: Emergency Room;

Table 3. 90-day primary and secondary study outcomes in Spanish population compared to non-Spanish HIP ATTACK-1 cohort.

	Spanish Cohort		Non-Spanish Cohort		p value
	N	%	N	%	
Randomized	534		2436		
Primary Outcomes					
Death	69	12.9	225	9.2	**0.0098**
Vascular Mortality	35	6.6	136	5.6	0.3828
Non-vascular Mortality	34	6.4	89	3.7	**0.0044**
Composite of Major Complications*	126	23.6	526	21.6	0.3113
Secondary Outcomes					
Cardiovascular Complications					
Myocardial injury**	189	35.4	712	29.2	**0.0050**
Congestive Heart Failure	21	3.9	41	1.7	**0.0010**
Myocardial Infarction	13	2.4	151	6.2	**0.0006**
New Clinically important Atrial Fibrillation	7	1.3	39	1.6	0.6229
Cardiac Revascularization Procedure	2	0.4	4	0.2	0.2951
Nonfatal Cardiac Arrest	0	0	3	0.1	1.0000
Peripheral Arterial Thrombosis	0	0	2	0.1	1.0000
Infection					
Infection with No Sepsis	86	16.1	291	11.9	**0.0089**
Infection with Sepsis	38	7.1	103	4.2	**0.0045**
Pneumonia	25	4.7	90	3.7	0.2843
Surgical Site infection	16	3.0	36	1.5	**0.0154**
Bleeding					
Major Bleeding	21	3.9	130	5.3	0.1810
Life-Threatening Bleeding	4	0.7	12	0.5	0.4634
Delirium within 7 days post-randomization	84	15.7	223	9.2	**<0.0001**
Pressure Ulcer at Discharge	32	6.0	57	2.3	**<0.0001**
Stroke	4	0.7	15	0.6	0.7631
Proximal Deep Venous Thrombosis	1	0.2	15	0.6	0.3330
Pulmonary Embolism	0	0	18	0.7	0.0579

*Death and non-fatal myocardial infarction, stroke, venous thromboembolism, sepsis, pneumonia, life-threatening bleeding, and major bleeding. **After randomization not meeting the third universal definition of myocardial infarction.

Table 4. Type of vascular and non-vascular mortality in the Spanish cohort.

	Spanish Cohort	
	N	**%**
Randomized	534	
Death	69	12.9
Vascular Mortality	35	50.7
Unknown	11	15.9
Congestive heart failure	8	11.6
Cardiac arrest	6	8.7
Myocardial infarction	3	4.3
Hemorrhage	5	7.2
Stroke	2	2.9
Non-vascular Mortality	34	49.3
Infection	20	29.0
Cancer/Malignancy	5	7.2
Respiratory failure	4	5.8
Renal failure	2	2.9
Aspiration	1	1.4
General deterioration	1	1.4
Acute abdominal	1	1.4

Figure 1. Kaplan Meier estimates for the primary outcome Mortality of the Spanish and non-Spanish cohorts

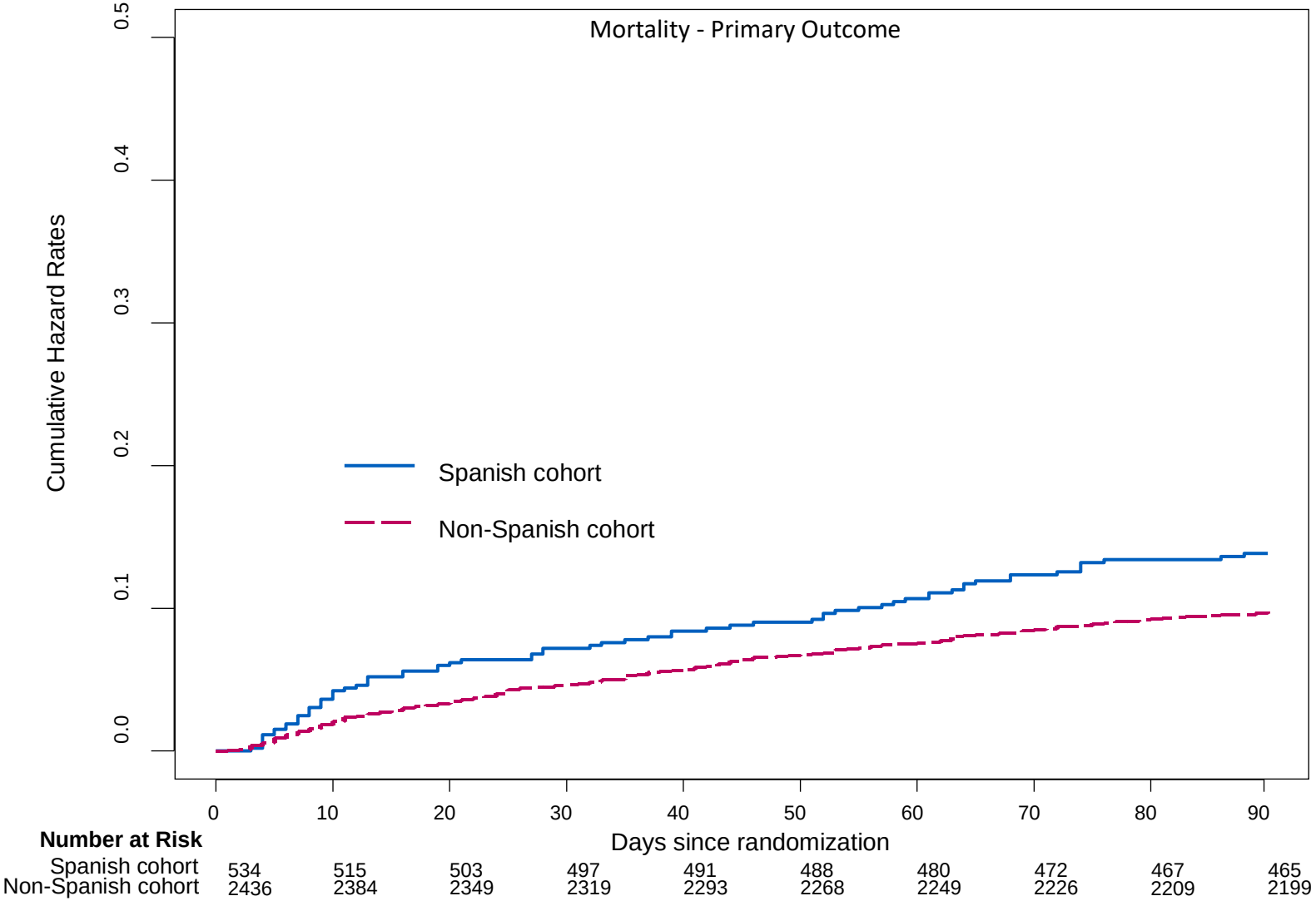
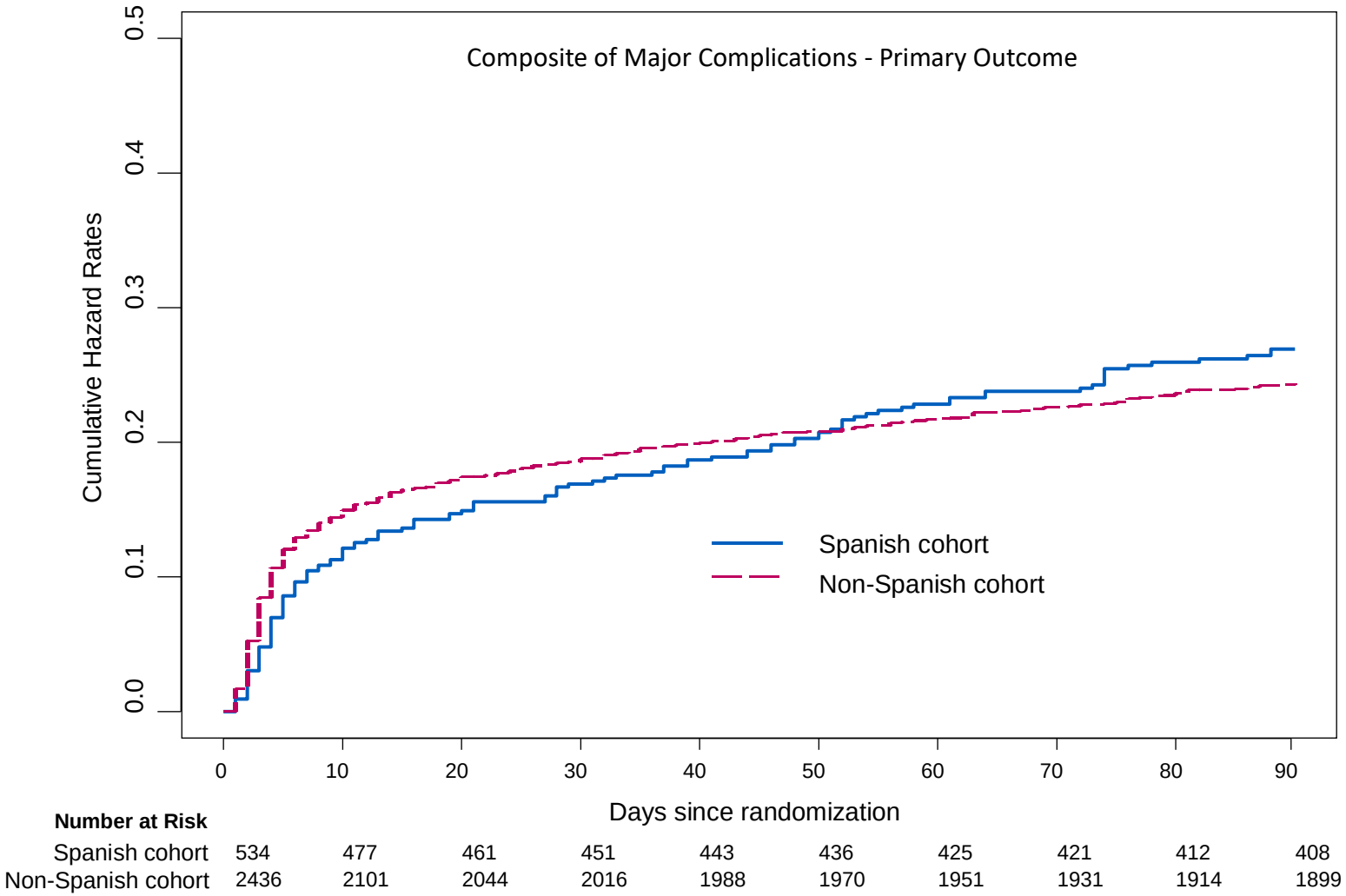


Figure 2. Kaplan Meier estimates for the primary outcome Composite of Major Complications of the Spanish and non-Spanish cohorts



Number at Risk										
Spanish cohort	534	477	461	451	443	436	425	421	412	408
Non-Spanish cohort	2436	2101	2044	2016	1988	1970	1951	1931	1914	1899

SUPPLEMENTARY APPENDIX

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