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Isolated Cardiac Troponin Rise Does Not Modify the Prognosis in Elderly Patients with Hip Fracture

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1   **Abreviation**

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3   ACS: acute coronary syndrome

4   ADL: Activities of Daily Living

5   CI : Confidence Interval

6   CIRS: Cumulative Illness Rating scale

7   CNIL : French National Commission on Computing and Liberty

8   CPP : ethics committee

9   cTn : cardiac troponin

10   ECG: electrocardiogram

11   IADL: Instrumental Activities of Daily Living

12   ICU: intensive care unit

13   ITR: isolated troponin rise

14   STEMI: ST-elevation myocardial infarction

15   UPOG: Unit for Peri-Operative Geriatric care

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1   **Abstract** (word count 253)

2   **Introduction**: Perioperative myocardial infarction remains a life-threatening complication in

3   non-cardiac surgery and even an isolated troponin rise (ITR) is associated with significant

4   mortality. Our aim was to assess the prognostic value of ITR in elderly patients with hip

5   fracture.

6   **Methods**: In this cohort study, all patients admitted between 2009 and 2013 in our dedicated

7   geriatric post-operative unit after hip fracture surgery with a cardiac troponin I determination

8   were included divided into Control, ITR and acute coronary syndrome (ACS) groups. The

9   primary end point was a composite criteria defined as 6 month mortality and/or re-

10   hospitalization. Secondary end points included 30-day mortality, 6 month mortality, and 6

11   month functional outcome.

12   **Results**: 312 patients were (age 85 ± 7 years) divided into Control (n=217), ITR (n=50) and ACS

13   (n=45) groups. There was no significant difference for any post-operative complications

14   between ITR and Control groups. In contrast, atrial fibrillation, acute heart failure, hemorrhage,

15   and ICU admission were significantly more frequent in the ACS group. Compared to the

16   Control group, 6-month mortality and/or rehospitalization was not significantly modified in the

17   ITR group (26 vs 28 %, P=.84, 95% CI of the difference -13 to 14%) whereas it was increased

18   in the ACS group (44 vs 28%, P=.02, 95% CI of the difference 2 to 32%). ITR was not

19   associated with a higher risk of new institutionalization or impaired walking ability at 6 month,

20   in contrast to ACS group.

21   **Conclusion**: In elderly patients with hip fracture, ITR was not associated with a significant

22   increase in death and/or rehospitalization within 6 months.

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1   **Introduction**

2   Perioperative myocardial infarction remains a frequent and life-threatening
3   complication in non-cardiac surgery.[1-3] In 2012, redefinition of acute myocardial infarction
4   highlighted the importance of troponin elevation in association with either electrocardiographic
5   changes, and/or clinical symptoms of ischemia, and/or new wall motion anomalies.[4] However,
6   large database analyses have recently extended the concept of perioperative myocardial
7   infarction to myocardial injury after non cardiac surgery, because even subtle and isolated
8   increase in troponin irrespective of ischemic features (*i.e.*, ischemic symptoms and ECG
9   findings) are associated with a significant mortality risk.[5,6] This result is in agreement with
10   previous studies showing that isolated troponin rise (ITR) is associated with an increased
11   mortality risk in various non-ischemic conditions such as sepsis,[7] pulmonary embolism,[8] renal
12   failure,[9] and acute respiratory failure in chronic obstructive pulmonary disease patient.[10]

13   Hip fracture is a frequent emergency condition in the geriatric population, associated
14   with a poor prognosis [11,12] and with a 5 to 8 fold increased mortality risk in the first 6 months
15   following hip fracture surgery.[13] Mortality rate at 6 months varies across studies between 19%
16   to 25%.[14,15] The prognostic significance of a cardiac troponin rise remains controversial in
17   elderly patients with hip fracture. Some studies reported an increase in short and long-term
18   mortality[16-18] while other did not.[19-21] Moreover, these studies did not distinguish ITR and
19   myocardial infarction according to its universal definition.[4] In these elderly patients with hip
20   fracture an ITR may occur more frequently because of events such as atrial fibrillation or
21   transient supply/demand mismatch. Moreover, the mortality risk related to non-ischemic causes
22   is higher and remains markedly increased over a longer perioperative period in these elderly
23   patients,[22] which may be greater than the risk associated with myocardial injury itself.
24   Therefore, there is a knowledge gap concerning the prognostic role of postoperative troponin
25   in elderly patients with hip fracture and results obtained in younger patients who undergo
26   scheduled surgery may or may not apply to this frail population.[23]

27   The aim of our study was to assess the prognostic value of ITR in elderly patients with
28   hip fracture. We tested the hypothesis that ITR increases the rate of death and/or
29   rehospitalization within 6 months after hip fracture. We also assessed other clinically important
30   prognostic variables in this elderly population such as functional status, walking ability, and
31   autonomy.

32   **MATERIAL AND METHODS**

1   This study was approved by the ethics committee (CPP Pitié-Salpêtrière, Paris, France)

2 and as the study was observational, informed consent was waived. Nevertheless, all patients

3 were informed about their inclusion in the database and had the option to refuse it. The database

4 was declared to the French National Commission on Computing and Liberty (CNIL, Paris,

5 France). This study was carried out in our ten-bed peri-operative geriatric unit (Unit for Peri-

6 Operative Geriatric care, UPOG) in a tertiary university teaching hospital.

7   The database was created in June 2009 and acquisition of data was prospective.

8 Nevertheless, this study should be considered as retrospective since the design of this study was

9 performed later. The statistical plan of the study was decided before the statistical analysis,

10 except the sensitivity analysis using multivariable matching (*vide infra*). A significant

11 proportion of these patients (n=203) have been included in a previous study.[24]

12

13 *Patients*

14   From June 2009 to June 2013, all consecutive patients admitted to our UPOG were

15 evaluated for eligibility. Detailed methodology has been previously reported.[24] Patients were

16 included if they were ≥70 years of age (requirement to be admitted in the UPOG) and if their

17 primary presentation was due to hip fracture, and if they had a post-operative cardiac troponin

18 measurement. Patients were excluded if they presented with multiple or metastatic fractures, a

19 redo surgery, if they were already hospitalized at the time of diagnosis, and if there was no

20 troponin measurement. We stopped recruiting patients in June 2013 for that study when

21 ultrasensitive troponin measurement was implemented in our institution to ensure that the same

22 method of measurement was used.

23

24 *Data collection*

25   Prospectively collected data included age, sex, living conditions, walking ability,

26 functional autonomy, previous medical history, medications, type of fracture and surgical

27 treatment, type of anesthesia (general vs locoregional), and any nerve block provided for

28 analgesia. Associated co-morbidities were assessed using the Cumulative Illness Rating scale

29 (CIRS).[25] Functional status was evaluated with the Activities of Daily Living (ADL) scale [26]

30 and the Instrumental Activities of Daily Living (IADL) scale.[27] We recorded hemoglobin level

1   during the acute care period, serum creatinine and estimated creatinine clearance using the

2   Cockroft formula.[28] Chronic renal failure was defined as an estimated creatinine clearance ≤

3   60mL.min^{-1}.

4   Considering silent myocardial infarction,[4,29] electrocardiogram (ECG) and cardiac

5   troponin I (cTnI) measurement were routinely performed within the first 3 days after surgery in

6   all patients. cTnI measurement at admission in the emergency department (preoperative value)

7   relied on the emergency physician decision. A 12 lead ECG was routinely performed at the

8   admission into the emergency department, at admission into the geriatric unit, and in presence

9   of any evocating clinical symptoms. ECGs were all reviewed by an expert panel unaware of the

10   troponin level, including two independent physicians, specialized in geriatrics and cardiology

11   (H.V., A.B, J.C.B, J.B.) as previously described.[30] The percentage of agreement between

12   experts was 97% (kappa score = 0.94, 95% confidence interval (CI) 0.85 to 0.99). A cTnI rise

13   was defined in presence of a value above 0.05 ng.L^{-1} (Dimension Xpand® analyser, Siemens

14   Healthcare Diagnostics France, Saint-Denis, France). Undetectable values were quoted as 0.05

15   ng.L^{-1} An acute coronary syndrome (ACS) was defined following the third universal definition

16   of myocardial infarction:[4] cTnI rise with at least one value above the 99th percentile upper

17   reference limit and with at least new significant ST-segment-T wave changes, new left bundle

18   branch block, development of pathological Q waves in the ECG, or new wall motion anomalies.

19   Patients were regrouped according to troponin level and ECG interpretation, as Control group

20   (no significant ECG change and no troponin rise), ITR Group (troponin rise without significant

21   ECG changes), and the ACS group (troponin rise with significant ECG changes).

22

23   *Outcomes and follow-up*

24   All complications during the acute care period were recorded including delirium, stool

25   impaction, urinary retention requiring drainage, pain, pressure ulcer, infection, thromboembolic

26   event, post-operative anemia and transfusion, swallowing disorders, acute cardiac failure, atrial

27   fibrillation, stroke and admission into intensive care unit (ICU), as previously described.[24]

28   Patients requiring coronary angiography and cardiologic transfer were considered as ICU

29   transfers. We also recorded therapeutic intensification (*i.e.* new administration of

30   antiaggregants, statin, converting enzyme inhibitor, or beta-blockers, or coronary stenting or

31   coronary artery bypass) as previously described.[31]

1   Patients were followed until death or 6 months after admission for living status and

2   functional outcome (ability to walk, ADL and IADL scores). Surviving patients or their

3   relatives were contacted and interviewed by telephone. For rehospitalization, day-case

4   admissions for chemotherapy, hemodialysis, pace-maker replacement, and geriatric assessment

5   were not considered as hospitalization. For any new institutionalization at 6 months, patients

6   who were dead were censored and patients who were already institutionalized before hip

7   fracture were excluded.

8

9   *End points*

10   The primary end point was a composite criteria defined as 6 month mortality and/or re-

11   hospitalization from any cause. Secondary end points included acute care and/or rehabilitation

12   mortality, 30-day mortality, 6 month mortality, 6 month functional outcome (ability to walk,

13   ADL and IADL), and new institutionalization.

14

15   *Statistical analysis*

16   The sample size was based on all available patients and thus no a priori power

17   calculation was conducted. Data are expressed as mean ± SD or median [25-75th interquartile]

18   for non-Gaussian variables, and number (percentages). Comparison between groups was

19   performed using analysis of variance and the Newman Keuls-test, the multiple comparison

20   Kruskall-Wallis test, and Fisher's exact method with Bonferroni correction, when appropriate.

21   Survival was estimated using the Kaplan-Meier method and comparisons were performed using

22   the log-rank test. The Cox proportional hazards model was used to determine the predictors of

23   death and re-hospitalization at 6 months, death at 6 months, and new institutionalization at 6

24   months. Only variables known to be previously associated with the prognosis (age, sex, CIRS)

25   [24] were entered into the Cox model and we added the group (control, ITR, and ACS). We

26   calculated the risk ratio and its 95% CI in association with these variables. We performed a

27   sensitivity analysis (post hoc test) and also conducted a multivariable matching aiming to create

28   two groups of patients with similar preoperative characteristics (*i.e.* age, sex and CIRS 52), one

29   with postoperative ITR and the other group without any troponin elevation. Matched

30   populations consisted in 50 patients with ITR and 100 control patients. Using conditional

1 logistic regression and double robust estimator, we then estimated the impact of ITR on study

2 primary outcome, *i.e.* 6 month mortality and/or re-hospitalization

3   Statistical analysis was performed using NCSS 7.0 software (Statistical solutions Ltd.,

4 Cork, Ireland). All P values were two-tailed and P values of less than .05 were considered

5 significant.

6

1 **RESULTS**

2 During the study period, 365 patients with a hip fracture were admitted. Of these, 53

3 were excluded because of pathological fracture (n=3), redo surgery (n=7), pre-existing

4 hospitalization (n=4), and absence of cTnI measurement (n=39), therefore 312 (85%) were

5 finally retained in the analysis (Fig. 1). Post-operative rise in cTnI occurred in 94 (30%) patients

6 and ACS was diagnosed in 45 (14%) patients (Table 1). Nine ACS were ST-elevation

7 myocardial infarction (STEMI) and 36 were non-STEMI. Thus, patients were divided in

8 Control group (n=217), ITR group (n=50) and ACS group (n=45) (Fig. 1). The main

9 characteristics of the patients are presented in table 1. Preoperative cTnI was available in only

10 65 patients and was elevated in only 13 patients (0.30 [0.16-1.11] ng.L-1. Six of these patients

11 belong to the ITR group and 7 to the ACS group. Median maximum postoperative cTnI values

12 was 0.05 [0.05-0.05] ng.L-1 in Control group, 0.11 [0.08-0.23] ng.L-1 in ITR group, and 0.60

13 [0.15-1.76] ng.L-1 in ACS group. ECG modifications that did not meet the ACS criteria were

14 observed in 70 (32%) patients in the control group.

15 Co-morbidities were similar between ITR and Control groups, except for creatinine

16 clearance, type of fracture and surgery, and IADL score. Coronary artery disease, heart failure,

17 and low creatinine clearance were more frequent in the ACS group than in the Control group.

18 There was no significant difference between ITR and ACS groups (Table 1). Most patients

19 underwent general anesthesia and half of them benefited from regional nerve block for

20 analgesia, without significant differences between groups (Table 1).

21

22 *Short-term outcome*

23 Table 2 shows the therapeutic intensification administered in the three groups. Patients

24 in the ACS group received more frequently new antiaggregants, statins, and beta-blockers.

25 Coronary angiography was performed in only 6 patients, all in the ACS group, showing

26 coronary stenosis in 4 patients and coronary occlusion in 3 patients, one of them had a coronary

27 stent. Tako-tsubo syndrome was diagnosed in one patient. Echocardiography was performed in

28 81 (26%) patients but we did not observe significant changes between the three groups. Ejection

29 fraction was $54 \pm 21\%$ (n=48), $53 \pm 20\%$ (n=17), and $43 \pm 25\%$ (n=16), in control, ITR, and

30 ACS groups, respectively without significant difference between groups (*P*=.24).

31 The main complications during hospital and rehabilitation stay until home return are

32 presented in table 3. There was no significant difference for any outcomes between the ITR and

33 Control groups. In contrast, atrial fibrillation, acute heart failure, stroke, infections, hemorrhage,

1 ICU admission, acute care and/or rehabilitation mortality were significantly more frequent in

2 the ACS group compared with the control group. Fewer patients were able to return at home in

3 the ACS group than in the control group.

4

5 *Long-term outcome*

6   Only 2 patients were lost on follow-up. Among the 310 patients with complete follow-

7 up, death occurred in 53 (17%) patients and rehospitalization occurred in 45 (15%) patients,

8 and 93 (30%) patients fulfilled the primary endpoint (death and/or rehospitalization). Death

9 occurred in 5 (11%) patients who were rehospitalized. The main causes of rehospitalization

10 were medical issues (n=23), falls (n=12) with refracture (n=10), postoperative infection (n=4),

11 postoperative mechanical complication (n=1), and non orthopedic surgery (n=3). Compared to

12 the Control group, 6-month mortality and/or rehospitalization was not significantly modified in

13 the ITR group (26 vs 27 %, P=.84; 95% CI of the difference -10 to 17%) whereas it was greater

14 in the ACS group (44 vs 27%, P=.02, 95% CI of the difference 2 to 32%) (Fig. 2). Similarly,

15 there was no significant difference between the ITR group and the Control group for 6-month

16 death and new institutionalization. In contrast, the risk of new institutionalization was

17 significantly increased in the ACS group compared with the Control group (Fig. 2). In the

18 multivariable cox proportional-hazards analysis, when taken in consideration variables known

19 to impact the long term outcomes (age, sex, and CIRS 52), ITR was not associated with a higher

20 risk of death and/or rehospitalization, death, or new institutionalization. In contrast, the risks of

21 death and/or rehospitalization, and new institutionalization were significantly increased in the

22 ACS group compared with Control group (Table 4). We also conducted a multivariate matching

23 aiming to create two groups of patients with similar preoperative characteristics (*i.e.* age, sex

24 and CIRS 52), but one with postoperative ITR (n=50) and the other group (n=100) without any

25 troponin elevation. Within this matched population, the odds ratio associated with postoperative

26 ITR to predict 6-month mortality and/or rehospitalization was 1.04 (95% CI 0.50 to 2.13;

27 P=.92). This result was consistent with that obtained with direct regression approach and

28 suggests that postoperative ITR after hip fracture surgery is not associated with worse long term

29 outcome.

30   There was no significant difference for the 6-month ability to walk, ADL and IADL

31 scores between the ITR and Control groups. In contrast, autonomy of patients in ACS group

32 was lower than patients in Control group since they were less able to walk and ADL score was

33 lower (Table 3).

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1 **DISCUSSION**

2   In this study, we found that ITR was not predictive of death and/or re-hospitalization

3 during the 6-month period following hip fracture in elderly patients. In addition, ITR did not

4 significantly influence any other outcomes including postoperative complications, in-hospital

5 stay, admission to ICU, new institutionalization, walking ability and functional status. By

6 contrast, a cTnI rise within the context of ACS was associated with a significant increase in

7 death and/or rehospitalization within 6 months, and a poorer outcome considering admission to

8 ICU, new institutionalization, walking inability and functional status.

9   The prognostic significance of troponin rise remains controversial in elderly patients

10 with hip fracture. A few studies have suggested that a troponin rise is not associated with intra-

11 hospital mortality.[19] In contrast, Dawson-Bowling et al.[18] reported an association with intra-

12 hospital mortality, Talsnes et al.[17] with 3 month mortality, and Chong et al.[16] with 1 year

13 mortality. More recently, Hietala et al.[32] also reported an association between cTnT rise and

14 30 day and 1 year mortality. However, this association should be carefully analyzed,

15 considering three points. First, these studies did not delineate ITR and ACS although ACS is

16 known to be associated with its own mortality risk, particularly in elderly patients.[33] Second,

17 most of these studies did not provide detailed information concerning co-morbidities. Lastly,

18 other important long term outcome variables, known to be clinically important in the elderly

19 population, were not considered. Taken altogether, ECG findings and co-morbidities could play

20 an important part in the association between ITR and outcome.

21   Our results contrast with those of a recent large study (n=15,065) of patients aged 45

22 years or older undergoing non-cardiac surgery with postoperative cTnT measurement.[6] In this

23 study, an ITR, irrespective of the presence of an ischemic ECG feature, independently predicted

24 30 day mortality. Van Weas et al. also reported that increase in postoperative troponin was

25 associated to an increase in 30-day mortality in patients over 60 years undergoing scheduled

26 non-cardiac surgery.[34] However, van Waes et al. did not separate patients with ITR and those

27 with ACS.[34] But our results are in agreement with those reported by Huddleston et al.[35] in

28 elderly patients with hip fracture who classified patients as clinically verified myocardial

29 infarction (equivalent to ACS), subclinical myocardial ischemia (isolated elevation of troponin

30 or CK-MB), or no myocardial ischemia. The 1-year mortality was higher in patients with

31 myocardial infarction but not in patients with subclinical myocardial ischemia.[35] Nevertheless

32 because patients were included between 1988 and 2002, CK-MB was used and this biomarker

33 has been clearly outdated by troponin. Our results emphasize the fact that a rise in troponin

1   levels should carefully be interpreted according to ECG modifications in elderly patients with

2   hip fracture.

3   Several points should be discussed to explain the discrepancy between our results and

4   those of previous studies. First, in these studies[6,34], only short-term outcome was assessed

5   whereas we assessed long-term (*i.e.* 6 month) outcome. Following hip fracture, in-hospital

6   mortality ranges from 2.3% to 13.9%, but the risk persists beyond the immediate surgical period

7   with 6 month mortality rates ranging from 12 to 23 %. Subsequently, the mortality risk returns

8   to that of an equivalent elderly population without hip fracture.[24] Thus our study was probably

9   underpowered to detect a change in in-hospital mortality but was appropriate to detect a

10 difference in long term outcome which is more clinically relevant in the elderly patients.[22]

11 Second, the proportion of elderly patients in the VISION study was low (24 %) and the

12 prognosis associated with ITR may be different in young and elderly patients, mainly because

13 the clinical significance of this elevation might be different. Third, our elderly population had

14 much many co-morbidities (Table 1) which are known to markedly interfere with postoperative

15 complication and outcome. Emergency conditions were also constant in our population whereas

16 they occurred only in a low proportion (14% in the VISION study, 21% in the Van Weas et al.

17 study) of patients, and these emergency conditions are also known to interfere with

18 postoperative complication and outcome. It should be noted that 30-day mortality was 1.8% to

19 3% in previous studies[6,34] vs 8.0% in our study. This greater exposure to high-risk conditions

20 may have overcome the hypothetical risk associated with ITR. Fourth, in a geriatric population,

21 an ITR may be more frequently due to non-ischemic events, such as pulmonary embolism, atrial

22 fibrillation, or congestive heart failure. Importantly, we have observed a lower clearance of

23 creatinine in the ITR group. This association has previously been reported and is not necessarily

24 associated with a cardiac ischemic event,[36-38] particularly when considering cTnI. Again, the

25 incidence of renal failure is markedly increased in comorbid elderly patients, particularly during

26 emergency conditions. Lastly, we performed a strict interpretation of ECG modifications using

27 an expert panel blinded for troponin values, offering a precise diagnosis of ACS, which was not

28 possible in the other studies.[6] This point is important since ECG analysis may be more difficult

29 in elderly patients who frequently present with age and/or co-morbidities-related ECG

30 modifications

31   Our study has several strengths. We prospectively collected detailed assessment of co-

32 morbidities and ECG modifications, to allow troponin rise interpretation. The definition of ACS

33 group responded strictly at the universal definition of myocardial infarction and all ECGs were

1 independently interpreted by an expert panel blinded to troponin values. The procedures used
2 in our UPOG were used for all patients, and we have previously demonstrated a significant
3 reduction of 6 month mortality and re-hospitalisation.[24]

4   Our study has several limitations. First, this study must be considered as essentially
5 retrospective. Nevertheless, data were collected prospectively and the statistical plan was
6 determined before the analysis. Second, the sample size in the ITR group was relatively low
7 (n=50) and thus the power of our study may have been insufficient to show a significant
8 difference. Nevertheless, it should be pointed that the difference observed between the ITR and
9 Control groups was very low (Fig. 2), suggesting that, even if it exists, this difference is
10 probably not clinically significant. Moreover, looking at many other outcome variables, we
11 failed to identify any poor prognosis signal in the ITR group. Third, we did not use the
12 ultrasensitive method of analysis of troponin. However, we do not think that this point may
13 have interfered with our results since ultrasensitive method may have only detected even more
14 subtle increase in troponin without clinical significance. Fourth, we did not systematically
15 measure preoperative cTnI and we cannot rule out the possibility that some patients had
16 chronically elevated cTnI concentrations that were unchanged postoperatively, particularly
17 those with chronic renal failure. Fifth, we did not measure preoperative cTnI in all patients but,
18 in previous studies, preoperative troponin measurements before elective surgery was not
19 significantly associated with poor outcome.[39] Lastly, our results may not apply to other
20 orthogeriatric models reported in the literature.[16-21] Our model is essentially characterized by
21 an early admission to a dedicated geriatric unit, a high rate of early surgery (*i.e.*, <24h after
22 admission),[22] and this model has been shown to markedly decrease mortality and improve
23 autonomy, walking ability, and functional status.[24]

24   In conclusion, in elderly patients with hip fracture, ITR is not associated with a
25 significant increase in death and/or rehospitalization within 6 months or any other outcome
26 variable. In this elderly and co-morbid population, troponin rise should be strictly interpreted
27 with consideration for universal definition of myocardial infarction, requiring a detailed
28 analysis of ECG modifications.

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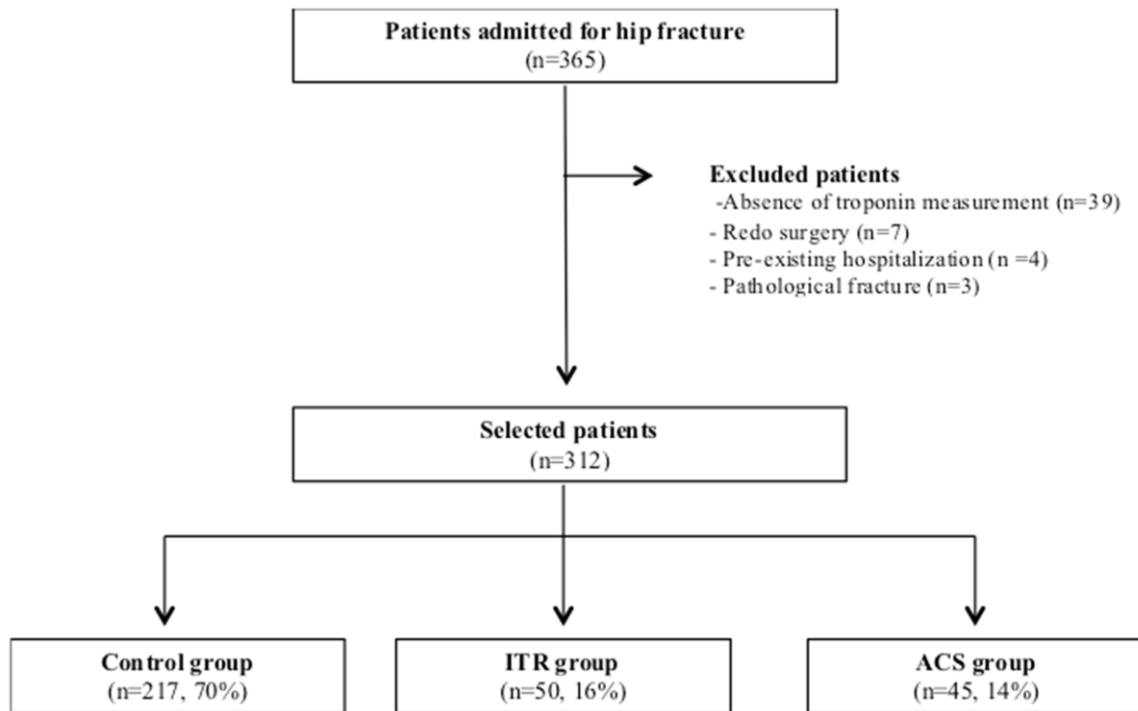2   the non-cardiac surgery setting. *Anaesthesia* 2014; 69: 484-93.

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1   **Figures**


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┌─────────────────────────────────────┐
│   Patients admitted for hip fracture │
│              (n=365)                 │
└─────────────────────────────────────┘
              │
              │──────────►  Excluded patients
              │                -Absence of troponin measurement (n=39)
              │                - Redo surgery (n=7)
              │                - Pre-existing hospitalization (n =4)
              │                - Pathological fracture (n=3)
              ▼
┌─────────────────────────────────────┐
│         Selected patients            │
│              (n=312)                 │
└─────────────────────────────────────┘
```

| Control group (n=217, 70%) | ITR group (n=50, 16%) | ACS group (n=45, 14%) |

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3   **Fig. 1**: Study flow chart. ITR : isolated troponin rise, ACS : acute coronary syndrome.
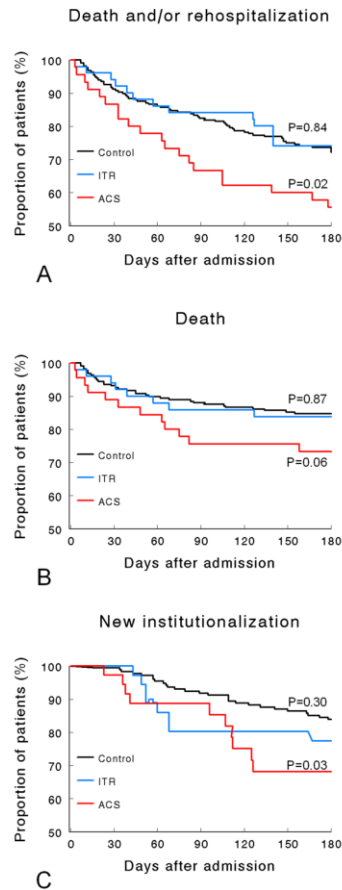
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Fig. 2: Non-adjusted survival curves for death and/or re-hospitalization (Primary endpoint, Panel A), death (Panel B), and new institutionalization (Panel C) in Control group (n=217), isolated troponin rise (ITR, n=50) group and acute coronary syndrome (ACS, n=45) group. For new institutionalization, death was considered as a censored observation and patients who were previously in an institution were excluded. *P* values refer to log-rank test.