UNIVERSITY
OF
MODENA AND REGGIO EMILIA

Post Graduate School Program
Neurosciences

XXXIV CYCLE

In agreement with
University of Parma

Postoperative dysfunctions in very elderly patients

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Academic Year 2020-2021

To my family,
ten years ago,
it was smaller

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Introduction

Italy is in the first positions for longevity globally. The life expectancy in Italy is constantly increasing, passing from the value of 82.75 for both sexes, (80.5 years old for male, and 85 for female) to a value of 84.01 for both sexes, 81.90 for male, and 85.97 for female recorded by the Italian Institute of Statistics in 2016. Differently, in the world, the mean life expectancy for both sex is 73.2 years old, 75.6 for females, and 70.8 for men [1,2]. This result could be related to many factors, lifestyle, diet, physical activity, and medicine [3–7]. So, in Italy is quite common finding an elderly patient with an age upper of 75 years old, a little bit less frequent a people with an age over life expectancy. The management of elderly patients in hospitals is a challenge for the healthcare system, especially for the consequences of elderly hospitalization and its problems. Furthermore, elderly hospitalized management has consequences on functional ability, autonomy in daily living [8]. Surgical elderly patients usually are frail and high risk of complications during the post operative period [9–12]. Postoperative cognitive impairment or dysfunction such as delirium or mental impairment is widespread in the postoperative period, and often, their insurgence is linked to loss of autonomy at home later the discharge [13]. In many cases a planned medical or surgical hospitalization can be the trigger of a cascade of loss of autonomy, often measured across Barthel Index Scale [14–17]. This last complication has a high social-economic, reducing the patient's quality of life, impacting the lives of relatives or next of kin, often requiring the presence of a caregiver. For that reason, in the last years medical literature has focused its attention on these topics.

Delirium

Postoperative delirium is a frequent complication in postoperative elderly patients: it comprises acute onset of disturbances in arousal, attention, and other domains of cognition, hallucinations, and delusions. Delirium can be hypoactive or hyperactive states or mixed. It is an acute disease that requires the following features: disturbance in attention [18,19]. It represents an acute change from baseline attention and awareness and tends to fluctuate in severity during a day; these above mentioned first two criteria are necessary but not sufficient to make a delirium diagnosis. It also needs one of the following features: an additional disturbance in cognition such as deficit of memory or disorientation, language, visual-spatial ability, or perception, and the disturbances in the two first criteria are not better explained by a pre-existing, established, or evolving neurocognitive disorder or coma. In the end, there is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies [20]. The most accredited theory regarding pathophysiology of delirium is that the disease is a consequence of acute multiple simultaneous molecular dysfunctions which bring to cerebral nervous system interaction failure [21]. Systemic inflammation, as a septic shock syndrome, can lead to neuroinflammation with microglial cells activation, neuronal dysfunction, synaptic dysfunction. Stress conditions, such as surgical operations, bone fractures, hospital admission, sleep deprivation can cause neuroinflammation with the unbalance of the limbic-hypothalamic-pituitary-adrenal axis and so by increasing cortisol blood levels. Prolonged exposure of neurons to high levels of cortisol and high levels of blood insulin and glucose leads to malfunction and damage of these cells because of continuous metabolic stress. The acetylcholine pathway is often dysregulated in patients with delirium with hyperactivation of microglia and consequent release of inflammatory cytokines and direct neuronal damage. Acetylcholine pathways depends also on dopamine and serotonin levels and misbalances on these can modify acetylcholine release. Drugs that activate the dopaminergic system as levodopa, can cause delirium. Abnormal hyperproduction of gamma-aminobutyric acid (GABA) in the nervous system actively contributes to the development of delirium. The use of drugs that increase GABA levels in synapses, such as benzodiazepine, increases the risk of delirium manifestation [22,23]. Postoperative presents a wide incidence to 15-25% in older adults after elective surgery in older adults reaching more than 50% of cases in high-risk elderly patients who undergo major surgery such as cardiac surgery requiring cardiopulmonary bypass or orthopedic hip fracture repair [24,25]. The most screening tool used with highest sensibility and specificity for delirium are clinical and not instrumental test: these tools are the 4 'A's test (Arousal, Attention, Abbreviated Mental Test – 4, Acute change) and the Confusion Assessment Method (CAM4) and CAM version for critically patients (CAM-ICU) [26–28]. People affected by delirium often develop postoperative cognitive dysfunction (POCD) after hospital discharge during hospitalization [29].

Postoperative cognitive dysfunction (POCD)

POCD is a frequent postoperative complication in the elderly, and it belongs to neuro-cognitive disorder (NCD). POCD diagnostic criteria have recently been aligned with the clinical diagnostic criteria already used in the Diagnostic and Statistical Manual for Mental Disorders, fifth edition [20,30]. POCD includes pre-existing cognitive impairment or changes during the preoperative period until 12 months later the surgical procedure. So POCD includes cognitive impairment measurable with objectively test at varying intervals after anesthesia and surgery, up to 3 months to 7.5 years later surgery. POCD is defined as individual patient decline measured such as postoperative decrement of ≥1 standard deviation of decline in a cognitive individual test [30–32]. The principal and the most accurate test to detect POCD is the Minimental test, but often quick and more feasible version are useful such as rapid cognitive screen or six items cognitive impairment test (6CIT) [33,34]. Many aspects in the development of POCD have tracts like the postoperative delirium pathophysiology, such as the acetylcholine pathway dysregulation or hyperactivation of microglia and unbalance between neurotrophic factors and neuroapoptosis [35,36]. Currently, the neuroinflammation theory is the most convincing one. The surgical act stresses the body and generates a powerful inflammatory response with direct or indirect damage on neuronal cells. Inflammation can directly damage by the activation of oxidative stress pathways with mitochondrial impairment and final cell damage, as demonstrated in animal studies [21].

One current hypothesis is that postoperative inflammation promotes the progression of POCD. Indirectly, several pathways have a role in neuronal damage and microglial cells activation with neuroinflammation as the NOD-, LRR- and pyrin domain–containing protein 3 (NLRP3) a multi-protein complex belonging to the inflammatory pathway of the innate immune system, inflammasome, together with the alteration of IL1 beta local and systemic concentration [37]. Furthermore, the release of pro-inflammatory cytokines acts on the brain-derived neurotrophic factor, which intracellular signaling is a crucial mediator of neurogenesis and neuronal plasticity. The consequence is a reduction in neurogenesis and neuronal plasticity, with cognitive impairment after surgery [38]. Risk factors of POCD or Delirium are similar for both diseases and very common in elderly patients, especially in case of planned major surgical operations with a high risk of blood loss, prolonged anesthesia, and length of stay [39–41]. Emergency conditions or surgical operations can worse the incidence of these complications. For that reason, the medical literature has focused on several medical strategies or multimodal approaches to reduce the risk of developing POCD or Delirium in the last years.

This disease presents a high correlation with mortality, loss of autonomy, and prolonged length of stay in hospital [42,43].

Aim of the study

In 2018, we planned a preliminary study in a particular category of elderly patients. The study's main objective is to measure the survival and the various comorbidities of a specific type of elderly patient who underwent a planned surgery or deferrable urgent surgery with age upper than the life expectancy found in Italy at the time of the study.

Primary endpoint

The primary endpoint describes this population, perioperative complications rate, mortality, variation of cognitive status, and Barthel index later the hospitalization of elderly with age upper the life expectancy record in Italy at the time of the study.

Secondary endpoint

Measuring if an anaesthesia can worse the daily live or the cognitive conditions, or survival measuring a possible risk’s factors.

Material and methods

We planned a single cohort longitudinal preliminary prospective study. After the ethics committee's approval was received on March 29, 2018 (Procedure protocol 0007425/18, Azienda Ospedaliero Universitaria of Modena, Italy). We enrolled from September 2018, in the II Department of Anaesthesia and Intensive Care of Policlinico teaching hospital, for six months, elderly with age upper the value of 80.5 years old for male and equal or upper to 85 years old for female who underwent a surgical operation, not in emergency.

Patient management

Consent to the study has been offered during the anesthetic evaluation, for this reason, interventions in an emergency were excluded. If possible, we explained the study in the presence of relatives or caregivers, in the case of legal tutor the consent was asked of him.

Exclusion criteria were represented by patient's refusal or emergency surgical condition. Elderly afferent to II Department of Anaestehsia and Intensive Care and candidates for surgical procedures of the following disciplines have been enrolled:

- general surgery;
- orthopedic surgery;

- plastic surgery;
- breast surgery;
- thoracic surgery;
- otolaryngologist surgery;
- maxillofacial and dermatologic surgery.

Collection data was performed:

- at admission;
- within 48 hours surgical operation;
- at discharge or 7 days later the admission;
- after one year of hospital admission.

We collected the followings clinical data:

- demographic data, phone number or phone number available;
- anamnesis co-pathologies expressed as Charlson Index correct for age;
- Index of Coexisting Disease, Cumulative Illness Rating Scale and Possum Score for morbidity and mortality
- reason for surgical operations;
- Barthel Index at admission, at hospital discharge; Barthel Index was considered pathological if lower 80 points;
- cognitive status, measured with 6CIT, at admission, within 48 hours of surgical operation, at discharge, later one year with a face to face follow

up or with a phone interview. 6CIT was considered pathological if equal or upper to 8 points;

- confusion Assessment Method (CAM) at admission, within 48 hours of surgical operation, at discharge;
- Type of surgery: major surgery has been defined as surgery with blood risk loss upper than 15-20%.
- Pre-established pre-operative examinations:
- preoperative vital signs;
- perioperative risk classification (ASA);
- established preoperative specialist consultations;
- anesthesia performed (general, regional, sedation)
- anesthesia drugs;
- any transfusions of blood products;
- clinical monitoring normally used;
- intraoperative vital signs;
- postoperative analgesia;
- life parameter at admission, within 24-48 hours, at discharge
- post-operative blood tests normally performed;
- post-operative complications (prolonging length of stay in hospital);
- in-hospital mortality;

- 30 days mortality from admission;
- One year survival (measured at follow up or in case of absence with electronics system).

Sample size

There are no data available for this type of patient; this study was planned to schedule a second study, make some comparisons, and determine an adequate power level of the subsequent study.

In the end, we extract from the Italian Institute of Statistics the risk of death for each patient, and we compare the mean risk estimated with our mortality.

Statistics calculates

We analyzed the data with Stata® software 16 (StataCorp, College Station, TX, USA) and using GraphPad (GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com").

The results are expressed as mean (M) and standard deviation (SD), and the percentage of subjects was expressed as a percent of the total number of observations (obs), and the p-value was considered significant if <0.05.

Confidence intervals (CIs) were calculated at 95%. All differences with a p-value (p) ≤ 0.05 (*) were considered statistically significant

Linear and non-linear regression were performed to detect any potential relation between two variables. Wilcoxon sign rank test and McNemar test were used to make longitudinal comparisons with continuous or binary variables. Multiple linear logistic regression was used to analyze the relationship between type of anaesthesia and cognitive function, type of anaesthesia and Barthel index, type of anaesthesia and hospital complications and type of anaesthesia and one year mortality: this relationship was also tested for the following covariates: type of surgery, sex, age, Charlson index and ASA score. Risk factor association were calculated as Odds ratio and were expressed associated with their CI.

Results

In six months, we found 137 patients with an age over life expectancy, we enrolled 76 patients (40.79 % men, 50.11 % female) over 85 patients eligible for inclusion criteria, 9 patients refused to participate, 73 were available at one year follow up to check mortality rate, 70 available for follow up visit or interview (figure 1).

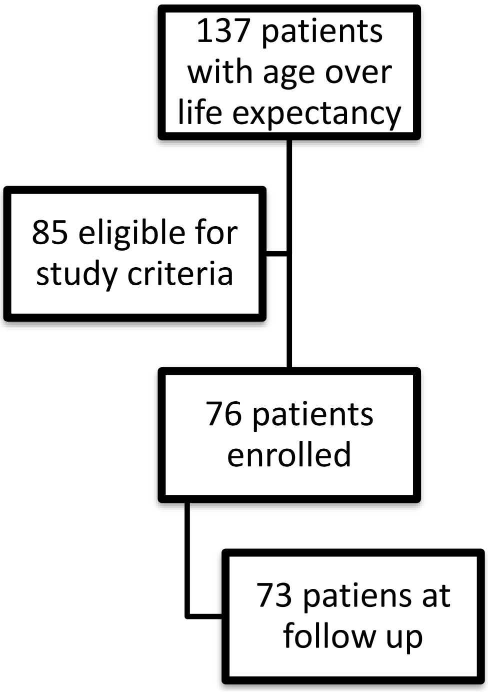

Figure 1: enrollment flow chart.

The mean age of the cohort was 86.89 years old with a standard deviation 4.22 years old, minimum value 80.5 years old, CI of 85.93 to 87.76 years old, 25° percentile value of 83.14, 75° percentile 89.63 years old and maximum value of 97.62 years old: age values normally distributed with Shapiro Wilk (R 0.9576) positive test with p value of 0.012 (figure 2).

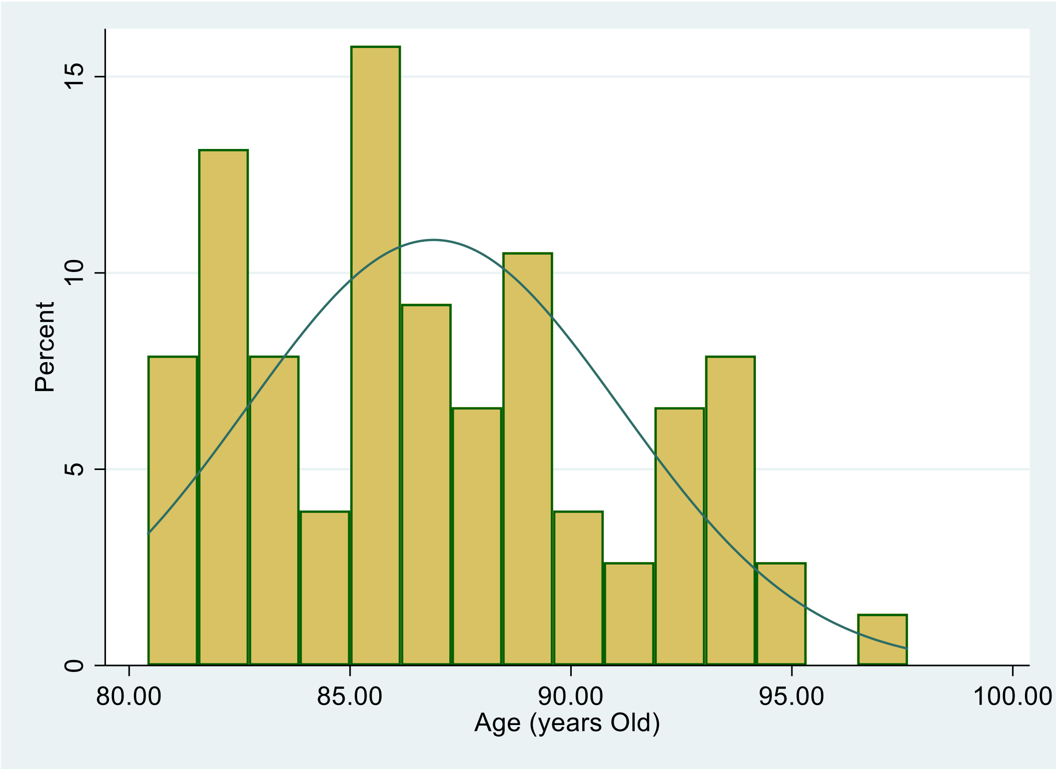

Figure 2: the age distribution of study cohort.

Most interventions are represented by orthopedic (34%) and maxillofacial and dermatological surgical procedures (40%). The remaining part underwent head-neck surgery, breast surgery, or thoracic surgery. In the 55.26 % of cases surgery was due to neoplastic reason. Major Surgery occurred in the 39.47%, and general anaesthesia in 40.79%. Patients showed an ASA classification of perioperative risk upper 3 in over 80% of cases. Charlson Comorbidities index was higher 4 in the 25% of cases. A pathological value (≥7) of Cumulative Illness Rating Scale was present in the 51.39%. We recorded also Barthel Index lower 80 points at admission in the 23.68% and a pathological cognitive test in the 39.47% (table 1). The mean value of Possum score percentage risk for complications was 65.88±2.43% with CI of 61.40-70.36 % and for mortality 10.99±1.35% with CI of 8.29-13.70%. The percentage of probability of death in one year estimated by Italian Institute of Statistics was 44.78±1.67% with CI of (41.05-47.69%).

Patients features at admission	Percentage (76 observations)
Major surgery	39.47%
General anesthesia	40.79%
ASA ≥ III	80.26%
Charlson Index ≥ 4	25%
Charlson Index Correct for Age ≥ 8	28.57%
Cumulative Illness Rating Scale ≥ 7	51.39%
Barthel Index ≤ 80 points	23.68%
6CIT ≥ 8	39.47%

Table 1: patient’s features at admission

We also highlighted a direct linear correlation between the cognitive test score and age and an inverse linear correlation between the Barthel score with respectively angular coefficient 0.60 and -1.47 and p-value <0.001 for both values.

From an initial analysis of the basal values of the blood-chemical tests, there are no significant alterations from the laboratory data, except for hemoglobin which is at the lower limits of normal. Bilirubin was expected in most cases (table 2).

Principal blood exames	Number of observations	Mean and Standard Deviation	Confidence Interval (CI)
Hemoglobin (gr / dl)	72	13,18 ± 0,19	12,81-13,55
Platelets ($x10^3/mm^3$)	71	214,48 ±7,98	198,57-230,39
Leukocytes ($x10^3/mm^3$)	72	7,14 ± 0,29	6,57-7,71
Na^+ (mEq/l)	71	140,31 ± 0,4	139,52-141,1
K^+ (mEq/l)	70	4,24 ± 0,06	4,12-4,36
aPTT	69	1,07 ± 0,02	1,02-1,12
Creatinine (mg/dl)	70	1,09 ± 0,05	0,99-1,18

Table 2: principal blood exams values at hospital admission

A first representation of the values at hospitalization of vital signs shows that, on average, the systolic blood pressure is higher than expected, and the diastolic value is lower than 80 mmHg. Heart Rate and body temperature were always average. We did not record any significant variations during life parameters detection (table 3a and table 3b).

Life parameters at admission	Observations	Mean and Standard Deviation	Confidence Interval
Heart rate (bpm)	68	73,79 ± 1,46	70,87-76,71
Systolic blood pressure (mmHg)	69	146,13 ± 2,49	141,15-151,1
Diastolic blood pressure (mmHg)	69	78,94 ± 1,42	76,11-81,77

Table 3a: principal life parameters at admission

Blood pressure Mean and Standard Deviation	Admission	Within 48 hours later surgical operation	Discharge
Systolic blood pressure (mmHg)	141,32 ± 2,55	136,46 ± 2,65	133,75 ± 1,95
Diastolic blood pressure (mmHg)	73,83 ± 1,51	70,74 ± 1,52	73,45 ± 1,88

Table 3b: principal life parameters during hospitalization.

The principal complication was delirium during the hospitalization, also recording CAM points alterations in 6.67% of cases.

Intra-hospital complications were present in the 26.32 cases, a lower value than parentage risk estimation by Possum Score with p-value <0.001. At the same time, Possum Score showed a ROC curve for complication of 0.65 with a CI of 0.51 to 0.79. ıntra-hospital mortality was lower than estimated by Possum Score with a p-value <0.001. The one-year mortality was like the value predicted by Possum Score with a p-value of 0.370, showing a ROC curve of

0.69 with a CI of 0.46-0.89. At the same time, the mortality rate was lower than the percentage probability of death estimated by the Italian Institute of Statistics with a p-value <0.001 (figure 2a-b) (Table 4).

Hospital and follow up Complications	Percentage and observations (obs)
CAM point increase	6.67% (76 obs)
6CIT ≥ 8 at discharge	55.26% (76 obs)
Barthel Index ≤ 80 points at discharge	42.47% (76 obs)
Hospital complications	26.32 (76 obs)
Hospital Delirium	5% (76 obs)
Blood loss and transfusion	5% (76 obs)
Infection	3.9% (76 obs)
Hospital mortality	2.63% (76 obs)
One year mortality	9.59% (73 obs)
6CIT ≥ 8 later one year	55.56% (54 obs)
Barthel Index ≤ 80 points later one year	37.50 % (56 obs)

Table 4: Principal complication during hospitalization and one year later the study

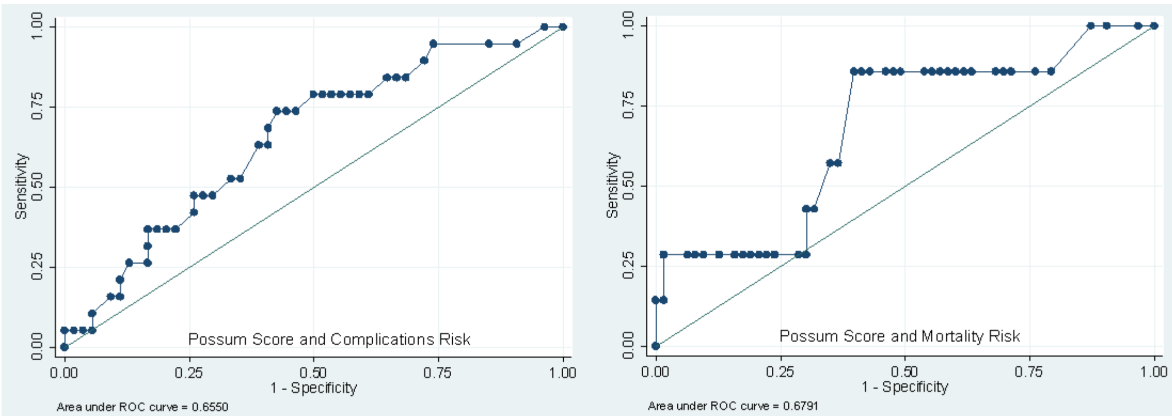

Figure 2a-2b: Possum Score and Its ROC curve for complications and mortality

In the end, we record an increased rate of pathological value of the 6CIT during the hospitalization, passing from a rate of 39.47%, reaching a rate of 55.26% with a p-value of <0.001 with McNemar test.

Also, the 6CIT values follow a linear regression with age with a p-value <0.001, but with a small sharper angular coefficient of 0.62. The same event happened with the Barthel Index at discharge, with an increased rate of pathological values from 23.68 to 42.68 with a p-value < 0.001 with McNemar test. The Barthel Index at discharge follows a linear regression with p value <0.001 and angular coefficient of -2.05.

Comparison for 6CIT and Barthel Index values at follow up deserves a sub-analysis among follow up data with the same number of observations.

Analyzing data of Barthel index at follow up, in 56 observations, we confirm the above results, passing from a pathological value in the 23.79% of cases, reaching a value of 37.50% with a p-value of 0.01, but these data do not follow a linear regression with age. Analyzing data of 6CIT at follow up, in 54 observations, we confirm the above results, passing from a pathological value in the 37.04% of cases, reaching a value of 53.7% with a p-value of 0.01, but these data do not follow a linear regression with age (figure 3).

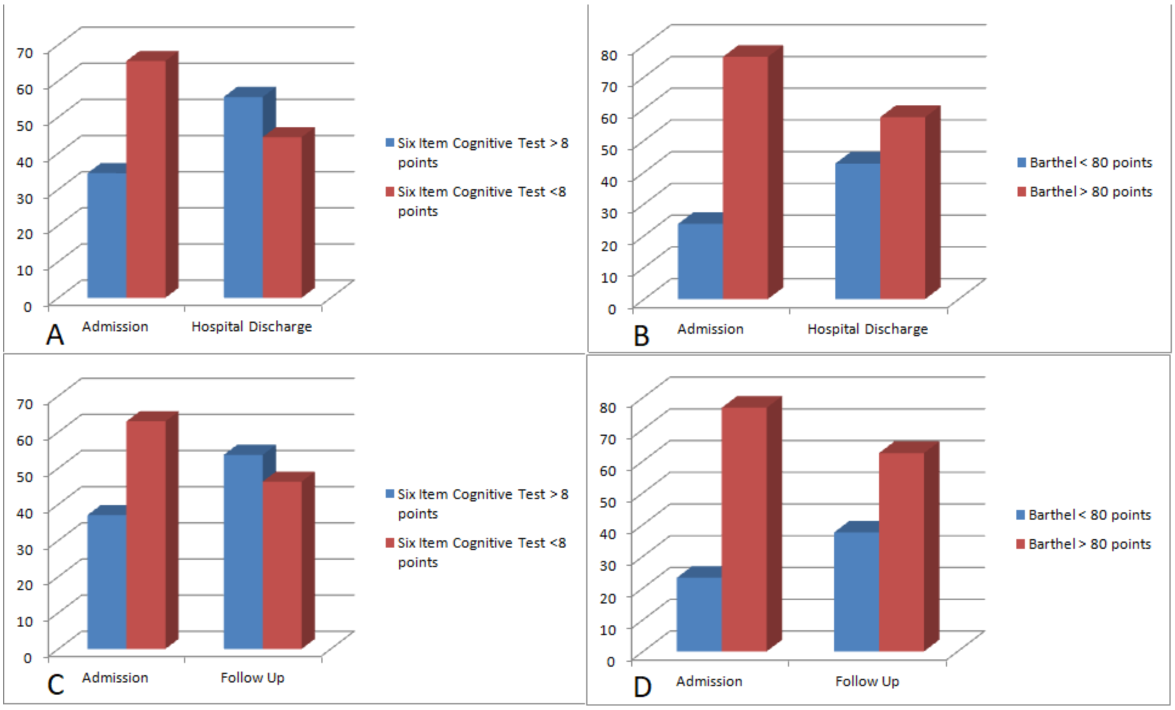

Figure 3: 6CIT and Barthel Index later hospital discharge and one year later in study cohort.

As we can see in table 5, the principal risk for loss of autonomy at discharge, decreased of cognitive status, is represented by the presence of co morbidities (table 5 and figure 4).

Variables	6CIT >8 at discharge OR and CI	Barthel index < 80 at discharge OR and CI	Hospital Complications OR and CI	One year mortality OR and CI
Type of Anaesthesia	1.01 (0.34-3.01)	1.88 (0.55-6.28)	0.77 (0.23-2.25)	12.68 (0.96-166)
p-value	0.981	0.312	0.671	0.053*
Type of Surgery	2.36 (0.82-6.78)	4.84 (1.4-15.89)	5.68 (1.7-18.84)	0.71 (0.08-5.88)
P value	0.108	0.009*	0.004*	0.754
Age	1.11 (0.95-1.30)	1.27 (1.06-1.53)	1.01 (0.86-1.18)	1.44 (1.033-1.99)
p-value	0.171	0.008*	0.861	0.029
Sex	0.92 (0.25-3.35)	0.50 (0.12-2.08)	0.39 (0.98-1.57)	0.16 (0.01.88)
P value	0.902	0342	0.187	0.146
Charlson Index	1.33 (1.05-1.69)	1.23 (0.99-1.53)	1.03 (0.82-1.29)	1.48 (1.01-2.17)
P value	0.016	0.052*	0.766	0.043*
ASA ≥ 3	0.59 (0.15-2.20)	0.76 (0.17-3.29)	1.75 (0.36-8.45)	0.12 (0.01-1.87)
p-value	0.435	0.710	0.485	0.131
LR	13.28	20.74	10.07	14.15
Prob > chi^2	0.038*	0.002*	0.122	0.028*
Pseudo R2	0.127	0.208	0.115	0.307
ROC R2 model	0.730	0.776	0.721	0.861

Table 5: Relation among type of anaesthesia and cognitive status, loss of autonomy at discharge, decrease cognitive status, hospitals complications and one year mortality for the following covariates: type of surgery, age, sex, Charlson Index and ASA score.

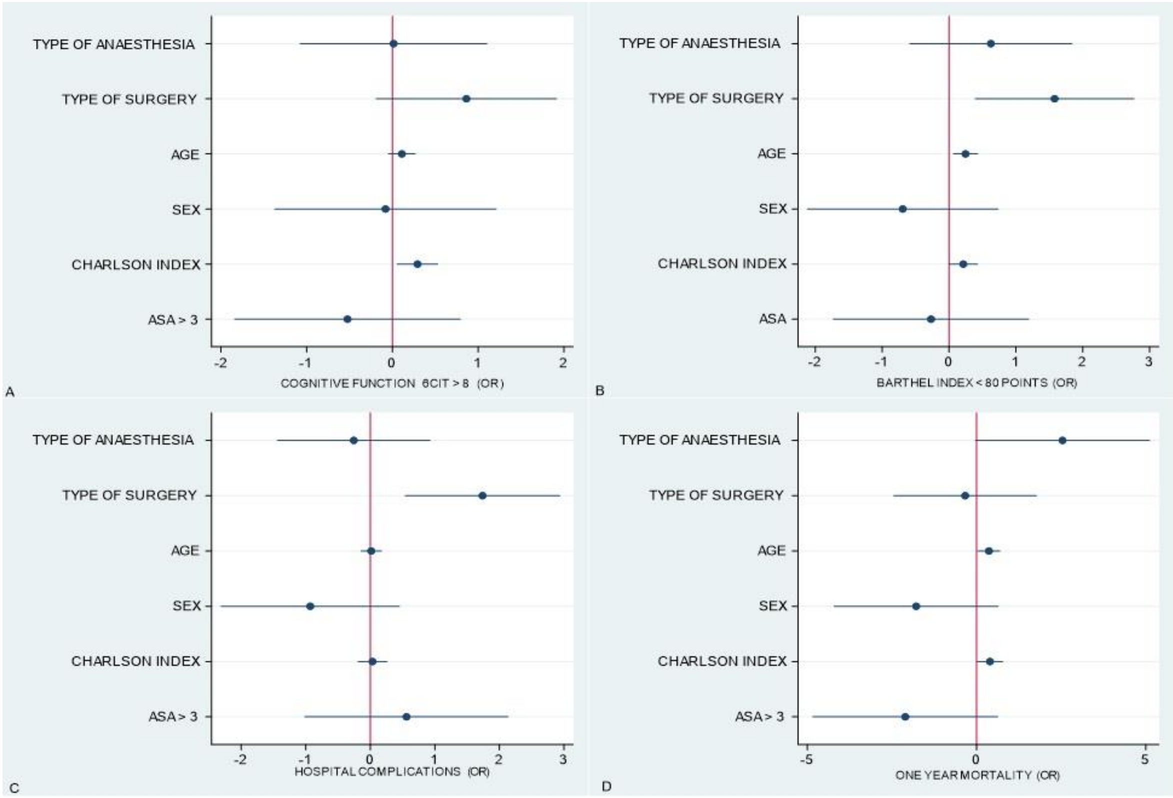

Figure 4: principal risk factor for loss of autonomy at discharge, decrease cognitive status, complications and one year mortality expressed as odds ratio.

Discussion

Doctors and hospitals are taking care of a substantial and rapidly growing number of very elderly individuals. This study showed that the percentage of the subgroup of elderly patients over 80 in the extensive overview of elderly patients has been increased in the last years and accounts for a large part of the work of health care workers in operating rooms [44,45]. In the past, surgery was rarely offered to the elderly between the eighth and ninth decade of life, but today many patients are 80 years old or older.

The decision phase and planning of significant surgeries for this category are difficult [46,47]. Considering that the studies published in this field and these patients are limited, we understand how the work becomes more and more complex. The concept of elderly patients with an age upper the life expectancy is something innovative, never described and could be a threshold in future studies. Although mortality and general complications increase in proportion with age, our study shows that survival is still very high even beyond 30 days after surgery and later one year (mortality measured in sample 9 out of 73 patients). Indeed, one reason for our value is related to the type of surgery and the absence of emergency surgery. Maybe the future literature of elderly should be divided into elective and non-elective and emergency surgery of elderly. Intra-hospital mortality rate reaches value upper the 20% in the emergency setting [46,49]. So, we can observe two different scenarios by dividing these types of surgery regimens. In the last years have been risen the number of studies regarding patients over 80 years old, their presence in hospital is increasing and they represent a challenge for medical and scientific community [50–52]. When is the surgical operation appropriate? Which type? What is the clinical impact on the outcome? How will it be their life expectancy of these patients? These are often un-answered medical questions of physician. With our study, we try to measure the stress impact induced by a surgical operations and perioperative period on cognitive status and level autonomy at home. We excluded the emergency setting because emergency conditions have a more profound and stronger impact. We measured the cognitive status using the 6CIT because it is easy: it does not require a motor competence or drowning ability, and it is functional in the emergency setting, and it can also be performed with a phone interview [53–56]. We also measured the Barthel Index score for every patient when possible; this score is one of the most used scores to describe autonomy in everyday life [14,15,17]. The cognitive condition and daily autonomy should be considered for importance like blood pressure or usual life parameters, especially in case of elderly patients. We tried measuring the correlation of the test and their age to find a sort of trend. During hospitalization, a worsening in cognitive status, daily activities, and autonomy occur and can be triggered by surgical operation and its consequences [33,55,57]. Once we observed a pathological increase rate of cognitive status or Barthel index Score, we tried to find a trend variation to distinguish a pathological worsening or worsening linked to age or time passing. The linear regressions showed a slight variation in angular coefficient, but it was minimal, especially for 6CIT; many confounding could act on this coefficient. Surgery represents the greatest stress for these individuals due to the invasiveness of the procedures. General anaesthesia showed an increased odds ratio for one-year mortality, especially in older people and in case of many comorbidities: this finding suggests avoiding general anaethesia in more frail subjects where possible. [45-48]. Furthermore, often general anaesthesia is necessary for the most invasive surgery with a higher risk of complications related to surgery. If the hospital stays increase, it can be associated with a worse recovery and loss of an independent life and cognitive reserve. This study is preliminary research to understand how to design and project future investigation with elderly with an age upper the life expectancy. The sample size is small, but it is not an easy setting working with very elderly patients.

Conclusion

The inclusion of only patients undergoing elective surgery could explain this study's low morbidity and mortality. A small fraction of those older than life undergoing surgery die or suffer from postoperative complications, but most have a good outcome with very low mortality for some types of surgery.

These findings could be of great help to patients, family members, and practitioners who can measure the risks and benefits of significant surgery. Furthermore, these results can also help us understand how and when to shift the objectives of health interventions from life extension to palliation for those patients belonging to a highly fragile age category who suffer most from peri and postoperative complications. Age upper life expectancy could be a new threshold in older adults. These types of elderly require a multimodal approach and all kinds of fast-track hospitalization, reducing the length of stay.

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Acknowledgments

I want to thank the Director of the Postgraduate School Program on Neurosciences, Professor Michele Zoli, and my tutor, Professor Stefano Meletti for their valuable contributions. I would Like also to thank Professor Alberto Barbieri for kind scientific collaborations in the last years.