

# Neuropsychiatric disorders in hip fracture

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## Summary

**Hip fractures most frequently occur in the elderly population. They are mainly caused by falls from standing position. The presence of several comorbidities, in particular neuropsychiatric disorders, are related to high percentages of falls, disability and mortality rates. Delirium and depression are the two most common mental disorders in this population.**

**Delirium is strongly related to an increase of functional limitation in activities of daily living, a decline in walking autonomy, and a higher rate of nursing home placement or death. A multi-factorial intervention program, consisting of oxygen supplementation, intravenous fluid supplementation and extra-nutrition, accurate monitoring of vital signs, adequate pain treatment, daily delirium screening, reduction in drug use, and modification in peri-operative management, should always be performed in good clinical practice.**

**Patients who undergo surgery frequently experience depression that can worsen functional outcome. An early detection and an adequate intervention based on psychological support and pharmacological treatment can give good results.**

**We propose a simple flow chart for the management of elderly hip fracture patients that should be used in both Orthopaedics and Rehabilitative settings.**

*KEY WORDS: hip fracture; elderly; neuropsychiatric disorders; delirium; depression.*

## Introduction

Hip fractures most frequently occur in the elderly population and represent a huge public health problem, above all in western countries, where there is a higher percentage of older people. According to the Italian National Institute for Statistics (ISTAT), in Italy, life expectancy is one of the highest in the world, reaching 77.8 years for men and 86.9 years for women. The 18% of the Italian

population is actually over 65 years of age, and 4% of this group is already > 80 years (1).

Increased life expectancy is associated with a greater frailty of elderly people and a higher prevalence of chronic and degenerative diseases, such as osteoporosis. Hip fractures are mainly caused by low-energy trauma (i.e. falls from standing position) in osteoporotic bone. Falls cause a hip fracture in 0.6% of people under 64 years, in 10.8% of people over 64 years, in 12.9% over 74, and in 14.2% over 79 (2). Hip fracture in the elderly has important consequences in terms of survival and functional outcome. The mortality rate after hip fracture surgery is 22% within the first year and 47% in the second year. Moreover more than 50% of the surviving patients do not return to the pre-fracture functional level.

The presence of several comorbidities, very common in the elderly, are related to high percentages of falls and mortality rates after hip fractures (3). Among the comorbidities, neuropsychiatric disorders represent a major challenge in terms of mortality and functional outcome of hip fracture patients.

## Type and frequency of neuropsychiatric disorders in hip fracture patients

In normal population severe cognitive impairment affects about 1% of adults aged 60-64 years and 30-40% of those over 85 years (4). Alzheimer Disease accounts for about 60-70% of dementia in the elderly with an estimated prevalence in Italy of over 1 million.

Delirium is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as a fluctuating level of consciousness and pervasive impairment in mental, behavioural, and emotional functioning. Delirium affects up to 30-40% of elderly hospitalized patients (5).

Depression is the most common of mood disorders in elderly people. The DSM-IV defines major depression as the occurrence of 5 or more of the following features: depressed mood, diminished interest or pleasure, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished energy to concentrate, and suicidal ideation. The prevalence of depression in the elderly is 17-37%, with 11-30% of that population having major depression (6). This prevalence might be underestimated in patients with any cognitive disorder.

There are several studies focusing on the prevalence of neuropsychiatric impairments in elderly patients at the time of the fracture.

Givens et al. have recently performed a prospective cohort study on 126 hip fracture inpatients, older than 65 years. The pre-fracture cognitive status was assessed using the Blessed Dementia Rating Scale. This scale had been specifically developed for proxy administration, and its reliability had been tested against direct patient assessment of cognitive status. In this population 41% had no evidence of pre-fracture cognitive impairment, no symptoms of depression or delirium during hospitalization; 30% had two specific conditions (59.5% had delirium and cognitive impairment, 21.6% had depression and cognitive impairment, 18.9% had delirium and depression); and 22% had one condition (51.85% delirium, 25.95% depressive symptoms, 22.2% cognitive impairments).

The authors also found that pre-fracture cognitive impairment or depression were related to a higher risk of mortality and institutionalization at 1 month (respectively OR 8.42 and 3.53). Delirium was strongly related to an increase of functional limitation in activities of daily living (ADL), a decline in walking autonomy, and a higher rate of nursing home placement or death (respectively OR 3.40, 4.39, 4.26) (7).

According to the National Health and Nutrition Examination Survey, depression is associated with a greater risk of hip fracture (HR 1.9) (8).

### Characteristics of delirium in hip fracture patients

#### Definition and epidemiology

The diagnostic criteria for delirium defined by DSM IV are shown in Table 1.

Table 1 - Diagnostic criteria for delirium (DSM-IV).

1. Disturbance in consciousness (reduced awareness of the environment) with impaired ability to focus, sustain or shift attention.
2. Change in cognitive (memory impairment, temporal-spatial disorientation, language disturbance) cannot be justified by a preexisting or evolving dementia.
3. Disturbance develops over a short period of time (usually hours to days) and has a fluctuation during the course of the day.
4. There is evidence from clinical history, physical examination, or other findings that the disturbance is caused by a general medical condition, drug intoxication or withdrawal syndrome.

Delirium is the most studied organic psychiatric disorder in patients who sustained a hip fracture, and it has been associated with increased morbidity and mortality rates, a longer length of hospital stay, and an increased risk of nursing home placement (9).

Its incidence ranges from 16% to 62% after surgery for hip fracture (10). It usually peaks between 2 and 5 days after surgery (11). Lipowski suggested that in elderly patients undergoing surgery for hip fracture there are three different clinical variants of delirium: "hyperactive-hyperalert", "hypoactive-hypoalert" (or lethargic) and "mixed" (12). Hyperactive-hyperalert patients present an overactivity of sympathetic nervous system, thus being restless and agitated; hypoactive-hypoalert patients are lethargic, confused, sedated, respond slowly to questions, and do not initiate voluntarily movements, they often wrongly receive a diagnosis of depression. All forms of delirium may also show disturbances in attention, memory, thought and language, sleep-wake, and visuo-constructional and perceptual abilities. Rabinowitz (13) assessed that the hypoactive form of delirium has a worse prognosis, while Marcantonio et al. (14) said that the hyperactive subtype is associated with a higher mortality rate.

A prodromal phase characterized by difficulties in concentrating and thinking clearly, changes in sleep-wake cycle with sleepiness during the day and restlessness at night, vivid dreams or disorientation immediately after the awake, and hallucination can occur before delirium. The result is that patients are often tired, restless, irritable, anxious and depressed and they may present cognitive and perceptual disturbances or hypersensitivity to sounds (15).

Duppils et al. report that anxiety, frequent requests for assistance, disorientation, reduced attention and psychomotor restlessness are frequent prodromic signs in elderly hip fracture patients who develop delirium after 6-48 hours (16).

De Jonghe et al. agree that delirium appears mostly within the fir-

st 48 h after surgery (respectively in 21% the day of the surgery and in 48% the day after). They also observed the following prodromic symptoms: disorientation (50-83% vs 23% in control), difficulty concentrating (60-83% vs. 43%), short-term memory impairment (50-83% vs 34%), long-term memory impairment (67-83% vs 53%) and an underlying somatic illness (40-76% vs. 17%) (15).

#### Pathophysiology and risk factors for delirium in hip fracture

The pathophysiology of post hip fracture delirium has not been yet clarified. Patients with hip fractures experience a high number of stressful events that may affect the development of delirium. The accident, the transfer to the hospital, the clinical and radiological examinations, the type of anesthesia and surgery, the administration of opioids, the sleep deprivation and the pain that is not always properly treated might have an important role in the development of delirium (10).

Recently Juliebo et al. run a prospective cohort study to identify risk factors for pre-operative and post-operative delirium in elderly patients with hip fracture. Pre-fracture cognitive impairment, indoor injury, fever, delayed surgical intervention were identified as independent risk factors and statistically significant for pre-operative delirium. BMI less than 20 and fracture occurring indoors were instead recognized as independent and statistically significant risk factors for post-operative delirium (9).

Other researches focused on the role of biological markers in the development of post-fracture delirium in elderly patients. Stress hormones as well as pro-inflammatory cytokines (Interleukins: IL-6, IL-8, IL-12) can affect some mental functions such as attention, memory, mood and perception. Several pro-inflammatory cytokines have been implicated in determining the development of the main symptoms of delirium in elderly patients. In humans, the most investigated pro-inflammatory cytokines are IL-6 and IL-8, even though only inconsistent correlations were shown. Van Munster et al. found that in a cohort of 120 hip fracture patients older than 65 years, with and without delirium, there were higher levels of cortisol and IL-8 before delirium, and of IL-6 and S100B during delirium (17).

#### Diagnosis of delirium

There are several screening tools to make diagnosis of delirium. The most used are the Confusion Assessment Method (CAM), the Delirium Rating Scale (DRS-R-98), and the Organic Brain Syndrome scale (OBS).

The CAM is a structured interview focusing on the main clinical issues of delirium: (1) acute change in mental status with fluctuating course, (2) inattention, (3) disorganized thinking and (4) altered level of consciousness. To make diagnosis of delirium it is required the presence of both symptoms 1 and 2 and at least one of the other two. This scale allows to distinguish delirium from dementia and depression with the 100% sensitivity and 94% specificity (18).

The DRS-R-98 is a useful tool not only to assess delirium but also to quantify its severity. It is made of 3 items for the diagnosis (temporal onset, fluctuation, and physical disorder), and 13 items concerning the severity of the symptoms (sleep-wake cycle disturbance, perceptual disturbances and hallucinations, delusions, lability of affect, language impairments, thought process abnormalities, motor agitation or retardation, orientation, alterations in attention, short and long-term memory deficits, visuo-spatial ability modifications) (19).

The OBS scale consists of two subscales: the first investigates principally on signs of confusion such as disturbances of awareness and orientation; while the second part covers a wide spectrum of symptoms such as emotional reactions, different types of time related variations and fluctuations in the clinical condition, suspiciousness and delusions, language and speech difficulties, neurological symptoms, spatial disorientation and impaired recogni-

tion, physical and practical disabilities, and social interaction skills (20).

*Interventions for preventing and treating delirium*

Bjorkelund et al. proposed a multi-factorial intervention program, consisting of oxygen supplementation, intravenous fluid supplementation and extra-nutrition, accurate monitoring of vital signs, adequate pain treatment, daily delirium screening, reduction in drug use, and modification in peri-operative management (see Table 2), in elderly patients with hip fracture. In a prospective study, they applied this program to a cohort of elderly hip fracture subjects, without any cognitive impairment at admission. The results, compared with an historical control group, showed a reduction of the 35% of patients who developed delirium during hospitalization (21). In our opinion, the extensive application of this protocol might significantly reduce the incidence of post-operative delirium.

Table 2 - The multi-factorial intervention program for delirium (adapted from Bjorkelund et al.).

1. Supplemental oxygen 3-4 l/min: in the ambulance and continually until day 2 post-operatively, during patient mobilization, or when patient's oxygen saturation is  $\geq 95\%$  without oxygen.
2. Intravenous fluid supplementation and extra nutrition: fructose/glucose 1.0 l in the ambulance or immediately after admittance. Additional i.v. supplementation in case of increased fasting. Extra oral multi-nutrient drinks daily post operatively.
3. Increased monitoring of vital physiological parameters: especially oxygen saturation starting at the place of injury until post-operatively, day 5. Systolic blood pressure should be maintained  $\geq 90-100$  mmHg. Red blood cell transfusion should be considered if hemoglobin  $< 100$  g/l. Avoid hypo-hyperthermia.
4. Pain relief: immediately after admittance with a combination of opioids and paracetamol i.v.
5. Avoid delay in transfer logistics: nurse assessment of patient immediately ( $\leq 5$  min) after admittance. Assessment by the orthopedic surgeon ( $\leq 30$  min) before referral to the X-ray department. After X-ray directly to the orthopedic ward.
6. Screen for delirium through daily testing with the OBS scale. All staff is educated and instructed to pay increased attention to symptoms of delirium.
7. Avoid polypharmacia: sedatives/hypnotics and drugs with anticholinergic properties should be administered with restriction.
8. Perioperative/Anesthetic period: for pre-medication paracetamol is recommended as a first choice. Propofol and/or alfentanil i.v. is recommended at arrival at the operating department before transfer to the operation table. Spinal anesthesia with bupivacain is recommended as a first choice. Systolic blood pressure should be maintained at  $< 2/3$  of baseline or  $>90$  mmHg. Red blood cell transfusion should be administered if there is a tendency toward increased blood loss ( $>0.3$  l) or hemoglobin  $< 100$  g/l. for sedation, propofol is recommended. Give adequate post-operative analgesia with paracetamol as a first choice or in combination with an opioid.

**Characteristics of depression in hip fracture patients**

*Definition and epidemiology*

Depression is a mood disorder, characterized by cognitive, behavioral, somatic and affective impairments that affect functional activity and social participation of a person. Patients who undergo surgery frequently experience depression that can worsen their functional outcome.

Prevalence of depression in older people after hip fracture ranged from 9% to 47% and largely exceed the 2% and 10% re-

spectively reported for major and minor depressive disorder in the aged-matched not affected people (3).

Depression is a highly disabling condition in itself and when associated with hip fracture significantly reduces functional outcome level. Mossey said that hip fracture older people with only few depressive symptoms were three times as likely to achieve independence in walking, and nine times to return to their pre-fracture level of function than those with more depressive symptoms (22).

*Diagnosis and interventions*

The diagnosis of depression is often performed by the Hamilton Depression Rating Scale (HDRS) and the Geriatric Depression Scale (GDS) (23, 24).

The original version of the Hamilton Scale contains 17 items (HDRS17) pertaining to symptoms of depression experienced over the past week. The questionnaire rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss.

The Geriatric Depression Scale allows to analyze also individuals with mild-moderate cognitive impairments. The scale is commonly used for a comprehensive geriatric assessment. The original GDS contains 30 items, but a short version of the GDS containing 15 questions has been developed. Recently, a further shortened version of GDS was proposed by van Marwijk et al. containing only 4 items and conserving high sensitivity and specificity (see Table 3).

Patients who are positive at the screening for depression should be considered for antidepressants and further assessed for cognitive impairments (25).

There are few studies focusing on the identification of risk factors

Table 3 - Geriatric Depression Scale 4 items.

1. Are you basically satisfied with your life?	Yes	<b>No</b>
2. Do you feel that life is empty?	<b>Yes</b>	No
3. Are you afraid that something bad is going to happen to you?	<b>Yes</b>	No
4. Do you feel happy most of the time?	Yes	<b>No</b>

Score 1 for answers in bold; 2-4=depressed, 1=uncertain, 0=not depressed

for depression after hip fracture and even less studies investigating prevention and/or intervention strategies.

Lenze et al. found that 18 of 126 patients (14%) with hip fracture developed a major depressive disorder (MDD). Of these patients, 61% showed early symptoms of MDD before discharge, furthermore no new case was identified after 14 weeks until the end of the study (24 weeks). Moreover he reported a higher incidence of MDD in hip fracture patients comparing with the general population, thus suggesting that hip fracture is a risk factor for depression. An alternative explanation could be that depressive symptoms are a risk factor for falls, osteoporosis and hip fracture. It seems that type of fracture and surgery, and degree of disability at discharge are not associated with depression, in contrast to other clinical events such as stroke, in which specific features as lesion location may be predictive of the risk of depression.

The first symptoms of depression usually appear within the 10<sup>th</sup> weeks, particularly the first 2 weeks, after the fracture, therefore this period is crucial to early detect and prevent it.

One of the most frequent early symptoms of MDD is apathy, that is the lack of interest, initiative and motivation (26).

Recently Oude Voshaar et al. published an interesting cohort study concluding that pain and anxiety after hip fracture surgery are other significant risk factors for depression (3).

Burns et al. recently published the results of two randomized con-

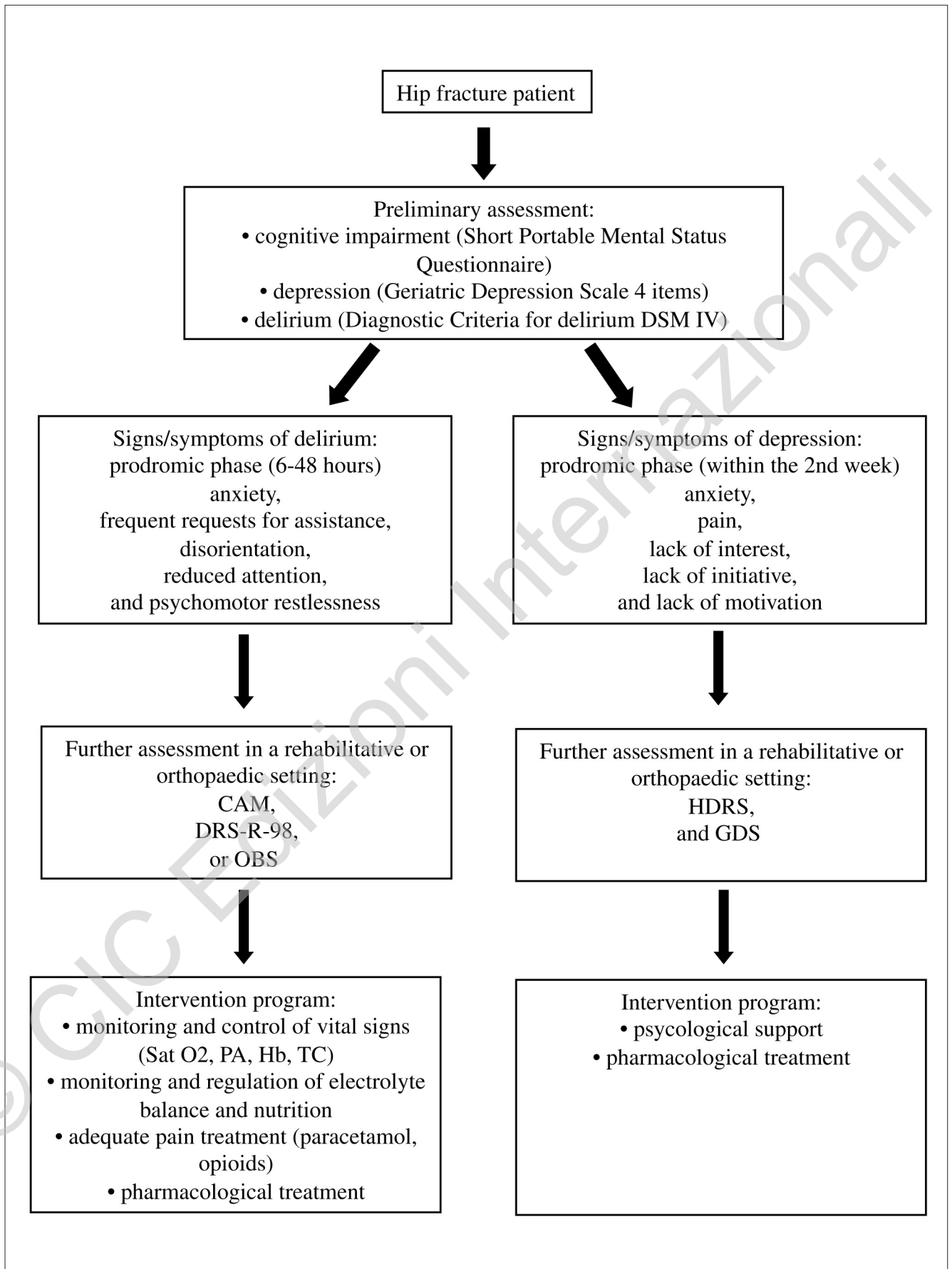


Figure 1 - Flow chart for diagnosis and treatment of post-fracture neuropsychiatric impairments.

trolled trials with the aim to evaluate the effect of a psychological approach in preventing depression and of a psychiatric intervention for its treatment. They concluded that there were no statistically significant benefits in both interventions for preventing and treating (27).

## Conclusion

Mortality and functional outcome in hip fracture patients are significantly related to the presence of neuropsychiatric comorbidities. The most frequent ones in elderly are delirium and depression. Early detection of these disorders can improve survival, and level of functional recovery. We strongly support the introduction of a routinely assessment of these impairments in order to start as soon as possible an adequate treatment. Therefore we propose a simple flow chart for the management of these patients that should be used in both Orthopaedics and Rehabilitative settings (see Figure 1).

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