Predictors of Postoperative Delirium in Geriatric Patients Following Surgical Fixation of Fractures.

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Purpose: The purpose of this study was to investigate risk factors associated with postoperative delirium (POD) in patients following surgical fixation of fractures. Additionally, a frailty assessment tool previously associated with POD was evaluated to determine whether each component was significantly associated with POD.

Methods: We performed a retrospective study of 608 patients aged ≥ 64 years admitted to the Massachusetts General Hospital for fractures. Medical, functional, and social data were collected at the initial assessment. A stepwise selection model was used to evaluate variables and create a model that predicted the risk of POD. Components of the FRAIL scale assessment were evaluated in an exploratory multivariable analysis to determine whether they were significantly associated with POD.

Results: POD occurred in 92 (15.1%) patients. Patients with POD were more likely to be older (OR 1.05, 95% CI 1.01-1.09), and have higher FRAIL scale scores (OR 1.35, 95% CI 1.07-1.71) and positive MiniCog (score < 3) (OR 2.52, 95% CI 1.22-5.20). Female gender was protective for POD (OR 0.39, 95% CI 0.21-0.74). Of the FRAIL scale components, fatigue was a risk factor for POD and the ability to ambulate was protective (β= 0.28, 95% CI 0.0025-0.56 and β= -0.34, 95% CI -0.65, -0.03, respectively).

Conclusions: In conclusion, older age, cognitive impairment, and frailty were risk factors for POD, whereas female gender was protective of POD in geriatric patients who underwent surgical repair of orthopedic fractures. MiniCog and FRAIL scale demonstrated predictive value in assessing patients' risk factors for POD. The FRAIL scale components that were found to be significantly associated with POD risk were fatigue and the inability to ambulate.

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Glossary of abbreviations

ADL	Activities of daily living
ASA	American Society of Anesthesiologists
BMI	Body mass index
CAM	Confusion Assessment Method
CCI	Charlson Comorbidity Index
CI	Confidence interval
GFR	Glomerular filtration rate
GIFTS	Geriatric Inpatient Fracture Service
ICU	Intensive care unit
MNA-SF	Mini Nutritional Assessment - Short Form
ORIF	Open reduction internal fixation
POD	Postoperative delirium
pRBC	Packed red blood cells
TSH	Thyroid stimulating hormone
UTI	Urinary tract infection

Section 1: Introduction

Postoperative delirium (POD) is a common acute brain dysfunction defined by disturbances or decline in attention, awareness, and cognition not explained by a pre-existing neurocognitive disorder. This acute confusional state typically occurs 24-72 hours after the completion of a surgical procedure and affects roughly 15–53% of patients with a higher prevalence in older populations of 60-65 years of age[1].

POD is associated with negative outcomes including prolonged hospitalization, persistent functional and cognitive deficits, and increased risk of dementia and mortality[2-5]. Its estimated healthcare cost in the the United States attributed to POD is $143-152 billion per year, surpassing the economic cost of diabetes and non-fatal falls combined[6]. The incidence of POD in geriatric patients with orthopedic fractures ranges from 12-51%[7]. Given the growth of the aging population, the incidence of orthopedic trauma and POD in geriatric patients is likely to increase along with the poor outcomes for elderly patients and economic concerns for the states.

Precipitating factors include acute illness, surgery, drugs, and stress[8]. Early interventions could prevent the occurrence of delirium and related detrimental outcomes. Recent studies suggest that clinical care protocols directed at elderly post-surgical patients may result in a reduced incidence of POD[9]. Therefore, principled strategies to preemptively identify and target patients at risk for POD may result in significantly improved perioperative outcomes. Predictive models may help identify risk factors for POD and stratify patients into risk categories for preventative care.

Several assessment tools have been associated with POD in elderly patients with fractures. Cognitive impairment as defined by MiniCog score < 3 is a risk factor for POD in patients with lower extremity fractures[10]. Additionally, the incidence of POD was significantly higher in frail patients determined by the FRAIL scale assessment[11]. We aim to validate these predictors in the cohort of orthopedic trauma patients admitted to the Geriatric Inpatient Fracture Service (GIFTS) at Massachusetts General Hospital to aid in the development of strategies for improved POD identification, prevention, and management.

Furthermore, assessment tools can be predictive of many events including POD, mortality, infections, increased length of stay, and other complications. The FRAIL scale is a short questionnaire consisting of self-reported fatigue, resistance status, ambulation status, illnesses, and loss of weight. The current scoring system of the FRAIL scale confers 1 point per component (**Extended Figure 1)**, but it is unclear if each component has equal strength in association with POD. We aim to evaluate the different components of the FRAIL scale to determine which of these are significant predictors of POD risk status.

Section 2: Student role

Patients were evaluated by geriatricians as a part of a routine initial assessment (**Extended Table 1**). I transferred the data collected from EPIC notes to REDCap and updated the patient database from record ID 233 to 692 (Note: Patients without evaluations from the geriatricians, had missing delirium statuses, or who did not undergo surgery were excluded from the final analysis). I assisted in the revision of the study questionnaires on REDCap to build variables of interest into the GIFTS clinical research database including number of insomnia medications and names of insomnia medications.

I completed a comprehensive literature review to create the current working hypothesis.

I worked alongside a statistician to implement univariate analysis comparing the incidence of POD with categorical and continuous variables and to create a model to predict POD using stepwise selection model. I also performed multivariable analysis using a generalized linear regression model comparing the incidence of POD with the individual components of the FRAIL scale.

Section 3: Methods

Data collection:

A retrospective study was performed using a cohort of 608 patients diagnosed with orthopedic fractures from January 2017 until June 2018. Participants were ≥ 64 years old with fractures admitted to Geriatric Inpatient Trauma Service at Massachusetts General Hospital for surgical fixation. Data of baseline patient characteristics including fracture type marital status, baseline

disposition, FRAIL scale score, ADL score, and MiniCog score were obtained in a face to face interview with geriatricians (**Extended Table 1**). Other variables such as admission hemoglobin/hematocrit and GFR, surgery type and date, ASA class, type of anesthesia, transfusion requirement, ICU stay, mortality, and postoperative complications (i.e. infections and AKI) were collected via chart review from the electronic medical records. Patients underwent surgical fixation of fracture which was either open reduction internal fixation (plate and screw or intramedullary nail), total hip arthroplasty, dynamic hip screw, hemiarthroplasty, or percutaneous pinning.

Patient evaluation/questionnaires:

The FRAIL scale score components and assessment questions are revealed in **Extended Figure 1**. Patients who scored 3+ on the FRAIL scale were identified as frail.

MiniCog consisted of 3 parts: 3 word registration, clock drawing, 3 word recall. Patients scored 0 or 2 points for correctly drawing the clock with hands. 1 point was assigned for each word recalled. Cognitive impairment, or a positive MiniCog, is defined by score <3.

Delirium was assessed daily by geriatricians using Confusion Assessment Method (CAM) (**Extended Figure 2**).

Statistical analysis:

A stepwise selection model was used to assess the variables of interest in predicting POD. A cutoff p-value of <0.35 was selected for inclusion in the model. Patients who had incomplete assessments of variables due to preoperative delirium or inability to assess were excluded from the analysis.

A generalized linear model was used to perform an exploratory multivariable analysis of the individual components of the FRAIL scale. Patients who had incomplete FRAIL scale assessments were excluded from the analysis.

Section 4: Results (observations, data analysis)

Results:

As presented in **Table 1**, 92 (15.1%) of the 608 patients experienced POD. Of those who had POD, 61 (66.3) were female and 31 (33.7%) were male, with an age range from 67-102 years and an average age of 84.8 ± 7.9 years. Of those who did not experience POD, 362 (70.3%) were female and 153 (29.7%) were male, with an age range from 64-99 years and an average age of 79.5 ± 8.5 years.

Compared to the non-POD cohort, patients who had POD typically were older and had a higher ASA class, greater requirement for transfusion during their hospitalization, greater incidence of positive MiniCog score, lower basic and instrumental ADL scores, higher FRAIL scale scores, and lower MNA-SF scores. The incidence of hemiarthroplasty was greater in the POD group compared to non-POD (32.9% vs 16.9%, respectively).

Predictors of POD were determined in a stepwise selection model (**Figure 1**). The results indicate that patients with POD were more likely to be older (OR 1.05, 95% CI 1.01-1.09), and have higher FRAIL scale scores (OR 1.35, 95% CI 1.07-1.71) and positive MiniCog (score < 3) (OR 2.52, 95% CI 1.22-5.20). Female gender was protective of POD (OR 0.39, 95% CI 0.21-0.74). The MNA-SF score does not have a statistically significant association with POD in the model.

Multivariable analysis of the FRAIL scale components revealed the ability to ambulate (β= -0.34, 95% CI -0.65, -0.03) had the strongest negative association with POD (**Figure 2**). In contrast, fatigue (β= 0.28, 95% CI 0.0025-0.56) was the only other component found to be significantly associated with an increased risk of POD. The ability to climb stairs (resistance), illnesses, and weight loss were not considered significant in the multivariable analysis.

Section 5: Discussion, Limitations, Conclusions, Suggestions for Future Work

Discussion:

In this study, our main findings revealed that only some of the components of the FRAIL scale were significantly associated with POD in geriatric patients who underwent surgical repair of orthopedic fractures. Of the components, ambulation status had the greatest negative effect on

POD, whereas fatigue had a smaller but positive effect on POD. Although age and frailty were also risk factors for POD, cognitive impairment was found to be the most predictive of POD.

Given that ambulation had a greater association with POD compared to resistance, it is possible that severe immobility is correlated with cognitive dysfunction. Data suggests that sedentary behavior is associated with cognitive impairment, and that high levels of physical activity are linked with a lower incidence of cognitive dysfunction[12-14].

The findings in the study are consistent with risk factors identified in current literature. A prior systematic review by Viramontes et al.[15] found that there was an association between cognitive impairment and an increased incidence of POD in patients with total hip arthroscopy (THA). A retrospective study by Aziz et al.[16] revealed that older age and male gender are risk factors for POD following THA. Lee et al.[17] also identified age and male gender as risk factors for POD in patients with hip fracture repair through a prospective cohort study.

The implication of this study is that healthcare providers can seek preemptive consultations for delirium precautions in patients who are fatigued or have poor mobility. Providers can also consider shortening the FRAIL scale to these two components when evaluating POD risk in the clinical setting. It is important to note that fatigue and ambulation are easy to assess, as opposed to illnesses and weight loss, which patients might not know and might not be documented in medical records.

There are several strengths of our study. First, the study utilized a large sample size of 608 patients. We also utilized a large set of variables that could be considered for possible association with POD outcome. There was also standardized evaluations with the same set of geriatricians who performed the initial assessments and daily CAMs. Additionally, patients with preexisting conditions were not excluded from the study, thus making the results more generalizable.

Limitations of the study include the fact that the design was done retrospectively. There was also a disproportionate incidence of hip fractures and female patients, which does not necessarily reflect the same risk for POD in patients with other types of fractures or male patients. This can

be addressed with future work that exclusively evaluates risk factors for POD in male or non-hip fracture patients. Second, some patients with concurrent delirium during the initial assessment were excluded due to an inability to answer questionnaires, which may have resulted in a final model that did not reveal risk factors accurately. Lastly, it was possible to miss CAM positive diagnoses depending on the onset of delirium and the time patients were evaluated.

Additional suggestions for future work include optimizing existing questionnaires (i.e. ADLs, CCI, MiniCog) to include only the most pertinent and predictive POD components. Another future study can identify the association between FRAIL scale scores and the duration and severity of delirium[18].

In conclusion, older age, frailty, and cognitive impairment were risk factors for POD, whereas female gender was protective of POD in geriatric patients who undergo surgical repair of orthopedic fractures. The FRAIL scale components that were significantly associated with POD risk were fatigue and the inability to ambulate.

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Table 1 Baseline characteristics

	No POD (n= 516)	POD (n= 92)	P-value
Sex			
Male	153 (29.7%)	31 (33.7)	0.44
Female	362 (70.3%)	61 (66.3)	

Age			
Mean (S.D)	79.5 (8.5)	84.8 (7.9)	
Median (range)	79.0 (64-99)	85.5 (67-102)	
Missing	1	0	
Age (group)			
<80	265 (51.5%)	22 (23.9)	<0.0001*
>80	250 (48.5%)	70 (76.1)	
Marital status			
Single/Widow/Separated/Divorced	315 (62.6%)	58 (65.9%)	0.56
Married/Living with partner	188 (37.4%)	30 (34.1%)	
Type of fracture[†]			
Hip	282 (61.3%)	61 (72.6%)	0.26
Knee/Above knee Fracture	80 (17.4%)	11 (13.1%)	
Below knee fracture	52 (11.3%)	6 (7.1%)	
Others	46 (10.0%)	6 (7.1%)	
Type of surgery			
ORIF	266 (54.2%)	40 (47.1%)	0.002*
Total hip arthroplasty	48 (9.8%)	2 (2.4%)	
Hemiarthroplasty	83 (16.9%)	28 (32.9%)	
Others	94 (19.1%)	15 (17.6%)	
Anesthesia type			
General	415 (85.2%)	74 (89.2%)	0.34
Spinal	72 (14.8%)	9 (10.8%)	
ASA class			
1-2	152 (32.1%)	14 (17.1%)	0.006*
3+	322 (67.9%)	68 (82.9%)	
Transfusion preop/intraop			
No	305 (95.6%)	41 (95.3%)	0.94
Yes	14 (4.4%)	2 (4.7%)	
Transfusion preop/intraop/postop			
No	305 (59.1%)	41 (44.6%)	0.009*
Yes	211 (40.9%)	51 (55.4%)	
MiniCog score			
Positive	101 (24.0%)	32 (62.7%)	<0.0001*

Negative	320 (76.0%)	19 (37.3%)	
Insomnia medications			
No	368 (71.3%)	62 (67.4%)	0.45
Yes	148 (28.7%)	30 (32.6%)	
Charlson Comorbidity Index score			
0-2	23 (4.9%)	0 (0%)	0.2
3-4	115 (24.5%)	14 (16.3%)	
>=5	331 (70.6%)	72 (83.7%)	
Basic ADL score			
Mean (S.D)	5.4 (1.4)	4.2 (2.3)	<0.0001*
Median (range)	6.0 (0-6)	6.0 (0-6)	
Missing	34	14	
Instrumental ADL score			
Mean (S.D)	5.3 (2.9)	2.7 (3.1)	<0.0001*
Median (range)	7.0 (0-8)	1.0 (0-8)	
Missing	30	11	
FRAIL scale score			
Mean (S.D)	1.4 (1.4)	2.4 (1.4)	<0.0001*
Median (range)	1.0 (0-5)	2.5 (0-5)	
Missing	39	12	
MNA-SF score			
Mean (S.D)	12.0 (2.4)	10.2 (3.2)	<0.0001*
Median (range)	13.0 (2-14)	10.0 (3-14)	
Missing	64	19	

† Hip fracture (Intertrochanteric, subtrochanteric, femoral neck); Knee/Above knee fracture (Femoral shaft, distal femur, patella, operative pelvis); Below knee fracture (Distal tibia, tibia plate, tibia shaft, ankle, foot); Other (Clavicle, scapula, humerus, elbow, forearm, wrist)

Figure 1 Stepwise selection model for POD

	OR (95% C.I.)	P-value
Female gender	0.39 (0.21-0.74)	0.004*
Age	1.05 (1.01-1.09)	0.009*
Positive MiniCog score	2.52 (1.22-5.20)	0.005*

MNA-SF score	0.89 (0.79-1.00)	0.056
FRAIL scale score	1.35 (1.07-1.71)	0.013*

Figure 2 Multivariable analysis of FRAIL scale components and POD

Deficit	Total Group Yes %	β	CI (95%)	P value
Fatigue	36.3%	0.28	(0.0025, 0.56)	<0.05*
Resistance	63.2%	-0.13	(-0.42, 0.16)	0.38
Ambulation	62.7%	-0.34	(-0.65, -0.03)	0.03*
Illness	31.0%	0.11	(-0.16, 0.36)	0.43
Loss of weight	15.9%	0.21	(-0.10, 0.50)	0.18

Extended Table 1: Patient Assessment Question Set

- Fracture data
    - Date of fracture
    - Type of fracture (periprosthetic fracture, side of fracture)
- Socio-Demographic Data
    - Name
    - Date of birth
    - Age at admission
    - Gender, language
    - Marital status
    - Baseline disposition
- Abbreviated Social Risk Score
    - English-speaking, cohabitation, availability of person during crisis, leisure activities
- Charlson Comorbidity Score
    - Myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue

disease, ulcer disease, mild liver disease, diabetes (without complications), diabetes with end organ damage, hemiplegia, moderate or severe renal disease, solid tumor (non-metastatic), leukemia, lymphoma/multiple myeloma, moderate or severe liver disease, metastatic solid tumor, AIDS
    - Age range
- Medications
    - Antihypertensives, warfarin, aspirin, clopidogrel, new oral anticoagulant, low molecular weight heparin, calcium, vitamin D, anti-osteoporotic medication, insomnia treatment
- Cognitive assessment
    - MiniCog
    - Global deterioration scale
- Basic ADL
    - Activities, bathing, dressing, toileting, transferring, continence, feeding
- Instrumental ADL
    - Telephone, shopping, preparing food, housekeeping, laundry, transportation, handling medications, handling finances
- Functional Ambulation Classification
- Ambulatory aid
- FRAIL scale index
    - Fatigued, ability to climb stairs and walk a block, presence of 5+ illnesses, weight loss
- Falls in the last year
- MNA-SF
    - Food intake, weight loss in last 3 months, mobility, psychological stress, neuropsychological problems, BMI
    - Supplements
- Lab data
    - Hemoglobin and hematocrit at admission, GFR at admission, Vitamin B12, TSH, total protein, albumin, Vitamin D
- Surgery data

    - Date of surgery
    - Time of anesthesia
    - ASA classification
    - Type of anesthesia
    - Type of surgery
    - Weight bearing status
- Transfusion data
    - None, preoperative, intraoperative, postoperative, units of pRBC
- ICU data
    - Date of ICU admission
    - Date of transfer from ICU to floor
- Mortality data
    - Date of in-hospital mortality
    - Cause of hospital mortality
- Complications data
    - Delirium assessed via Confusion Assessment Method including date of positive CAM
    - Acute kidney injury, respiratory infection, urinary tract infection, atrial fibrillation, heart failure, ischemic heart disease, pressure ulcers, urinary retention, paralytic ileus, deep vein thrombosis/pulmonary embolism, stroke, wound/hardware complication, others
- Discharge data
    - Date of discharge
    - Discharge service (orthopedic, medicine, ICU, etc.)
    - Discharge disposition
    - Home services at discharge
    - Health insurance problems

Extended Figure 1 FRAIL scale components and score breakdown

	Scoring	**Assessment Question**

Fatigue	Yes +1 No +0	"Over the last two weeks before your trauma, how often do you feel tired or fatigued?"
Resistance	Yes +0 No +1	"In the last month, did you climb a flight of stairs without an assistive device?"
Ambulation	Yes +0 No +1	"In the last month, did you walk a block without an assistive device?"
Illness	Yes +1 No +0	"Did a doctor ever tell you that you have [illness]*?"
Loss of weight	Yes +1 No +0	"Have you lost more than 5% of your weight unintentionally within the last year?"

*hypertension, diabetes, cancer, chronic lung disease, myocardial infarct, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease

Extended Figure 2 Confusion Assessment Method (CAM)

	Assessment*
1	**Acute onset** or **Fluctuating course**
2	**Inattention**
3	**Disorganized thinking** or **Altered level of consciousness**

*Positive CAM is defined as scoring positive for all 3 components.