Title: Does anticholinergics drug burden relate to global neuro-disability outcome measures and length of hospital stay?

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Abstract

Primary Objective: To assess the relationship between disability, length of stay (LOS) and anticholinergic burden (ACB) with people following acquired brain or spinal cord injury.

Research Design: A retrospective case note review assessed total rehabilitation unit admission.

Methods & Procedures: Assessment of 52 consecutive patients with acquired brain/spinal injury and neuropathy in an in-patient neuro-rehabilitation unit of a United Kingdom university hospital. Data analysed included: Northwick Park Dependency Score (NPDS), Rehabilitation complexity Scale (RCS), Functional Independence Measure and Functional Assessment Measure FIM-FAM (UK version 2.2), LOS and ACB. Outcome was different in RCS, NPDS and FIM-FAM between admission and discharge.

Main Outcomes & Results: A positive change was reported in ACB results in a positive change in NPDS with no significant effect on FIM-FAM, either Motor or Cognitive, or on the RCS. Change in ACB correlated to the length of hospital stay (regression correlation: -6.64; SE: 3.89). There was a significant harmful impact of increase in ACB score during hospital stay, from low to high ACB on NPDS (OR=9.65; 95% CI: 1.36 to 68.64) and FIM-FAM Total scores (OR=0.03; 95% CI: 0.002 to 0.35).

Conclusions: There was a statistically significant correlation of ACB and neuro-disability measures and LOS amongst this patient cohort.

Introduction

Medications with anti-cholinergic properties are widely prescribed particularly in older people [1,2] with approximately 20-50% of older people being prescribed at least one [3]. These medications have been associated with dizziness, sedation, confusion, delirium, and a decline in physical function, in addition to other side-effects such as dry mouth, dry eyes, constipation, blurred vision and increased heart rate [1,3,4]. A recent systematic review reported that medicines with anti-cholinergic properties in the general population have a significant adverse effect on cognitive and physical function, but limited evidence exists for adverse effects in delirium or on mortality [5]. Consequently, to avoid inappropriate prescribing of anti-cholinergic drugs, caution has been advised [1].

Current evidence suggests that cognitive impairment associated with anticholinergic use is reversible on discontinuation of medications in the general population. However this has been questioned with trials reported anticholinergic medications may be associated with increased risk of longer term mild cognitive impairment or dementia post suspension of this medication [6-8].

Medications with anti-cholinergic properties are used in populations within neuro-rehabilitation units frequently. This is the first published study reporting on anti-cholinergic in neuro- rehabilitation Units. As Table 1 demonstrates, a variety of medications with anti-cholinergic properties are frequently prescribed for people in neuro-rehabilitation units to manage symptoms such as urinary incontinence and pain subsequent to brain injury and spinal cord injury.

Insert Table 1 here

Given the acknowledged potential side-effects of these medications, it is hypothesised that they may have a detrimental effect on hospital length of stay. Currently length of stay is a major performance marker for hospitals and individual departments in the United Kingdom (UK) and the United States of America (USA). In 2013, as part of a national service reconfiguration for neuro-rehabilitation, the UK Department of Health (DoH) included length of stay, alongside response times and discharge destinations, as contributors to defining local population needs [9]. The proposed tariff system provides financial incentives for specialist units to discharge patients as soon as safe. There is, however, a paucity of evidence regarding what factors may contribute to increasing length of stay in neuro-rehabilitation units where patients with cognitive deficits are treated. Therefore investigating whether the anti-cholinergic burden impacts on length of stay could have important financial as well as quality of life implications for neuro-rehabilitation service provision.

The Anti-cholinergic Burden (ACB) scale measures the net load of such medication [10]. This scale was developed through a review of the literature to identify drugs with documented anticholinergic activity and a consensus meeting involving experts in the area. To our knowledge, no published evidence exists regarding the prevalence of ACB in neurologically impaired populations and its impact on length of stay in neuro-rehabilitation units. Accordingly, the purpose of this paper is to examine firstly what the impact of the ACB could be on both the functional recovery of people following traumatic brain injury and spinal cord injury secondly to determine whether ACB scores impact on rehabilitation centre length of stay.

Methods

Design

A retrospective case note review was chosen for this pilot study. Data were routinely collected as part of UK Rehabilitation Outcome Collaboration (UKROC) which is a mandatory requirement for specialist neuro-rehabilitation units in the UK [11]. Formal approval was obtained from the East Kent University's NHS Trust Neurorehabilitation Unit's Audit Director who authorises such "practice-based evidence" category research. The UKROC data collection was approved by the East Kent University Hospital's ethical review board.

Participants

The cases notes of fifty-two consecutive patients with acquired brain or spinal injury admitted to a 19-bedded in-patient neuro-rehabilitation centre of a UK university hospital were reviewed.

Data Collection

Data were extraction from each set of case notes by a senior neurology registrar (FM) and a medical student (MM), overseen by the director of the service (MS). All data were extracted onto a standardised data collection proforma. Data collected included:

- Patient demographic data (age and gender)
- Hospital length of stay as defined as the date of admission to date of discharge
- The Functional Independence Measure and Functional Assessment Measure (FIM-FAM UK version 2.2) score already calculated for each patient as a mandatory outcome measures. These are global measures of disability in the brain injured population. The scale measures separately FIM Motor & FIM Cognitive disability. It has an ordinal

scoring system for all 30 items from 1-7 (1=complete dependence and 7=fully independent) [11]

- The Rehabilitation Complexity Scale (RCS). This is part of minimum dataset in neurology units, it is a 22-point measure providing a simple overall measure of Care, Nursing, Therapy, Medical and Equipment needs, and is designed to offer a crude banding of complexity.

- The Northwick Park Nursing Dependency tool (NPDS) provides an assessment of patient care needs. It is an ordinal scale incorporating activities of daily living, safety awareness, behavioural management and communication.

- Anticholinergic burden assessed using the ACB Score [3,10]. The Anti-cholinergic Burden (ACB) scale measures the net load of such medication [10]. This scale was developed through a systematic review of the literature to identify drugs with documented anticholinergic activity. Medications were identified to have absent, possible or definite anticholinergic properties based on the ACB properties. Drugs with possible anticholinergic effects were defined as those with serum anticholinergic activity or in vitro affinity to muscarinic receptors but with no known clinically relevant negative cognitive effects (ACB score 1). Drugs with established and clinically relevant cognitive anticholinergic effects were considered to be definite anti-cholinergics (ACB score 2–3).

- This scale was validated in a large longitudinal study of participants enrolled in the Medical Research Council Cognitive Function and Ageing Study [12]. Using the ACB, we categorised patients' ACB status into 3 categories (no ACB = total score 0; low ACB = total score 1 and moderate to high = total score >= 2).

Data Analysis

The data was assessed for distribution prior to analysis. Based on this a statistical operation was undertaken to include multiple linear regression analysis of the effect of change in ACB between admission and discharge. The primary analysis was to assess the relationship between LOS and ACB. The secondary analyses were to assess the relationship between ACB and RCS, NPDS and the FIM-FAM. Resulting change in outcome was evaluated with mean and standard errors. We also evaluated the relationship between type of ACB change (no change, change to lower level and change to higher level) at discharge compared to admission, and outcomes around the median (below-above) with logistic regression, adjusted for age, sex, and clinical diagnosis.

Post-hoc sample size calculation

As part of this pilot study, a post-hoc power calculation was undertaken to determine the required sample size for a definitive study. All inferential analyses were regression coefficients and standard errors (SE). All analyses were performed by a statistician (AB) using the MATLAB R2014 software (MathsWorks, Natick, Massachusetts, USA).

A power calculation, using power=0.80, effect size=0.35 and probability level=0.05, for a multiple linear regression was undertaken to detect a significantly large predictor of effect. From this, when using a single predictor, the power calculation suggests that using more than 25 participants will allow the detection of a sufficiently large effect and to detect medium size effect, 54 observations are needed. Therefore this pilot study is only likely to detect a large to medium effect if they exist.

Results

Cohort Characteristics

Notes of 52 people following admission to a neuro-rehabilitation unit were examined. The mean age of the cohort was 61 years (range 31 years to 92 years), and there were 37 males and 15 females; everyone in the cohort was Caucasian. The ACB characteristics and functional scores for the cohort on admission and discharge are presented in Table 2.

Insert Table 2 here

Overall, the median ACB Score on admission was 1.5 and 2 at discharge. There was no statistically significant difference between ACB on admission compared to discharge (p=0.31; 95% CI: -0.20 to 0.62). Median length of stay was 59.5 days. The medications with anticholinergic properties prescribed on admission and at discharge are presented in Table 1.

Relationship between ACB Score and Outcomes

The change in ACB negatively correlated to the length of hospital stay (coefficient: -6.64; SE: 3.89) where higher ACB score related to longer length of hospital stay. Graphically the mean regression coefficient and standard error are shown demonstrating potentially significant effects of ACB on the outcome for NPDS and length of hospital stay (red bars) but not for the other outcomes (blue bars) for the complete dataset (Figure 1). Figure 2 represents the change in ACB between admission and discharge. This indicates that as there was a decrease in ACB (positive change), was related to a shorter length of hospital stay. An increase in the Δ (delta)

ACB was associated with a decreased length of stay. Therefore if the anti-cholinergic prescription drug at discharge had a lower score on the ACB scale compare to admission, there was a positive Δ and the length of stay for the patient would be reduced. Conversely, if the anti-cholinergic prescription drug at discharge had a higher score on the ACB scale compare to admission, the Δ would be negative, and the length of hospital stay would be longer.

Insert Figure 2 here

The analysis of ACB score and FIM-FAM indicated no significant relationship between these two variables for the cognitive (coefficient: 0.15; SE: 1.10) or motor (coefficient: 1.29; SE: 1.83) subsets. Similarly, there was no statistical significant relationship between ACB score and RCS at discharge (coefficient: 0.00; SE: 0.29). However, the results suggest that there was a statistical relationship between ACB score and NPDS, where higher ACB causes poorer functional recovery following brain or spinal injury.

Relationship between type of ACB change and outcomes around the median:

The outcomes suggest that a higher ACB at discharge compared to admission, was associated with increase the NPDS score (higher than median value of the cohort) with an Odds Ratio: 9.65 (95% CI: 13.36 to 68.64) and to decrease the FIM-FAM Total number of OR 0.03 (95% CI: 0.002 to 0.35). There were no significate differences for lower change of ACB for these outcomes (Table 3).

Insert Table 3 here

Discussion

The findings of this study suggest that there may be a statistically significant relationship between ACB score and length of stay in a neuro-rehabilitation unit following traumatic brain injury or spinal cord injury. There appears limited evidence for a relationship between ACB score and functional outcomes for this population in this context. Nevertheless, we observed that those who's ACB increased during hospital stay as a group had higher likelihood of NPDS and FIM-FAM total scores above the group median.

It is important to remember that this was a pilot study and therefore the results may have been influenced by type two statistical error. Nonetheless these pilot results provide an indication and trend. A power calculation has been presented to inform the design of a definitive evaluation of the impact of ACB score on length of stay in patients admitted to a neuro-rehabilitation unit.

Previously there has been limited data on the prevalence and impact of medications with ACB on patients in a neuro-rehabilitation unit. Often drugs like oxybutynin are needed to treat urge incontinence a common complication of patients at NRU who sustain injury to brain and/or spinal cord. Cognitive impairment due to anti-cholinergic activity [13] may adversely affect patient's ability to engage in the rehabilitation process potentially increasing the LOS. This may partly account for why rehabilitation length of stay was longer in those who had a higher ACB score.

Kidd et al [14] explored the relationship between ACB and length of stay. Their results were inconclusive. A recent systematic review of the impact of ACB score on function reported similar inconclusive results between an associated reduction in cognitive function and ACB score within the general population [5]. However, in a subgroup analysis of people with dementia, there appeared to be a strong trend towards an association between reduced cognitive function and increased ACB score [5]. It may be argued that a similar trend is reported in this pilot study, where another group of patients with existing cognitive impairment through acquired brain

injury, demonstrate a greater length of stay. Further examination of this with a larger cohort to give a sufficiently powered analysis is required to definitively determine the association between these factors.

This current study has multiple limitations. Our sample size was small and from a single specialist centre; all participants were Caucasian. Nevertheless, the statistically significant correlation was sufficiently powered to detect a large effect size. We used routine data from clinical documentation for ACB calculations hence we were unable to test the accuracy of these data. We cannot exclude the possibility of other confounding factors for length of stay in this cohort. For example, the seasonal variation may impact on length of stay [15]. Therefore, whilst acknowledging that "practice based evidence" will often influence, complement and inform formulation of "evidence based policy" we would recommend a prospective study design to definitively answer the research question [16].

The findings of this study may be valuable in the current health care setting. From a quality of care perspective, reduced length of stay in rehabilitation units can facilitate improvements in healthcare efficiency to allow earlier admission to specialist rehabilitation rather than delayed admission whilst waiting for bed-spaces. This is important as early rehabilitation has previously been acknowledged to be more clinically and cost effective [17]. Within the current NHS funding model this more efficient use of bed-spaces can also provide financial rewards for the providing neuro-rehabilitation unit.

This study has provided an indication that medications with anti-cholinergic properties may be a modifiable factor which could have a positive significant effect on length of stay and potentially functional outcome. This study also provides evidence of the range of medications with anti-cholinergic properties which are used in neurorehabilitation units for this population. There was no pattern of medication classes which seemed to make patient's stay longer. However we cannot with certainty rule this out as in an observation study such as this, we cannot imply causality and there may also be unknown confounders and the possibility of

residual confounding. Nonetheless based on these findings, further exploration with sufficiently powered cohorts is warranted.

Conclusion

This paper described the prevalence of anti-cholinergic prescribing and the burden score in people with brain injury or spinal cord injury in a single rehabilitation centre in the UK. The findings suggest that there is a correlation between ACB and length of stay where greater ACB is associated with longer length of hospital stay. There is also a significant association between an ACB change increasing during hospitalisation and worsening of NPDS and FIM-FAM Total disability scores. However, we recommend larger epidemiological research and caution with prescribing drugs with anti-cholinergic properties for patients with brain injury.

Declarations of Interest

The authors report no declarations of interest.

Figure and Table Legends

Figure 1: Mean and standard error values for the association of ACB Score with clinical outcomes include length of stay.

Figure 2: Scatter graphs to demonstrate the mean change in ACB between admission and discharge with 95% confidence intervals.

Table 1: Anticholinergic medications prescribed and Anticholinergic Burden on admission and at discharge.

Table 2: Descriptive Statistics from the cohort

Table 3: Odd Ratios (95% Confidence Intervals) of NPDS, RCS, FIM-FAM and Length of Stay below or above the median based on no change of ACB at discharge compare to admission

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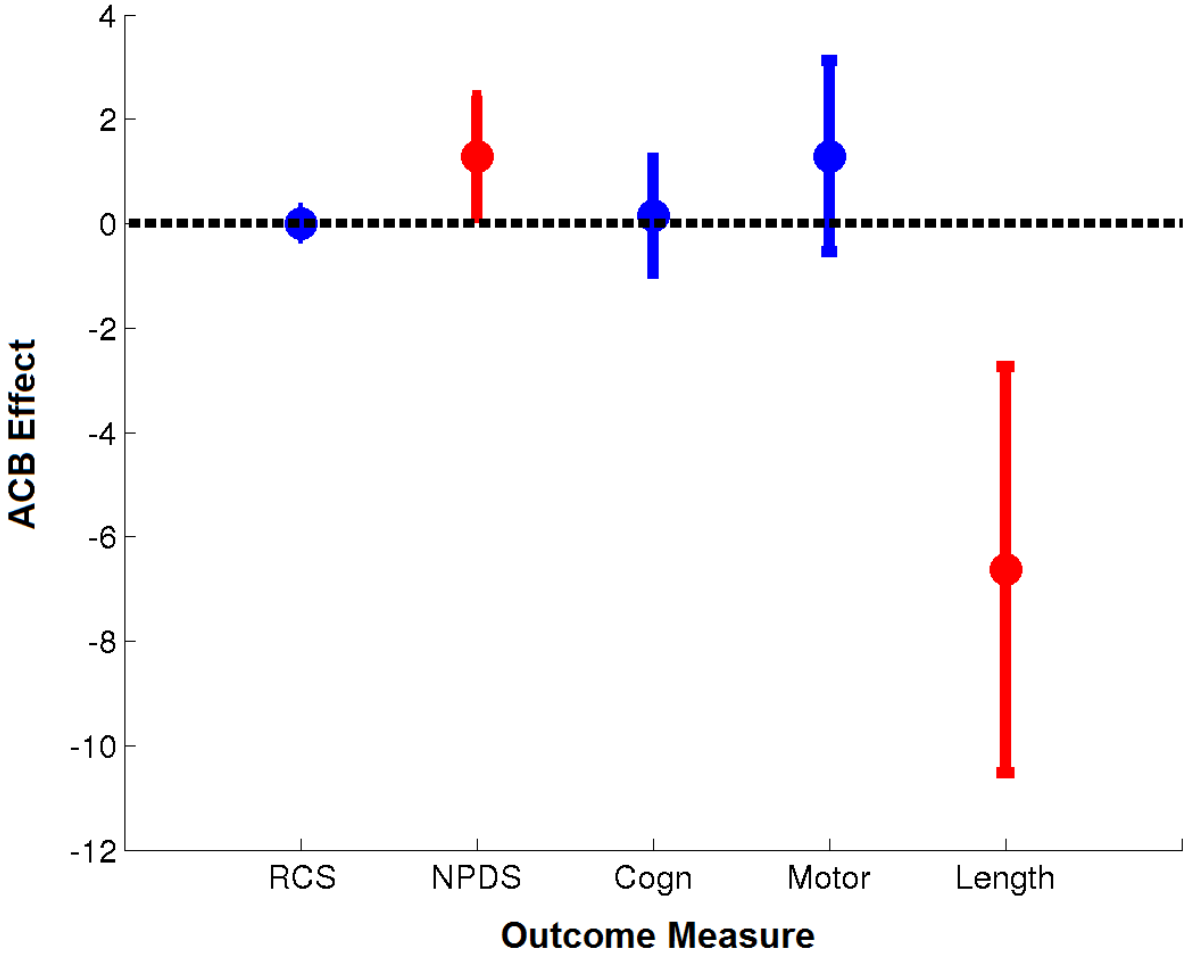
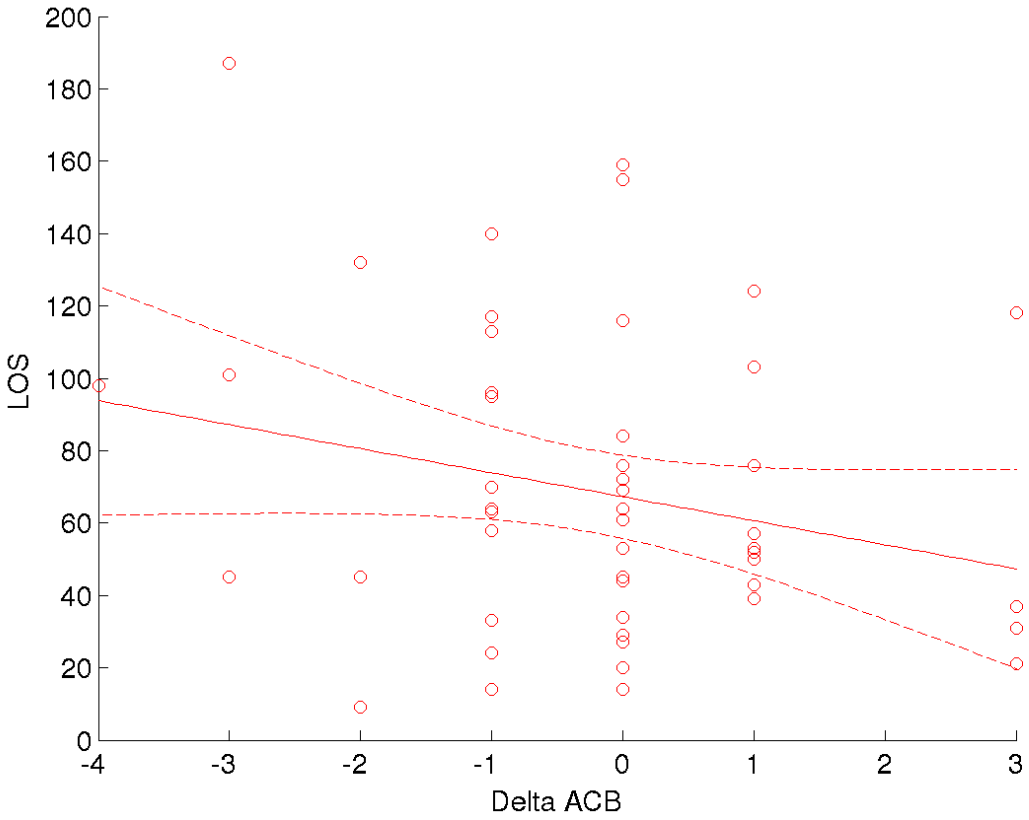
Figure 1: Mean and standard error values for the association of ACB Score with clinical outcomes include length of stay.



* *Red bars demonstrate significant effects, blue bars are non-significant*

Cogn – FIM-FAM Cognitive Disability; Length – Length of Hospital Stay; Motor – FIM-FAM Motor Disability; NPDS - Northwick Park Nursing Dependency tool; RCS - Rehabilitation Complexity Scale (RCS)

Figure 2: Scatter graphs to demonstrate the mean change in ACB between admission and discharge with 95% confidence intervals.



ACB – anticholinergic burden; LOS – Length of stay.

Table 1: Anticholinergic medications prescribed and Anticholinergic Burden on admission and at discharge.

Frequency of Medications Prescribed	Admission	Discharge
Bisoprolol	6	8
Ramipril	4	6
Lorazepam	1	0
Prednisolone	4	4
Frusemide	4	4
Lisinopril	2	2
Metoprolol	2	0
Amlodipine	9	8
Tramadol	3	4
Perindopril	3	2
Nifedipine	1	0
Ranitidine	4	6
Morphine	2	1
Buprenorphine	1	1
Amitriptyline	4	6
Zopiclone	4	3
Mirtazepine	2	1
Warfarin	1	2
Nimodipine	1	0
Fludrocortisone	1	1
Carbamazepine	1	1
Codeine	4	6
Hydroxyzine	1	1
Atenolol	3	1
Promethazine	1	0
Quetiapine	1	1
Chorophenamine	1	0
Paroxetine	1	1
Duloxetine	1	1
Clonazepam	0	2
Diazepam	0	1
Fentanyl	0	1
Oxybutinin	0	3

Anticholinergic Medication	Admission	Discharge
Anticholinergic Burden ACB*	1.5 (1 to 4.5)	2 (0 to 4)
ACB 0: no anticholinergic burden**	11 (21.2)	15 (28.9)
ACB 1: low anticholinergic burden**	15 (28.9)	10 (19.2)
ACB ≥2: moderate to high anticholinergic burden**	26 (50.0)	27 (51.3)

Table 2: Descriptive Statistics from the cohort

Characteristics	N=52	
Mean Age (Range)	61 years (31- 92)	
Gender (% Males)	71.2%	
Ethnicity (% Caucasian)	78.8%	
Handedness (% Right)	92.3%	
Diagnosis – Acquired Brain Injury (%)	82.7%	
Diagnosis – Spinal Cord Injury (%)	17.3%	
Length of Stay* (Days)	68.7 (9 to 187)	
Baseline Data	**Admission**	**Discharge**
FIM-FAM (total) *	197.0 (57.7 to 152.0)	184.0 (37.2 to 104.5)
RCS*	11 (10 to 12)	8 (6 to 10.8)
NPDS*	29.5 (16 to 40.5)	22 (12 to 38)
Anticholinergic Burden ACB*	1.5 (1 to 4.5)	2 (0 to 4)
ACB 0: no anticholinergic burden**	11 (21.2)	15 (28.9)
ACB 1: low anticholinergic burden**	15 (28.9)	10 (19.2)
ACB ≥2: moderate to high anticholinergic burden**	26 (50.0)	27 (51.3)

*** (Median; IQR)**

**** (Frequency; N)**

Table 3: Odd Ratios (95% Confidence Intervals) of NPDS, RCS, FIM-FAM and Length of Stay below or above the median based on no change of ACB at discharge compare to admission.

		Lower Change	No Change	Higher Change
NPDS * (26/26)	Model A	2.22 (0.57 – 8.60)	1.0	5.54 (0.98 – 31.25)
	Model B	1.70 (0.38 – 7.74)	1.0	**9.65 (1.36 – 68.64)**
RCS* (31/21)	Model A	1.13 (0.29 – 4.39)	1.0	1.27 (0.28 – 5.68)
	Model B	1.00 (0.23 – 4.38)	1.0	2.63 (0.46 – 14.98)
FIM-FAM Total* (26/26)	Model A	0.39 (0.10 – 1.54)	1.0	**0.07 (0.01 – 0.62)**
	Model B	0.47 (0.10 – 2.21)	1.0	**0.03 (0.002 – 0.35)**
LoS * (26/26)	Model A	1.49 (0.39 – 5.74)	1.0	0.85 (0.19 – 3.80)
	Model B	1.54 (0.37 – 6.46)	1.0	0.49 (0.09 – 2.55)

*** (Below/ Above Median)**

Model A : Unadjusted
Model B : Adjusted for Age, Sex, Diagnosis