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Journal Club: Long-term functional outcome in patients with acquired infections after acute spinal cord injury

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Infections, particularly pneumonia, are the primary cause of mortality in individuals with spinal cord injury (SCI).[1] Several factors may contribute to the high rate of infections in the SCI population, including motor paralysis and reduced reflexes resulting in aspiration, invasive procedures, and so-called SCI-induced immune depression syndrome (SCI-IDS).[2,3] SCI-IDS is thought to occur when the connection between the CNS and the immune system are disrupted by a lesion in the spinal cord, resulting in a decrease in immune function.[3] In addition to increased morbidity and mortality, infections after SCI may affect neurologic recovery.[2,3] A recent study found that infections impaired the return of muscle strength up to 1 year postinjury; however, the long-term consequences remain uncertain.[2]

The aim of this study was to investigate whether infections occurring in an acute care setting after SCI affected long-term functional recovery and survival.[4]

METHODS **Data source and inclusion criteria.** The study by Kopp et al.[4] used data gathered from the multicenter National Spinal Cord Injury Database (NSCID). The NSCID prospectively gathers data from 25 specialized traumatic SCI care centers.[2] Inclusion criteria were admission within 24 hours after injury between 1995 and 2005, age between 17 and 75, a cervical SCI, complete baseline and infection data, and an American Spinal Cord Injury Association Impairment Scale (AIS) grade of A, B, or C (see table e-1 at Neurology.org for a full description of the AIS grading system). Participants were excluded if they resided in a hospital or nursing home prior to injury, had serious concomitant injuries affecting consciousness, or were rehospitalized for unspecified infectious or parasitic diseases during the follow-up period.

Exposures and outcomes. The primary outcomes were the motor items of the Functional Independence Measure (FIM; FIM_{motor} total score and 4 additional FIM_{motor} subscores) at 4 timepoints (admission, discharge, 1 year, and 5 years postinjury). The secondary outcome measure was infection-associated mortality at 10 years postinjury. Hospital-acquired infections included pneumonia and postoperative wound infections that occurred during acute care or inpatient rehabilitation.

Statistics. FIM_{motor} scores as a dependent variable were analyzed in 3 ways: an explorative analysis of scores at each of the 4 timepoints, a linear mixed model (LMM), and an adjusted LMM. Both models used multiple imputation and a sensitivity analysis using only complete cases. The measure of interest was a time × infection interaction term; that is, if early infection had a time-dependent effect on the recovery of FIM_{motor} scores. The LMMs included the initial model (adjusted only for baseline FIM_{motor} scores), an additional model (adjusted for AIS, level of injury, age, ethnic group, and working status), and finally 3 models stratified for AIS grade and adjusted for the aforementioned variables.

Mortality data were analyzed using an exploratory analysis and a Cox regression model (adjusted and unadjusted) over 10 years. Similar to the LMM, the Cox models were adjusted for AIS, stratified for AIS, and further adjusted for neurologic level of injury, age, working status, and educational level.

RESULTS A total of 1,203 individuals were included in the study, with 47% (564) acquiring an infection during early care, the majority of which were pneumonia (540 acquired pneumonia, 11 postoperative wound infections, and 13 both). The group that acquired infections was significantly different from the group that did not with regards to sex (a higher proportion of males), injury severity (a higher proportion of AIS As), level of injury (a higher proportion of C1–C4 injuries), and median baseline FIM_{motor} scores (a smaller interquartile range).

The exploratory analysis in the complete cohort and the AIS A group identified significantly higher FIM_{motor} scores in those without acute infections at each time point. The AIS B and C group analyses only found a significant difference between the 2 groups at discharge.

Supplemental data at Neurology.org

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The FIM_{motor} score LMMs not stratified by AIS (imputed and complete cases models) all revealed a significant association between acquired infections and impaired recovery of FIM_{motor} scores at each time point, and overall. Specifically, the imputed model adjusted for all variables revealed a −7.4 point difference (95% confidence interval [CI] −11.5 to −3.3) and the complete cases model revealed a −5.2 point difference (95% CI −8.4 to −2.0). The model was then stratified by AIS and adjusted for level of injury and sociodemographic variables. When the model was stratified by AIS grade, there was an overall significant association between infections and impaired recovery in AIS A (both models) and in AIS B at 5 years for the imputed model only. The AIS C model did not confer an overall significant association.

In-hospital mortality was not significantly different between the groups with and without infections; however, Kaplan-Meier survival curves indicated a significant difference in survival in both the total cohort and AIS subgroups over a 10-year period. Initial Cox regression confirmed a significant association between infection and mortality in the total cohort with and without adjustment for AIS grade, and stratification by AIS grade revealed an association in AIS A and B. Further adjustment for level of injury and sociodemographic variables (age, working status, and educational level) confirmed the significant association in the complete cohort (hazard ratio 1.65, 95% CI 1.26–2.16) and the AIS A stratification.

INTERPRETATION This work indicates that pneumonia and postoperative infections in acute care after SCI negatively affect both long-term functional recovery and survival. This study was conducted using an observational database. Although this design introduces the possibility of additional factors related to the exposure (infections) influencing the outcomes, the study design is suitable for the nature of the study as it is not possible to randomize individuals to the study exposure.

The authors provide a strong statistical analysis investigating the association between early infections after SCI and long-term functional recovery and mortality utilizing multiple imputation to account for attrition bias. Attrition, or loss to follow-up, can occur for numerous reasons, and is of particular concern in longitudinal studies.[5] These missing data can introduce bias when the lack of data is related to the outcome measure, and is not missing at random.[5] One strategy to avoid this bias is multiple imputation, in which missing values are predicted through other observed values in the dataset, creating multiple imputed datasets, and averaging these imputed estimates.[5] This is a common method of accounting for missing data, with varying outcomes.[5,6] Presented in conjunction with the complete case sensitivity analysis, the imputed data allow for a transparent interpretation of the results. In addition, the authors also adjust for variables known to be related to functional recovery after SCI (e.g., level of injury, AIS). The results consistently confirm that early infections are associated with impaired functional outcomes after SCI in complete SCI. The authors note that these effects are likely due to pneumonia, as this accounted for the majority of recorded infections.

Based on stratified sensitivity analyses, the authors reported that attrition bias existed in AIS groups B and C, but not A, due to the fact that the imputed and complete case only models produced differing results. This could indeed be due to attrition bias, or inaccuracy in the imputations. It would be of interest to examine whether this was due to a nonrandom dropout in the groups AIS B and C, and not A.

Given that the cohort included patients enrolled between 1995 and 2005, it would be of interest to know how the management of care after SCI (e.g., infections and treatments for infections) changed throughout this time frame,[7,8] or if year of admission differed significantly between the groups. Perhaps related to care, length of acute care stay has also been shown to affect functional outcomes after SCI, and could provide further insight.[9,10]

Regarding inclusion/exclusion criteria, the authors provided valid reasoning for the inclusion of specific injury characteristics (limiting heterogeneity and ceiling effects in recovery), though no reason was given for the exclusion of individuals in prior care. Second, patients who were rehospitalized for unspecified infectious or parasitic diseases during follow-up were also excluded, and a justification was also not provided. Both prior care and rehospitalization could potentially confound the relationship between infection and function/survival, which may have been the reason for their exclusion. However, it would be interesting to quantify how these factors affected the study outcomes in a sensitivity analysis. Third, of all the individuals who were enrolled in NSCID and met the initial selection criteria (n = 1,427), 1,203 (84%) remained after the application of the exclusion criteria. Exclusion was largely due to age and missing baseline assessments. Although the proportion of patients recruited was high, it would be of interest to know if those excluded due to missing data differed significantly with regards to injury characteristics or outcomes.

Overall, this article provides a strong statistical analysis of the available data and presents a comprehensive report of the outcomes. Future analyses on novel cohorts and potential confounding and mediating variables could increase our understanding of how

acute infections after SCI are related to long-term functional recovery.

AUTHOR CONTRIBUTIONS

F.M. Warner: drafting/revising the manuscript, analysis or interpretation of data. B. Tong: revising the manuscript, analysis or interpretation of data. Dr. Jutzeler: revising the manuscript, analysis or interpretation of data. Dr. Cragg: revising the manuscript, analysis or interpretation of data. P.S. Scheuren: revising the manuscript. Dr. Kramer: drafting/revising the manuscript, analysis or interpretation of data.

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DISCLOSURE

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