# The Time Course of Acute Pain in Hospitalized Patients: Exciting Progress in Data and Methods

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Acute pain has historically been considered a time-limited experience.[2] However, this notion has begun to clash with the increasingly recognized phenomena of chronic postsurgical pain.[4] The last few years have witnessed an escalating number of examinations of the elapsed days contribution to pain resolution, attempting to determine whether certain temporal "cut offs" can delineate boundaries between acute and chronic pain.

Research findings regarding temporal trajectories of acute pain have refuted many historical assertions concerning the predictable, near-universal resolution of postoperative pain in the early days following surgery. Work by Chapman et al. measuring the progression of daily average postoperative pain scores using mixed modeling techniques taught us that 37% of patients suffer flat, or even increasing, postoperative pain trajectories through postoperative day 6 [3]. Follow-up work by Lavand' Homme and colleagues demonstrated remarkably different early temporal trajectories of postoperative pain following total knee arthroplasty in patients developing chronic postsurgical pain versus those with anticipated early resolution of their surgical pain[5]. Deeper investigation into the interaction of psychosocial modulators of postoperative pain, such as depression and anxiety, also revealed that temporal considerations could impact the interpretation of effects that had previously been considered as static in nature. For instance, Althaus et al. demonstrated faster resolution of acute postoperative pain despite higher initial pain intensity in patients with increased preoperative anxiety[1].

Postoperative pain provides a clinical platform for the study of acute pain that commonly includes a baseline pain intensity, a "scheduled injury," and recurring postoperative assessment and treatment captured as part of standard clinical documentation. This model is imbued with certain key assumptions: that baseline preoperative pain represents a "baseline", despite the fact that pain is often a key motivator to pursue surgical treatment; that surgery is often performed with some expectation by both patient and surgeon that it will eventually lead to less overall pain; and that pain in surgical models is nearly always related to exogenous mechanisms of tissue injury.

While prior investigations of the temporal nature of acute pain have largely focused on surgical populations, this month's article by Kannampallil and colleagues significantly builds upon prior investigations of acute pain in hospitalized patients by exploring the

temporal domain of pain within the medical hospital population. Moreover, this article applies several uncommon, yet quite apropos, statistical methodologies that better address the inherent challenges in studying temporal patterns in this patient population. Ther work by this research team differs from similar prior investigations in that it includes a mixed population of patients admitted by a range of inpatient services ranging from psychiatry to medicine to surgery. Such aggregations of patient populations present several analytical challenges given the overlapping distributions of sociodemographics, comorbidities, admitting diagnoses, and courses of hospitalization. To address this challenge, Kannampallil et al. combined sociodemographic, service-level, treatment, and temporal aggregations via K-means clustering to identify four distinct clusters of patients. Kannampallil and colleagues also use mixed-effects regression with a polynomial function for measuring temporal effects, refining the quantification of each individual patient's variation from the mean trajectory with empirical Bayesian estimation. This allowed for intra-subject considerations across irregularly timed assessments to highlight the variance contribution of time, and which enabled investigators to move beyond simple linear functions of effects over time. In addition, the differentiation of temporal trajectories according to cluster analyses is also notable, capturing not only rates of pain decrease but also the presence of pain rebound in a cluster consisting of older, non-surgical patients with lower opioid utilization and higher rates of only non-opioid analgesics or no medications. The proposal for the use of an area under the curve of a temporal trajectory as a marker for the quality of pain treatment is a particularly noteworthy opportunity that addresses existing limitations with current measures relying on pain intensity and opioid consumption. This approach is important because it underscores the need to focus on addressing longer-term recovery rather than addressing each pain intensity rating as an independent point.

Epidemiological investigations into the acute pain of hospitalized patients are critically important contributions to our understanding of the clinical suffering of these patients. It is important to also note that currently available statistical frameworks commonly used in such investigations are unable to address three important facets of acute pain management of the hospitalized patient: 1) A lack of context regarding activity level at the time of pain assessment, 2) a lack of inputs on irregular timing of analgesic interventions, and 3) a lack of linkage to medical surgical and functional outcomes.

In terms of activity level at the time of pain assessment, many clinical assessments of pain intensity fail to capture data on the clinical context of the intensity rating. Ratings captured before, during, or after physical therapy, unrelated to the admitting diagnosis, or in relation to "minor and common" hospital procedures that nevertheless can be quite painful (e.g., phlebotomy, Foley catheter insertion) carry important contextual information that may influence the anticipated impact of the acute pain experience on measures of functional outcome.

Regarding a lack of inputs on irregular timing of analgesic interventions, one of the most important contextual details about pain intensity relates to the type and timing of analgesic interventions. Such irregularly timed interventions are often interspersed among irregularly timed pain assessments, with different anticipated pharmacokinetic profiles of analgesic interventions further obfuscating potential temporal associations among effects. Even simple

models of such sequential interactions can necessitate moving beyond traditional statistical methods of clustering, classification, and regression, instead pushing investigators to explore the realms of mathematical simulation.

In considering the lack of linkage to medical surgical and functional outcomes, it is important to note that, to date, large-scale electronic medical record-based epidemiological investigations of pain in primary care and hospitalized patient populations have largely focused on core descriptors of the population at hand. Indeed, this is quite appropriate given the need to establish a foundational base in this research domain. The work by Kannampallil, and others before, importantly extends this avenue of research into the temporal domain. However, further work is necessary to expand temporal domain investigations into linkages with longer-term surgical and functional outcomes in order to determine the contribution of acute pain and analgesic strategies to post-discharge functional outcomes. Once these additional foundations are set, future work in this area will also need to consider the spatial effects of both hospital location and patient residence before and following hospitalization.

Altogether, these observations point to the need for researchers in the pain community not only to expand upon their epidemiological investigations into the pain experience of hospitalized patients, but also to expand the repertoire of the analytical tools they utilize.

## Acknowledgments

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