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Association between fibromyalgia and adverse perioperative outcomes

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Editor's key points

- Fibromyalgia has features that may increase perioperative risk.
- This retrospective review could not identify an association between fibromyalgia and major complications.
- There was an unexpected reduction in mortality in those with fibromyalgia.
- A diagnosis of fibromyalgia may lead to treatments that otherwise reduce perioperative risk, but an alternative explanation is unmeasured or residual confounding.

Background. Fibromyalgia, the classic non-inflammatory pain syndrome, has been associated with chronic inflammatory makers which are linked with increased morbidity and mortality. We tested the primary hypothesis that patients with fibromyalgia undergoing hospital procedures have a high risk of cardiovascular complications. Our secondary goals were to evaluate the association of fibromyalgia with: (i) in-hospital thromboembolic events, (ii) in-hospital mortality, and (iii) in-hospital microvascular complications.

Methods. We obtained 21.78 million discharge records from 2009 to 2010 from the US Agency for Healthcare Research and Quality censuses across the seven states. We matched fibromyalgia records and compared records with controls based on age, gender, state of discharge, principal procedure, and a propensity score developed from the set of diagnosis-related predictors. A multivariable logistic regression was used to compare matched fibromyalgia patients and controls on the primary and secondary outcomes.

Results. We matched 89 589 pairs for a total sample size of 179 178 discharge records. The adjusted odds ratio for in-hospital cardiovascular complications was 1.04 [99% confidence interval (CI): 0.90–1.19, $P=0.51$], for thromboembolic events was 1.03 (99% CI: 0.93–1.15, $P=0.46$), for in-hospital mortality was 0.81 (99% CI: 0.73–0.89, $P<0.001$), and for microvascular complications was 0.96 (99% CI: 0.88, 1.04, $P=0.18$). Two separate sensitivity analyses produced results similar to that of the primary analysis for all three complication outcomes.

Conclusions. We found no evidence that the diagnosis of fibromyalgia increased the risk of in-hospital complications. Fibromyalgia seems to be associated with a reduction in in-hospital mortality, but this requires confirmation with a large prospective controlled study.

Keywords: anaesthesia, general; chronic pain; complications, death; risk; surgery, non-cardiac

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Fibromyalgia is a debilitating pain syndrome characterized by widespread generalized pain, affecting 2% of the US population and more than 3% of women totalling to ~5 million adult cases.[1] Although the term fibromyalgia was first introduced in 1976,[2] the condition is not new. Clinical manifestations of muscular pain were recognized as early as 1592, and identified by the term muscular rheumatism; there have since been numerous refinements in nomenclature as our understanding of this entity evolved.[3]

Fibromyalgia is classically described as a non-inflammatory pain syndrome, but increased concentrations of inflammatory markers including C-reactive protein,[4] interleukin-10, interleukin-8, and tumour necrosis factor-α[5] challenge this notion. Chronic inflammation, even at low levels, is associated with heart disease.[6] Autonomic dysfunction is common in patients with fibromyalgia,[7] and includes postural orthostatic tachycardia syndrome[8] and abnormal heart rate responses during and after exercise.[9] Moreover, impaired baroreceptor reflexes in fibromyalgia reduce responsiveness to changes in arterial pressure.[10] During episodes of acute stress, hypotension and hypertension may remain unchecked, either of which may lead to cardiac ischaemia by decreased coronary perfusion.

Chronic autonomic dysfunction, including poor cardiac rate control,[9 11] is associated with increased risk of coronary artery disease possibly mediated by endothelial dysfunction.[12 13] There is evidence to suggest increased arterial wall stiffness and endothelial dysfunction in patients with fibromyalgia, leading to impaired endothelium-mediated vasodilation, thus compromising blood flow.[14 15] Endothelial dysfunction, aside from being a risk for cardiac disease, is also linked to thromboembolic events. It is thus not surprising that hypertension, dyslipidaemia, and coronary atherosclerosis are highly associated with fibromyalgia.[16 17] Autonomic nervous system hyperactivity and impaired endothelial functions as seen in

fibromyalgia may also be associated with end-organ damage to sensitive organs such as the kidney.[18] This concept is supported by a study that noted microvascular changes and decreased functioning of the smaller vessels in patients with fibromyalgia.[19]

There are common underlying processes between fibromyalgia and myocardial infarction, thromboembolic events, impaired microcirculation, all of which can lead to increased mortality, but the clinical relationships have yet to be evaluated. Myocardial infarction risk appears to be increased in patients with various rheumatological diseases, notably systemic lupus erythematosus, which shares clinical features with fibromyalgia.[20] However, the association between fibromyalgia and cardiovascular complications has yet to be established.

Our primary goal was thus to evaluate the association between fibromyalgia and cardiovascular complications in the perioperative period. Specifically, we tested the primary hypothesis that patients with fibromyalgia have a higher risk of postoperative myocardial infarctions. Our secondary goals were to evaluate the association of fibromyalgia with: (i) in-hospital thromboembolic events characterized by deep vein thrombosis, pulmonary embolism, pulmonary infarction, transient ischaemic attack, and stroke; (ii) in-hospital mortality; and (iii) microvascular complications characterized by impaired renal function and impaired wound healing.

Methods

Under authorization by the US Agency for Healthcare Research and Quality, censuses of inpatient hospital discharge data across the following seven states were obtained: Arizona, California, Florida, Iowa, Maryland, Michigan, and New Jersey.[21] A total of 21.78 million discharge records from 2009 to 2010 were reviewed. Discharge data included basic patient characteristics such as age and gender, diagnosis codes with present-on-admission (POA) indicators, and procedure codes. All diagnosis and procedure codes were based on the International Classification of Diseases and Injuries, Version 9, Clinical Modification coding system.

We excluded medical visits (as defined by zero procedures performed) and visits associated with patients aged <40 yr. Fibromyalgia was identified using the POA diagnosis code 729.1 (myalgia and myositis, unspecified). We considered year of discharge, state of discharge, gender, age, principal procedure code, and all POA diagnosis codes (excluding that specified above for fibromyalgia) as potential confounding variables.

Diagnosis and procedure codes are hierarchical in nature. Each diagnosis code is represented by a maximum of five digits and each procedure code is represented by a maximum of four digits. Truncating trailing digits thus results in an aggregation of detailed diagnoses (or procedures) to a more general diagnosis (or procedure) class. For example, the diagnosis code 550.03 represents bilateral recurrent inguinal hernia with gangrene, while 550.0 represents all inguinal hernias with gangrene (unilateral, bilateral, or unspecified), and 550 represents all inguinal hernias. Five-digit diagnosis codes are thus more sparsely represented than three-digit codes—some to the extent that they can potentially introduce stability issues relating to small cell sizes during estimation of regression models. Therefore, in encoding baseline diagnosis-related predictors for analysis, we aggregated POA diagnoses if they were represented by fewer than 50 000 patients (which represented 0.56% of the patients meeting study inclusion criteria). Coupled with an assumed fibromyalgia incidence of $\sim$1%, this implied a minimum cell size of about 500 discharges for any predictor in our propensity model. Diagnoses not meeting the minimum cell size criterion were truncated down to a minimum of three digits, and three-digit diagnosis codes still not meeting the criterion were removed. Likewise, patients' primary procedures were aggregated from four digits to a minimum of two digits.

Cardiovascular, thromboembolic, and microcirculatory complication outcomes were encoded from the diagnosis codes not recorded as POA. In-hospital mortality was available as a binary indicator variable in the discharge record. Neither mortality nor any of the complication outcomes were mutually exclusive; therefore, a record may have more than one outcome. However, multiple events in the same outcome category would only result in one outcome.

Statistical analysis

We matched fibromyalgia discharges to a single control discharge before modelling. Matches were based on age, gender, state of discharge, (aggregated) principal procedure, and a propensity score developed from the set of aggregated POA diagnosis-related predictors. Propensity scores (i.e. the estimated probability of having fibromyalgia based on patients' other POA diagnoses) were estimated using elastic net logistic regression.[22 23]

Elastic net logistic regression is a 'shrinkage' methodology, wherein the overall size of fitted model coefficients is purposely biased towards zero in order to maximize predictive accuracy in external samples. In short, coefficients pertaining to highly correlated diagnoses tend to be averaged together, while coefficients pertaining to irrelevant diagnoses are 'shrunk' entirely to zero, effectively removing the diagnosis from the model altogether. The R statistical software (The R Foundation for Statistical Computing, Vienna, Austria) package 'glmnet' was used to fit the propensity model from the aggregated POA diagnosis-related predictors.[24]

Successful matched pairs were restricted to those with common gender, common state of discharge, common principal procedure, a difference in age of <5 yr, and a difference in diagnosis-based propensity score of <0.01. We used a greedy distance-based algorithm for the matching;[25] that is, observations were randomly ordered and for each successive fibromyalgia discharge in the data set, the nearest qualifying discharge without fibromyalgia according to age and propensity score was selected as the matched control.

After matching, the balance between fibromyalgia and normal controls on the aforementioned baseline variables