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Evaluation of risk factors for pseudo-obstruction in systemic sclerosis

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Abstract

OBJECTIVE: Although up to 90% of systemic sclerosis (SSc) patients are affected by gastrointestinal (GI) dysmotility, the clinical phenotype of patients with pseudo-obstruction is not well-defined. We sought to identify this phenotype by studying a large cohort of SSc patients with and without pseudo-obstruction.

METHODS: We performed a retrospective analysis of patients seen at the Johns Hopkins Scleroderma Center between February 2003 and September 2017. All SSc patients had clinical data prospectively collected in a longitudinal database. Cross-sectional analyses were performed comparing autoantibody status and clinical and demographic features of patients with and without pseudo-obstruction. Cox proportional hazards regression was used to identify risk factors for pseudo-obstruction.

RESULTS: 175 patients with SSc had a history of pseudo-obstruction, and 2,637 SSc patients did not. After adjusting for significant variables from the univariate analysis and potential confounders, the Cox proportional hazards multivariable analysis demonstrated that older age (HR 1.02; 95% CI 1.00-1.04), male sex (HR 1.75; 95% CI 1.42-2.43), diffuse cutaneous disease (HR 2.52; 95% CI 1.59-3.99), myopathy (HR 1.83, 95% CI 1.09-3.08), and opioid use (HR 2.38; 95% CI 1.50-3.78) were predictive of pseudo-obstruction. Autoantibodies to RNA polymerase-3 were negatively associated with pseudo-obstruction (HR 0.34; 95% CI 0.17-0.66).

CONCLUSION: We identified clinical features associated with pseudo-obstruction in a large US SSc cohort. This study identifies characteristics of patients with SSc who are at a higher risk of developing pseudo-obstruction and suggests that opioids may be a modifiable risk factor. These clinical features may allow for earlier diagnostic evaluation and/or therapeutic intervention for patients at risk for pseudo-obstruction.

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INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by a progressive vasculopathy, fibrosis, and internal organ dysfunction. The gastrointestinal (GI) tract is affected in over 90% of patients with this disease [1]. Severe involvement of the lower GI tract, however, is less common, and is often characterized by episodes of recurrent pseudo-obstruction, malabsorption, and refractory constipation that require multiple hospitalizations or total parenteral nutrition [2–5]. To that end, multiple studies have reported severe GI involvement is associated with high morbidity and mortality [1, 2, 6, 7, 8, 9].

Pseudo-obstruction is a rare but severe GI complication in SSc with a prevalence of <10% in patients with diffuse cutaneous disease [5, 6, 8]. Patients can experience severe abdominal pain, distention, bloating, and the inability to tolerate an oral diet [5–6]. The risk factors associated with SSc-associated pseudo-obstruction are poorly defined and therefore this often severe GI complication is challenging to predict. We previously reported risk factors and clinical features associated with severe SSc GI disease requiring parental nutrition [10]; however, few studies focusing on risk factors for pseudo-obstruction exist. A detailed characterization of predisposing factors, clinical phenotype, and the natural history of GI progression to pseudo-obstruction is needed to identify at-risk patients for earlier evaluation and potentially the adjustment of modifiable risk factors. In this report we utilize the Johns Hopkins Scleroderma Center database to identify clinical features associated with pseudo-obstruction and define baseline risk factors that are predictive of this complication.

METHODS

Study population

The Johns Hopkins Scleroderma Center Cohort was established in 1991 to study the natural history of the disease among patients seen in our Center. We performed a retrospective analysis of patients seen between February 2003 and September 2017, as 2003 was the first year of our electronic medical record. All patients had data prospectively collected in our longitudinal database if they met 2013 ACR/EULAR criteria for systemic sclerosis, 1980 American College of Rheumatology (ACR) criteria, had at least three of five features of CREST syndrome, or minor criteria (Raynaud's, abnormal nailfold capillaries, SSc-specific autoantibodies) [11]. At each visit, an assessment of the clinical involvement of systemic sclerosis and a detailed medication reconciliation were recorded. Patients with pseudo-obstruction were identified by having a modified Medsger GI severity score of 3 (i.e. evidence of pseudo-obstruction or malabsorption) at least one time during follow-up. Of these SSc patients with Medsger GI score of 3, a chart review was performed to confirm that the patients met our predefined criteria for pseudo-obstruction, which required that at least 3 of the following findings were present at the visit during which they were scored a 3: abdominal pain, nausea, vomiting, failure to pass flatus, bloating, distention, tympany to percussion, or high-pitched bowel sounds. In addition, patients were also required to have documentation of imaging and/or physician notes to rule out alternative causes of obstruction. For a sensitivity analysis, a more stringent case definition of pseudo-obstruction was utilized requiring patients to have dilated bowel documented on imaging. Patients without pseudo-obstruction were defined as having a maximum modified GI Medsger

severity score of 2 or less. Written informed consent was obtained from all patients. The present study was approved by the Johns Hopkins Institutional Review Board.

Clinical Phenotyping

The Center's database includes demographic and clinical data, including age at first clinical visit, sex, race, smoking status, disease duration from first Raynaud's or non-Raynaud's symptom, SSc skin subtype, and autoantibody status. Specific organ involvement is defined at baseline by Medsger's severity scores and objective measures, and then approximately every 6 months at follow-up visits on all actively followed patients.

In this study, the presence of lung and/or cardiac involvement was defined by a score of 1 or greater on the respective Medsger severity scores (lung or heart) [6]. Severe Raynaud's was defined as a Medsger Raynaud's severity score of ≥ 2 (i.e. presence of digital pits, ulcers, or gangrene). Myopathy was identified by the physician and was dependent on the presence of at least one of the following abnormal test results at any visit: an elevation in creatinine phosphokinase (CPK), myopathic features on electromyography (EMG), magnetic resonance imaging (MRI) consistence with muscle inflammation, or abnormal muscle biopsy. The presence of tendon friction rubs and cancer (ever/never) was also recorded. Specific measures of pulmonary function were recorded (minimum forced vital capacity [FVC] and minimum single breath diffusing capacity for carbon monoxide [DLCO] at any visit, measured as the absolute value as well as the percent predicted value all standardized for sex and age). Estimated right ventricular systolic pressure (RVSP) was measured by transthoracic echocardiogram and obtained as part of routine clinical screening. All analyses were performed using the maximum score estimate for any study. Data on the use of opioids, promotility agents, and immunosuppressive medications (mycophenolate mofetil, methotrexate, cyclophosphamide, and IVIG) were collected at each visit. Information on death was collected through the National Death Index as is the standard practice in the management of our database. The end of follow-up was determined by the date of pseudo-obstruction, the date of last visit/patient contact, or the date of administrative censoring (September 2017), whichever came first.

Autoantibody profile

Autoantibody data was systematically obtained on all patients using the commercially available line immunoblot assay (Systemic Sclerosis Profile Euroline [IgG]; Euroimmun, Lubeck, Germany). This assay provides the ability to screen for autoantibodies to Scl-70, centromere (CENP A or CENP B), RNA polymerase-3 (RP11 or RP155), Fibrillarin (U3RNP), Nor90, Th/To, Ku, PmScl75, PmScl100, and PDGFR. Patients were considered positive for anti-centromere, RNA polymerase-3, or PM-Scl antibodies if they were positive for either of the respective subunits on the Euroline profile (i.e. anti-centromere positive if positive for either CENP-A or CENP-B). Moderate to strong titers were considered positive. Sensitivity analyses were performed using different cut-off values for a positive result.

Statistical methods

Cross-sectional analysis.—We compared SSc patients with a history of pseudo-obstruction (prevalent and incident cases) to those without a history of pseudo-obstruction.

We performed Chi-square or Fischer's exact tests to evaluate for associations between dichotomous variables. Student's t-tests were used for parametric data to examine differences between the means of continuous variables between two groups. Non-parametric continuous variables compared across two groups were evaluated with the Wilcoxon-Mann-Whitney test. The association between the presence of pseudo-obstruction (dependent variable) and the independent variables (SSc characteristics and autoantibody type) was expressed as the odds ratio (OR) and the corresponding 95% confidence interval (95% CI), or as a P-value (considered significant when ≤ 0.05). A multi-variable logistic regression model was constructed and the following covariates were included in the model based on their clinical relevance: age at first symptom (Raynaud's or non-Raynaud's), age at first symptom (first non-Raynaud's only), sex, race (Caucasian vs. non-Caucasian), and cutaneous subtype. Additional significant variables from the univariate analysis were also included.

Cox proportional hazards model.—Cox proportional hazards regression was performed using the study population limited to incident cases of pseudo-obstruction and patients without a history of pseudo-obstruction. Opioid exposure was included as a time-varying covariate prior to the first observed outcome of incident pseudo-obstruction, death, or administrative censoring. We included the same covariates into the Cox proportional multivariable model as in our multi-variable logistic regression model. We also explored model fit using Cox non-proportional hazards. By comparing these models to the Cox proportional hazards model, we confirmed the assumption of proportional hazards and determined that there was no significant improvement in model fit using alternative models. Two Cox proportional hazards models were developed utilizing two different time origins: (1) onset of first symptom (Raynaud's or non-Raynaud's and using only the first non-Raynaud's symptoms) as reported by the patient at their first visit in our Center and (2) first visit in our Center. This second analysis was performed to determine whether eliminating the time patients were unobserved impacted the results of the analysis.

Competing risks survival analysis.—As death is common among patients with scleroderma, and it prevents pseudo-obstruction events from occurring altogether, we adjusted our analysis to specifically account for this. We implemented competing-risks analysis, according to Fine and Gray's proportional subhazards model [12]. We estimated the cumulative incidence to determine the probability of pseudo-obstruction when accounting for the competing risk of death.

Sensitivity analysis.—In order to determine whether isolating the analyses to include only SSc patients with imaging would impact our results, we performed a sensitivity analysis using a more stringent case definition of pseudo-obstruction requiring dilation on imaging.

RESULTS

Cross-sectional univariate analysis comparing SSc patients with and without pseudo-obstruction

Among the 2,812 SSc patients studied, 175 patients had a history of pseudo-obstruction between February 2003 and September 2017. Table 1 provides the demographic and clinical characteristics of the patients with and without a history of pseudo-obstruction. Patients with SSc who developed pseudo-obstruction were more likely to be male (23% vs. 15%; $p=0.009$), have diffuse cutaneous disease (48% vs. 36%; $p=0.001$), cardiac involvement (44% vs. 26%; $p<0.001$), myopathy (29% vs. 15%; $p<0.001$), severe Raynaud's (66% vs. 53%; $p<0.001$), an elevated RVSP (43mmHg vs. 37mmHg; $p<0.001$), opioid exposure (43% vs. 26%; $p<0.001$), prokinetic exposure (63% vs. 16%; $p<0.001$), an antibody to U3RNP (7% vs. 3%; $p=0.011$), and were more likely to die (44% vs. 24%; $p<0.001$) than SSc patients without pseudo-obstruction. Patients with pseudo-obstruction were significantly less likely to have antibodies to RNA polymerase-3 (11% vs. 19%; $p=0.011$) than SSc patients without pseudo-obstruction. Exposure to immunosuppression, specifically mycophenolate mofetil, cyclophosphamide, methotrexate, and IVIG, was not significantly different between the two groups.

Cross-sectional multivariable model

We then sought to determine which clinical, demographic, and serologic features remained associated with pseudo-obstruction after adjusting for relevant clinical covariates and potential confounders. Covariates that were found to be significantly associated with pseudo-obstruction in the univariate analysis were included in the multivariable model (Table 2). After adjusting for significant variables from the univariate logistic regression analysis and relevant clinical confounders (i.e. age, sex, race, and cutaneous subtype), older age (OR 1.02; 95%CI 1.00-1.04), longer disease duration (OR 1.04, 95%CI 1.02-1.06), male sex (OR 1.61, 95%CI 1.03-2.51), diffuse cutaneous disease (OR 2.45; 95%CI 1.57-3.83), myopathy (OR 1.67, 95%CI 1.10-2.54), cardiac involvement (OR 1.70, 95%CI 1.13-2.56), and opioid use (OR 1.88; 95%CI 1.28-2.75) remained significantly associated with pseudo-obstruction in SSc. Anti-RNA polymerase-3 antibodies were protective of this complication (OR 0.36; 95%CI 0.19-0.67). There was no longer a significant association with antibodies to U3RNP.

Evaluating the effect of opioid exposure on the development of pseudo-obstruction in SSc using Cox proportional hazards: univariate and multivariable models

As an association between opioid use and pseudo-obstruction was identified in the univariate and multivariable cross-sectional analyses, we sought to determine the relationship of opioids to the development of pseudo-obstruction modeling opioid use as a time-varying covariate in a Cox proportional hazards model. In the univariate analysis, patients who were exposed to opioids had a HR of 2.27 of developing pseudo-obstruction compared to patients not exposed to opioids (95%CI 1.46-3.53; $p<0.001$). Kaplan Meier curves were generated using time of disease onset at first symptom (Raynaud's or non-Raynaud's) and first non-Raynaud's symptom (Figures 1 & 2, respectively), and the difference between the time to pseudo-obstruction was statistically different based on opioid exposure by the log rank test

($p < 0.001$). Using first symptom (Raynaud's or non-Raynaud's) as the disease starting point, and after adjusting for age at baseline visit, diffuse cutaneous skin disease, race, male sex, myopathy, and antibodies to U3RNP and RNA polymerase-3, opioid usage remained significantly associated with pseudo-obstruction, with a HR of 2.38 (95% CI 1.50-3.78; $p = 0.002$) (Table 3). Similar results were observed using the disease starting point as the patient's first non-Raynaud's symptom, with an association between pseudo-obstruction and opioid exposure remaining statistically significant (HR 2.54, 95% CI 1.53-4.24; $p < 0.001$). Other features associated with pseudo-obstruction in this model were older age (HR 1.02, 95% CI 1.00-1.04; $p = 0.019$), diffuse cutaneous disease (HR 2.97, 95% CI 1.80-4.89; $p < 0.001$), baseline myopathy (HR 1.85, 95% CI 1.85, 95% CI 1.03-3.30; $p = 0.039$), and the presence of anti-U3RNP antibodies (HR 2.49, 95% CI 1.10-5.64; $p = 0.028$). Anti-RNA polymerase-3 antibodies were inversely associated with pseudo-obstruction (HR 0.28, 95% CI 0.13-0.59; $p = 0.001$).

To determine if the unobserved person-time had a significant impact on the hazard of pseudo-obstruction following opioid exposure, we performed a sensitivity analysis using the time of origin as the baseline visit in our Center. In the univariate Cox proportional hazards analysis, opioid usage was associated with a 2.24 increased hazard of pseudo-obstruction (95% CI 1.44-3.48; $p < 0.001$). In the adjusted model, opioid exposure was associated with a 2.14 increased hazard of pseudo-obstruction (95% CI 1.31-3.49; $p = 0.002$) (Supplemental table).

Given that death is not uncommon among patients with SSc, we modeled death as a competing risk for pseudo-obstruction in opiate exposed and unexposed patients and calculated the relevant subhazard ratio. In the univariate analysis, the subhazard ratio of opioid exposure was 1.86 (95% CI 1.19-2.90; $p = 0.007$). After adjusting for age, diffuse cutaneous subtype, race, sex, myopathy, and antibodies to U3RNP and RNA polymerase-3, the subhazard ratio associated with opioid exposure was 1.95 (95% CI 1.16-3.26; $p = 0.011$).

Sensitivity analysis including only cases of pseudo-obstruction with imaging data available in the medical record

We then performed a sensitivity analysis to determine whether limiting the analysis to patients with pseudo-obstruction and imaging data ($n = 66$) changed our results. This analysis included 66 cases and 2,637 controls. Patients with pseudo-obstruction were more likely to be older (57 vs. 53 years; $p = 0.025$), have a longer disease duration from the first symptom (Raynaud's or non-Raynaud's) (6.4 vs. 9.8 years; $p = 0.008$) or the first non-Raynaud's symptom (8.6 vs. 4.2 years; $p < 0.001$), more likely to be male (27 vs. 15%; $p = 0.009$), smokers (59% vs. 44%; $p = 0.021$), have myopathy (38.5 vs. 16.8%; $p < 0.001$), have a higher RVSP (42 vs. 37; $p = 0.028$), have anti-U3RNP antibodies (11% vs. 3%; $p = 0.003$), and have been exposed to opioids (39.4 vs. 26.0; $p = 0.014$). They were less likely to have antibodies to RNA polymerase-3 (6% vs. 19%; 0.010). In the multivariable model, older age (OR 1.03, 95% CI 1.00-1.05; $p = 0.047$), longer disease duration (OR 1.03, 95% CI 1.01-1.07; $p = 0.009$), male sex (OR 2.00, 95% CI 1.01-3.97; $p = 0.046$), myopathy (OR 3.11, 95% CI 1.67-5.80; $p < 0.001$), and anti-U3RNP antibodies (OR 3.67, 95% CI 1.30-10.4; $p = 0.014$) were positively associated with pseudo-obstruction. A negative association with anti-RNA

polymerase-3 antibodies trended towards significance (OR 0.31, 95%CI 0.09-1.03; $p = 0.056$), as did the association with opioid exposure (OR 2.02, 95%CI 0.97-4.22; $p = 0.193$).

In order to specifically evaluate the association between incident cases of pseudo-obstruction and opioid use, we then performed a univariate analysis using only incident cases with imaging ($n=38$). We found that longer disease duration (10 vs. 4 years, $p<0.001$), male sex (32 vs. 15%; $p = 0.007$), diffuse cutaneous disease (53% vs. 36%, $p = 0.035$), myopathy (45% vs. 17%, $p < 0.001$), high RVSP (43 mmHg vs. 37 mmHg, $p = 0.023$), absence of anti-RNA polymerase-3 antibodies (6% vs. 19%, $p=0.044$), the presence of anti-U3RNP antibodies (11% vs. 3%, $p = 0.010$), and opioid exposure (50% vs. 26%, $p < 0.001$) were all associated with incident pseudo-obstruction. In the multivariable model, longer disease duration (OR 1.09, 95%CI 1.05-1.12; $p<0.001$), male sex (OR 2.65, 95%CI 1.20-5.83, $p = 0.016$), diffuse cutaneous disease (OR 3.05, 95%CI 1.30-7.15; $p=0.010$), myopathy (OR = 2.67, 95%CI 1.22-5.86), and anti-U3RNP antibodies (OR 3.35, 95%CI 1.03-10.9; $p = 0.045$) were associated with pseudo-obstruction. The negative association between pseudo-obstruction and anti-RNA polymerase-3 antibodies (OR 0.26, 95%CI 0.06-1.17, $p = 0.050$) remained. The positive association of incident pseudo-obstruction with opioid exposure was of borderline statistical significance (OR 2.02, 95%CI 0.97-4.22; $p = 0.060$).

Finally, we completed a univariate Cox proportional hazards analysis limited to the incident cases of pseudo-obstruction with imaging and found that the association between pseudo-obstruction and opioid use remained approximately the same, but statistical significance was lost as the number of cases dropped from 66 to 38 (HR 1.89, 95%CI 0.71-5.07; $p = 0.20$) (Supplemental Figure).

DISCUSSION

We performed a retrospective study using a cohort of SSc patients to explore risk factors for the development of pseudo-obstruction. We identified older age, male sex, diffuse cutaneous disease, myopathy, anti-U3RNP antibodies, and opioid use as risk factors for the development of pseudo-obstruction, and determined that opioid usage is a time-dependent risk factor. In contrast, we found that patients with antibodies to RNA polymerase-3 have a lower risk of developing pseudo-obstruction. The ability to risk stratify for pseudo-obstruction potentially allows for earlier diagnostic evaluation and/or therapeutic intervention in high risk patients.

Our research suggests that patients who develop pseudo-obstruction are a phenotypically distinct population. Nishimagi and colleagues described distinct phenotypic features of patients predisposed to severe GI involvement (malabsorption and/or pseudo-obstruction). Our findings are similar to Nishimagi's study, as they found that patients with diffuse cutaneous disease and/or myositis are a subgroup that are significantly more likely to have pseudo-obstruction. Their study also found that such patients were more likely to have erosive esophagitis and less likely to have interstitial lung disease (as defined as abnormal findings on chest radiography, high-resolution computed tomography, or forced vital capacity on pulmonary function testing) [13]. In our study, we did not confirm the association between pseudo-obstruction and ILD, and did not assess for erosive esophagitis

as a predictor. Pulmonary involvement, as assessed by the Medsger severity score and pulmonary function parameters (FVC and DLCO), was not significantly associated with pseudo-obstruction. Also in contrast to Nishimagi's study, we identified statistically significant associations between pseudo-obstruction and age and sex [13]. These discrepancies may be attributable to the relatively small sample size in the Nishimagi study (14 patients with severe GI involvement, including 10 with pseudo-obstruction), which inherently limited the power to identify differences between groups.

Our findings are consistent with our prior work, which sought to identify the clinical features of SSc patients dependent on supplemental nutrition (i.e. enteral or parenteral tube feeding). In both studies, we found that male sex and myopathy were associated with severe GI disease [10]. Whether these GI phenotypes represent a continuous spectrum or discrete subtypes warrants further study.

Our study also demonstrated that opioid usage in SSc is an important and potentially modifiable risk factor for pseudo-obstruction. Opioid use in our database is documented in 42.9% of SSc patients with a history of pseudo-obstruction and 26.9% of patients across the whole cohort. In SSc patients with pseudo-obstruction, 42% of the patients were prescribed opioids for musculoskeletal-related pain and 19% were prescribed for digital ischemia and/or ulcerations. Twenty-one (21%) percent did not have an indication for opioid prescription listed, including those prescribed for unspecified pain. Eighteen (18%) percent had various other indications including oral pain, cough, headaches, and cancer-related pain. These commonly prescribed medications are known to directly affect μ opioid receptors throughout the gastrointestinal tract inducing reduced gastric emptying, decreased intestinal motility, and greater ileocecal and anal sphincter tone [14]. Through these effects, opioid medications can increase risk of pseudo-obstruction in non-SSc patients [14]. While others have described opioid usage as an "effective and safe" treatment for digital ulcerations in SSc, 51.7% of patients reported constipation as a side effect after one month of treatment [15]. Our study adds valuable information for clinicians when weighing the risks and benefits of prescribing opioids for pain in scleroderma.

Our univariate analysis demonstrated an association between the use of prokinetic agents and pseudo-obstruction (63.4% as compared to 15.8%, $p < 0.001$). This correlation reflects the fact that these patients had more severe gastrointestinal involvement and were therefore prescribed more medications than the patients without GI involvement. As this was not felt to be a causal relationship, we did not carry this variable further into multivariate analysis.

Another insight our study provides is the notion that clinical features and antibody profiles are helpful in the risk stratification of SSc patients for pseudo-obstruction. We identified several risk factors for pseudo-obstruction including older age, male sex, diffuse cutaneous disease, baseline myopathy and anti-U3RNP antibodies. Nishimagi et al observed that 57% of the 14 patients with severe lower GI involvement had myositis-related autoantibodies, including five patients with U3RNP [13]. The association of U3RNP and other myositis-related autoantibodies supports the clinical findings that myopathy is predictive of pseudo-obstruction. Importantly, a negative association between antibodies to RNA polymerase-3 and the development of pseudo-obstruction in SSc, suggests that anti-RNA polymerase-3

positive patients might have a reduced pseudo-obstruction risk. Antibodies to RNA polymerase-3 were also identified in only 10.7% of the SSc patients with pseudo-obstruction in our cohort, compared to 19.1% in the patients in the group without pseudo-obstruction, which provides additional support of this idea.

The strengths of our study include a large number of SSc patients who had pseudo-obstruction, as well as a large SSc comparator cohort without this complication. Standardized data collection, including documentation of medications at each visit, as well as long follow-up time and the systematic screening of a spectrum of SSc-specific and SSc-associated autoantibodies also strengthened this work. We are limited by the retrospective study design, which relied upon chart review to confirm the diagnosis of pseudo-obstruction. While we defined pseudo-obstruction *a priori* for inclusion in our study, it is a subjective clinical diagnosis with reliance on the physician's diagnostic acumen. Though cross-sectional imaging is part of a gold standard definition of pseudo-obstruction, we did not require imaging confirmation of the diagnosis, as it is not routinely performed at our site for all patients with pseudo-obstruction if clinical suspicion is high. We, therefore, relied upon the physician judgment in some patients to rule out mechanical obstruction as a competing diagnosis. This may have resulted in misclassification. To evaluate the role of misclassification, we performed a sensitivity analysis on the few patients who had imaging confirmation in the medical record for their incident pseudo-obstruction. Though the hazard ratio remained about the same, the association lost statistical significance, likely due to the small number of cases in this analysis. In addition, despite documenting medication prescriptions at each visit, we do not record the actual usage of opioids (e.g. how many tablets do the patient actually take on average each day). This limits our interpretation of how the dose and formulation of opioid medications relate to pseudo-obstruction.

Our research demonstrates that older age, male sex, diffuse cutaneous disease, baseline myopathy, and opioid usage are associated with pseudo-obstruction in SSc, whereas RNA polymerase-3 may be protective against pseudo-obstruction. One of the two Cox multivariable models also demonstrated a significant association between anti-U3RNP antibodies. Additional research is needed to further characterize the sub-population of patients at increased risk of gastrointestinal dysmotility to study disease mechanism, disease course and response to treatment. In particular, opioid usage should be further evaluated in prospective studies to better understand its role as a modifiable risk factor and explore how opioid indication, formulation, dosing, timing, and cessation affect the development of pseudo-obstruction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Time to incident pseudo-obstruction from first symptoms (Raynaud's or non-Raynaud's) by preceding opioid exposure; Opioid exposure = patient-reported taking opioids during follow-up time in our Center; No opioid exposure = patient did not report taking opioids during follow-up time in our Center.

Kaplan-Meier curve: time to pseudo-obstruction from first symptom (Raynaud's or non-Raynaud's).

Fig. 2.

Time to incident pseudo-obstruction from first non-Raynaud's symptoms by preceding opioid exposure; Opioid exposure = patient-reported taking opioids during follow-up time in our Center; No opioid exposure = patient did not report taking opioids during follow-up time in our Center.

Kaplan-Meier curve: time to pseudo-obstruction from first non-Raynaud's symptom.

Table 1.

Demographic and clinical characteristics of SSc patients with pseudo-obstruction compared to SSc patients without pseudo-obstruction

Clinical Feature	No pseudo-obstruction (Medsger 2) (n=2,637)	Pseudo-obstruction (Medsger GI 3) (n=175)	p-value
Age at first symptoms, mean (SD)	42.8 (15.1)	44.1(15.5)	0.274
Disease duration from 1 st symptoms to baseline visit, median (IQR)	4.9 (1.7, 12.5)	5.0 (2.0, 17.8)	0.258
Follow-up interval in years, median (IQR)	4.8 (1.0, 11.4)	3.5 (0.7, 8.8)	0.016
Male sex, n (%)	407 (15.4)	40 (22.9)	0.009
<i>Race/Ethnicity</i>			
White, n (%)	2017 (78.1)	132 (77.6)	0.878
Ever smoker, n (%)	1150 (44.1)	81 (46.6)	0.525
<i>SSc Type</i>			
Diffuse cutaneous disease, n (%)	949 (36.0)	84 (48.0)	0.001
Max GI score at their first visit, n (%)			
Medsger GI score 0	617 (23.5)	14 (8.0)	<0.001
Medsger GI score 1	1615 (61.4)	63 (36.0)	
Medsger GI score 2	399 (15.2)	37 (21.1)	
Medsger GI score 3	0 (0)	61 (34.9)	
Cardiac involvement (>1), n (%)	604 (25.6)	72 (44.2)	<0.001
Myopathy, n (%)	401 (15.4)	50 (28.9)	<0.001
Raynaud's severity (>1), n (%)	1397 (53.1)	115 (65.7)	<0.001
Lung involvement, n (%)	1459 (63.7)	105 (71.4)	0.062
Cancer, n (%)	460 (17.5)	39 (22.3)	0.106
Tendon friction rubs, n (%)	418 (15.9)	33 (19.2)	0.259
Dead, n (%)	624 (23.7)	73 (43.5)	<0.001
<i>Pulmonary function parameters</i>			
FVC, % predicted, median (IQR)	72.1 (56.2, 86.0)	70.3 (57.9, 82.9)	0.492
DLCO, % predicted, median (IQR)	61.8 (43.9, 79.3)	61.7 (42.0, 80.1)	0.833
RVSP by echo (mmHg), median (IQR)	37 (30.0, 49.6)	42.5 (35.0, 51.0)	<0.001
<i>Medications</i>			
Opioids, n (%)	682 (26.0)	75 (42.9)	<0.001
Prokinetic, n (%)	414 (15.8)	111 (63.4)	<0.001
Mycophenolate mofetil, n (%)	546 (24.7)	31 (19.5)	0.139
Cyclophosphamide, n (%)	146 (5.6)	12 (6.9)	0.471
Methotrexate, n (%)	381 (14.5)	32 (18.3)	0.172
IVIG, n (%)	86 (3.9)	11 (6.9)	0.063
<i>Autoantibodies</i>			
Anti-Scl-70, n (%)	420 (21.5)	29 (19.5)	0.549
Anti-CENP, n (%)	552 (28.3)	42 (28.2)	0.972
Anti-RNA pol-3, n (%)	373 (19.1)	16 (10.7)	0.011

Clinical Feature	No pseudo-obstruction (Medsger 2) (n=2,637)	Pseudo-obstruction (Medsger GI 3) (n=175)	p-value
Anti-Ro52, n (%)	444 (22.8)	33 (22.1)	0.859
Anti-Ku, n (%)	43 (2.2)	1 (0.7)	0.208
Anti-Th/To, n (%)	72 (3.7)	7 (4.7)	0.535
Anti-PM-Scl, n (%)	40 (2.1)	2 (1.3)	0.551
Anti-U3RNP, n (%)	65 (3.3)	11 (7.4)	0.011

* Cardiac involvement = maximum Medsger cardiac severity score 1; Lung involvement = maximum Medsger lung severity score 1; FVC = forced vital capacity; DLCO = diffusing capacity of carbon monoxide; RVSP = estimated right ventricular systolic pressure by echo

Table 2.

Cross-sectional multivariable model evaluating the association between clinical, demographic, autoantibodies and pseudo-obstruction after adjusting for clinically important covariates and potential confounders

Covariate	Odds Ratio	95%CI	p-value
Age at first symptom	1.02	1.00, 1.04	0.011
Disease duration from 1 st symptoms to baseline visit	1.04	1.02, 1.06	0.001
Male sex	1.61	1.03, 2.51	0.035
Diffuse cutaneous disease	2.45	1.57, 3.83	<0.001
Myopathy	1.67	1.10, 2.54	0.015
Cardiac involvement	1.70	1.13, 2.56	0.011
Raynaud's severity	1.44	0.93, 2.24	0.100
RVSP	0.99	0.98, 1.00	0.150
Anti- RNA polymerase-3	0.36	0.19, 0.67	0.001
Anti-U3RNP	1.83	0.86, 3.92	0.117
Ever Opioids	1.88	1.28, 2.75	0.001

* Cardiac involvement = maximum Medsger cardiac severity score 1; RVSP = estimated right ventricular systolic pressure by echo

Table 3.

Cox proportional hazards multivariable model evaluating the time to pseudo-obstruction among SSc patients with and without opioid exposure after adjusting for clinically important covariates and potential confounders

Covariate	Hazard Ratio	95%CI	p-value
Age at baseline	1.02	1.00, 1.04	0.026
Male sex	1.75	1.42, 2.43	0.013
Diffuse cutaneous disease	2.52	1.59, 3.99	<0.001
Baseline Myopathy	1.83	1.09, 3.08	0.023
Anti- RNA polymerase-3	0.34	0.17, 0.66	0.002
Anti-U3RNP	1.73	0.77, 3.85	0.182
Opioids	2.38	1.50, 3.78	0.002

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Date of origin = first RP or non-RP symptom of SSc