ORIGINAL ARTICLE

Clinical outcomes and resource utilization analysis in patients with rheumatoid arthritis undergoing endoscopic retrograde cholangiopancreatography

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Abstract

Background and Aim: The literature is lacking on associations of endoscopic retrograde cholangiopancreatography (ERCP) related outcomes in rheumatoid arthritis (RA) patients. The aim of this study is to evaluate the effects of RA on clinical outcomes and hospital resource utilization in patients undergoing ERCP.
Methods: The National Inpatient Sample database was used to identify hospitalized patients who had underwent an ERCP study from 2012 to 2014 using International Classification of Diseases-Ninth Edition (ICD-9) codes. Primary outcomes were mortality, hospital charges, and length of stay. Secondary outcomes were ERCP-related complications. Chi-squared tests for categorical data and independent t-test for continuous data were utilized. Multivariate analysis was performed to assess the primary outcomes.
Results: There was 83 890 ERCP procedures performed, of which 970 patients had RA. In patients with RA, 74.2% were female, and the average age was 65.7 years. RA primary outcomes of mortality rate and hospital cost were lower and statistically significant. There was no statistically significant difference in secondary outcomes except for lower cholecystectomy rates in RA patients.
Conclusion: With a high inflammatory state, it was hypothesized that RA would be associated with worse outcomes after ERCP. Yet, the primary outcomes of mortality and hospital cost were found to be lower than controls, with no difference in secondary outcomes. We posit that immunosuppressants used to treat RA provides a protective effect to overall complications with ERCP.

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by systemic inflammation. It affects 0.5–1% of the population in the United States and Europe and women twice as often as men.[1–3] The inflammatory state in RA primarily affects the joints and may be present before the onset of symptoms, as shown by increased inflammatory markers.[4,5] RA is known to be associated with several other autoimmune diseases and has been associated with complications such as interstitial lung disease and vasculitis. Moreover, RA has been associated with pancreatic and biliary complications, including acute pancreatitis, primary biliary cirrhosis, and a potential increased risk of gallstones.[6–13] Given the inflammatory nature of RA, and the various pancreatic and biliary associated diseases, it is important to consider this diagnosis in patients undergoing treatments or procedures that may lead to further inflammation and complications.

Endoscopic retrograde cholangiopancreatography (ERCP) is an example of a procedure that may lead to further

inflammation. ERCP is indicated for the diagnosis and treatment of patients with biliary pancreatitis, choledocholithiasis, and sphincter of Oddi dysfunction and as a palliative treatment for patients with pancreatic cancer obstructing the common bile duct.[14] Although it is a relatively safe procedure, ERCP has many risks, with the most common complication being post-ERCP pancreatitis (PEP) and others including post-ERCP bleeding, perforation, and infection.[15] Furthermore, the risk of complications after ERCP has been associated with post-procedural increased levels of inflammatory markers.[16–18] Despite this association, the literature is lacking on the relationship between ERCP-related outcomes and complications in patients with inflammatory conditions, such as RA. Understanding this relationship may clarify additional risk factors and possible preventative measures to decrease that risk. This study aims to provide a quantitative analysis evaluating the effects of RA on clinical outcomes, hospital resource utilization, and inpatient mortality in patients undergoing ERCP.[19]

Methods

Data source. The data used in this study were obtained from the National Inpatient Sample (NIS), which is the largest all-payer publicly available database in the United States, containing more than 7 million hospital stays and representing approximately 20% of all nonfederal hospitals in the United States. The NIS was queried from 2012 to 2014 using the International Classification of Diseases-Ninth Edition Revision - Clinical Modification (ICD-9 CM) codes to identify hospitalized patients with RA undergoing ERCP. The NIS is a product of the Agency for Healthcare Research and Quality and contains deidentified patient information. The data used are a nationally representative sample obtained through hospital discharge records. Although a proportion of the national population has been sampled, yearly sampling weight has been applied, which provides adequate national estimates. Years of data and several studies have verified the value of this sampling tool, and as a result, this tool was used for this study.

Study design and inclusion criteria. This was a cross-sectional study and included all patients aged >18 years with a primary procedural code for ERCP from 2012 to 2014. The ICD-9 CM procedural code used was 51.10. The database was then queried to include all patients with a diagnosis code for RA, 714.0. Patients included in the study were required to have a procedural code for ERCP. Included patients were then divided into two groups, those with and without RA. Primary outcomes measured were mortality, hospital charges, and length of stay (LOS). Secondary outcomes included ERCP-related complications, such as pancreatitis, sepsis, perforation, gastrointestinal (GI) bleed, and fistula/abscess formation. Various patient demographics (age, race, gender, income, and insurance status) and comorbidities were obtained. The severity of the comorbidities was analyzed via the Deyo modification of the Charlson Comorbidity Index (CCI). CCI measures 17 common medical conditions and assigns different weights to develop a score from 0 to 33, which is then used to correlate the overall level of illness severity.

Statistical analysis. All statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA). Chi-squared tests and independent *t*-tests were used to compare outcomes for categorical and continuous data, respectively, between the two groups. A multivariate logistic regression model was designed to investigate the associations between ERCP complications and RA. The hierarchical model included both patient characteristics (age, race, gender, comorbidities) and the CCI. To limit the effect of cofounders, this was the primary means by which adjustments were made in the data for patient characteristics. Univariate analysis was conducted on the aforementioned factors. Complicated diabetes mellitus, anemia, renal failure, cardiovascular disease, congestive heart failure, age, race, insurance status, and gender were included in the multivariate analysis, with $P < 0.05$ indicating statistical significance. Adjusted odds ratios were calculated for each primary outcome with 95% confidence intervals.

Results

This study examined the associations between RA and ERCP complications. There was a total of 83 890 patients undergoing ERCP procedures between 2012 and 2014 who were included in this analysis, of which 970 had RA. General characteristics of patients with and without RA are shown in Table 1. Patients who had RA were older (65.7 years *vs* 59.9 years) and included more women (74.6 *vs* 69.9%) compared to patients who did not have RA. More patients with RA were insured by Medicare (68.6%) compared to those without RA (47.0%).

The primary outcomes of LOS and hospital charges are shown in Table 1, and inpatient mortality with all secondary outcomes are shown in Table 2. The primary outcomes of LOS (7.91 days *vs* 7.21 days) and total hospital charges ($77 684 *vs* $67 160) were lower for patients with RA, although the difference was only statistically significant for total hospital cost. Inpatient mortality was significantly lower for patients with RA compared to those without (1.0 *vs* 2.3%). In the secondary outcomes, a higher rate of patients with RA had sepsis compared to those without RA (16.5 *vs* 13.4%), although it was not found to be significant. They also had higher rates of stricture formation (26.8 *vs* 24.9%), although this was not significant. RA patients were also found to have statistically significant lower rates of cholecystectomy compared to controls. Finally, patients with RA had lower rates of fistula formation (0.0 *vs* 0.2%), pancreatitis (27.8 *vs* 28.8%), abscess formation (0.0 *vs* 0.1%), perforation (0.0 *vs* 0.3%), and GI bleeds (0.5 *vs* 0.7%) compared to those without RA, although none of these differences were statistically significant. The CCI in RA patients was also higher and statistically significant compared to the control group.

Discussion

RA is an autoimmune disorder associated with a high inflammatory state, often occurring before the onset of symptoms.[4,5] Although rare, GI manifestations can be severe in RA. Specifically, rheumatoid vasculitis may lead to ulcerations of the small and large intestine, as well as necrosis and perforation in some patients.[20,21] In the setting of endoscopy, the risk of these complications may be amplified. In addition, RA is associated with other autoimmune conditions, such as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis with a possible shared genetic basis.[3,9,10,20,22] More recently, literature has shown that RA and other autoimmune diseases affect the gut microbiome and may play a role in the inflammatory nature of the disease.[23–25] Initially, little was known about GI manifestations of RA, but as more is learned about the impacts of RA on the GI system, it will become important to understand how they might affect GI medical and procedural treatments.

It was hypothesized that the inflammatory state of RA would contribute to complications, mortality, and hospital costs in patients undergoing ERCP. Although RA is known to be a systemic, inflammatory disease, little is known about how this may impact outcomes in GI procedures and even common surgeries such as appendectomy and cholecystectomy. Most studies on RA outcomes are in orthopedic surgery, where it has been associated with an increased risk of infection, possibly due to the

Table 1 Demographics and resource utilization of endoscopic retrograde cholangiopancreatography (ERCP) patients with and without rheumatoid arthritis

	ERCP Without RA *n* = 82 920	ERCP With RA *n* = 970	*P*-value	95% CI
Age	59.9 (18.8 SD)	65.7 (13.8 SD)	**<0.05**	−7.1 to −4.7
Gender			**<0.05**	
Female	46 100 (55.6%)	720 (74.2%)		
Male	36 820 (44.4%)	250 (25.8%)		
Race			**<0.05**	
White	51 910 (69.9%)	690 (74.6%)		
Black	9265 (11.7%)	85 (9.2%)		
Hispanic	11 160 (14.2%)	105 (11.4%)		
Asian or Pacific Islander	2970 (3.8%)	10 (1.1%)		
Native American	440 (0.5%)	20 (2.2%)		
Others	2960 (0.4%)	15 (1.6%)		
Primary payer			**<0.05**	
Medicare	38 930 (47.0%)	665 (68.6%)		
Medicaid	12 095 (14.6%)	80 (8.2%)		
Private insurance	23 970 (29.0%)	190 (19.6%)		
Self-pay	4595 (5.6%)	20 (2.1%)		
Others	3175 (3.8%)	15 (1.5%)		
Median household income			**<0.05**	
Lowest quartile	22 515 (27.8%)	250 (26.5%)		
Second quartile	21 105 (26.1%)	220 (23.3%)		
Third quartile	20 085 (24.8%)	240 (25.4%)		
Highest quartile	17 230 (21.3%)	235 (24.9%)		

CI, confidence interval; RA, rheumatoid arthritis.
The bold terms emphasis of statistical significance.

Table 2 Complications and outcomes in endoscopic retrograde cholangiopancreatography (ERCP) patients with and without rheumatoid arthritis (RA)

	ERCP Without RA *n* = 82 920	ERCP With RA *n* = 970	*P*-value	Adjusted odds ratio (95% CI)
GI bleed	870 (0.7%)	5 (0.5%)	0.10	0.48 (0.20–1.18)
Perforation	210 (0.3%)	0 (0.0%)	0.26	0.20 (0.01–3.25)
Abscess	90 (0.1%)	0 (0.0%)	0.60	0.47 (0.03–7.60)
Pancreatitis	23 865 (28.8%)	270 (27.8%)	0.52	1.17 (1.17–1.34)
Stricture	20 630 (24.9%)	260 (26.8%)	0.17	0.96 (0.83–1.11)
Fistula	170 (0.2%)	0 (0%)	0.33	0.25 (0.02–4.02)
Sepsis	11 145 (13.4%)	160 (16.5%)	<0.05	1.11 (0.93–1.32)
Cholecystectomy	21 425 (25.8%)	215 (22.2%)	**<0.05**	0.82 (0.70–0.95)
Inpatient mortality	1920 (2.3%)	10 (1.0%)	**<0.05**	0.38 (0.20–0.71)
Length of stay in days	7.91 (10.1 SD)	7.21 (6.9 SD)	<0.05	0.065–1.34
Total charges	$77 684.85 (107 984 SD)	$67 160 (78 875 SD)	**<0.05**	3620–17 428
Charlson Comorbidity Index	3.3 (2.7 SD)	4.6 (2.1 SD)	**<0.05**	−1.46 to −1.11

The bold terms emphasis of statistical significance.

immunosuppressive effect of disease-modifying antirheumatic drugs (DMARDs).[26–28] Another study looked at cardiovascular outcomes in patients with RA undergoing any type of surgery but found no significant difference between RA patients and patients without RA.[29] In comparison to the literature from other surgeries and procedures, along with the inherent risk of infection with ERCP, this analysis shows that patients with RA had no statistically significant increased risk of developing complications when compared to the control group.

In patients with other autoimmune conditions who underwent ERCP, PSC has several studies looking at ERCP outcomes as the procedure is therapeutic and is a screening tool for cancer in the disease. In general, these studies showed similar rates of post-ERCP complications in patients with PSC *versus* patients without it, except for an increased rate of postprocedure infections for PSC patients.[30–32] Despite PSC primarily affecting the bile duct and potentially leading to an increased risk of infection, other outcomes are largely the same in this disease. However, in comparison to RA, another autoimmune disease, the data presented in this study suggest that, while most outcomes are largely the same, there is a decreased risk of mortality in patients with RA. Thus, there might be another factor playing a role in the perceived benefit of having RA.

One theory about these results is that the treatment of RA with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and DMARDs is suppressing the inflammatory response and providing benefit to RA patients. Although the evidence is mixed, some studies show a benefit of using NSAIDs either before or after ERCP to decrease rates of PEP.[33–37] Thus, patients taking NSAIDs at the beginning of their disease course, or to treat an acute flare-up, may be experiencing a secondary benefit. No studies have been conducted to assess the effectiveness of DMARDs in post-ERCP complications, but these medications may also have a role in reducing complications after ERCP in RA patients. Methotrexate, a commonly used DMARD, has been found to have anti-inflammatory properties in addition to its antimetabolite activity.[38,39] As in NSAIDs, this anti-inflammatory property may play a role in the reduction of post-ERCP complications. Moreover, corticosteroids, which is also used as an RA therapy, has immunosuppressive properties that help reduce the inflammatory state and has been widely studied in different contexts from autoimmune disease to septic shock. While patients developed pancreatitis at the same rate, the effect of DMARDs or anti-inflammatory medications may be seen in reducing progression to sepsis by limiting the cascade of inflammatory responses, resulting in lower rates of sepsis in this study, although not statistically significant. However, it is possible that such anti-inflammatory medications provided the mortality benefit that was seen in this study. Moreover, although not statistically significant, the decreased LOS was likely impacted by the effects of anti-inflammatory therapies and possibly by a more prompt, aggressive approach in therapy for RA patients as they would be considered higher risk or immunosuppressed. Such a bias could have led to the early performance of an ERCP procedure or the initiation of empiric, broader spectrum antibiotics, which could have affected the LOS. Although LOS was not statistically significant, the total hospital cost was found to be lower in RA patients. Although our study showed a nonsignificant decreased LOS in RA patients and lower rates of sepsis complications, the decrease in rates could have contributed to the lower total hospital cost. Further research on the specific effects of anti-inflammatory therapies and DMARDs on post-ERCP complications may elucidate beneficial therapies to reduce poor outcomes.

While these results are interesting, there are important limitations to this study. First, due to the nature of the database, long-term outcomes could not be analyzed. In addition, while ICD-9 codes were used to identify patients, they may not always be accurately documented. Moreover, characteristics about the patients, such as time since diagnosis, severity of disease, and medication use and adherence, that could impact outcomes could not be analyzed. In addition, although complications such as fistula formation, stricture formation, and sepsis are possible post-ERCP complications, it should be noted that they are also possible indications for ERCP. As sepsis from cholangitis and cholecystitis may be an indication for ERCP, the rates of cholecystectomy were analyzed between the two groups to determine if there was any statistical significance (Table 2). It was discovered that patients with RA were less likely to undergo a cholecystectomy than the control group. Such a finding does not necessarily indicate that the complication of sepsis or obstruction was an indication for ERCP or the result of the actual ERCP during that hospital stay; however, it should be noted that this anomaly may have affected results, and a database study is limited in its ability to distinguish the two. Moreover, one can argue that surgical complications may have affected the primary outcomes between the two groups; however, as already discussed, based on literature review, this study illustrated distinct findings of no significant differences in complications and a lower mortality rate in RA patients. Finally, as this is an observational study, there is the possibility of confounding variables, and causality is limited.

In conclusion, it was hypothesized that the inflammatory state of RA would contribute to increased cost, mortality, LOS, and complication rates in patients with RA. However, this analysis demonstrated that mortality rate and hospital cost were lower, while LOS was not significantly different between the two groups. In terms of complication rates, the rate of sepsis was lower but not statistically significant, and all other studied complications, including GI bleeds, abscess formation, pancreatitis, perforation, stricture, and fistula formation, were not significantly different between the two groups. We postulate that the treatment for RA, which usually involves anti-inflammatory therapies, is suppressing the inflammatory response and reducing the chance that complications escalate into a more severe response while providing an overall mortality benefit during ERCP. We also theorize that a bias in initiation of aggressive therapies could have affected LOS and hospital costs. Further research on the effects of DMARDs and other anti-inflammatory therapies on post-ERCP complications would be beneficial in clarifying the relationships described in this study.

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