Original Article

Impact of connective tissue diseases on inpatient outcomes in gastrointestinal bleeding: insights from a national database analysis

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Background: Connective tissue diseases (CTDs) are characterized by immune system dysregulation, which can profoundly impact the gastrointestinal (GI) system. While GI bleeding is a well-recognized cause of mortality and morbidity in the USA, its occurrence in patients with CTD remains documented but underexplored in terms of inpatient outcomes. GI bleeding in CTD is attributed to factors such as vasculopathy and drug-related risks, notably steroids and non-steroidal anti-inflammatory drugs (NSAIDs). This research seeks to conduct a comprehensive national-level analysis, utilizing the National Inpatient Sample (NIS), to compare GI bleeding outcomes between patients with CTD and those without this condition.

Methods: Utilizing the extensive NIS database covering 2020, we conducted a retrospective analysis of GI bleeding patients with CTD, identified through the International Classification of Diseases, 10th Revision (ICD-10). The primary outcome was in-hospital mortality. The secondary outcomes included rate of urgent esophagogastroduodenoscopy (EGD) and colonoscopy-endoscopy in 1 day or less, total rate of EGD and colonoscopy, rate of EGD and Colonoscopy with intervention, rate of complications including acute kidney injury (AKI), blood transfusion, sepsis, pneumonia, pulmonary embolism (PE) and healthcare utilization. Employing Stata software, we utilized multivariate logistic and linear regression analyses to adjust for confounders.

Results: There were 455,494 hospitalizations for GI bleeding and 19,874 involved patients with CTDs. The in-hospital mortality rate was significantly lower for CTD patients at 2.1%, compared to 2.4% for non-CTD patients [adjusted odds ratio (aOR): 0.79, 95% confidence interval (CI): 0.63–0.99, P=0.04]. CTD patients showed increased odds of total EGD, urgent colonoscopy, and total colonoscopy; however, these changes were not statistically significant. CTD patients had higher odds of complications, including PE (6.87% *vs.* 4.12%, P=0.009). However, there were no significant differences in mean length of hospital stay and total hospital charges (THCs) compared to non-CTD patients.

Conclusions: Patients with CTD exhibited a lower in-hospital mortality rate compared to those without CTD. The elevated risk of PE underscores the importance of implementing prophylactic measures for these patients.

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Keywords: Connective tissue disease (CTD); gastrointestinal bleeding (GI bleeding); in-hospital mortality; pulmonary embolism (PE)

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Introduction

This research investigates the intricate interplay between the connective tissue, immune, and gastrointestinal (GI) systems, focusing on the impact of connective tissue diseases (CTDs) on GI bleeding. The connective tissue system, with its multifaceted roles in protection, structural support, metabolic functions, and wound healing across organ systems, is integral to the vitality of the GI system. Notably, CTD often involves immune system dysregulation, which can significantly affect the GI system, leading to inflammation, autoimmunity, barrier dysfunction, alterations in the microbiome, and a spectrum of secondary GI pathologies encompassing both intestinal and extraintestinal organs (1). Additionally, medications commonly prescribed for CTD treatment, such as steroids, immunomodulators, and non-steroidal anti-inflammatory drugs (NSAIDs), may influence the GI system through side effects or immunosuppression (2,3), highlighting the intricate interconnectedness of the immunological, GI, and connective tissue systems.

Amongst the various GI manifestations observed in patients with CTD, GI bleeding has been a paramount area of research. Despite its clinical significance, more comprehensive data must be collected on the in-hospital outcomes of GI bleeding in patients with CTD. GI manifestations have been reported across a spectrum of CTD, including systemic lupus erythematosus (SLE), mixed CTDs (MCTDs), rheumatoid arthritis (RA), scleroderma, Sjogren's syndrome, polymyositis, psoriatic arthritis and vasculitis syndromes (4-7).

Multiple factors contribute to GI bleeding in CTD patients, encompassing direct disease activity of the specific CTD (4) and the effects of medications employed in CTD management (8,9). Determining the precise etiology of GI bleeding in this population group can be challenging. CTDs may directly cause GI bleeding through mechanisms such as gastric or intestinal vasculopathy, erosions leading to ulceration, and micro thrombosis, resulting in tissue ischemia and bleeding (4). While disease activity-associated gastric manifestations often respond to high-dose pulsed methylprednisolone (10), studies suggest that long-term steroid use carries an independently increased risk of GI bleeding due to factors such as heightened gastric acid production, suppression of gastric prostaglandins protective to the stomach lining, impaired blood clotting, and interactions with other medications that augment the risk (11-13). The association between steroid use and the independent risk of GI bleeding has been a topic of debate since the mid-1990s, with individual small-scale studies yielding conflicting results (14). However, it is well-established that the concomitant use of NSAIDs and steroids substantially elevates the risk of GI bleeding, showing a synergistic effect (12-fold increase compared to 1.8-fold increase in steroid users alone) (13).

Given the widespread use of steroids and NSAIDs in the treatment of CTD and recognizing that patients with CTDs retain an independent risk of GI bleeding due to the underlying pathophysiology of their condition, this

Highlight box

Key findings

- The in-hospital mortality rate was significantly lower for patients with connective tissue disease (CTD) and gastrointestinal (GI) bleeding at 2.1%, compared to 2.4% for non-CTD patients.

What is known, and what is new?

- GI bleeding is a significant manifestation of CTD, influenced by disease activity and medications like steroids and non-steroidal anti-inflammatory drugs.
- Patients with CTD exhibited a low mortality rate of 2.1%, in contrast to the higher rate of 2.4% observed among non-CTD patients. These findings retained significance even after meticulous adjustments for various covariates, including demographic factors, patient-specific characteristics, and comorbidities.

What is the implication, and what should change now?

- The lower mortality rate seen in patients with GI bleeding and comorbid CTD warrants further investigation and understanding.
- Recognition of the heightened risk of pulmonary embolism in CTD patients with GI bleeding suggests the need for prophylactic measures.

research endeavors to conduct a comprehensive national-level comparison of GI bleeding inpatient outcomes in individuals with and without CTDs. We present this article in accordance with the STROBE reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-5/rc).

Methods

The research made use of data from the National Inpatient Sample (NIS) database, which is a component of the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP). The NIS holds the most extensive collection of inpatient care information within the USA, comprising billing information submitted by hospitals to state-wide data organizations. The NIS offers comprehensive insights drawn from around 7 million unweighted hospitalizations each year, constituting approximately 20% of hospital admissions in the USA (15). This study utilized data from the year 2020, the most recent available, and employed weighted data to obtain national estimates.

The databases utilize the International Classification of Diseases, 10th Revision, and Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) for coding. Diagnoses in the NIS are categorized into a principal diagnosis (DX1) and secondary diagnoses (DX2 to DX40). The principal diagnosis refers to the primary ICD-10 code for the hospitalization, while secondary diagnoses encompass any additional ICD-10 codes. Patient identifiers are not included in the NIS, and like other HCUP databases, Institutional Review Board approval is not required for analysis. The study followed the guidelines in the Declaration of Helsinki (as revised in 2013).

Utilizing the comprehensive NIS 2020 datasets, we gathered demographic data and clinical outcomes for all adult patients admitted for GI bleeding with a concurrent CTD. The number of patients with GI bleeding and CTDs determined the sample size for this study.

We performed a retrospective analysis, identifying individuals aged 18 and greater with a primary diagnosis of GI bleeding (inclusive of both upper and lower GI bleeding) and a secondary diagnosis of comorbid CTDs, encompassing conditions such as SLE, RA, scleroderma, Sjogren syndrome, inflammatory myositis, MCTD, giant cell arteritis, polymyalgia rheumatica, and psoriasis. This amalgamation of CTDs was systematically defined using the ICD-10-CM/PCS coding system (Table S1).

To facilitate a rigorous comparative analysis, we established two distinct groups: one composed of individuals with GI bleeding and coexisting CTDs, and another consisting of patients with GI bleeding but without CTDs. Notably, individuals below age 18 and those with documented coronavirus disease 2019 (COVID-19) infection were excluded from both groups. This strategic exclusion was implemented to mitigate potential confounding factors related to age and the impact of COVID-19, ensuring a more focused investigation into the association between CTDs and GI bleeding.

Baseline characteristics considered encompassed patient sociodemographic and hospital characteristics, including age, race, gender, and medical conditions during admissions, including diabetes mellitus, congestive heart failure, cigarette smoking, chronic kidney disease, hypertension, chronic obstructive pulmonary disease (COPD), myocardial infarction, cerebrovascular accident, liver cirrhosis, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), peripheral vascular disease, dementia, and malignancy. Patients were additionally classified according to socio-demographic factors, including primary payer, mean household income by quartile, disposition, hospital bed size, hospital location, and hospital teaching status, all of which were documented in the database.

Outcome measures

The primary outcome was analyzing in-hospital mortality in patients with CTD. Secondary outcomes included rate of urgent esophagogastroduodenoscopy (EGD) and colonoscopy (endoscopy in 1 day or less), Total rate of EGD and colonoscopy, rate of EGD and colonoscopy with intervention, factors influencing endoscopic evaluation and intervention, rate of complications including acute kidney injury (AKI), blood transfusion, sepsis, pneumonia, deep venous thrombosis (DVT), pulmonary embolism (PE). Additionally, we conducted comparisons involving the mean length of stay (LOS), mean total hospital charges (THCs), and transfers to another acute care hospital.

Statistical analysis

Given the intricate survey design and clustering, our analyses were carried out using Stata/MP 17.0 (Stata Corp, College Station, TX, USA). Due to the NIS representing a 20% stratified random sample of US hospitals, we applied

hospital-level discharge weights provided by the NIS to derive national estimates of total inpatient hospitalizations. Univariate logistic regression analysis was employed to compute unadjusted odds ratios (ORs) for both primary and secondary outcomes. To account for confounding variables, multivariate logistic regression using hospital-level variables was utilized. A secondary logistic regression model was developed using variables linked to the outcome of interest in univariate regression analysis with a significance level of P<0.2. Proportions were assessed using the Fisher exact test, Continuous variables underwent comparison utilizing the student *t*-test. All P values were two-sided, with 0.05 as the threshold for statistical significance. Independent multivariate predictors were identified with logistic regression models. The findings are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CIs). Patients with missing data for any variables in the regression analyses were excluded.

Results

Patient and hospital characteristics

Among the 455,494 hospitalizations for GI bleeding, 19,874 patients had CTDs. Notably, patients with both GI bleeding and CTD were, on average, older (mean age 70.07 *vs.* 68.41 years) and comprised a significantly higher proportion of females compared to males (67.95% *vs.* 32.05%, P<0.01). In contrast, males were the majority (53.47% *vs.* 46.58%) among patients without CTD. The majority of CTD patients with GI bleeding were of White ethnicity (71.28%). Additionally, most of these patients had Medicare insurance (74.42% *vs.* 66.97%, P<0.001) and were more likely to seek care at urban teaching hospitals (73.94% *vs.* 71.74%, P=0.01). The distribution of comorbidities varied between the two study groups. Patients with CTD and GI bleeding had a higher likelihood of co-existing chronic pulmonary disease (20.05% *vs.* 16.65%, P<0.001) and congestive heart failure (28.55% *vs.* 24.43%, P<0.001). They also exhibited elevated rates of hypertension, chronic kidney disease, peripheral vascular disease, and myocardial infarction, although these differences did not reach statistical significance. Statistically significant variations were observed in annual median household income, the expected primary payer (insurance), hospital region, and the hospital's teaching status (*Table 1*).

Outcomes

Primary outcome: in-hospital mortality

The in-hospital mortality among patients admitted with GI bleed and comorbid CTD was markedly lower at 2.1%, in contrast to the 2.4% mortality rate observed in non-CTD patients (*Table 2*). This substantial difference persisted after adjusting for key factors, including demographics, hospital characteristics, and comorbidities, with an aOR of 0.79 (95% CI: 0.63–0.99, P=0.04) (*Table 2*).

In the multivariate analysis controlling for age, gender, comorbidities, and socioeconomic status, we found that being female (OR 0.84, 95% CI: 0.63–0.99), comorbidities such as hypertension (OR 0.66, 95% CI: 0.59–0.75), and chronic kidney disease (OR 0.62, 95% CI: 0.55–0.70), patients admitted to hospitals situated in the Midwest region (OR 0.81, 95% CI: 0.70–0.94), were significantly associated with lower odds of mortality during the hospitalization of patients with CTD and GI bleed.

Increasing age (OR 1.02, 95% CI: 1.02–1.03), higher Charlson comorbidity index (OR 1.17, 95% CI: 1.152–1.203), presence of comorbidities such as liver cirrhosis (OR 1.71, 95% CI: 1.50–1.94), and dementia (OR 1.32, 95% CI: 1.16–1.51), all well as management in a medium-sized (OR 1.20, 95% CI: 1.05–1.36), and large sized hospitals (OR 1.21, 95% CI: 1.07–1.37), were significantly associated with higher odds of in-hospital mortality among patients with CTD and GI bleed.

Secondary outcomes

Patients with both GI bleeding and CTDs showed trends toward increased rates of EGD and colonoscopy, although these differences were not statistically significant in multivariate analysis (*Table 2*).

Furthermore, we analyzed other factors influencing endoscopic evaluation and intervention within our cohort. We observed significant associations and the likelihood of interventions during EGD in advancing age (OR 1.004, 95% CI: 1.003–1.006), higher Charlson comorbidity index scores (OR 1.08, 95% CI: 1.08–1.09), and the presence of comorbidities such as smoking (OR 1.11, 95% CI: 1.08–1.15), liver cirrhosis (OR 1.06, 95% CI: 1.01–1.13), and myocardial infarction (OR 1.09, 95% CI: 1.03–1.15). Additionally, admission to hospitals located in the Midwest (OR 1.15, 95% CI: 1.06–1.24) and teaching hospitals (OR 1.22, 95% CI: 1.17–1.27) emerged as significant predictors

Table 1 Patient and hospital characteristics of hospitalizations with gastrointestinal bleed with and without connective tissue disease

Patient characteristics	GI bleed with CTD, total (n=19,874)	GI bleed without CTD, total (n=455,494)	P value
Mean age (years)	70.07	68.41	<0.001
Sex, %			<0.001
Female	67.95	46.53	
Male	32.05	53.47	
Race, %			0.005
White	71.28	68.81	
Black	15.25	15.96	
Hispanic	7.8	9.0	
Asian	2.49	3.04	
Native American	1.13	0.83	
Others	2.05	2.36	
CCI, %			<0.001
0	2.06	12.42	
1	12.93	21.24	
2	19.32	16.62	
≥3	65.69	49.72	
Median annual income national quartile for patients zip code ($), %			<0.001
1–49,999	28.28	30.88	
50,000–64,999	27.57	27.47	
65,000–85,999	21.96	22.66	
≥86,000	22.19	19	
Insurance, %			<0.001
Medicare	74.42	66.97	
Medicaid	7.66	11.76	
Private insurance	16.25	17.08	
Others	1.67	04.19	
Region of hospital, %			<0.001
Northeast	18.21	17.62	
Midwest	25.26	22.29	
South	37.53	40.36	
West	18.99	19.72	
Relative bed size category of hospital, %			0.62
Small	22.04	22.49	
Medium	29.01	29.4	
Large	48.96	48.11	

Table 1 (*continued*)

Table 1 (*continued*)

Patient characteristics	GI bleed with CTD, total (n=19,874)	GI bleed without CTD, total (n=455,494)	P value
Location/teaching status of the hospital, %			0.01
Rural	7.97	8.67	
Urban nonteaching	18.09	19.59	
Urban teaching	73.94	71.74	
Comorbidities, %			
Hypertension	38.09	36.59	0.05
Chronic kidney disease	26.72	25.72	0.17
Chronic obstructive pulmonary disease	20.05	16.65	<0.001
Smoking	39.57	42.47	<0.001
Congestive heart failure	28.55	24.43	<0.001
Diabetes mellitus	30.19	33.53	<0.001
Myocardial infarction	11.7	11.33	0.48
Cerebrovascular accident	3.27	3.46	0.50
Liver cirrhosis	9.56	10.07	0.29
Human immunodeficiency virus/ acquired immunodeficiency syndrome	0.1	0.54	<0.001
Peripheral vascular disease	4.33	3.87	0.13
Dementia	6.77	8.59	<0.001
Malignancy	0.7	0.79	0.57

GI, gastrointestinal; CTD, connective tissue diseases; CCI, Charlson comorbidity index.

of intervention during EGD.

Conversely, there was a decreased likelihood of interventions during EGD in female gender (OR 0.86, 95% CI: 0.83–0.89), having comorbid dementia (OR 0.61, 95% CI: 0.56–0.65) or malignancy (OR 0.83, 95% CI: 0.69–1.00), and possessing Medicaid insurance (OR 0.76, 95% CI: 0.71–0.82) or self-pay status (OR 0.78, 95% CI: 0.71–0.86).

In regards to colonoscopy, we observed significant associations and the likelihood of interventions during colonoscopy in advancing age (OR 1.02, 95% CI: 1.01–1.03), female gender (OR 1.28, 95% CI: 1.06–1.54) and the presence of comorbidities such as smoking (OR 1.37, 95% CI: 1.13–1.65) and congestive heart failure (OR 1.39, 95% CI: 1.08–1.80). Additionally, admission to large hospitals (OR 1.36, 95% CI: 1.05–1.77) emerged as a significant predictor of intervention during EGD.

On the contrary, our analysis revealed a reduced likelihood of interventions during colonoscopy among patients with dementia (OR 0.61, 95% CI: 0.43–0.88), as well as those covered by Medicaid (OR 0.59, 95% CI: 0.38–0.92) or private insurance (OR 0.70, 95% CI: 0.50–0.98), and those admitted to hospitals in the western region (OR 0.64, 95% CI: 0.46–0.89).

Interestingly, patients with CTD and GI bleeding were at risk of complications, including PE (6.87% *vs.* 4.12%, aOR: 1.42, 95% CI: 1.24–1.63, P<0.001) (*Table 2*). They also had higher odds of requiring blood transfusion, experiencing pneumonia, and facing malnutrition, although these differences did not reach statistical significance. There were no significant differences in LOS, THCs, or transfer to other facilities compared to patients without CTDs (*Table 2*).

Discussion

Utilizing a nationwide database, we aimed to compare mortality and other outcomes such as those who underwent urgent endoscopy (i.e., <24 hours from admission day),

Table 2 Outcomes of gastrointestinal bleeding in patients with coexisting connective tissue diseases

Outcome	GI bleed with CTD	Univariate		Multivariate	
		OR (95% CI)	P value	OR (95% CI)	P value
Primary outcome					
In-hospital mortality	2.1%	0.87 (0.69–1.09)	0.22	0.75 (0.59–0.95)	0.04
Secondary outcomes					
Urgent EGD	35.65%	0.98 (0.91–1.04)	0.47	0.97 (0.91–1.04)	0.40
Urgent colonoscopy	6.29%	0.95 (0.84–1.08)	0.44	1.05 (0.93–1.20)	0.42
Total EGD	44.18%	1.07 (1.00 –1.13)	0.047	1.02 (0.96–1.09)	0.55
EGD with intervention	20.18%	1.09 (1.01–1.18)	0.04	1.02 (0.94–1.11)	0.56
Total colon	19.65%	1.05 (0.97–1.14)	0.24	1.08 (0.99–1.17)	0.07
Colonoscopy with intervention	0.53%	1.05 (0.66 –1.66)	0.83	0.96 (0.60–1.53)	0.86
AKI	22.52%	0.92 (0.86–0.99)	0.047	0.88 (0.81–0.96)	0.03
Acute respiratory failure	4.08%	0.94 (0.79–1.11)	0.44	0.84 (0.71–0.99)	0.03
Blood transfusion	36.1%	1.08 (1.01–1.16)	0.02	1.04 (0.96–1.11)	0.34
Sepsis	1.81%	0.83 (0.65–1.05)	0.12	0.79 (0.62–1.00)	0.05
Pneumonia	4.68%	1.14 (0.98–1.33)	0.09	1.05 (0.89–1.24)	0.52
PE	6.87%	1.71 (1.51–1.95)	<0.001	1.42 (1.24–1.63)	<0.001
Ventilator	2.49%	0.76 (0.62–0.93)	0.008	0.76 (0.62–0.93)	0.009
Malnutrition	10.06%	1.15 (1.03–1.28)	0.01	1.02 (0.92–1.14)	0.61
The mean length of stay (days)	4.74	0.19 (0.03–0.35)	0.02	–0.04 (–0.19–0.12)	0.65
Mean total hospital charges (USD)	56,891	42.33 (–2,857 to 2,942)	0.98	–2,101.59 (–50,317 to 828)	0.16
Transfer to another acute care hospital	2.32%	1.00 (0.92–1.09)	0.90	0.92 (0.84–1.01)	0.10
Transfer to another type of healthcare facility	14.35%	1.00 (0.92–1.09)	0.90	0.92 (0.84–1.01)	0.10

GI, gastrointestinal; CTD, connective tissue diseases; OR, odds ratio; CI, confidence interval; EGD, esophagogastroduodenoscopy; AKI, acute kidney injury; PE, pulmonary embolism.

endoscopy with intervention, odds of developing AKI, acute renal failure, sepsis, the need for transfusion, pneumonia, DVT, mechanical ventilation, mean LOS, THCs and transfer to other facilities among patients admitted for GI bleeding with CTDs *vs.* those without CTDs in USA.

GI bleeding represents a significant cause of hospital admissions in the USA and is associated with mortality rates ranging from 5% to 10% (16). However, despite the clinical importance of this condition, limited data are available regarding mortality in patients with concomitant CTD.

Within our cohort of 19,874 patients admitted for GI bleeding, a noteworthy discrepancy in-hospital mortality rates emerged when comparing those with CTD to those without this comorbidity. Specifically, patients with CTD exhibited a lower mortality rate of 2.1%, in contrast to 2.4% observed among non-CTD patients. These findings retained significance even after meticulous adjustments for various covariates, including demographic factors, patient-specific characteristics, and comorbidities.

While these findings suggest a potential protective effect associated with CTD or factors that enhance survival in the context of GI bleeding, it is essential to recognize the absence of a standardized mortality rate for CTD-related GI bleeding. The variance in mortality rates is influenced by several factors, encompassing the severity of bleeding episodes, the underlying health status of the patient, and the promptness of medical interventions. Nonetheless, this notable contrast in mortality outcomes between CTD

and non-CTD patients warrants further investigation and exploration.

In patients with CTD, significant contributors to GI bleeding included intestinal vasculitis and thrombotic events, which may culminate in ischemia, ulcerations, bowel perforations, and subsequent GI bleeding (4). Additionally, the concurrent presence of inflammatory bowel disease (IBD) within the spectrum of CTD entities is recognized as a common etiology of GI bleeding (17). Prompt and precise diagnoses play pivotal roles in managing GI bleeding in patients with CTD, often relying on advanced imaging modalities, including computed tomography (CT) scans (18). Recent trends suggest an increasing utilization of CT scans, particularly in patients presenting with abdominal symptoms (19,20), further underscoring the imperative need for timely diagnosis and intervention. This diagnostic approach serves to mitigate fatal complications and significantly enhance patient outcomes, as exemplified in the context of conditions such as lupus mesenteric vasculitis (LMV) and ulcerative colitis, where abdominal CT scans facilitate early diagnosis (21,22) and enable the prompt initiation of immunosuppressive therapies such as pulsed corticosteroids (23). These therapeutic strategies, in turn, hold the potential to improve the prognosis of CTD-associated GI bleeding substantially.

Beyond the direct association between CTD and GI bleeding, emerging research highlights a distinct concern related to the concomitant use of steroids and NSAIDs commonly used in the management of different CTD. These medications significantly escalate the risk of peptic ulcer disease, a notable precursor to GI bleeding. An illustrative nested case-control study demonstrated a marked elevation in the risk of developing ulcers among patients concurrently using both medications (24). Consequently, proton pump inhibitors (PPIs) are often prescribed to mitigate the potential ulcerogenic effects, particularly in patients necessitating both steroid and NSAID therapies, particularly in those with significant comorbidities and receiving high-dose prednisone (25). However, this practice has been accompanied by an upsurge in PPI utilization and associated healthcare expenditures, with a substantial proportion of patients potentially receiving PPIs unnecessarily (26). Recent meta-analyses have revealed that peptic ulcer formation is a relatively rare complication of systemic corticosteroid therapy alone, occurring in less than 0.4–1.8% of patients (27). Consequently, routine prophylactic PPI use with systemic corticosteroids alone is not recommended (27).

Nevertheless, prescribing PPIs is contingent on several pertinent factors in the context of CTD. CTD encompasses a diverse spectrum of heterogeneous disorders that often manifest with significant comorbidities (28). Notably, our study underscores that a considerable percentage of CTD patients exhibit a higher Charlson comorbidity index, a prognostic indicator reflecting long-term survival and prognosis based on comorbidities, compared to patients without CTDs (65.69% *vs.* 49.72%, P≤0.001). Moreover, CTD patients frequently experience platelet dysfunction, a key pathogenic process predisposing them to vascular conditions that may necessitate antiplatelet or anticoagulant therapy, thereby further elevating their susceptibility to GI bleeding (29). Consequently, a substantial proportion of CTD patients may require PPI therapy more frequently than the general population. A pivotal meta-analysis conducted by Scally and colleagues has provided compelling evidence that PPI administration results in a fivefold reduction in ulcer incidence and a fivefold improvement in ulcer healing. This observation aligns with our finding of decreased mortality among CTD patients, suggesting a plausible mechanism through which ulcer management in CTD patients may contribute to GI bleed prevention and ultimately reduce mortality (30).

Additionally, our study coincides with the long-term cohort analysis conducted by Sultan *et al.* at the Center for Rheumatology in London, which followed 266 SLE patients over 20 years. Remarkably, no deaths attributed to peptic ulcer disease were recorded (10), further underscoring the effective management of ulcerative conditions in CTD patients and its potential role in preventing GI bleeding and reducing mortality.

In our study, we noted a modest adjusted increase of 2% and 8% in the likelihood of patients with CTDs undergoing EGD (44.18% *vs.* 42.61%) and colonoscopy (19.65% *vs.* 18.9%), respectively. However, these differences did not attain statistical significance, suggesting that factors beyond our scope likely influenced these heightened odds. Nevertheless, when examining these procedures independently of other variables, a statistically significant difference surfaced, indicating that CTD patients with GI bleeding were more inclined to receive EGD, including cases with intervention.

This observation may be attributed to the prevalence of GI manifestations in certain CTDs, which often impact the upper GI tract (31). Consequently, this heightened likelihood of intervention underscores the intricate relationship between CTDs and GI bleeding.

However, it's worth noting that many of the potentially severe GI complications manifest in the small and large intestines due to vasculitis (32). This can progress to ischemic enteritis and subsequent life-threatening GI bleeding (6,32). This might explain why patients with GI bleeding and comorbid CTD had adjusted odds of undergoing urgent colonoscopy. However, this finding did not achieve statistical significance compared to the control group. To the best of our knowledge, limited data comprehensively defines the rate of endoscopy utilization in patients with GI bleeding and CTD, nor does it specifically outline the occurrence rate of GI bleeding in different GI tract segments in these patients. This represents a promising avenue for further exploration and research in this field.

It's noteworthy that our study revealed a predominance of Caucasians (White race) among the US population with both CTD and GI bleeding. Interestingly, existing literature suggests that CTD is not only more prevalent but also exhibits higher disease activity and greater damage in non-Caucasian populations (33,34). A retrospective trend analysis conducted between 2008 and 2018 demonstrated a statistically significant increase in the overall incidence of variceal upper GI bleed, with a particular rise observed in the White and Hispanic populations. In contrast, the Asian and Black populations showed a stable trend (35). This trend aligns with our findings, where we observed a significantly higher proportion of GI bleeding cases in the White population (71.28%) compared to other racial groups.

It's essential to note that while Black patients exhibited higher odds of mortality, there has been a noted decrease in mortality rates from variceal upper GI hemorrhage in Black (P=0.03 for trend) and Hispanic (P=0.004 for trend) individuals (36). Addressing future challenges will require a comprehensive investigation into the genetic, environmental, and socio-economic factors that may predispose the Caucasian population with CTD to have increasing rates of GI bleeding. Furthermore, our study aligns with existing literature, indicating that CTD is more common among females (37). This may help explain the significant occurrence of GI bleeding among female patients with CTD compared to their male counterparts (67.95% *vs.* 32.05%, P<0.001), in contrast to the general population.

A noteworthy discovery in our study reveals a 42% increased likelihood of developing PE during hospitalization for patients experiencing GI bleeding alongside CTDs (6.87%, aOR: 1.42, 95% CI: 1.24–1.63; P≤0.001). This heightened risk is intricately linked to the interplay between CTD and other antibodies, notably antiphospholipid antibodies, which predispose these individuals to clot formation (36,38). These findings emphasize the crucial need for vigilant monitoring and considering prophylactic anticoagulation measures for these patients during hospitalization. This approach aligns with the strategy employed for patients with IBD, even in GI bleeding, underscoring the importance of a comprehensive clinical management approach. It's essential to recognize that patients with CTD often present with comorbid chronic lung conditions (36). In our study population, we observed a higher prevalence of comorbid COPD among patients with CTD and GI bleeding despite a lower smoking rate compared to the other population group. Notably, COPD has recently been identified as an independent risk factor for PE, with a reported prevalence of 25% in patients hospitalized due to COPD exacerbations (39,40). Additionally, our study revealed an increased likelihood of requiring blood transfusions among patients with CTD and GI bleeding. However, this difference did not achieve statistical significance compared to the other population group.

Strength and limitation

We acknowledge that, like other studies utilizing the NIS, our research has certain limitations. The retrospective design of our study allows for the establishment of associations but cannot imply causality. It's important to note that while ICD-10-CM codes for GI bleed and CTD have been previously validated and employed, variations in coding accuracy across different hospitals cannot be ruled out. Moreover, the NIS provides data on hospitalizations rather than individual patients, which means that patients hospitalized multiple times cannot be counted repeatedly. One notable observation is the overrepresentation of the White population in our study, which warrants consideration. It is essential to recognize that more severe cases and higher disease activity associated with CTD are often found in non-Caucasian populations. Therefore, further research in this specific population subset may be necessary to validate or replicate our findings.

Additionally, our study could not ascertain the use of GI prophylaxis, steroid administration per patient, direct access endoscopic findings to evaluate the cause of GI bleeding, or the extent of endoscopic interventions in the patients included. These factors could confound the outcomes. Furthermore, the NIS dataset does not contain information

on physical examinations, vital signs, laboratory values, or medications, preventing an assessment of patients' CTDs and the severity of bleeding episodes. This limitation underscores the complexity of managing patients with both GI bleeding and CTD, emphasizing the importance of individualized care and consideration of various clinical factors in decision-making and treatment.

Despite these limitations, our study possesses several strengths. It is one of the few investigations that have delved into the outcomes of GI bleeding in patients with CTDs. Utilizing the largest inpatient database in the USA enhances the robustness of our study. The study uses the NIS, an extensive, nationally representative database that enhances external validity. Including a diverse range of patients from different regions and healthcare settings in the USA increases the likelihood that the findings can be generalized to the broader population. Our scientific inquiry and analytical approach contribute valuable new insights to a relatively underexplored topic. Notably, our findings highlight significantly lower odds of mortality in patients with GI bleed and comorbid CTD.

Conclusions

These results present intriguing implications, suggesting patients with CTD experience lower in-hospital mortality when admitted with GI bleeding. Further research is warranted to substantiate and gain a deeper understanding of these findings and their clinical relevance. Delving into the underlying mechanisms and patient-specific variables contributing to this observed difference is imperative for advancing our comprehension of this medical domain. The heightened risk of PE underscores the significance of implementing prophylactic measures to mitigate thrombotic events in patients with both CTD and GI bleeding. Despite statistical significance in other complications such as blood transfusion, pneumonia, and malnutrition, healthcare providers should remain vigilant for these potential adverse outcomes, even without statistical confirmation.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-5/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-24-5/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Used ICD-10 codes

Diagnosis codes	ICD-10 codes
Gastrointestinal bleeding	K228, I8501, K251, I8511, K255, K285, K255, K261, K271, K281, K275, K265, K2211, K3182, K5521, K6381, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2941, K2961, K2921, K2961, K2971, K2981, K31811, K5711, K5713, K5731, K5733, K226, K2931, K2951, K2991, K31811, K50111
SLE (systemic lupus erythematosus)	M32.x
Rheumatoid arthritis	M05.x, M06.x, M08.x
Scleroderma	M340, M341, M342, M348, M3481, M3482, M3483, M3489, M349
Sjogren syndrome	M332, M3320, M3321, M3322, M3329
Inflammatory myositis	M3500, M3501, M3502, M3503, M3504, M3509, M331, M332, M339, M3381, M3389
Mixed connective tissue disease	M351, M332, M339, M3381, M3389
Giant cell arteritis	M315, M316
Psoriasis	L40.x
Polymyalgia rheumatica	M353
Esophagogastroduodenoscopy without intervention	0DJ68ZZ, 0DJ08ZZ, 0D958ZX, 0DD58ZX, 0D998ZX, 0D968ZX, 0DD68ZX, 0DD98ZX, 0DB58ZX, 0DB68ZX, 0DB98ZX, 0D987ZX, 0DDC8ZX, 0DDB8ZX, 0DDA8ZX, 0DD88ZX, 0DBC8
Esophagogastroduodenoscopy with intervention	06L34CZ, 0D518ZZ, 0D528ZZ, 0D538ZZ, 0D548ZZ, 0D558ZZ, 0W3P8ZZ, 3E0G8TZ, 0D568ZZ, 0D578ZZ, 0D598ZZ, 0DQ98ZZ, 0DQ68ZZ, 0DQ78ZZ, 0W3P8ZZ, 0DL58ZZ, 0DL68ZZ, 0DL98ZZ, 0DLA8ZZ, 0DLB8ZZ, 0DTB8ZZ
Colonoscopy without Intervention	0DJD8ZZ, 0D9E8ZX, 0D9H8ZX, 0D9N8ZX, 0DBE8ZX, 0DBH8ZX, 0DBN8ZX, 0DDE8ZX, 0DDH8ZX, 0DDN8ZX, 0DBP8ZZ, 0DBQ8ZZ, 0DDH
Colonoscopy with Intervention	0D5E8ZZ, 0D5F8ZZ, 0D5G8ZZ, 0D5H8ZZ, 0D5K8ZZ, 0D5L8ZZ, 0D5M8ZZ, 0D5N8ZZ, 0D5P8ZZ, 0DLH8ZZ, 0D5Q8ZZ, 0DLP8ZZ, 0DLQ8ZZ, 0DQH8ZZ, 0DQQ8ZZ, 0D5Q8ZZ, 0DTH8ZZ, 0DTP8ZZ, 0DTQ8ZZ
Diabetes mellitus	E08.x, E09.x, E10.x, E11.x, E12.x, E13.x, O24.x, E0837X1, E0837X2, E0837X3, E0837X9, E1037X1, E1037X2, E1037X3, E1037X9, E1137X1, E1137X2, E1137X3, E1137X9, E1337X1, E1337X2, E1337X3, E1337X9,
Smoking	Z87891, F17200, F17201, I501, F17208, F17209, F17210, F17211, F17213, F17218, F17219, F17220, F17221, F17223, F17228, F17229, F17290, F17291, F17293, F17298, F17299, F17210, F17211, F17213, F17218, F17219, F17220, F17221, F17223, F17228, F17229, F17290, F17291, F17293, F17298, F17299
Hypertension	I15.X, I10
Myocardial infarction	I21.x, I22.x, I23.x, I252
Cerebrovascular accident	I69.x, I68.x, I67.x, I67848
Congestive heart failure	I502.x, I503.x, I504.x, I110, I130, I132, I501
Chronic obstructive pulmonary disease	J44, J440, J441, J449
Chronic kidney disease	N181, N182, N183, N184, N185, N186, N189
Liver cirrhosis	K703.x, K704.x, K74.x, K717, K720, K7210, K7211, K7290, K7291, K7681, P7881, K7460
Human immunodeficiency virus/acquired immunodeficiency syndrome	B20, B9735, Z21
Peripheral vascular disease	173.x, I739, Z958, Z959
Dementia	F01.x, F02.x, F03.x, G310.x, F1027, F1327, F1827, F1927, G3183
Malignancy	C00.x, C26.x, C30.x, C34.x, C37.x, C41.x, C45.x, C93.x, C91.x, C85.x, C81.x, C76.x, C95.x, C96.x, C58, C60, C883, C887, C889, C900, C901, C940, C943, C945, C947

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