Glomerular Diseases

Research Article

Glomerular Dis 2023;3:233–240
DOI: 10.1159/000534062

Received: May 30, 2023
Accepted: September 7, 2023
Published online: September 30, 2023

Kidney Biopsy Findings and Clinical Outcomes of US Veterans with Inflammatory Bowel Disease

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Keywords
Inflammatory bowel disease · Immunoglobin A nephropathy · Histopathology

Abstract
Introduction: Patients with inflammatory bowel disease (IBD; ulcerative colitis [UC] and Crohn's disease [CD]) may have unique patterns of kidney injury related to their underlying or coexisting disease or to medications. We present the kidney biopsy findings and clinical outcomes of veterans with UC or CD from the US Department of Veteran's Affairs (VA) health system. ***Methods:*** Histopathologic and clinical data were extracted by retrospective review of the VA electronic health record of patients with IBD and a kidney biopsy between 2000 and 2018. Incident end-stage kidney disease (ESKD) was defined as requirement of kidney replacement therapy. Statistical analyses were performed using SAS. ***Results:*** A total of 140 patients (UC: 91 and CD: 49) underwent kidney biopsy. The three most common diagnoses were IgA nephropathy (17.1%), diabetic nephropathy (14.3%), and acute interstitial nephritis (9.3%). Significant interstitial fibrosis, tubular atrophy, and arteriosclerosis were present in 45% of biopsies. Twenty-six percent of patients with UC and 20% of those with CD progressed to ESKD, with a mean time from kidney biopsy of 3.1 and 1.9 years, respectively. Forty-five percent of patients with UC and 34% of those with CD died, with a mean time from kidney biopsy of 4.3 and 4.6 years, respectively. ***Conclusion:*** Among US veterans with IBD who underwent a kidney biopsy, IgA nephropathy, diabetic nephropathy, and interstitial nephritis were among the most common findings. Additionally, features of advanced kidney disease with rapid clinical progression to ESKD or death were observed. These findings suggest a delay and possibly a low rate of diagnosis.

Introduction

Inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory disorders of the intestine thought to occur from an abnormal immune response to the intestinal

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microbiota in a genetically susceptible host [1]. Dermatologic, ocular, myeloid, and kidney abnormalities are among the extraintestinal manifestations of IBD. The most common kidney pathology associated with IBD is that of immunoglobin A nephropathy (IgAN), but other glomerular and tubulointerstitial diseases have been described [2, 3]. Many reports are limited to single centers, with short follow-up. Accordingly, we aim to describe the indications and findings for kidney biopsy, as well as the clinical outcomes among a nationwide cohort of US veterans with IBD to better characterize the role of intrinsic renal disease in these patients.

Methods

Objectives

Among US veterans diagnosed with IBD within the VA who underwent a kidney biopsy, this study had two major objectives:

1. to compare, by IBD subtype, the baseline clinical characteristics and indications for biopsy,
2. to describe, by IBD subtype, the kidney histopathologic findings.

In addition, we sought to explore the clinical outcomes of patients with attention to (1) medical and surgical treatments and (2) loss of glomerular filtration rate (GFR), initiation of dialysis therapy, and all-cause mortality.

Concise Methods

In this retrospective study, national veteran data contained within the VA Corporate Data Warehouse (CDW) was first used to identify veterans with IBD between January 1, 2000, and June 30, 2018. The IBD cohort was identified as the presence of either CD or UC, defined by ICD9 and ICD10 (556.* and K50.*, respectively), combined with the presence of a standardized current procedural terminology code (CPT) for kidney biopsy ("50200") with a full pathology report available for review. In addition, subjects required documentation of a gastroenterologist evaluation citing the presence of disease (through review of individual endoscopic findings and available pathologic reports). Exceptions for endoscopic evidence were made in the event of colectomy for UC with no available endoscopy reports. IBD disease onset was recorded by year, extracted from gastroenterology provider notes, and noted as January 1st of the given year.

Baseline subject demography along with available serologic parameters were obtained. Race was recorded as documented in the electronic health record. Creatinine at the time of kidney biopsy was defined as serum creatinine (sCr) measured within 7 days of the procedure. Date of normal renal function was defined as the last known date when sCr was less than 1.4 mg/dL or estimated GFR (eGFR) >60 mL/min. This was based on the chronic kidney disease (CKD)-EPI equation without race adjustment, whereas for a 55-year-old male, sCr of 1.4 estimates GFR at <60, and sCr of 1.3 estimates GFR at >60. The presence of hematuria (defined as >3 red blood cells per high-powered field) or proteinuria (as measured urine protein to creatinine ratio (UPCR) or 24-h urine protein collection) within 3 months of biopsy was recorded.

Manual review and data extraction for both primary and secondary histopathologic diagnoses were performed. The degree of arteriosclerosis was categorized into one of 4 categories: none, mild, moderate, or severe, based on the description contained within the pathology report. Similarly, the degree of interstitial fibrosis and tubular atrophy (IFTA) was categorized as none, mild, moderate, or severe (mild: <25%, moderate: 26–49%, severe: 50% or greater). Incident end-stage kidney disease (ESKD) was defined as the first date of kidney replacement therapy (defined as dialysis or kidney transplantation). The primary healthcare outcomes of interest included GFR loss, initiation of kidney replacement therapy, and all-cause mortality. χ^2 analysis and linear regression comparisons were performed for categorical and continuous variables by IBD diagnosis, respectively. Percentages and median follow-up times for outcomes of interest were calculated over the available timeframe. SAS Enterprise v7.1 (Cary, NC, USA) was used for all analyses.

Results

A total of 480 subjects with available data were identified, of whom 197 had a confirmed diagnosis of UC or CD. Fifty-seven subjects were excluded from this analysis as they underwent kidney biopsy for oncologic cause. The final cohort (n = 140; 91 UC, 49 CD) of subjects underwent kidney biopsy to evaluate for intrinsic kidney disease and were analyzed.

Baseline characteristics are presented in Table 1. Patients were predominantly male and white. The mean age in years (SD) at IBD diagnosis was 45.2 (16.4) for UC and 37.9 (15.5) for CD. At baseline, 26 patients with UC (28.6%) underwent colectomy for disease management or dysplasia, and 28 patients with CD (57.1%) had some form of intestinal surgery (bowel resection or fistula intervention). The indications for kidney biopsy were acute kidney injury or CKD in 107 patients (76.5%), proteinuria in 28 patients (20%), and hematuria in 5 patients (3.5%). At kidney biopsy, the mean age in years (SD) was 62 (14.1) for UC and 60.5 (12.6) for CD. The mean sCr (SD) was 2.9 mg/dL (2.5) for UC and 3.4 mg/dL (3.2) for CD. The mean UPCR (SD) was 3.8 g/g (3.9) for UC and 3.0 g/g (3.3) for CD.

2 lists the most common medications prescribed for the overall cohort and by IBD diagnosis. Mesalamine/balsalazide and prednisone were the most prescribed medications (42.1% and 33.6%, respectively), followed by tumor necrosis factor inhibitors and rectal hydrocortisone (each 9.3%). Overall prescribing patterns significantly differed and varied by disease type (p = 0.005). Compared to patients with CD, those with UC were more likely to be prescribed mesalamine/balsalazide (47.3% vs. 32.6%), tumor necrosis factor inhibition (13.2% vs. 2%) and less likely to be prescribed prednisone (31.9% vs. 36.7%) or rectal hydrocortisone (2.2% vs. 22.4%).

Table 1. Baseline characteristics overall and by IBD diagnosis (n = 140)

	Overall	UC	CD	p value
N	140	91	49	
Age at IBD diagnosis	42.5 (28.7–55.7)	45.2 (30.3–58.6)	37.9 (22.9–48.8)	<0.05[a]
At kidney biopsy				
Age	61.3 (55.5–71.1)	61.7 (57.6–71.8)	60.5 (54.6–79.9)	0.64
UPCR	3.5 (1.0–4.9)	3.8 (1.0–5.3)	3 (0.8–3.8)	0.38
sCr	3.1 (1.4–3.4)	2.9 (1.4–3.3)	3.4 (1.7–3.5)	0.36
eGFR, mL/min	36.7 (17.9–51.3)	37 (17.9–53.7)	36 (18.0–45.3)	0.85
Age, ESKD	64.2 (58.4–73.1)	64.4 (58.5–73.9)	63.7 (58.2–72.2)	0.86
Age, death	70.8 (67.6–77.3)	70.3 (67.7–77.3)	71.7 (67.5–77.4)	0.88
Race				0.45
White	80.0	80.2	79.6	
Black	12.9	14.3	10.2	
Other	6.4	4.4	10.2	
Unknown	0.7	1.1	0	
Sex				0.30
Male	92.9	91.2	95.9	
Female	7.1	8.8	4.1	
Diabetes	41.7	41.5	43.8	0.86
Smoking status				0.87
Current	15.7	14.3	18.4	
Former	43.6	44	42.9	
Never	17.1	16.5	18.4	
Unknown	23.6	25.3	20.4	
Surgery				<0.05[a]
Yes	38.6	28.6	57.1	
No	56.4	65.9	38.8	
Unknown	5.0	5.5	4.1	
Dialysis				0.36
Yes	24.2	26.3	20.4	
Death				0.34
Yes	41.4	45.1	34.7	

Values are percentages (%) and interquartile ranges (IQR) unless otherwise noted. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; *N*; number; UPCR; urine protein/Cr ratio (g/g); sCr, serum creatinine (mg/dL); eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); ESKD; end-stage kidney disease. [a]$p = < 0.05$; χ^2 test.

Table 2. Medication use overall and by IBD diagnosis

	Overall	UC	CD	p value
Medication				<0.05[a]
Mesalamine/balsalazide	42.1	47.3	32.6	
Prednisone	33.6	31.9	36.7	
TNFi	9.3	13.2	2.0	
Rectal HC	9.3	2.2	22.4	
Sulfasalazine	2.9	3.3	2.0	
6-MP/azathioprine	2.8	2.2	4.0	

Values shown are percentages (%). UC, ulcerative colitis; CD, Crohn's disease; TNFi, tumor necrosis factor inhibitor; HC, hydrocortisone; 6-MP, 6-mercaptopurine. [a]$p < 0.05$; χ^2 test.

Of the unique pathologic findings on kidney biopsy, the 5 most common primary diagnoses on kidney biopsy were IgA nephropathy (17.1%), diabetic nephropathy (14.3%), interstitial nephritis (9.3%), focal segmental glomerulosclerosis (FSGS; 8.6%), and membranous nephropathy (MN; 5.7%). Compared to patients with CD, those with UC were more likely to have biopsy findings consistent with IgAN (17.6% vs. 16.3%) or diabetic nephropathy (18.7% vs. 6.1%), and less likely to have findings consistent with interstitial nephritis (8.8% vs. 10.2%), FSGS (5.5% vs. 14.3%), or MN (4.4% vs. 8.2%). Additional information regarding additional biopsy findings overall and by IBD diagnosis is shown in Table 3. Moderate or severe IFTA or arteriosclerosis were found in

Table 3. Kidney biopsy results by IBD diagnosis

	Overall	UC	CD	*p* value
Primary finding (5 most common diagnoses)				<0.01[b]
IgAN	24 (17.1%)	16 (17.6%)	8 (16.3%)	
Diabetic nephropathy	20 (14.3%)	17 (18.7%)	3 (6.1%)	
Interstitial nephritis	13 (9.3%)	8 (8.8%)	5 (10.2%)	
FSGS	12 (8.6%)	5 (5.5%)	7 (14.3%)	
MN	8 (5.7%)	4 (4.4%)	4 (8.2%)	
Secondary finding				<0.05[a]
Interstitial nephritis	19 (13.6%)	12 (13.2%)	7 (14.3%)	
ATI	16 (11.4%)	9 (9.9%)	7 (14.3%)	
Arteriosclerosis				0.73
None	7 (5.0%)	5 (5.4%)	2 (4.1%)	
Mild	26 (18.6%)	17 (18.7%)	9 (18.4%)	
Moderate	38 (27.1%)	23 (25.3%)	15 (30.6%)	
Severe	25 (17.9%)	19 (20.9%)	6 (12.2%)	
Unknown	44 (31.4%)	27 (29.7%)	17 (34.7%)	
IFTA				0.99
<25%	39 (27.9%)	25 (27.4%)	14 (28.6%)	
25–50%	35 (25.0%)	23 (25.3%)	12 (24.5%)	
>50%	28 (20.0%)	18 (19.8%)	10 (20.4%)	
Unknown	38 (27.1%)	25 (27.5%)	13 (26.5%)	

Values are numbers and percentages (%). UC, Ulcerative colitis; CD, Crohn's disease; IgAN, immunoglobulin A nephropathy; FSGS, focal segmental glomerulosclerosis; ATI, acute tubular injury; IFTA, interstitial fibrosis/tubular atrophy. [a]$p < 0.05$; [b]$p < 0.01$ reflects a difference in distribution of diagnoses overall between UC and CD; χ^2 test.

46.2% and 42.8% of biopsies, respectively. The two most common secondary diagnoses were acute or chronic interstitial nephritis (13%) and acute tubular injury (11%). Regarding interstitial nephritis, it was described as "acute" in 15 patients, "chronic" in 11 patients, "acute on chronic" in 3, and the acuity was not described in 3 cases. The full list of primary biopsy diagnoses can be found in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000534062).

A total of 24 patients with UC (26%) and 10 with CD (20%) progressed to ESKD, with a mean time (SD) from kidney biopsy of 3.1 (4.2) and 1.9 (1.8) years, respectively. Forty-one patients with UC (45%) and 17 with CD (34%) died with a mean time from kidney biopsy of 4.3 (SD) and 4.6 years (SD), respectively.

Among the 3 most common diagnoses, progression to ESKD occurred in 9 of 24 (38%) patients with IgAN, 6 of 21 (29%) patients with diabetic nephropathy, and 4 of 12 (33%) with interstitial nephritis. Patients on average carried a diagnosis of IBD for at least 10 years prior to referral for kidney biopsy. Additionally, patients had a decline in GFR to less than 60 mL/min (CKD stage 3) for more than a year prior to kidney biopsy. Among patients with interstitial nephritis, patients presented with severely compromised kidney function (mean eGFR 17.6 mL/min), and mean time to dialysis from kidney biopsy was less than a year (10.8 months) (Table 4).

Discussion

In this cohort of US Veterans with IBD who underwent kidney biopsy for cause with relevant clinical outcome data, our findings of IgAN and interstitial nephritis being the two most common findings are consistent with previous literature [3]. At the time of kidney biopsy, a large proportion of patients had significant kidney dysfunction and histopathologic findings of advanced chronic scarring (IFTA). These findings were associated with a short latency between kidney biopsy and development of ESKD and death.

Ambruzs et al. [3] first described that IgAN was the most common diagnosis among a cohort of 83 IBD patients and also demonstrated that the frequency of IgAN in IBD was higher when compared to the biopsy findings of non-IBD patients during the same time period of their review. The link between IgAN and mucosal disease has been a topic of interest and research for some

Table 4. Characteristics and time to clinical event for patients with IgA nephropathy (IgAN), diabetic nephropathy (DN), and interstitial nephritis (IN)

	Characteristics at kidney biopsy			Time (years) from IBD diagnosis			Time (years) from last known eGFR >60			Time (years) from kidney biopsy	
Group	Age	eGFR	UPCR	To kidney biopsy	To ESKD	To death	To kidney biopsy	To ESKD	To Death	To ESKD	To death
IgAN	59.1 (15.4)	40.3 (28.9)	2.8 (2.9)	21.6 (17.45)	29.1 (27.9)	34.1 (21.5)	1.3 (1.6)	3.0 (0.5)	4.8 (4.1)	1.4 (1.1)	3.4 (2.3)
DN	65.1 (10.5)	44.0 (22.9)	5.0 (4.6)	15.6 (11.6)	17.8 (6.6)	18.0 (11.4)	1.7 (1.9)	5.0 (2.3)	5.2 (2.7)	2.3 (2.4)	4.5 (3.9)
IN	59.1 (12.6)	17.6 (12.2)	2.1 (3.6)	13.7 (14.9)	19.3 (14.8)	25.2 (19.7)	2.0 (3.6)	2.9 (3.6)	9.8 (5.2)	0.9 (0.9)	5.0 (3.5)

Values are means and standard deviations (SD) unless otherwise noted. SD, standard deviation; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; ESKD, end-stage kidney disease.

time, with the initial observations of synpharyngitic hematuria in patients with IgAN, as well as the observed higher prevalence of IgAN in patients with celiac disease [4]. Since those initial observations, epidemiologic studies have confirmed the increased risk of IgAN in patients with celiac disease. A recently published study from Sweden found that among patients with IgAN, IBD was more prevalent and associated with a worse prognosis compared to patients with IgAN without IBD [5]. Along with genome-wide association studies of patients with IgAN identifying loci in genes involved in the intestinal mucosal integrity, our understanding of the link between inflammatory gastrointestinal disease and IgAN has continued to grow. Our findings of IgAN being the most common primary diagnostic finding among our cohort of IBD patients further support the potential link between intestinal mucosal disease and IgAN, and continued research to elucidate the underlying mechanisms is needed.

Interstitial nephritis is a known potential adverse effect of aminosalicylic acid (ASA) therapy which is commonly used for the management of IBD. However, previous case series and reports have proposed that interstitial nephritis itself could be an extraintestinal manifestation of IBD [6, 7]. Although most patients in our cohort had ASA or another drug exposure possibly associated with interstitial nephritis, a culprit agent could not be identified by the treating physician in 6 patients. Of the patients with consensus on potential culprit agents, ASA was predominant, but there were two cases where NSAID exposure was noted, one case of cephalosporin exposure, and lastly, a case of IgG4-related interstitial nephritis. The cases where a culprit agent could not be identified may represent instances where interstitial nephritis was thought to be an extraintestinal manifestation of IBD.

Our findings of a high incidence of diabetic nephropathy differed from previous biopsy series of IBD patients [3, 8, 9]. These findings are likely related to both the IBD as well as the high prevalence of diabetes in the population studied. Multiple national studies indicate that the risk of type 2 diabetes is higher among patients with IBD (both UC and CD) than the general population and not explained by corticosteroid exposure alone [10, 11]. Additionally, diabetes is more prevalent among US veterans than the general US population [12]. In our study, patients with UC were more likely to have diabetic nephropathy compared to those with CD. Data differ regarding whether there is a higher risk of diabetes in patients with UC compared to CD. A population-based study in Korea showed that patients with CD were at higher risk of diabetes compared to UC, as opposed to a cohort from Denmark which found no difference between IBD subtype [10, 11]. Among our cohort, patients with CD were more likely to have had surgical intervention, which may have negatively impacted their hydration, nutrition, and metabolic parameters, resulting in less frequent diabetes.

Closer evaluation of the three most common diseases highlights some of the potential reasons for the findings of advanced kidney disease at biopsy. On average, the patients had a decline in kidney function for more than a year prior to referral for biopsy, a relatively long period of disease activity. In particular, patients with interstitial nephritis had a longer average duration of compromised kidney function (2 years vs. 1.3 [IgAN]/1.7 [DN] years),

presented with much lower eGFR at time of biopsy, and had a very short latency to development of ESKD. Given the interstitial nephritis was described as chronic in a significant number of patients, it may also have contributed to the short timeframe between biopsy and development of ESKD. Kidney injury can result in significant damage prior to changes in sCr; thus, at the point a patient's renal function has declined by creatinine-based GFR assessment, a potentially significant amount of damage has occurred. Accordingly, alternatives to screening for kidney disease other than sCr may be of benefit to clinicians in identifying kidney disease earlier (i.e., proteinuria, urinary biomarkers, cystatin C).

Regarding other glomerular diseases, FSGS, MN, and paraprotein-related diseases were the 4th, 5th, and 6th most common findings, respectively. Although some biopsy reports reflected a suspicion of either primary or secondary FSGS, we opted to combine these into one category given the difficulty in retrospectively distinguishing these entities. Regarding MN, previous evidence from childhood MN demonstrated a potential link between gut microbiota and development of antibodies targeting cationic bovine serum albumin, resulting in nephrotic syndrome [13]. A more recent study evaluating gut dysbiosis and MN demonstrated significant differences in the gut microbiome composition in patients with MN compared to healthy controls. These findings suggest that altered gut flora, potentially caused by intestinal inflammation, may contribute to the pathogenesis of MN [14]. Lastly, amyloidosis can be a result of chronic, sustained inflammation and is a known potential complication of long-standing IBD [15]. Three patients (2 with CD and 1 with UC) were noted to have AA-amyloid, and all had long-standing, difficult-to-control IBD.

Regarding secondary diagnoses, acute tubular injury was found to be more common among patients with CD than UC. The numbers in our study are small, and the reason for this difference is unclear. Given CD can have esophageal and/or gastroduodenal involvement, patients with CD experience more issues with malabsorption and nutrient deficiency [16, 17], which can lead to hemodynamic and metabolic tubular injury. The burden of malabsorption, either due to GI surgery or uncontrolled disease, is highlighted by the finding of oxalate nephropathy only among CD patients in our cohort. Additionally, given several UC patients had curative colectomy, they may have been at less risk of developing hemodynamic tubular injury. Current practice in terms of kidney function monitoring in IBD patients is provider dependent. Both American and British gastroenterology consensus guidelines do recommend periodic renal function monitoring for those patients treated with 5-ASA [18, 19]. However, no clear guidelines exist with respect to other therapeutic agents. In a 2013 survey of 249 private practice gastroenterologists in France, 82% reported monitoring kidney function once or twice a year when patients are on 5-ASA. However, only 29% reported evaluating kidney function prior to initiating therapy. If a patient has an abnormal creatinine while on therapy initiation, 80% would obtain a nephrology opinion, and 48% of providers would stop therapy if a 30–50% increase in sCr was observed [20]. These findings suggest a significant heterogeneity in practice patterns in terms of assessment of kidney function or changes thereof. Our findings of advanced IFTA on kidney biopsy, high mean sCr at biopsy, and relatively short time from biopsy to development of ESKD suggest a delay in diagnosis or perhaps under-recognition of kidney disease in IBD patients. It is possible that earlier and more frequent assessment of GFR, UPCR, and hematuria may detect kidney disease at an earlier stage and halt its progression to ESKD.

There are multiple limitations of this study. The large male predominance of US Veterans limits generalizability. The retrospective study design limits complete data extraction and outcome data is subject to confounding variables. Many patients at the VA also seek care outside the VA system, including laboratory monitoring, which may underestimate the true number of patients with IBD who underwent kidney biopsy or sought nephrology care. These factors also limited our ability to distinctly capture episodes of acute kidney injury or hospitalizations, which could help inform reasons for the apparent accelerated decline in kidney function. In addition, as this population of patients is older with a large multimorbidity burden, use of additional markers of kidney function such as cystatin C may be particularly useful but were not widely available. Cystatin C may provide additional insights into baseline function as well as the severity of kidney disease at the time of biopsy. Given the relatively long timeframe of the study, and a nonuniform approach to pathologist biopsy reporting, classification error may exist, notably with respect to ascribing "primary" versus "secondary" diagnoses. In an attempt to mitigate these issues, data abstraction and interpretation was performed in a uniform manner to apply our proposed definitions. Strengths of this study include the relatively large size of the cohort, specificity of patients having true UC or CD, and uniform laboratory and pathology reporting stemming from the use of a single VA EHR. Our selection process does highlight the potential pitfalls of utilizing ICD codes to study IBD, as after chart review, we could not confirm a diagnosis of UC or CD in a large portion of patients who carried a relevant ICD code.

Conclusion

Among US veterans with IBD who underwent kidney biopsy, IgAN, acute or chronic interstitial nephritis, and diabetic nephropathy were the most common findings. Patients had advanced kidney disease at biopsy, and ESKD or death was common within a relatively short time period. The findings of advanced kidney disease at the time of biopsy and short time to ESKD suggest a delay in diagnosis and possibly a low rate of diagnosis. Additional research evaluating the potential benefit of screening for renal disease should be considered.

Acknowledgments

This research was presented as an abstract at the American Society of Nephrology's 2021 Annual Meeting.

Statement of Ethics

All work was carried out in compliance with ethical principles for medical research involving human subjects as outlined in the Helsinki Declaration. The need for informed consent was waived by the Institutional Review Board at the Minneapolis VA, who ultimately approved this study (IRB# 1594650-3).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

Prasanth Ravipati, MD: conceptualization; data curation; writing – original draft; and writing – review and editing. Scott Reule, MD, MS: conceptualization; data curation; formal analysis; methodology; writing – original draft; and writing – review and editing. Prasanth Ravipati and Scott Reule contributed equally as first authors. Alyssa Bren, BS: data curation and writing – review and editing. Lihong Bu, MD, PhD: conceptualization; methodology; and writing – review and editing. Byron P Vaughn, MD, MS: conceptualization and writing – review and editing. Patrick H Nachman, MD, MS: conceptualization; methodology; supervision; writing – original draft; and writing – review and editing.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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