Intradural spinal arachnoid cyst resection: implications of duraplasty in a large case series

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OBJECTIVE Optimal diagnosis and management strategies for intradural spinal arachnoid cysts (SACs) are still unresolved given the rare nature of this entity, with few large case series and virtually no statistical analyses of patient characteristics in the literature. Here, the authors studied a large patient cohort with these lesions to determine whether pre- or postoperative attributes could be used to aid in either diagnosis or prognosis.

METHODS A chart review was completed at a single institution for the period from 2002 to 2016 to determine the preoperative characteristics and postoperative outcomes of 21 patients with exclusively intradural SACs. Patients were assessed for symptoms such as weakness, pain, sensory changes, bowel and/or bladder dysfunction, and gait changes. Postoperatively, patients were analyzed for symptom improvement, complication occurrence, and duration of follow-up.

RESULTS Approximately two-thirds of the patients in this series had developed SACs idiopathically, and the mean duration of symptoms prior to diagnosis was 15 months among all patients. A slight majority (57%) underwent CT myelography in the course of diagnosis, and a quarter of the patients had a syrinx. There was a statistically significant association between location of the SAC and number of presenting signs and symptoms; that is, patients with cysts in the lumbar-sacral region had more symptoms than those with cysts at the cervical or thoracic levels (p = 0.031). Overall, outcomes were largely positive, with approximately 60%–70% of patients experiencing postoperative improvement in symptoms, with motor weakness showing the highest response rate (71%) and pain symptoms the least likely to subside (50%). In the cohort with preoperative pain, those who had undergone expansile duraplasty were significantly more likely to experience relief of their pain symptoms (p = 0.028), which may have been a result of the superior restoration of cerebrospinal fluid pathways allowing for more adequate reduction in compression.

CONCLUSIONS In this large case series on intradural SACs, new light has been shed on aspects of both pre- and postoperative care for patients with these rare lesions. Specifically, the authors revealed that lumbosacral intradural SACs may be associated with a higher disease burden and that patients who undergo expansile duraplasty may have an increased likelihood of experiencing postoperative pain relief.

KEY WORDS spine; arachnoid cyst; intradural; congenital

Abbreviations: CSF = cerebrospinal fluid; SAC = spinal arachnoid cyst.

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cells leading to scar formation that produces a diverticular cyst. Secondary cysts can be caused by alterations in cerebrospinal fluid (CSF) flow that produce diverticulation of the arachnoid layer at regions of decreased resistance.

As rare entities, intradural SACs have been the focus of very few large case series reporting the characteristics and outcomes of treated adults. At least 2 large studies on 21 and 17 patients, respectively, who were surgically managed for intradural SAC were unable to correlate the resolution of symptoms with characteristics such as patient age, cyst size, or duration of symptoms. Moreover, the authors of one of these studies did not report whether the patients underwent duraplasty, and in the other study, despite a number of patients who underwent expansile duraplasty, there was no report of how duraplasty affected surgical outcomes. While the role of expansile duraplasty has been extensively studied in Chiari malformation, its role in intradural spine surgery has not been evaluated.

Here, we report on a series of 21 adults surgically treated for intradural SAC at our institution.

Methods

Through a chart review, we identified 21 patients (12 male, 9 female) who had undergone surgery for intradural SAC between 2002 and 2016. Patients were assessed for symptoms such as weakness, pain, sensory changes, bowel and/or bladder dysfunction, and gait changes. Postoperatively, patients were analyzed for symptom improvement, complication occurrence, and duration of follow-up. Basic statistical analyses were performed for the entire cohort using a software package (MATLAB, The MathWorks Inc.). We performed ANOVA for comparisons among groups based on intradural SAC location, and independent samples t-tests were performed to compare primary versus secondary cysts. A Fisher’s exact test was used to compare complication rates in patients based on whether they had undergone expansile duraplasty. A p < 0.05 was considered statistically significant.

Surgical Procedure

All patients underwent surgery via laminectomy or laminoplasty. Localization of the cyst and appropriate spinal levels was performed with lateral fluoroscopy. Somatosensory and motor evoked potentials were monitored with intraoperative electrophysiology. After the spinous process, lamina, and facet complex were exposed, the lamina and facets at the relevant levels were thinned with a high-speed drill. Intraoperative ultrasonography was used for visualization of the cyst location to confirm localization prior to durotomy. We typically expose one level above and below the cyst to allow adequate space to mobilize the spinal cord and prevent excessive tension during dissection. Exposure typically revealed a thickened arachnoid band that was dissected with microscissors. Representative images from one of the cases are featured in Fig. 1. A duraplasty was used in instances in which it was believed necessary to increase the size of the intradural space to prevent spinal cord adherence and tethering.

Results

Patient ages ranged from 19 to 78 years old, with a mean age of 55.1 years. All patients had undergone preoperative evaluation, including a detailed history and physical examination. Follow-up visits also included complete physical examinations and documentation of improvements in preoperative signs and symptoms. In all cases, diagnosis was confirmed with preoperative imaging, including MRI and CT myelography in selected cases. Baseline demographic data and surgical details are provided in Table 1.

All cysts identified in this series were dorsal to the spinal cord. Fifteen patients (71%) had cysts in the thoracic region, 4 (19%) in the cervicothoracic region, and 2 (10%) in the lumbosacral region. Figure 2 displays a breakdown of the frequency of levels affected by intradural SACs across all patients. The mean number of presenting symptoms in patients with cervicothoracic, thoracic, and lumbosacral cysts was 3.3, 2.2, and 4.5, respectively, when they were assessed for signs and symptoms such as weakness, pain, sensory changes, bowel and/or bladder dysfunction, and gait changes.

We identified 7 patients with a potential antecedent mechanism, while 14 patients were thought to have developed the cysts idiopathically. The mean duration of symptoms prior to neurosurgical evaluation or diagnosis was 15 months, although there was wide variation from as little as several days to as much as 4+ years. Presenting symptoms included weakness (67%), sensory disturbances (67%), pain (57%), gait changes (52%), and bowel and/or bladder dysfunction (24%; Fig. 3). Twelve patients underwent CT myelography to aid in diagnosis, which suggested intradural arachnoid cyst in two-thirds of the cases. A quarter (25%) of the patients had a syrinx during the course of radiological evaluation (Fig. 4).

Eight of 21 patients underwent duraplasty. Eighteen of 21 patients underwent laminectomy, while 3 underwent laminoplasty. The diagnosis was confirmed by histopathological evaluation (Fig. 5).

One-way ANOVA revealed that patients with lumbosacral cysts had significantly more presenting signs and

![FIG. 1. A: Intradural cyst identified after dural opening. B: Tack-up sutures are placed for enhanced visualization. C: Resection of arachnoid cyst wall. D: Primary dural closure with running suture. Figure is available in color online only.](image)
symptoms than those with cervicothoracic or thoracic cysts ($F = 4.25, p = 0.031$). The overall variance of difference in the number of presenting conditions attributable to the location of the cyst was $R^2 = 0.32$. The difference in presenting signs and symptoms between patients with cervicothoracic and thoracic cysts was not statistically significant ($p = 0.14$, t-test). Additionally, while the 2 patients with lumbosacral cysts did have a lower mean duration of symptoms (4 months vs 16.7 and 13.8 months for patients with thoracic and cervicothoracic cysts, respectively), this difference was not significant ($F = 0.59, p = 0.6$, 1-way ANOVA). There was also no difference in the number ($p = 0.24$, t-test) or duration ($p = 0.94$, t-test) of presenting symptoms for patients with primary versus secondary causes.

In terms of postoperative improvement, weakness improved most robustly with 10 (71%) of 14 patients recovering motor ability. Fifty percent of the patients reported decreased postoperative pain, while 64% had at least some resolution of their sensory disturbances (Fig. 3). Sixty percent of the patients with preoperative bowel and/or bladder dysfunction reported improvement, and 55% had improved gait. There were no significant differences based on cyst location in the number ($F = 0.28, p = 0.8$, 1-way ANOVA) or percentage ($F = 0.21, p = 0.8$, 1-way ANOVA) of preoperative symptoms that improved postoperatively. In addition, when organizing the patients into 2 groups based on whether their arachnoid cyst spanned more or fewer than 2 levels, there was no difference in the number and percentage of preoperative symptoms that improved postoperatively ($p = 0.66$ and 0.82, respectively, t-test). Similarly, patients with primary and secondary cysts did not experience any postoperative difference in these measures ($p = 0.40$ and 0.82, respectively, t-test). Neither did we find any differences in outcome based on demographic characteristics. For instance, there was no difference in the number of symptoms improving postoperatively based on male or female sex ($p = 0.60$, t-test). Similarly, there was no difference in the percentage of improved symptoms based on an age greater or lower than 60 years ($p = 0.36$, t-test). Finally, there was no difference in this measure based on a preoperative symptom duration of less than or greater than 12 months ($p = 0.79$, t-test).

Interestingly, we found that patients who had undergone duraplasty were significantly more likely to experience postoperative improvement in pain symptoms than were those who had not undergone duraplasty ($p = 0.028$, 1-way ANOVA).

### TABLE 1. Demographic and surgical management data in 21 patients treated for SAC

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Potential Etiology</th>
<th>Levels Affected</th>
<th>Operation</th>
<th>Duraplasty</th>
<th>Fusion</th>
<th>Syrnix</th>
<th>FU Period (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>F</td>
<td>Idiopathic</td>
<td>T6–7</td>
<td>T6–7 laminec, T-8 superior laminec (redo)</td>
<td></td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>Idiopathic</td>
<td>T-3</td>
<td>T2–3 laminec, C7–T5 PSF</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>Idiopathic</td>
<td>T4–5</td>
<td>T-4 &amp; partial T-5 laminec, T3–5 spino-porous process wiring/fusion, revision of T4–5 laminec (redo)</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>156</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>F</td>
<td>Idiopathic</td>
<td>T4–9</td>
<td>T-3 laminec, T4–9 laminop</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>F</td>
<td>Idiopathic</td>
<td>-</td>
<td>T7–9 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LTFU</td>
</tr>
<tr>
<td>6</td>
<td>78</td>
<td>M</td>
<td>Idiopathic</td>
<td>T2–6</td>
<td>T4–6 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LTFU</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>M</td>
<td>Idiopathic</td>
<td>C2–T4</td>
<td>T3–6 laminop</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>F</td>
<td>Posttraumatic (remote MVC)</td>
<td>T2–5</td>
<td>T1–5 laminop</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>M</td>
<td>Congenital (spina bifida/CM)</td>
<td>C2–T8</td>
<td>T-9 laminec</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>M</td>
<td>Idiopathic</td>
<td>T-5</td>
<td>T-6 laminec</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>M</td>
<td>Post-SAH (ruptured VA aneurysm)</td>
<td>C2–T3, T8–9</td>
<td>T1–4 laminec</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>F</td>
<td>Idiopathic</td>
<td>S1–2</td>
<td>S-1 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>13</td>
<td>63</td>
<td>F</td>
<td>Post-SAH (ruptured PICA aneurysm)</td>
<td>C6–T1</td>
<td>C3–6 laminec</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>43</td>
</tr>
<tr>
<td>14</td>
<td>61</td>
<td>F</td>
<td>Idiopathic</td>
<td>T-4</td>
<td>T3–5 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>15</td>
<td>64</td>
<td>F</td>
<td>Idiopathic</td>
<td>L1–2</td>
<td>L1–2 laminec</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>78</td>
<td>M</td>
<td>Idiopathic</td>
<td>T4–5</td>
<td>T3–6 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>74</td>
<td>M</td>
<td>Postmeningitis</td>
<td>T1–2</td>
<td>T2–3 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LTFU</td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>M</td>
<td>Idiopathic</td>
<td>T4–5</td>
<td>T3–7 laminec (redo), cyst fenestration</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>LTFU</td>
</tr>
<tr>
<td>19</td>
<td>19</td>
<td>M</td>
<td>Congenital (aspects of Shprintzen-Goldberg &amp;/or DiGeorge syndromes)</td>
<td>T3–5, T8–10</td>
<td>T3–5 laminop, T8–10 laminop</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>35</td>
<td>M</td>
<td>Idiopathic</td>
<td>T6–7</td>
<td>T6–7 laminec</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>21</td>
<td>60</td>
<td>F</td>
<td>Posttraumatic (fall)</td>
<td>T4–5</td>
<td>T4–5 laminec, w/ T2–7 posterior fusion</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

CM = Chiari malformation; FU = follow-up; laminec = laminectomy; laminop = laminoplasty; LTFU = lost to follow-up; MVC = motor vehicle collision; PICA = posterior inferior cerebellar artery; PSF = posterior spinal fusion; SAH = subarachnoid hemorrhage; VA = vertebral artery; − = no; + = yes.
Fisher’s exact test, OR 24.2, 95% CI 0.93–629.4; Table 2). A similar effect was not seen for other postoperative symptoms, including weakness, sensory changes, or gait change (p > 0.05, Fisher’s exact test). Patients who had undergone duraplasty did not differ from those who did not undergo duraplasty in terms of characteristics such as age (p = 0.93, t-test) or duration of preoperative symptoms (p = 0.22, t-test).

Complete resection was achieved in 17 patients, whereas incomplete resection occurred in 4. Four patients experienced complications, one who required an additional operation due to pseudomeningocele, one who developed a pseudomeningocele managed conservatively, one who required reexploration and washout due to poor wound healing, and another who developed a postoperative epidural hematoma. A Fisher’s exact test did not reveal an association between undergoing a duraplasty and experiencing a postoperative complication (p > 0.05, OR 1.11, 95% CI 0.14–8.7). Additionally, 2 patients developed symptomatic cyst recurrence and required a second operation, whereas 1 patient who had undergone resection at an outside institution had to have an operation at our institution for symptomatic cyst recurrence. Follow-up periods ranged from 1 month to 13 years, with a mean follow-up duration of 18 months (SD ± 3.9 months). Nine patients underwent postoperative imaging, as symptomatically warranted, and 7
of them showed improvement following surgery. Of the 4 patients with a syrinx on preoperative imaging, 3 showed improvements, while the fourth did not undergo follow-up imaging. Four patients were lost to follow-up.

Discussion

Intradural SACs are uncommon outpouchings of the arachnoid layer that are generally found in the thoracic and cervical regions of the spinal cord. Herein, we report on a series of patients with SACs, some of whom had predisposing factors. Two patients had histories of congenital anomalies: one with spina bifida and Chiari malformation, the other with an undefined syndrome that shared features of Shprintzen-Goldberg and DiGeorge syndromes. Another patient had long-standing thoracic discomfort stemming from a motor vehicle accident from more than 20 years ago, and 2 other patients suffered aneurysmal subarachnoid hemorrhages within 2–3 years prior to presentation. Additionally, 1 patient was diagnosed with an arachnoid cyst in the context of an admission for meningitis. We did not find any differences between the 2 groups of primary idiopathic and secondary SACs when analyzing clinical factors in the two. Thus, our series represents a “real-world” cohort of patients consisting of both idiopathic and secondary causes of SAC development.

In adults, intradural SAC seems to present most commonly in the 3rd and 4th decades of life, with the average age of several case series in the range of 35–52 years, which is slightly lower than the mean age of 55 years among our patients. In our study, all of the identified intradural SACs were dorsal to the spinal cord, a rate consistent with those in prior series demonstrating rates above 90%, though higher than rates in other more recent series showing approximately a quarter of the cysts occurring anteriorly. Presenting symptoms commonly include weakness, pain, sensory disturbances (for example, paresthesias, hypesthesias), gait changes, and bowel or bladder dysfunction. Symptoms typically last for several months and have been postulated to be shorter for thoracic cysts than for lumbar or sacral cysts, perhaps as a result of the smaller spinal cord diameter in this region. However, our results do not corroborate this hypothesis and, if anything, indicated that thoracic cysts took longer to present, although this difference was not significant. When looking at the half of the patients with arachnoid cysts spanning 2 or fewer levels compared with the group harboring more extensive cysts, there was no difference in the number of presenting symptoms. Interestingly, we found that the 2 patients with intradural arachnoid cysts of the lumbosacral region had significantly more presenting symptoms than the patients with cysts of the cervicothoracic or thoracic region. While our sample size for this group is indeed limited, it is consistent with those in prior studies demonstrating small percentages of cysts at the lumbosacral region, and the finding that more than one-third of the variation in the number of presenting symptoms can be explained by cyst location leaves open the possibility that other factors are also influential in affecting this measure.

Radiological evaluation of intradural SACs is most often conducted with MRI and CT myelography. A communicating arachnoid cyst will show contrast filling on CT myelography (Fig. 6), while a noncommunicating cyst will demonstrate a filling defect. With MRI, cysts typically demonstrate heterogeneous signal intensity, although poorly communicating cysts are hyperintense compared

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Duraplasty Group</th>
<th>No Duraplasty Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Mean age in yrs</td>
<td>54.8</td>
<td>55.4</td>
<td>0.93*</td>
</tr>
<tr>
<td>No. of preop symptoms</td>
<td>3.1</td>
<td>2.4</td>
<td>0.21*</td>
</tr>
<tr>
<td>Average no. of levels affected</td>
<td>4.3</td>
<td>2.9</td>
<td>0.30*</td>
</tr>
<tr>
<td>Postop pain improvement</td>
<td>5/5 (100%)</td>
<td>2/7 (29%)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Postop weakness improvement</td>
<td>5/6 (83%)</td>
<td>5/8 (63%)</td>
<td>0.58†</td>
</tr>
<tr>
<td>Postop gait change improvement</td>
<td>2/5 (40%)</td>
<td>4/6 (67%)</td>
<td>0.57†</td>
</tr>
<tr>
<td>Postop bladder dysfunction improvement</td>
<td>1/2 (50%)</td>
<td>2/3 (67%)</td>
<td>1.00†</td>
</tr>
<tr>
<td>Postop complication</td>
<td>1/8 (13%)</td>
<td>3/13 (23%)</td>
<td>1.00†</td>
</tr>
</tbody>
</table>

Boldface type indicates statistical significance (p < 0.05).
* t-test.
† Fisher’s exact test.
with CSF, while those that are communicating may have hypointense bands resulting from spin dephasing because of the movement of CSF within the cyst. In our series of patients, slightly more than half underwent CT myelography when clinical uncertainty remained following MRI. These studies helped prove two-thirds of the time, especially if a filling defect was observed, since idiopathic herniation, the other main differential diagnosis of spinal cord compression, is typically characterized by the free flow of contrast material at the level of herniation. Histopathology typically demonstrates a sheet of flattened arachnoid cells that surround fibrocollagenous connective tissue. Epithelial membrane antigen staining often labels cells lining the cyst wall (Fig. 5).

In terms of surgical management, the removal of intradural SAC is typically accomplished by posterior decompression via laminectomy. Ventral cysts are commonly extirpated via a posterolateral approach. More recently, endoscopic techniques allowing for a less invasive procedure have been described. In cases in which direct cyst resection is not feasible, other methods include cysto-peritoneum or atrium shunting or even percutaneous cyst resection is not feasible, other methods include cyst-resection compared with that in patients who underwent duraplasty following SAC resection alone. This finding concurs with results in a case report by Kikuta et al., who described a patient with an extradural arachnoid cyst who had undergone expansile duraplasty given that the SAC could not be fully resected. The patient had complete resolution of his preoperative pain and dysesthesia. The authors hypothesized that these symptoms were probably related to entrapment neuropathy and that the expansile duraplasty resolved the symptoms by relieving the compression. While complete resection was achieved in most patients in our series, it is possible that the additional volume afforded by expansile duraplasty plays a role in relieving the dysesthetic pain associated with SACs. In informal conversations and personal communications with other experts and colleagues regarding intradural spinal surgery, expansile duraplasty to prevent dorsal tethering and increase CSF flow around the surgical site was commonly discussed. This idea was applied in our experience with SAC to potentially help reduce cyst recurrence, dorsal tethering, and dural constriction. Improvements in pain symptoms have also been described following expansile duraplasty for the management of other spinal pathologies, including posttraumatic syringomyelia and myelomalacic myelopathy, potentially related to the restoration of CSF pathways in the subarachnoid space.

Finally, in terms of postoperative management, 2 patients in this series required reoperations for recurrent arachnoid cyst while 4 patients experienced complications, including epidural hematoma, pseudomeningocele, and poor wound healing. Overall, most patients experienced postoperative recovery, with roughly two-thirds of the preoperative symptoms improving or resolving postoperatively.

While this report represents one of the largest case series of patients surgically treated for SAC, it is worthwhile to note a few limitations inherent to our study design, including its retrospective nature. As mentioned above, the statistical power of our subdivided analyses would certainly benefit from larger sample sizes, and our hope is that this matter will be addressed in future meta-analyses that incorporate findings from multiple large case series. Another limitation is the absence of standardized outcome measures, such as health-related quality of life assessments.
Conclusions

Intradural SACs are rare entities that cause weakness, sensory changes, and gait disturbances and can ultimately produce spinal cord compression or syringomyelia. Here, we report on a case series of 21 patients from our institution that underwent resection of these cysts. We demonstrated that cyst location is associated with the quantity of preoperative signs and symptoms but has little prognostic significance for postoperative recovery. We also found that CT myelography still plays a useful role in distinguishing arachnoid cysts when MRI results are equivocal. Most cysts were amenable to surgical intervention via laminectomy and resection, and postoperative symptom resolution was widespread. Duraplasty may play a role in postoperative pain relief following arachnoid cyst resection. Case series of this pathological entity are extremely rare, but this study represents a large, real-world cohort of patients.

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References


Disclosures

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Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chi. Statistical analysis: all authors. Administrative/technical/material support: Chi. Study supervision: Chi.

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