



Systematic Reviews /Meta-analyses

Iatrogenic spinal cord ischemia: A patient level meta-analysis of 74 case reports and series [☆]



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A B S T R A C T

Background: We seek to characterize the features of iatrogenic spinal ischemia, determine which spinal levels are affected, and evaluate the efficacy of management strategies.

Methods: We performed a meta-analysis of case reports and series of spinal ischemia in the past 10 years. 343 full-length case reports and case series were screened against predefined inclusion/exclusion criteria. 89 patients were included for our final meta-analysis using PRISMA guidelines.

Results: Mean age of patients was 59.62 years (range: 9 months-88 years). 66% of all cases were male. Endovascular surgery (32.6%) and aortic surgery (36.0%) were most common causes of iatrogenic injury, followed by non-aortic surgery (32.6%), and non-surgical procedures (22.47%). A- and B-level ASIA Impairment was found in 66% of all patients. Rehabilitation was the most common management (49.44% of cases), followed by blood pressure management (40.45%). Non-aortic surgeries had the poorest overall outcomes (OR = 0.28, $p = 0.016$), whereas aortic and endovascular surgeries saw significant improvement in outcomes measured at discharge (OR = 2.6, OR = 2.3, respectively, $p < 0.05$). Therapeutic surgical infarctions were found to be associated with improved outcomes (OR = 5.33, $p = 0.032$). Ischemic injury to T4–T7, and T10 were associated with significantly poorer outcomes. Autonomic impairment was associated with a likelihood of infarction at T10 (OR = 4.54, $p = 0.0183$).

Conclusions: In this paper, we compare outcomes following iatrogenic spinal ischemia. We demonstrate the need for more comprehensive randomized controlled trials to test effective treatment strategies.

Introduction

Iatrogenic spinal cord ischemia (ISCI) is a rare, debilitating complication of various surgical procedures, including aortic and spine surgery. Up to 45% of ISCI has been attributed to iatrogenic causes, including the repair of thoracoabdominal or aortic aneurysm [1], precipitating various degrees of permanent injury. Previous observational studies have reported the most frequent level of injury of iatrogenic SCI to be in the cervical and low thoracic regions [2].

Specifically, the risk of ISCI following aortic grafting has been reported to be up to 6.5% [3]. Ischemia can often occur during clamping due to hypoperfusion and de-clamping due to hyperperfusion of radicular arteries [4]. ISCI during percutaneous and endovascular surgeries has also been reported. Other sources of iatrogenic SCI have been reported to be due to steroid injections, nerve blocks, spine surgery, interventional embolization, and cerebral spinal fluid catheter placements.

A variety of intra-operative strategies have been proposed to prevent spinal cord ischemia. Intraoperative neuromonitoring is commonly used to predict, prevent, and minimize the impact of ischemic events. For ex-

ample, somatosensory evoked potentials and transcranial motor evoked potentials (tcMEPs) are frequently used in cervical and thoracic spine surgery to help surgeons diagnose intraoperative SCI [5]. In addition, existing studies investigate the use of protocols involving cerebrospinal fluid (CSF) drainage and hypothermia. Lumbar CSF drainage has been widely accepted as a preventive measure aiding in spinal cord perfusion variability during anesthesia and aortic maneuverings [6]. Intra-operative monitoring of mean arterial pressures has also been used in this regard. Medical management has included administration of corticosteroids, anticoagulation and antiplatelet medications.

Despite efforts to predict and prevent ischemia, insufficient evidence has been presented to manage iatrogenic ischemic injury after it has occurred. Some notable studies investigate all causes of ischemic injury or consider iatrogenic spinal cord injury altogether, including neuronal damage due to direct compression of the spinal cord. While these studies offer some insight into iatrogenic ischemic injury, they fall short because ischemic injury in any nervous structure makes use of different pharmacological processes, and additionally, the iatrogenic nature of injury lends itself to unique management protocols. Additionally, the

[☆] **Summary Statement:** In our meta-analysis of 74 case reports and series, we evaluate the utility of known therapies for instances of iatrogenic spinal cord ischemia and compare how location of the infarction influences patient outcomes.

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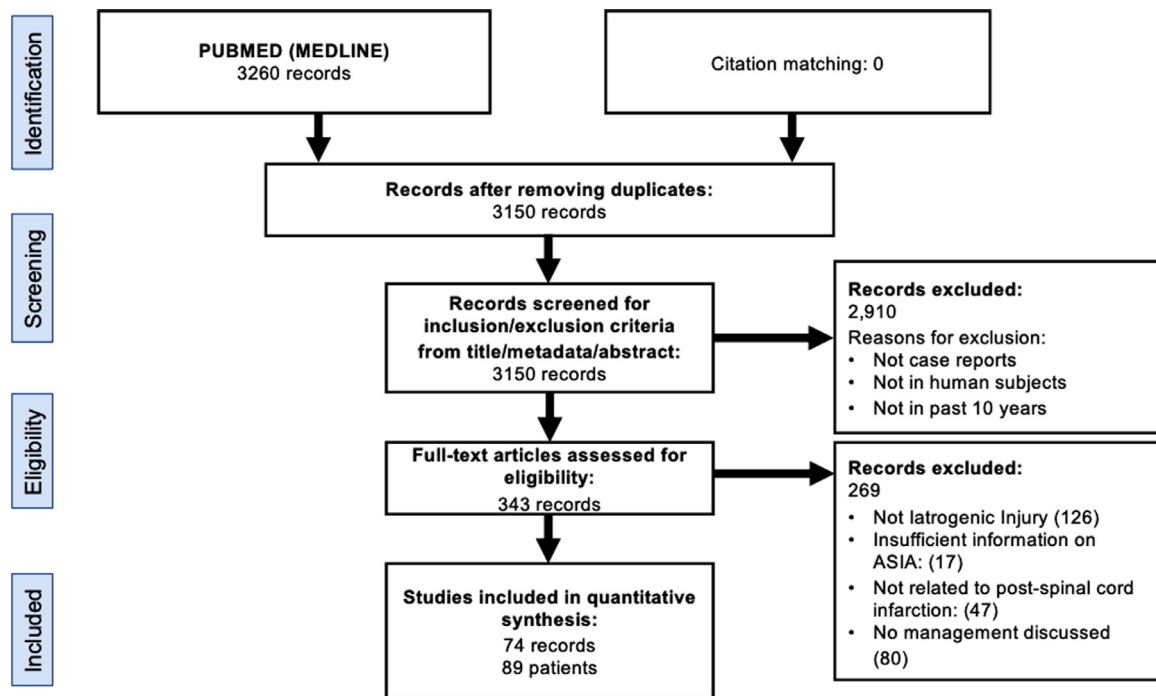


Fig. 1. PRISMA Diagram elucidating the process of record identification.

literature that has been published is limited to small single-center experiences and observational studies. To our knowledge, no meta-analyses exist that investigate post-infarct management. We sought to characterize the features of iatrogenic spinal cord ischemic injury in patients and understand what treatment strategies play a role in optimizing outcomes for patients. We additionally sought to understand whether certain types of injuries were increased in prevalence at specific regions of the spinal column.

Methods

This systematic review was undertaken and reported in accordance with the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines (Fig. 1) [7]. The references of included studies are included in the supplemental materials. This meta-analysis was not registered, though a complete *a priori* protocol can be made available by contacting the corresponding author. Because no protected patient data was used, this study was exempt from the institutional review board (IRB) at our institution.

Eligibility criteria

Eligibility criteria were defined prior to the literature search. We sought to gather information on management of iatrogenic spinal ischemia in human patients via case reports or series over the past 10 years. Cases were restricted to this window to prevent era effects in the causes of spinal ischemia. If case reports and series did not include the ASIA impairment scale score or provided insufficient information to generate an ASIA Impairment score (reproduced in Supplemental Table 1) [8], they were excluded. Additionally, we excluded cases that provided ambiguous language about management, such as “conservative therapy.” If cases provided specific language about the treatment provided to the patient, they were considered part of the analysis. Additionally, cases also considered included information about discharge of the patient or patient status after a follow-up period. Cases without this information were excluded. Finally, cases were excluded if they included non-iatrogenic causes of spinal infarction, such as chronic conditions, idiopathic presentations, etc.

Search strategies and information sources

Case reports and series were searched and identified via an exhaustive search on PUBMED (MEDLINE). Our complete search criteria included the following terms: (“spinal cord ischemia”) OR (“spinal cord infarction”) OR (“spinal cord stroke”). Throughout the search process, citations and reference matching was performed to ensure that no additional cases of spinal prior to our search date were excluded. This initial search yielded 3260 records.

Study selection

After deletion of duplicates, 3150 records were initially screened by metadata, abstracts and titles for publication type, relevance, for publication date, and species. This process yielded 343 full length records for review. After the identification of these records, full length articles were evaluated against the predefined eligibility criteria. Each record was screened twice for eligibility and flagged in cases of ambiguity. In such cases, consensus was used to evaluate the inclusion or exclusion of the study. All excluded studies were maintained and re-evaluated at the conclusion of the review of records prior to data-analysis to ensure that no records that matched eligibility criteria were mistakenly excluded. At the conclusion of the review of full-length articles, 74 case reports and case series, including 89 patients, were included in the statistical analysis.

Data collection process and data items

Features and data collected from each case report were defined prior to the execution of the primary search and determined by pilot searches performed. A spreadsheet was utilized to tabulate patient age, sex, cause of injury, spinal levels affected by injury (verified by imaging or clinical exam), severity of injury (determined by ASIA Impairment scale), presence of motor, sensory, or autonomic impairment as a result of the injury, and types of treatment used, including anticoagulation, antiplatelet therapy, rehabilitation, etc. In cases where specific therapies were listed, they were listed explicitly in our data record. Additionally, information about the inciting factors of iatrogenic injury were collected and

classified under four broad categories – aortic surgeries, endovascular surgeries, non-aortic surgeries (including spinal surgery), and non-aortic procedures (e.g., lumbar puncture, epidural anesthesia).

In some cases, patients were eligible for multiple inciting factors. Endovascular aortic surgeries were included in the “aortic surgery” subgroup in addition to the “endovascular surgery” subgroup for analysis. Three outcome measures were determined for patients, depending on what data was available – discharge outcome, follow-up outcome, and most recent available outcome (also titled overall outcome), a composite variable of discharge and follow-up outcome. Outcomes were scored from -2 to 3, with -2 being patient death and 3 being complete recovery of patient. A score of 0 indicated no change in condition. This is further elucidated in Supplemental Table 2. This custom scale was used instead of the Rankin score or the ASIA impairment scale due to the lack of consistency across case reports obtained during pilot searching. Due to the lack of standardized symptom reporting, it was determined to use a broad categorical scale to include as many articles as reasonably possible for outcome metrics. Each data entry was verified by at minimum two reviewers.

Summary measures and statistical analysis

Data analysis was performed using GraphPad Prism 9.0 (GraphPad Software, Inc., San Diego, CA) and MATLAB 2020b (MathWorks, Inc., Natick, MA) software. To determine significance of contingency tables, Fisher's Exact Test or Chi-Goodness-of-fit test was computed, depending on the appropriateness of use. Odds ratios were computed to determine association between patient treatment and cause of injury and outcome features. In some cases, one cell in our contingency table had no data. In this case, as is standard, the Haldane-Anscombe correction was applied. In order to determine significance in cases where confounding features were identifiable, the Cochran-Mantel-Haenszel test was utilized. For associations relating to locations of infarction, odds ratios were computed as standard with the assumption that each spinal level was independent.

Results

From a total of 3150 unique records for our search criteria, 343 full length articles were examined for eligibility against our inclusion/exclusion criteria. Of these articles, 74 records of 89 patients of patients with iatrogenic spinal infarctions and were included in our final analysis. Articles that did not contain sufficient information about the ASIA criteria were excluded (17 records) and articles that did not discuss the management of spinal infarctions were also excluded in final analysis (80 records). Another 47 records were excluded as they discussed spinal cord infarction as a potential differential, but ultimately excluded spinal ischemia in their workup.

Table 1 provides general descriptive statistics of the patient sample included for analysis. Of the total iatrogenic injuries, mean patient age was 59.62 (standard deviation = 18.66). Ages ranged from nine months to 88 years. 59 (66.29%) patients were male, and six records did not include information about biological sex. Inciting factors were categorized into four groups – endovascular surgical complications (32.58%), aortic surgical complications (35.96%), non-aortic surgical complications (23.60%), and non-surgical procedures (22.47%). In some cases, aortic surgeries were also endovascular, in which case the record was considered part of both groups. Grade of disability was evaluated in two ways – first by type of impairment, and second utilizing the ASIA Impairment scale. The relationship between both classification systems has been shown empirically in Supplemental Figure 1. Motor impairment was present in 87/89 patients, and sensory impairment was present in 64/89 patients. Autonomic impairment, however, was present in 47.19% of all patients. Approximately 66% of all infarctions caused A- or B-level impairment. C level impairment was seen in 22 patients, while D-level impairment was found in 8 patients. No patients presented with ASIA grade

Table 1
Descriptive Statistics of Patient Population.

Continuous Patient Features	μ (σ)	Range
Age (in years)	59.62 (18.66)	0.75 – 88
Categorical Patient Features	N	% of total patients
Sex		
Male	59	66.29%
Females	24	26.97%
Unknown	6	6.74%
Inciting Factors		
Endovascular Surgical Complication	29	32.58%
Aortic Surgical Complication	32	35.96%
Non-aortic Surgical Complications	21	23.60%
Non-surgical Procedure	20	22.47%
Grade of Disability		
Motor impairment	87	97.75%
Sensory impairment	64	71.91%
Autonomic Impairment	42	47.19%
ASIA A	38	42.70%
ASIA B	21	23.60%
ASIA C	22	24.72%
ASIA D	8	8.99%
ASIA E	0	0.00%
Patients with infarction of known spinal level	63	70.79%
Treatment Methods		
anti-coagulation	12	13.48%
anti-platelets	12	13.48%
BP management	36	40.45%
Mannitol	4	4.49%
Naloxone	2	2.25%
Steroids	25	28.09%
CSF drainage	29	32.58%
Therapeutic surgery	14	15.73%
Endovascular Revascularization	5	5.62%
Rehab	44	49.44%
Hyperbaric Oxygen	8	8.99%
Hypothermia	1	1.12%
Edavarone	2	2.25%

E in our meta-analysis. We additionally found an injury location validated by radiographic findings for 63 (70.79%) patients. In some cases, infarction was diagnosed clinically, but radiographic findings were either not used to confirm the infarction, or insufficient information was provided in the reports (26 records). In such cases, these records were excluded in the comparisons of location analysis.

Management of spinal ischemia in iatrogenic cases was heterogeneous. Post-infarction rehabilitation (49.44% of records) was the most common treatment strategy utilized for patients, followed by blood pressure management (40.45% of records). Steroid use and CSF drainage were also commonly used (28.09%, and 32.58%, respectively). In some cases, we saw the use of therapeutic surgical procedures aimed at reversing ischemic injury (8 records). Supplemental Table 4 breaks down the type of surgeries – 4 surgeries were direct revascularization, while 4 other cases were discectomies, laminectomies or laminoplasties. Other less commonly used treatment strategies included Naloxone (2 patients), Mannitol (4 patients), Hyperbaric Oxygen (8 patients) and Edavarone (2 patients).

Inciting factors and management strategies utilized for spinal infarctions were evaluated for their efficacy in Fig. 2A and 2B. Non-aortic surgeries had significantly poorer overall outcomes (OR = 0.2797 (0.1005-0.7784), $p = 0.016$) and discharge outcomes (OR = 0.207 (0.0649 – 0.6605), $p = 0.007$). While not significantly favored in total outcomes, at discharge, patients with iatrogenic ischemia caused by endovascular (OR = 2.931 (1.0537, 8.155), $p = 0.05$) and aortic (OR = 2.967 (1.104–7.98), $p = 0.035$) surgeries were significantly improved compared to other patients. Outcomes for non-surgical procedures did not favor or disfavor improvement at any timepoints. For management strategies (Fig. 2B), there were no significant differences in overall outcomes. However, any surgical intervention after infarction was associated with a significant improvement in outcomes (OR = 5.33 (1.095–

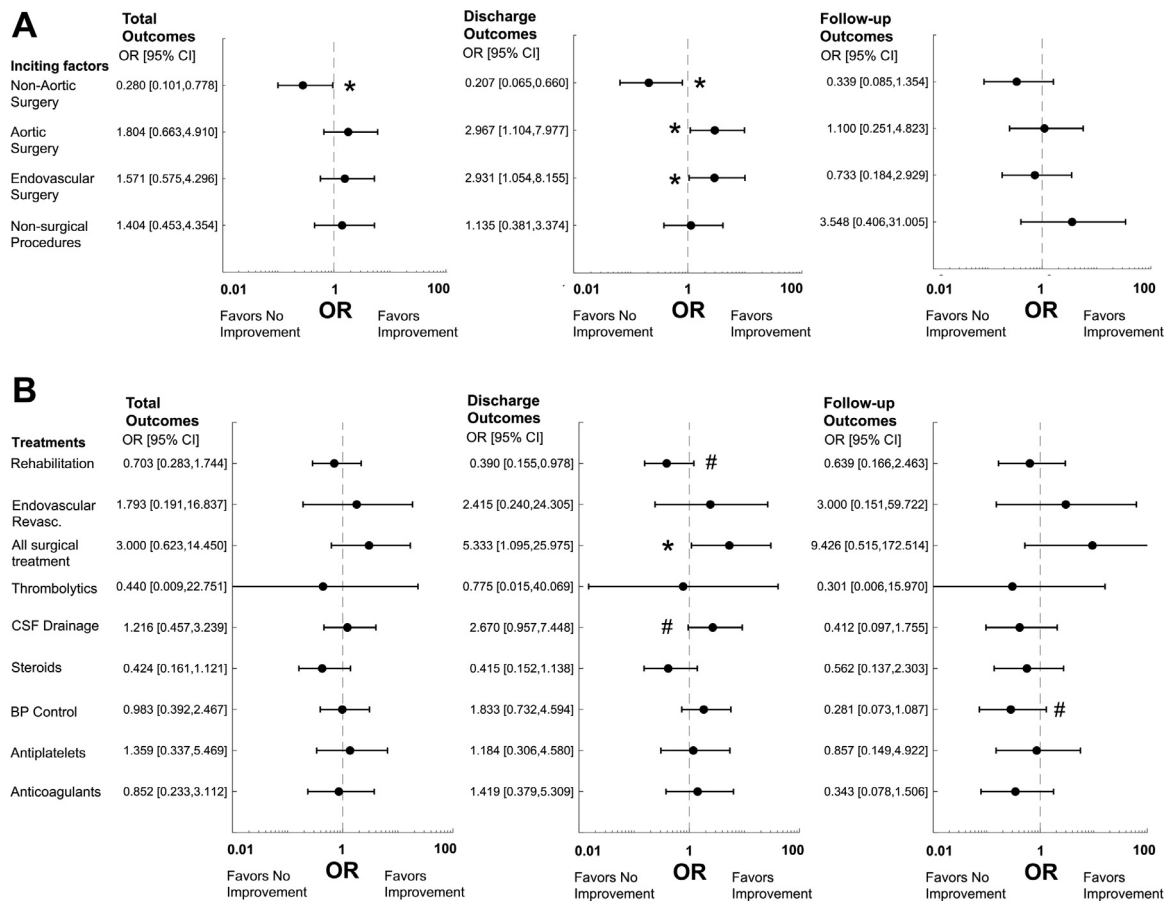


Fig. 2. Forest Plots of Primary Comparisons. A demonstrates the odds ratio of inciting factors for spinal cord infarction to result in improvement. B demonstrates the odds ratio of treatment strategies for spinal cord infarction to result in improvement. Asterisk (*) denotes significance ($p < 0.05$). Hash (#) denotes trend towards significance ($p < 0.10$).

25.97), $p = 0.032$). There also were some notable trends in outcomes observed. CSF drainage was associated with a trend in improved discharge outcomes (OR = 2.67 (0.9574 – 7.448), $p = 0.0861$). Additionally, blood pressure control was marginally associated with poorer follow-up outcomes in patents (OR = 0.2813, $p = 0.076$). Degree of impairment, age, and biological sex were also compared to outcomes (Supplemental Fig. 2). There was no significant association between outcomes and ASIA impairment. Additionally, autonomic dysfunction, sensory dysfunction and motor dysfunction were not significantly associated with an improvement in outcomes. With the exception of patients between ages 40 and 60 years, who had improved discharge outcomes (OR = 5.33 (1.095-25.975), $p = 0.0322$), age and biological sex were not significantly associated with an improvement in outcomes.

Subgroup comparisons were also performed, shown in Supplemental Table 3. For each classified inciting factor, treatments were evaluated by improvement. For cases of ischemia caused by non-surgical procedures at discharge, blood pressure management was associated with a significant improvement in outcomes (OR = 4.33 (1.093 – 17.73), $p = 0.05$). This was not seen in other causes of iatrogenic ischemia. Patients with ischemia due to complication from aortic surgery also saw significantly poorer overall outcomes when treated with steroids (0.033 (0.003–0.397), $p = 0.01$) and poorer discharge outcomes when administered rehabilitation (0.133 (0.021–0.856), $p = 0.04$). Other notable trends in the subgroup comparisons were also observed. Non-aortic surgical causes of ischemia receiving mannitol after infarction saw a trend towards improved outcomes (OR = 19.286 (0.743–500.414), $p = 0.07$). Rehabilitation was also observed to trend towards poorer outcomes in other subgroups of patients. Non-surgical procedure-associated infarctions (OR = 0.292, $p = 0.10$) and endovascular surgery-associated infarctions

(OR = 0.121 (0.012–1.214), $p = 0.08$) trended towards poorer discharge outcomes for rehabilitation. Rehabilitation also was associated with a trend towards poorer outcomes for overall outcomes (OR = 0.115 (0.012–1.129), $p = 0.08$).

The location of the infarction was also compared to the causes of infarction and severity of infarction (Fig. 3). Across all patients, there was broadly a bimodal distribution of spinal levels affected – cervical and lower thoracic/lumbar regions. In general, upper thoracic injuries occurred less frequently. There were also notable differences in spinal columns for various comparisons. When comparing pediatric and adult cases of iatrogenic spinal infarctions, pediatric cases presented with ischemia at cervical regions more significantly, notably at C3 (OR = 0.11 (0.018–0.691), $p = 0.031$) and C7 (OR = 0.157 (0.027–0.9167), $p = 0.05$). C2 and C3 also trended towards favoring pediatric cases ($p = 0.06$, $p = 0.089$, respectively). The severity of impairment was also compared against the spinal levels. ASIA A- and B-level impairments, noted to be more severe, were not more common than C- and D-level impairment in any specific spinal level. However, when looking at symptoms of impairment, there was a significant association between autonomic impairment and increased frequency of injury at T10 (OR = 4.54 (1.347–15.28), $p = 0.0183$). Aortic surgery was associated with a significantly increased frequency of ischemia in L1-L2 region ($p = 0.027$, $p = 0.045$, respectively).

Outcomes were also compared to location of spinal cord injury. Ischemic injury from T4–T7 and T10 were significantly associated with poorer outcomes ($p < 0.05$). Worse outcomes with ischemia to lower thoracic region was also observed in discharge and follow-up outcomes. Infarction of T6 was associated with poorer discharge outcomes ($p = 0.0475$), whereas T3–T6 was associated with poorer outcomes in

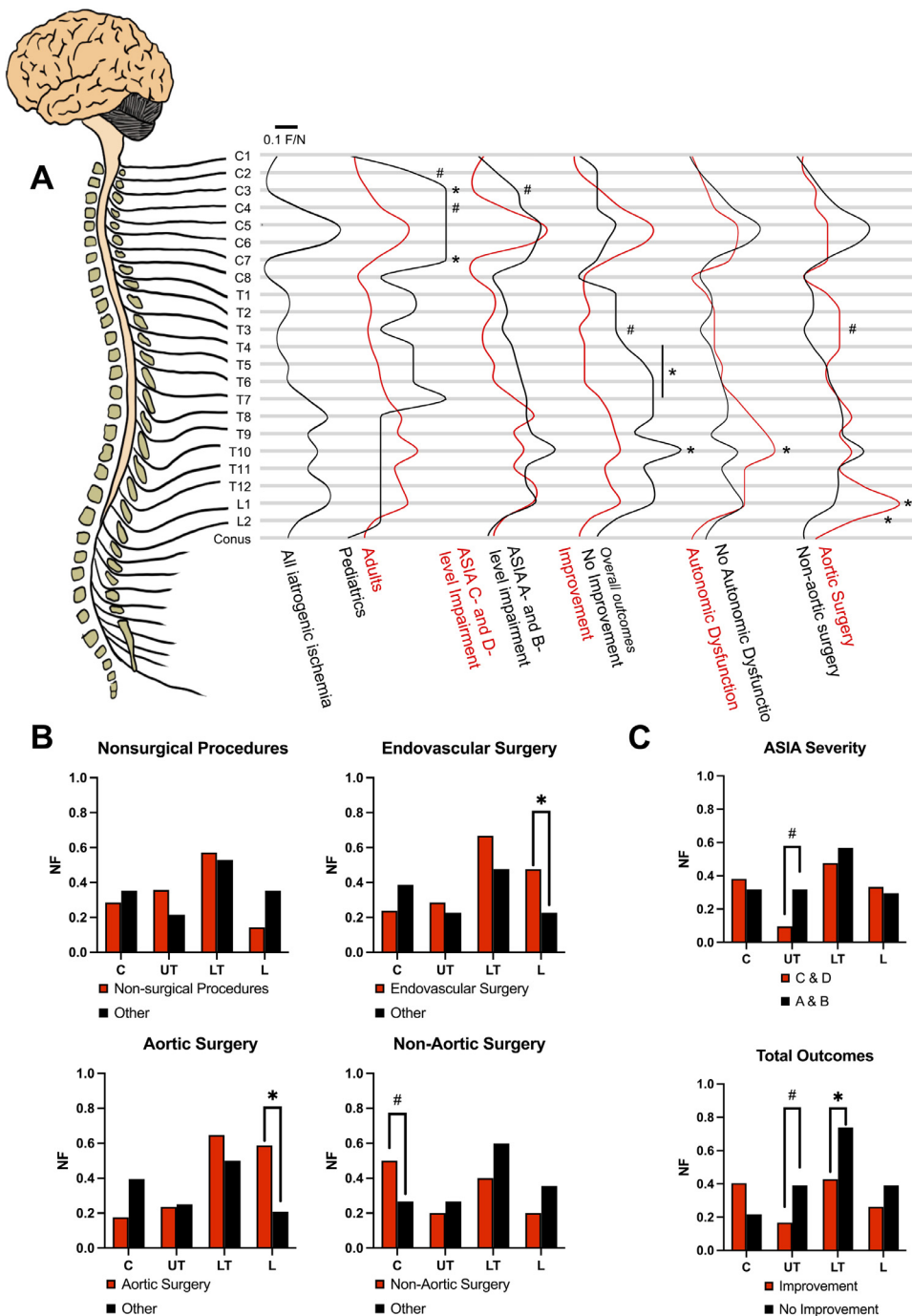


Fig. 3. Associations of Patient Features with Location of Ischemia. **A** shows the frequency distribution normalized to number of individuals in each cohort for different patient features, defined to be (F/N). A scale bar representing the value of 0.1 F/N is shown. **B** shows the normalized frequency distribution for cervical, upper thoracic (T1-T6), lower thoracic (T6-T12) to lumbar regions for inciting factors of spinal infarction. **C** shows the normalized frequency distribution for C, UT, LT, L regions for severity and total outcomes.

follow-up ($p < 0.05$). Fig. 3B also compares the inciting factors of injury at a broader stratification of spinal levels. Endovascular procedures were associated with increased frequency of ischemia in lumbar regions (OR = 3.09 (1.02–9.37), $p = 0.05$). There was a similar association with all aortic surgeries (OR = 5.43 (1.65–17.859), $p = 0.006$). Non-aortic surgeries were marginally associated with an increase in ischemia to cervical regions ($p = 0.09$), but no other regions differed significantly.

We finally compared outcomes for emergent and less frequent therapeutics (Table 2). Due to the diminished sample size and low frequency of administration, there were no statistically significant associations with these therapeutics. However, some had impressive outcomes in the small group of patients that were observed. Hyperbaric oxygen (HBO) was found to be administered in eight patients, out of which seven pa-

tients had improvement. Out of these seven, six patients had a near-complete to complete recovery. Many of these patients had B- and A-level impairment. This was also observed with hemoglobin transfusion, where all four patients had a near-complete to a complete recovery. Other therapies had unclear outcomes. Out of the two patients observed to receive Edavarone, one patient had full recovery, while the other had no change in overall outcome. With mannitol, 3/4 patients improved, whereas with naloxone, 1/2 patients experienced improvement in symptoms.

Discussion

While ischemic injury to the spinal cord has been characterized as an infrequent complication of a variety of interventions, iatrogenic cases

Table 2
Outcomes for Emergent and Less Frequent Therapeutics and Surgeries.

Treatment	Patient #	ASIA Score	Death	Worsened	No Change	Some Improvement	Mostly Improved	Full Improvement
Treatment								
HBO	1	B					x	
	2	A						x
	3	A				x		
	4	C						x
	5	A		x				
	6	A					x	
	7	A					x	
	8	A						x
Hemoglobin Transfusion	1	A						x
	2	C						x
	3	C					x	
	4	B					x	
Edavarone	1	B			x			
	2	C						x
Mannitol	1	A			x			
	2	B						x
	3	A					x	
	4	C						x
Naloxone	1	C			x			
	2	C						x
Therapeutic Surgery								
Endovascular Revascularization Procedure	1	A				x		
	2	A						x
	3	A				x*		
	4	D						x
	5	A			x			
Open Revascularization	1	B						x
	2	D					x	
	3	A						x
	4	A						x
	5	A						x
	6	A					x	
Discectomy/ Laminectomy/ Laminoplasty	1	B						x
	2	B					x	
	3	A				x*		
Removal of Pathology (tumor, AVM, hematoma)	1	B			x			

x* refers to the same patient with both procedures.

have not been previously characterized and studied as their own entity. These cases represent a smaller subset of iatrogenic spinal cord injury but necessitates a unique management approach due to need to target vascular supply to the spine as opposed to neuronal damage [2]. This has led to a variety of heterogenous treatment strategies to be developed parallely – for example, vascular surgeons performing open and endovascular surgery have developed their own guidelines to prevent ischemia [9,10], while the prevention of spinal ischemia in spine surgery has warranted independently arrived recommendations [11]. In this meta-analysis of 74 case reports and series, we sought to unify the study of iatrogenic spinal cord ischemia (SCI) by collecting data within the past 10 years on the different features of SCI and management strategies associated with improved outcomes.

During the eligibility period of our systematic review, we excluded 126 patients that met all inclusion criteria except the iatrogenic classification. 41.2% of all cases identified were iatrogenic. A previous study by Robertson et al. in 2012 described the rate of perioperative spinal cord ischemia as 45%, with 69% of those cases being from aortic surgeries [1]. A study published in 2001 describes aortic surgery constituting 25% of all cases of ischemia [12]. In our study, while the overall rate of iatrogenic cases is similar, aortic surgeries constituted 36% of total iatrogenic ischemic cases, and 14.8% of all ischemic cases identified. These numbers are markedly lower than previous reported in the past two decades. This could potentially be explained by advances in aortic surgery, including the use a variety of intraoperative techniques to protect against spinal ischemia, but also to perioperatively identify and manage suspected ischemia. Additionally, we found non-surgical proce-

dures, including epidural anesthesia and lumbar punctures, to constitute 22.47% of all iatrogenic spinal cord ischemia. A retrospective analysis of 54 cases revealed epidural anesthesia to cause 1.8% of all ischemic cases [13], which is lower than observed, even when adjusting our observed rate for all ischemic injuries. We also found no association between age, sex, and severity of injury on outcomes for iatrogenic cases. This differed from previous observational studies [13], which demonstrated that biological sex and severe initial impairment were independent predictors of unfavorable outcomes in SCI.

Uniquely in our study, we characterized the impairment due to iatrogenic spinal cord infarction. Severe ASIA impairment (A and B) was most frequently observed (66.3%). In studies comparing all iatrogenic spinal injury, including non-vascular injury, ASIA C was observed in 43% of cases. Additionally, across all cases of SCI, mild impairment was more common. In either case, this suggests that iatrogenic spinal cord ischemia presents uniquely with severe impairment.

As discussed previously, management of iatrogenic SCI varies across specialty. Intraoperative neuroprotective interventions and specific protocols post-operatively have been shown to improve outcomes in endovascular and aortic cases [14,15]. This explains our observation that aortic and endovascular cases had improved discharge outcomes. The lack of clearly defined management guidelines following SCI in non-aortic surgery, such as spinal surgery, also explain the notably worse overall and discharge outcomes for patients. We also demonstrate the utility of key therapeutic strategies. Therapeutic surgical intervention was shown to significantly improve discharge outcomes for all patients. This is consistent with anecdotal evidence from observational studies

that show surgical revascularization is an effective strategy following ISCI secondary to spinal surgery [11].

In our subgroup analysis, blood pressure management for non-surgical procedures, and a trend towards improved outcomes for mannitol use in non-aortic surgeries, was also observed. This suggests that these strategies, more frequently observed in aortic surgery, may be effective to incorporate in management algorithms post-SCI in non-surgical procedures and non-aortic surgeries. Interestingly, rehabilitation, the most commonly observed management strategy used, was found to be associated with worse outcomes for all patients and in some subgroups. This perhaps suggests the need for better tools and metrics to evaluate which patients would benefit from rehabilitation programs. In some cases, the use of advanced robotics in rehabilitation has shown substantial benefit to patients, specifically with spinal cord infarctions [16,17]. We also evaluated the efficacy of rarely reported therapeutic strategies, such as HBO, hemoglobin transfusion, and Edavarone. While not statistically significant due to a small sample size, HBO and hemoglobin transfusion therapy was found to have generally improved outcomes. This suggests the need for further investigation in the form of prospective observational studies.

We also sought to compare causes and features of spinal ischemia relative to the location of infarction. The greatest frequencies of infarctions were noted in the cervical and thoracolumbar regions. This observation has previously been validated in several retrospective studies [18,19]. Additionally, we observed aortic surgeries cause increased frequency of ischemic infarcts in the lumbar region. This could be explained by iatrogenic damage to the Artery of Adamkiewicz and other spinal segmental arteries, which has previously been shown to result in ischemia to the lower thoracic and lumbar regions [20]. Autonomic dysfunction, including bowel and bladder incontinence was also found to be associated with increased ischemia at T10. Previous studies for spinal cord injury have demonstrated bowel and bladder dysfunction in patients with injuries in the T10-L2 region, as the sympathetic efferent to the bladder are from this region [21–23]. Not previously reported is the location of the infarction in comparison to outcomes and the severity of initial impairment. Upper thoracic injuries were associated with increased severity in ASIA Impairment, while lower thoracic SCI were associated with poorer overall outcomes.

There are several limitations to the conclusions of this study. First, case reports and series are considered the lowest tier of evidence [24], and considered a source of significant publication bias [25]. However, given the absence of widely used treatment algorithms, single-center retrospective studies are subject to selection bias, and may not provide an accurate assessment of what the optimal management strategies are to manage SCI. Additionally, given the lack of recent studies and rarity of the occurrence of iatrogenic spinal cord ischemia, this methodology provides the capacity to compare different treatments used for patients and their subsequent impact on patient outcomes. For rarely occurring pathologies, meta-analyses of case reports and case series are often the only mechanism for reporting these events [26,27]. Related to the use of case reports and variable reporting of SCI across the different inciting factors identified, this also presents a source of heterogeneity in the data. This may explain why cases of SCI due to epidural anesthesia were 1.8% of all cases in the literature, while in our dataset, we observed procedural SCI complications to come close to 22.5% of all iatrogenic cases, and nearly 10% of all SCI identified.

In this study we performed a meta-analysis of iatrogenic spinal cord ischemia. We defined characteristics of spinal cord ischemia in patients with different inciting factors and evaluated how the grade of disability and the treatment provided to the patients impacted overall outcomes. In addition to more frequently observed therapeutic strategies, we also observed the efficacy of less frequently prescribed outcomes, such as hyperbaric oxygen hypothermia, Edavarone, mannitol. In summary, we present a comprehensive evaluation of the factors causing iatrogenic spinal cord ischemia and management strategies. We additionally demonstrate that while some therapeutics may be frequently

utilized, their efficacy remains to be tested in large patient samples. Emergent therapies demonstrate some promising outcomes and should be tested in multicenter randomized controlled trials.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Informed Patient Consent

The authors declare that informed patient consent was taken from all the patients.

Declaration of Competing Interest

The authors have no conflicts of interest related to this work to declare.

Acknowledgements

None.

Statement of Ethics

As a systematic review and meta-analysis, the study is exempt from institutional review board review. However, the authors do confirm that components to this study were in bounds with local research policies at the University of Illinois and Carle Foundation Hospital, in addition to generally accepted ethical guidelines for systematic reviews and meta-analyses.

Authors' contributions

AN, CM, SH were responsible for designing the review protocol, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, and writing the paper. TKK and PMA provided invaluable feedback and critical edits for this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.nxj.2021.100080](https://doi.org/10.1016/j.nxj.2021.100080).

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