Trends in High-Impact Neurosurgical Randomized Controlled Trials Published in General Medical Journals: A Systematic Review

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■ BACKGROUND: **The neurosurgery literature lacks a comprehensive report of neurosurgical randomized controlled trials (RCTs) published in general medical journals. RCTs published in these journals have high visibility and impact on decision-making by general medical practitioners and health care policymakers.**

■ METHODS: **A systematic review of neurosurgical RCTs in the *New England Journal of Medicine, The Lancet, Journal of the American Medical Association, The BMJ,* and *Annals of Internal Medicine* was completed.**

■ RESULTS: **There were 78 neurosurgical RCTs published in the selected high-impact journals from 2000 to 2017. The most common study topics were neurovascular (n = 39, 50%) and spine (n = 24, 30.8%). Of these RCTs, 44 (56.4%) compared operative with nonoperative management. For studies published before 2017, the mean number of citations was 899. Approximately half of the studies showed superiority of operative management over nonoperative management in the intent to treat primary outcome of interest (n = 24, 54.5%). However, stratified by subsubspecialty, 7 (87.5%) of the functional RCTs, 9 (50%) of the neurovascular RCTs, 1 (50%) of the trauma RCTs, and 7 (43.8%) of the spinal RCTs demonstrated superiority of operative management over nonoperative management. Additionally, there were large subspecialty differences in study characteristics, such as rate of double blinding, proportion of patient enrollment from patients screened, and proportion of crossover from nonsurgical to surgical arm.**

■ CONCLUSIONS: **Neurosurgical RCTs in general medical journals have large subspecialty differences in characteristics such as crossovers from nonsurgical to surgical treatment arms and the proportion of studies demonstrating benefit of operative intervention over nonoperative management.**

INTRODUCTION

The pinnacle of evidence-based medicine is randomized, double-blinded, multicenter, clinical trials.[1-4] Randomized controlled trials (RCTs) are the tipping points for new therapeutics and interventions and the benchmarks for allocation of health care resources. As health care and neurosurgical care delivery continue to be analyzed, critiqued, and changed by payors, regulators, providers, and patients, the medical, financial, and medico-legal impact of RCTs continues to grow.[5,6] In particular, neurosurgical RCTs published in high-impact journals, such as the *New England Journal of Medicine* (NEJM) and *The Lancet*, are given the highest visibility to medical and nonmedical professionals involved in health care innovation.[7-9] Furthermore, highly publicized stories of recent developments in science and medicine are most often communicated to the general public from the findings published in these high-impact journals.[10] As such, a new neurosurgical RCT can quickly and heavily influence opinions of referring general practitioners, patients seeking care, and policymakers enacting regulations. It is imperative for the practicing neurosurgeon to be thoroughly familiar with the body of neurosurgical RCTs published

Key words
- Evidence-based care
- High impact
- Medical management
- Neurosurgery
- Operative management
- Randomized controlled trials

Abbreviations and Acronyms
NEJM: *New England Journal of Medicine*
RCT: Randomized controlled trial

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in general medical journals and, furthermore, to quickly assess the methodologic characteristics that influence the study directions of these RCTs.

In a previous study of RCTs published in high-impact medical journals, Nwachukwu et al.[11] characterized orthopedic RCTs published between 2005 and 2015 in 5 high-impact medical journals. Of the relatively few orthopedic studies published in high-impact medical journals studying operative intervention, there were more studies published that supported nonoperative management.[11] Furthermore, Nwachukwu et al.[11] found evidence of methodologic characteristics that influenced the direction of RCT findings toward nonoperative management. We previously examined funding, adjustments to reported outcome measures, and accrual of patients in neurosurgical RCTs comparing surgery with nonoperative management; however, to our knowledge, no study in neurosurgery has yet examined high-impact general medical

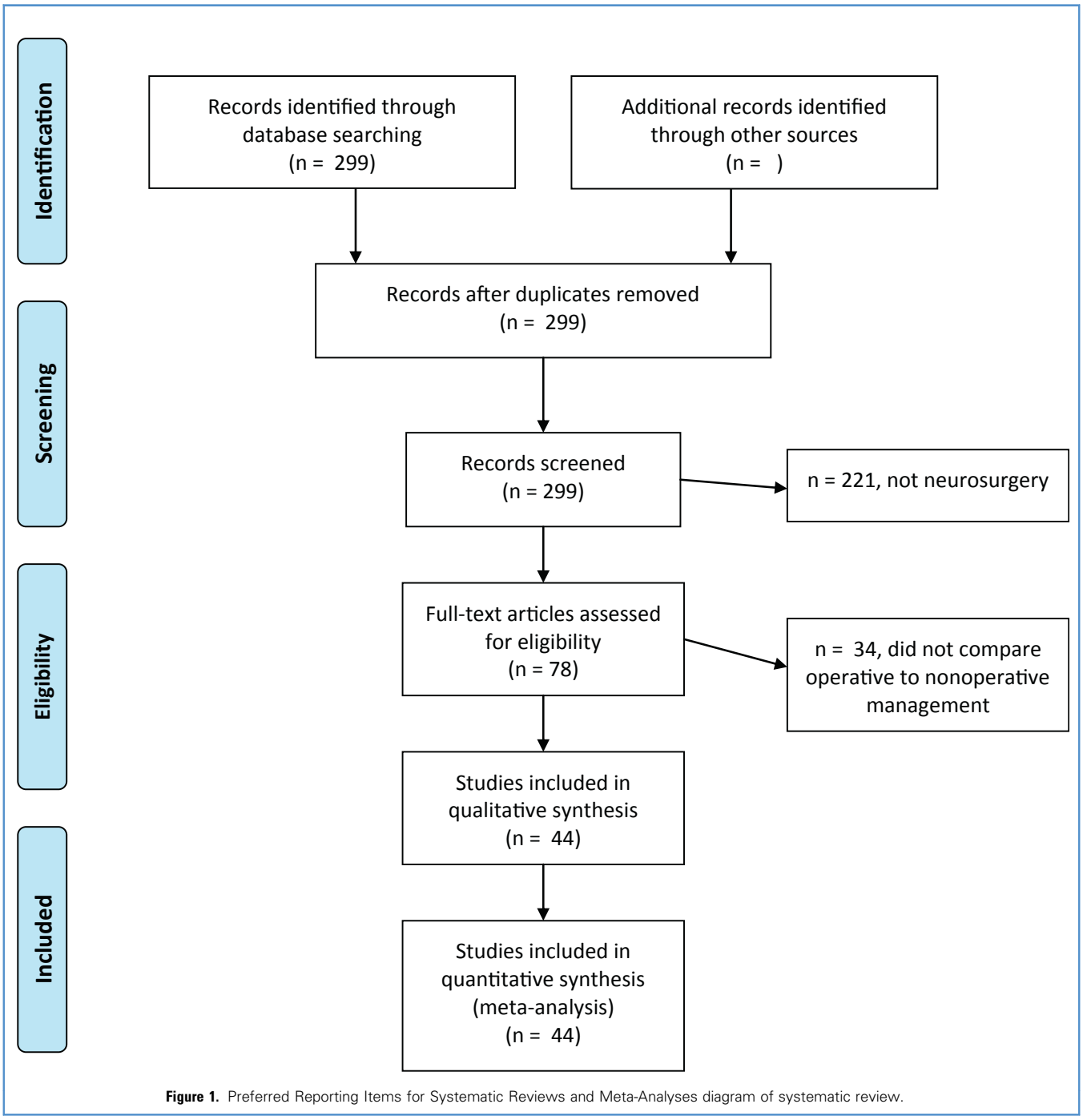

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of systematic review.

Table 1. Descriptive Statistics of Neurosurgery Randomized Controlled Trials Published in General Medical Journals

Study Topic	Number of Patients (%)
Neurovascular	39 (50)
Spine	24 (30.8)
Functional	9 (11.5)
Cranial oncology	3 (3.85)
Trauma	3 (3.85)

journals specifically.[12] Neurosurgeons would benefit from understanding what portion of the subset of neurosurgical RCTs comparing operative with nonoperative management in general medical journals shows benefit of surgical intervention. Similarly, for these RCTs, neurosurgeons would benefit from understanding the key characteristics, such as proportion of patients enrolled from patients screened, of these studies and how these trends verify by neurosurgical subspecialty.

As such, the purpose of this study was to characterize RCTs published in 5 high-impact medical journals. A second aim of this study to examine the subset of neurosurgery RCTs that compared operative with nonoperative management in these journals. For this subset of RCTs, this study further analyzed the direction of the study findings, determined trends within the RCT literature, and sought to provide quick rules of thumb for the practicing neurosurgeon to parse the methodologic characteristics of neurosurgical RCTs published in high-impact general medical journals.

METHODS

Systematic Review

Neurosurgery studies published between 2000 and 2017 in 5 high-impact general medical journals were screened. This selection of journals was based on previous studies of high-impact general medical journals by Van Spall et al.[13] and by Nwachukwu et al.[11]

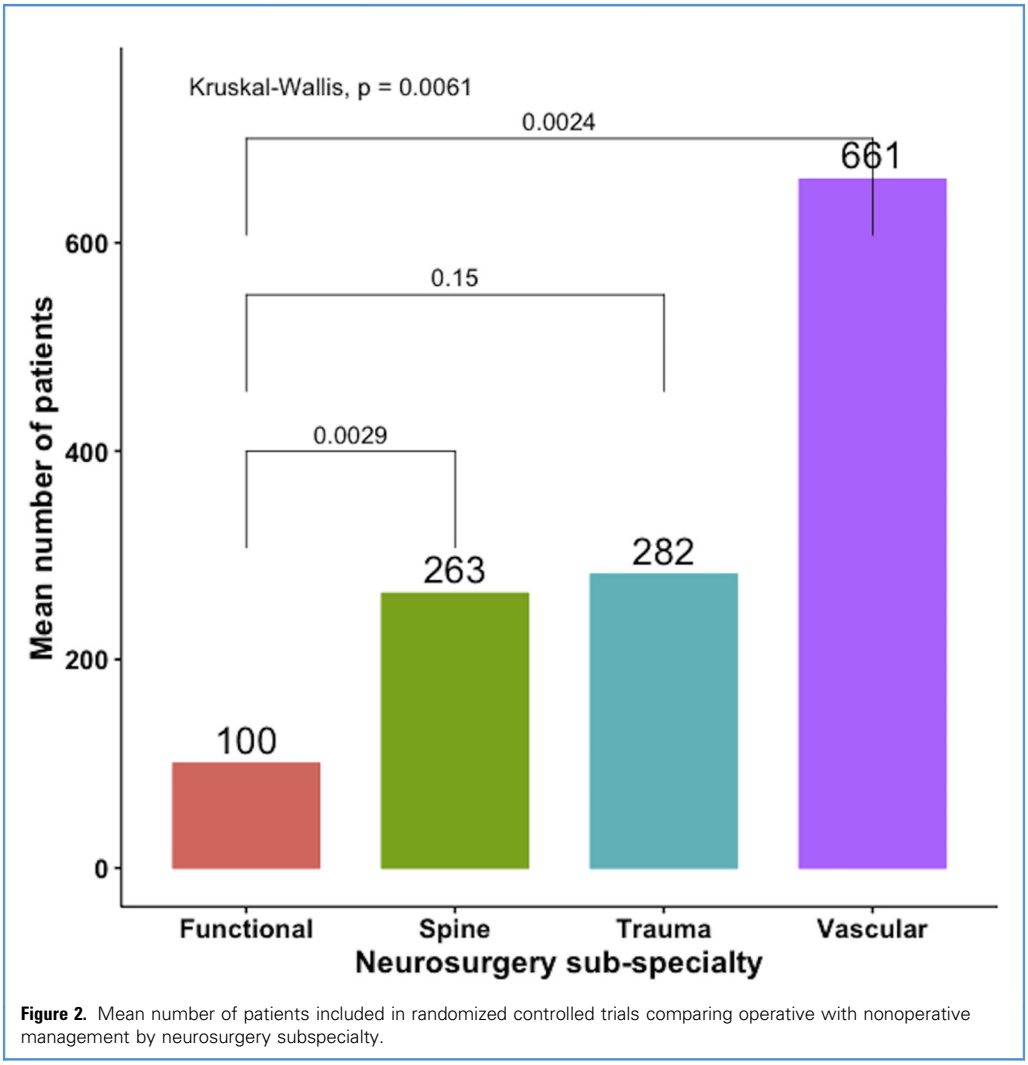

Figure 2. Mean number of patients included in randomized controlled trials comparing operative with nonoperative management by neurosurgery subspecialty.

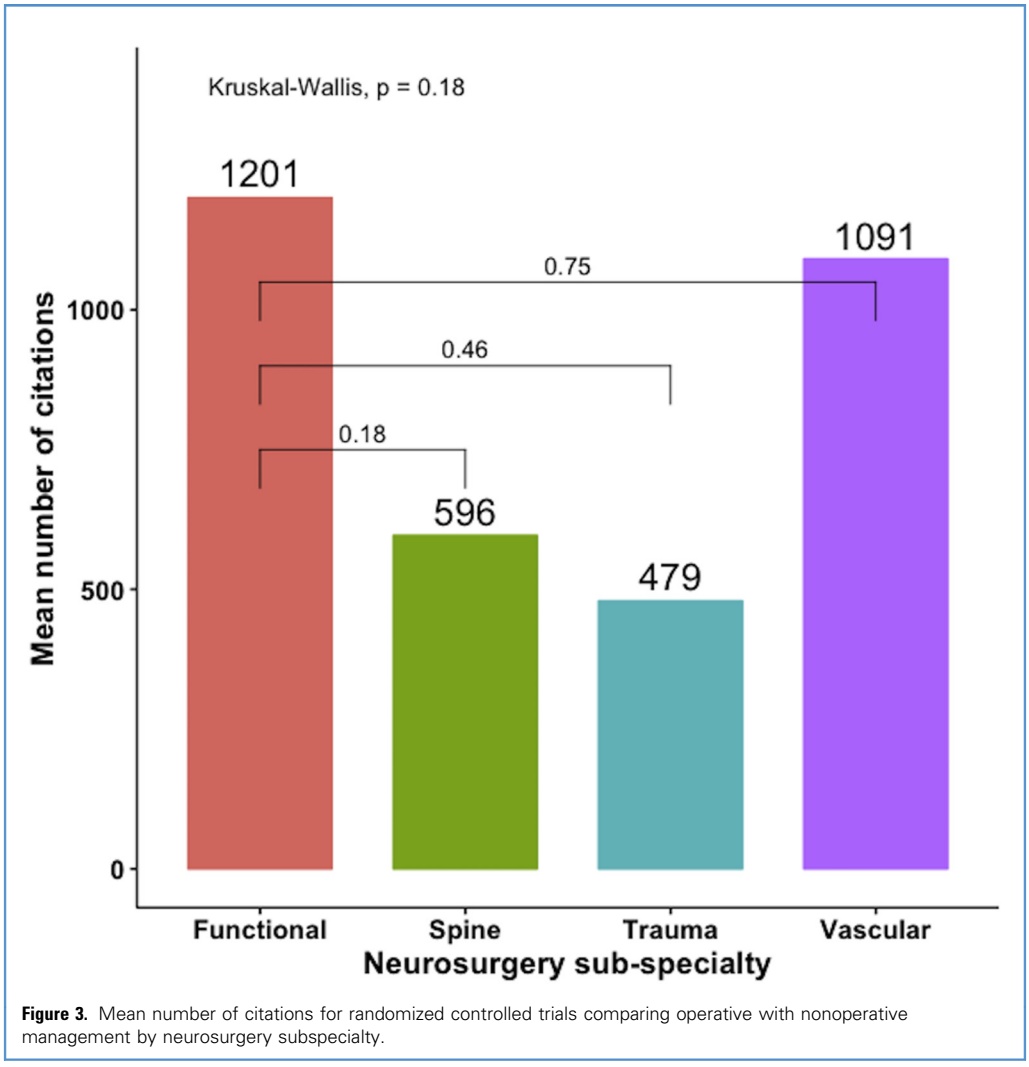

Figure 3. Mean number of citations for randomized controlled trials comparing operative with nonoperative management by neurosurgery subspecialty.

The NEJM, *The Lancet*, *Journal of the American Medical Association*, *The BMJ*, and *Annals of Internal Medicine* were assessed. The screen was completed on December 3, 2017, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews (**Figure 1**). The search strategy is included in **Supplementary Table 1**. The PubMed and Embase databases were searched using the journals (previously listed), study type (RCT), and year (2000–2017) criteria.

Analysis

In the first phase of analysis, all RCTs dealing with the field of neurosurgery were included. Descriptive statistics were generated for the body of studies by topic of study. Next, the following selected demographic data were extracted from the subset of RCTs comparing operative versus nonoperative intervention: journal of publication, date of publication, study sample size, study comparisons, citation rates (obtained using a Google Scholar search, completed on December 3, 2017), double blinding, presence and proportion of crossover to surgical arm from nonsurgical arm, and proportion of patients enrolled from patients screened. In our previous study, we also examined the impact of funding and deviations from prior end points.[12] Studies published in 2017 were excluded for the mean citation rate calculation. Mean number of patients, percent double blinding, percent of patients enrolled from patients screened, and percent crossover from nonsurgical to surgical arms were calculated for all RCTs comparing operative with nonoperative management and by subspecialty. For these factors, Wilcoxon tests were used for pairwise comparisons and Kruskal-Wallis tests were used for comparing across all neurosurgery subspecialties. R version 3.5.1 (The R Foundation, Vienna, Austria) and RStudio version 1.0.153 (RStudio, Boston, Massachusetts, USA) were used for data analyses.

RESULTS

Neurosurgery RCTs

From 2000 and 2017, there were 78 neurosurgery RCTs published in the selected high-impact general medical journals. The most

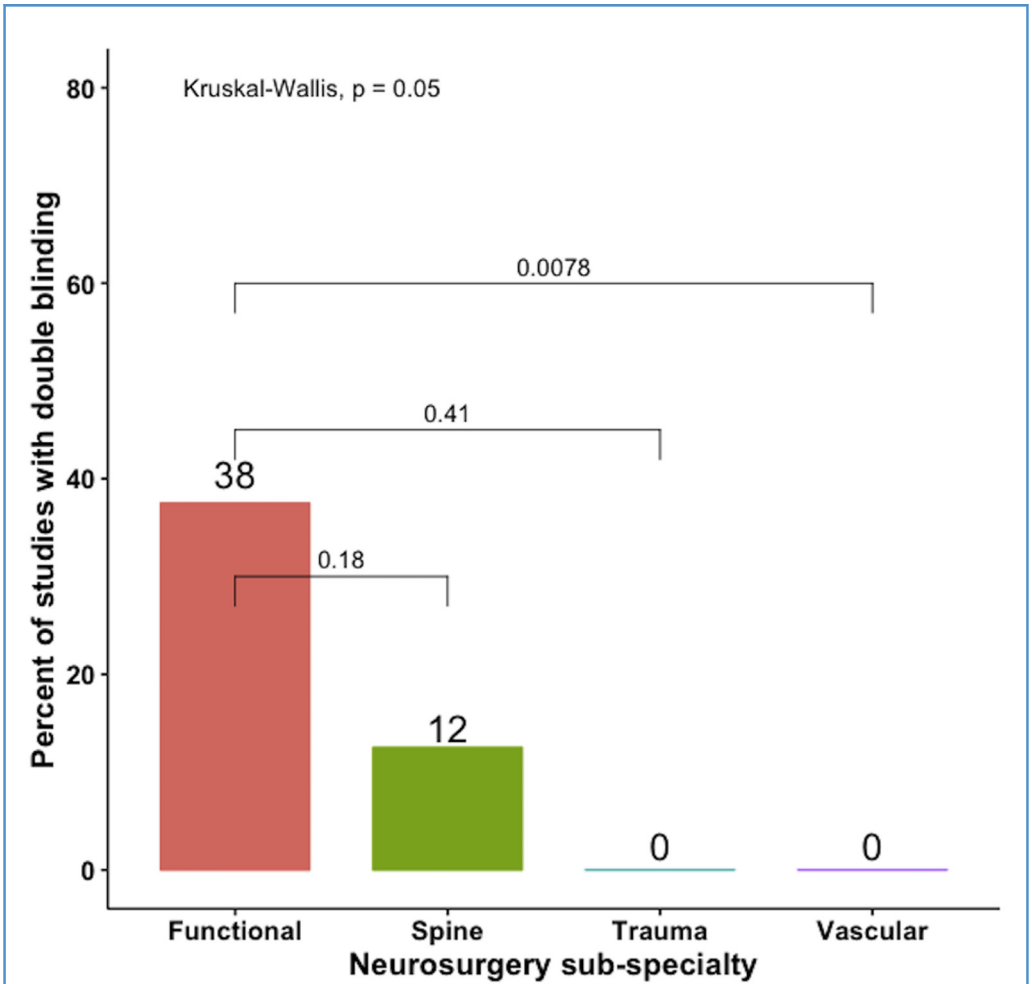

Figure 4. Percent of studies with double blinding for randomized controlled trials comparing operative with nonoperative management by neurosurgery subspecialty.

common topics of RCTs were neurovascular (n = 39, 50%), spine (n = 24, 30.8%), functional (n = 9, 11.5%), cranial oncology (n = 3, 3.85%), and trauma (n = 3, 3.85%) (Table 1).

RCTs Comparing Operative with Nonoperative Management

From 2000 to 2017, 44 neurosurgery RCTs (56.4%) compared operative with nonoperative management.[14-57] The most common journals of publication were NEJM (n = 23, 52.3%) and *The Lancet* (n = 10, 22.7%). For studies published before 2017, the mean number of citations was 899. Approximately half of the studies showed superiority of operative management over nonoperative management in the intent to treat primary outcome of interest (n = 24, 54.5%). Overall, the mean sample size was 400, the mean proportion enrolled from patients screened was 41%, the proportion of studies with double blinding was 11%, and the mean proportion crossover from nonsurgical to surgical arms was 13%.

Subspecialty Analysis

Stratified by subspecialty, 7 (87.5%) of the functional RCTs, 9 (50%) of the neurovascular RCTs, 1 (50%) of the trauma RCTs, and 7 (43.8%) of the spinal RCTs demonstrated superiority of operative management over nonoperative management in the reported intent to treat primary outcome of interest. Figures 2–6 compare the mean number of patients, mean number of citations, mean percent double blinding, mean percent enrollment, and mean percent crossover from nonoperative to operative arms across the subspecialties. Spinal RCTs had a mean number of 263 patients, had a mean enrollment of 32% of patients from those screened, had a 24% mean rate of crossover from nonsurgical to surgical arms, had a 12% rate of double blinding, and had a mean citation rate of 596 (Table 2). The highest cited spinal RCT was "Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial" by Patchell et al. in *The Lancet*.[20] Functional RCTs had a mean number of 100 patients, had the highest mean rate (77%) of enrollment from patients screened, had the lowest mean rate of 5% crossover from nonsurgical to surgical arms, had the highest double blinding rate of 38%, and had the highest mean citation rate of 1201 (Table 3). The highest cited functional RCT, and the highest cited neurosurgical RCT overall, was "Transplantation of embryonic dopamine neurons for severe

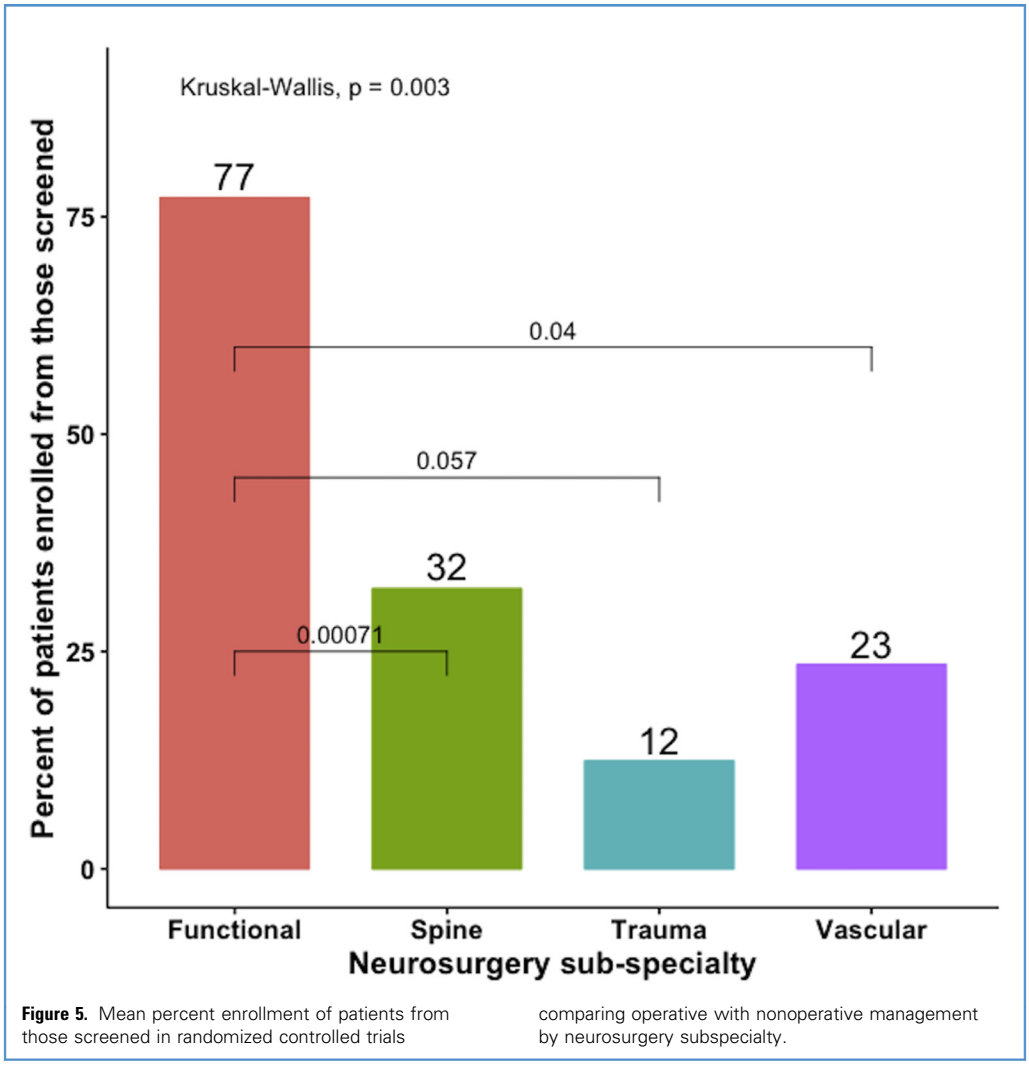

Figure 5. Mean percent enrollment of patients from those screened in randomized controlled trials comparing operative with nonoperative management by neurosurgery subspecialty.

Parkinson's disease" by Freed et al. in the NEJM.[32] Vascular RCTs included the highest mean number of patients (n = 661), had a mean 6% crossover from the nonsurgical to surgical arms, enrolled a mean of 23% of patients from those screened, and had a mean citation rate of 1091 (Table 4). The highest cited vascular RCT was "Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial" by Halliday et al. in *The Lancet*.[43] Trauma RCTs had a mean number of 282 patients, had a mean 21% crossover from nonsurgical to surgical arms, enrolled a mean of 12% of patients screened, and had a mean citation rate of 479 (Table 5). The highest cited trauma RCT was "Decompressive craniectomy in diffuse traumatic brain injury" by Cooper et al. in the NEJM.[53]

DISCUSSION

To our knowledge, this is the first study in the neurosurgery literature to analyze neurosurgical RCTs published in 5 high-impact general medical journals. The study characterized the body of neurosurgical RCT literature for the practicing neurosurgeon and offered heretofore unexamined insights into the subspecialty differences in neurosurgical RCT methodology. Overall, there were more RCTs published comparing operative with nonoperative management, and of these RCTs, 24 (54.5%) were in favor of surgery. The subspecialty analysis revealed significant differences in the direction of study findings and methodologies. The overwhelming majority of functional RCTs (n = 7; 87.5%) supported operative management over nonoperative management, whereas a minority of spinal RCTs (n = 7; 43.8%) supported operative management over nonoperative management. Approximately half of vascular (n = 9, 50%) and trauma RCTs (n = 1, 50%) supported operative management over nonoperative management. However, functional and spinal RCTs greatly differed with respect to methodologic characteristics as subsequently detailed.

Nwachukwu et al.[11] previously conducted a study of all orthopedic operative studies published in high-impact medical journals and found that most studies supported nonoperative management over operative management. Unlike in orthopedics,

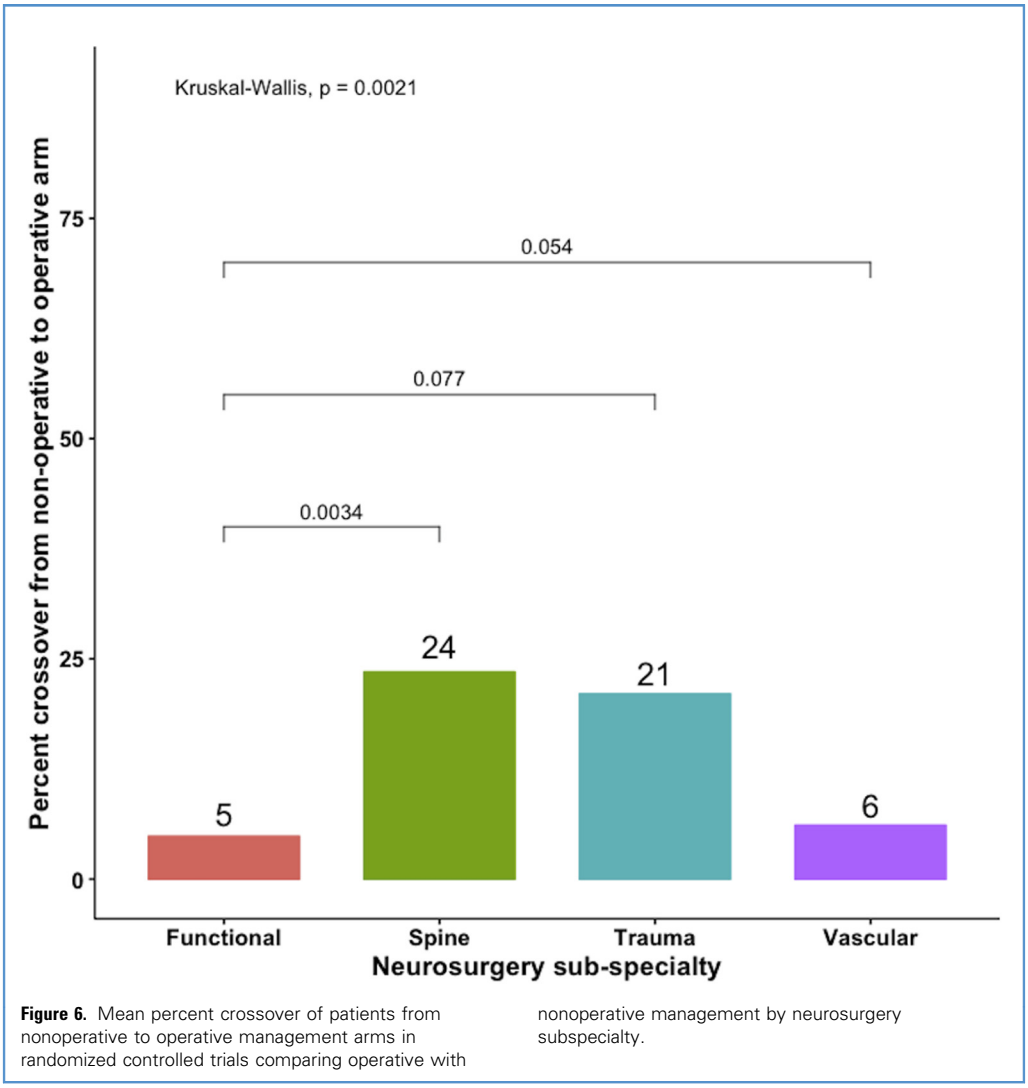

Figure 6. Mean percent crossover of patients from nonoperative to operative management arms in randomized controlled trials comparing operative with nonoperative management by neurosurgery subspecialty.

we found that slightly greater than half of neurosurgery RCTs in general medical journals supported operative management. Nwachukwu et al.[11] also found that the mean rate of crossover from nonsurgical to surgical arms was 33% in orthopedic RCTs published in general medical journals. The mean overall rate for neurosurgery RCTs was much lower at 13%.

Nwachukwu et al.[11] argued that with a high rate of crossover from nonsurgical to surgical arm, the preferred reporting of intent to treat analysis was inappropriate given the high rate of crossover to surgery. This remains relevant for neurosurgery, with the relatively high rate of crossover in spine (23%) and trauma RCTs (21%). For instance, if a large percent of patients assigned to conservative management ultimately underwent surgery by the time of the analysis, analyzing these patients in the nonsurgical group attenuated the effect of surgery on the primary outcome of interest. For neurosurgery, the rate of crossovers was highest for spine and lowest for functional. Interestingly, as previously stated, most functional RCTs (n = 7, 87.5%) supported operative management, whereas a minority of spine RCTs (n = 6, 40%) supported operative management. Rate of crossovers, as a result, may influence the direction of study findings in the intent to treat analysis.

Furthermore, the mean proportion of patient enrollment from those screened was highest for functional RCTs at 77% versus the mean proportion enrollment of 32% for spine, 23% for vascular, and 12% for trauma. Van Spall et al.[13] conducted a review of all RCTs, including neurosurgical, published in high-impact general medical journals between 1994 and 2006 and found only 47.2% of exclusion criteria could be strongly justified in the context of the specific RCT. As such, prestudy exclusion of surgical candidates remains an important metric for practicing neurosurgeons to assess while interpreting the results of a neurosurgical RCT. It is imperative to understand why groups of patients were excluded from study inclusion. In the study of surgical versus nonsurgical treatment for lumbar spinal stenosis by Delitto et al.,[15] even among the 418 of patients (9.4%) that met the

Table 2. Operative Versus Nonoperative Management Spine Randomized Controlled Trials Published in General Medical Journals (2000–2017)

Study	Study Title	Journal	Comparisons
Buchbinder et al., 2009[14]	"A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures"	NEJM	Vertebroplasty versus sham procedure for osteoporotic vertebral fracture
Delitto et al., 2015[15]	"Surgery versus nonsurgical treatment of lumbar spinal stenosis: a randomized trial"	*Annals of Internal Medicine*	Surgical decompression with physical therapy for lumbar spinal stenosis
Fairbank et al., 2005[55]	"Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial"	*The BMJ*	Lumbar spine fusion versus intensive rehabilitation program based on principles of cognitive behavioral therapy for patients with chronic back pain of at least 1 years' duration
Geurts et al., 2003[16]	"Radiofrequency lesioning of dorsal root ganglia for chronic lumbosacral radicular pain: a randomised, double-blind, controlled trial"	*The Lancet*	Percutaneous radiofrequency lesioning of dorsal root ganglia versus sham control
Hellum et al., 2011[17]	"Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study"	*The BMJ*	Surgery with disk prothesis versus rehabilitation in patients with degenerative disk disease
Juch et al., 2017[18]	"Effect of radiofrequency denervation on pain intensity among patients with chronic low back pain: the Mint Randomized Clinical Trials"	*JAMA*	Radiofrequency denervation versus exercise and psychologic support alone for chronic low back pain
Kallmes et al., 2009[19]	"A randomized trial of vertebroplasty for osteoporotic spinal fractures"	NEJM	Vertebroplasty versus sham procedure for osteoporotic vertebral fracture
Klazen et al., 2010[57]	"Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial"	*The Lancet*	Vertebroplasty versus nonsurgical management
Patchell et al., 2005[20]	"Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial"	*The Lancet*	Surgery plus radiotherapy versus radiotherapy alone for metastatic cancer causing spinal cord compression
Peul et al., 2008[21]	"Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: two year results of a randomised controlled trial"	*The BMJ*	Early surgery versus prolonged conservative care for sciatica
Peul et al., 2007[22]	"Surgery versus prolonged conservative treatment for sciatica"	NEJM	Early surgery versus prolonged conservative management for patients with severe sciatica
van den Hout et al., 2008[23]	"Prolonged conservative care versus early surgery in patients with sciatica from lumbar disc herniation: cost utility analysis alongside a randomised controlled trial"	*The BMJ*	Cost of faster recovery of early surgery versus prolonged conservative care of sciatica
Wardlaw et al., 2009[24]	"Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial"	*The Lancet*	Balloon kyphoplasty versus nonsurgical care for vertebral compression fracture
Weinstein et al., 2006[27]	"Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial"	*JAMA*	Standard decompressive laminectomy (with or without fusion) or usual nonsurgical care for lumbar degenerative spondylolisthesis

NEJM, *New England Journal of Medicine*.

Continues

Table 2. Continued

Study	Study Title	Journal	Comparisons
Weinstein et al., 2007[25]	"Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis"	NEJM	Standard decompressive laminectomy (with or without fusion) or usual nonsurgical care for lumbar degenerative spondylolisthesis
Weinstein et al., 2008[26]	"Surgical versus nonsurgical therapy for lumbar spinal stenosis"	NEJM	Decompressive laminectomy (with or without fusion) vs nonsurgical care for lumbar spinal stenosis

NEJM, *New England Journal of Medicine*.

inclusion and exclusion criteria for the trial from the 5119 patients screened for eligibility, 65% declined to participate because they did not want to risk the chance of being randomized to the nonsurgical arm. In addition, of the patients ultimately enrolled and randomized to the nonsurgical arm, 57% of the patients crossed over from the nonsurgical arm to the surgical arm. Of the neurosurgical RCTs analyzed in this study, 38.6% did not report the total population screened. The Consolidated Standards of Reporting Trials statement for randomized controlled trials requires reporting of the total population screened and requires reasons patients were excluded.[58] For example, in a randomized trial of vertebroplasty for osteoporotic spinal fractures, 300 of 1813 patients screened met eligibility criteria but declined to participate; ultimately 131 were enrolled.[19,58] The study did not list the reasons for patients declining participation. Proportion of patient enrollment and reasons for patient exclusion are critical to understand in determining the generalizability of RCT findings.

We previously conducted a systematic review of 82 neurosurgical RCTs published from 2000 to 2017 with 25.6% failing to report funding sources and relatively high changes to anticipated accrual.[12] Similar to the subspecialty differences noted in the present study, we found subspecialty differences in trial registration rates and changes to primary and secondary outcome measures. As sophisticated consumers of these trial designs, neurosurgeons should be aware of these overall trends and the high-impact general medical journal specifics highlighted here.

There are several limitations to this study, including the analysis of a subset of general medical journals and a subset of the time period. In addition, we were unable to directly compare our systematic review of RCTs in general medical journals to such a review of RCTs published only in neurosurgical journals. Yarascavitch et al.[59] previously reviewed clinical studies in 3 neurosurgical journals but only from the time period of 2009–2010. Furthermore, we are unable to examine the trends in publication of neurosurgical RCTs from those submitted to general medical journals. Analyses of the defining

Table 3. Operative Versus Nonoperative Management Functional Randomized Controlled Trials Published in General Medical Journals (2000–2017)

Study	Study Title	Journal	Comparisons
Deuschl et al., 2006[28]	"A randomized trial of deep-brain stimulation for Parkinson's disease"	NEJM	Deep-brain stimulation versus medical management in patients with advanced Parkinson disease
Dwivedi et al., 2017[29]	"Surgery for drug-resistant epilepsy in children"	NEJM	Surgery versus medical therapy for patients 18 years of age or younger with drug-resistant epilepsy
Elias et al., 2016[30]	"A randomized trial of focused ultrasound thalamotomy for essential tremor"	NEJM	Unilateral focused ultrasound thalamotomy versus sham procedure for essential tremor
Engel et al., 2012[31]	"Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial"	*JAMA*	Continued anti-epileptic drugs versus anteromesia temporal resection for mesial temporal lobe epilepsy and disabling seizures
Freed et al., 2001[32]	"Transplantation of embryonic dopamine neurons for severe Parkinson's disease"	NEJM	Transplant of embryonic dopamine neurons versus sham surgery for severe Parkinson disease
Kupsch et al., 2006[33]	"Pallidal deep-brain stimulation in primary generalized or segmental dystonia"	NEJM	Neurostimulation of internal globus pallidus versus sham stimulation
Weaver et al., 2009[34]	"Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial"	*JAMA*	Deep-brain stimulation versus medical therapy for advanced Parkinson's disease
Wiebe et al., 2001[35]	"A randomized, controlled trial of surgery for temporal-lobe epilepsy"	NEJM	Surgery versus treatment with antiepileptic drugs for 1 year for patients with temporal lobe epilepsy

NEJM, *New England Journal of Medicine*.

Table 4. Operative Versus Nonoperative Management Vascular Randomized Controlled Trials Published in General Medical Journals (2000—2017)

Study	Study Title	Journal	Comparisons
Berkhemer et al., 2015[36]	"A randomized trial of intraarterial treatment for acute ischemic stroke"	NEJM	Intraarterial treatment versus medical management alone for acute ischemic stroke
Broderick et al., 2013[37]	"Endovascular therapy after intravenous t-PA versus t-PA alone for stroke"	NEJM	Endovascular therapy versus t-PA alone for stroke
Campbell et al., 2015[38]	"Endovascular therapy for ischemic stroke with perfusion-imaging selection"	NEJM	Endovascular therapy versus alteplase alone for stroke
Ciccone et al., 2013[39]	"Endovascular treatment for acute ischemic stroke"	NEJM	Endovascular therapy versus IV t-PA for stroke
Derdeyn et al., 2014[40]	"Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial"	*The Lancet*	Stenting versus medical management in high-risk patients with intracranial artery stenosis
Goyal et al., 2015[41]	"Randomized assessment of rapid endovascular treatment of ischemic stroke"	NEJM	Endovascular treatment versus standard care for patients with proximal intracranial occlusion in the anterior circulation
Halliday et al., 2004[43]	"Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial"	*The Lancet*	Immediate CEA versus indefinite deferral of any CEA
Halliday et al., 2010[42]	"10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial"	*The Lancet*	Immediate carotid enterectomy versus indefinite deferral of any carotid procedure for asymptomatic patients with carotid artery disease
Jovin et al., 2015[44]	"Thrombectomy within 8 hours after symptom onset in ischemic stroke"	NEJM	Endovascular therapy versus medical therapy alone for patients with proximal anterior circulation occlusion
Juttler et al., 2014[45]	"Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke"	NEJM	Hemicraniectomy versus conservative treatment for patients with malignant middle cerebral artery infarction
Kidwell et al., 2013[46]	"A trial of imaging selection and endovascular treatment for ischemic stroke"	NEJM	Mechanical embolectomy (Merci Retreiver or Penumbra System) versus standard care for patients within 8 hours after onset of large-vessel, anterior circulation strokes
Mendelow et al., 2005[47]	"Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial"	*The Lancet*	Early surgery combined hematoma evacuation (within 24 hours of randomization) versus initial medical treatment for spontaneous supratentorial intracerebral hemorrhage
Mendelow et al., 2013[48]	"Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial"	*The Lancet*	Early surgical hematoma evacuation within 12 hours of randomization versus initial medical treatment alone for conscious patients with superficial lobar intracerebral hemorrhage and no interventricular hemorrhage
Mohr et al., 2014[49]	"Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial"	*The Lancet*	Medical management with interventional therapy (i.e., neurosurgery, embolization, or stereotactic radiotherapy, alone or in combination) or medical management alone for unruptured brain arteriovenous malformations
Powers et al., 2011[50]	"Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial"	*JAMA*	Extracranial-intracranial bypass surgery versus no surgery for symptomatic atherosclerotic internal carotid artery occlusion and hemodynamic cerebral ischemia
Saver at al., 2015[51]	"Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke"	NEJM	Thrombectomy plus IV t-PA versus IV t-PA alone
van den Berg et al., 2017[52]	"Two-year outcome after endovascular treatment for acute ischemic stroke"	NEJM	Endovascular treatment or conventional treatment for acute ischemic stroke
Zaidat et al., 2015[56]	"Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial"	*JAMA*	Balloon-expandable stent plus medical therapy versus medical therapy alone for symptomatic intracranial stenosis

NEJM, *New England Journal of Medicine*; IV, intravenous; t-PA, tissue plasminogen activator; CEA, carotid endarterectomy.

Table 5. Operative Versus Nonoperative Management Trauma Randomized Controlled Trials Published in General Medical Journals (2000—2017)

Study	Study Title	Journal	Comparisons
Cooper et al., 2011[53]	"Decompressive craniectomy in diffuse traumatic brain injury"	NEJM	Bifrontotemporoparietal decompressive craniotomy or standard care for adults with severe diffuse traumatic brain injury and intracranial hypertension refractory to first-tier therapies
Hutchinson et al., 2016[54]	"Trial of decompressive craniectomy for traumatic intracranial hypertension"	NEJM	Decompressive craniectomy versus ongoing medical care for patients, 10—65 years of age, with traumatic brain injury and refractory elevated intracranial pressure (>25 mm Hg)

NEJM, *New England Journal of Medicine*.

characteristics of manuscripts accepted and rejected from general medical journals would be of interest to the neurosurgery community, particularly segmented by subspecialty, and may the subject of future studies. Future studies should seek to broaden the findings presented here for neurosurgery and examine these trends across multiple surgical subspecialties. Additionally, future studies should seek to characterize the rates of crossovers and proportion of enrollment for neurosurgical RCTs with different surgical modalities.

Despite these limitations, this work is particularly relevant to the practicing neurosurgeon by providing an analytical overview of the neurosurgical RCTs published in general medical journals. These studies are likely to be the ones cited by nonneurosurgical medical practitioners and policymakers, and the most likely to be nationally publicized to the general public. Furthermore, as previously stated, it is extremely important for neurosurgeons to be critically aware of the following parameters while interpreting the validity and generalizability of the study findings: total number of patients screened, reasons for patient exclusion, proportion of crossovers between treatment arms, and type of analysis presented (intent to treat vs. as treated).

CONCLUSIONS

Neurovascular, functional, and spinal RCTs are the most commonly published neurosurgery topics in general medical journals, and more than half are RCTs comparing operative with nonoperative management. There is a large subspecialty difference in study characteristics such as crossovers from nonsurgical to surgical treatment arms and the proportion of studies demonstrating benefit of operative intervention over nonoperative management.

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SUPPLEMENTARY DATA

Supplementary Table 1. PubMed and Embase Search Strategies

PubMed, December 3, 2017	"Neurosurgical Procedures"[Mesh] OR neurosurgery[tiab] OR "Nervous System Diseases/surgery"[Mesh] OR "Skull/surgery"[Mesh] OR "Spine/surgery"[Mesh] OR ("Nervous System Diseases"[Mesh] AND Surgical Procedures, Operative) OR ("Back Injuries"[Mesh] AND Surgical Procedures, Operative) OR ("Neck Injuries"[Mesh] AND Surgical Procedures, Operative)
Embase, December 3, 2017	'neurosurgery'/de OR 'spine surgery'/de OR 'neck injuries'/de OR 'back injuries'/de OR "neurosurgery"/exp OR "neurosurgical procedures"/exp OR "spine"/exp OR "brain"/exp OR "central nervous system"/exp OR "nervous system"/exp OR neurosurger*:ab,ti OR spine surger*:ab,ti OR cranial*:ab,ti OR spinal*:ab,ti OR spine*:ab,ti OR brain*:ab,ti