Timing of surgery in cauda equina syndrome with urinary retention: meta-analysis of observational studies

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Object. The authors performed exploratory meta-analyses of observational cohort studies, evidence level III, examining whether earlier surgery makes a difference in outcome in terms of urinary function once cauda equina syndrome (CES) from a herniated lumbar disc has progressed to urinary retention (CESR).

Methods. Literature search identified 27 studies of CESR patients with clear definition of surgical timing. Relative risk (RR) could not be calculated in 11 studies, leaving 16 for meta-analysis. Urinary retention related to surgical timing at 5 breakpoints: 12, 24, 36, 48, or 72 hours. Urinary outcome was classified as Normal, Fair, or Poor. Meta-analysis was performed for “Event = Fair/Poor” or “Event = Poor.” Eight studies allowed separation into CESR and incomplete CES (CESI), and 5 of these had enough data for meta-analysis to compare CESR and CESI. A random effects meta-analysis model was used because of heterogeneity across the studies. A best-evidence synthesis was performed for the 4 largest studies that had 24- and 48-hour breakpoints.

Results. For “Event = Fair/Poor,” meta-analyses using the 5 breakpoints predicted a more likely Fair/Poor outcome for later surgery (RR range 1.77–2.19). The RR for later timing of surgery was statistically significant for 24- and 72-hour breakpoints and was elevated but not statistically significant for the other 3. For “Event = Poor,” the RR range was 1.09–5.82, statistically significant for the 36 hour breakpoint only. Meta-analysis comparing CESR patients with CESI patients predicted a Fair/Poor result for CESR (RR 2.58, 95% confidence interval 0.59–11.31). The best-evidence synthesis did not disclose reasons for differences in the results of the 4 studies.

Conclusions. This study supports early surgery for CES and indicates that CESR and CESI cases should not be analyzed together. (DOI: 10.3171/SPI/2008/8/4/305)

KEY WORDS • cauda equina syndrome • evidence-based medicine • meta-analysis • neurogenic bladder • spinal nerve root • urinary retention

This study was performed to evaluate the timing of surgery for CESR arising from herniated lumbar discs, with or without spinal stenosis.

Cauda equina syndrome describes the clinical condition that results from compressive, ischemic, and/or inflammatory neuropathy of multiple lumbar and sacral nerve roots in the lumbar spinal canal. The syndrome includes varying combinations of lower extremity weakness, sensory loss in the lower extremities and/or saddle area, pain in the low back and/or lower extremities, and visceral impairment of bladder, rectal, and/or sexual function. Although CES is sometimes used to describe a syndrome without impairment of bladder and bowel function, generally in the literature the term “cauda equina syndrome” means a syndrome that includes impairment of urinary function and saddle sensory deficits.⁷⁸,⁷⁹

Cauda equina syndrome can arise from many types of nerve root compromise.¹³,¹¹² Podnar¹¹⁸ found an annual incidence of CES from intervertebral disc herniation of 1.8 per million in Slovenia. Extrapolating to the annual incidence of herniated discs in the US (150 per 100,000), he calculated that 0.12% of herniated discs in the US result in CES.

Tandon and Sankaran¹⁶⁶ described the ways in which CES can present: suddenly, over a period of a few hours, either as the first sign of lumbar disc pathology (Type I) or as the end point in a long history of chronic low back pain and/or sciatica (Type II); or slowly and insidiously, progressing gradually to severe visceral impairment with urinary retention (Type III).
The majority of authors who have addressed the issue of surgical timing and the outcome of CES appear to be of the opinion that patients with CES due to a herniated disc should receive surgical treatment on an urgent basis.\textsuperscript{2,3,7, 16,18,30,42,46,48,49,59,60,63,67,72–74,79,82,87,88,94,106,119,120,123,134,141,152,157,166,168–170}

Some of these authors hold this opinion in spite of the fact that their studies have not demonstrated a statistical advantage to early surgery.\textsuperscript{7,18,79,106,119,120,157} Even Gleave and Macfarlane\textsuperscript{52} and Hussain et al.,\textsuperscript{65} who feel that surgery should not be considered as an emergency once the bladder has become paralyzed, have expressed the opinion that “... the disc prolapse should be removed at the earliest opportunity.”\textsuperscript{52} and that “... these operations should be performed under the most favorable conditions and quite necessarily ‘on the next available list’.”\textsuperscript{65}

Gleave and Macfarlane\textsuperscript{50} identify 2 stages of CES: incomplete cauda equina syndrome, termed CESI, and cauda equina syndrome with retention, termed CESR. They characterize CESI as “altered urinary sensation, loss of desire to void, poor urinary stream, and the need to strain in order to micturate,” and CESR as “painless urinary retention and overflow incontinence, where the bladder is no longer under executive control.”\textsuperscript{50} They feel that patients with CESI who have surgery uniformly do well, while patients with CESR do considerably more poorly with or without surgery.

Gleave and Macfarlane\textsuperscript{52} analyzed 33 of their cases of CESR and concluded that the timing of surgery bore no relationship to the outcome. They presented their data as a correlation between mean delay to surgery and urinary outcome, which does not allow inclusion with data from other studies in a meta-analysis regarding the timing of surgery and postoperative outcome.

Discussing the work of Shapiro,\textsuperscript{141} Gleave and Macfarlane\textsuperscript{50} state, “... we would not dispute his assertion that CESI is best treated by early surgery.”\textsuperscript{50} Therefore, the issue of early versus delayed surgery for CES revolves around the timing of surgery in cases of CESR in which the syndrome has progressed to bladder paralysis. Unfortunately, in accordance with Gleave and Macfarlane, we found that most of the studies in the literature do not allow a clear division of the cases into CESI and CESR, nor do they clearly define the timing of surgery in relation to the development of full-blown CESR. Gleave and Macfarlane are concerned that emergency surgery for CES, when carried out under less than optimal circumstances, can do more harm than good.\textsuperscript{50,51,169}

Clinical Materials and Methods

Our null hypothesis is that later surgery does not increase the RR of a fair or poor outcome of urinary function once CES from a herniated lumbar disc has progressed to urinary retention (CESR). We adhered as much as possible to the MOOSE group’s criteria for performing a meta-analysis of observational studies.\textsuperscript{156}

Data Collection and Definition of Variables

Literature Search. We searched the medical literature extensively, beginning with basic searches of the MEDLINE/PubMed service of the US National Library of Medicine, using the MeSH (medical subject heading) terms “cauda equina,” “neurogenic bladder,” “polyradiculopathy,” and “intervertebral disc displacement” in various combinations. We saved our searches to a PubMed “My NCBI” account and signed up for automatic email updates to the searches. We searched the Latin American and Caribbean LILACS (Literatura Latino Americana e do Caribe em Ciências da Saúde) database.\textsuperscript{2} We searched 2 ISI Web of Knowledge databases, BIOSIS Previews and Web of Science, as well as 2 dissertational databases, ProQuest Digital Dissertations and WorldCat Dissertations,\textsuperscript{92,171} all available through the institutional subscriptions of the UCSF Library and Center for Knowledge Management. Embase was not directly available to us and we made the assumption that it would contain very few references that we had not already located with Medline, BIOSIS Previews, or Web of Science.\textsuperscript{132} We obtained the full text of each article of interest and obtained further articles from the reference lists of the articles through a highly iterative process. We examined full-text copies of the 42 articles upon which Ahn et al.\textsuperscript{2} relied for their meta-analysis of CES.\textsuperscript{2,76} We obtained translations of pertinent non-English articles in French, Danish, Hebrew, Serbian, and Slovak. We searched the Internet itself for leads to articles appearing in journals not indexed in the databases. We eventually accumulated approximately 800 full-text articles pertaining to various aspects of CES, experimental dorsal root regeneration, and the meta-analysis of observational studies. We terminated our searches on November 19, 2007. Only 27 articles met our inclusion criteria of reporting cases of CES that had progressed to a paralyzed, insensate bladder, thus distinguishing CESR from CESI patients, of defining the interval between the development of bladder paralysis and surgery, and of adequately describing postoperative urinary function.\textsuperscript{7,18,22,26,30,58,59,61,67,73, 74,82,87,88,94,120,122,134,141,152,157,168,170,176}

Raw Data and Zero Cells. The raw data from these 27 studies are presented in the Appendix to this article, along with the probability values for the individual studies. Eleven of the 27 studies could not be included in our meta-analysis because there were no Fair or Poor results in the urinary outcome for CESR patients, because there were no Normal results, or because there were no cases in which patients underwent surgery within 72 hours of the onset of CESR, and as a consequence no early surgery data were available for any of the breakpoints.\textsuperscript{7,22,26,58,65,90,122,152,166,170,176}

It is our opinion, as well as the consensus among a majority of statisticians, that such studies should not be included in a meta-analysis.\textsuperscript{17,162,174} Major meta-analytical software packages (for example, Comprehensive Meta-Analysis from Biostat [http://www.meta-analysis.com], Stata from StataCorp [http://www.stata.com], the Cochrane Collaboration’s RevMan [http://www.cc-ims.net/RevMan], and the R Project [http://www.r-project.org]) default to the condition of dropping studies in which “events” equal 0% or 100%, or in which there are no subjects in 1 arm or the other of the study (M. Borenstein, personal communication, 2007). The other 16 studies contained data for earlier and later surgery around 1 of the 5 breakpoints.

Contact With Authors. For relatively recent articles in which there were questions about the data or discrepancies between the text and tables, we wrote or emailed the authors for clarification. We heard back from Drs. Bhandari and Busse,\textsuperscript{39} Buchner,\textsuperscript{18} Grevitt and McCarthy,\textsuperscript{53} McMan-
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us,73 Nikolić and Radulović,120 Sell,119 Shapiro,141 and Sul-

la.157 Both Shapiro and Sullivan confirmed that all the patients

included in their studies had CESR (S. Shapiro, personal

communication, 2006; I. Sullivan, personal communication,

2006).

Comparison of CESR and CESI Cases. Dinning and

Schaeffer30 noted that the time at which placement of an

indwelling catheter is required preoperatively constitutes

“an easily identifiable and uniform marker of disability.”30 In

these 27 papers it was possible to define the CESR patients

as those who developed a distended paralyzed bladder ex-
hibited by clear-cut overflow incontinence or by the re-

quirement for catheterization. It is true that bladder paraly-
sis does not manifest itself for several hours after onset, but

overflow incontinence and/or the requirement for catheter-

ization is probably the best we can do in regard to defining

the onset of full-blown CESR. Nineteen studies reported

only on CESR patients.18,26,58,60,61,74,82,87,88,90,93,94,120,122,134,141,152,157,176,177 Eight reported on both CESR and CESI patients.7,22,30,67,73,93,156,170

Timing of Surgery. In these 27 studies surgical timing was

defined as the interval between the onset of full-blown

CESR (catheterization or the recognition of clear-cut over-

flow incontinence) and the time that surgery was per-

formed. Overflow incontinence is termed “ischuria para-
doxa” in some of the European literature74 (I. Sullivan, personal

communication, 2007). A number of studies outside these

27 did not meet our inclusion criteria because the authors

reported surgical timing as the interval between hospital

admission and the operation and/or were unclear in regard

to the number of hours or days that had elapsed between the

onset of CESR and the surgery.

Breakpoints. We determined the 5 breakpoints by care-

ful reading of the text in the 27 articles and by comparing

it with data in their tables. We were able to identify 5 peri-

ods during which surgery was performed, using the onset of

CESR (the recognition of bladder paralysis) as the start-

ing point: onset–12 hours after onset;18,26,60,84,141 onset–24

hours;18,22,30,60,82,87,88,90,93,94,141,157,168,177 onset–36 hours;22

onset–48 hours;22,26,60,82,87,88,90,93,94,120,141,157,168,177

and onset–72 hours.18,22,26,30,58,67,74,82,87,88,94,122,134,152,157,158,170,176 The end of each period was designated as a “breakpoint,” and statistical comparisons were made between the number of pa-

tients who were treated surgically before and after each of

the 5 breakpoints. The data did not allow the development of

other breakpoints, such as 6 hours, 18 hours, or 60 hours.

Urinary Function Outcome. The description of urinary

function outcome varies from study to study. In their origi-
nal paper, Gleave and Macfarlane52 classified urinary out-

come as “excellent if full bladder control was regained

within six weeks, good if recovery was ultimately full but
delayed, fair if the patient had voluntary control but suf-
f ered from stress incontinence or lack of urinary sensation,
and poor if they remained incontinent.” In the current study
we use 3 categories of urinary outcome: Normal, Fair, and

Poor, with Normal including the 2 groups that Gleave and

Macfarlane called “Excellent” and “Good.”

This system of grading urinary outcome depends upon

the patient’s subjective perception of bladder function and
does not necessarily express adequately the true neurolo-
gical status of the bladder, since many patients with bladder
dysfunction may void by abdominal straining, unaware

or only marginally aware that they are doing so.3,59,77

However, since few studies report the results of postopera-
tive urodynamic evaluation, we chose this system for the

purposes of this meta-analysis.

Therefore, “Normal” means the patient perceives his or

her urinary function to be normal; “Fair” means the patient

has some degree of difficulty with urination, such as hav-
ing to strain actively to void, having stress or nocturnal in-
continence, or having signs of abnormal postvoiding resid-

ual urine, such as urinary frequency or frequent urinary

infections; and “Poor” means the patient requires catheter-

ization, either intermittent or indwelling, or requires the

constant use of pads or absorbent undergarments. We also

considered the outcome as “Poor” if the patient had persis-
tent incontinence of stool or flatus.

Meta-Analysis

We performed a meta-analysis of the 16 studies that had
Fair or Poor “events” for the CESR patients, or more ex-

actly, 10 meta-analyses, 1 for each of the 5 breakpoints

combined with 1 of the 2 possible outcomes of urinary

function (Fair/Poor vs Normal; or Poor vs Normal/Fair).

We performed an additional meta-analysis to compare

patients with CESR and patients with CESI with regard to

outcome. Calculations were performed using Biostat’s CMA

software (CMA version 2.2.046). These computa-

tions were verified with the R Project (R Foundation for

Statistical Computing) software (using the “meta” library).

The CMA software adds a 0.5 continuity correction to all
cells in studies that contain zero-value cells, other than the
2 cases described above (“events” equal 100% or 0%, or
zero data for either early surgery or late surgery around 1 or
more of the breakpoints).

Relative Risk, Definition of “Events,” and Tests for Hetero-
geneity. We used RR instead of odds ratios to quantify the
association between surgical timing and urinary function

because the data represent a prospective follow-up of pa-

tients in the epidemiological sense, with the dependent

variable (outcome) occurring later in time than the inde-

pendent variable (timing of surgery). Relative risk is the

natural choice for prospective studies and can be used here,

although it cannot be used in some other sampling frame-

works, such as case-control studies, where the odds ratio

would be required.87

We estimated the RR of negative urinary function out-

comes for patients with longer waiting times for surgery
relative to patients with shorter waiting times using stan-
dard meta-analysis for binary outcomes.29,31 The analysis
pooled results from the 16 studies that had the Normal,
Fair, or Poor outcomes distributed in ways that allowed sta-
tistical comparisons, appropriately weighting the size of
each study. The negative urinary function outcome was

defined and analyzed in each of 2 ways: 1) as Fair or Poor

(Fair/Poor) outcome, and 2) as Poor outcome. An “Event”
is the outcome upon which the statistical operations are

focusing. Therefore, we defined an Event as the occurrence

of an unfavorable outcome of urinary function—as a Fair

or Poor outcome (vs a Normal outcome), or as a Poor out-

come (vs a Normal or Fair outcome). The data were input

into the CMA meta-analytic application in a way that gave
us the RR of an Event occurring with later surgical timing.
The Q statistic tests the null hypothesis that all studies share a common effect size with minimal dispersion of the effect size across the studies. It quantifies the amount of dispersion across the effect sizes and displays the percentage of observed variance between studies that is due to real differences in effect sizes. We regard $I^2 < 25\%$ as low heterogeneity, $25\% - 75\%$ as moderate heterogeneity, and $> 75\%$ as severe heterogeneity.

Even though heterogeneity was statistically absent or mild in 6 of 10 meta-analyses, we used the DerSimonian–Laird random effects method throughout rather than a fixed effects model because we observed a number of differences in study design, methods, and RRs among the individual studies.

**Exclusion of Studies.** A number of studies did not meet our inclusion criteria, even though some of them have been cited quite regularly in the CES literature (Table 1). We could only accept 10 of the 42 studies upon which Ahn et al. relied. We eliminated earlier studies that appeared to duplicate data included in a subsequent more comprehensive study.

**Assumptions.** Extracting data from the included studies was demanding and in some cases involved making several judgments and assumptions (Table 2).

**Language Restrictions.** We evaluated the effect of our not having imposed a linguistic restriction on our search for articles. We performed “English only” meta-analyses on the 24-hour and 48-hour breakpoints for “Event = Fair or Poor” and compared them with the unrestricted analyses.

**Publication Bias.** We evaluated the meta-analyses for publication bias, using funnel plots and the “trim and fill” method of Duval and Tweedie, as well as the Egger regression test.

**Best-Evidence Synthesis**

In an effort to identify sources of heterogeneity across the studies, we analyzed the 4 largest studies that had data for the 24- and 48-hour breakpoints along the lines of a best-evidence synthesis suggested by Slavin.

### Results

**Meta-Analysis**

**Combined RR and 95% CIs.** Across the 5 breakpoints, the RR for “Event = Fair or Poor” ranged from 1.77 to 2.19 (Table 3), indicating a more likely Fair or Poor outcome for later surgery than for earlier surgery. For the 24-hour and 72-hour breakpoints, the RRs were statistically significant with probability values of 0.045 and 0.002, respectively; the RRs were elevated but not statistically significant for the 12-, 36-, and 48-hour breakpoints with probability values of 0.37, 0.19, and 0.12, respectively. For “Event = Poor” the RR ranged from 1.09 to 5.82, again indicating a

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Reasons For Exclusion From Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dandy, 1942</td>
<td>chronic case of &gt; 1 yr duration, dense intradural scar, urinary outcome not described</td>
</tr>
<tr>
<td>French &amp; Payne, 1944</td>
<td>timing of surgery not specified, CESR &amp; CESI cases could not be separated</td>
</tr>
<tr>
<td>O'Connell, 1951</td>
<td>10/500 disc patients had CES, timing of surgery not specified</td>
</tr>
<tr>
<td>Fairburn &amp; Stewart, 1955</td>
<td>3 isolated case reports; 2 CESR w/ normal recovery, 1 CESI; transdural excision in all 3</td>
</tr>
<tr>
<td>Shephard, 1959</td>
<td>CESR &amp; CESI patients could not be separated</td>
</tr>
<tr>
<td>Gurdjian et al., 1961</td>
<td>10/1176 disc patients had CESR, timing of surgery not specified, outcome vague: “No sphincter disturbances following surgery were noted.”</td>
</tr>
<tr>
<td>Scott, 1965</td>
<td>timing of surgery not specified</td>
</tr>
<tr>
<td>Schaeffer, 1966</td>
<td>data duplicated in a later study*</td>
</tr>
<tr>
<td>Taher et al., 1966</td>
<td>42/46 CES patients had CESR, timing of surgery &amp; urinary outcome not specified</td>
</tr>
<tr>
<td>Aho et al., 1969</td>
<td>urinary outcome could not be correlated w/ timing of surgery</td>
</tr>
<tr>
<td>Spangfort, 1972</td>
<td>31/2504 patients had CES, CESR &amp; CESI patients could not be separated, timing of surgery not specified</td>
</tr>
<tr>
<td>Gindin &amp; Volcan, 1978</td>
<td>3 cases of CESR, timing of surgery not defined</td>
</tr>
<tr>
<td>Nielsen et al., 1980</td>
<td>CESR &amp; CESI patients could not be separated</td>
</tr>
<tr>
<td>O’Laioire et al., 1981</td>
<td>urinary outcome could not be correlated w/ timing of surgery</td>
</tr>
<tr>
<td>Fager, 1985</td>
<td>6/243 central disc patients had CES; timing of surgery not specified for 4 of them</td>
</tr>
<tr>
<td>Hellström et al., 1986</td>
<td>CESR &amp; CESI cases could not be separated</td>
</tr>
<tr>
<td>Kostuik et al., 1986</td>
<td>timing of surgery could not be correlated w/ onset of CESR in 1/23 CESR patients</td>
</tr>
<tr>
<td>Fantacciullacci et al., 1989</td>
<td>20 cases of CESR, timing of surgery not defined, outcomes for CESR &amp; CESI could not be separated</td>
</tr>
<tr>
<td>Gleave &amp; MacFarlane, 1990</td>
<td>urinary outcome could not be correlated w/ timing of surgery</td>
</tr>
<tr>
<td>Shapiro, 1993</td>
<td>data duplicated in a later study†</td>
</tr>
<tr>
<td>Busse et al., 2001</td>
<td>urinary outcome not specifically described</td>
</tr>
<tr>
<td>Kabre et al., 2001</td>
<td>timing of surgery not specified, urinary outcome not specifically associated w/ etiology of CES</td>
</tr>
<tr>
<td>Hussain et al., 2003</td>
<td>urinary outcome could not be correlated w/ timing of surgery</td>
</tr>
<tr>
<td>Qureshi &amp; Sell, 2007</td>
<td>urinary outcome could not be correlated w/ timing of surgery</td>
</tr>
</tbody>
</table>

* References 30 and 173.
† References 141 and 173.
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TABLE 2
Assumptions necessary in some included studies

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ver Brugghen, 1945</td>
<td>assumed Normal urinary outcomes although descriptions were vague</td>
</tr>
<tr>
<td>Jennett, 1956</td>
<td>urinary outcomes of CESR patients were determined by coordinating data in text with Table II; CESI patients were assumed to have Normal outcome because Fair and Poor outcomes were mentioned only in connection with CESR patients</td>
</tr>
<tr>
<td>Wilson, 1962</td>
<td>assumed Normal urinary outcome although description was vague</td>
</tr>
<tr>
<td>Liebergall et al., 1989</td>
<td>assumed all 9 patients were CESR preop because all required catheterization postop; assumed 2 patients w/out postop cystometrography had Normal outcome; assumed all 4 patients with &quot;pathological&quot; postop cystometrography findings had Fair outcome &amp; the 3 patients with &quot;normal&quot; cystometrography results had Normal outcome</td>
</tr>
<tr>
<td>Šulla, 1996</td>
<td>email from Dr. Šulla confirmed that all 58 patients were CESR &amp; required catheterization preop; text allowed separation of CESR &amp; CESI patients only at 36-hr breakpoint; communication with Dr. McManus confirmed data for other breakpoints were no longer available</td>
</tr>
<tr>
<td>Kennedy et al., 1999</td>
<td>email from Dr. Šulla confirmed that all 44 patients were CESR w/ either urinary retention or overflow incontinence</td>
</tr>
<tr>
<td>Shapiro, 2000</td>
<td>email from Dr. Buchner resolved outcome discrepancies between text and tables</td>
</tr>
<tr>
<td>Buchner &amp; Schiltenwolf, 2002</td>
<td>email from Dr. Buchner and Dr. Šulla allowed correlation of urinary outcome with timing of surgery</td>
</tr>
<tr>
<td>Radulović et al., 2004</td>
<td></td>
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</table>

Poor outcome for later surgery (Table 3). The RR for 36 hours was statistically significant, with a probability value of 0.008. The probability values for the 12-, 24-, 48-, and 72-hour breakpoints were not statistically significant (Figs. 1 and 2).

For a Fair/Poor result, there is a trend toward worsening of the outcome as the breakpoint intervals increase (12 hours, RR 1.77; 24 hours, RR 1.85; 36 hours, RR 2.11; 48 hours, RR 2.09; 72 hours, RR 2.19). However, the lack of statistical significance for the RR at the 12-, 36-, and 48-hour breakpoints renders this apparent trend uncertain.

Comparison of CESR and CESI Cases. Five studies allowed the comparison of urinary outcome for CESR and CESI patients (Fig. 3). In all these studies combined, 6 of 44 CESI patients had a Fair or Poor outcome, compared with 26 of 70 CESR patients. These figures cannot be compared directly with a single statistical operation because of the risk of Simpson paradox. Meta-analysis of the 5 studies is required, yielding an RR of 2.58 (95% CI 0.59–11.31, p = 0.2) for a Fair or Poor outcome for CESR patients relative to CESI patients.

Heterogeneity. Within the 5 meta-analyses used for Fair/Poor outcome, heterogeneity across the studies was absent or low for 3, moderate for 1, and high for 1. It was absent or low for 3 and high for 2 meta-analyses of the 5 used for Poor outcome. It is likely that the significant study effect in some of the meta-analyses results from the varying ways in which the patients were treated and/or cases were analyzed from center to center. In studies of CES the number of potential confounding factors is considerable (Table 4). Our meta-analyses do not allow a formal evaluation of these factors since the numbers were too small for subgroup analysis.

TABLE 3
Summary of meta-analyses

<table>
<thead>
<tr>
<th>Event Outcome</th>
<th>Breakpoint (hr)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>I²</th>
<th>Studies w/ Estimable RRs (used in the meta-analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair/Poor</td>
<td>12</td>
<td>1.77 (0.51–6.15)</td>
<td>0.4</td>
<td>44.75</td>
<td>McLaren &amp; Bailey, 1986; Shapiro, 2000; Henriques et al., 2001; Buchner &amp; Schiltenwolf, 2002; Mangialardi et al., 2002</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>24</td>
<td>1.85 (1.01–3.39)</td>
<td>0.045</td>
<td>6.13</td>
<td>Malloch, 1965; McLaren &amp; Bailey, 1986; Liebergall et al., 1989; Dinning &amp; Schaeffer, 1993; Šulla, 1996; Shapiro, 2000; Henriques et al., 2001; Buchner &amp; Schiltenwolf, 2002; Mangialardi et al., 2002; McCarthy et al., 2007</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>36</td>
<td>2.11 (0.69–6.41)</td>
<td>0.2</td>
<td>27.67</td>
<td>McLaren &amp; Bailey, 1986; Liebergall et al., 1989; Kennedy et al., 1999; Henriques et al., 2001; Mangialardi et al., 2002</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>48</td>
<td>2.09 (0.83–5.24)</td>
<td>0.1</td>
<td>65.14</td>
<td>Malloch, 1965; McLaren &amp; Bailey, 1986; Liebergall et al., 1989; Šulla, 1996; Shapiro, 2000; Radulović et al., 2004; McCarthy et al., 2007</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>72</td>
<td>2.19 (1.34–3.57)</td>
<td>0.003</td>
<td>0.00</td>
<td>Schneider, 1949; Jennett, 1956; Malloch, 1965; Knudsen, 1967; McLaren &amp; Bailey, 1986; Liebergall et al., 1989; Šulla, 1996; Buchner &amp; Schiltenwolf, 2002</td>
</tr>
<tr>
<td>Poor</td>
<td>12</td>
<td>4.35 (0.71–26.57)</td>
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<td>16.08</td>
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<td>1.58 (0.40–6.27)</td>
<td>0.5</td>
<td>62.18</td>
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<tr>
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<td>5.82 (1.57–21.56)</td>
<td>0.008</td>
<td>0.00</td>
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<td>55.47</td>
<td>McLaren &amp; Bailey, 1986; Radulović et al., 2004; Šulla, 1996; Shapiro, 2000; McCarthy et al., 2007</td>
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<td>1.09 (0.40–2.98)</td>
<td>0.9</td>
<td>0.00</td>
<td>Jennett, 1956; McLaren &amp; Bailey, 1986; Šulla, 1996; Buchner &amp; Schiltenwolf, 2002</td>
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Language Restrictions. With no language restrictions, the RR for a Fair/Poor result was 1.85 (95% CI: 1.01–3.39) at the 24-hour breakpoint. The English-only RR at 24 hours was 3.02 (95% CI: 1.40–6.53). The RR for the unrestricted meta-analysis at the 48-hour breakpoint was 2.09 (95% CI: 0.83–5.24) with a probability value of 0.1 and high heterogeneity. The English-only meta-analysis yielded an RR of 4.49 (95% CI: 1.80–11.18) with a probability value of 0.001 and virtually no heterogeneity (Table 5).

Publication Bias. Explorations using funnel plots and the “trim and fill” method suggested possible publication bias for a Fair/Poor outcome at the 12-, 24-, 48-, and 72-hour breakpoints (Table 6). A formal test by means of the Egger regression method supported the evidence of bias. (Fig. 2.)
Timing of surgery in cauda equina syndrome

**FIG. 3.** Forest plot for meta-analysis of the RR of obtaining a Fair/Poor outcome of urinary function in CESR patients compared with CESI patients.

Publication bias at the 48-hour (p = 0.02) and 72-hour (p = 0.03) breakpoints for a Fair/Poor result, but not at the 12-hour (p = 0.3), 24-hour (p = 0.2), or 36-hour (p = 0.3) breakpoints. There was evidence of publication bias for a Poor result at the 48-hour breakpoint (p = 0.08, Egger regression).

Meta-analysis is particularly subject to publication bias because studies that do not produce results reaching levels of statistical significance are less likely to be published. Studies that are “...not coherent with current prevailing paradigms or a body of knowledge” also fall into this category. There is debate, however, concerning the accuracy of the operations used to test for publication bias. Sources of heterogeneity other than publication bias, such as differences in study design and execution, can also contribute to asymmetry in the funnel plot.

**Best-Evidence Synthesis**

Our best-evidence synthesis analyzed the studies of McCarthy et al., Radulović et al., Shapiro, and Šulla for a “Fair/Poor” result at the 24- and 48-hour breakpoints (Table 7).

The authors of all 4 of these studies advocate emergency surgery for CES. All 4 studies indicated which of the patients in the study population had CESR. Involved levels were not documented by Shapiro or Šulla. Neither the patients of McCarthy and colleagues nor those of Radulović and colleagues had involved levels superior to L2–3, nor did either group include patients with involvement of multiple vertebral levels. Shapiro noted the presence of “lumbar spondylotic stenosis” in association with a disc herniation in 8 of his 44 cases. McCarthy et al. excluded patients with stenosis at the involved level and the authors of the other 2 studies did not mention stenosis. McCarthy and colleagues do not indicate the degree of experience possessed by the operating surgeon. Shapiro performed the surgery in 30 of the 44 cases he studied, and Šulla personally performed the surgical procedures in most of his cases (I. Šulla, personal communication, 2006). Nikolić indicated that none of the operations in the case series reported by Radulović and colleagues were

**TABLE 4**

Potential confounding factors leading to heterogeneity across studies*

<table>
<thead>
<tr>
<th>Epidemiological factors</th>
<th>CESR vs CESI onset</th>
<th>Clinical picture</th>
<th>Periop &amp; postop support</th>
<th>Pathological features</th>
<th>Surgical procedure</th>
<th>Urinary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, sex, location of study, cultural factors</td>
<td>Specificity of separating groups, variation of preop urinary function</td>
<td>Different combinations of motor deficits, sensory deficits, saddle anesthesia, bladder &amp; anal sphincter impairment, sexual dysfunction</td>
<td>Diagnostic studies available (myelography, CT, MRI), preop corticosteroids administered or not, preop opioids &amp; effect on bladder function, surgeon (experienced spine surgeon or inexperienced surgeon), experienced surgical team, postop rehabilitation (bladder/bowel training, gait training, sexual counseling, chronic pain management &amp; effect on bladder/bowel function)</td>
<td>HNP, HNP w/ stenosis, level(s) involved (multiple levels, compromise of conus medullaris at T12–L1 &amp; L1–2), configuration of herniation (central, posterolateral, intrathecal, posterior migration), arachnoiditis present or absent, degree of cross-sectional canal compromise, degree of cauda equina edema</td>
<td>Laminectomy with or without partial facetectomies, interlaminar approach, unilaminal approach, excision of intrathecal disc herniation, transdural excision of epidural herniation, intradural exploration of cauda equina</td>
<td>Adequacy of description, pre- &amp; postop UDS, duration of preop bladder distention (myogenic decompensation), postop rehabilitation</td>
</tr>
</tbody>
</table>

* CT = computed tomography; FU = follow-up; HNP = herniated nucleus pulposus; LBP = low back pain; MRI = magnetic resonance imaging; UDS = urodynamic study.
performed by residents (I. Nikolić, personal communication, 2007). The operation performed was a full laminectomy in almost all the cases studied by Shapiro and ˘Sulla and in 34% of the cases reported by Radulović et al. McCarthy and colleagues did not document the actual surgery performed. None of the studies of Radulović et al., Shapiro, or ˘Sulla included an intradural approach (I. Nikolić, personal communication, 2007; I. ˘Sulla, personal communication, 2007). McCarthy et al. did not comment on this point. Formal postoperative urodynamic evaluation or systematic determination of postvoiding residual urine volume was performed in very few of the cases in any of the studies. It appears that the assessment of the outcome of urinary function in all 4 studies depended primarily on the patient’s perception of his or her urinary status and on the patient’s report of whether or not he or she had to strain to initiate or complete urination.

This analysis does not answer the question of why Shapiro’s results were much better for early surgery but worse for late surgery compared with the other studies. At the 48-hour breakpoint the risks of Fair/Poor urinary outcome with early surgery were 19, 57, 5, and 33% for McCarthy et al.,93 Radulović et al.,120 Shapiro, and ˘Sulla,157 respectively. For later surgery their respective risks for a Fair/Poor outcome were 50, 19, 63, and 33%, respectively. It is possible that some of Shapiro’s patients with Fair/Poor results might have experienced further improvement with more time, since the residual effects of CES can take years to improve, but Shapiro’s mean follow-up time was 5.3 years.

**Discussion**

Meta-analysis is a complex multiple-step process. Metaanalytic software takes variations across studies into account and weights each study appropriately.36,38,148–150 Egger and Davey Smith describe the process well.36,38,148–150 There is discussion in the literature concerning the validity of meta-analysis of observational (nonexperimental) studies.34,45,55,117,139,140,142,150,154,172 Black,14 among others,24,69,135 discusses the limitations of RCTs and the complementary roles that RCTs and observational studies play in evalu-

---

**TABLE 5**

<table>
<thead>
<tr>
<th>Breakpoint &amp; Language Restriction</th>
<th>RR (95% CI)</th>
<th>p Value</th>
<th>Q Value</th>
<th>I^2</th>
<th>Studies w/ Estimable RRs (used in meta-analysis)</th>
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<td>24-hr breakpoint</td>
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<tr>
<td>no restriction</td>
<td>1.85 (1.01–3.39)</td>
<td>0.045</td>
<td>9.59</td>
<td>6.13</td>
<td>Malloch, 1965; McLaren &amp; Bailey, 1986; Liebergall et al., 1989; Dinning &amp; Schaeffer, 1993; Šulla, 1996; Shapiro, 2000; Henriques et al., 2001; Buchner &amp; Schiltenwolf, 2002; Mangialardi et al., 2002; McCarthy et al., 2007</td>
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<td>English only</td>
<td>3.02 (1.40–6.53)</td>
<td>0.005</td>
<td>5.65</td>
<td>0.00</td>
<td>Malloch, 1965; McLaren &amp; Bailey, 1986; Dinning &amp; Schaeffer, 1993; Shapiro, 2000; Henriques et al., 2001; Buchner &amp; Schiltenwolf, 2002; Mangialardi et al., 2002; McCarthy et al., 2007</td>
</tr>
<tr>
<td>48-hr breakpoint</td>
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<td></td>
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<tr>
<td>no restriction</td>
<td>2.09 (0.83–5.24)</td>
<td>0.1</td>
<td>17.21</td>
<td>65.12</td>
<td>Malloch, 1965; McLaren &amp; Bailey, 1986; Liebergall et al., 1989; Šulla, 1996; Radulović et al., 2004; Shapiro, 2000; McCarthy et al., 2007</td>
</tr>
<tr>
<td>English only</td>
<td>4.49 (1.80–11.18)</td>
<td>0.001</td>
<td>1.9</td>
<td>0.00</td>
<td>Malloch, 1965; McLaren &amp; Bailey, 1986; Shapiro, 2000; McCarthy et al., 2007</td>
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</tbody>
</table>

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**TABLE 6**

<table>
<thead>
<tr>
<th>Event Outcome</th>
<th>Breakpoint (hrs)</th>
<th>Original CMA Analysis</th>
<th>Results of Trim &amp; Fill Analysis</th>
<th>Egger Regression</th>
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<tr>
<td></td>
<td></td>
<td>RR (95% CI)</td>
<td>p Value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>12</td>
<td>1.77 (0.51–6.15)</td>
<td>0.4</td>
<td>0.82 (0.21–3.26)</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>24</td>
<td>1.85 (1.01–3.39)</td>
<td>0.045</td>
<td>1.48 (0.74–2.95)</td>
</tr>
<tr>
<td>Fair/Poor</td>
<td>36</td>
<td>2.11 (0.69–6.41)</td>
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<td>2.11 (0.69–6.41)</td>
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<tr>
<td>Fair/Poor</td>
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<td>2.09 (0.83–5.24)</td>
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<td>1.22 (0.52–2.90)</td>
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<tr>
<td>Fair/Poor</td>
<td>72</td>
<td>2.19 (1.34–3.57)</td>
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<td>1.82 (1.18–2.82)</td>
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<tr>
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<td>4.35 (0.71–26.57)</td>
<td>0.1</td>
<td>4.35 (0.71–26.57)</td>
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<tr>
<td>Poor</td>
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<td>1.58 (0.40–6.27)</td>
<td>0.5</td>
<td>1.58 (0.40–6.27)</td>
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<tr>
<td>Poor</td>
<td>36</td>
<td>5.82 (1.57–21.56)</td>
<td>0.008</td>
<td>ND*</td>
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<tr>
<td>Poor</td>
<td>48</td>
<td>2.26 (0.54–9.45)</td>
<td>0.3</td>
<td>2.26 (0.54–9.45)</td>
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<tr>
<td>Poor</td>
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<td>1.09 (0.40–2.98)</td>
<td>0.9</td>
<td>1.09 (0.40–2.98)</td>
</tr>
</tbody>
</table>

* Only 2 studies; analysis could not be performed. Abbreviations: NA = not applicable; ND = not done.
ing the effectiveness of health care. The MOOSE group has advanced criteria for the construction of meta-analyses from observational studies.

The overwhelming number of opinions expressed in the world literature regarding the urgency of surgery for CES precludes setting up an RCT to study surgical timing in CES, because “equipoise” is lacking. Equipoise is the condition that exists when the participants in a proposed RCT have no preference among the treatment options. Without equipoise, an RCT cannot ethically be run. Therefore, we are stuck with observational cohort studies regarding CES and its appropriate treatment, which constitute, by definition, Level III evidence.

There is uncertainty over how exhaustive the search for articles must be when embarking on a meta-analysis. Egger and colleagues have studied the question of whether or not exhaustive studies produce enough of an increment of reliability to be worth the time and expense. They concluded that it is more worthwhile to put one’s resources into assessing the quality of the included studies, rather than into laborious and tedious searches for obscure publications. In a study of meta-analyses with and without language restrictions, Grégoire et al. noted little change in results when non-English articles were added to the meta-analyses that they analyzed, although they caution that even a small change that converts a nonsignificant result to a significant one may alter the impact of a study. The elimination of non-English articles from our current study would have had an important impact on our results (Table 5).

Gleave and Macfarlane believe that the issue of whether or not earlier surgery bestows a significant benefit on patients with CES has been clouded by studies that analyze
CESR and CESI cases together, since patients with CESI generally tend to do better with surgery than do those with CESR. They concluded this was the case in the studies of 3 of the authors whose studies we analyzed in this current paper.5,30,51,112,113 This conclusion, however, reflects a misinterpretation of the data from these studies. Dinning and Schaeffer50 separate out their cases of CESR;30,50 Shapiro’s 44 patients all had CESR by definition; and in the study of Kennedy et al.,73 of 19 patients had CESR and the other 7 had CESI (their CESR cases can be separated from the CESI cases using a 36-hour breakpoint). Our meta-analysis of CESI and CESR cases supports Gleave and Macfarlane’s view in regard to the issue of not grouping CESI and CESR cases together. We found an RR of 2.58 (95% CI 0.59–11.31) for a Fair/Poor result for CESR compared with CESI cases, although this result is not statistically significant.

However, the definition of CESI is itself extremely cloudy in the literature—there are numerous studies that demonstrate bladder involvement without full-blown CES in cases of disc herniation and/or spinal stenosis, and there is no indication in the literature concerning which, if any, of these studies might have progressed to full-blown CES had they been left unattended.5,12,28,39,40,43,44,53,56,77,84,95,105,116,125,128,143,159,163 We attempted to follow the advice of Gleave and Macfarlane and perform meta-analyses only on those studies in which we could, with reasonable confidence, separate cases of CESR and CESI (or more exactly “non-CESR”).

The reasons for the moderate or high heterogeneity across 4 of 10 meta-analyses are not clear from the data available. It seems likely, although not proven, that surgical results are related to the experience of the surgeon and to the operation performed. Perhaps patients with CES need more aggressive decompression. It is interesting that in 1929 Dandy 26 described 2 patients with severe CESR, of at least 1 and 3 weeks’ preoperative duration, in whom bladder function recovered postoperatively in 2 weeks and 10 days, respectively. In both patients the dura mater had been opened and the herniated disc removed transdurally.

Schneider reported 2 cases of CESR from herniated discs in the lumbar region. In Case 2, after removing the herniated disc, he opened the dura and inspected the cauda equina: “. . . a few cauda equina roots showed a reddish-purple discoloration but otherwise there was no abnormality. Spinal fluid flowed freely, and, since the cauda equina did not appear markedly swollen, the dura was closed tightly.”134 Jennett reports opening the dura in a number of his cases, as do others.107 It is unusual these days to open the dura in the course of removing a herniated disc or performing decompression in patients with spinal stenosis, but a markedly swollen cauda equina might benefit from expansion of the intradural volume with a dural graft. Perhaps this issue should be revisited.

Emergency surgical treatment of cauda equina compression is supported by the fact that deleterious changes occur in the spinal cord itself soon after the onset of cauda equina compression.24,30,51,112,113,158 Marsala et al.53 demonstrated the development of nitric oxide synthase immunoreactivity in neurons of the dorsal horn and elsewhere in the spinal cord 2 days after multiple cauda equina constrictions in a dog model.

Autologous nucleus pulposus induces inflammatory and possibly immunological changes in adjacent spinal nerve roots, dorsal root ganglion, and nerve roots intradurally in the cauda equina.20,21,28,99,108–110,146,165 It seems logical that early surgery to remove the offending herniated disc material would offer at least some measure of protection against these changes.

In peripheral nerve injury, the concepts of metabolic conduction block, neuropraxia, axonotmesis, and neurotmesis are well-developed.85 These concepts generally hold true for spinal nerve roots as well, although there are major structural and vascular differences between the spinal roots and peripheral nerves.107 If surgery is performed early, compression on the cauda equina may be relieved while the nerves are still in the stage of metabolic conduction block or neuropraxia. Nerve impairment will ultimately reach the point of irreversibility through direct mechanical pressure, the development of progressive edema through pressure or venous occlusion, or impairment of nutrition by vascular occlusion or interference with the diffusion of nutrients from the cerebrospinal fluid.75,107,111,110,131 Once axonotmesis of the sensory roots has occurred, regeneration is unlikely and the sensory side of the reflex arc subserving bladder emptying will be absent. Progress is being made, however, in encouraging sensory axons to bridge the dorsal root entry zone and become established in the central nervous system environment of the spinal cord.1,2,24,26,136,155,167,175 Since we do not know, in an individual patient, when axonotmesis will occur or when deleterious spinal cord plasticity will become permanent and we cannot yet produce reliable regeneration of sensory axons into the central nervous system, it seems reasonable to relieve cauda equina compression as soon as possible.

Since the RR of the meta-analysis at each of our 10 breakpoint/outcome combinations indicates a favorable effect for earlier surgery on the outcome of urinary function in patients with CESR, the results of our study suggest that Gleave and Macfarlane are incorrect in drawing the conclusion that surgical timing has no effect on urinary function once the bladder is paralyzed and insensate. They do have a point, of course, that it makes no sense to do emergency surgery for CES unless an experienced surgeon and adequate operative support are available. It does, however, make sense to bring the patient and an appropriate surgical team together on an urgent basis and proceed with surgery as soon as possible.

We urgently need a multicenter study of CES with oversight and registration of the cases, carefully defining and separating CESI and CESR cases, to bring focus to the issues raised by Gleave, Macfarlane, Shapiro, Sulla, and all the other authors who have thus far contributed to the currently diffuse field of CES literature.

Conclusions

The findings of this study support early surgery for CES and indicate that patients with CESR and those with CESI should not be combined in a single study analyzing the results of surgical timing in regard to urinary outcome.

Appendix

Please see pp 315–316.
**APPENDIX**

Raw data for meta-analysis of outcome of urinary function, with individual probability values for each study calculated for Fair/Poor vs Normal and for Poor vs Normal/Fair

<table>
<thead>
<tr>
<th>Breakpoint</th>
<th>Authors &amp; Year</th>
<th>Timing of Surgery (hr)</th>
<th>Urinary Function Outcome</th>
<th>p Value</th>
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<td>Shapiro, 2000</td>
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<td>15</td>
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(continued)
APPENDIX (continued)

Raw data for meta-analysis of outcome of urinary function, with individual probability values for each study calculated for Fair/Poor vs Normal and for Poor vs Normal/Fair

<table>
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<tr>
<th>Breakpoint</th>
<th>Authors &amp; Year</th>
<th>Timing of Surgery (hr)</th>
<th>Urinary Function Outcome</th>
<th>p Value</th>
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* Fisher exact test.
† Chi-square.

Disclaimer

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