Systematic review of outcome parameters following treatment of chronic exertional compartment syndrome in the lower leg

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Objective: Surgery is the gold standard in the management of chronic exertional compartment syndrome (CECS) of the lower extremity, although recent studies also reported success following gait retraining. Outcome parameters are diverse, and reporting is not standardized. The aim of this systematic review was to analyze the current evidence regarding treatment outcome of CECS in the lower leg.

Material and Methods: A literature search and systematic analysis were performed according to the PRISMA criteria. Studies reporting on outcome following treatment of lower leg CECS were included.

Results: A total of 68 reports fulfilled study criteria (n = 3783; age range 12-70 year; 7:4 male-to-female ratio). Conservative interventions such as gait retraining (n = 2) and botulinum injection (n = 1) decreased ICP ($\overline{x}$ = 68 mm Hg to $\overline{x}$ = 32 mm Hg) and resulted in a 47% ($\pm$42%) rate of satisfaction and a 50% ($\pm$45%) rate of return to physical activity. Fasciotomy significantly decreased ICP ($\overline{x}$ = 76 mm Hg to $\overline{x}$ = 24 mm Hg) and was associated with an 85% ($\pm$13%) rate of satisfaction and an 80% ($\pm$17%) rate of return to activity. Return to activity was significantly more often achieved (P < .01) in surgically treated patients, except in one study favoring gait retraining in army personnel.

Conclusion: Surgical treatment of CECS in the lower leg results in higher rates of satisfaction and return to activity, compared to conservative treatment. However, the number of studies is limited and the level of evidence is low. Randomized controlled trials with multiple treatment arms and standardized outcome parameters are needed.

Keywords: chronic exertional compartment syndrome, conservative treatment, fasciotomy, lower extremity, systematic review

1 | INTRODUCTION

Chronic exertional compartment syndrome (CECS) may affect muscle compartments mostly of the lower limb and is characterized by a sensation of tightness and pain during or after performing repetitive physical activity. Symptoms are likely the result of a mismatch between swelling of muscular tissue within a relatively noncompliant fascia, leading to supranormal intracompartmental pressures (ICP). However, strong evidence supporting this hypothesized pathogenetic mechanism of CECS is currently lacking.1

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The diagnosis of CECS is often delayed as familiarity with the disorder among physicians is limited. Moreover, clues in patient history or physical examination in patients possibly suffering from CECS are not universally accepted. The diagnostic gold standard is invasive needle or catheter manometry that can provide values of ICP before, during, and after provocative exercise. However, the validity of these ICP measurements is seriously doubted and cutoff criteria (Box 1) are questioned.\textsuperscript{2-10} As a consequence of all these uncertainties, diagnostic delay in CECS can be unacceptably long.

Once CECS is diagnosed, intervention is advised as its natural course is not beneficial.\textsuperscript{7} Conservative therapy may entail cessation of provocative physical activity, therapeutic massage, taping, stretching, or strengthening. In addition, gait retraining and shoe modifications may be tried.\textsuperscript{11,12} Surgical intervention entails opening of the enveloping fascia via a fasciotomy using an open, a minimally invasive, or an endoscopic technique.\textsuperscript{12-14}

Traditionally, management of CECS starts with conservative measures, followed by surgical intervention in case of treatment failure or severely disabling symptoms.\textsuperscript{31} This sequence is merely based on clinical experience; a surgery first approach, or a combination of surgery and conservative measures, might also be beneficial.

Apart from clinical therapeutic considerations, presentation of treatment outcome in scientific literature is far from standardized. Commonly used outcome measures are return to physical activity, improvement of symptoms or patient-reported satisfaction, though applied methodologies often vary. At present, clinical outcome seems largely dependent on population characteristics, in particular military versus civilian athletes.\textsuperscript{12,15-17} In addition, outcome measures may even differ between military and civilian athletes; for example, the Single Assessment Numeric Evaluation (SANE) score\textsuperscript{18} is a validated single question instrument increasingly applied in military populations, yet rarely used with civilian patients. Conversely, these factors do influence whether a conservative or surgical approach is preferred.

A systematic review focusing on outcome following various treatments for CECS in the lower leg is currently not available. The aim of this systematic review is to analyze the current evidence regarding the most commonly reported treatment outcomes of CECS in the lower leg. Results of this review may aid in proposing a standardized report for treatment outcome regarding CECS in future research.

\section{2 | MATERIALS AND METHODS}

\subsection{2.1 | Search strategy}

The search strategy and systematic analysis were performed according to the PRISMA statement methodology. A search was conducted in PubMed, EMBASE, Web of Science, Cochrane, CENTRAL, and Emscare. Key words used included “chronic exertional compartment syndrome,” “anterior compartment,” “posterior compartment,” “peroneal compartment,” “exertional leg pain,” “medial tibial pain,” “overuse injuries,” “therapy,” “surgical treatment,” and “conservative treatment.” All related MeSH terms, synonyms, and plurals were entered. Language was restricted to English and Dutch. Studies published between January 1, 1970, and May 1, 2019, were selected. In addition, relevant publications that were found outside this strategy were manually added, based on opinions of experts in the field.

\subsection{2.2 | Inclusion criteria}

Clinical studies with fully available text including at least five subjects diagnosed with CECS of the lower leg were considered. The diagnosis was based on a suggestive history and physical examination in the presence of elevated ICP values. Outcome following a conservative and/or surgical intervention was reported as drop in ICP values, complication rate, or recurrence rates. Moreover, studies using patient-reported outcome measures such as return to activity, satisfaction, Lower Leg Outcome Survey (LLOS),\textsuperscript{19} or the SANE,\textsuperscript{18} which numerically scores functioning of affected joints or other sections of the leg, were also included. The commonly encountered, yet heterogeneous outcome variable patient satisfaction was summarized dichotomously, using the categories “satisfied and/or improvement of symptoms” or “very satisfied and/or free of symptoms.”

\subsection{2.3 | Exclusion criteria}

Studies concerning acute compartment syndrome, compartment syndrome secondary to a condition other than repetitive physical activity, or a compartment syndrome in body parts other than the lower leg were excluded. Moreover, papers on combinations of CECS with medial tibial stress syndrome (MTSS) or popliteal artery entrapment syndrome were not considered, as were...
FIGURE 1  Flow chart of selected studies.
| Author               | Design | Level of Evidence | patients (n) | Patient population? | Male/Female | µ age in year (min-max) | Affected compartments | µ duration symptoms in months (min-max) | n conservative patients/n surgical patients |
|----------------------|--------|-------------------|--------------|---------------------|-------------|------------------------|------------------------|------------------------------------------|-------------------------------------------|
| Akermark et al⁴²      | R      | 4                 | 30           | C                   | 19/11       | 23 (15-36)            | DP                     | -                                         | -/30                                      |
| Ali et al³⁴           | P      | 4                 | 20           | -                   | -           | -                     | A                      | -                                         | -/46                                      |
| Allen & Barnes⁴³      | P      | 4                 | 110          | C                   | 86/24       | - (12-44)             | A, DP                  | -                                         | -/110                                     |
| Baliani et al⁴⁴       | P      | 4                 | 7            | C                   | -           | 26 (18-34)            | A                      | -                                         | -/7                                       |
| Beck et al⁴⁵          | R      | 4                 | 135          | C                   | -           | -                     | A, L, DP, SP            | -                                         | -/135                                     |
| Biedert & Marti²⁹     | R      | 4                 | 15           | C                   | 14/1        | 29 (-)                | DP                     | 54 (12-180)                             | -/15                                      |
| Blackman et al⁴⁶      | P      | 4                 | 7            | C                   | 6/1         | 25 (21-29)            | A                      | -                                         | 7/-                                       |
| Breen et al²¹         | P      | 4                 | 10           | C                   | 9/1         | 31 (-)                | -                      | -                                         | 10/-                                      |
| Cook & Bruce⁴⁷        | R      | 4                 | 14           | M                   | 10/4        | 27 (22-38)            | A, L, DP, SP            | 63 (6-120)                              | -/14                                      |
| de Brujin et al⁴⁸     | P      | 4                 | 14           | C                   | 5/9         | 26 (18-48)            | A                      | - (6-240)                               | -/14                                      |
| de Fijter et al³³     | R      | 4                 | 72           | C + M               | 65/7        | 21 (18-37)            | A                      | -                                         | -/72                                      |
| Detmer et al³⁹        | R      | 4                 | 100          | C                   | 51/49       | 26 (-)                | A, L, DP, SP            | 22 (-)                                  | -/100                                     |
| Dieball et al¹⁹       | P      | 4                 | 10           | M                   | 8/2         | 20 (-)                | A, L                   | -                                         | 10/-                                      |
| Drexler et al⁵⁰       | R      | 4                 | 53           | C                   | 49/4        | 24 (16-43)            | A, L                   | 22 (1-120)                              | -/53                                      |
| Edmundsson et al³¹    | P      | 4                 | 18           | C                   | 8/10        | 36 (16-65)            | -                      | 31 (6-180)                              | -/18                                      |
| Finestone et al²      | R      | 4                 | 36           | C + M               | -           | 24 (16-54)            | A                      | -                                         | -/36                                      |
| Fronek et al²⁵        | R      | 4                 | 18           | C                   | 8/10        | 24 (12-43)            | A, L                   | -                                         | 5/13                                      |
| Garcia-Mata et al³     | R      | 4                | 23           | C                   | 10/13       | 16 (14-18)            | A, L, DP, SP            | 24 (7-72)                               | -/23                                      |
| Gatenby et al⁵²       | R      | 4                 | 20           | C                   | 8/12        | 28 (16-50)            | A, L                   | 32 (1-131)                              | -/20                                      |
| Helmhout et al³¹      | P      | 3                 | 19           | M                   | 18/1        | 25 (19-53)            | -                      | -                                         | 19/-                                      |
| Helmhout et al³³      | P      | 4                 | 6            | M                   | 6/0         | 21 (18-27)            | -                      | - (6-36)                                | 6/-                                       |
| Howard et al⁵⁴        | R      | 4                 | 39           | C                   | 14/25       | 32 (-)                | A, L, DP, SP            | -                                         | -/39                                      |
| Irion et al⁵⁵         | R      | 4                 | 13           | C                   | 6/7         | 20 (17-24)            | A, L, DP, SP            | - (0-4)                                 | -/13                                      |
| Islam & Robbs.³⁹      | P      | 3                 | 120          | C                   | 86/34       | 28 (18-53)            | A, L, DP, SP            | 42 (12-72)                              | -/120                                     |
| Isner-Horobeti et al²² | R      | 4                 | 16           | C + M               | 13/3        | 23 (18-36)            | A, L                   | 40 (4-240)                              | -/16                                      |
| Jarvinnen et al⁵⁶     | R      | 4                 | 34           | C                   | 26/8        | 24 (15-41)            | DP                     | 18 (3-60)                               | -/34                                      |
| Lohrer & Nauck.⁵⁷     | R      | 4                 | 17           | C                   | 8/9         | 24 (14-43)            | A, L, DP               | 38 (6-360)                              | -/17                                      |
| Maffulli et al⁵⁸      | P      | 4                 | 18           | C                   | 12/6        | 27 (18-35)            | A, L                   | 17 (5-31)                               | -/18                                      |
| Maher et al⁵⁹         | R      | 4                 | 21           | C                   | 5/16        | 25 (-)                | -                      | 15 (-)                                  | -/21                                      |
| McCallum et al⁶⁰      | R      | 4                 | 46           | M                   | 38/8        | 30 (19-50)            | A, L, DP, SP            | -                                         | -/46                                      |
| Micheli et al³⁶       | R      | 4                 | 47           | C                   | -           | 17 (14-21)            | A, L, DP, SP            | 15 (-)                                  | -/47                                      |
| Moeyersoons et al⁶¹    | R      | 4                 | 100          | C                   | 81/19       | 14 (-)                | -                      | 24 (-)                                  | -/100                                     |
| Conservative | Surgical | μ Follow-up in months (min-max) | Outcome measurements used |
|--------------|----------|---------------------------------|--------------------------|
|              | Intervention(s) |                                   |                          |
|              | Open       | 34 (6-85)                        | ICP Patient satisfaction | Return to activity | SANE LLOS Complications (in %) | Recurrence (in %) | Reoperations (in %) |
| PT           | ES         | 6 (-)                           | N Y Y N N N              | -                  | -                              | -                  |
|              | MI         | -                               | Y N Y N N N              | 0                  | 1                              | -                  |
|              | MI         | 25 (12-38)                      | N N Y N N N              | -                  | -                              | -                  |
|              | MI         | 25 (6-28)                       | N N Y N N N              | 11.2               | -                              | 19                 |
|              | Open, MI & ES | 27 (8-72)                     | N Y N N N N              | -                  | -                              | -                  |
|              | MI         | 12 (-)                          | N Y N N N N              | -                  | -                              | -                  |
|              | MI         | 37 (11-90)                      | N Y N N N N              | 11.1               | 3.7                            | 3.7                |
|              | MI         | 21 (16-25)                      | N Y Y N N N              | 3.6                | -                              | -                  |
|              | MI         | 62 (-)                          | N N Y N N N              | 18                 | 2                              | 2                  |
|              | Open & MI | 5 (0-47)                        | N Y Y N N N              | 7.7                | 3.4                            | 3.4                |
|              | MI         | 50 (5-98)                       | N Y N N N N              | 16.8               | 8.4                            | -                  |
|              | Open       | 12 (-)                          | N Y N N N N              | 10.5               | -                              | -                  |
|              | -          | 116 (-)                         | N N N N N N              | 4.9                | -                              | 1.6                |
| AM           | Open       | 50 (-)                          | Y Y Y N N N              | 10                 | -                              | 5                  |
|              | Open       | 58 (12-84)                      | Y Y Y Y N N N            | 2.3                | 0                              | 2.3                |
|              | Open       | -                               | N N Y N N N              | 5.6                | 5.6                            | 2.8                |
|              | GR         | 4 (-)                           | Y N N Y Y Y              | -                  | -                              | -                  |
|              | GR         | 9 (-)                           | N N N Y Y Y              | -                  | -                              | -                  |
|              | Open       | 185 (-)                         | N Y Y N N N              | 13                 | -                              | 6                  |
|              | Open       | 11 (2-60)                       | N N Y N N N              | 7.7                | 31                             | 7.7                |
|              | Open       | 12 (-)                          | N Y N N N N              | 11                 | 0.5                            | 0.5                |
| BI           | -          | 4 (3-9)                         | Y Y Y Y N N N            | -                  | -                              | -                  |
|              | Open       | - (12-120)                      | N Y N N N N              | 9                  | 6                              | 6                  |
|              | ES         | 47 (5-84)                       | N Y Y N N N              | 10.5               | 0                              | 5.3                |
|              | MI         | 8 (5-12)                        | N Y Y N N N              | 14.8               | 0                              | -                  |
|              | Open       | 213(32-329)                     | N N Y N N N              | -                  | -                              | -                  |
|              | -          | 26 (8-51)                       | N Y Y Y N N              | 20                 | -                              | 1.4                |
|              | MI         | 50 (3-162)                      | N Y Y N N N              | -                  | -                              | -                  |
|              | Open       | -                               | N Y Y N N N              | -                  | -                              | -                  |

(Continues)
| Author                | Design | Level of Evidence | patients (n) | Patient population? | Male/ Female | µ age in year (min-max) | Affected compartments | µ duration symptoms in months (min-max) | n conservative patients/ n surgical patients |
|-----------------------|--------|-------------------|--------------|---------------------|--------------|------------------------|------------------------|----------------------------------------|---------------------------------------------|
| Mouhsine et al62      | R      | 4                 | 18           | C                   | 10/8         | 25 (19-38)             | A, L                   | -                                      | -/18                                        |
| Orlin et al63         | R      | 4                 | 37           | C                   | 17/20        | 37 (-)                 | A, L, DP, SP           | -                                      | -/37                                        |
| Packer et al26        | R      | 3                 | 100          | C                   | 32/68        | 26 (-)                 | -                      | 27/73                                 |                                             |
| Pandya & Ganley.64    | R      | 4                 | 6            | C                   | -            | - (15-17)              | A, L                   | -                                      | -/6                                         |
| Pasic et al65         | R      | 4                 | 46           | C                   | 23/23        | 30 (16-57)             | A, L, DP, SP           | 48 (0-252)               | -/46                                        |
| Puranen & Alavaikko.66| R      | 4                 | 24           | C                   | 11/13        | 29 (16-63)             | A, DP                  | -                                      | -/24                                        |
| Qvarfordt et al34     | R      | 4                 | 15           | C                   | 8/7          | 29 (17-50)             | A, L                   | 36 (5-108)               | -/15                                        |
| Raikin et al155       | R      | 4                 | 16           | C                   | 6/10         | 25 (14-50)             | A, L, DP               | 30 (7-72)                | -/16                                        |
| Reneman.36            | R      | 4                 | 61           | C + M               | 58/3         | 21 (18-57)             | A, L                   | -                                      | -/61                                        |
| Rettig et al67        | R      | 4                 | 12           | C                   | 1/11         | 21 (15-30)             | A, L, DP               | 17 (1-36)                | -/12                                        |
| Roberts et al68       | R      | 4                 | 98           | M                   | 88/10        | 28 (-)                 | A                      | -                                      | -/98                                        |
| Rorabeck et al69      | R      | 4                 | 12           | C                   | 9/3          | 21 (18-26)             | A, L, DP, SP           | 11 (5-18)                | -/12                                        |
| Rorabeck et al70      | R      | 4                 | 25           | C                   | 14/11        | 22 (-)                 | A, L, DP               | - (12-84)                | -/25                                        |
| Schepsis et al71      | P      | 4                 | 20           | C                   | 8/12         | 23 (16-37)             | A, L                   | - (4-30)                 | -/20                                        |
| Schepsis et al37      | R      | 4                 | 28           | C                   | 15/13        | - (15-39)              | A, L, DP               | - (2-30)                 | -/28                                        |
| Sebik & Dogan38       | P      | 4                 | 6            | C                   | 4/2          | 28 (-)                 | A                      | -                                      | -/6                                         |
| Simpson et al4        | R      | 4                 | 41           | M                   | -            | -                      | A                      | 40 (9-110)               | -/41                                        |
| Singh et al72         | R      | 4                 | 15           | C + M               | 13/2         | 31 (20-43)             | A, L, DP, SP           | -                                      | -/15                                        |
| Simmon et al73        | R      | 3                 | 62           | C                   | 27/35        | 26 (-)                 | -                      | 30 (2-300)               | -/62                                        |
| Styf & Korner.74      | R      | 4                 | 19           | C                   | 14/5         | 26 (17-51)             | A                      | 30 (10-84)               | -/19                                        |
| Sudmann.75            | R      | 4                 | 29           | C + M               | 11/18        | - (14-70)              | A                      | - (1-120)                | -/29                                        |
| Takebayashi et al76   | R      | 4                 | 9            | C                   | 6/3          | 22 (18-24)             | A, L, DP, SP           | -                                      | -/9                                         |
| Thein et al31         | R      | 4                 | 55           | C                   | 36/7         | 24 (-)                 | A                      | -                                      | 12/43                                       |
| Turnipseed.5          | R      | 4                 | 796          | C                   | 279/517      | -                      | A, L, DP, SP           | -                                      | -/796                                       |
| van den Brand et al30 | P      | 3                 | 10           | C + M               | 8/2          | 23 (-)                 | A                      | -                                      | -/10                                        |
| van den Brand et al77 | P      | 3                 | 42           | M                   | -            | -                      | A                      | -                                      | -/42                                        |
| van der Wal et al37   | R      | 4                 | 12           | M                   | 11/1         | 30 (-)                 | A                      | 50 (-)                   | 12/6                                         |
| van Zantvoort et al38 | R      | 4                 | 30           | C                   | 14/16        | 29 (17-65)             | A, L, DP, SP           | -                                      | -/30                                        |
| van Zoest et al77     | R      | 4                 | 46           | C                   | 19/27        | 35 (-)                 | DP                     | -                                      | 19/27                                       |
| Verleisdonk et al68   | P      | 4                 | 53           | C + M               | 47/6         | - (18-41)              | A                      | 24 (-)                   | 3/50                                         |
| Verleisdonk et al28   | R      | 4                 | 81           | C + M               | 77/4         | 24 (18-54)             | A, L                   | 6 (1-60)                 | -/81                                        |
| Waterman et al79      | R      | 4                 | 611          | M                   | 561/50       | 28 (-)                 | A, L, DP, SP           | -                                      | -/611                                       |
| Winkes et al80        | P      | 4                 | 52           | C                   | 23/29        | 33 (-)                 | A, L, DP               | -                                      | -/52                                        |

**TABLE 1** (Continued)
| Conservative Intervention(s) | Surgical approach | μ Follow-up in months (min-max) | Outcome measurements used |
|-----------------------------|------------------|--------------------------------|--------------------------|
|                            |                  | ICP | Patient satisfaction | Return to activity | SANE | LLLOS | Complications (in %) | Recurrence (in %) | Reoperations (in %) |
| -                           | Open             | 24 (-) | N | N | Y | Y | N | N | 0 | 0 | 0 |
| -                           | Open             | 34 (24-52) | N | Y | N | N | N | N | 2.7 | - | - |
| AM                          | -                | 67 (-) | N | Y | Y | N | N | N | 6.4 | - | - |
| -                           | ES               | -    | N | N | Y | Y | N | N | 9.1 | - | 0 |
| -                           | Open             | 55 (4-127) | N | Y | Y | N | N | N | - | - | 11 |
| -                           | -                | - (2-8) | Y | N | N | N | N | N | - | - | - |
| -                           | Open             | 3 (-)  | Y | Y | N | N | N | N | - | - | - |
| -                           | Open             | 16 (6-48) | N | Y | Y | N | N | N | - | - | - |
| -                           | Open             | - (2-48) | Y | N | Y | N | N | N | - | - | - |
| -                           | -                | - (6-24) | N | Y | Y | N | N | N | 4.8 | - | - |
| -                           | Open             | 23 (-)  | N | Y | N | N | N | N | - | - | - |
| -                           | Open             | 12 (6-24) | N | Y | Y | N | N | N | - | - | - |
| -                           | Open             | - (24-42) | N | Y | Y | N | N | N | 4 | 12 | 8 |
| -                           | Open             | 26 (12-42) | N | Y | N | N | N | N | 3.3 | - | - |
| -                           | Open             | 50 (-)  | N | Y | N | N | N | N | 8.7 | - | 2.2 |
| -                           | ES               | 24 (-)  | N | Y | Y | N | N | N | 0 | - | - |
| -                           | MI               | -     | N | N | Y | N | N | N | - | - | - |
| -                           | Open             | 3 (1-6)  | N | Y | N | N | N | N | - | - | - |
| -                           | Open             | 51 (24-107) | N | Y | Y | N | N | 3.4 | 11 | 11 |
| -                           | Open             | 25 (19-46) | N | Y | Y | N | N | - | 6.7 | 6.7 |
| -                           | MI               | - (8-30) | N | Y | N | N | N | N | - | - | - |
| -                           | -                | -     | N | Y | N | N | N | N | - | - | - |
| AM                          | Open             | 28 (-)  | N | N | Y | N | N | N | 7.4 | - | - |
| -                           | Open & MI        | -     | N | Y | N | N | N | N | 7 | 3.9 | - |
| -                           | MI               | -     | Y | N | N | N | N | N | - | - | - |
| -                           | MI               | -     | Y | N | N | N | N | N | - | - | - |
| LM                          | MI               | 2 (-)  | Y | Y | N | N | N | 0 | - | - | - |
| -                           | Open             | - (12-108) | N | Y | Y | N | N | N | - | - | - |
| LM                          | Open             | 36 (19-44) | N | Y | N | N | N | N | - | - | - |
| AM                          | MI               | -     | Y | Y | N | N | N | N | - | 5.7 | 1.4 |
| -                           | MI               | 6 (-)  | Y | Y | Y | N | N | N | 2.6 | - | - |
| -                           | Open             | -     | N | N | Y | N | N | 14.3 | 45 | 5.9 |
| -                           | Open             | 39 (3-89) | N | Y | N | N | N | N | - | - | - | (Continues)
reviews, case reports, letters, expert opinions, and narrative articles. Finally, if two selected articles were reporting on the same (retrospective) cohort, the smallest study was excluded.

### 2.4 Data analysis

Data extracted from included studies were study design, demographics of participants, diagnostics, type of intervention, comparator groups, and all available outcome measures. All relevant data were independently entered into an Excel spreadsheet (Microsoft, Redmond, Washington, 2010) by two researchers (SV & ER). If absolute numbers were available, rates of recurrence, reoperation, or complication were calculated by dividing by the total number of legs. Discrepancies between reviewers were resolved by discussion.

For quantitative data, results from comparable groups of studies were pooled and means with corresponding standard deviations were calculated. The homogeneity of results was tested by calculating the Chi-squared statistic with Yate's correction for continuity and the probability value. The level of significance was set at 5% (P < 0.05).

### Table 2: Treatment outcome following conservative intervention in CECS

| Author                | Design | Level of Evidence | Patients (n) | Patient population? | Male/Female | µ age in year (min-max) | Affected compartments | µ duration symptoms in months (min-max) | n conservative patients/ n surgical patients |
|-----------------------|--------|-------------------|--------------|---------------------|-------------|------------------------|-----------------------|----------------------------------------|---------------------------------------------|
| Winkes et al\(^{21}\) | P      | 4                 | 42           | C                   | 23/19       | - (17-52)              | DP                    | - (3-72)                              | 42/42                                       |
| Wittstein et al\(^{22}\) | R      | 4                 | 9            | C                   | 4/5         | 24 (13-54)             | A, L, DP, SP           | -                                     | 9/9                                         |
| Zimmermann et al\(^{20}\) | R      | 3                 | 37           | M                   | 32/5        | 23 (19-30)             | A                     | 11 (3-28)                              | 37/3                                |

Abbreviations: -, information not available; A, anterior compartment; AM, Activity modification; BI, botulinum injection; C, civil population; DP, deep posterior compartment; ES, endoscopic; GR, Gait retraining; L, lateral compartment; LM, Lifestyle modification; M, military population; MI, minimally invasive; N, no; P, prospective; PT, Physical therapy; R, retrospective; SP, superficial posterior compartment; Y, yes.

Abbreviations: -, information not available; AM, Activity modification; BI, botulinum injection; GR, Gait retraining; ICP, intracompartmental pressure; LLOS, Lower Leg Outcome Survey (0-60, with 60 being normal); LM, Lifestyle modification; M, Massage; PE, post-exercise; PT, Physical therapy; SANE, Single Assessment Numeric Evaluation (0-100 scale, with 100 being normal).
deviations (SD) were calculated. \( P \)-values < .05 were considered significant.

### 2.5 Assessing the quality of evidence

The quality of studies was evaluated according to Cochrane's GRADE evidence profile. Subsequently, levels of evidence were established for all selected studies.

### RESULTS

A total of 7421 studies were identified (Figure 1). Following removal of duplicates and screening of title and abstract, 286 articles were reviewed for potential eligibility. Subsequently, 92 articles fitted all study criteria. After studying outcome variables, 68 studies were included (patients \( n = \); 3783). The majority of the studied populations received surgical treatment (\( n = \); 3612), whereas only 171 patients were treated conservatively.

| Conservative Intervention(s) | Surgical approach | \( \mu \) Follow-up in months (min-max) | ICP | Patient satisfaction | Return to activity | SANE | LLLOS | Complications (in %) | Recurrence (in %) | Reoperations (in %) |
|-----------------------------|-------------------|--------------------------------------|-----|-------------------|-------------------|------|-------|---------------------|-----------------|------------------|
| -                           | Open              | 26 (12-42)                           | N   | Y                 | Y                 | N    | N     | 6.3                 | 6.2             | 1.6              |
| -                           | ES                | 45 (5-90)                            | N   | N                 | Y                 | N    | N     | 14.3                | 0               | 0                |
| GR                          | -                 | 11 (3-28)                            | N   | Y                 | N                 | Y    | N     | -                   | -               | -                |

| After intervention (±SD) | Change (P-value) | Before intervention (±SD) | After intervention (±SD) | Change (P-value) | Satisfaction (in %) | Very satisfied or symptom free | Return to activity (in %) |
|-------------------------|------------------|-------------------------|-------------------------|------------------|---------------------|-------------------------------|--------------------------|
| -                       | -                | -                       | -                       | -                | 0                   | -                             | -                        |
| -                       | -                | -                       | -                       | -                | -                   | -                             | -                        |
| -                       | -                | -                       | -                       | -                | 17                  | 83                            | -                        |
| 90 (±10)                | <0.01            | 67.3 (±13.7)            | 91.5 (±8.5)             | <0.01            | -                   | -                             | 100                      |
| -                       | -                | -                       | -                       | -                | 20                  | -                             | 0                        |
| 77 (±22)                | 0.00             | 72.0 (±11.3)            | 84.6 (±15.5)            | 0.00             | -                   | -                             | -                        |
|                         |                  |                         |                         |                  | 94                  | 94                            |                          |

| -                       | -                | -                       | -                       | -                | 56                  | -                             | -                        |
| -                       | -                | -                       | -                       | -                | 25                  | -                             | -                        |
| -                       | -                | -                       | -                       | -                | 0                   | -                             | -                        |
| -                       | -                | -                       | -                       | -                | 84                  | -                             | -                        |
| -                       | -                | -                       | -                       | -                | 0                   | -                             | -                        |
| 73 (±22)                | <0.01            | -                       | -                       | -                | 70                  | 19                            | -                        |
## Table 3: Treatment outcome following surgical intervention for CECS

| Study                  | Legs (n) | Compartments (n) | Type of Surgery | ICP in mm Hg | Before intervention μ (±SD) | After intervention μ (±SD) | Change (P-value) |
|------------------------|----------|------------------|-----------------|--------------|----------------------------|----------------------------|-----------------|
| Akermark et al42        | 60       | 60               | Open            |              | -                          | -                          | -               |
| Ali et al24             | 24       | 24               | ES              | -            | -                          | -                          | -               |
| Allen & Barnes33        | 73       | 84               | MI              | -            | -                          | -                          | -               |
| Balius et al44          | 9        | 9                | MI              | -            | -                          | -                          | -               |
| Beck et al45            | 250      | 741              | Open, MI & ES   | Rest         | 6 (-)                      | 2 (-)                      | <0.005          |
| Biedert & Marit.29      | 15       | -                | Open            | PE           | 19 (-)                     | 2 (-)                      | <0.0001         |
| Cook & Bruce57          | 27       | 56               | Open            |              | -                          | -                          | -               |
| de Bruijn et al48       | 28       | 28               | MI              | -            | -                          | -                          | -               |
| de Fijter et al33       | 118      | 118              | MI              | -            | -                          | -                          | -               |
| Detmer et al59          | -        | 233              | Open & MI       |              | -                          | -                          | -               |
| Drexlser et al50        | 95       | 95               | MI              | -            | -                          | -                          | -               |
| Edmundsson et al51      | 57       | 121              | Open            | -            | -                          | -                          | -               |
| Fronck et al25          | 20       | 40               | Open            | -            | -                          | -                          | -               |
| Garcia-Mata et al5      | 43       | -                | Open            | -            | -                          | -                          | -               |
| Gatedby et al52         | 36       | 72               | Open            | -            | -                          | -                          | -               |
| Howard et al54          | 39       | 78               | Open            | -            | -                          | -                          | -               |
| Irion et al55           | 20       | 48               | Open            | -            | -                          | -                          | -               |
| Islam & Robbs.39        | 216      | 376              | Open            | -            | -                          | -                          | -               |
| Jarvinnen et al56       | 34       | 48               | Open            | -            | -                          | -                          | -               |
| Lohrer & Nauck57        | 38       | 38               | ES              | -            | -                          | -                          | -               |
| Maffulli et al58        | 27       | 38               | MI              | -            | -                          | -                          | -               |
| Maher et al59           | 36       | -                | Open            | -            | -                          | -                          | -               |
| McCallum et al60        | 70       | 114              | -               | -            | -                          | -                          | -               |
| Micheli et al16         | 72       | 103              | MI              | -            | -                          | -                          | -               |
| Moeyersoons & Martens61 | 85       | -                | Open            | -            | -                          | -                          | -               |
| Mouhsine et al62        | 29       | 36               | Open            | -            | -                          | -                          | -               |
| Orlin et al63           | 74       | 296              | Open            | -            | -                          | -                          | -               |
| Packer et al26          | 125      | -                | -               | -            | -                          | -                          | -               |
| Pandya & Ganley64       | 11       | 22               | ES              | -            | -                          | -                          | -               |
| Pasie et al65           | 84       | 244              | Open            | -            | -                          | -                          | -               |
| Qvarfordt et al64       | 30       | 60               | Open            | -            | -                          | -                          | -               |
| Raikin et al45          | -        | -                | Open            | -            | -                          | -                          | -               |
| Reneman et al36         | 119      | -                | Open            | -            | -                          | -                          | -               |
| Rettig et al57          | 20       | 21               | -               | -            | -                          | -                          | -               |
| Roberts et al58         | 189      | 189              | Open            | -            | -                          | -                          | -               |
| Rorabeck et al69        | 24       | 56               | Open            | -            | -                          | -                          | -               |
| Rorabeck et al70        | -        | -                | Open            | -            | -                          | -                          | -               |
| Schepsis et al71        | 30       | 45               | Open            | -            | -                          | -                          | -               |
| Treatment outcome following surgical intervention for CECS | Legs (n) | Compartments (n) | Type of Surgery | ICP in mm Hg | Likert Scale (in %) | Satisfaction (in %) | Return to activity (in %) |
|----------------------------------------------------------|----------|-----------------|----------------|--------------|--------------------|---------------------|-------------------------|
|                                                         |          |                 |                | Measurement  | Excellent | Good | Fair | Poor | Bad | Satisfied/impro | Very satisfied/ symptom free | Previous level | Full activity |
|                                                         |          |                 |                | Before        | -         | -    | -    | -    | -    | -                | -                   | -              | -            |
|                                                         |          |                 |                | After         | -         | -    | -    | -    | -    | -                | -                   | -              | -            |
|                                                         |          |                 |                | Change        | -         | -    | -    | -    | -    | -                | -                   | -              | -            |
|                                                         |          |                 |                | P-value       | -         | -    | -    | -    | -    | -                | -                   | -              | -            |
| Akermark et al 42                                       | 60       | 60              | Open           | -            | -         | -    | -    | -    | -    | 30                | 57                  | -              | 67           |
| Ali et al 24                                            | 24       | 24              | ES             | -            | -         | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Allen & Barnes 43                                       | 73       | 84              | MI             | -            | -         | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Balius et al 44                                        | 9        | 9               | MI             | -            | -         | -    | -    | -    | -    | -                | -                   | -              | 86           |
| Beck et al 45                                           | 250      | 741             | Open, MI & ES  | -            | -         | -    | -    | -    | -    | -                | -                   | -              | 86           |
| Biedert & Marti 29                                     | 15       | -               | Open Rest      | PE           | 6        | (-)  | 19   | (-)  | 2    | 2                | (-)                 | <0.005         | -            |
| Cook & Bruce 47                                         | 27       | 56              | Open           | -            | 78.5     | -    | -    | -    | -    | -                | -                   | -              | -            |
| de Bruijn et al 48                                      | 28       | 28              | MI             | -            | 31       | 31   | 23   | 8    | 8    | -                | -                   | 100            | -            |
| de Fijter et al 33                                      | 118      | 118             | MI             | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 94           |
| Detmer et al 49                                         | -        | 233             | Open & MI      | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Drexler et al 50                                        | 95       | 95              | MI             | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Edmundsson et al 51                                     | 57       | 121             | Open           | 11           | 11       | 61   | 23   | 8    | 8    | -                | -                   | 100            | -            |
| Fronek et al 25                                         | 20       | 40              | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 94           |
| Garcia-Mata et al 3                                     | 43       | -               | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 100          |
| Gatenby et al 52                                        | 36       | 72              | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 50           |
| Howard et al 54                                         | 39       | 78              | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 78           |
| Irion et al 55                                          | 20       | 48              | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 86           |
| Islam & Robbs 39                                        | 216      | 376             | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Jarvinnen et al 56                                      | 34       | 48              | Open           | 41           | 34       | 34   | 48   | 15   | 7    | -                | -                   | 100            | -            |
| Lohrer & Nauck 57                                       | 38       | 38              | ES             | 53           | 57       | 57   | 24   | 18   | 18   | -                | -                   | -              | 94           |
| Maffulli et al 58                                       | 27       | 38              | MI             | 47           | 94      | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Maher et al 59                                          | 36       | -               | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| McCallum et al 60                                       | 70       | 114             | -              | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 90           |
| Micheli et al 16                                        | 72       | 103             | MI             | 47           | 28       | 15   | 9    | 9    | 15   | -                | -                   | 75             | -            |
| Moeyersoons & Martens 61                                | 85       | -               | Open           | 31           | 85      | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Mouhsine et al 62                                       | 29       | 36              | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Orlin et al 63                                          | 74       | 296             | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Packer et al 26                                         | 125      | -               | -              | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 79           |
| Pandya & Ganley 64                                      | 11       | 22              | ES             | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Pasic et al 65                                          | 84       | 244             | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Qvarfordt et al 34                                      | 30       | 60              | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 94           |
| Raikin et al 35                                         | -        | 80              | Open           | -            | 20       | 80   | 15   | 9    | 9    | -                | -                   | 83             | -            |
| Reneman et al 36                                        | 119      | -               | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Rettig et al 67                                         | 20       | 21             | Open           | -            | 83       | 17   | 25   | 75   | 25   | -                | -                   | 66             | -            |
| Roberts et al 68                                        | 189      | 189             | Open           | -            | -        | -    | -    | -    | -    | -                | -                   | -              | 96           |
| Rorabeck et al 24                                       | 24       | 56              | Open           | -            | 83       | 17   | 25   | 83   | 25   | -                | -                   | 66             | -            |
| Rorabeck et al 70                                       | -        | 21             | Open           | -            | 92       | -    | -    | -    | -    | -                | -                   | -              | 90           |
| Schepsis et al 71                                       | 30       | 45              | Open           | 43           | 30       | 30   | 23   | 15   | 7    | -                | -                   | 90             | -            |

(Continues)
An overview of study characteristics is found in Table 1. The majority (72%) was of retrospective design. An overall 7:4 male-to-female ratio was found. Study populations were dominated by adults between 20 and 30 years of age, although CECS cases up to 70 years old were identified. Additionally, more than half of the studies (56%) reported on CECS in multiple compartments, whereas 22 (32%) studies analyzed results of only one compartment. In eight (12%) articles, the affected compartments were not specified.

Inclusion of CECS patients was done by using a suggestive history of pain during exercise as a criterium in 62 articles (91%). In a total of 58 studies (85%), ICP manometry was performed, of which 24 studies applied the Pedowitz criteria. Additional imaging using radiographic images, MRI, or scintigraphy, for exclusion of stress fractures, was performed in 23 (34%), eight (12%), and 20 (29%) articles, respectively. Ultrasonography either traditionally and/or with Doppler, for exclusion of vascular pathologies, was conducted by ten studies (15%).

## Outcome following conservative treatment

Studies reporting on ICP measurements, SANE, LLOS, patient satisfaction, or return to physical activity following conservative interventions are depicted in Table 2. Interestingly, none of the studies used similar intervention strategies (Appendix S1) or outcome measurements.

A significant drop in ICP was reported in two studies using gait retraining and one applying botulinum...
injections. Moreover, lower ICP values were associated with an improved outcome as reflected by SANE and LLOS scores. Improvement of symptoms or satisfaction was reported by 47% (±42%) of the patients who completed a follow-up analysis, whereas 50% (±45%) returned to a form of physical activity. The well-structured gait retraining programs and treatment with botulinum injections scored highest with satisfaction rates ranging from 89% to 100%, whereas all studies with patients alone initiated modifications in activity and/or lifestyle scored between 0% and 84% satisfaction.

Among the 171 conservatively treated patients, six cases were reported to eventually opt for surgery. Additionally, a significant reduction of individuals requiring subsequent surgery was found in military populations (not mentioned in Table 2).

### 3.2 Outcome following surgical treatment

Clinical outcome with respect to lowered ICP values, patient satisfaction, return to activity, rates of complication, recurrence, and reoperation after surgical intervention is depicted in Table 3.

ICP values were obtained both before and after surgical intervention in nine of thirty studies. Five of these found a statistically significant reduction of ICP, suggesting that surgical intervention is effective in reducing muscle compartment pressures.

Patient-reported outcome measures and rates of return to activity reveal that the majority of CECS patients were satisfied and returned to previous levels of activity. In addition, 58% (±29.6%) were satisfied with the treatment results and experienced reduction of symptoms, whereas 78% (±21.2%)
were very satisfied and/or free of symptoms. Combining these results allows for calculating an 85% (±13%) overall satisfaction rate. Moreover, the average proportion that returned to some form of physical activity after surgery was 80% (±17.3). However, return to previous level and/or full activity was on average 69% (±25.5%) and 65% (±25.0%), respectively.

Surgical complications and rates of recurrence and reoperations (Table 1) indicate that approximately 8% (±5.3%) of the studied CECS patients experienced surgical complications, mainly wound problems or nerve damage. Irrespective of surgical technique or operated compartment, recurrence, and reoperation rates were 7% (±10.8%) and 5% (±4.3%), respectively. Comparing studies that focused on civilian (n =; 32) or military patients (n =; 3) revealed a significantly higher complication rate among patients that serve in the armed forces (civilian 7.1%±4.6% versus military 15.1%±4.5%, P =; .01). Similar results are found with respect to recurrence (civilian 5.6%±7.7% versus military 24.4%±29.2%, P =; .03) and reoperations rates (civilian 5.2%±4.8% versus military 21.4%±32.6%, P =; .03).

A list of different postoperative treatment protocols after surgical intervention is found in Appendix S2. Days of rest, weight bearing, use of compressive bandages, and sport limitations varied widely among studies.

### 3.3 | Comparison of conservative and surgical interventions

Table 4 lists studies comparing conservative and surgical interventions. Packer et al26 and Thein et al31 compared rates of return to activity and found significant differences favoring surgical intervention. However, Packer et al26 found similar satisfaction rates. Interestingly, Zimmermann et al20 reported in a military population a higher percentage that returned to active duty following conservative treatment compared to surgical intervention.

### 4 | DISCUSSION & CONCLUSION

This systematic review is the first to analyze studies reporting on outcome following conservative and surgical treatment in patients with CECS in any compartment of the lower leg, not just the posterior compartment.32 No randomized controlled trials were found.

Most CECS studies report on beneficial effects of surgical therapy, with an overall 85% satisfaction rate and an 80% rate of return to physical activity. In contrast, conservative interventions were seemingly associated with lower rates of satisfaction and return to activity (47% and 50%, respectively). Only two studies compared both modalities in one
model, reporting statistically superior results following a fasciotomy. However, caution regarding an interpretation is required due to the limited number of studies on conservative treatment with substantial smaller study populations.

This review demonstrates that ICP measurements are infrequently used as a treatment outcome parameter, even though they are considered the gold standard in diagnosing CECS. Only sixteen of the included studies measured ICPs before and after intervention, with only nine studies reporting on corresponding P-values. The use of ICP measurements as outcome measure cannot be confirmed, nor discarded with current literature.

Another interesting finding is that this overview consistently found a potential difference between surgically treated civilian and military study populations with significant higher rates of postoperative complications, recurrence, and reoperations in the military, as was already suggested by previous literature. Even though these observations were made on the basis of different population sizes (civilian n =; 1975, military n =; 671), these findings may suggest conservative treatment in military patients may be preferred compared to surgery.

This review was subject to a number of limitations, the most prominent being the lack of uniformity among outcome measures. Moreover, follow-up data were often obtained in substantially smaller number of patients than initially treated, potentially introducing selection bias. This principle also applies to the exact determination of overall recurrence rates and complications, especially when information on unilaterality or bilaterality of symptoms was missing.

This review was further hampered by the heterogeneity among study populations. Variation was found in studies with respect to the inclusion of patients with fascial herniae, presence of concomitant MTSS or affected upper extremities. An attempt to overcome this heterogeneity was made by solely including studies that allowed for extraction of data only concerning CECS in the lower extremity. Nevertheless, any conclusion based on the present review must be taken with caution.

Defining uniform and generally applicable outcome parameters will likely simplify future data comparison. This process is facilitated by initiating a consensus via the Delphi method as was already conducted for various other entities by the International Consortium for Health Outcomes Measurement. Based on the content of Hip & Knee osteoarthritis set, we wish to propose a potential outline from which standardization can be initiated (Figure 2). The use of a 5-point Likert scale is preferred for all questions related to symptoms or performance. Currently, such a set of standardized outcome measurements will be applied by our study group to military civilian collaboration, with special

| Satisfaction (in %) | Overall Difference (p-value) | Conservative | Surgical | Return to activity (in %) | Overall Difference (p-value) |
|---------------------|-----------------------------|--------------|----------|--------------------------|-----------------------------|
|                     |                             | Satisfied/improved | Satisfied/improvement | Satisfied/improved | Difference | Previous level | Full activity | Previous level | Full activity | Difference |
|                     |                             | Very satisfied/symptom free | Very satisfied/symptom free | Very satisfied/symptom free | (p-value) | (p-value) | (p-value) | (p-value) | (p-value) | (p-value) |
| NS                  |                             | -              | 0        | -                        | -                        | -              | -              | -              | -              | -              |
| <0.05               |                             | -              | 20       | -                        | -                        | -              | 0              | -              | 94             | -              |
| <0.05               |                             | -              | 0        | 100                      | -                        | -              | -              | -              | -              | -              |
| NS                  |                             | 56             | 81       | -                        | 0.011                    | 30             | 77             | 79             | <0.001         |
| <0.05               |                             | 84             | 52       | -                        | -                       | -              | -              | -              | -              |
| <0.05               |                             | -              | 0        | 100                      | -                        | -              | -              | -              | -              |

This review was subject to a number of limitations, the most prominent being the lack of uniformity among outcome measures. Moreover, follow-up data were often obtained in substantially smaller number of patients than initially treated, potentially introducing selection bias. This principle also applies to the exact determination of overall recurrence rates and complications, especially when information on unilaterality or bilaterality of symptoms was missing.

This review was further hampered by the heterogeneity among study populations. Variation was found in studies with respect to the inclusion of patients with fascial herniae, presence of concomitant MTSS or affected upper extremities. An attempt to overcome this heterogeneity was made by solely including studies that allowed for extraction of data only concerning CECS in the lower extremity. Nevertheless, any conclusion based on the present review must be taken with caution.

Defining uniform and generally applicable outcome parameters will likely simplify future data comparison. This process is facilitated by initiating a consensus via the Delphi method as was already conducted for various other entities by the International Consortium for Health Outcomes Measurement. Based on the content of Hip & Knee osteoarthritis set, we wish to propose a potential outline from which standardization can be initiated (Figure 2). The use of a 5-point Likert scale is preferred for all questions related to symptoms or performance. Currently, such a set of standardized outcome measurements will be applied by our study group to military civilian collaboration, with special
emphasis on prevention, conservative treatment, and non-invasive diagnostics.

In conclusion, the present review found that surgical treatment for CECS resulted in a minimal 80% overall satisfaction and return to physical activity rate. In contrast, conservative interventions were associated with lower rates of satisfaction and return to activity up to 50%. As these findings are based on low-quality studies demonstrating a large heterogeneity, higher quality studies including randomized controlled trials with univocal endpoints are required for determining any superior treatment regimen in the lower leg CECS.

5 | PERSPECTIVE

Surgery is currently the gold standard in the management of CECS of the lower extremity, although recent studies also reported success following gait retraining. This review provides an extensive overview of all published evidence regarding treatment outcome for both conservative and surgical therapy. This study therefore serves educational purposes for healthcare professionals working with CECS patients, who can be found among all areas of sport in both civil and military populations. The presented overview aids evidence-based and shared decision making in the discussion between healthcare provider and patients; it offers clear implications and guidelines for future treatment and research.

CONFLICT OF INTEREST
There is no conflict of interest to declare.

AUTHOR CONTRIBUTION
SV and ER contributed equally to this manuscript. SV, ER, and RH conceptualized the study. SV wrote the study protocol. SV and ER conducted the literature searches, the study selection, the data extraction, and the study quality.
assessment. SV and ER performed all statistical analyses. SV and ER drafted all sections of the manuscript. All authors critically revised the draft manuscript and contributed to the subsequent revisions and the final version of the manuscript.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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