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CRITICAL REVIEW

Efficacy and safety of corticosteroids and ACTH in epileptic syndromes beyond Infantile Epileptic Spasms Syndrome (IESS): A systematic review and meta-analysis

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Abstract

We conducted a systematic review investigating the efficacy and tolerability of adrenocorticotropic hormone (ACTH) and corticosteroids in children with epilepsies other than infantile epileptic spasm syndrome (IESS) that are resistant to anti-seizure medication (ASM). We included retrospective and prospective studies reporting on more than five patients and with clear case definitions and descriptions of treatment and outcome measures. We searched multiple databases and registries, and we assessed the risk of bias in the selected studies using a questionnaire based on published templates. Results were summarized with meta-analyses that pooled logit-transformed proportions or rates. Subgroup analyses and univariable and multivariable meta-regressions were performed to examine the influence of covariates. We included 38 studies (2 controlled and 5 uncontrolled prospective; 31 retrospective) involving 1152 patients. Meta-analysis of aggregate data for the primary outcomes of seizure response and reduction of electroencephalography (EEG) spikes at the end of treatment yielded pooled proportions (PPs) of 0.60 (95% confidence interval [CI] 0.52–0.67) and 0.56 (95% CI 0.43–0.68). The relapse rate was high (PP 0.33, 95% CI 0.27–0.40). Group analyses and meta-regression showed a small benefit of ACTH and no difference between all other corticosteroids, a slightly better effect in electric status epilepticus in slow sleep (ESES) and a weaker effect in patients with cognitive impairment and "symptomatic" etiology. Obesity and Cushing's syndrome were the most common adverse effects, occurring more frequently in trials addressing continuous ACTH (PP 0.73, 95% CI 0.48–0.89) or corticosteroids (PP 0.72, 95% CI 0.54–0.85) than intermittent intravenous or oral corticosteroid administration (PP 0.05, 95% CI 0.02–0.10). The validity of these results is limited by the high risk of bias in most included studies and large heterogeneity among study results. This report

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KEYWORDS

ACTH, childhood epilepsy, corticosteroid drugs, epileptic encephalopathy, resistant epilepsy, systematic review

1 | INTRODUCTION

Adrenocorticotropic hormone (ACTH) and corticosteroids have been used for over 70 years to treat childhood epilepsies and epileptic encephalopathies that are unresponsive to conventional anti-seizure medication (ASM). However, authors have reported their experiences mostly in retrospective and a few uncontrolled prospective case series undergoing regimens relying on experience and expert consensus. In infants with infantile epileptic spasms (IESS) including West syndrome (WS), adequately powered clinical trials comparing ACTH and corticosteroids with active controls have only been conducted in recent years. National and international controlled trials have shown that in these patients, relatively short courses of ACTH or prednisolone are well tolerated and effective in alleviating seizure severity and frequency, and in improving electroencephalographic results and psychomotor development.[1,2] Therefore, systematic reviews and practice guidelines now rank these medications as the first choice in the treatment of IESS.[3,4]

The knowledge and evidence about the role of ACTH and corticosteroids in ASM-resistant epilepsies and encephalopathies beyond the first year of life and throughout childhood are much weaker than for IESS. There are hardly any controlled studies involving these patients. Several narrative reviews have been published based on retrospective case series and a few open cohort studies.[5-8] A Cochrane review on the treatment of pediatric epilepsies other than infantile spasms with ACTH and corticosteroids, last updated in 2015, found mainly low-evidence reports and one randomized cross-over trial of a new synthetic $ACTH_{4\text{-}19}$ analogue that included only five children and yielded no interpretable results. The authors were, therefore, unable to make an evidence-based treatment recommendation.[9]

Herein we provide a current systematic review on this topic. Our aim was to identify all available studies in the field and include them when appropriate. Following the PICO (patient, investigated condition, comparison condition, outcome) criteria, our inclusion criteria were reports of childhood epilepsy other than West syndrome/IESS (P), treatment with ACTH or a corticosteroid drug (I), and information on a comparison period or group (individual baseline or parallel group) (C). We aimed to collect data on efficacy, measured as seizure and/or EEG response and/or improvement in behavior and cognition, and tolerability, measured by the occurrence of typical CST adverse effects (O). The objective of this systematic review was to provide a comprehensive overview of the "state of the art" and the best available evidence. Knowing that the largest number of studies published in this field were of low methodological quality, we decided to include all types of publications, from retrospective case series to randomized-controlled trials. At the beginning of our work, we published the protocol of our systematic review on International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42022313846 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=313846). This report was prepared in accordance with the

Key points

- Systematic review resulting in low to moderately solid evidence on the efficacy and tolerability of adrenocorticotropic hormone (ACTH) and corticosteroid treatment in children with epilepsy other than infantile spasms.
- Meta-analysis based on aggregate data from 2 controlled prospective, 5 uncontrolled prospective, and 31 retrospective studies.
- Pooled data showing a seizure response in 60% and electroencephalography (EEG) response in 56% of patients, with no major differences between drugs. However, 30%–40% of patients relapse after the cessation of treatment.
- The most frequent adverse effects are obesity and Cushing's syndrome, occurring in 70% of patients under continuous treatment for some weeks, but in less than 10% undergoing pulsed, intermittent regimens.
- More prospective, randomized-controlled studies are needed to improve the level of evidence and define the optimal doses and treatment duration.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guideline for systematic reviews and meta-analyses.[10]

2 | METHODS

2.1 | Information sources

We performed a systematic literature search in the following databases and registers: MEDLINE via PubMed (MeSH [medical subject headings] and text search), AWMF-register of guidelines (https://register.awmf.org/de/leitlinien), Cochrane Register of Systematic Reviews and Cochrane Register of Clinical Trials (https://www.cochrane.de/cochrane-library), Google-Scholar, OpenGrey (http://www.opengrey.eu), BASE (Bielefeld Academic Search Engine) https://www.base-search.net, Clinicaltrials.gov (https://clinicaltrials.gov/), German clinical trials register (DRKS) (http://www.bfarm.de/EN/BfArM/Tasks/German-Clinical-Trials-Register/_node.html), and EU clinical trials register (https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-024262-22/DE).

2.2 | Search strategy

For the MEDLINE search we applied the MeSH search terms (epilepsy AND drug therapy (MESH)) AND (corticosteroids (MESH) or ACTH (MESH)) NOT (West syndrome (MESH) OR infantile spasms); and the text terms (epilepsy OR epileptic syndromes) AND (ACTH OR adrenocorticotropic hormone OR prednisone OR prednisolone OR dexamethasone OR methyl-prednisolone) NOT (West syndrome or infantile spasms)" (see also the Table S1). The registers and other sources were searched more simply with the combination "epilepsy AND corticosteroid treatment". Our first search took place on November 11 to 13, 2021, including all years since the start of the database. An update including records from January 1, 2022, onward was done on February 21, 2023. We also screened the reference lists of the identified reviews, original articles, and some international textbooks on pediatric epilepsy (see Figure 1). We captured all findings in the bibliographic management system CITAVI 4.6, at the same time identifying and deleting duplicate findings.

2.3 | Eligibility criteria and selection process

Two of the authors together screened and selected the identified records applying the following inclusion criteria: (1) reports on childhood epilepsy other than West syndrome with available full-text publication in English, German, French, or Spanish; (2) treatment with ACTH or any corticosteroid drug; (3) inclusion of more than five patients; (4) clear case definition of the epileptic disorder and seizures; (5) reliably described treatment schedule; (6) reliably described outcome criteria for efficacy measured as seizure and/or EEG response and/or improvement in behavior and cognition; (7) information about adverse effects. We regarded items (1–5) as absolutely necessary, whereas only partial information in 6 and 7 were allowed when the existing information was sufficient for at least one outcome. If the reviewers came to divergent conclusions, they resolved this by discussion.

2.4 | Study risk of bias assessment

The risk of bias of the identified full-text publications was assessed using a self-constructed assessment sheet based on published items (National Institutes of Health [NIH] and Joanna Briggs Institute [JBI] checklists, Cochrane ROBINS-I tool; [11] http://joannabriggs.org/research/critical-appraisal-tools.html).[12] Two of the authors assessed each report in parallel; divergent conclusions were solved by discussion. Manuscripts were assessed based on reporting of and adherence to the following criteria: (1) patient selection and inclusion in the study; (2) clear definition of epileptic disorder including etiology, electroclinical syndrome, seizure type, EEG findings, and cognitive comorbidity; (3) clear definition of indication for corticosteroid treatment; (4) definition of drug(s), dose, and duration of treatment; (5) assignment to treatment groups in cohort studies; (6) reporting of possible confounding factors affecting treatment outcome; (7) definition of valid outcome criteria related to seizures, EEG findings, neuropsychological status, and side effects; (8) completeness and timing of outcome data; and (9) adequacy of statistical analysis and reporting. Following the suggestions in the ROBINS-I tool for non-randomized cohort studies, we summarized these factors in separate risk-of-bias domains (selection, confounding, intervention, outcome, statistics, reporting, and so on) and graded the resulting risks of bias as low, moderate, severe, or critical as compared with a theoretically well-conducted prospective randomized trial investigating the same topic (for our assessment and scoring sheet see Appendix S2). For the sole randomized-controlled trial we found, we applied the revised Cochrane Group RoB_2.0 tool.[13]

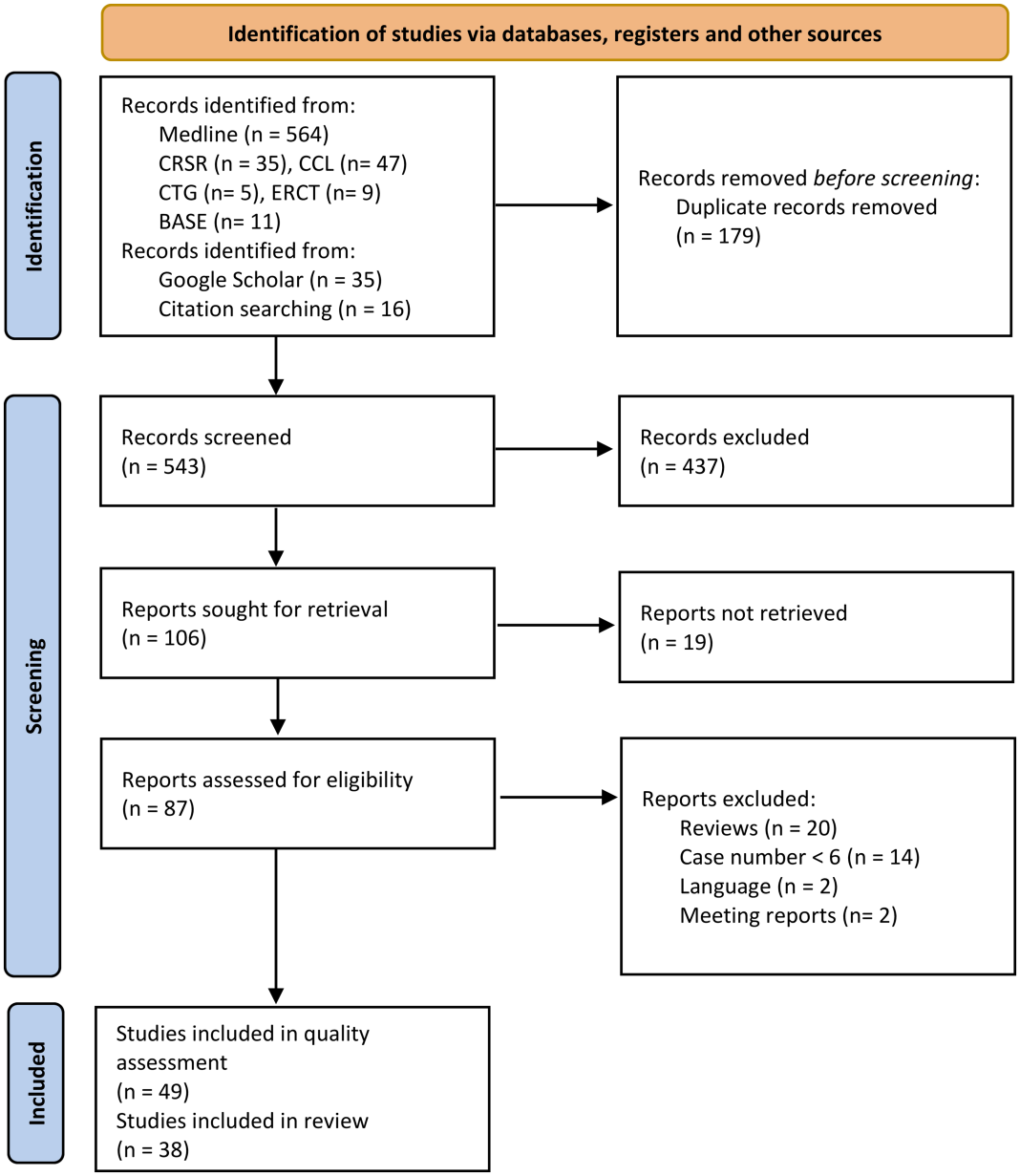

FIGURE 1 Search of records and selection of studies included in the review. BASE, Bielefeld Academic Search Engine; CCL, Cochrane Central Library; CTG, Clinical trials.gov; CRSR, Cochrane Register of Systematic Reviews; ERCT, European Register of Clinal Trials.

2.5 | Data collection

Two authors in parallel extracted all relevant data from the study reports and listed them in a detailed, descriptive format in two separate Excel files for "aggregate data" and "individual participant data." If important questions remained open in more recent publications (e.g., timing of outcome investigations), we attempted to contact authors via e-mail.

2.6 | Data items

A complete listing of the extracted outcome data and other variables is found in the respective Excel tables in Tables S1 and S2. The variable list of aggregate data (AD) was predefined before starting the extraction process by discussion between all authors of this review. The variables in the individual participant data (IPD) table include the contents of tables in the individual reports. For both analyses (AD and IPD) we determined the proportion of early reduction in seizures by more than 50% ("early seizure response") and of early improvement in EEG by more than 50% spike reduction ("early EEG response") as primary outcome variables. We defined proportions to be free of seizures and normalized EEG, and less well-defined improvements in seizures and EEG, proportions of improvement in psychology, relapses, adverse effects, and all late outcome data as secondary outcome variables.

2.7 | Preparation of individual study data for synthesis

To prepare for the statistical analyses, the extensive extracted data were reduced to the variables of interest and coded into machine-readable formats. Lists of the coded variables for AD and IPD are found in the respective Excel sheets in Tables S3 and S4.

We allocated the study drugs to five drug groups (Table 1). Furthermore, we transformed data on drug dose, treatment duration, follow-up scheme, and timing of the outcome measures to a comparable format. The very different treatment protocols usually followed an initial, high-dosed treatment period over a defined number of weeks, frequently (but not always) followed by an ill-defined period of tapering of dose and dosing frequency individualized according to the state of the patient. In an attempt to make different drugs and dosages comparable, we calculated the cumulative doses of ACTH and corticosteroids over the initial treatment period and converted them for corticosteroids with published factors into cortisol-equivalents.[14] In addition, and relying on two recent publications from one U.S. pharmacological institute, we converted synthetic ACTH and natural ACTH international units into prednisolone and cortisol milliequivalents (Table 2).[15,16]

Concerning the timing of collected outcome data, we were interested in separating "early outcome" at the termination of treatment or shortly thereafter from "late outcomes" off-corticosteroid treatment and after the occurrence of relapses. Some authors had reported early and late outcomes separately, but in most of the retrospective studies the follow-up schedules varied widely, and only seizure relapses were reported in the longer term. Based on the distribution of the time lines noted in our tables, we designated results reported at the end of treatment (EoT) and up to 3 months later as "early" and from more than 3 months later to several years as "late." If necessary, we calculated "late" results by subtracting seizure and/or EEG relapses from their early results. Thirty-five authors reported early outcomes at EoT, and three 7–12 weeks after EoT. Twenty-five of them also reported later outcomes, but 13 reported only early outcomes. Adverse effects data were included in statistical analyses only when the authors had credibly reported to have collected them prospectively and systematically.

TABLE 1 Drugs and grouped drugs.

Interventional drug	Drug group
Intravenous methylprednisolone (ivMP) followed by oral prednisone	Pulsed + contin. CST
ivMP, repeated pulses	Pulsed CST
Dexamethasone, repeated pulses	
Hydrocortisone, oral	Continuous CST
Dexamethasone, oral	
Deflazacort, oral	
Prednisone or prednisolone, oral	
MP, oral	
Natural ACTH, intramuscular	ACTH
Synthetic ACTH1–24, intramuscular	
Optimized ASM	Control

Note: ACTH, adrenocorticotropic hormone; CST, corticosteroid; ivMP, intravenous methylprednisolone; MP, methylprednisolone.

2.8 | Synthesis methods

2.8.1 | Aggregate data

For the AD, we coded the primary endpoint and most secondary endpoints as binary outcomes (yes/no). We used the proportion of events in a study as the outcome measure, except for the outcome "adverse events," where we used the rate of events per individual as outcome measure because an individual could experience more than one adverse event. For meta-analysis, we pooled the logit-transformed proportions (for adverse events, the log-transformed rates) using a three-level random-effects model with random effects for study and author (as authors could contribute more than one study to an analysis). To investigate the impact of covariates, we ran subgroup analyses and univariable and multivariable meta-regression. Covariates were study type, drug group, epilepsy type, the proportion of patients with symptomatic etiology, and dose, measured in cumulated cortisol-equivalents. We presented results as forest plots with a 95% confidence interval (CI) for the pooled effect and a 95% prediction interval providing a range for 95% of the study-specific estimates.

2.8.2 | Individual participant data

We pooled the individual data from patients across studies for which IPD was available applying a generalized mixed model with epilepsy type as fixed effect and study as random effect for all analyses. Covariates were mean age, drug group, etiology, epilepsy type, and disability. We presented results as regression tables.

We performed a sensitivity analysis in which we compared the results of our statistical tests in the entire sample of 38 included studies with those of 19 studies that had at most a moderate risk of bias for the outcome criteria.

Statistical analyses were conducted using the open statistical environment R, version 4.3.0.[17] For meta-analysis

TABLE 2 Cortisol-equivalents.

Drug	Conversion factor
Hydrocortisone 1 mg	1
Prednisolone, prednisone 1 mg	4
Methylprednisolone 1 mg	5
Dexamethasone 1 mg	25–30
Deflazacort 1 mg	3.3
Natural ACTH 1 IU	1.6 mg
ACTH1-24 (tetracosactide) 1 IU	7 mg

Note: Reference: Aktories[14];Poola[16]; Wang et al.[15]

of aggregate data, we used the R package meta, version 7.0-0.[18] For analysis of IPD, we used the R package lme4, version 1.1-34.[19]

3 | RESULTS

3.1 | Results of study selection

Our literature search resulted in a total of 722 citations. Elimination of duplicates reduced the number of findings to 543. The subsequent selection resulted in 106 potentially relevant titles and 93 abstracts for further selection. Twenty of these publications were identified as review articles or editorials not contributing original data. Sixty-seven were original reports for which full-text versions could be downloaded from online versions of the journals or purchased via the German online library system SUBITO (https://www.subito-doc.de/). After reading the full-text versions, we excluded 18 manuscripts (2 meeting reports, 2 in Chinese, and 14 case reports with five or less patients). We contacted the authors of three recent studies to resolve ambiguities regarding the timing of outcome measurement. One of them responded by telephone, and two failed to respond to our e-mail inquiries. The flow-chart of this selection process is depicted in Figure 1.

3.2 | Risk of bias in included studies

Forty-nine full texts of original reports were subjected to systematic quality and risk-of-bias (RoB) assessment. Studies rated by reviewers as "critical" in important domains (especially regarding selection, intervention, and outcome) were excluded from further review. Manuscripts were also excluded if they reported multiple different corticosteroid drugs but did not separately describe the outcome parameters per drug. A tabulated quality report and description of the excluded studies is found in Table S5, and their references in Appendix S3. After an assessment of RoB as described in methods, 38 reports were included in the further detailed presentation and data analyses. A shortened list of risk of bias in our included studies is depicted in Figure 2; the full version is found in Table S6.

3.2.1 | Study design

The first-ever published randomized cross-over study with only four of five patients treated failed to meet our inclusion criteria.[58] However, we identified one recently published, prospective, randomized, open-label parallel study comparing intravenous methylprednisolone (ivMP) with ongoing ASM treatment (Rangarajan, 2022).[20] A second prospective, open-label parallel trial compared oral hydrocortisone to deflazacort with alternating allocation.[21] Another five studies prospectively enrolled patients in single-arm, open-label single-center trials[22-25] (Qian 2016).[50] The remaining included studies were retrospective case series addressing treatment with one ($N=25$), two ($N=6$), or more ($N=1$) different corticosteroids or ACTH. Thus most of the included studies reveal a high risk of bias due to their study design.

3.2.2 | Indication for ACTH or corticosteroids

In 30 of the included studies the indication was clearly stated as severe childhood epilepsy resistant to at least two or three ASMs, with severe, usually generalized or diffuse spike waves on EEG, and cognitive or behavioral deterioration. In some studies, investigating only patients with electric status epilepticus in slow sleep (ESES) or Landau–Kleffner syndrome (LKS), only the latter two criteria were required. However, most studies failed to report how many of the children with a corticosteroid indication were eventually treated. In all but one[23] of the studies, patients were corticosteroid- or ACTH-naive, with isolated exceptions for single patients.

FIGURE 2 Selected items of risk-of-bias assessment for the included studies; for the full list see supplements. Low (green) – moderate (yellow) – serious (orange) – critical (red): estimated risk of bias as compared to a theoretical prospective randomized study on the same intervention (following ROBINS-I). The only randomized controlled trial[20] was assessed with the ROB-2 tool.[5,20-57]

Author	Year	*B: selection*	*F1: seizure outcomes*	*F2: EEG outcomes*	*F3: psych outcomes*	*F4: side effect outcomes*
Almaabdi	2014	ser	mod	ser	ser	ser
Altunel	2013	ser	ser	mod	ser	ser
Bakker	2015	mod	mod	mod	not rep	not rep
Bast	2014	mod	ser	ser	not rep	mod
Buzatu	2009	ser	ser	mod	mod	mod
Cao	2019	mod	mod	mod	mod	mod
Charuvanij	1992	ser	ser	not rep	not rep	mod
Chatterjee	2021	ser	ser	ser	ser	mod
Chen	2016	ser	mod	mod	mod	mod
Dooley	1989	ser	ser	ser	not rep	ser
Gencpinar	2016	ser	ser	ser	not rep	not rep
Gobbi	2014	mod	mod	mod	not rep	not rep
Gofshteyn	2021	mod	mod	mod	ser	mod
Grosso	2008	ser	mod	not rep	not rep	mod
Haberlandt	2010	ser	ser	ser	not rep	not rep
Hasaerts	1989	ser	ser	ser	ser	ser
Heyman	2012	ser	ser	ser	ser	ser
Kimizu	2020	ser	mod	not rep	mod	mod
Kramer	2006	mod	mod	mod	not rep	not rep
Kramer	2009	mod	not rep	mod	mod	not rep
Nasiri	2017	mod	mod	mod	not rep	mod
Oguni	2005	mod	mod	mod	not rep	not rep
Okumura	2006	mod	mod	mod	not rep	mod
O'Regan	1998	ser	ser	ser	not rep	not rep
Pera	2015	mod	mod	mod	mod	mod
Qian	2016	ser	ser	ser	not rep	not rep
Rangarajan **ROB-2**	2022	RCT, low	some concern	some concern	low	low
Sevilla-Castillo	2009	low	mod	not rep	not rep	mod
Sinclair	2003	ser	ser	not rep	not rep	ser
Sinclair	2005	ser	not rep	ser	ser	ser
Snead	1983	ser	ser	not rep	not rep	mod
Syed	2017	ser	ser	not rep	not rep	not rep
Tang-Wai	2017	ser	mod	ser	not rep	ser
van den Munckhof	2018	mod	not rep	ser	ser	not rep
Verhelst	2005	mod	ser	ser	ser	ser
Yamatogi	1979	ser	mod	crit	not rep	not rep
Yang	2021	low	mod	mod	not rep	mod
You	2008	ser	mod	mod	ser	mod

3.2.3 | Study inclusion

Inclusion in the seven prospective studies was based on the indication for corticosteroid treatment over a period of 1–5, mostly 2, years. The retrospective studies relied on chart reviews from one, two ($N=3$), four ($N=1$), or six ($N=1$) specialty clinics. Here, the period covered ranged from 2 to 26 years, usually 10 to 12 years. Almost all authors stated that "all patients treated consecutively during the period" were included in their study. However, only eight reported the number of cases excluded because of refusal or contraindications to steroid treatment, insufficient data, premature discontinuation, serious adverse events, or lack of follow-up.

3.2.4 | Confounding variables

Etiology, electroclinical syndrome, seizure types, comorbid mental retardation, age of manifestation, and previous ASM treatment are essential for both research and routine clinical practice. These characteristics were, therefore, usually recorded in both the prospective and retrospective studies. However, the nomenclature of epilepsies has changed considerably over the last decades. In etiological terms, the advent of high-resolution magnetic resonance imaging (MRI) and molecular genetics has resulted in a substantial number of cases initially classified as idiopathic turning out to be symptomatic or genetic. Only six studies reported systematic MRI examinations in all included patients.[20,21,23,26,27,28] Although more than half of the studies classified a symptomatic etiology in their patients further as perinatal, malformative, or postinfectious, nine studies merely distinguished "symptomatic" from idiopathic or cryptogenic, and six did not report an etiology at all. These basic features were addressed in most reports; however, potentially important intercurrent variables such as non-ASM co-medications, acute illness, or adherence to treatment were rarely mentioned in the retrospective series.

3.2.5 | Definition of intervention

Corticosteroid or ACTH treatment, including type of drug, use, dose, and duration of treatment, was accurately reported in all the included prospective studies, and in the retrospective studies when they were based on a fixed in-house protocol. However, the longer the period of patient enrollment and the higher the number of participating physicians, the more the choice of drugs and dosage varied.

3.2.6 | Definition of outcome variables

The number of seizures was the main outcome parameter in most studies. This was usually estimated from parent/guardian observations and diaries. In one prospective study, parents were trained via video instruction to recognize their children's seizures.[22] Two studies conducted an objective count based on 24-h video-EEG[29] (Qian 2016). Only a few studies defined a baseline of 2 weeks to 3 months to which seizure outcome was compared. Change was hardly ever reported as median number of seizure reduction, but usually as proportion of patients becoming free of seizures, improved >50% (defined as "response"), or any percentage in-between. EEG was usually performed while the patient was awake or asleep, with nap EEG, or with video-EEG monitoring over 4 to 24 or more hours. EEG findings were described in terms of background activity and epileptic features, but the nomenclature was inconsistent among studies. When ESES was studied, usually the spike–wave index (SWI, percentage of spike–wave activity over a few minutes) was calculated and compared to baseline. Most authors adhered to the definition of ESES "with bilateral spike waves occurring in at least 85% of slow wave sleep time." Others applied the broader definition of ">50% of SW time."[30] One study even relied on an SWI > 15% for a treatment indication with ACTH, based on their observation that an SWI > 15% was associated with neuropsychological dysfunction (Altunel 2013).[35] Regarding the cognition and behavior outcome, few studies reported psychological testing results. But even these had to rely on the clinical impression of parents or guardians to describe improvement in the larger number of patients unable to comply with testing. Fourteen studies systematically assessed their patients for adverse events (AEs), especially during inpatient treatment. Others collected spontaneous reports on AEs from parents/caregivers only. Few authors provided detailed lists of observed AEs; many just indicated "no serious and only transient" side effects.

3.2.7 | Statistics

Most authors reported a 100% seizure reduction ("free of seizures") and >50% reduction as "response," with some calculating these values from diaries and others only estimating them. Two studies documented a combined response of seizure reduction and EEG improvement.[31,32] All studies provided descriptive statistics of their data. Most also calculated correlations with covariates such as age at treatment, time since epilepsy diagnosis, etiology,

electroclinical syndrome, seizure type, and EEG changes. Some also applied multivariable statistics.

3.2.8 | Reporting

Most studies reported seizures, but in studies on ESES where seizures are often not a major clinical problem, three studies did not. EEG data, although usually assessed, were not reported in eight studies. Behavioral and cognitive findings were not reported in 20 studies with mixed epilepsy types and in 1 study with ESES. AEs were reported rather inconsistently, with 12 studies not reporting side effects at all.

3.3 | Meta-analysis of aggregate data (AD)

The full extracted data of all studies and variables selected for statistical analyses are found in Tables S1 and S3. Meta-analysis of the aggregated data (or AD) of all 38 included reports using random effects models showed the mean proportions of the primary outcomes "early seizure response" and "early EEG response" over all included studies and their treatment arms to be 0.60 (95% CI 0.52–0.67) and 0.56 (95% CI 0.43–0.68). After treatment cessation or already during tapering, the proportion of relapsing patients among all those treated was 0.33, leaving over the longer term a seizure response in 39% and EEG response in 52% of patients. These and results of other secondary outcome variables are listed in Table 3.

Subgroup analyses for drugs and drug groups showed a 10%–15% higher pooled proportion in trials with ACTH compared with corticosteroids for the primary outcome of "early seizure response." However, the residual heterogeneity between the ACTH studies was much larger than this possible drug effect (Figure 3). As seen in Table 3 and Figure 3, the heterogeneity between outcome measures was generally very large, and this was not associated with drug group or epilepsy type. Of interest, the heterogeneity of the primary outcome "early response of seizures" was lower in prospective studies than in retrospective series (Figure 4). The second primary outcome—"early response of EEG"—revealed no systematic differences between drug groups. The most impressive finding of our meta-analyses is a strong association between the treatment schedule and adverse event "overweight or Cushing syndrome." Its pooled proportion is low with pulsed ivMP or dexamethasone and high with continuous treatment with ACTH or oral corticosteroids (Figure 5). All other outcome parameters yielded only marginal differences between subgroups, precluding a further explanation of heterogeneity (see Appendixes S4 and S5 for all forest plots).

Results of multivariable meta-regression tests showing the primary outcome measures and their relevant covariables are listed in Tables 4 and 5. These findings suggest a positive effect of ACTH treatment and the epilepsy type ESES/LKS, and a negative effect of symptomatic etiology on one or both of the primary outcome measures (seizure and/or EEG response). Further findings and the reports of all other analyses performed are found in Appendixes S4 and S5.

TABLE 3 Meta-analysis of 38 studies, AD, random-effects model.

Outcome measure	No. of patients	Mean proportion	95% CI	Heterogeneity I^2 (%)
Early free of seizures	983	0.31	0.23–0.40	77
Early response of seizures[a]	987	0.60	0.52–0.67	71
Early improved seizures	1037	0.61	0.53–0.67	71
Early normalized EEG	575	0.20	0.12–0.30	71
Early EEG response[a]	418	0.56	0.43–0.68	78
Early improved EEG	826	0.49	0.30–0.59	78
Early improved psych	449	0.55	0.48–0.62	43
Relapse (proportion of treated)	780	0.33	0.27–0.40	72
Late response seizures	653	0.39	0.30–0.49	69
Late improved seizures	674	0.39	0.30–0.48	70
Late improved EEG	270	0.52	0.38–0.66	70
Late improved psych	97	0.52	0.28–0.74	67
Overweight or Cushing's	515	0.29	0.10–0.60	90

Note: Early = at EoT or 7–12 weeks later, late = >3 months after EoT.

[a]Primary outcome variables.

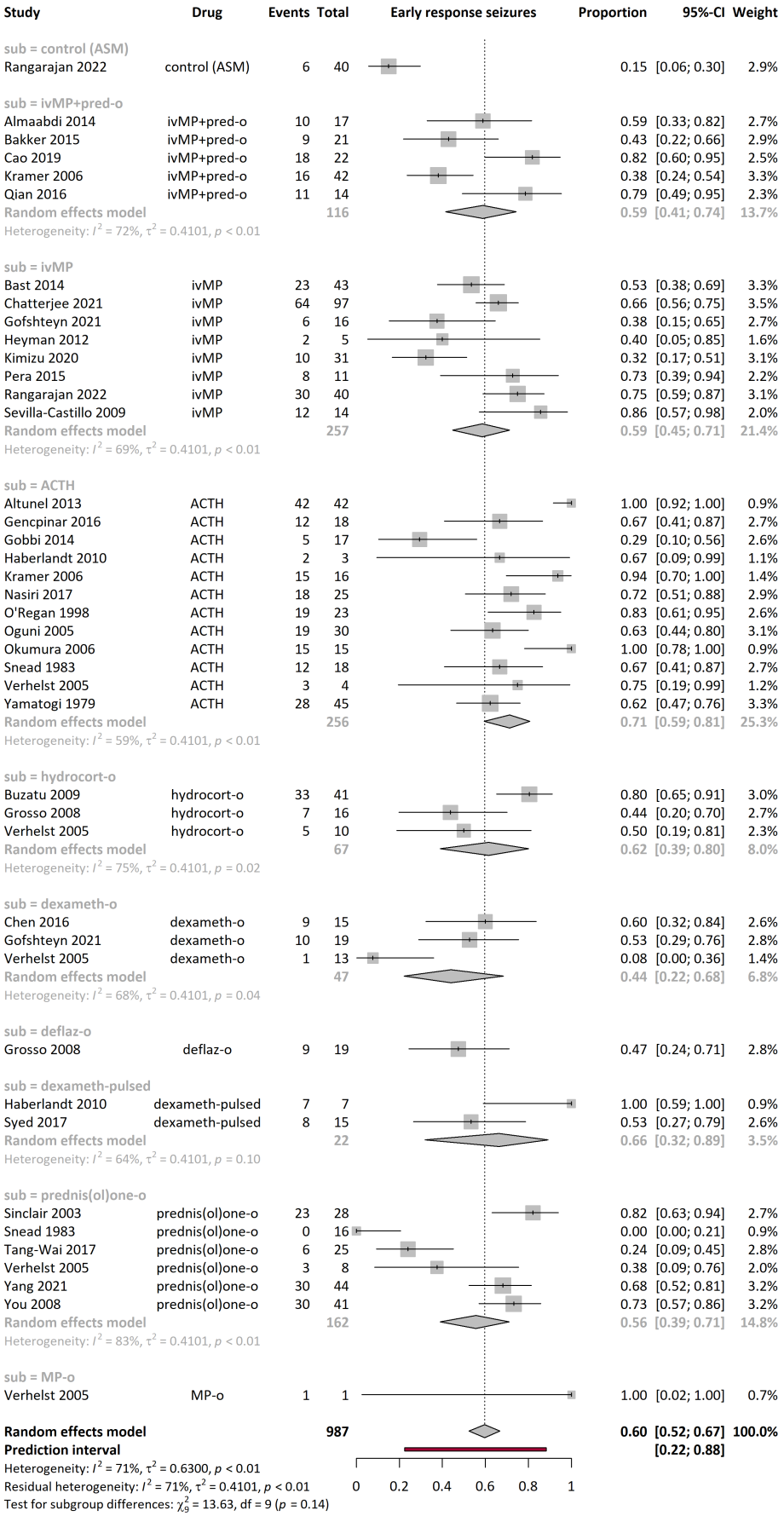

FIGURE 3 Forest-plot of the primary outcome "early response of seizures," subgroup analysis drug, ACTH, continuous intramuscular ACTH; deflaz-o, continuous oral deflazacort; dexameth-o, continuous oral dexamethasone; hydrocort-o, continuous oral hydrocortisone; ivMP, pulsed intravenous methylprednisolone; prednis(ol)one-o, continuous oral prednisone or prednisolone; ivMP-pred-o, ivMP followed by continuous oral prednisolone; MP-o, oral methylprednisolone.

3.4 | Analysis of individual participant data (IPD)

In 18 of the 38 included reports, the authors tabulated IPD, although not always incorporating the same variables. We combined these data from altogether 401 patients in the Excel sheet "Individual Participant Data" (Tables S2 and S4).

First, to see whether the IPD would be representative for the entire sample of 38 studies, we compared the distribution of relevant covariables between the reports contributing IPD tables and those without such tables. We identified no distinct differences between the two in the variables study type, epilepsy syndrome ESES/LKS vs mixed, drug group, mean age at treatment, male/female ratio, proportion of symptomatic etiology (Appendix S4, page 2). There is thus no indication that the IPD data are not representative for our review.

Table 6 shows the pooled proportions of the outcome measures calculated applying a generalized mixed model with study as random effect (results in Appendix S6). The numbers of reported outcomes differ considerably between studies. Notably, the proportions of the primary and secondary outcomes (0.49 and 0.33) tend to be somewhat lower than in the AD full-set of all 38 reports (Table 3).

Table 7 shows the descriptive statistics of the covariates. Also here, the numbers of reported features vary considerably, making statistical evaluation and interpretation difficult. We noted a significant correlation between symptomatic etiology and a more severe disability (proportional odds model, average odds ratio 2.27, $p = .0013$, Appendix S7, page 5).

We performed univariate and multivariate logistic regression analyses with different models. Probably because of the fewer cases that could be included, the regression models often failed to deliver interpretable results. However, similar to the meta-analyses of aggregate data, we can assume positive effects of ESES/LKS in comparison to other epilepsy syndromes and negative effects of symptomatic etiology and significant disability on treatment outcome. Patient age at treatment, epilepsy types other than ESES/LKS, individual drugs, and drug-groups were not associated with outcome in univariate analyses (Tables 8 and 9). For more details see the statistics output in Appendix S8.

3.5 | Sensitivity analysis

When choosing studies to include in our review, we excluded reports with important or multiple domains with a critical risk of bias but included those with serious RoB. This resulted in the data extraction and analyses described above. To test for sensitivity and goodness of fit, we now further excluded all reports with serious RoB in the domains of the primary outcomes "response of seizures" and "response of EEG." This yielded 19 reports that we subjected to the same analyses as described in Sections 3.3 and 3.4. These showed similar findings as in the previous analyses on the 38 reports, both regarding meta-analyses of the AD and the IPD analysis. As an example, Figure 6 shows the forest plot with subgroups "drug group" for the primary outcome variable "early response of seizures." In addition, the meta-regression and multivariable meta-regression analyses on the AD set and the logistic regression analyses on the IPD set yielded similar findings, as depicted in Sections 3.3 and 3.4. The full statistic output and figures for these data sets are found in Appendixes S9 (AD set) and S10 (IPD set). There was, therefore, no reason not to interpret the data sets of the 38 studies.

The data in .rda (R data) format and R Markdown scripts to reproduce all statistical analyses, including instructions (readme.txt), are found in a .zip folder (Appendix S11).

3.6 | Description of selected prospective controlled trials

A recently published randomized-controlled study compared pulsed treatment with ivMP with standard ASM.[20] After the screening of 100, a total of 91 children meeting the inclusion criteria entered the study. Central nervous system (CNS) imaging, short-term EEG including a nap, and Vineland Social Maturity Scale (VSMS) as a developmental test were performed in all. In the first 4 weeks ASM was optimized in all children and parents were trained to observe and record their children's seizures. After this baseline period, 40 patients each were randomized for open label treatment with ivMP + ASM or unchanged standard ASM (11 had dropped out before randomization). IvMP (30 mg/kg) was administered

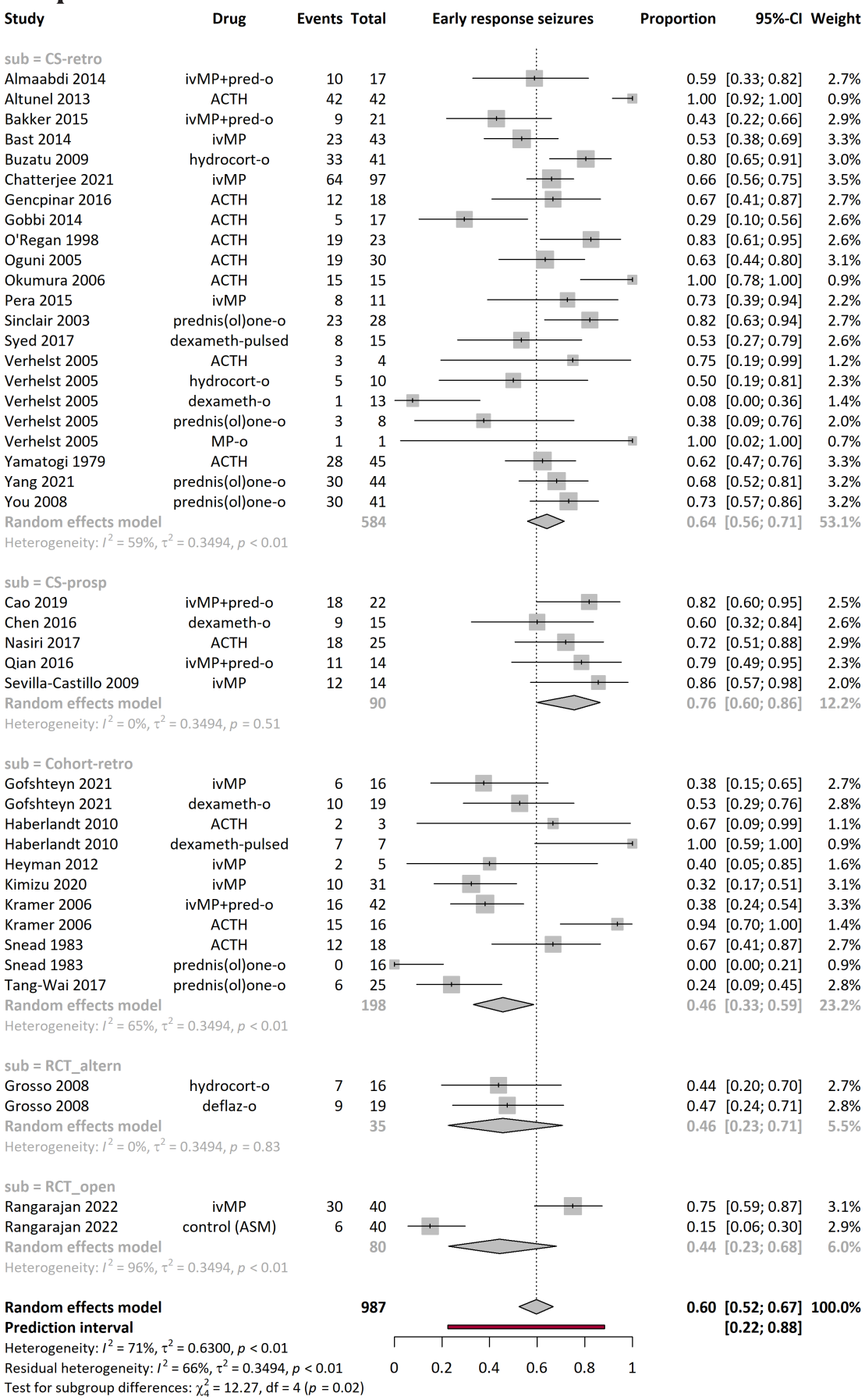

FIGURE 4 Forest-plot of the primary outcome "early response of seizures," subgroup study type. Note the lower heterogeneity in prospective vs retrospective studies. The high heterogeneity in the Rangarajan trial reflects the difference between ivMP and the control arm. CS-retro, retrospective case series; CS-prosp, prospective case series; Cohort-retro, retrospective cohort series; RCT_open, open-label randomized-controlled trial; RCT_altern, open-label, controlled trial with alternating allocation. For further abbreviations see Figure 3.

over 4–6 h for 5 days/month for 3 consecutive months (12 weeks). The primary and secondary outcomes seizure frequency, EEG, and VSMS were assessed 4 weeks after the last dose of third pulse of IVMP. The evaluators were blinded to the treatment allocation. ITT analysis showed that the primary outcome median percentage of change in seizure frequency after ivMP + ASM was significantly higher than in the ASM-only group: 91.4 (interquartile range [IQR] 47.37–100) vs 10 (IQR 0–25); $p < .001$. The seizure response rate (>50% decrease) was 0.75 in the intervention group as compared to 0.15 in the ASM-only arm ($p < .001$). In multivariate analysis, no factors other than treatment allocation had any influence on seizure outcomes. There was also significant improvement in the EEG results, and social age in VSMS rose slightly. No serious adverse drug reactions besides slight infections were observed in the ivMP group. Unfortunately, the authors did not report longer term effects beyond 4 weeks after treatment, so information on relapses that would be expected to occur after ending treatment is missing. Furthermore, the lack of blinding the primary observers and the changes of ASMs during the 4-week baseline triggers concern about the risk of bias.

Another prospective, comparative trial allocated patients with drug-resistant epilepsy to open-label treatment with oral hydrocortisone or deflazacort on an alternating sequence in the order of hospitalization.[21] ASMs were unchanged during the baseline period of 2 months and over the following 6 months. Seizure frequency and types were recorded by parents or caregivers. Hydrocortisone was administered at daily doses of 10 mg/kg for 1 month, 5 mg/kg for 1 month, 2.5 mg/kg for 1 month, 1 mg/kg for 1 month, and 1 mg/kg on alternate days for 2 months. Deflazacort was administered at a daily dose of 0.75 mg/kg for the whole 12-month study period. The efficacy and tolerability of the corticosteroids were evaluated after 6 months and at the 12-month follow up. All patients initially underwent brain MRI, waking and sleep EEG, metabolic screening, and chromosomal analysis. Clinical investigations, EEG, and structured monitoring of adverse effects including lab test and body mass index (BMI) measurements were done at each visit. Sixteen patients were treated with hydrocortisone (group 1) and 19 with deflazacort (group 2). After 6 months, there were 44% of responders (>50% seizure improvement) in group 1 and 47% in group 2. In group 1, 87% of responders relapsed to baseline 2 weeks to 3 months after cessation of hydrocortisone. In group 2, the relapse rate was only 22% ($p = .04$). In group 1, 37% of patients had at least one adverse effect (BMI > 97%ile, Cushing's syndrome, hypertonus, and others), only one patient in group 2 ended deflazacort after 12 months due to gastric pain. EEG results and cognitive effects were not reported. This was the first (and to date only) trial to show that deflazacort at a low dose is as effective in epilepsy as the higher hydrocortisone dose. The much lower relapse rate at 12 months is probably attributable to continuous treatment for this duration, and not a drug-specific effect.

4 | DISCUSSION

Two Cochrane reviews (CRs) and several narrative reviews have been published on our topic during the past decade. A CR on the treatment of Lennox–Gastaut syndrome (LGS) identified nine randomized-controlled trials, but none on ACTH or prednisone.[33] Another CR on the treatment of pediatric epilepsies other than West syndrome identified one randomized cross-over trial of synthetic $ACTH_{4\text{-}9}$ in five children with LGS. One of these children did not start treatment; of the others, none achieved seizure reduction exceeding 50%.[9] We did not include this study in our review because of the low number of patients.[58] Dontin et al[6] summarized 19 studies in a narrative review of corticosteroid therapy for epileptic encephalopathies other than West syndrome. Except for two studies on ESES and one on pulsed methylprednisolone, all were retrospective series and case reports. The authors suggested promising potential for pulsed treatment and emphasized the need for more research and an international consensus. Bakker et al[5] published a review of 14 retrospective studies reporting on over five patients in addition to their own case series. ACTH appeared superior to corticosteroid in this compilation, with 69% of 103 vs 48% of 192 short-term responders (>50% seizure reduction). However, the 50%–70% relapse rate was very high in both groups. The highly variable treatment durations did not seem to influence the treatment outcomes; however, the reviewers suspected differential effectiveness of ACTH and corticosteroid in different types of epilepsy, although this statement remained purely descriptive.

Our systematic review included 38 studies with 1152 patients in the AD analysis and 401 patients in the IPD analysis. Thirty-one of the 38 studies were retrospective case series (4

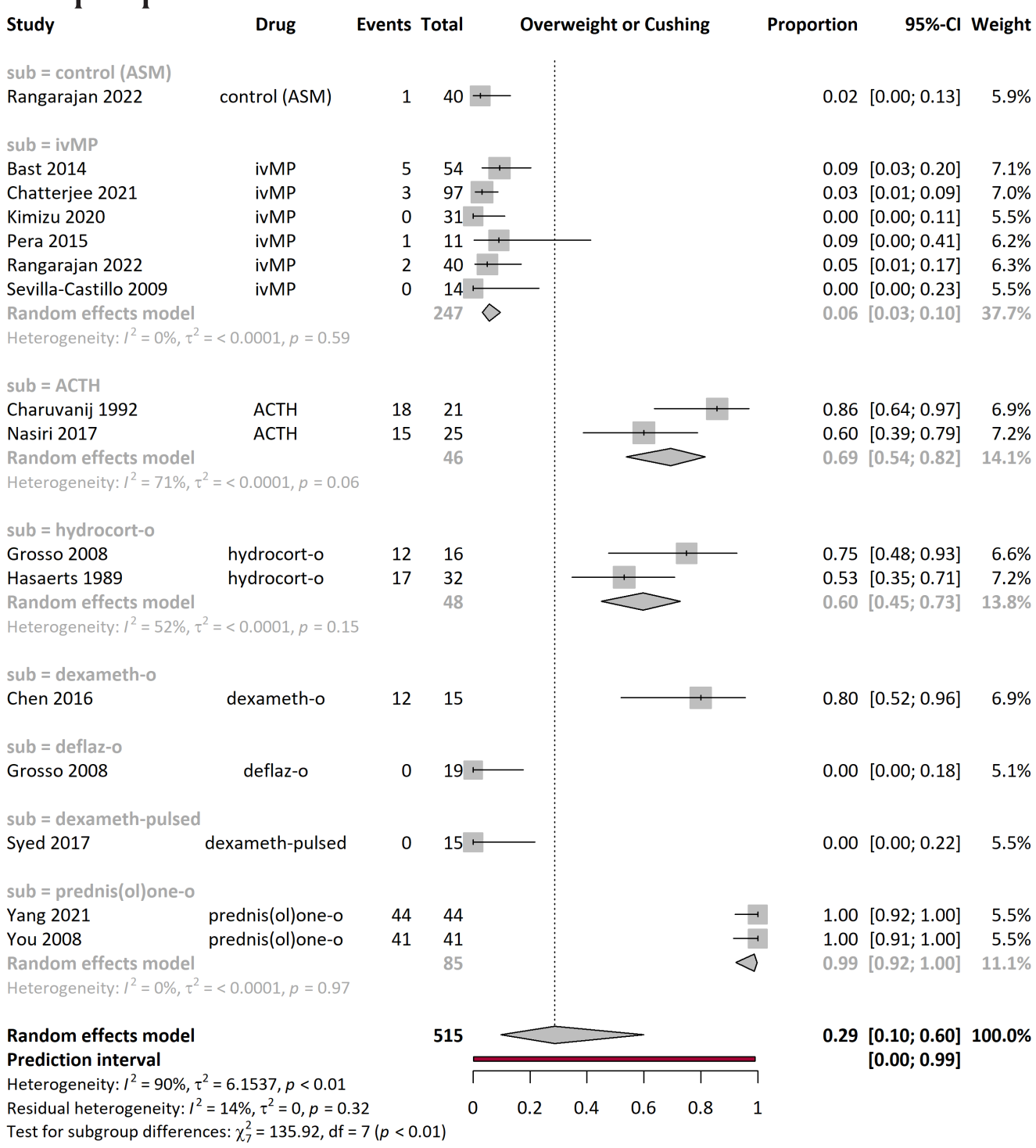

FIGURE 5 Forest plot subgroup analysis drug of the secondary outcome "side effect overweight or Cushing's syndrome," legend see Figure 3.

with two different treatment arms and 1 with five different treatment arms), 5 were prospectively treated and recorded case series, and 2 were open-label prospective controlled trials with alternating or randomized treatment assignment. Overall, similar to the previous narrative reviews, we found a pooled early 50% response rate for seizures and EEG in about 60%, and seizure freedom or EEG normalization in 20%–30% of patients. Behavioral or cognitive improvement occurred in 50% of patients. Several authors reported that the improvement usually occurred after 1–2 (maximum 4) weeks of treatment. However, a pooled 33% of all treated or 50%–60% of initially improved patients experienced

TABLE 4 Results of multivariable meta-regression, AD: early response seizures.

	Estimate	95% CI	*p*-value
Intercept	−0.52	−2.30 to 1.27	
Drug group ivMP/Dex pulsed	0.16	−0.65 to 0.97	.6959
Drug group oral CST cont	−0.18	−0.90 to 0.54	.6260
Drug group ACTH	0.64	−0.18 to 1.47	.1272
Epilepsy type ESES/LKS	0.94	0.19 to 1.70	.0142
Cortisol-equivalents (log-transformed)	0.16	−0.11 to 0.43	.2480
Proportion with symptomatic etiology	−0.87	−1.94 to 0.20	.1126

TABLE 5 Results of multivariable meta-regression, AD: early EEG response.

	Estimate	95% CI	*p*-value
Intercept	−1.42	−4.20 to 1.35	
Drug group ivMP/Dex pulsed	−0.03	−1.04 to 0.98	.9513
Drug group oral CST cont	−0.18	−1.77 to 1.42	.8279
Drug group ACTH	1.45	0.48 to 2.42	.0035
Epilepsy type ESES/LKS	1.32	0.21 to 2.42	.0192
Cortisol-equivalents (log-transformed)	0.22	−0.21 to 0.66	.3140
Proportion with symptomatic etiology	−1.74	−3.58 to 0.09	.0630

TABLE 6 Pooling of IPD outcome variables using a generalized mixed model with study as random effect.

Outcome variables	*N* total	*N* outcome	Proportion	95% CI
Early response of seizures[a]	316	139	0.49	0.27-0.71
Early EEG response[a]	193	78	0.33	0.14-0.53
Relapse seizures (proportion of responders)	121	69	0.61	0.43–0.82
Relapse EEG (proportion of responders)	43	20	0.47	0.31–0.74
Late response of seizures	239	70	0.30	0.10–0.60
Late EEG response	80	26	0.32	0.22–0.44
Improved behavior	110	50	0.49	0.27–0.74
Improved cognition	162	80	0.47	0.23–0.73
Overweight	92	20	0.24	0.12–0.40

[a]Primary outcome variables.

recurrences after discontinuing ACTH and corticosteroids or even while tapering. This resulted in a longer-term outcome of a remaining 30%–40% responders.

In our AD meta-analysis, all primary and secondary outcome measures revealed very large heterogeneity among studies, which could only be somewhat explained by different drugs or other covariates. Studies using ACTH showed a 10%–15% higher pooled response rate than the others, but this differed dramatically among individual ACTH series. Other than this, we detected no differences in efficacy among the various steroids. We also failed to demonstrate an association between cumulative steroid or ACTH dose and effect. Most of the studies we included had investigated whether factors such as patient age, time since epilepsy diagnosis, etiology, type of epilepsy, seizure type, and EEG changes were predictive of treatment effect. By and large, these variables demonstrated no influence in more than one study. Low patient numbers in subgroups, lack of statistical power, and often the problem of multiple and "a posteriori" testing complicate any serious interpretation of the published results. As far as the data quality enables a conclusion, our meta-regression (AD) and logistic regression (IPD) analyses did identify positive effects in ESES/LKS vs other epilepsies, and negative effects of symptomatic etiology and more severe disability on EEG and cognitive improvement. Although these results should be viewed with caution due to methodological factors, they make sense from a clinical perspective. Systematic monitoring of drug-specific adverse effects

TABLE 7 Descriptive statistics of covariates used in IPD regression analysis.

Covariates	*N* total	*N* true	Proportion
Symptomatic etiology	373	136	0.36
Disability, moderate–severe	214	143	0.67
Corticosteroid (CST)			
Dexamethasone	401	32	0.08
Hydrocortisone	401	52	0.13
ivMP	401	105	0.26
oMP	401	1	0.002
Prednisone	401	95	0.24
sACTH	401	116	0.29
CST drug group			
CST pulsed	401	73	0.18
CST pulsed + cont	401	39	0.09
CST cont	401	173	0.43
ACTH	401	116	0.29
Type of epilepsy			
Unclassified	401	52	0.13
Location-related	401	70	0.17
Generalized	401	46	0.11
LGS	401	43	0.10
MAE	401	16	0.04
SMEI	401	21	0.05
ESES	401	93	0.23
LKS	401	28	0.07
Rasmussen	401	3	0.007
Epileptic spasms	401	29	0.27
Epilepsy type grouped			
ESES & LKS	401	121	0.30
All others	401	280	0.70

TABLE 8 Results of multivariable regression, IPD: early seizure response.

	Estimate	95% CI	*p*-value
Intercept	0.34		
Age	−0.003	−0.01 to 0.00	.38
Proportion symptomatic etiology	−0.22	−0.86 to 0.40	.48
Epil-type ESES/LKS	0.53	−0.44 to 1.55	.28
Drug group continuous CST	−1.44	−3.23 to 0.20	.08
Drug group pulsed CST	0.30	−1.43 to 2.29	.73
Drug group pulsed+continuous CST	−1.15	−3.50 to 1.06	.28

was reported in 14 studies. Our pooled data show that the development of obesity and/or Cushing's syndrome strongly correlates with the treatment protocol; these were frequently observed under continuous treatment with ACTH and oral corticosteroids, but rarely under pulsed intravenous or oral therapy with steroids or continuous deflazacort.

4.1 | Limitations

Weaknesses of this review a priori result from the risk of bias of the included studies. We included a wide range of clinical trial types to incorporate as many different treatment protocols with ACTH or corticosteroid as possible. We accepted a higher risk of bias and studies with lower

TABLE 9 Results of multivariable regression, IPD: early EEG response.

	Estimate	95% CI	*p*-value
Intercept	0.04		
Age	0.00	−0.0 to 0.01	.53
Proportion symptomatic etiology	−0.95	−1.75 to 0.19	.02
Epil-type ESES/LKS	1.48	0.22 to 2.79	.02
Drug group continuous CST	−1.53	−4.02 to 0.62	.11
Drug group pulsed CST	−0.99	−2.88 to 0.86	.26
Drug group pulsed+continuous CST	−1.36	−4.46 to 0.80	.28

validity so long as the study design enables us to discern a relationship between a specific therapy and essential outcome measures. In our meta-analyses, the enormous heterogeneity of outcome results is striking among studies, even with very similar treatment protocols. Apart from deviations from the reported dose and therapy duration, this could be due to unknown differences in the patients treated. Despite similar clinical and electroencephalographic manifestations, early childhood epilepsies, in particular, may be caused by a variety of small brain lesions and genetic variants, which would only be detectable via advanced MRI examinations and molecular genetic testing methods not available to authors of the older studies. In addition, we cannot expect consistent nomenclature of seizure types, epilepsy syndromes, and EEG anomalies over such a long time-span. The detection and documentation of seizures is an inherent problem in epilepsy trials. Although convulsive seizures and drop seizures are relatively easy to recognize, this is not true for a myriad of minor seizure manifestations, some of which occur only during sleep. This situation is made even more difficult in disabled children and adolescents, whose seizures are often assessed by alternating caregivers and in changing surroundings. Thus high-quality trials can be achieved only by prospective study designs with clearly defined inclusion criteria, observational methods, and training of relevant individuals, or must be compensated by a randomized-controlled study design with adequate case numbers.

In our AD analysis, we examined study arms defined by a uniform drug, a fairly uniform age group of patients, and similar dosing and treatment duration. Because eight studies had enrolled patients with ESES or LKS exclusively, we could match those in the AD analysis with the 30 others with mixed epilepsies. However, gender distribution, illness duration, cause of epilepsy, extent of comorbid disability, and other covariates were distributed differently within and between studies. We could only capture these indirectly in our analyses, for example, as a proportion of patients with symptomatic etiology in a study. From the IPD analysis, we had expected the possibility of more-detailed association analyses. However, because of the highly variable IPD composition of contributing studies, statistical evaluation proved to be difficult.

Although the dose and duration of the initial full-dose treatment were relatively uniform within individual studies, the subsequent maintenance phase and tapering varied widely depending on patient response, adverse effects, and secondary deterioration. Even some of the higher-ranked trials reported results only up to the end of treatment, leaving open the question of relapse and long-term outcomes. We, therefore, limited our attempt to carry out dose–response calculations to the initial high-dose treatment phase and calculated the cumulative dose for that phase. Because the various corticosteroids applied entail different glucocorticoid potency, we converted the actual doses into cortisol-equivalents according to published data. A particular challenge was converting different ACTH preparations. We relied on two recent pharmacological publications that had been unknown in the field. Our evaluations on ACTH's cortisol-equivalent should, therefore, be interpreted with caution.

4.2 | Summary and recommendations on the clinical use of ACTH and corticosteroids

Based on this systematic review on retrospective case series and a few prospective trials including only one randomized-controlled trial, we are unable to make strong recommendations based on high-level evidence data. However, there is some low-level evidence that ACTH and various corticosteroids are effective in ASM-resistant childhood epilepsies beyond IESS. In the pooled results of our meta-analysis, 60% responded with a >50% reduction in seizures, half of them becoming seizure-free. The EEG response was similar. In addition,, there might have been improved psychological function in half of the patients. However, at or up to several months after treatment withdrawal, at least half of responders relapse, resulting in long-term seizure alleviation in 30%–40% of patients. We observed

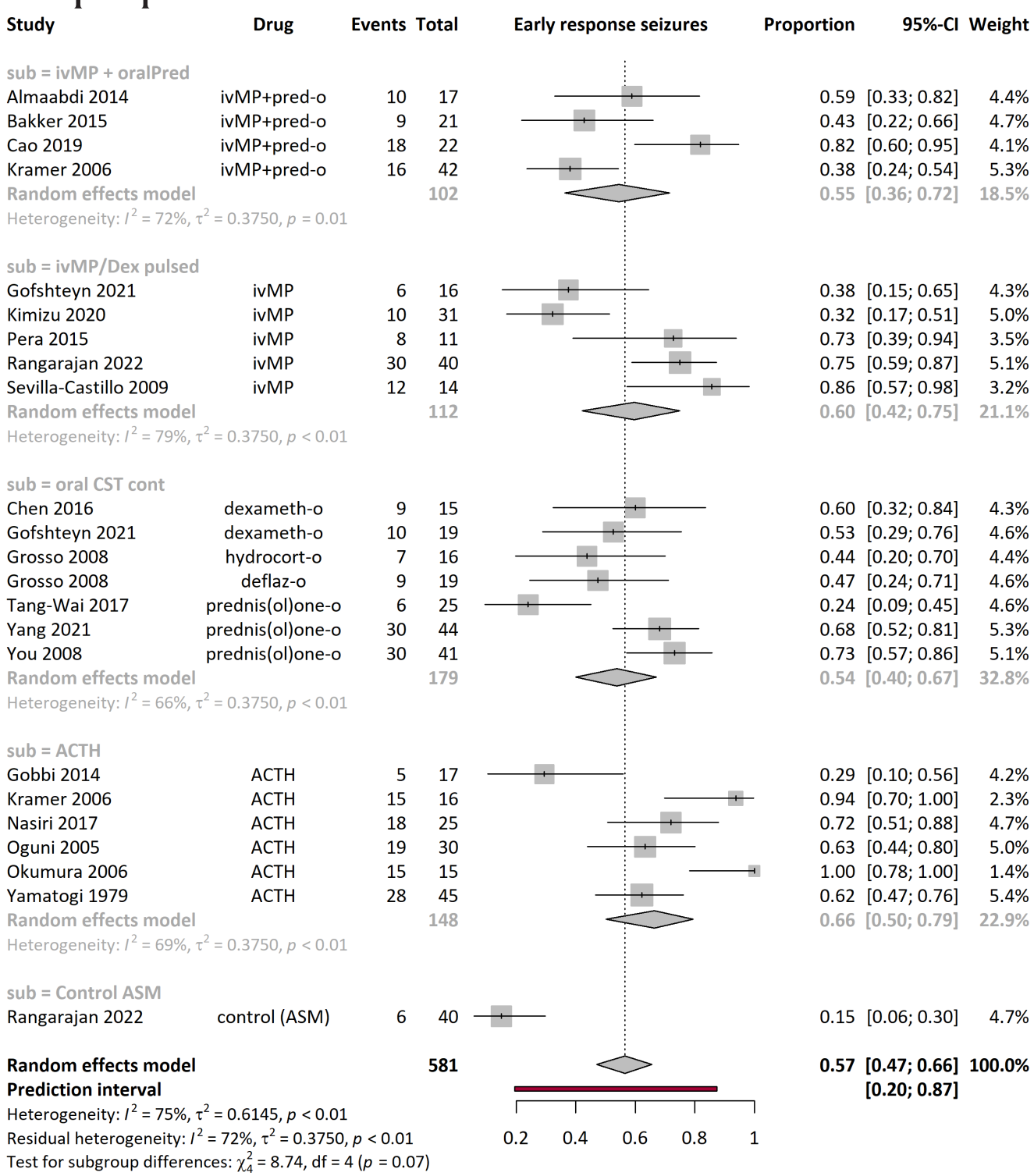

FIGURE 6 Sensitivity analysis that included 19 reports with at most "moderate" risk of bias for the seizure outcome, example. Forest plot of the primary outcome "early response of seizures," subgroup analysis drug group. Legends as in Figure 3.

only minor, clinically irrelevant differences in efficacy between ACTH and the various corticosteroid drugs including pulsed ivMP. Concerning EEG and cognitive improvement, patients with ESES or LKS seem to respond somewhat better than those with other epileptic syndromes, and children with symptomatic etiology and more severe disability do worse. The most frequent adverse effect is abnormal weight gain and Cushing's syndrome. However, these are associated nearly exclusively with continuous ACTH and oral corticosteroid regimens, whereas the pulsed protocols seem to have only slight and transient side effects. In conclusion,

also in children beyond IESS, ACTH or corticosteroids can be tried in epilepsies that are unresponsive to ASMs, especially in epileptic encephalopathies with deteriorating cognitive function. Under the assumption that there are no proven differences in effectiveness among drugs, we recommend applying those protocols with the fewest side effects, namely, pulsed ivMP or pulsed oral corticosteroids. Continuous low-dose deflazacort has been reported to trigger few side effects as well, but such novel data should be verified in further studies.

4.3 | Suggestions for future clinical trials

More prospective and well-organized studies are mandatory to improve what is very weak evidence currently. Patients must be investigated by applying the best current clinical, radiological, metabolic, and genetic methods, and inclusion and exclusion criteria must be derived accordingly. Ultimately, only randomization and, when feasible, blinding will enable researchers to control for additional unknown influencing factors. For example, a comparison of ivMP with oral deflazacort, both in a pulsed regimen, is a potentially worthwhile study question derived from the present data. A comparison of different ivMP doses (10 versus 30 mg/kg), two different dexamethasone pulse doses, or pulsed dexamethasone vs continuous deflazacort are also suitable study designs.

AUTHOR CONTRIBUTIONS

Rudolf Korinthenberg: design of study, search of literature, selection of literature, quality assessment of publications, data extraction, drafting of the manuscript, editing of the manuscript. Thomas Bast: literature selection, quality assessment of publications, data extraction, editing of the manuscript. Edda Haberlandt: literature selection, quality assessment of publications, data extraction, editing of the manuscript. Ulrich Stephani: literature selection, quality assessment of publications, data extraction, editing of the manuscript. Adam Strzelczyk: literature selection, quality assessment of publications, data extraction, editing of the manuscript. Gerta Rücker: study design, data extraction, statistical analysis, editing of the manuscript.

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CONFLICT OF INTEREST

U.S: nothing to declare concerning any steroid treatment evaluation. A.S. has received personal fees and grants from Angelini Pharma/Arvelle Therapeutics, Desitin Arzneimittel, Eisai, Jazz (GW) Pharmaceuticals, Marinus Pharma, Medtronic, Takeda, UCB (Zogenix) Pharma, and UNEEG Medical, but these are not related to the topic of this review. T.B. and E.H. have published their own data on steroids in epilepsy 9 and 14 years ago. R.K. is coauthor of the current German guidelines on treatment in IESS. G.R. has no conflicts of interest to declare.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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