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REVIEW

Incidence of fatigue and low-dose corticosteroid use in prostate cancer patients receiving systemic treatment: a meta-analysis of randomized controlled trials

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Abstract

Background Cancer-related fatigue (CRF) is a complex condition that is reported in > 50% of cancer patients. In men with castration-resistant prostate cancer (CRPC), CRF was reported in 12–21% of patients. Approved systemic therapy against CRPC is commonly administered in combination with androgen-deprivation treatment (ADT) and, in some cases, with daily, low-dose corticosteroids. Importantly, the use of low-dose corticosteroids is associated with multiple negative effects, including reduced muscle mass. On these grounds, we hypothesized that the chronic use of corticosteroids may increase the incidence of fatigue in patients with prostate cancer.

Methods We reviewed all randomized trials published during the last 15 years conducted in patients with prostate cancer receiving systemic treatment and we performed a sub-group analysis to gather insights regarding the potential differences in the incidence of fatigue in patients receiving vs. not receiving daily corticosteroids as part of their systemic anti-neoplastic regimen.

Results Overall, 22,734 men enrolled in prospective randomized phase II and III trials were evaluable for fatigue. Estimated pooled incidence of grade 1–2 fatigue was 30.89% (95% CI = 25.34–36.74), while estimated pooled incidence of grade 3–4 fatigue was reported in 3.90% (95% CI = 2.91–5.02). Sub-group analysis showed that grade 3–4 fatigue was approximately double in patients who received daily corticosteroids as part of their anti-neoplastic treatment (5.58; 95% CI = 4.33–6.98) vs. those who did not (2.67%; 95% CI = 1.53–4.11).

Conclusion Our findings highlight the need for ad hoc-designed prospective clinical trials to investigate whether the benefits associated with low-dose, daily corticosteroids outweigh the risks associated with corticosteroid-related adverse events such as fatigue.

Keywords Prostate cancer · Meta-analysis · Fatigue · Corticosteroids

Introduction

Cancer-related fatigue (CRF) is a complex condition that is reported in > 50% of cancer patients [1],

and it is related to cancer itself or anti-neoplastic medications [2]. Although CRF is considered by patients as having a profound effect on their daily functioning [1], in common clinical practice, only a minority of patients receive any anti-fatigue intervention among those recommended [2]. In men with castration-resistant prostate cancer (CRPC), CRF was reported in 12–21% of patients [3], and prospective clinical trials report a prevalence of Grade 3/4 fatigue according to Common Toxicity Criteria in the range of 0–18%.

Approved systemic treatments against CRPC include hormonal, chemotherapy, immunotherapy as well as radiopharmaceutical agents [4]. These agents are commonly administered in combination with androgen-deprivation treatment (ADT) and, in some cases, with daily, low-dose

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corticosteroids, as it is the case of abiraterone [5], docetaxel [6] and cabazitaxel [7]. Importantly, the use of low-dose corticosteroids is associated with multiple negative effects, including reduced muscle mass, increased adipose tissue and impaired glucose tolerance [8]. These deleterious effects are implicated in the pathogenesis of CRF [2] and can also be caused or worsened by long-term ADT [9]. On these grounds, we hypothesized that chronic use of corticosteroids may affect the risk of reporting fatigue in patients with prostate cancer. In this meta-analysis, we reviewed all randomized trials published during the last 15 years and conducted in patients with prostate cancer receiving systemic treatment. A sub-group analysis was performed to explore differences in fatigue incidence in patients receiving vs. patients not receiving daily corticosteroids as part of their systemic anti-neoplastic regimen.

Evidence acquisition

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10].

Data source and search

We reviewed MEDLINE/PubMed for articles published since December, 2004 until December, 2017. The search criteria were limited to articles published in the English language and phase III or phase II randomized in prostate cancer patients. The MeSH terms used for the PubMed search were 'prostate cancer' and 'randomized trial'. If more than one publication was found for the same trial, the most recent, complete and updated version was included in the final analysis.

Study selection

Screening of all the titles and abstracts retrieved was performed by PP, AS, VC, while two reviewers (PP and VC) evaluated full texts of the articles. In case of disagreement, disagreement was resolved by consensus or, if consensus was not reached, by consulting a third reviewer (MF). The findings of interest from the articles included were collected using a dedicated spreadsheet.

Inclusion criteria

Included studies were randomized phase II or phase III trials testing a systemic agent in prostate cancer.

Exclusion criteria

Studies were excluded if adverse events were not grade according to Common Toxicity Criteria (https://www.eortc.be/services/doc/ctc/) or if data about incidence of adverse events were not reported.

Outcomes

The data obtained for each trial included the first author's name, year of publication, trial phase, inclusion of patients with metastatic disease, inclusion of patients with castration-resistant and number of experimental arms. For each arm, information about the number of evaluable patients, type of systemic agent administered, use of ADT, use of daily corticosteroids, number of patients with fatigue of grade 1–2 and grade 3–4 was retrieved.

Statistical analysis

Statistical heterogeneity between studies was assessed using the Cochrane Q statistic (with a p value < 0.1 reflecting a significant heterogeneity) and I2 statistic, which measures the percentage of total variability across studies not due to sampling error. Due to an expected large heterogeneity across trials, the random-effects model of DerSimonian and Laird was a priori selected to obtain pooled incidence estimates. To correct for over-dispersion, which refers to a variability in the individual observations larger than that expected under the theoretical model and which is particularly common when proportions are < 0.30 and/or > 0.70, the raw incidences were converted using the Freeman–Tukey transformation and back transformed after quantitative data synthesis (please see [11] for further explanations). A subgroup analysis, based on the use of daily corticosteroids as part of the therapeutic regiment, was planned to explore whether this covariate may have an impact on fatigue burden in these subgroups of patients.

Statistical analysis was performed using the R statistical programming environment, Version 3.5 (http://www.r-project.org).

Quality assessment

Study quality was assessed using the Jadad 5-item scale [12], as described. The final score ranged from 0 to 5.

Evidence synthesis

The systematic literature search performed on PUBMED retrieved 2267 abstracts. Fifty full texts were finally included in the quantitative meta-analysis [13–62]. There was no disagreement between the reviewers on the articles that met the inclusion criterion. Detailed information on the article retrieval process is illustrated in Fig. 1. Most of the trials included in the quantitative meta-analysis had a Jadad score ≥ 3, with only 4 trials that presented a Jadad score of 1. Characteristics of the studies included are summarized in Table 1.

Overall, 22,734 men enrolled in prospective randomized phase II and III trials were evaluable for fatigue. Estimated pooled incidence of grade 1–2 fatigue was 30.89% (95% CI = 25.34–36.74) (Fig. 2), while estimated pooled incidence of grade 3–4 fatigue was reported in 3.90% (95% CI = 2.91–5.02) (Fig. 3). There was significant heterogeneity for both grade 1–2 and grade 3–4 fatigue in the entire population considered as well as in the subgroups divided by daily corticosteroids use. Importantly, no significant differences in incidences of grade 1–2 fatigue were reported between patients receiving daily corticosteroids and those who did not (Fig. 4), while sub-group analysis showed that grade 3–4 fatigue was approximately double in patients who received daily corticosteroids as part of their anti-neoplastic treatment (5.58; 95% CI = 4.33–6.98) vs. those who did not (2.67%; 95% CI = 1.53–4.11) (Fig. 5). A persistent heterogeneity between the trials in each of these two subgroups was noted; so, the pooled incidence estimates in each group may be biased.

Discussion

In our meta-analysis involving more than 22,000 prostate cancer patients receiving systemic therapy in prospective clinical trials, we found that about one-third of the patients received concomitant daily corticosteroids. Docetaxel was approved in combination with low-dose prednisone

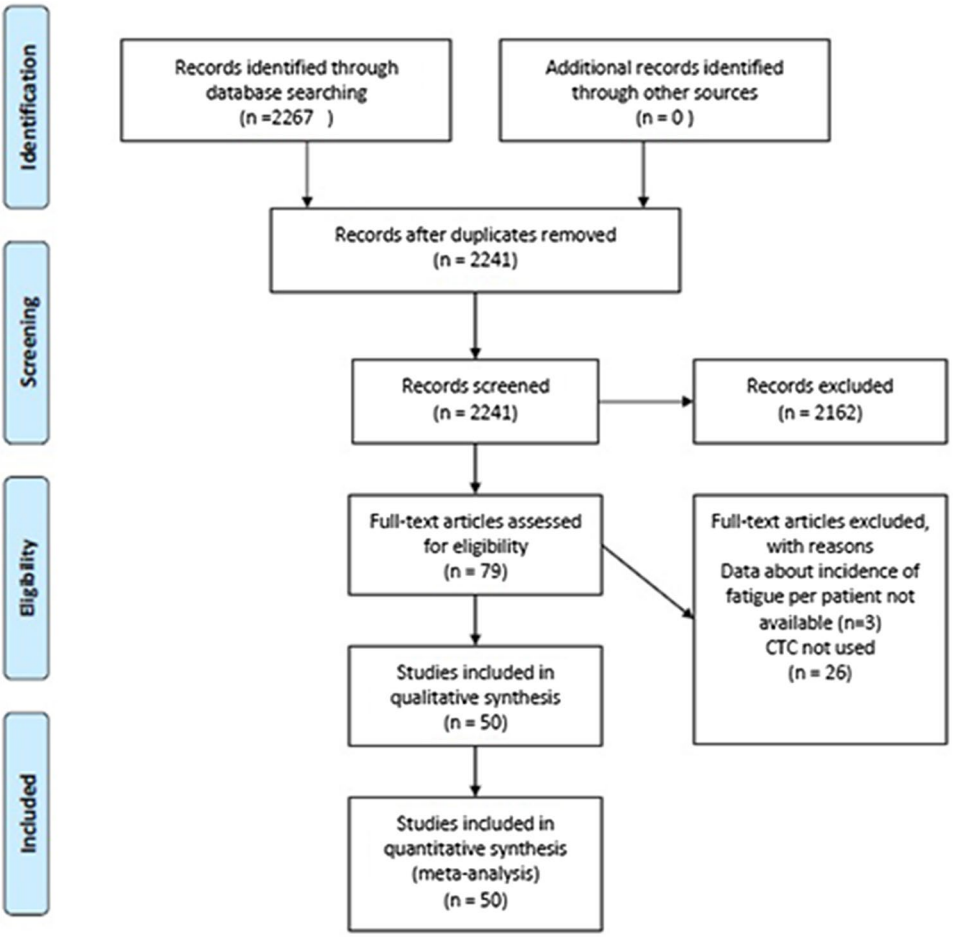

Fig. 1 Flow diagram of the evidence acquisition

Table 1 Characteristics of individual trials included in the meta-analysis and oftrial arms

Characteristics of individual trials of the quantitative analysis ($n=50$)	
Variable	Number
Phase II	27
Phase III	23
Jadad score	
1	4
2	13
3	11
4	6
5	16
Version of the CTC employed	
1.0	1
2.0	13
3.0	22
4.0	14
Metastatic disease	
Yes	43
No	7
CRPC	
Yes	31
No	19
Characteristics of individual arms of the trials included in the quantitative analysis ($n=106$)	
Variable	Number
Chronic corticosteroid administered	
Low-dose (≤ 10 mg daily) prednisone/prednisolone	45
Other	1
ADT administered	
Yes	88
No	18
Type of systemic intervention besides ADT	
Chemotherapy	25
Hormonal agent	12
Immunotherapy	3
Radiopharmaceutical agent	2
Targeted agent	15
Inert placebo	15
Combination of agents belonging to the classes above	26
Other agents not belonging to the classes above	8

on the grounds of the TAX 327 results [61], which may have influenced investigators to use concomitant low-dose corticosteroids with active treatments in subsequent trials [63–65]. The concomitant use of corticosteroids in the TAX 327 trial was based on the results by Tannock et al., who reported that low-dose prednisone treatment (7.5–10 mg daily) could lower serum testosterone, androstenedione and dehydroepiandrosterone sulfate levels in men with CRPC, with a clinically meaningful palliative effect [66]. In more recent clinical trials, prednisone alone was associated with a palliative effect in 12% of patients in a randomized phase III trial comparing mitoxantrone plus prednisone vs. prednisone [67]; while in randomized studies of abiraterone, the use of prednisone alone demonstrated measurable clinical benefits including PSA declines (10% after docetaxel, 24% before docetaxel) and RECIST responses (3% and 16%, respectively) [5, 31]. With the growing number of effective systemic agents available in prostate cancer, the clinical benefit associated with concomitant corticosteroid use remains uncertain, especially in patients who have received multiple lines of treatments. In fact, apart from the known negative metabolic effects due to their prolonged use, corticosteroids may even promote prostate cancer growth by activating some AR variants that make tumors sensitive to glucocorticoids even at low concentrations [68]. In a recently published pooled analysis [69] including the control arms of 18 randomized controlled trials that had (n = 2831) or had not ($n=2784$) administered single-agent prednisone, no significant differences were reported for overall survival or adverse events of any grade, except for a trend towards more frequent grade ≥ 3 fluid retention (1.0% vs. 0.4%; $P=0.097$) that was seen in the prednisone group. Unfortunately, incidence of fatigue was not evaluated in this meta-analysis [69]. In our work, we focused on the potential relationship between fatigue and the chronic use of low dose of corticosteroids. In a large pooled sample including > 22,000 patients, we found that grade 3–4 fatigue incidence was approximately double in patients receiving daily corticosteroids as part of their systemic therapy vs. patients who did not. No differences were found in the incidence of grade 1–2 fatigue. Incidence of grade 1–2 vs. grade 3–4 fatigue showed a numerically higher heterogeneity (97 vs. 91%, respectively), which may be related to the fact that fatigue is often underreported [70], and mild fatigue may be more likely not to be reported at all than severe fatigue.

Our meta-analysis presents multiple limitations. First, the trials included employed different versions of the Common Toxicity Criteria, which slightly differ in the definition of fatigue. Second, our meta-analysis was not designed to account for the multitude of confounding factors related to fatigue, such as line and type of treatment, patient and disease characteristics (disease stage, patient comorbidities, concomitant medications including steroids, etc.).

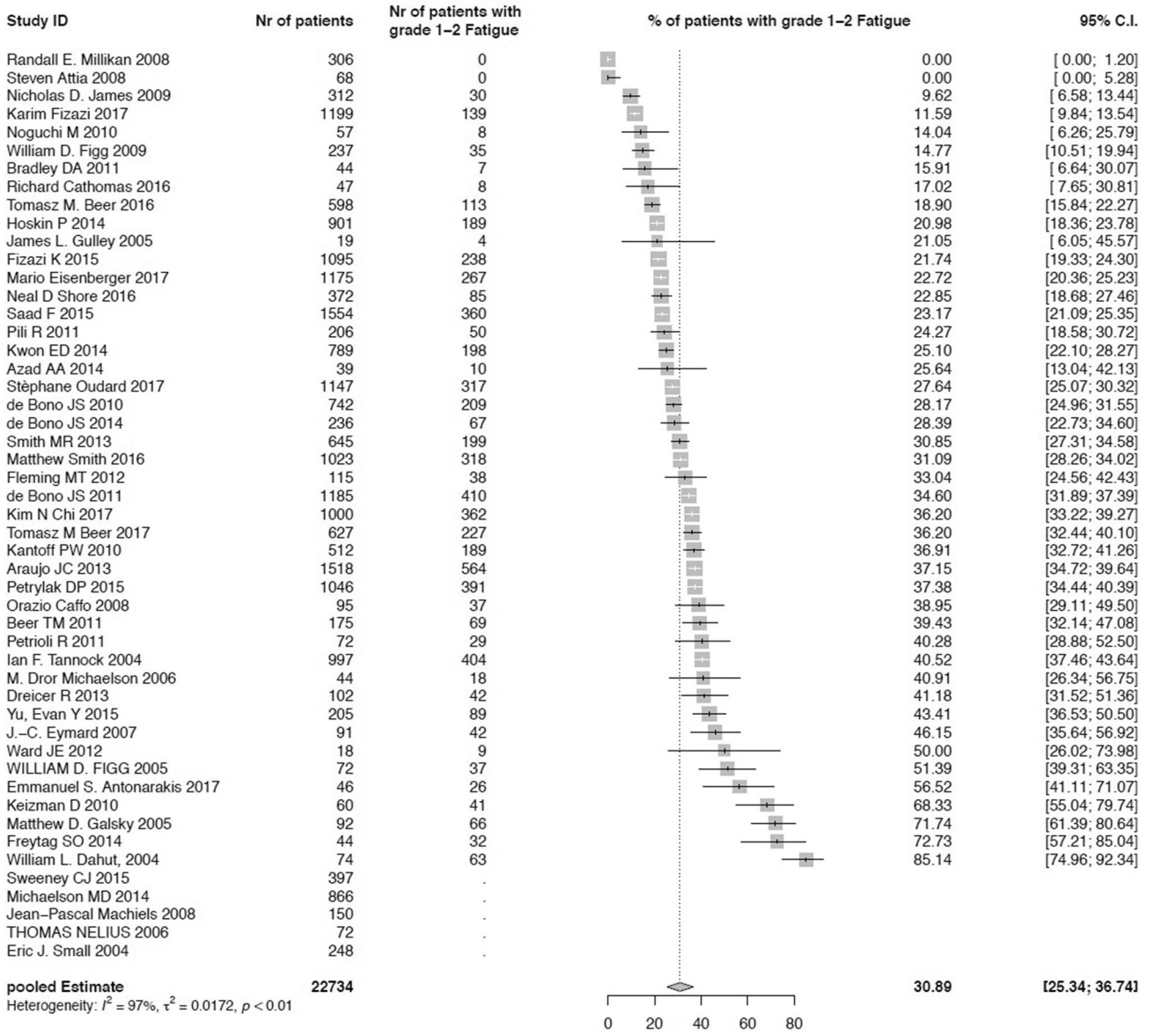

Fig. 2 Pooled estimated incidence of grade 1–2 fatigue

Third, there was significant heterogeneity among the studies included. Fourth, 17 of the 50 trials included showed a Jadad score of less than 3; so, the underlying data of poor quality may ultimately undermine the strength of our results. The systematic selection of prospective, randomized trials, as well as the large size of the pooled sample is among the strengths of our meta-analysis. In brief, we have shown that low-dose, daily corticosteroids are commonly administered with systemic agents in prostate cancer patients enrolled in clinical trials, without any convincing evidence that their benefits outweigh the risks associated with possible adverse events such as fatigue. In this regard, the results of the subgroup analysis performed in patients treated with vs. without daily corticosteroid further highlight the need for ad hoc-designed, prospective, randomized controlled trials. In this regard, useful data will be provided by the ongoing randomized phase II CABACARE trial, which was designed to compare safety and efficacy of cabazitaxel administered with vs. without daily prednisone in CRPC patients [71].

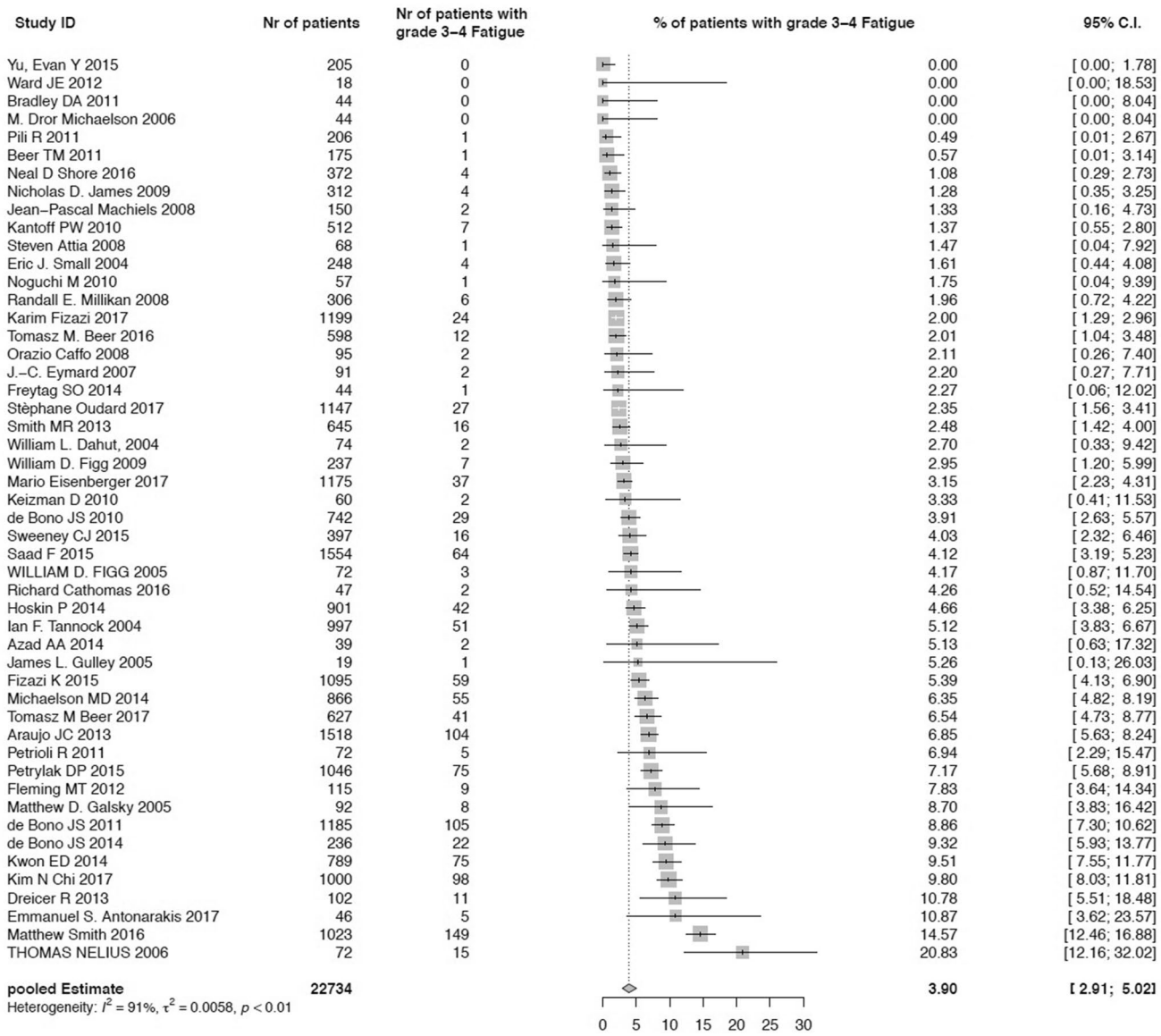

Fig. 3 Pooled estimated incidence of grade 3–4 fatigue

Authors' contribution Ferro: Project development; Manuscript editing. Di Lorenzo: Project development; Manuscript editing. de Cobelli: Project development; Manuscript editing. Bruzzese: Data analysis. Pignataro: Data collection. Borghesi: Project development. Musi: Project development. Vartolomei: Project development. Cosimato: Data collection. Serino: Data collection. Ieluzzi: Data collection. Terracciano Project development. Damiano Project development; Manuscript editing. Cantiello Project development; Manuscript editing. Mistretta Project development; Manuscript editing. Muto Project development; Manuscript editing. Lucarelli Project development; Manuscript editing. De Placido Project development; Manuscript editing. Buonerba Project development; Data management; Manuscript writing.

Compliance with ethical standards

Conflict of interest No relevant conflicts by any of the authors are to be disclosed.

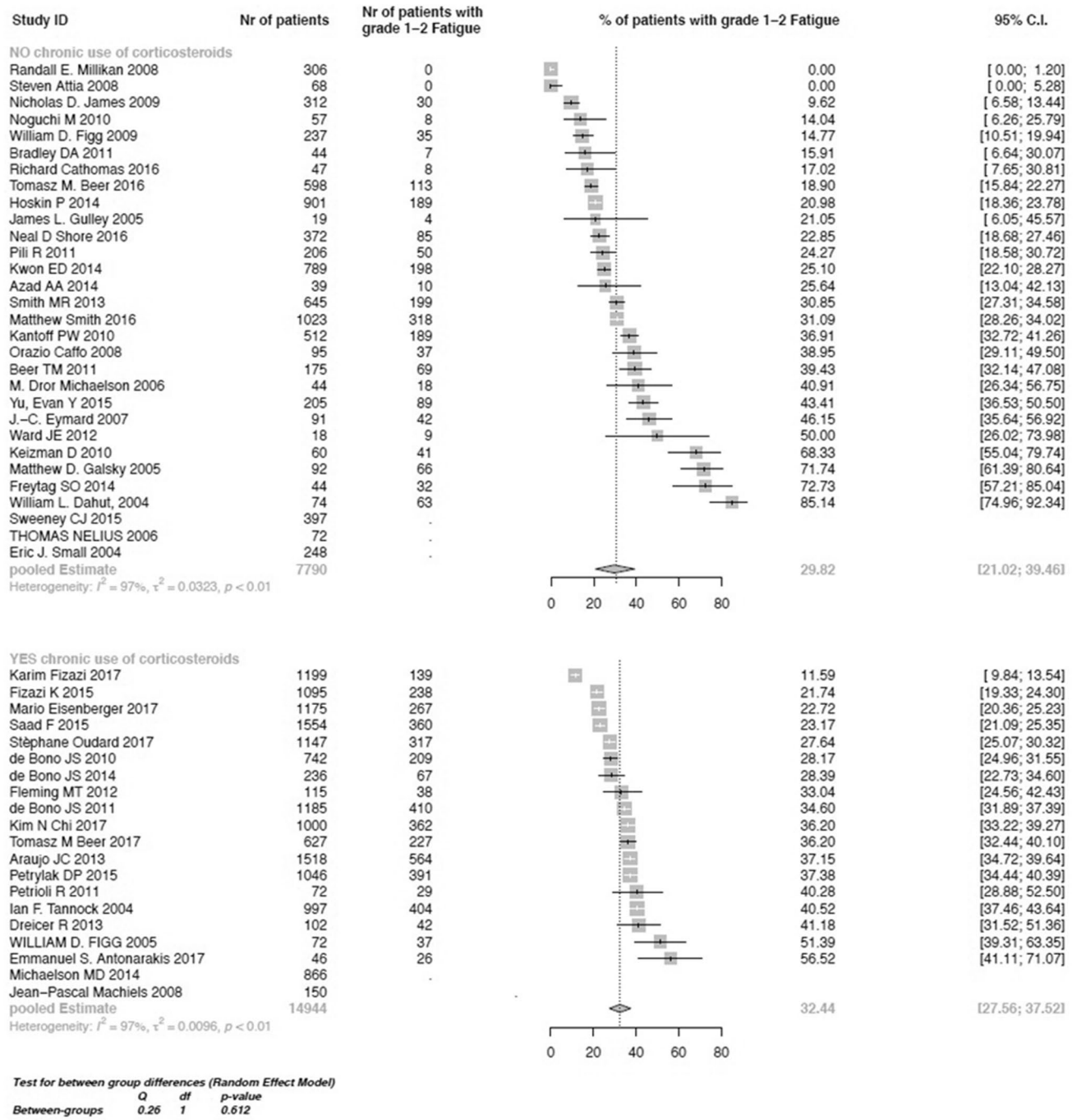

Fig. 4 Pooled estimated incidence of grade 1–2 fatigue in patients treated with vs. without daily corticosteroids in combination with systemic treatment

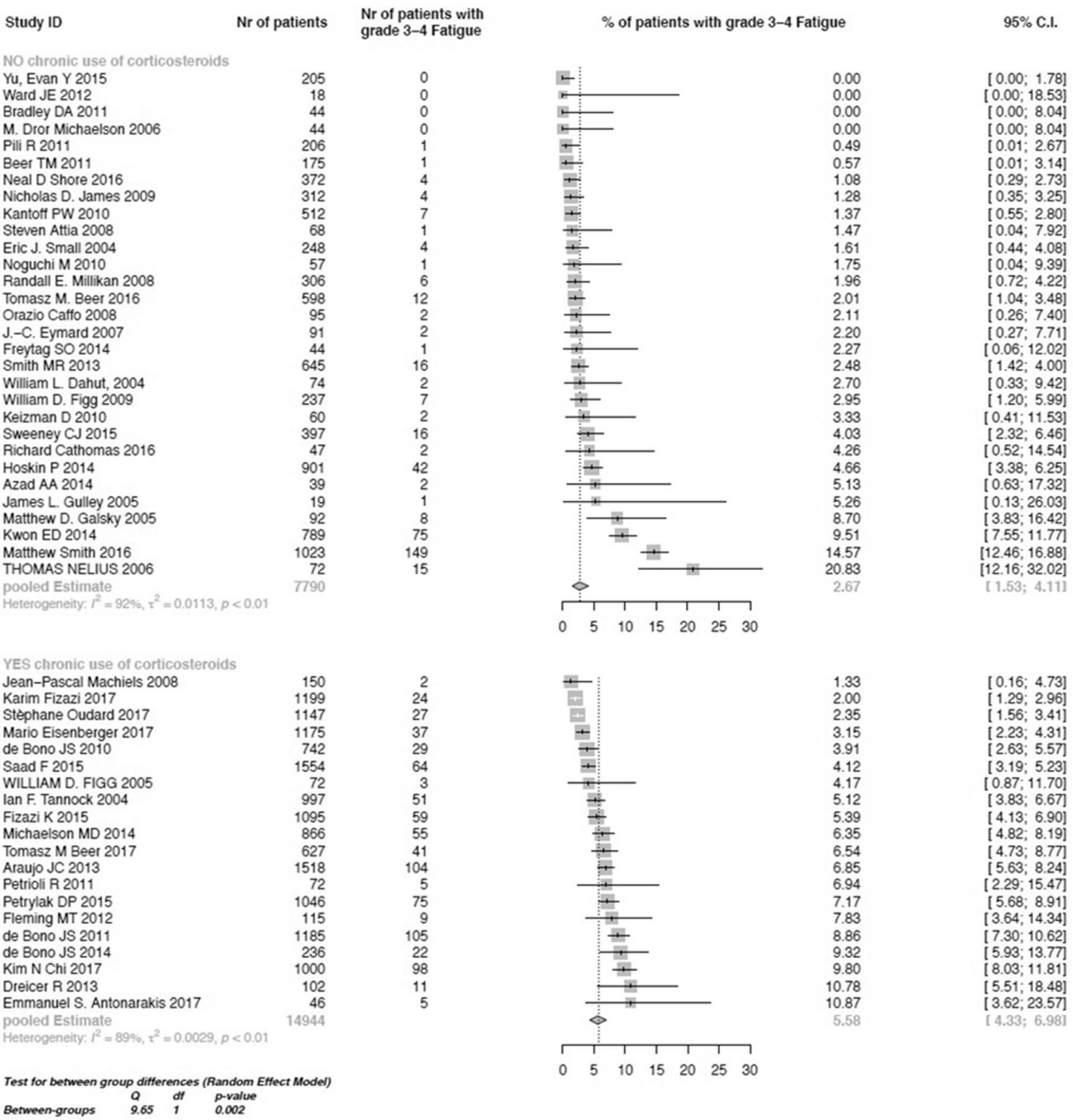

Fig. 5 Pooled estimated incidence of grade 3–4 fatigue in patients treated with vs. without daily corticosteroids in combination with systemic treatment

Ethical statements The authors have no potential conflicts of interest to disclose relevant to this work. This work is a systematic review of published data, so it does not directly involve human participants and/or animals, not did it require any informed consent or ethics committee approval.

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