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Do patients with reduced or excellent performance status derive the same clinical benefit from novel systemic cancer therapies? A systematic review and meta-analysis

Sierra Cheng,[1] Mahin Qureshi,[1] Eleanor Pullenayegum,[2,3] Adam Haynes,[4] Kelvin KW Chan[1,3,4]

[1]Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, Canada
[2]The Hospital for Sick Children, University of Toronto, Toronto, Canada
[3]Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
[4]Canadian Centre for Applied Research in Cancer Control, Toronto, Canada

Correspondence to
Dr Kelvin KW Chan; kelvin.chan@sunnybrook.ca

ABSTRACT

Background Whether patients with excellent and reduced performance status (PS) derive different net clinical benefit from novel anticancer systemic therapies on clinical trials is unclear.

Materials and methods A systematic review was conducted of randomised controlled trials (RCTs) cited for drug approvals between 2006 and August 2015 by the Food and Drug Administration, the European Medicines Agency and Health Canada. Included studies had overall survival (OS) and/or progression-free survival (PFS) primary endpoints. Meta-analyses of OS/PFS based on PS dichotomised into excellent and reduced subgroups were performed using random effects.

Results The systematic review identified 110 RCTs, with none reporting PS subgroup analyses for toxicity and 66 (60%) for efficacy. For these 66 RCTs involving 44 511 patients, pooled HRs for excellent and reduced groups were 0.65 (95% CI 0.61 to 0.70) and 0.67 (95% CI 0.62 to 0.72), respectively, with no difference between the two groups (p=0.68). Sensitivity analyses based on drug or cancer type and type of endpoints (OS or PFS) demonstrated similar results.

Conclusions No decrease in *relative* efficacy from novel systemic therapy was found for patients with reduced PS when compared with patients with excellent PS for the range which were included in modern RCTs. Reporting of PS subgroup analyses of toxicities and more inclusion of patients with borderline low PS in RCTs should be considered for a more comprehensive understanding of the net clinical benefits of contemporary systemic therapies in patients across the spectrum of different PS.

Key questions

What is already known about this subject?
► Commonly, the net clinical benefit derived for patients of different PS is thought of as being different with respect to efficacy and toxicity of systemic therapies.
► Most literature has been focused on specific cancer settings and is not representative of modern practice with use of novel systemic therapy.

What does this study add?
► No difference in relative efficacy benefits derived amongst levels of PS for anticancer systemic therapies within the range of PS examined in current RCTs.
► Results were consistent across all drug types (chemotherapy, targeted agent, oral and intravenous), as well as all analysed cancer types (lung, colorectal, prostate, breast and ovarian).
► Lack of reporting of PS-based subgroup analyses for toxicity prevented the net clinical benefit from being determined

How might this impact on clinical practice?
► Reporting PS subgroup analyses of toxicities and more inclusion of patients with borderline low PS in clinical trials should be considered for a more comprehensive understanding of the net clinical benefits across the PS spectrum.

INTRODUCTION

Performance status (PS) is the classification of a patient's physical well-being based on his or her level of function.[1] PS is a common inclusion criterion for clinical trials. There are two scales for assessing PS that are commonly employed: the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale/WHO scale, a six-point scale ranging from 0 to 5 with lower numbers representing increased function, and the Karnofsky Performance Status scale (KPS), a scale ranging from 0 to 100 with greater numbers indicating increased function.[2]

Commonly, the net clinical benefit derived for patients of different PS is thought of as being different with respect to efficacy and toxicity of systemic therapies, thereby contributing to a reluctance to provide certain treatments to patients of reduced PS. Similarly, in some jurisdictions, reimbursement

recommendations and funding criteria for new therapies may be specific to patients with good PS. Despite this tendency to believe there is a differential level of relative clinical benefit among levels of PS, there has been no systematic evidence to support this, and individual trials are often not sufficiently powered to test for interaction between subgroups lending to the necessity of meta-analysis.

Most literature on this issue focused on a specific cancer setting and was not representative of modern practice with the use of novel systemic therapy. For example, a pooled analysis of five non-small cell lung cancer trials comparing postoperative cisplatin-based chemotherapy to no chemotherapy reported a significant overall survival (OS) benefit for ECOG PS 0 patients receiving chemotherapy, while patients of ECOG PS 1 and 2 did not benefit or even benefited more from no chemotherapy (p=0.01 for interaction, p=0.009 for trend test).[3] One may hypothesise that novel systemic therapies are more tolerable in patients with reduced PS.

Understanding how PS affects drug efficacy and toxicity may facilitate discussion of treatment selection as well as explanation of risks, benefits and survival based on a patient's specific PS. Furthermore, it is not clear whether PS levels can be used to predict the relative efficacy or toxicity for only chemotherapy drugs, only targeted agent drugs or both drug types.

We therefore aim to conduct a systematic review and meta-analysis of randomised clinical trials (RCTs) examining novel systemic therapies to determine whether the benefits derived with respect to both efficacy and toxicity for patients of reduced PS are similar or different to those derived for patients of excellent PS.

METHODS
Selection of studies
The Food and Drug Administration's (FDA) Hematology/Oncology Approvals & Safety Notification web page, the European Medicines Agency's (EMA) Public Assessment Reports and Health Canada's Summary of Basis Decision documents were searched for clinical trials cited as clinical efficacy evidence in oncology drug approvals of any indication between January 2006 and August 2015.[4–6] Appendices of all identified trials were collected. Companion studies were also collected by searching citing articles from Web of Science and each study's ClinicalTrials.gov Identifier/NCT number.

All clinical trials were screened by two reviewers. Trials were required to record patient baseline PS characteristics, have OS and/or progression-free survival (PFS) primary endpoints and report PS subgroup analyses including OS/PFS HRs with 95% CIs. Exclusion criteria were single-arm, phase I and non-randomised trials. Studies that did not test chemotherapy, molecularly targeted agent or hormone therapy cancer drugs were also excluded.

Data extraction and meta-analyses for drug efficacy
All phase II and III RCTs with primary endpoints of PFS and/or OS were screened for PS subgroup analyses, and the percentage of studies reporting PS subgroup analyses was calculated. Data were collected, and the same methods were applied for the toxicity subgroup analyses.

Two independent reviewers extracted OS/PFS HRs with 95% CIs for each PS. Data from studies that did not report numerical values, but did provide a forest plot, were extracted using DigitizeIt V.2.1. Upper and lower limits were extracted, and mean standard errors were used in forest plots. Data from studies that stratified patients by KPS or Gynecologic Oncology Group (GOG) PS (which also uses a six-point scale similar to the ECOG PS scale) rather than ECOG PS was collected, and PS scores were converted to ECOG PS (conversion table, online supplementary table S1). If the interim analysis for a study was cited for clinical efficacy and collected, and the final analysis companion study reported the ECOG PS subgroup analysis, data were extracted from the final rather than the interim analysis.

PS was dichotomised into excellent and reduced PS subgroups for each trial. If HR data were provided as three categories in the forest plot (eg, ECOG 0, 1 and 2 were available for a particular trial) instead of as two categories, the data for ECOG 0 were designated as the excellent ECOG PS data and the data for ECOG 2 were designated as the reduced ECOG PS data. The primary analysis was based on primary endpoint OS or PFS HRs only.

Sensitivity analyses were conducted based on OS HRs only, PFS HRs only, systemic therapy type (chemotherapy or molecularly targeted agent), route of drug administration, cancer type, PS-stratifying studies only, non-PS stratifying studies only, as well as removal of KPS/GOG PS studies. Sensitivity analyses comparing the PS subgroups as reported in the original publications were also conducted (comparison of ECOG PS levels 0, 1 and 2, comparison of ECOG PS 0 vs 1, comparison of ECOG PS 0 vs ≥1 and comparison of ECOG PS 0–1 vs 2).

Forest plots were constructed for each comparison, and pooled HRs with 95% CIs were calculated. PS group differences (ie, excellent PS vs reduced PS) were calculated using the test for subgroup differences based on the random-effects model, and significance of variability was determined with the I^2 statistic.[7] The value of I^2 statistic lies between 0% (no observed heterogeneity between subgroups) and 100% (considerable significant heterogeneity between subgroups).[8] All meta-analyses were conducted using Review Manager V.5.3 software (Copenhagen, Denmark).

RESULTS
Study characteristics
As seen in the figure 1 online supplementary figures S1 and S28, studies were identified. Of the collected studies, 56 were duplicates cited by the different drug approval
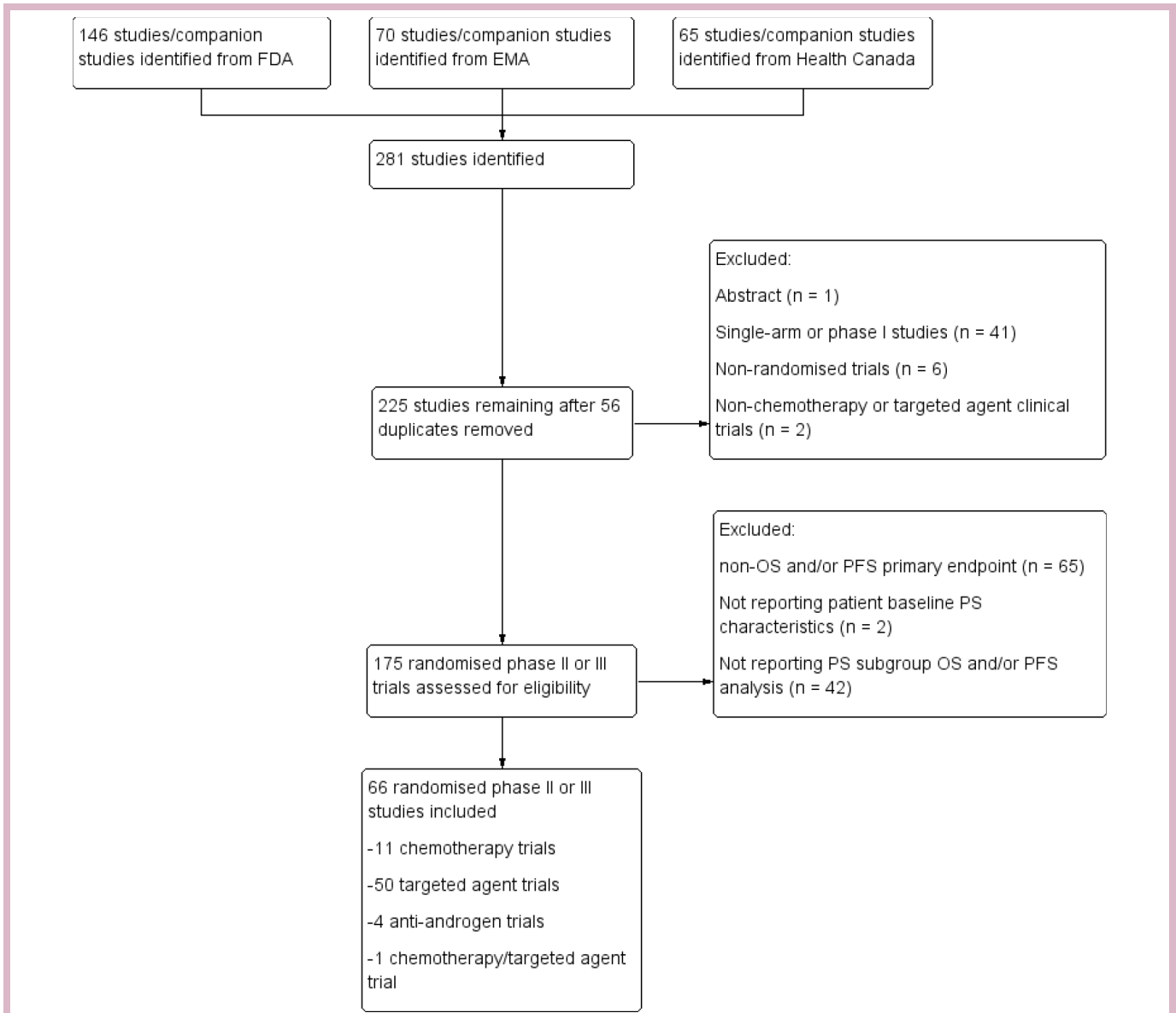
Figure 1 PRISMA study flow diagram. EMA, European Medicines Agency; FDA, Food and Drug Administration; OS, overall survival; PFS, progression-free survival; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; PS, performance status.

agencies, 41 were single-arm or phase I studies, 1 was an abstract publication, 2 did not test chemotherapy or targeted drugs in their experimental arms and 6 were non-randomised trials. Of the remaining 175 studies, 66 met the full eligibility criteria of this systematic review and were therefore included. The characteristics of these 66 studies are summarised in table 1, as well as in online supplementary table S2. These studies enrolled 44 511 patients, with 25 862 and 16 515 in the excellent and reduced PS groups for analysis, respectively.

Twenty-nine of the included studies had inclusion criteria of ECOG PS 0–1, while 32 studies had inclusion criteria of ECOG PS 0–2. Four studies enrolled ECOG PS 3 patients as protocol deviations or violations.[9–12] Only one study permitted the enrolment of ECOG PS 0–3 but did not actually pursue the enrolment of any patients of ECOG PS 2–3.[13]

Twenty of the included studies did not report explicit numerical HRs for PS subgroups but did include forest plots from which HRs were extracted.

Of the 66 studies with PFS and/or OS primary endpoints, none reported PS subgroup analyses for toxicities. In fact, only one study reported toxicities by subgroups, which was by age and not by PS.[14]

Excellent versus reduced PS comparison

As seen in table 2 and figure 2, a comparison of excellent and reduced PS among all studies demonstrated no subgroup differences (p=0.68, I^2=0%). Pooled HRs for the excellent and reduced PS subgroups were 0.65 (95% CI 0.61 to 0.70) and 0.67 (95% CI 0.62 to 0.72), respectively (complete forest plot, see online supplementary 1).

Table 1 Summary of included studies and patient characteristics

Characteristic	Number of studies	Percentage
Studies	66	
Patients (total enrolled)	44 511	
Patients (excellent PS subgroup)	25 862	
Patients (reduced PS subgroup)	16 515	
Drug type (experimental arm)		
Targeted agent	50	76
Chemotherapy	11	17
Antiandrogen	4	6
Chemotherapy and targeted agent	1	2
Route of administration (experimental arm)		
Oral	36*	55
Intravenous	30*	46
Subcutaneous injection	1	2
Type of cancer		
Lung	17	26
Colorectal	9	14
Melanoma	5	8
Prostate	5	8
Renal	4	6
Breast	4	6
Gastric or gastro-oesophageal	4	6
Ovarian	3	5
Others	15	23
Primary endpoint		
OS	32	49
PFS	30	46
OS and PFS (coprimary)	4	6
Secondary endpoint		
OS	31	47
PFS	28	42
Response rate	6	9
Not stated	1	2
Performance status scale		
ECOG PS	61	92
KPS	4	6
GOG PS	1	2
Inclusion criteria		
ECOG PS 0–1	29	44
ECOG PS 0–2	32	48
ECOG PS 0–3	1	2

Continued

Table 1 Continued

Characteristic	Number of studies	Percentage
KPS 70–100	3	5
KPS 60–100	1	2
GOG PS 0-1	1	2
Phase		
III	63	95
II	2	3
IIb/III	1	2

*One study was a three-arm trial, with one experimental therapy being an oral drug and one being an intravenous drug. Thus, the study is reflected twice under route of administration and the total number of studies listed is 67.
ECOG PS, Eastern Cooperative Oncology Group Performance Status; GOG PS, Gynecologic Oncology Group Performance Status; KPS, Karnofsky Performance Status; OS, overall survival; PFS, progression-free survival; PS, performance status.

Sensitivity analyses

Results of the sensitivity analyses conducted are summarised in table 2. Sensitivity analyses based on comparison of excellent and reduced PS for only OS HRs and only PFS HRs demonstrated no difference between the two groups (see online supplementary figure S2). For the OS analysis, the test for the difference between the two groups was negative (p=0.31, I^2=3.1%). For the PFS analysis, the test for the difference between the two groups was also negative (p=0.91, I^2=0%).

Tests for difference between the two groups were not significant for analyses of chemotherapy drugs or targeted agent drugs only (OS and PFS HRs combined) (for chemotherapy: p=0.93, I^2=0%; for targeted agents: p=0.72, I^2=0%) (forest plots, see online supplementary figure S2). No difference between the two groups were observed when comparing PFS or OS HRs only for either chemotherapy or targeted agent drugs (see online supplementary figures S5 and S6). Similarly, analysis of oral therapies only or intravenous therapies only all demonstrated no significant subgroup differences (see online supplementary figures S7–S10).

Cancer-specific analyses of lung, colorectal, prostate, breast and ovarian cancer studies all demonstrated no significant differences between the two groups (see online supplementary figures S7–S15).

Removal of studies that reported subgroup analyses using KPS or GOG PS rather than ECOG PS from the primary analysis still demonstrated no significant difference between the two groups (see online supplementary ure S16). Similarly, analyses of only studies that stratified patients for PS at baseline and studies that did not stratify for PS at baseline also demonstrated no significant differences (see online supplementary figure S17).

As seen in figure 2, no group differences were observed when comparing ECOG PS levels (0 vs 1 vs 2) (p=0.95, I^2=0%). Pooled ECOG PS 0, 1 and 2 OS HRs were 0.80

Table 2 Summary of analyses

| Analysis	Number of trials	Number of patients	Excellent PS HR (95% CI)	Reduced PS HR (95% CI)	p Value test for subgroup differences	I^2 for subgroup differences (%)
All drugs: OS and PFS	67*	42 377	0.65 (0.61 to 0.70)	0.67 (0.62 to 0.72)	0.68	0
All drugs: OS only	35*	26 006	0.77 (0.72 to 0.82)	0.80 (0.76 to 0.85)	0.31	3.1
All drugs: PFS only	32	16 371	0.53 (0.47 to 0.60)	0.53 (0.47 to 0.60)	0.91	0
Chemotherapy drugs: OS and PFS	12*	8407	0.77 (0.69 to 0.86)	0.77 (0.70 to 0.85)	0.93	0
Targeted agent drugs: OS and PFS	50	27 790	0.62 (0.56 to 0.68)	0.63 (0.57 to 0.70)	0.72	0
Chemotherapy drugs: OS only	8*	5617	0.78 (0.67 to 0.90)	0.80 (0.70 to 0.91)	0.81	0
Chemotherapy drugs: PFS only	4	2790	0.74 (0.62 to 0.87)	0.69 (0.59 to 0.82)	0.61	0
Targeted agents: OS only	23	15 190	0.78 (0.72 to 0.85)	0.81 (0.76 to 0.86)	0.51	0
Targeted agents: PFS only	27	12 600	0.50 (0.44 to 0.57)	0.49 (0.42 to 0.58)	0.88	0
Oral therapies: OS and PFS	36	23 129	0.58 (0.52 to 0.66)	0.59 (0.52 to 0.67)	0.92	0
Oral therapies: OS only	15	13 398	0.78 (0.69 to 0.88)	0.79 (0.73 to 0.86)	0.87	0
Oral therapies: PFS only	21	9731	0.76 (0.39 to 0.53)	0.46 (0.38 to 0.56)	0.95	0
Intravenous therapies: OS and PFS	30	19 152	0.74 (0.70 to 0.78)	0.76 (0.71 to 0.82)	0.49	0
Intravenous therapies: OS only	21	12 512	0.76 (0.72 to 0.81)	0.81 (0.75 to 0.88)	0.22	33.8
Intravenous therapies: PFS only	9	6640	0.67 (0.59 to 0.77)	0.67 (0.60 to 0.74)	0.94	0
Lung cancer: OS and PFS	17	13 261	0.68 (0.58 to 0.80)	0.73 (0.63 to 0.83)	0.52	0
Colorectal cancer: OS and PFS	9	5352	0.69 (0.63 to 0.77)	0.76 (0.66 to 0.88)	0.30	6.1
Prostate cancer: OS and PFS	5	5954	0.71 (0.65 to 0.77)	0.76 (0.65 to 0.89)	0.46	0
Ovarian cancer: OS and PFS	3	2289	0.85 (0.68 to 1.06)	0.74 (0.57 to 0.97)	0.45	0
Breast cancer: OS and PFS	4	2086	0.59 (0.46 to 0.77)	0.55 (0.39 to 0.78)	0.75	0
Stratified by PS: OS and PFS	37*	31 231	0.68 (0.62 to 0.74)	0.71 (0.65 to 0.77)	0.46	0
Not stratified by PS: OS and PFS	30	18 353	0.61 (0.54 to 0.69)	0.62 (0.55 to 0.71)	0.84	0
All drugs: OS and PFS (ECOG PS only)	62*	39 920	0.64 (0.60 to 0.69)	0.66 (0.61 to 0.72)	0.60	0
All drugs: OS and PFS (ECOG PS 0 vs 1)	39	26 545	0.64 (0.58 to 0.71)	0.67 (0.61 to 0.73)	0.58	0
All drugs: OS and PFS (ECOG PS 0 vs ≥1)	15*	7231	0.62 (0.52 to 0.72)	0.63 (0.53 to 0.74)	0.88	0
All drugs: OS and PFS (ECOG PS 0–1 vs 2)	13	10 636	0.71 (0.63 to 0.82)	0.79 (0.69 to 0.92)	0.29	11.2

*One trial provided two pair-wise comparisons (comparing three different drugs total).
ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall status; PFS, progression-free survival; PS, performance status.

(95% CI 0.65 to 0.99), 0.77 (95% CI 0.61 to 0.96) and 0.80 (95% CI 0.58 to 1.11), respectively (complete forest plot, see online supplementary figure S18). No group differences were demonstrated when comparing OS and PFS HRs only (online supplementary figure S19). Similarly, comparisons of ECOG PS subgroups as reported in the original publications (0 vs 1, 0 vs ≥1 and 0–1 vs 2) all demonstrated no significant differences between
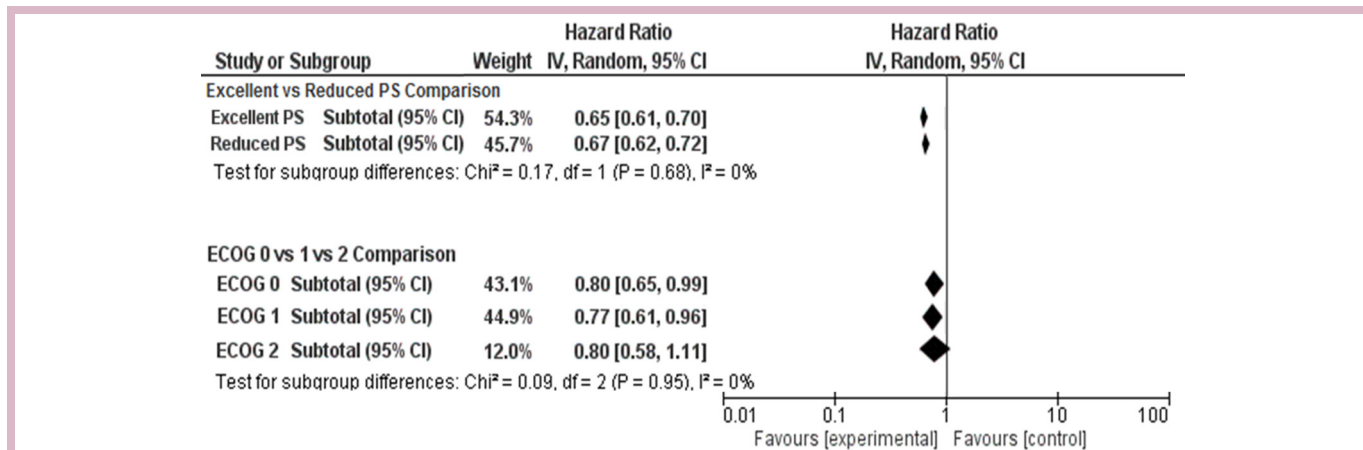
Figure 2 Forest plots for all drugs (OS and PFS HRs combined): excellent versus reduced PS comparison and ECOG PS levels comparison (see online supplementary 1). ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; PFS, progression-free survival; PS, performance status.

the groups (see online supplementary figures S20-S22, respectively).

DISCUSSION

No significant subgroup differences were found when comparing excellent and reduced PS. All sensitivity analyses supported this, with no significant differences found for only chemotherapy drugs, targeted agent drugs, oral drugs, intravenous drugs, OS HRs, PFS HRs, ECOG PS HRs and only stratifying or non-stratifying studies. Analyses of studies for specific cancer types—lung, colorectal, prostate, breast and ovarian—were not significant. All analyses comparing the PS subgroups as reported in the original study publications were also not significant (comparing ECOG PS 0 vs 1, ECOG PS 0 vs ≥1, ECOG PS 0–1 vs 2 and ECOG PS 0 vs 1 vs 2). While it is well known that PS is a prognostic factor for survival[15–22] indicating that absolute survival length is known to be greater for good PS compared with poorer PS, our results suggest that, based on reported values, there is no statistical difference in *relative* survival (whether it be OS or PFS) by treatment between excellent and reduced PS groups included in RCTs.

This supports the findings of many individual trials cited for drug approvals, the majority of which studied targeted agents and reported no interaction of efficacy and PS subgroup analyses.[23–26] That is, no difference in *relative* survival benefit was found across PS subgroups. While studies are often not powered to test for interaction individually, the results of this meta-analysis may provide the necessary power to extend the negative results of these individual trials to be generalisable to most chemotherapy and targeted agent drugs. Similar results have been presented by a pooled analysis of nine metastatic colorectal cancer trials studying first-line chemotherapy (monotherapy) that reported no OS or PFS difference between patients of ECOG PS 0 and 1 with patients of ECOG PS 2 (PFS: ECOG PS 0–1 hour 0.81 (0.77–0.86),

ECOG PS 2 hour 0.79 (0.66–0.96), p=0.68 for interaction; OS: ECOG PS 0–1 hour 0.87 (0.82–0.93), ECOG PS 2 hour 0.88 (0.73–1.07), p=0.41 for interaction).[27] This analysis involved older trials and older drugs that may have been considered to have greater toxic effects in reduced PS patients compared with novel drugs. While caution should be exercised in applying our results to older drugs or newer regimens that use older drugs, our meta-analysis may also extend this analysis' results to novel systemic therapies covering multiple cancer types from an efficacy perspective.

Despite this, there have been older studies demonstrating significant differential levels of effect (survival) of the treatment based on PS. One trial included in this analysis assigned patients with ovarian cancer to carboplatin and paclitaxel with or without bevacizumab and found a significant PFS benefit for patients of reduced PS (ECOG PS 1 hour 0.66 (95% CI 0.54 to 0.81), ECOG PS 2 hour 0.78 (95% CI 0.46 to 1.30)), while no benefit was found for patients of excellent PS (ECOG PS 0 hour 1.01 (0.81–1.27)) (interaction test p=0.022).[28] However, our ovarian cancer-specific analyses indicate no HR benefit to PS levels. It may be possible that a differential level of benefit across PS levels is only observed for specific drug–cancer setting combinations. As a result, the PS subgroups differences are not seen in aggregate based on cancer types or drug types. In the case of a significant interaction test from an individual trial, further research may be required for the specific drug–cancer combination.

While there may be under-reporting of PS subgroup analyses in RCTs in general, it is more likely that trials that demonstrated positive significant subgroup differences will have reported these results.[29] Thus, there is likely overall reporting bias towards demonstrating significant differences between PS subgroups. Despite this, our study demonstrated no significant subgroup differences, lending to increase the robustness of our result.

Among the included studies, there was a limited number that reported HRs for each of ECOG 0, 1 and 2 instead of dichotomising PS levels. The study is further limited by the small absolute number of chemotherapy trials collected and therefore included in the analysis.

Taking into account the efficacy, toxicity and cost-effectiveness, there is still uncertainty regarding the net clinical benefit for patients of excellent and reduced PS. Cost-effectiveness was not analysed in our study. While no difference in drug relative efficacy was noted based on OS and PFS HRs, PS subgroup-based toxicity data were not reported in any of the studies. Despite the fact that subgroup analyses may often be insufficiently powered, awareness of balancing efficacy benefits and toxicity is increasingly important for decision making. A meta-analysis of trials of newly approved cancer drugs demonstrated significantly increased rates of toxic-related deaths, toxic-related reasons for treatment discontinuation and grade 3 or 4 adverse events in comparison with control treatments.[30] Therefore, in addition to knowing that there is no *relative* difference in survival benefit for patients of different PS, it is important to understand if there may be incremental improvement or worsening of toxicity for novel systemic therapies.

Based on our analysis, it is unclear if the lack of relative efficacy differences among PS levels can be generalised beyond patients of ECOG PS 2 or not due to these patients generally not being enrolled in trials. Only four of the included studies enrolled patients of ECOG PS 3 or greater, and those which did enrol ECOG PS 2 patients generally enrolled a low number of patients. Thus, reduced PS subgroups in our analyses are heavily weighted by ECOG PS 1 patients and can be considered to be borderline low PS. Furthermore, it has recently been described that the eligibility criteria between protocols and publications only matches in only 44.0% of cancer trials, with ECOG PS study populations being narrower in publications.[31] Thus, it may be necessary to conduct further research on drug efficacy for patients with higher levels of impairment. Additionally, none of the included studies reported toxicity subgroup analyses for PS leading to uncertainty as to whether PS might contribute to different levels of the toxic effects of treatment. We cannot, therefore, generalise our conclusions to state that PS has no implications on differences to patient care. Subgroup analyses of toxicities based on PS are encouraged.

Based on the conducted systematic review and meta-analysis, there is no difference in efficacy benefits derived among levels of PS for anticancer systemic therapies within the range of PS examined in current RCTs (primarily ECOG 0–2), and generalisability outside this range is limited due to highly selective patient populations included in trials. In the absence of direct evidence from a specific trial, treatment or funding decisions for novel anticancer systemic therapies should not strictly rely on PS for differential treatment effect; however, whether a differential effect of PS for toxicity exists remains unknown, and therefore, PS-based toxicity analyses and the inclusion of patients of lower PS in trials when safe and feasible should be considered.

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