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Effectiveness and safety of immunotherapy in NSCLC patients with ECOG PS score ≥2 – Systematic review and meta-analysis

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) are standard of care in advanced non-small cell lung cancer (NSCLC), however their status in patients with poor performance status (PS) is poorly defined. We aimed to evaluate the efficacy and safety of ICIs in NSCLC patients with PS ≥ 2.

Methods: We conducted a systematic review and meta-analysis of interventional and observational studies, which reported efficacy and safety data on ICIs in PS ≥ 2 comparing to PS ≤ 1 NSCLC patients. Efficacy endpoints included: Objective Response Rate (ORR), Disease-Control Rate (DCR), Overall Survival (OS), Progression-Free Survival (PFS). Safety endpoint was the incidence of severe (grade≥3) Adverse Events (AE). Random-effects model was applied for meta-analysis. Heterogeneity was assessed using I^2. The review is registered on PROSPERO (CRD42020162668).

Findings: Sixty-seven studies (n = 26,442 patients) were included. In PS ≥ 2 *vs.* PS ≤ 1 patients, the pooled odds ratios were: for ORR 0.46 (95 %CI: 0.39–0.54, I^2:0 %); for DCR 0.39 (95 %CI: 0.33–0.48, I^2:50 %) and for AEs 1.12 (95 %CI: 0.84–1.48, I^2:39 %). The pooled hazard ratio for PFS was 2.17 (95 %CI: 1.96–2.39, I^2:65 %) and for OS was 2.76 (95 %CI: 2.43–3.14, I^2:76 %). The safety profile was comparable regardless of the PS status.

Interpretation: Patients with impaired PS status are, on average, twice less likely to achieve a response when exposed to ICIs when compared with representative PS ≤ 1 population. For lung cancer patients treated with ICIs, the impaired PS is not only prognostic, but also predictive for response, while the safety profile is not affected. Prospective randomized studies are indispensable to determine whether poor PS patients derive benefit from ICIs.

1. Introduction

Immune checkpoint inhibitors (ICIs), encompassing antibodies against programmed death receptor (PD-1), PD-1 ligand (PD-L1) and cytotoxic-T-lymphocytes antigen 4 (CTLA-4), vastly improved the outcome of patients with non-small cell lung cancer (NSCLC) and are now standard of care in this population [1]. The superior efficacy of ICIs has been documented in several randomized clinical trials (RCTs) comparing them with chemotherapy in both first and subsequent lines of therapy [2].

The Eastern Cooperative Oncology Group Performance Status Score (PS) is one of the most powerful prognostic factors available to oncologists [3]. In the past, stratification between PS ≤ 1 *versus* PS ≥ 2 patients was obligatory and provided evidence that PS is not only prognostic but also predictive for response and toxicity in NSCLC population treated with chemotherapy [4]. In contrast, patients with poor

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PS were consistently excluded from registrational ICI trials, which precludes reliable assessment of the treatment in this population (constituting about 34–48 % of all patients diagnosed with NSCLC worldwide [5]). Despite this shortfall, US Food and Drug Administration together with European Medicines Agency have granted approval for ICIs in NSCLC regardless of the patient PS status. As a consequence, now and for several years previously, ICIs are offered to a significant number of NSCLC patients, who are not representative of the population tested in RCTs.

As of now, the results of only five prospective ICI trials (all single-arm) that included PS $\geq$ 2 patients have been published [6–10]. However, except for the recently published PePS2 study [9], these trials primarily included PS $\leq$ 1 patients with a minor additional subsets termed "special populations", *i.e.* elderly and patients with comorbidities preventing any specific conclusions for PS $\geq$ 2 patients. The activity and safety of ICIs (predominantly nivolumab and pembrolizumab) was investigated in several national expanded access programs (EAPs) and a growing number of retrospective reports. These "real-world" reports are the best currently available evidence to address the important clinical evidence gaps for the PS $\geq$ 2 population.

We therefore performed a systematic review and meta-analysis of randomized clinical trials, observational studies (retrospective and prospective), reports from EAPs and compassionate use programs to assess the effectiveness and safety of immunotherapy in NSCLC patients with PS score of 2 or more with reference to PS 0-1 population.

2. Methods

This systematic review with meta-analysis was conducted in accordance with Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and reported according to PRISMA guidelines (Appendix A) [11,12]. A protocol was prepared prior to the study and prospectively registered at the PROSPERO database (number CRD42020162668, Appendix B). Each step of the study was conducted by two independent researchers with disputes resolved by discussion. We declare that all results are reported and discussed in the paper.

2.1. Search strategy

Electronic searches were conducted from origin to 22nd of May 2020 in OVID MEDLINE®, EMBASE, Cochrane Database of Systematic Reviews (CDSR), American Society of Clinical Oncology (ASCO) meeting abstracts' database, International Association for the Study of Lung Cancer (IASLC) meeting (World Conference on Lung Cancer – WCLC) abstracts' database, EORTC (European Organization for Research and Treatment of Cancer) website, European Society for Medical Oncology (ESMO) website, American Association for Cancer Research (AACR) website, European Cancer Organization (ECCO) website and pubmed.com. The searches were rerun before the final analysis of data as of 17th July 2020. Searches were supplemented by reviewing the reference lists of the publications, previous meta-analyses, and guidelines. The main search terms encompassed: non-small cell lung cancer (NSCLC), immunotherapy (ICI), anti-PDL1, anti-PD1, anti-CTLA4, pembrolizumab, nivolumab, atezolizumab, durvalumab, urelumab, ipilimumab, tremelimumab, efficacy, effectiveness, toxicity, safety. The full search strategy is available in Appendix C. No language restrictions were applied to the search.

2.2. Assessing for eligibility

The inclusion criteria for articles were as follows: **P**opulation criterion - patients with locally advanced or metastatic/ advanced non-small cell lung cancer (as defined in the National Comprehensive Cancer Network guidelines); **I**ntervention criterion - immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab, urelumab, ipilimumab, tremelimumab and any other ICI registered for treatment of NSCLC) in >10 patients with PS $\geq$ 2; **C**omparator criterion – (a) ICIs in patients with PS $\leq$ 1 or (b) any other active treatments, placebo or best supportive care in patients with PS $\geq$ 2; **O**utcomes criterion – Effectiveness: Objective Response Rate (ORR), Disease-Control Rate (DCR), Overall Survival (OS), Progression-Free Survival (PFS) and Safety: incidence of severe (grade$\geq$3) Adverse Events (AE); **S**tudy design - randomised controlled trial (RCT), non-randomised registered clinical trials, retrospective and prospective cohort, cross-sectional, case-control, case series studies.

Articles retrieved from the electronic searches were firstly screened for eligibility using their titles and abstracts. Full-text papers of potentially relevant trials were obtained and examined by assessing their population, intervention, comparison, outcome measurements and study design (PICOS) characteristics. The process of the selection of studies is reported in PRISMA flowchart (Fig. 1).

2.3. Quality assessment

For quality assessment, dependent on study design, two tools recognized by Cochrane Handbook for Systematic Reviews of Interventions were selected: i) revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for randomised clinical trials [13]; ii) Newcastle-Ottawa Scale for cohort and registry studies [14,15]. All full-text article studies were assessed for bias following the checklist respective to the tool applied. Detailed evaluation for each study was tabularised and final evaluation was presented in a semi-quantitative score.

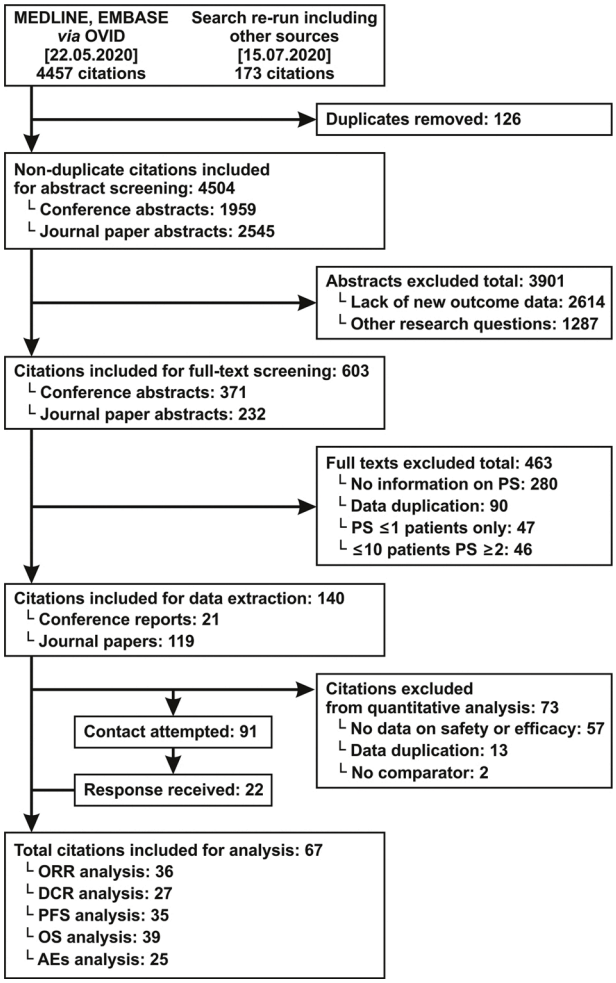

Fig. 1. PRISMA flowchart.

2.4. Data extraction and definition of outcomes

Features of included and excluded studies were tabularized with reason for inclusion or exclusion in tables designed for this study. Descriptive data on methods, participants, intervention and control, outcome measures, trial/study name, group, centre, ID number, address for correspondence, funding, sample size, detailed treatment modality, accrual period, length of follow up, patients lost to follow up, subgroup analyses were obtained. The following quantitative data were extracted: the number of patients with PS $\leq$ 1 and PS $\geq$ 2 (and detailed values for each 0–4 group if available), the number of responses (CR + PR, SD, PD) and grade $\geq$3 AEs for each PS subgroup, OR with 95 % confidence interval (95 %CI) for ORR, DCR and AE (the odds ratios were calculated from the direct numbers when available) as well as HR together with 95 %CI for OS and PFS. Data for the following subgroups were sought: disease stage (IV or other), race, histological type (squamous *vs.* adenocarcinoma), druggable oncogenic mutation status (EGFR, ALK, ROS1, BRAF *vs.* none), age (75 and younger *vs.* older), treatment line (first *vs.* subsequent), brain metastases (yes *vs.* no), autoimmune disorders (yes *vs.* no), immunohistochemical status of PD-L1 (0 % *vs.* 1–50 % *vs.* >50 %). The potential (partial or complete) overlap between the studies was assessed based on the lists of authors and participating centres, accrual period, applied treatment, patients' characteristics and outcome measures [16]. In case of complete overlap, only the most comprehensive study was included. Studies with potential partial overlap were marked as separate subgroups and an additional analysis was performed including only the largest study from each subgroup.

If specific data were not accessible through article (including supplementary material), the corresponding Author was contacted *via* academic e-mail. In case of no response within two weeks, the queries were repeated with the time for closure of data accrual within a month from the initial e-mail. If meta-analysis was not applicable (*e.g.* because of the lack of data) the results were reported descriptively (tabularized and discussed).

2.5. Data analysis

Meta-analysis was conducted for differences between PS $\leq$ 1 *vs.* PS $\geq$ 2 groups using random effects model on all prespecified outcome measures (ORR, DFS, OS, PFS, Safety). Total and subtotal odds ratios (OR) or hazard ratios (HR) with 95 % CI, prediction intervals (PI) [17,18] and overall effect (p-value). The results were presented as forest plots and L'Abbé plots [19]. For the assessment of heterogeneity between studies I^2 values were calculated (between-study variance was assessed according to DerSimonian and Laird method [20]). Publication bias was assessed with funnel plots and tests for funnel plot asymmetry [21,22], and "Trim and Fill" method [23]. R version 4.0.0 [24] and the *meta* package [25] were used for data analysis and visualisation (code available upon request and will be publicly available in the companion Data in Brief paper).

2.6. Role of the funding source

The funder of the study played no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

3. Results

A total of 4504 publications were retrieved through the literature search, and 67 studies with a total of 26,442 patients (individual study median: 217, range: 44−2,302) were included in the final analyses (Fig. 1, Table D.01) [6,7,26–90]. Among these, there were 3890 PS $\geq$ 2 patients (median: 39, range: 11–241) and 22,552 PS $\leq$ 1 patients (median: 170, range: 32−2,129). ICIs were administered as first line treatment in four studies, as the second or further line in thirty-four studies, twenty-six studies included both treatment-naïve and pre-treated patients, while no data was available for three studies. Twelve studies included only specific populations of patients: with PD-L1 tumour proportion score $\geq$50 % (four studies); older age (three studies); with oncogenic driver mutations (two studies); with squamous cell carcinoma, with concurrent TBC/HBV infection and with African American descent or chronic viral infections (one study each).

3.1. Objective response rate

Thirty-six studies provided data on objective response rate (n = 9888 patients; 1937 PS $\geq$ 2 and 7951 PS $\leq$ 1); for 33 of these, direct responder numbers were also available (Fig. 2). The odds ratio for ORR in PS $\geq$ 2 *vs.* PS $\leq$ 1 patients was 0.46 (95 %CI: 0.39−0.54; PI: 0.39−0.54) with low heterogeneity (I^2 = 0 %) (Fig. 3A). The results did not differ significantly in the following subgroups of studies: with different lines of treatment (Fig. D.01), with different quality according to Newcastle-Ottawa Scale (Fig. D.02), with a focus on specific populations (Fig. D.03), with different source of data (Fig. D.04) and after exclusion of the studies with potential partial overlap of patients (Fig. D.05, OR range: 0.42−0.60). The analysis of funnel plot asymmetry identified the potential publication bias (rank correlation test [21] p = 0.003, linear regression test [22] p = 0.015; Fig. D.06); however, accounting for the potentially missing studies using the "trim and fill" method [23] did not affect the pooled result (OR = 0.48, 95 %CI: 0.41−0.56; Fig. D.07).

The proportion of responders among the PS $\geq$ 2 patients showed a higher degree of heterogeneity, ranging from 0 % to 42 % (I^2 = 59 %) with the pooled rate of 15 % (95 %CI: 0.12−0.19; PI: 0.06−0.34; Fig. D.08). In the subgroup analysis (Fig. 4), patients treated with first-line ICI had significantly better response rates (0.32, 95 %CI: 0.22−0.44), than patients treated with ICI as a subsequent line (0.11, 95 %CI: 0.09−0.14; p < 0.001).

3.2. Disease-control rate

Twenty-seven studies provided data on disease control rate (n = 8325 patients; 1473 PS $\geq$ 2 and 6852 PS $\leq$ 1), including direct numbers of non-progressors (Fig. 2). The odds ratio for DCR in PS $\geq$ 2 *vs.* PS $\leq$ 1 patients was 0.39 (95 %CI: 0.33−0.48; PI: 0.20−0.78) with moderate heterogeneity (I^2 = 45 %, Fig. 3B). The results did not differ significantly in the following subgroups of studies: with different lines of treatment (Fig. D.09), with different quality according to Newcastle-Ottawa Scale (Fig. D.10), with a focus on specific populations (Fig. D.11), with different source of data (Fig. D.12) and after exclusion of the studies with potential partial overlap of patients (Fig. D.13, OR range: 0.36−0.53). The analysis of funnel plot asymmetry identified no potential publication bias (rank correlation test [21] p = 0.19, linear regression test [22] p = 0.54; Fig. D.14) and accounting for the potentially missing studies using the "trim and fill" method [23] did not affect the pooled result (OR = 0.41, 95 %CI: 0.33−0.50; Fig. D.15).

The proportion of non-progressors among the PS $\geq$ 2 patients showed a higher degree of heterogeneity, ranging from 15 % to 72 % (I^2 = 73 %) with the pooled rate of 39 % (95 %CI: 0.33−0.45; PI: 0.17−0.65; Fig. D.16). In the subgroup analysis (Fig. D.17), patients treated with first-line ICI had significantly better response rates (0.61, 95 %CI: 0.49−0.73) than patients treated with ICI as a subsequent line (0.37, 95 %CI: 0.29−0.24; p < 0.001).

3.3. Progression-free survival

Thirty-five studies provided data on progression-free survival (n = 12,491 patients; 1843 PS $\geq$ 2 and 10,648 PS $\leq$ 1). The hazard ratio for PFS in PS $\geq$ 2 *vs.* PS $\leq$ 1 patients was 2.17 (95 %CI: 1.96–2.39; PI: 1.36–3.44) with considerable heterogeneity (I^2 = 63 %, Fig. 5A). The results did not differ significantly in the following subgroups of studies:

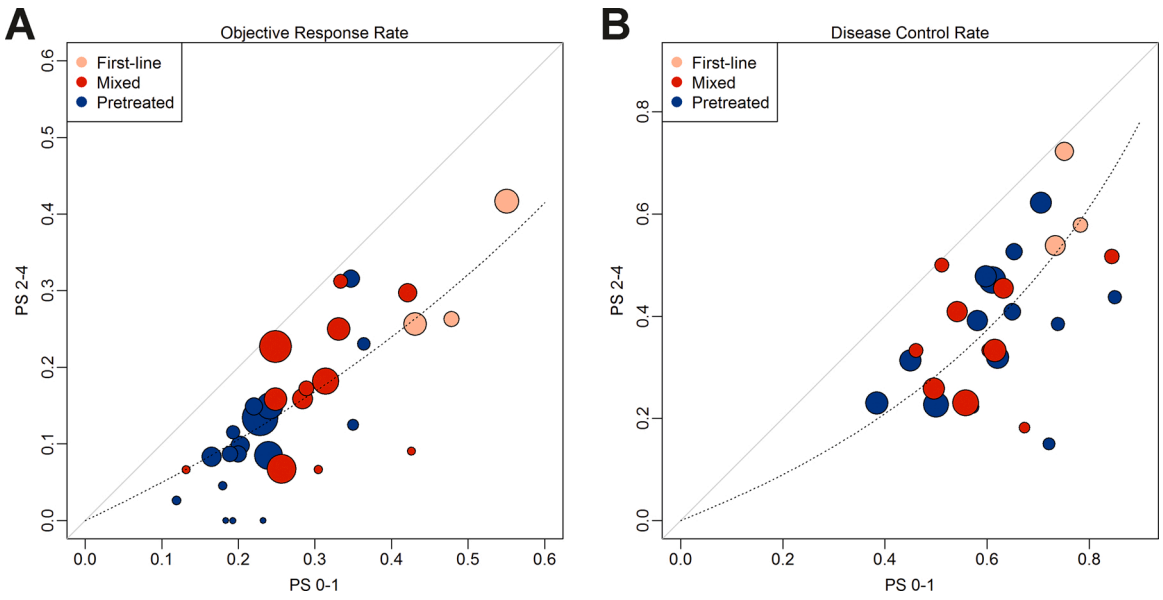

Fig. 2. L'Abbé plots for Objective Response Rate and Disease Control Rate. The size of each point is scaled according to the weights of random effects model.

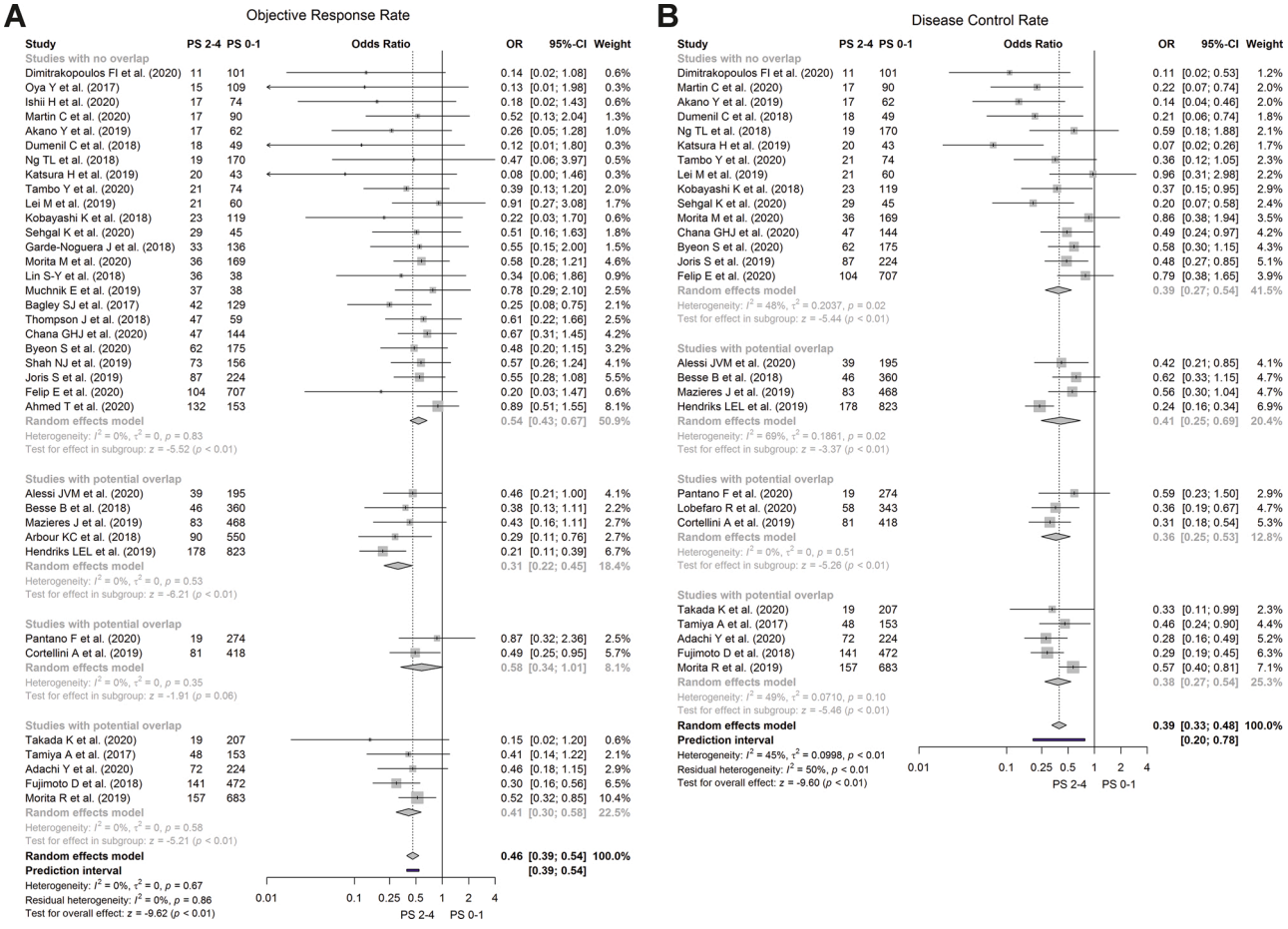

Fig. 3. Forest plots for the Odds Ratio of Overall Response Rate (A) and Disease Control Rate (B).

with different lines of treatment (Fig. D.18), with different quality according to Newcastle-Ottawa Scale (Fig. D.19), with a focus on specific populations (Fig. D.20), with different source of data (Fig. D.21) and after exclusion of the studies with potential partial overlap of patients (Fig. D.22, HR range: 1.79–2.22). The analysis of funnel plot asymmetry identified no potential publication bias (rank correlation test [21] p = 0.250, linear regression test [22] p = 0.320; Fig. D.23) and accounting for the potentially missing studies using the "trim and fill" method [23] did not affect the pooled result (HR = 2.07, 95 %CI: 1.87–2.30; Fig. D.24).

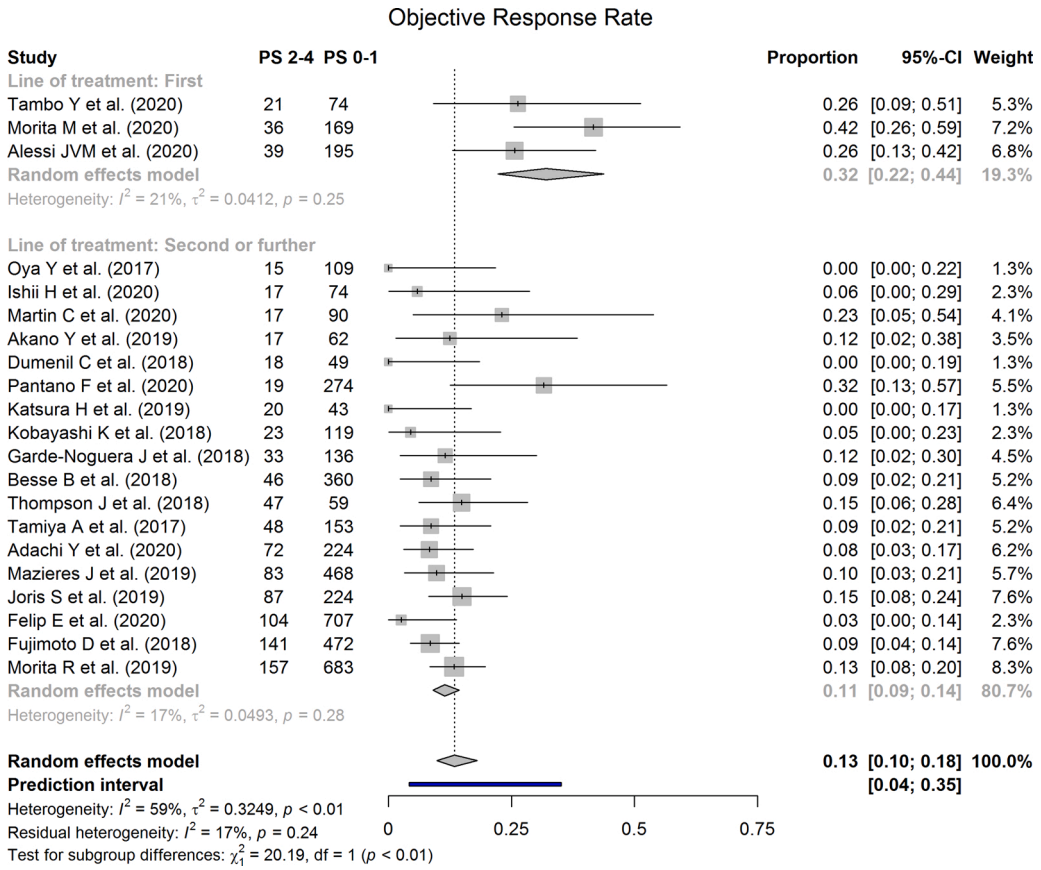

Fig. 4. Forest plot for the Objective Response Rate subgroup analysis according to the line of treatment in PS ≥ 2 patients.

3.4. Overall survival

Thirty-nine studies provided data on overall survival (n = 17,600 patients; 2373 PS ≥ 2 and 15,227 PS ≤ 1). The hazard ratio for OS in PS ≥ 2 *vs.* PS ≤ 1 patients was 2.76 (95 %CI: 2.43–3.14; PI: 1.38–5.53) with marked heterogeneity (I^2 = 77 %, Fig. 5B). The results did not differ significantly in the following subgroups of studies: with different lines of treatment (Fig. D.25), with different quality according to Newcastle-Ottawa Scale (Fig. D.26), with a focus on specific populations (Fig. D.27), with different source of data (Fig. D.28) and after exclusion of the studies with potential partial overlap of patients (Fig. D.29, HR range: 2.20–3.11). The analysis of funnel plot asymmetry identified no potential publication bias (rank correlation test [21] p = 0.640, linear regression test [22] p = 0.090; Fig. D.30) and accounting for the potentially missing studies using the "trim and fill" method [23] did not affect the pooled result (HR = 2.36, 95 %CI: 2.07–2.70; Fig. D.31).

3.5. Adverse events

Twenty-five studies provided data on adverse effects (n = 7302 patients; 1339 PS ≥ 2 and 5963 PS ≤ 1). The odds ratio for AEs in PS ≥ 2 *vs.* PS ≤ 1 patients was 1.12 (95 %CI: 0.84–1.48; PI: 0.46–2.73) with moderate heterogeneity (I^2 = 37 %, Fig. 6). The results did not differ significantly in the following subgroups of studies: with different lines of treatment (Fig. D.32), with different quality according to Newcastle-Ottawa Scale (Fig. D.33), with a focus on specific populations (Fig. D.34), with different source of data (Fig. D.35) and after exclusion of the studies with potential partial overlap of patients (Fig. D.36, OR range: 0.63–1.27). The analysis of funnel plot asymmetry identified no potential publication bias (rank correlation test [21] p = 0.460, linear regression test [22] p = 0.670; Fig. D.37).

4. Discussion

The pooled results from 67 studies identified in our systematic review and meta-analysis have demonstrated a significant reduction in both ORR and DCR in PS ≥ 2 NSCLC patients treated with ICIs when compared with PS ≤ 1 patients. The safety analysis showed that the ratio of severe AEs was similar regardless of the PS score.

The management strategy of NSCLC patients with poor PS remains the subject of a debate [91]. The body of prospective evidence addressing this unmet need is very limited. The CheckMate 153 and 171 trials of nivolumab in previously treated patients with NSCLC showed favourable safety profile in PS = 2 patients, but the median OS in this group was only 4–5 months [6,7]. The TAIL trial provided similar results (presented during ESMO 2019) for atezolizumab in pretreated NCSLC patients with stage IIIb-IV disease [10]. A median OS for PS = 2 patients in this study was merely 3.5 months, considerably shorter than in the overall population (11.1 months). The CheckMate 817 trial evaluates both nivolumab and ipilimumab in the previously untreated stage IV or recurrent NSCLC [92]. The full results have not been published yet, but the early data presented at the ESMO Immuno-Oncology Congress 2019 indicate both fair safety profile and promising OS outcomes in patients with co-morbidities or poor PS. Still, the median OS was much shorter in this group (*i.e.* 9.9 months *vs.* 17.0 months in PS ≤ 1 patients). The PePS2 study is the first prospective single arm trial that specifically enrolled only PS = 2 patients with NSCLC to be treated with pembrolizumab in both first and subsequent line [9]. Similarly to CheckMate trials, the treatment was safe in this population and the median OS of 9.8 months was comparable with the results of CheckMate 817 study. Importantly, all aforementioned trials were performed in unselected populations with a very low proportion of PS = 2 patients (10–15 % in CheckMate and TAIL studies). The authors of PePS2 study suggested a greater clinical benefit with higher PD-L1 expression, but due to limited

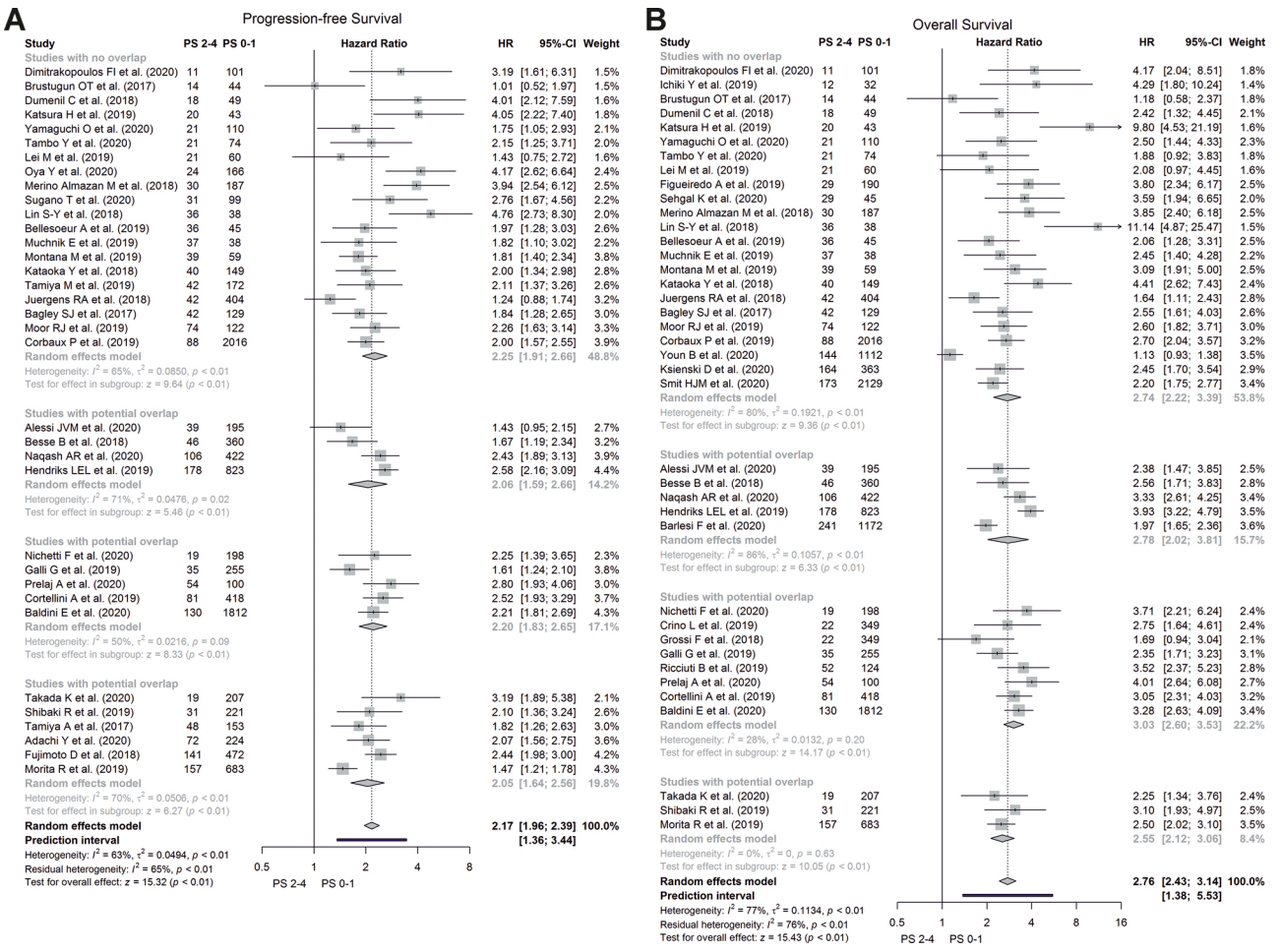

Fig. 5. Forest plots for the Hazard Ratio of Progression-free Survival (A) and Overall Survival (B).

sample size, a robust conclusion could not be drawn. Currently, there are two ongoing phase III RCTs comparing ICIs with chemotherapy, which include PS $\geq$ 2 patients. The eNERGY trial (NCT03351361) evaluates first-line nivolumab plus ipilimumab *versus* carboplatin-based chemotherapy, while the IPSOS trial (NCT03191786) compares first-line atezolizumab with single agent chemotherapy by investigator choice (vinorelbine or gemcitabine). Nevertheless, results of these trials are not expected soon, thus, no new, high quality prospective data to support treatment decisions may not be available in the near future.

Importantly, patients with PS $\geq$ 2 represent a heterogeneous population [93]. A recent study by Facchinetti et al. showed that in advanced NSCLC patients with impaired PS and a PD-L1 TPS $\geq$ 50 % treated with first-line pembrolizumab, outcomes were strongly dependent on the reason constituting the poor PS [94]. Patients with PS = 2 due to comorbidities had a significantly better prognosis compared with patients whose poor PS was determined by the disease burden. The limited inter- and intra-rater reliability of PS assessment adds another layer of complexity [95]. Nevertheless, PS remains a strong prognostic factor in NSCLC patients treated with ICIs [96]. Still, the key question whether poor PS is also predictive of immunotherapy efficacy remains open. This is of particular importance in NSCLC management in which the benefit from ICIs has been proven in trial populations which were unrepresentative for the average clinical populations (*i.e.* younger patients with less comorbidities). The issue of sorafenib for hepatocellular carcinoma exemplifies the case that if a drug is administered to 'real-world' patients who mostly do not meet its trial inclusion criteria, the results might be significantly poorer than those reported in the trial [97]. Thus, in such cases, there is a non-negligible risk of doing more harm than good. In fact, a recent study found that in patients with poor PS, the use of ICIs near death was more frequent than in PS $\leq$ 1 patients, and this treatment was associated with increased hospitalizations and in-hospital deaths, decreased referral to hospice, and shorter duration of hospice stay [98].

Our systematic search provided data an unprecedented number of NSCLC patients with poor PS treated with ICIs. We applied a random-effects model of meta-analysis due to the high number of retrospective studies of various designs and research questions. Crucially, we noted a twofold decrease of ORR in PS $\geq$ 2 patients when compared to the PS $\leq$ 1 group, with all included studies consistently reporting worse ORR in patients with impaired PS (Fig. 2). The subgroup analyses showed that the proportion of responses was greater in patients treated with ICIs in the first-line setting when compared to the subsequent lines. A higher proportion of responders in this setting is probably related to enrolment of patients with tumours showing high PD-L1 expression, whereas later line-patients are typically treated independently of PD-L1 status. This, however, did not translate to a difference in odds ratios between the first-line treatment (0.49) and the subsequent lines (0.43). Thus, the benefit of early ICI introduction in patients with high PD-L1 TPS seems to be independent of the PS. This is supported by the only prospective trial evaluating previously untreated NSCLC patients with PS $\leq$ 2 (CheckMate 817), which reported the median OS about twofold greater than survival reported in other trials which included poor PS patients. Furthermore, our analysis indicates that the OR for DCR (also termed clinical benefit rate) is even poorer than for ORR (0.38). Similarly to ORR analysis, the proportion of responses and disease stabilization was greater in patients treated with ICIs in the first-line setting than in subsequent lines, but, again, it did not translate to a difference in odds

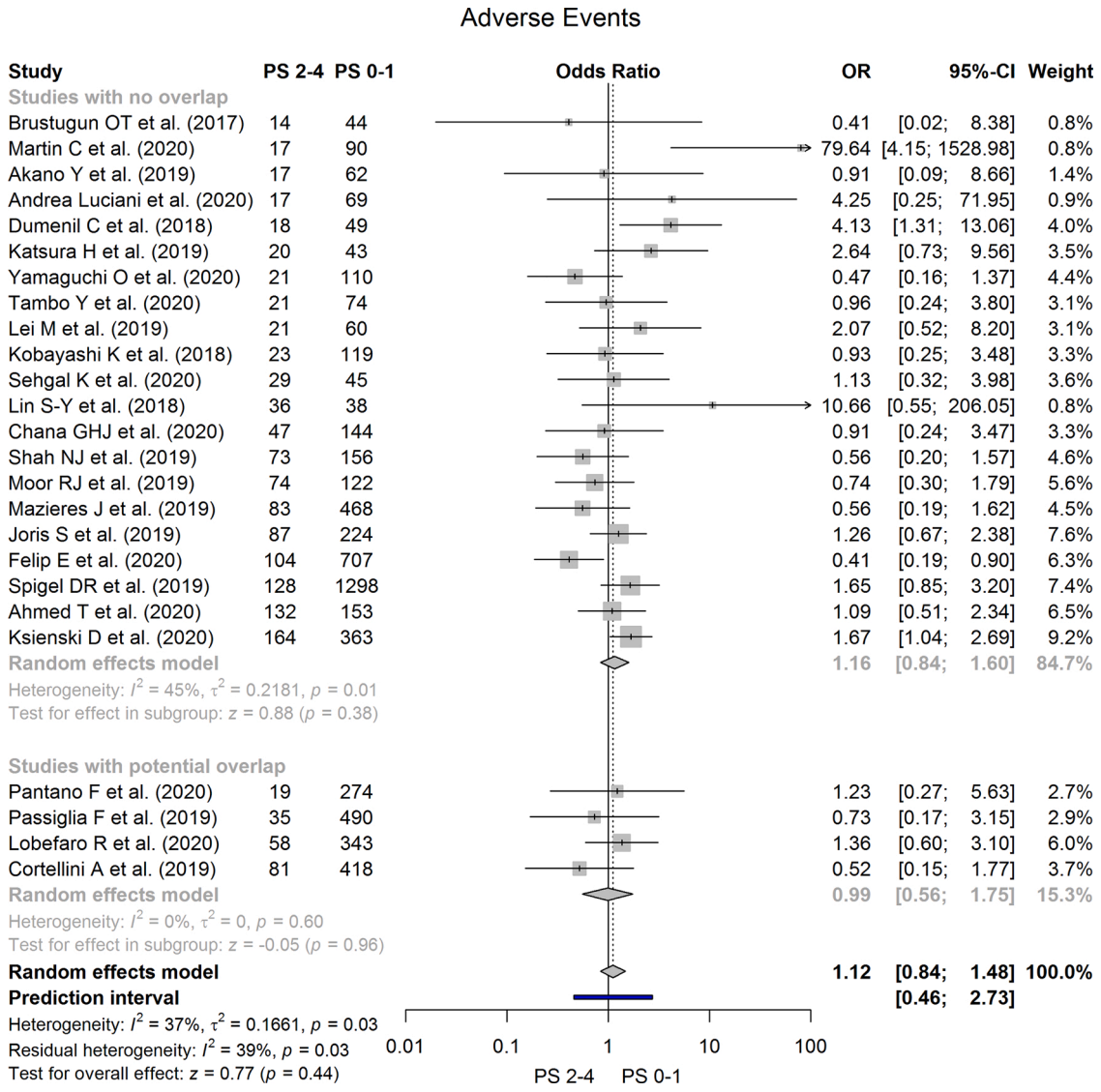

Fig. 6. Forest plot for the Odds Ratio of Adverse Events.

ratios. Although planned, the subgroup analysis evaluating the response regarding treatment line was imbalanced with the vast majority of studies reporting subsequent lines of therapy. Hence, these results should be viewed with caution and as hypotheses-generating for future clinical trials. We have also performed analyses evaluating the prognostic significance of PS status. Similar to other authors we found that this variable has a strong prognostic impact regardless of the treatment line. However, worse outcomes were noted in subsequent lines for both PFS and OS. Importantly, in both PFS and OS, we noted a greater level of heterogeneity with I^2 exceeding 50 %. The same issue was reported by authors of a meta-analysis focused on the prognostic significance of PS [96]. The described high heterogeneity within PS $\geq$ 2 subgroup appears to be the most possible explanation. However, the retrospective nature of many included studies has to be also taken into account. Many were single centre reports with PFS assessed by the investigators (not by an independent panel). Availability of other therapy options and opportunity to participate in early phase clinical trials could also have impacted the results. Finally, the analysis of severe AEs did not show differences between PS $\leq$ 1 and PS $\geq$ 2 patients, confirming the results from prospective trials. However, a high level of heterogeneity should be also noted. The vast majority of studies reported insignificant differences in severe AE rates between the groups, however, studies with a significantly lower [7] or higher [32,65] rates of treatment-related toxicity were present. This analysis might be biased by toxicity underreporting which is well-described in retrospective studies where toxicity is reported by clinicians [99].

The first to be named among limitations of this meta-analysis is that the majority of included studies were retrospective with no blinded independent central review of response assessment. However, a recent analysis of large number of phase III RCTs in patients with solid tumours found no systematic bias between local and central assessments [100]. Moreover, we applied the Newcastle-Ottawa Score for Quality Assessment and it accounts for the reported and factual methodology of outcome assessment across studies [14,15]. The majority of the included studies reported satisfying and robust methodology for outcome assessment, which could be partially explained by the fact that treatment with ICIs is still under tight control across economical medical systems due to its high cost. On the other hand, adverse events are often underreported in retrospective studies, and even in the more rigorously controlled setting of clinical trial [101]. This may also be noted in this analysis as there were relatively fewer studies reporting safety data. A lower amount of heterogeneity observed for ORR and DCR may partially result from the fact that some patients did not survive long enough to undergo a radiological assessment of response. However, we noted that a significant publication bias was present only in ORR analysis. It should be emphasized that different studies specified different outcome

measures – for nearly all studies reporting DCR, ORR was also available, but not *vice versa*, as seen in Fig. 3, panels A and B. In result, ORR analysis included the smallest studies which often tend to overestimate the true effect size (selection bias due to a phenomenon known as the "winner's curse") [102]. Nevertheless, trim and fill analysis showed that these deviations did not affect the pooled result. When results of the studies were not reported in a format suitable for meta-analysis, we tried to contact the study authors and pharmaceutical company sponsors with a request for additional data. While none of the pharmaceutical companies have responded to our messages, in contrast, the responses from individual investigators were very helpful. We received 22 responses which greatly improved the quality of our paper and allowed an increase in the study sample size. Finally, the absence of studies with a control group consisting of patients treated with cytotoxic agents makes it impossible to evaluate whether patients with poor PS should be offered chemotherapy instead. Such head-to-head comparisons are of utmost importance and we believe that they should be rigorously tested in prospective RCTs. This suggestion stands in line with the recent statements calling to broaden the eligibility criteria to make RCTs more generalizable [103]. Future clinical trials should include a very detailed evaluation of patients' PS, similar to the PePS2 study, together with the assessment of the reason of poor PS determination. Due to the fact that the vast majority of industry-funded clinical trials are done solely in PS 0-1 patients, we suggest that such an initiative may be started by the academic community. The example of the recently reported LungART trial [104] shows that properly designed academic trials investigating the most important clinical endpoints, *i.e.* OS and QoL, could be practice changing.

While data from RCTs are lacking, the presented herein meta-analysed "real-world" and trial data suggest caution with the use of ICI in NSCLC patients with PS $\geq$ 2 or higher. Such patients are, on average, twice less likely to achieve CR, PR or even SD when exposed to ICIs when compared to a representative PS $\leq$ 1 population. The prognostic significance of poor PS status was confirmed for both PFS and OS. Nonetheless, the safety profile is comparable irrespective of the PS score. In our opinion, future studies should primarily investigate whether there is an actual benefit of ICIs *versus* chemotherapy in PS $\geq$ 2 NSCLC patients, and focus on identifying tools to allow patient selection for those who may benefit more from ICI therapy.

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Contributors

BT, M Bieńkowski and M Braun did the literature search, collected the data, analysed and interpreted the data and did the quality assessment. RD and SP supervised the study. All authors designed the study, drafted the manuscript and revised and approved the manuscript for submission.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

BT, M Bieńkowski and M Braun declared no competing interests. RD received compensation for advisory boards or lectures from Roche, AstraZeneca, Pfizer, Novartis, Boehriner-Ingelheim, Takeda, FoundationMedicine, MSD and SeattleGenetics. SP received compensation for consultancy from BMS, Roche, Takeda, AstraZeneca, Novartis, Pfizer, MSD, EMD Serono, Guardant Health, AbbVie, Boehringer Ingelheim, Tesaro, Incyte, Paradox, and BeiGene. COI forms are provided in Appendix E.

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Appendix A. Supplementary data

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