Peer Review File

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Reviewer A

1. First, in the title the authors need to indicate the outcomes of this study, the incidence rate and associated factors of endocrine adverse events, and the clinical research design, i.e., a retrospective cohort study.

Response: According to reviewer's insightful suggestion. We have corrected the title. Please see the changes on line 3-4, page 1 in the revised manuscript (A real-world retrospective study of incidence and associated factors of endocrine adverse events related to PD-1/PD-L1 inhibitors).

2. Second, the abstract needs some revisions since it is not adequate. In the background, the authors did not describe the clinical needs for the real-world data on endocrine adverse events and their potential clinical contributions. In the methods, inclusion criteria of eligible subjects, baseline clinical variables collected, the diagnostic criteria for endocrine adverse events, and how the factors associated with endocrine adverse events were analyzed. In the results, the authors need to report findings from multiple regression analysis, not univariate analyses. The conclusion on the favorite efficacy of patients with endocrine AEs need to be made with cautions since the authors did not adjust for the confounding effects of other variables.

Response: We thank the reviewer a lot for this valuable comment for improving our manuscript. According to the advice of reviewer, we have modified the abstract. Please see the changes on line 27-31, page 1 and line 4-21, page 2 in the revised manuscript. The results of univariate and multivariate analysis were added in the "Results" section of Main text (Seen on line 5-12, page 7), attached with Table 4 and Table 5 (Seen on page 17-19).

3. Third, in the introduction of the main text, the authors need to have comments on the limitations of endocrine AE data from clinical trials, why real-world data are needed, and the clinical questions can be answered and the knowledge gaps can be filled by the real-world data. These questions are important for this research focus.

Response: As suggested by the reviewer, we have underlined the limitations of endocrine AE data from clinical trials and the importance of real-world data. Modification can be seen on line 14-18, page 3 in the revised manuscript.

4. Fourth, in the methodology of the main text, please describe the clinical research deign, the assessment of baseline clinical characteristics, and outcome assessment of treatment response and endocrine AEs. In statistics, please describe the details of the multiple logistic regression analysis and how to ascertain the independent association of endocrine AEs with treatment response. Please ensure P<0.05 is two-sided.

Response: We're sincerely sorry that we didn't make the methodology clear. The clinical research design, the assessment of baseline clinical characteristics, and outcome assessment of treatment response and endocrine AEs were described in the "Study design and patients" and "Endocrine adverse events and evaluation of efficacy" of the Methods section (seen on line 1-11 18-29, page 4). In statistics, according to the reviewer's instruction, we have added the details of the multiple logistic regression analysis and how to ascertain the independent association of endocrine AEs with treatment response. We also ensure that P<0.05 is two-sided (seen on line 31-33, page 4; line 1-7, page 5).

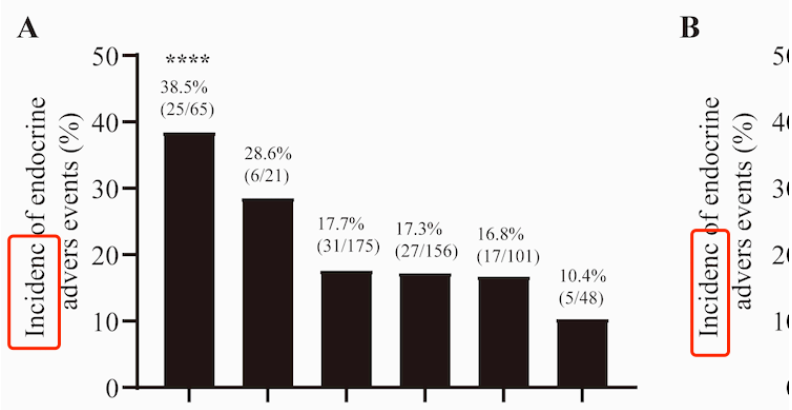
Reviewer B

1. All abbreviations should be defined the full term when they are first used in the Abstract Please check carefully and revise; such as: PD-1/PD-L1, AEs.

Response：We have defined the full term of PD-L1/PD-L1 and AEs in the abstract (Seen on line 30-31, page 1 and line 4, page 2).

2. Figure 1

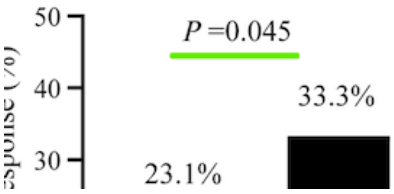
Check the spelling.



Response: We sincerely apologize for the stupid mistake, and have revised it (Seen Figure 1-revised).

3. Please check the data.

(33.3% vs. 23.1%, P=0.0.045) and DCR (91.1% vs. 79.1%, P=0.008) compared to the nonendocrine AE group (Figure 2A ,2B). In multivariate analysis, endocrine AEs remained an independent factor for both ORR (OR = 1.764, 95%CI 1.052–2.957, P =



Response: We have been ashamed for the careless, and made modification (Seen line 4, page 7).

4. Table 1

1) Some boxes are empty, please confirm whether they are correct. Such as:

Measured variables	Total (n=581)	AE group (n=116)	AE group (n=465)	P value	P value*
Gender				0.108	
Male	425	78 (18.4)	347 (81.6)		
Female	156	38 (24.4)	118 (75.6)		
Age (years)				0.527	
≥65	164	30 (18.3)	134 (81.7)		
<65	417	86 (20.6)	331 (79.4)		
Type of drug				0.189	
Anti-PD-L1	15	5 (33.3)	10 (66.7)		
Anti-PD-1	566	111 (19.6)	455 (80.4)		
Anti-PD-L1 agents				0.119	
Atezolizumab	7	4 (57.1)	3 (42.9)		
Durvalumab	8	1 (12.5)	7 (87.5)		
Anti-PD-1 agents				0.001	0.002

2) The sum-up of these numbers is not 581.

Lines of immunotherapy	
1	281
2	174
≥3	109
Others	18

3) The sum-up of these numbers is not 465.

Lines of immunotherapy				0.189
1	281	56 (19.9)	225 (80.1)	
2	174	28 (16.1)	146 (83.9)	
≥3	109	29 (26.6)	80 (73.4)	
Others	18	3 (16.7)	15 (83.3)	

Response: (1) Some boxes in the P-value* column were empty, because we only selected the variables with a P value <0.1 identified in univariable analysis and simultaneously with clinic significance for the multivariable analysis.

(2) (3) We apologize for the miscalculation and have corrected them (Seen revised Table 2).

5. Table 3

1) Please check if below data are correct.

Table 3 Impact of endocrine adverse events on the efficacy of treatment

Tumor response	Total (n=458)	Endocrine AE group (n=90)	Non-endocrine AE group (n=368)	P
CR	0	0	0	0.012
PR	115 (25.1)	30 (33.3)	85 (23.1)	
SD	258 (56.3)	52 (57.8)	206 (56.0)	
PD	85 (18.6)	8 (8.9)	77 (20.9)	
ORR%	115 (25.1)	30 (33.3)	85 (23.1)	0.045
DCR%	373 (81.4)	60 (91.1)	291 (79.1)	0.008

AE, adverse event; CR, complete response; PR, partial response; SD, stable disease;

2) If this p value (0.012) is for “CR, PR, SD, PD”, or only for “CR”.

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AE, adverse event; CR, complete response; PR, partial response; SD, stable disease;

PD, progressive disease; ORR, objective response rate; DCR, disease control rate. P

Response: (1) We apologize for the confusion. CR plus PR was categorized as the objective response rate (ORR), while CR, PR, plus SD was defined as the disease control rate (DCR) (mentioned in part of Method). Therefore, we checked and confirmed the above data were correct. (2) We confirm this p value (0.012) is for “CR, PR, SD, PD”.

6. Table 4 and table 5

1) Some boxes are empty, please confirm whether they are correct.

Table 4. Univariate and multivariate analyses of clinical variables on ORR(n=458)

Variables	No.	ORR	Univariate analyses		Multivariate analyses		
		N (%)	χ2	*P*-value[a]	OR	95%CI	*P*-value[b]
Gender							
Male	336	92(27.4)	3.462	0.063			
Female	122	23(18.9)					
Age(y)							
≥65	126	34(27.0)	0.325	0.569			
<65	332	81(24.4)					
Cancer types							
Head and neck cancer	41	14(34.1)	19.283	0.004	0.857	0.772-1.016	0.075
Lung cancer	237	72(30.4)					
Digestive tract cancer	90	8(8.9)					
Urinary tumor	35	9(25.7)					

2) It seems that some data are in the wrong boxes, please check and revise.

Table 4. Univariate and multivariate analyses of clinical variables on ORR(n=458)

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Cancer types							
Head and neck cancer	41	14(34.1)	19.283	0.004	0.857	0.772-1.016	0.075
Lung cancer	237	72(30.4)					

Response: (1) Some boxes in the P-value[b] column were empty, because we only selected the variables with a P value <0.1 identified in univariable analysis and simultaneously with clinic significance for the multivariable analysis. (2) We have adjusted the data to the correct boxes.

7. The word "studies" is inconsistent with the number of references cited here, please check if "studies" should be changed into "study". Otherwise, here should cite more than 2 studies.

system (9,10). Endocrine AEs are some of the most common irAEs. Previous studies have revealed that approximately 5–10% of patients who receive ICIs are prone to endocrine AEs of any grade, with a median time to onset of 9 weeks (range, 5–36 weeks) from treatment initiation (11). In this study, endocrine AEs occurred in 116 (20.0%)

Response: We have corrected it (Seen on line 16, page 7).

8. Please check if here should add citations (more than 2) as you mentioned "many meta-analyses".

Although many meta-analyses have reported ICI-related endocrine toxicity, most of these data are derived from clinical trials, but there is short of data in real world. Clinical trials are limited by strict inclusion and exclusion criteria and the results can only reflect a small subset of population. Patients in real-world situation are more complicated and heterogeneous. Therefore, gathering real-world evidence is helpful to answer clinical questions and fill the knowledge gaps.

Response: We have corrected it.

9. STROBE Reporting Checklist

This is a cohort study, please refill item 14c and item 15(cohort study), and fill "N/A" for inappropriate study type.

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page5/Line8-21	Results/Paragraph3
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable	Not Applicable
		(c) ***Cohort study*** —Summarise follow-up time (eg, average and total amount)	Not Applicable	Not Applicable
Outcome data	15*	***Cohort study*** —Report numbers of outcome events or summary measures over time	Not Applicable	Not Applicable
		Case-control study —Report numbers in each exposure category, or summary measures of exposure	Not Applicable	Not Applicable
		Cross-sectional study —Report numbers of outcome events or summary measures	Page5/Line23-33	Results/Paragraph4
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	Not Applicable	Not Applicable

Response: We have corrected it (Seen STROBE Reporting Checklist).