

Abstract

Immune checkpoint inhibitors (ICIs) are efficient against cancers but can lead to adverse events (AE). Traditionally, a statistical model with normal distributions for both inter- and intra-trial variabilities (normal-normal, N-N) is used as a standard approach to calculate AEs rates in meta-analysis. However, this can be problematic in case of rare events, where many groups within the studies have few or even zero events, since the standard errors then become highly variable or not even defined and continuity correction method introduce bias into results. We replaced the approximate normal within-study likelihood by the corresponding exact likelihood and compared results for both approaches using Bayesian model-based meta-analysis (BMA). Use of a N-N model led to significant overestimation (up to two times) of rare treatment related adverse events (itrAE) rates, comparing to use of an exact binomial-normal (B-N) model.

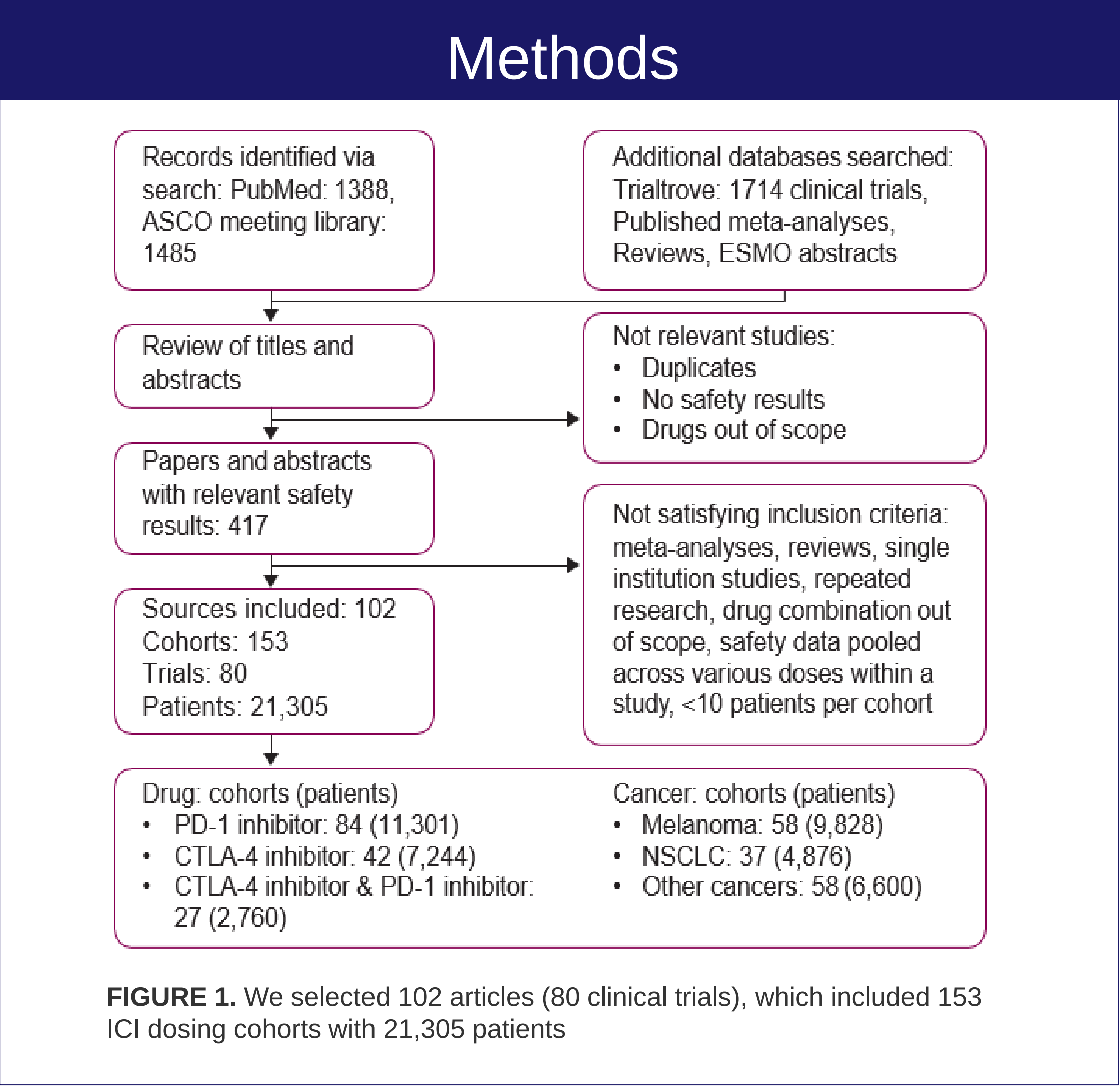
Introduction

Immune checkpoint inhibitors (ICIs) are promising anti-cancer therapies; yet, they are associated with immune-mediated adverse events (imAE), especially in combination therapies. The objective of this study was to apply a BMA towards the quantification of dose dependence of different AEs for PD-1 (nivolumab, pembrolizumab) and CTLA-4 (ipilimumab, tremelimumab) inhibitor monotherapies and combinations and to estimate AE rates for treatment related (trAEs) and immune mediated (imAEs) adverse events. In addition, as reported previously for standard meta-analyses, use of a statistical model with normal distributions for both inter- and intra-trial variabilities (normal-normal, N-N) can lead to biased results for rare events. In such cases, a binomial-normal (B-N) model should be used. We thus compared N-N and B-N models when studying rare AEs for ICIs therapies.

Methods

Data search and statistical analysis

We searched PubMed and TrialTrove databases, ASCO and ESMO abstracts to identify relevant ICI safety data. In order to quantitatively study the dose dependences, we converted the dosing regimens into drug exposures derived with published pharmacokinetic modes and normalized exposure by the drug potency (IC 50) to compare different drugs to the same target [1]. To explore dose dependence, we split the dosing interval into lower and higher dosing subgroups and compared their AE rates. The BMA was performed for all-grade and high-grade (Grades 3-4) treatment-related (trAEs) adverse events and for imAEs associated with specific organ groups (gastrointestinal, dermatological, hepatic, endocrine, pulmonary). Software STAN and the *brms* package in R software were used to perform the BMA and *metafor* package to perform standard meta-analysis. B-N and N-N models were compared using clinical trial data and simulated datasets. We used meta-regression to assess the quantitative dependence of AE rates on drug exposure.



Bayesian modeling

Bayesian meta-analysis was implemented in STAN *rstan* and *brms* packages in R. We used random effects normal-normal model and binomial-normal model for rare events (following Stijnen 2010) [2]..

Target		Total trAE		Total Grade 3/4 trAE		Gastrointestinal imAE		Hepatic imAE		Skin imAE		Endocrine imAE		Pulmonary imAE	
Dose/Exposure Subgroup		Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher	Lower	Higher
PD-1	AE %	71 (72)	74 (74)	17 (17)	19 (19)	1.5 (1.5)	3.8 (4.1)	1.9 (1.8)	0.04 (0)	1.1 (1.0)	1.3 (0.5)	0.38 (0.3)	0.4 (0)	0.8 (0.8)	1.2 (0.4)
	CI	68-75 (68-75)	70-77 (70-78)	15-19 (15-20)	15-22 (15-24)	1.2-2.0 (1.2-2.0)	1.8-8.0 (1.0-12)	1.4-2.5 (1.1-2.5)	0-80 (-)	0.8-1.6 (0.6-1.5)	0.3-6.2 (0-4.8)	0.2-0.9 (0-0.7)	0-19 (-)	0.4-1.5 (0.2-1.4)	0.2-8 (0-6.2)
	N	7506	2377	8899	2402	3644	247	3557	227	3644	247	2838	227	3557	227
PD-1 dose difference		P=.34		P=.41		P=.08		P=.42		P=.87		P>.9		P=.66	
CTLA-4	AE %	83 (84)	89 (90)	23 (22)	37 (34)	9.5 (9.2)	13 (11.5)	1.1 (0.6)	7.0 (6.7)	1.4 (1.0)	2.9 (2.7)	2.6 (2.3)	4.3 (4.0)	0.14 (0)	1.0 (1.0)
	CI	75-89 (76-90)	85-92 (84-95)	18-28 (17-27)	32-42 (27-41)	7.2-12 (6.4-12)	10-16 (7.7-15)	0.4-3.2 (0-1.8)	5.3-9.1 (4.6-9.2)	0.5-3.4 (0-3.5)	1.8-4.5 (1.3-4.4)	1.6-4.2 (0.9-4.3)	2.6-7.0 (2.0-7.0)	0.02-1.0 (-)	0.5-2.0 (0-80)
	N	1934	4907	1934	4931	1549	2701	1652	2615	1652	2701	1652	2104	719	817
CTLA-4 dose difference		P=.12		P<.001		P=.09		P<.001		P=.165		P=.15		P=.06	
CTLA-4 + PD-1 (CTLA-4 dose)	AE %	83 (83)	92 (92)	35 (34)	53 (53)	6.4 (6.8)	16.8 (17.6)	8.6 (7.7)	18 (15)	3.8 (3.6)	6.3 (4.9)	3.8 (3.6)	5.3 (2.9)	1.8 (1.4)	1.6 (1.6)
	CI (95%)	76-88 (75-88)	86-95 (86-96)	30-41 (29-40)	46-59 (44-62)	3.1-13 (3.8-13)	14-20 (11-23)	6.1-12 (4-13)	15-22 (10-24)	2.9-5.1 (1.9-6.1)	4.5-8.6 (1.2-11)	2.9-5.1 (2.2-5.7)	3.7-7.6 (0-8.5)	0.9-1.6 (0.4-3)	0.8-3.1 (0.1-5.5)
	N	2064	654	2106	654	1183	509	1183	509	1203	544	1203	509	1203	509
CTLA-4 + PD-1 dose difference (CTLA-4)		P=.016		P<.001		P=.008		P<.001		P=.02		P=.17		P=.8	

TABLE 1 Subgroup Analysis of AE Rates and ICI Dose/Exposure for total and grade 3&4 organ classes AEs. Results of Bayesian meta-analysis (in brackets) are compared with the standard meta-analysis results. B-N model was used.

Methods

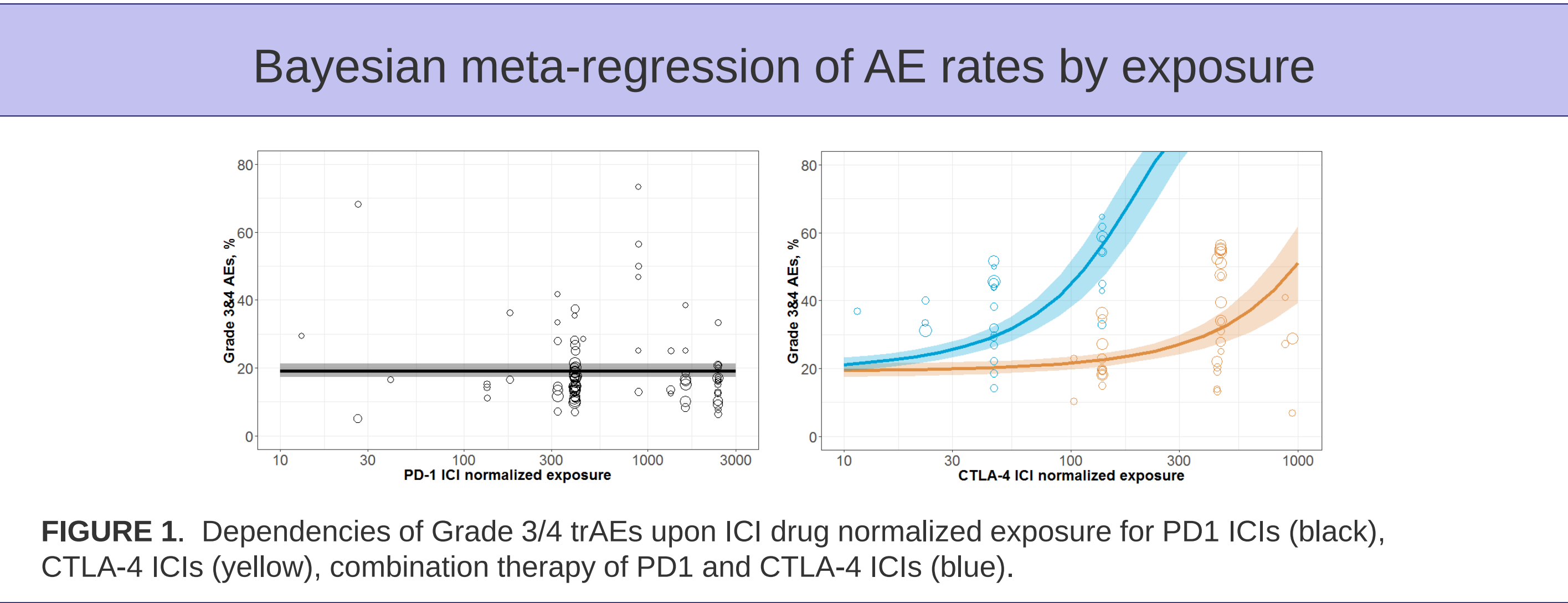
Normal-Normal and Binomial-Normal Bayesian models were:

$$\begin{aligned} \text{logit}(\mathbf{y}) &\sim \text{Normal}(\boldsymbol{\theta}, \boldsymbol{\sigma}^2) & \mathbf{Y} &\sim \text{Binomial}(\mathbf{n}, \boldsymbol{\pi}) \\ \boldsymbol{\theta} &\sim \text{Normal}(\boldsymbol{\alpha} + \boldsymbol{\beta}\mathbf{x}, \tau^2) & \text{logit}(\boldsymbol{\pi}) &\sim \text{Normal}(\boldsymbol{\alpha} + \boldsymbol{\beta}\mathbf{x}, \tau^2) \end{aligned}$$

Where $\mathbf{y}$ is the proportion of patients with AE in clinical trials, $\mathbf{Y}$ is the number of patients with AE, $\mathbf{x}$ is the matrix of the trial-level patient baseline characteristics (covariates), such as dose/exposure, line of therapy, etc., $\mathbf{n}$ is numbers of patients in trials, $\boldsymbol{\pi}$ is the probability of AE, $\boldsymbol{\beta}$ are the regression coefficients, $\boldsymbol{\alpha}$ is the effect size in the absence of covariates for logit transformed probabilities. Vectors are marked in bold. 95% quantiles of the inverse logit transformed posterior distribution were used as confidence intervals. Non-informative priors were used.

Results

A total of 102 articles were identified, representing 21,305 patients in 153 dosing cohorts treated with ICI monotherapies or combinations (Figure 1). No relationship between AE rates and dose of anti PD-1 monotherapy was observed. Dose dependence was observed for CTLA-4 inhibitor monotherapy for total grade 3/4 trAEs (AE rates for lower and higher doses subgroups - 22% vs. 34%, respectively) and hepatic imAEs (0.6% vs. 6.7%) and for combination therapy of CTLA-4 + PD-1 ICIs for total grade 3/4 trAEs (34% vs. 53%), and for organ imAE (gastrointestinal (6.8% vs. 17.6%), hepatic (7.7% vs. 15%) and skin (3.6% vs. 4.9%)) The results of Bayesian and standard meta-analysis agrees (Table 1). AE rates for CTLA-4 + PD-1 ICIs combinations were supra-additive for imAEs vs respective monotherapies (more than a sum). Use of a N-N model led to significant overestimation (up to two times) of rare AEs rates (Tables 2-4), while use of a B-N model gave more accurate results confirmed by external validation exercises. Both Bayesian and standard meta-analyses showed similar advantage of B-N model over N-N model.



Comparison AE rates obtained with N-N and B-N models

	Rash		Diarrhea		Colitis		Pneumonitis		Hyperthyroidism		Hypothyroidism	
	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N
AE,%	0.71	0.41	1.32	0.96	1.53	1.03	1.75	1.41	0.36	0.06	0.42	0.14
CI	0.56-0.89	0.3-0.56	1.1-1.59	0.76-1.21	1.07-2.15	0.65-1.64	1.41-2.17	1.11-1.78	0.23-0.67	0.02-0.19	0.3-0.59	0.08-0.22
N	13790		15575		3890		8757		4867		11789	

TABLE 2 Grade 3-5 trAEs for PD-1 ICIs monotherapies.

	Rash		Diarrhea		Colitis		Pneumonitis		Hyperthyroidism		Hypothyroidism	
	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N
AE,%	0.79	0.45	1.39	1.14	1.17	0.86	1.35	0.96	0.31	0.09	0.34	0.13
CI	0.52-1.19	0.25-0.8	1.06-1.82	0.82-1.58	0.97-1.42	0.67-1.1	1.09-1.66	0.73-1.27	0.22-0.45	0.05-0.17	0.25-0.48	0.08-0.21
N	5187		4377		10932		11237		11005		12204	

TABLE 3 Grade 3-5 imAEs for PD-1 ICIs monotherapies.

	Rash		Diarrhea		Colitis		Pneumonitis		Hyperthyroidism		Hypothyroidism	
	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N	N-N	B-N
AE,%	1.96	1.34	5.16	4.28	7.25	6.26	1.96	1.7	1.67	0.71	0.66	0.26
CI	1.51-2.53	0.88-2.04	3.91-6.78	3.12-5.85	5.74-9.12	4.45-8.76	1.21-3.15	1.04-2.76	1.06-2.65	0.24-2.04	0.38-1.14	0.12-0.59
N	3411		3502		1074		941		1439		2277	

TABLE 4 Grade 3-5 trAEs for PD-1 + CTLA-4 ICIs combination therapies.

Conclusions

Significant AE dependences on ICIs dose/exposure for anti CTLA-4 ICIs monotherapy and combination therapy of PD1+CTAL4 ICIs were observed with Bayesian and standard meta-analysis. The B-N model showed better performance and should be used for the meta-analysis of rare imAEs. This novel model-based meta-analysis methodology provides a quantitative framework for selecting ICI doses and dosing regimens with respect to specific AE rates.

References

- Shulgin B, Kosinsky Yu, Omelchenko A et al., Dose dependence of treatment-related adverse events for immune checkpoint inhibitor therapies: a model-based meta-analysis. Oncoimmunology 2020 May 21;9(1):1748982. PMID: 32934874
- Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med. 2010 Dec 20;29(29):3046-67. doi: 10.1002/sim.4040. PMID: 20827667.

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